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Presentation number: P1.01

Topic: Neuroanatomy

Ultrastructural sublamina-specific diversity of excitatory synaptic boutons in layer 1 in the adult human temporal lobe neocortex: A qualitative and quantitative electron microscopic analysis

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Introduction:The intricate nature of synapses profoundly influences synaptic transmission and plasticity within brain networks. While extensive studies exist on synaptic boutons (SBs) in various animal brains, quantitative data for human brains remain limited. This doctoral thesis focused on quantitatively analyzing excitatory SBs in layer 1 (L1) of the human temporal lobe neocortex (TLN), employing transmission electron microscopy (TEM) and 3D volume reconstructions.

Method: The study aimed to delineate the synaptic organization of L1 in the human TLN, presenting comprehensive data absent thus far. Parameters including SB size, presynaptic active zones (PreAZs), postsynaptic densities (PSDs), and pools of synaptic vesicles (SVs) were meticulously examined. Notably, L1 SBs exhibited medium size (~6 µm²) with distinct sublaminae showing no significant differences. Mitochondria within SBs played a pivotal role in SV organization.

Discution: Comparison with layer 6 (L6) revealed layer-specific differences in SV pools, suggesting varying synaptic efficacy and modulation. Furthermore, electron microscopic tomography and multivariate analysis elucidated structural characteristics and synaptic parameters, yet failed to identify distinct SB classes.

Astrocytic ensheathment of SBs exhibited layer-specific differences, influencing spatial glutamate concentration and synaptic transmission modulation. Human L1 SBs, positioned strategically as receiving associational and commissural layers, function as signal amplifiers and discriminators.

Result: Overall, profound layer-specific differences in SBs of the human TLN were observed, impacting synaptic efficacy and modulation. These findings enhance understanding of synaptic complexes in both normal and pathological brains, facilitating numerical simulations of synaptic parameters crucial for human brain function.

Presentation number: P1.02

Topic: Neuroanatomy

Interference with Sprouty is neuroprotective and improves axonal regeneration

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Intracellular negative feedback inhibitors of receptor tyrosine kinase signaling, such as the Sprouty (Spry) proteins, play important roles in the development and maintenance of the nervous system. Sprouties function as growth factor antagonists by specific interference mainly with processes upstream of extracellular regulated kinases. Applying different in-vivo lesion models we demonstrate that reduction of Spry2 and -4 in neurons and glial cells promotes neuronal survival and axonal regeneration in the central and peripheral nervous system. Injection of Spry2/4 siRNAs into rat brains reduces the lesion size in response to endothelin-induced vasoconstriction (a model for stroke) three weeks after the injury. In kainate-induced epileptogenesis, secondary brain damage is decreased as well. Heterozygous Spry2/4 knockout mice exhibit reduced neuronal loss three weeks after kainate injection into the hippocampus which is accompanied by increased astrocytosis and reduced neuronal migration (dispersion of granule cells). In the peripheral nervous system, primary sensory neurons dissociated from Spry2 knock-out ganglia reveal stronger ERK activation and enhanced axon outgrowth. Following sciatic nerve crush, significantly more myelinated axons regenerate in Spry2+/- mice which is accompanied by faster recovery of sensomotor performance, higher number of motor endplates in distal muscles and increased expression of GAP43. Taken together, our results suggest a role for Spry as a potential target for pharmacological inhibition to accelerate long-distance regeneration in peripheral nerves and to promote long-term neuron survival in neurodegenerative disease. Supported by the Austrian Science Fund (FWF, SPIN PhD program).

Presentation number: P1.03

Topic: Neuroanatomy

VEGFD signaling balances stability and activity-dependent structural plasticity of dendrites.

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Introduction:

Stable dendritic architecture is a feature of mature neurons which is necessary for proper nervous system function. Mature neurons still possess the capacity for structural flexibility, which is essential to facilitate adaptive processes such as memory formation. What molecular and cellular mechanisms regulate this fine balance between dendritic structural stabilization and flexibility is unknown. Anomalies of the nervous system are linked to abnormal connectivity resulting from failures in the retention of optimal dendritic structure caused by maladaptive plasticity or atrophy. The upkeep of mature dendritic trees depends on vascular endothelial growth factor D (VEGFD).

Methods:

Live imaging, in vivo and in vitro morphometrics, machine learning tracking of dendrite dynamics, phosphoproteomic, rAAV, mouse behaviour, biochemistry, analyses of mRNA and protein levels, immunocytochemistry, immunohistochemistry.

Results:

We describe how VEGFD affects the neuronal cytoskeleton and that VEGFD stabilizes dendrites by modulating the actin cortex and microtubule dynamics. Further, we found that during synaptic activity-induced structural plasticity VEGFD is downregulated. We observed that VEGFD opposes structural changes by negatively regulating dendrite growth in cultured hippocampal neurons and in vivo in the adult mouse hippocampus. A phosphoproteomic screening identified several regulatory proteins of the cytoskeleton modulated by VEGFD. VEGFD induces dephosphorylation of ezrin at tyrosine 478 via activation of the striatal-enriched protein tyrosine phosphatase (STEP). Activity-triggered structural plasticity of dendrites was impaired by expression of a phospho-deficient mutant ezrin in vitro and in vivo.

Discussion:

VEGFD governs the equilibrium between stabilization and plasticity of dendrites by acting as a molecular brake of structural remodeling.

Presentation number: P1.04

Topic: Neuroanatomy

MiRNA changes in adolescents with Anorexia nervosa at admission, discharge, and 1-year follow-up

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Introduction

Anorexia nervosa (AN) is a chronic eating disorder characterised by pathological low body weight and multifactorial pathophysiology, including endocrine dysfunctions, functional/morphological brain alterations, and intestine malfunction. The role of miRNAs in AN has not been investigated in greater depth. However, previous results suggest a dysregulation in the acute state.

Methods

The miRNA levels in the blood serum of AN patients were evaluated at three time points using next generation sequencing: at admission to the hospital, discharge and after 1-year follow-up. The sequencing results were compared to an age-matched control group. Cross-sectional and longitudinal evaluations were performed as well as correlations to clinical parameters.

Results

At the acute state, a total of 220 significantly deregulated miRNA candidates in AN were identified. Correlations with clinical data revealed that a high number of miRNAs were associated with body weight, inflammation, depression, and anxiety behaviour. MiRNA levels altered over the course of the disease leading to the identification of some sequences with specific state or trait characteristics.

Discussion

MiRNAs are pathologically altered in AN and hold great potential as biomarkers to better classify patients into high- and low-risk groups for chronic progression of AN. Future research should focus on determining the specific cells and tissues expressing these miRNAs and identifying the targets they regulate, thereby influencing the severity of the illness.

Presentation number: P1.05

Topic: Neuroanatomy

Cytokine and microbiome changes in adolescents with Anorexia nervosa at admission, discharge, and one-year follow-up

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Abstract:

Introduction: Anorexia nervosa (AN) is a severe eating disorder typically manifesting during ado-lescence. There is increasing evidence that serum cytokine levels are altered in individuals with AN. Previous research has largely focused on adult patients, assuming a low-grade pro-inflammatory state.

Methods: Serum levels of the cytokines tumour necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6 and IL-15, which are pro-inflammatory, were examined in 63 female adolescents with AN and 41 age-matched healthy controls (HC). We included three time-points (admission, discharge, and 1-year follow-up) and investigated whether clinical data and the gut microbiota were associated with cytokine alterations.

Results: Relative to the HC group, serum levels of IL-1β and IL-6 were significantly lower during the acute phase (admission) of AN. IL-1β normalised to control levels after weight recovery. TNF-α levels were not significantly different between the AN and HC groups. IL-15 level were significantly elevated in patients with AN at all time-points. Associations of cytokines with body-weight, illness duration, depressive symptoms, and the microbiome were found.

Conclusion: In contrast to most findings for adults, we observed lower levels of the pro-inflammatory cytokines IL-1β and IL-6 in adolescent patients, whereas IL-15 was consistently increased. Thus, the presence of inflammatory dysregulation suggests a varied rather than uniform pro-inflammatory state.

Presentation number: P1.06

Topic: Neuroanatomy

Extracellular Matrix Alterations in Epileptic Brain Pathologies: A Proteomic Analysis of FCD, MOGHE, and TLE

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Introduction

The extracellular matrix (ECM) of the brain is a complex network crucial for maintaining the physiological structure and function. Consequently, alterations in the ECM may contribute to pathological dysfunction, such as malformations of cortical development (MCDs). MCDs represent major underlying causes of epilepsy, including focal cortical dysplasia (FCD) and mild malformation of cortical development with oligodendroglial hyperplasia in epilepsy (MOGHE). Understanding the role and the composition of the ECM is essential for deciphering its involvement in both physiological and pathological conditions. In this study, ECM protein alterations in epilepsy are investigated, focusing on FCD, MOGHE, and temporal lobe epilepsy (TLE).

Methods

To study the composition of ECM proteins in human brain tissue, we performed proteomics using mass spectrometry. We utilized brain tissue from patients with FCD, MOGHE, and TLE. To identify possible region-specific differences, the tissue samples were taken from various brain regions, including the neocortex, hippocampus, and white matter.

Results

Our proteomics revealed significant alterations in the brain's ECM protein composition across the different brain pathologies. Key ECM proteins displayed varying expression levels in pathologic samples, indicating ongoing ECM remodeling linked to each pathology.

Discussion

This study highlights the pivotal role of the ECM in maintaining brain structure and functionality under physiological conditions, as well as its involvement in the underlying pathologic processes in epilepsy. The differential expression patterns of ECM proteins in FCD, MOGHE, and TLE emphasizes the potential of targeting ECM components as a promising therapeutic approach.

Acknowledgement

German Research Foundation (DFG) project 460333672 CRC1540 EBM

Presentation number: P1.07

Topic: Neuroanatomy

Exploring Age-Related Changes in the Mouse Brain: A Single-Cell Analysis of Male and Female Microglia

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Introduction

Novel technologies such as single-cell RNA and single-nucleus RNA sequencing have shed new light on the complexity of different cell populations in physiological and pathological states. This project aims to investigate the molecular and cellular alterations of microglia occurring in the brains of aging male and female mice at the single-cell and spatial level.

Methods

Utilizing advanced single-cell sequencing technologies Chromium and Visium from 10x Genomics, we profiled the transcriptomes of microglia from young (6 months-old) and aged (24 months-old) wildtype mice of both sexes for specific gene signatures. Sequencing was done with Illumina and data was analyzed using 10x Loupe Browser.

Results

In total we could identify 26 clusters and 11,258 genes from 4 groups (N=2). First results show differences in the expression profile of female and male microglia-specific genes as well as between the two age groups. Phagocytic and activation markers are upregulated in the aged group compared to younger samples. Genes associated with the neurodegenerative phenotype of microglia are upregulated in the aged group as well. Moreover, male and female cells differ in their expression levels of classical activation markers and genes involved in TGFβ signaling.

Discussion

By comparing gene expression patterns and functional pathways between age groups and sexes, we identified different molecular signatures associated with aging. Insights gained from this project may pave the way for future comprehensive studies elucidating the mechanisms driving age-related brain dysfunction and may contribute to the development of novel therapeutic strategies for age-related cognitive impairment and neurodegenerative diseases.

Presentation number: P1.08

Topic: Neuroanatomy

Alteration of brain glial cells in rats after fecal microbiota transplantation from patients with anorexia nervosa

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Introduction: Anorexia nervosa (AN) is a metabo-psychiatric illness, which typically manifests during adolescence. Bidirectional interactions between the gut microbiome and structural brain differences in patients with AN have been identified and were also shown in animal models. This study wanted to examine whether fecal microbiota transplants (FMT) from patients can affect the host-microbiome, cause structural brain changes, and potentially induce AN-like symptoms in rats.

Methods: We included four groups of female Wistar rats with free access to food and a running wheel. The treatment groups received an antibiotic-mixture to deplete endogenous microbiome prior to FMT. During the four-week transplantation period, control and vehicle rats were given water, while the FMT groups were gavaged with feces obtained from either healthy controls or patients diagnosed with AN. To examine the influence of FMT, we analyzed gene expression and staining of different glial cell markers.

Results: Analysis revealed no AN-specific changes in glial cell gene expression or in the cell count of the corresponding target brain cells. There was a trend towards a reduction of oligodendrocyte-related genes and a reduced expression of the neurogenesis marker BDNF in all antibiotic-treated groups.

Discussion: Our experiment did not report AN-specific effects of FMT on healthy rats. However, significant changes in oligodendrocyte-specific genes were observed in the antibiotic-treated groups, which should be further analyzed. The presented data support the hypothesis that changes in the microbiome alone are not sufficient to induce an AN-phenotype, as other factors may contribute to the development of AN such as food restriction.

Presentation number: P1.09

Topic: Neuroanatomy

Increased Serum Neurofilament Light Chain Concentration in Chronically Starved Mice

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Anorexia nervosa (AN) is characterized by hyperactivity, amenorrhea, and brain atrophy. While weight restoration reverses these symptoms, the underlying pathophysiological mechanisms remain largely unknown. Patients with AN demonstrate elevated serum levels of neurofilament light chain protein (NfL), indicating neuronal damage. This study aimed to investigate the association between NfL levels, brain atrophy, and behavior in a starvation-induced hyperactivity mouse model.

Female C57BL/6J mice were given limited food once daily and had continuous access to a running wheel until they reached a 25% weight reduction, which was maintained for two weeks to mimic chronic starvation. This was followed by a three-week refeeding period. Running activity was measured using running wheel sensors, and amenorrhea was assessed through vaginal smear analysis. Brain sections were examined to measure brain volumes, and behavioral changes were evaluated using forced swim and elevated plus maze tests.

Chronic starvation in mice resulted in AN-related symptoms, including hyperactivity and amenorrhea. Elevated serum NfL levels after chronic starvation were accompanied by reduced cerebral cortex and hippocampus volumes. Additionally, chronically starved mice exhibited reduced anxiety-like behavior, which normalized after refeeding.

Chronic starvation led to an increase in NfL levels in a mouse model of AN, suggesting that neuronal pathophysiology may contribute to the disease.

Presentation number: P1.10

Topic: Neuroanatomy

Analysis of a human mutation in the transcription factor Bcl11a using a mouse model

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Introduction:

The zinc-finger transcription factor Bcl11a has been previously demonstrated to be essential for the development of the murine central nervous system (Simon et al., 2020). Mutations in the human BCL11A gene are known to be associated with neurodevelopmental disorders, including intellectual disability, speech and language delay, as well as autism spectrum symptoms (Dias-Logan syndrome; Dias et al., 2016). Yet, the pathogenetic mechanisms underlying this syndrome remain unclear.

Methods:

To determine the precise cellular and molecular mechanisms of the Dias-Logan syndrome, we generated a mouse model carrying a previously described human mutation within exon 4 of BCL11A (Bcl11a$^{em3(c.529_530del)Cw}$) using *i*-GONAD (Wiegreffe et al., 2023). This mutation disrupts transcription of the zinc finger domains crucial for DNA binding. We systematically analyzed mice homozygous for the Bcl11a$^{em3(c.529_530del)Cw}$ allele and compared their phenotypes to mice with a forebrain-specific conditional deletion of the murine Bcl11a gene (Bcl11a$^{flox/flox}$; Emx1^{IRESCre}).

Results:

Homozygous Bcl11a$^{em3(c.529_530del)Cw}$ mice die perinatally and do not express intact Bcl11a protein. To determine whether truncated protein is generated from the Bcl11a$^{em3(c.529_530del)Cw}$ locus, we carried out western blot analyses and detected a mutant fragment of approximately 50-60 kDa. Morphological analysis further revealed striking phenotypic similarities between Bcl11a$^{em3(c.529_530del)Cw}$ homozygous and Bcl11a$^{flox/flox}$; Emx1^{IRESCre} mice.

Discussion:

Our preliminary analysis indicates that homozygous Bcl11a$^{em3(c.529_530del)Cw}$ mice recapitulate major phenotypic aspects observed in Bcl11a$^{flox/flox}$; Emx1^{IRESCre} mutant animals. This suggests that the mouse line we generated in this study serves as a valid model for the functional genetic analysis of the pathophysiology of the Dias-Logan syndrome.

Presentation number: P1.11

Topic: Neuroanatomy

Effects of glucose starvation on glioblastoma cells.

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Introduction

Glioblastoma (GBM) is a fast-expanding and aggressive brain tumor with a median survival of approximately 14 month. The poor prognosis is largely due to cellular invasion, which enables escape from resection and drives inevitable recurrence. Since high levels of glucose have been linked to increased tumor invasion, the central aim of this study was to obtain a more comprehensive understanding of glucose contribution to processes associated with tumor spreading.

Methods

We examined the effects of high glucose and glucose starvation on two different GBM cell lines, U138 and LN229. Changes in collective migration, cell proliferation, cell-cell adhesion, morphology, and mRNA and protein expression of genes responsible for GBM progression were evaluated over time. Furthermore, cell metabolic analysis via seahorse was performed.

Results

A significant difference in collective migration, but not in single cell migration was observed after glucose starvation in both U138 and LN229 cell lines. The speed under low glucose concentration in LN229 increased significantly, in contrast to U138, which showed initially a decreased speed but exceeded control conditions after 60 h. Assessing cell-cell adhesions showed increased ß-catenin staining levels in LN229. Furthermore, the number of cell division and the number of BrdU (S-Phase), but not Ki67 (non-G0 cells) positive cells was significantly decreased in low glucose groups in both cell lines.

Discussion

Taken together, glucose deprivation in LN229 and U138 cell lines changed tumor features essential for GBM progression. A thorough understanding of the metabolic traits that define invasive GBM cells may provide novel therapeutic targets.

Presentation number: P1.12

Topic: Neuroanatomy

The leptomeningeal compartment as regulatory interface of brain inflammation and immune surveillance

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Recent studies associate the meninges with immune surveillance and immune cell recruitment into the central nervous system (CNS). The underlying mechanisms, as well as characteristics of meningeal immune cell populations have barely been addressed. We hypothesize that leptomeninges play a vital role for immune cell recruitment into the CNS during neuroinflammation by establishment of a proinflammatory meningeal compartment.

Juvenile and adult human post-mortem meningeal tissues were analyzed (immuno-)histochemically for morphology and spatial distribution of immune cells and blood vessels in distinct regions. Meningeal gene expression and immune cell distribution under neuroinflammatory conditions were analyzed in a multiple sclerosis mouse model. Human arachnoid fibroblast cultures derived from meningeal biopsies were treated with proinflammatory cytokines to analyze proinflammatory gene expression by quantitative real-time PCR and next-generation sequencing and cytokine secretion by ELISA.

In the neuroinflammatory mouse model, meninges exhibited increased proinflammatory gene expression and immune cell accumulation. The distribution pattern of immune cells along penetrating blood vessels strongly suggested immune cell migration from the meninges towards the parenchyma. Post mortem human meninges revealed distinct regional differences in meningeal morphology and vascularization. Both juvenile and adult leptomeninges harbored heterogeneously distributed resident immune cell populations, mainly macrophages. Single cell sequencing revealed distinct and highly specialized subpopulations potentially orchestrating inflammatory leptomeningeal events. Under inflammatory stimulation, cultured meningeal fibroblasts secreted proinflammatory cytokines.

Leptomeninges are populated with resident immune cells and capable of proinflammatory signal secretion. This suggests that meninges function as an independent proinflammatory compartment and origin of perivascular immune cell migration towards the CNS.

Presentation number: P1.13

Topic: Neuroanatomy

Astrocytic factors as modulators of blood-brain barrier integrity - Insights from in vitro studies

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Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) marked by demyelination, immune cell infiltration, and blood-brain barrier (BBB) breakdown. Astrocytes, forming the glia limitans perivascularis, are key in maintaining BBB integrity and can influence immune cell infiltration based on their activation status. This study explores the mechanisms by which activated astrocytes affect endothelial barrier integrity.

Primary astrocyte-enriched glial cultures were exposed to tumor necrosis factor alpha (TNFα) to induce pro-inflammatory activation. After 8 h of stimulation, cells were given fresh medium to remove residual TNFα, followed by an additional 18 h growth period to produce astrocyte conditioned medium (ACM). This ACM was then used to stimulate brain microvascular endothelial cells (hCMEC/D3) for 24 h. The impact of astrocytic secreted factors on endothelial barrier properties was evaluated through gene and protein expression analysis, xCELLigence, and live cell microscopy. Proteomics were employed to identify factors within the ACM that can modulate endothelial barriers.

ACM from TNFα-stimulated glial cells disrupted endothelial barrier functions compared to control ACM. This disruption was indicated by increased expression of VCAM1 and ICAM1, but not ICAM2. Additionally, astrocytic factors reduced the expression of tight junction and adherens junction proteins.

Our findings suggest that factors secreted by activated glial cells play a crucial role in MS lesion formation by facilitating leukocyte adhesion and increasing barrier permeability. Future research will focus on elucidating the exact mechanisms by which these secreted factors within ACM exert their effects.

Presentation number: P1.14

Topic: Neuroanatomy

Accumulation of distinct PUFAs in ACDB5-deficient mice imply a disruption in the transfer of DHA pathway intermediates from the ER to peroxisomes

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Objectives

A major hallmark of the pathology of the peroxisomal disorder “Retinal Degeneration with Leukodystrophy” (RDLKD) is already expressed in its OMIM name. RDLKD is caused by the absence of the peroxisomal membrane protein ACBD5, which is involved in the import of very long-chain fatty acids (VLCFA) into peroxisomes but also in facilitating membrane contacts between the endoplasmic reticulum and peroxisomes. To unravel the pathologic mechanism of RDLKD, we correlated the retinal pathology of Acbd5-deficient mice (Acbd5$^{-/-}$) with tissue-specific lipidome alterations.

Methods

Retinae from Acbd5$^{+/+}$ and Acbd5$^{-/-}$ mice were analysed by confocal immunofluorescence, block face scanning electron microscopy, multifocal electroretinography (mfERG), ultra-high performance liquid chromatography / high-resolution mass spectrometry (UPLC-HRMS) and 2D-MALDI imaging.

Results

Acbd5$^{-/-}$ mice exhibit a progressive inflammatory cone-rod retinopathy as revealed by immunofluorescence microscopy and mfERG. The pathology in the optic retina was accompanied by a retinal pigment epithelium (RPE) pathology presented by declined cell numbers, increased binucleated cells and cell membrane distortions. Retinal phospholipids from Acbd5$^{-/-}$ mice unexpectedly exhibited normal DHA levels but a remarkable increase in its pathway intermediates synthesized at the ER. Moreover, polyunsaturated very long chain fatty acids (PUFA) were distinctly and highly elevated.

Conclusions

We hypothesize that the loss in ER-peroxisome membrane contacts in ACBD5 deficient mice leads to less efficient transfer of DHA synthesis pathway intermediates to peroxisomes. These accumulating C24-PUFAs are as a consequence elongated to extremely long PUFAs by the VLCFA elongase ELOVL4, which might disrupt the tightly controlled lipid environment in photoreceptor outer segments thereby triggering degenerative processes

Presentation number: P1.15

Topic: Neuroanatomy

Axon-Carrying Dendrite Diversity in Interneurons of the Mouse and Human Brain

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Introduction

Principal neurons with dendritic axon origins offer privileged pathways for information flow through the hippocampal network and between brain hemispheres. Traditionally overshadowed in research, the GABAergic interneurons play a crucial role in modulating network activity.

Methods

Our research leverages genetic and immunofluorescent markers to dissect the morphological variance among inhibitory neuron subpopulations, focusing on the axon initial segment (AIS) — a key site for action potential generation.

Results

Our study captures the extensive diversity of proximal interneuron morphologies within the murine hippocampus and neocortex, highlighting spatial patterns and interactions guiding interneuron morphology as well as hitherto undescribed configurations of the AIS in hippocampal interneurons. By extending our analysis to human tissue both from post-mortem samples and surgical resections, we establish a comparative framework that can translate the relevance of our murine findings to human neuroanatomy.

Discussion

The spatial pattern of cells with dendritic axon origins suggests critical roles in hippocampal network dynamics and sets the stage for exploring its implications in human brain function.

Presentation number: P1.16

Topic: Neuroanatomy

Characterization of LCN2 Receptor Expression and Signaling Pathways in Glial Cells under Healthy and Inflamed CNS Conditions

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Lipocalin 2 (LCN2), a 25-kDa secreted protein, possesses bacteriostatic properties and plays a crucial role in innate immunity. Recent findings show that LCN2 is secreted by activated astrocytes and significantly influences brain inflammation. Although six putative receptors for LCN2 have been identified, the mechanisms by which these receptors transmit and amplify signals remain poorly understood. We aim to characterize the expression patterns and signaling pathways of distinct LCN2 receptors in healthy and inflamed CNS.

We conducted a detailed analysis of existing research on LCN2 receptor expression and signaling. Given the limited knowledge on cell type-specific receptor expression within the CNS, we performed immunohistochemical staining in inflammatory animal models. Additionally, gene and protein expression studies were conducted on primary glial cells. To further elucidate the signaling mechanisms and functional relevance of the receptors NGALR and LRP2, shRNA was used to knock down their expression in astrocytes.

LCN2 receptors are expressed in various cell types and organs. In the CNS, we observed high expression of NGALR and LRP2 in glial cells. Astrocytes expressed these receptors at mRNA and protein levels. Inflammatory conditions did not alter their expression. Similar findings were noted in brain endothelial cells. shRNA experiments indicated that receptor expression might not be critical for astrocyte survival and metabolism.

LCN2 is involved in numerous biological processes and disease states, yet a significant gap remains in understanding how its receptors function. Further studies are needed to determine how NGALR and LRP2 signaling impacts inflammatory processes within the CNS.

Presentation number: P1.17

Topic: Neuroanatomy

High-resolution 3D mapping of cytoarchitectonic areas 44 and 45 reveals new anatomical details of Broca's region

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Broca's region is involved in key aspects of language processing. But its detailed functional diversity is in contrast to classical anatomical subdivisions of this region into two cortical areas (44 and 45). Previous work of our lab resulted in 3D cytoarchitectonic maps of areas 44 and 45, and later revealed further subdivision based on multiple neurotransmitter receptor distributions.

Based on the hypothesis that a more detailed parcellation of the two areas in receptor architecture would have a correlate in cytoarchitecture, we now mapped the cytoarchitecture of Broca's region in ten post-mortem human brains using an observer-independent border definition approach.

We identified two subdivisions of area 44 (44a and 44p) and two of area 45 (45a and 45p) arranged in anterior posterior orientation. 3D maps of all four subdivisions were computed in common stereotaxic spaces (MNI 152, Colin 27). Interindividual differences were expressed through probabilistic maps of these areas. In addition, high-resolution 3D reconstructions of these areas in a microscopical template brain, the BigBrain, have been generated at 20-micron resolution isotropic, to reveal fine details of anatomy.

The maps will be provided with the Julich-Brain Atlas and made accessible on the EBRAINS infrastructure as FAIR data. They may serve for education purposes in brain anatomy, facilitate neuroimaging studies on structure-function relationships and inform modelling, simulation and brain stimulation.

Presentation number: P1.18

Topic: Neuroanatomy

Characterization of Bcl11a/b transcription factors in multi-protein complexes during corticogenesis

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Transcription factors orchestrate gene expression and interact with multi-protein complexes during corticogenesis. Bcl11a/b transcription factors have been shown to control diverse functions in the developing central nervous system. However, the molecular mechanisms through which Bcl11a/b regulate neocortical development remain unclear.

To uncover changes in gene regulatory network upon the knockout of Bcl11a/b, ATAC-seq was performed on conditional knockouts (cKO) of Bcl11a, Bcl11b, and double cKO (dcKO) at E14.5. These data were further combined with genome-wide binding site analysis of Bcl11a/b. Moreover, *in vivo* biotinylation of Bcl11a/b in pyramidal neurons was carried out to identify interacting proteins of Bcl11a/b.

The absence of Bcl11a/b leads to dramatic changes in epigenetic landscapes. While most differentially accessible (DA) peaks are dcKO-specific, there are substantial overlaps in dcKO and Bcl11a cKO. This suggests that Bcl11a serves a compensatory function upon the loss of Bcl11b but not vice versa. Furthermore, most DA peaks are not bound by Bcl11a/b in wild-type situations. These results strongly suggest that Bcl11a/b influence chromatin accessibility through indirect mechanisms but not direct DNA binding. Gene ontology analysis showed that unbound DA peaks are enriched for terms including forebrain development and neuron projection guidance. In addition, motif analysis on unbound DA peaks revealed candidate transcription factors related to cell fate commitment and pattern specification process.

These results give robust indications for an indirect function of Bcl11a/b during corticogenesis. Mapping interacting proteins to open chromatin areas will further elucidate the mechanism of how Bcl11a/b regulate the neuron subtype specification during neocortical development.

Presentation number: P1.19

Topic: Neuroanatomy

Advancing Tract-Tracing in the Postmortem Human Brain: Mapping Cellular Origins of Intralobar Fibers in the Occipital Lobe

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To enhance neuronal tracing in fixed postmortem human brains, we developed rotating field tracer electrophoresis (RFTE), significantly improving the distribution of polar lipophilic tracers. This technique allowed us to reveal a network of intralobar fibers originating from the calcarine cortex and projecting to the prestriate cortex, prompting us to address the challenge of tracing the exact cellular origin of these fiber connections.

In this study, the cationic lipophilic tracer *FAST*-DiI was applied at previously identified projection sites of the calcarine cortex. To facilitate rapid tracer distribution along different fiber orientations, the tissue was placed in our RFTE chamber. The tracer application site was centrally aligned to the anode, while the cathode location was constantly rotated relative to the tissue. Cryostat-prepared sections were sealed with a 1-thioglycerol-based mounting medium to prevent signal deterioration and examined with a fluorescence microscope.

Upon tracer application into the white matter of the middle occipital gyrus, we observed fibers originating from the calcarine cortex. Data suggest that cell bodies are primarily found infragranularly. These fibers projected transversely and laterally from the calcarine cortex to the middle occipital gyrus, fitting the description of the transverse fascicle of the cuneus.

This detailed mapping confirmed and complemented our previous findings and align with historical data and known anatomical connections in non-human primates. The use of RFTE and polar lipophilic dyes enables the anatomical tracing of cortical projections in humans, confirming and expanding upon previously hypothesized pathways.

Presentation number: P1.20

Topic: Neuroanatomy

The role of muscularis macrophages in mediating local immune responses in a mouse model of multiple sclerosis

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Introduction

Multiple sclerosis (MS) is an autoimmune disorder affecting the central nervous system. The enteric nervous system (ENS) has been identified as an additional target in MS and its mouse model, experimental autoimmune encephalomyelitis (EAE). The ENS communicates closely with gut wall-resident muscularis macrophages (MM). MM can develop a pro- or anti-inflammatory phenotype and actively regulate inflammation and gut motility. We hypothesize that MM play a crucial role in mediating the local immune response in the ENS in MS and EAE.

Methods

We established a model that combines MM depletion with EAE in C57BL/6 mice. Transient MM depletion was achieved by intraperitoneal injections of the anti-CD115 blocking antibody AFS98. EAE was induced three days after initial injection using MP4, a fusion protein of myelin basic protein and proteolipid protein. Mice were immunized and treated with either AFS98 or an isotype control and sacrificed at a preclinical stage or at peak of disease.

Results

AFS98-induced depletion was specific for MM and could not be observed in other tissue-resident macrophages. Depletion was stable for two weeks. We observed an elevated EAE incidence and a significantly increased clinical score. Before symptom onset, we also observed a decreased whole gut transit time in MM-depleted mice compared to isotype control-treated mice.

Discussion

Initial data suggest that MM act in an anti-inflammatory manner during EAE development and that depletion of MM might be associated with a higher susceptibility for EAE. Serum and tissue samples were collected and will be further processed to analyse the underlying mechanisms.

Presentation number: P1.21

Topic: Neuroanatomy

Characterization, number, and spatial organization of nerve fibers in the human cervical vagus nerve and its superior cardiac branch

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Introduction: Electrical stimulation of the vagus nerve (VN) is a therapeutic intervention for epilepsy, obesity, depression, and heart diseases. VN stimulation involves the entire nerve, resulting in unwanted side effects. We conducted a neuroanatomical examination of the mid-cervical segment of the human VN and its superior cardiac branch to gain insight into the side effects of VN stimulation and aid in developing targeted stimulation strategies.

Methods: Nerve specimens were harvested from eight human body donors, then subjected to immunofluorescence and semiautomated quantification to determine the signature, quantity, and spatial distribution of different axonal categories.

Results: The right and left cervical VN (cVN) contained 25,489 ± 2,781 and 23,286 ± 3,164 fibers, respectively. Two-thirds of the fibers were unmyelinated and one-third were myelinated. About three-quarters of the fibers in the right and left cVN were sensory (73.9 ± 7.5% *versus* 72.4 ± 5.6%), while 13.2 ± 1.8% *versus* 13.3 ± 3.0% were special visceromotor and parasympathetic, and 13 ± 5.9% *versus* 14.3 ± 4.0% were sympathetic. Special visceromotor and parasympathetic fibers formed clusters. The superior cardiac branches comprised parasympathetic, vagal sensory, and sympathetic fibers with the left cardiac branch containing more sympathetic fibers than the right (62.7 ± 5.4% *versus* 19.8 ± 13.3%), and 50% of the left branch contained sensory and sympathetic fibers only.

Discussion: The study indicates that selective stimulation of vagal sensory and motor fibers is possible. However, it also highlights the potential risk of activating sympathetic fibers in the superior cardiac branch, especially on the left side.

Presentation number: P1.22

Topic: Neuroanatomy

Pupillary light reflex circuit: the pretectal olivary nucleus in monkey and man

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Introduction

The olivary pretectal nucleus (PON) is a key structure within the pupillary light reflex pathway receiving retinal afferents and projecting to the preganglionic Edinger-Westphal nucleus (EWpg). The PON has been described in numerous mammals including monkey, but its histochemical properties are poorly characterized allowing identification and comparison with the human PON.

Methods

Sections of macaque monkey and human pretectum were immunostained for parvalbumin (PAV), calretinin (CR), calbindin (CB), aggrecan (ACAN), glutamate decarboxylase (GAD), vesicular glutamate transporter 1 (vGlut1) and potassium-chloride transporter 2 (KCC2). Tracer-labelled neurons in PON with projections to the EWpg were simultaneously labeled by immunofluorescence to explore their histochemical characteristics in monkey.

Results

Strongly PAV- and CB-positive neurons highlight the PON in monkey, whereas CR-positive neurons are confined to its outer border. Retrogradely labelled projections neurons in PON expressed PAV and/or CB, and some of them were characterized by ACAN-positive perineuronal nets. However, in human PON these markers were only weakly expressed. Both primate species displayed strong punctate immunolabelling for GAD, KCC2 and vGlut1.

Conclusion

Neurons projecting from PON to EWpg do not form a homogeneous population, instead different neuron sets showed differential expression of calcium-binding proteins and aggrecan. However, the human PON displays poor expression of these markers. The source of the strong GABAergic and glutamatergic input (by vGlut1) to PON in monkeys and humans remains to be determined as we expand our knowledge of the pathways and transmitters that control the pupillary reflex.

Funding: DFG HO-1639/5-1

Presentation number: P1.23

Topic: Neuroanatomy

Reversibility of Endoplasmic Reticulum Stress Markers During Long-Term Glucose Starvation in Astrocytes

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Introduction: Brain volume decrease is linked to long-term starvation in patients with anorexia nervosa (AN). Food intake is critically diminished in this disorder, leading to one of the highest mortality rates. Data from animal models indicate that, astrocytes are the most affected cell type in AN. An elevated unfolded protein response (UPR) was observed in long-term glucose semi-starved astrocytes. A well-functioning protein machinery is essential for every cell, and prolonged UPR will lead to cell death. We have particularly investigated the nucleic acid stress-sensing pathway with the activator located in the endoplasmic reticulum, the cGAS-STING pathway (cyclic GMP-AMP synthase/stimulator of interferon genes).

Method: Primary astrocytes were obtained from rat pups. To induce glucose semi-starvation cells were supplied with a reduced amount (2 mM) of glucose in the medium for 15 days. Subsequently, the protocol was prolonged with an additional 6-day long recovery period during which the glucose concentration was re-established to 25 mM.

Results: Increased UPR mRNA expression was reversible after re-establishing the glucose concentration. Furthermore, we verified the presence of cGAS and STING in astrocytes with a characteristic presence of cGAS in the astrocyte nucleus during starvation.

Discussion: Cell dynamics, like alterations in cell numbers and stress responses, are important regulatory mechanisms in the impaired brain of patients with AN. If we understand these processes and their implications on brain function, AN pathophysiology and chronic manifestation of the illness could be better addressed.

Presentation number: P1.24

Topic: Neuroanatomy

Analysis of glutamatergic, GABAergicand adenosinergic neurotransmitter receptor densities in the striatum of 6-OHDA-hemiparkinson rats following botulinum neurotoxin-A injection

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Introduction: Parkinson's disease (PD) is characterized by a degeneration of striatal dopaminergic terminals and of dopaminergic neurons in the substantia nigra pars compacta that causes a dopamine deficit in the caudate-putamen (CPu) that is accompanied by compensatory changes not only in dopaminergic receptors. Many other neurotransmitter systems are involved resulting in severe motor and non-motor symptoms.

Methods: To disclose the role of various receptor binding sites for glutamate, adenosine and GABA in the hemiparkinsonian (hemi-PD) rat model induced by unilateral 6-hydroxydopamine injection (right medial forebrain bundle), the densities of AMPA, NMDA, $mGLU_{2/3}$, kainite, $GABA_A$, $GABA_B$, $GABA_{benzodiazepine}$, and A_1 and A_2 receptors were longitudinally visualized and measured in the CPu of hemi-PD rats by quantitative in vitro receptor autoradiography.

Results: We found that most binding sites were unaltered in hemi-PD rats. Only $GABA_A$ and A_2 binding sites were reduced in the right CPu. In a second step, the consequence of intrastriatally injected Botulinum neurotoxin-A (BoNT-A) known to reduce apomorphine-induced rotations in hemi-PD rats, on these receptors was analyzed. Following the application of BoNT-A all these receptor densities mainly remained unaltered.

Discussion: Our results provide novel data for an understanding of the postlesional plasticity of $GABA_A$ and A_2 receptors in the hemi-PD rat model. The therapeutic effect of BoNT-A on the impaired motor behavior of hemi-PD rats cannot be explained by BoNT-A-induced changes of the here investigated receptor densities.

Presentation number: P1.25

Topic: Neuroanatomy

Microglial and neuronal communication via exosomes under inflammatory conditions

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Objective: Spinal cord injury (SCI) is an acute injury accompanied by neuroinflammation, which has a pivotal role in a variety of neuronal diseases. The transcription factors Nrf2 and NF-κB are implicated in the regulation of inflammation. Neurons are one of the most vulnerable cell types in the human system and, therefore, a proper regulation of inflammatory processes is essential. Extracellular vesicles (EVs) represent one form of intercellular communication, and exosomes, as a subgroup of EVs, have become increasingly important in the understanding of inflammatory diseases.

Methods: We applied the SC contusion model on ARE-luciferase mice to quantify Nrf2 activity in the spinal cord and brain. Exosomes were isolated from lipopolysaccharides-stimulated BV-2 cells and characterized by nanoparticle tracking analysis. Nrf2 and NF-κB activity of N2a-cells in response to these exosomes was quantified by ARE- or NF-κB-driven luciferase reporter gene assays. Gene expression of Nrf2 and NF-κB targets was measured via RT-qPCR.

Results: Studies in SCI mice revealed an activation of Nrf2 in the SC but also in the brain. Exosomes isolated from BV-2 cells and given to N2a cells induced Nrf2 and NF-kB activity and the expression of their target genes.

Discussion: Based on our results, we hypothesize that microglia-derived exosomes transmit Nrf2- and NF-kB-related signals to neurons under inflammatory conditions. This form of communication may protect neurons by priming them for upcoming events. The identification of the exosome cargo and the biological consequences for neurons is part of our ongoing work.

Presentation number: P1.26

Topic: Neuroanatomy

The gaseous transmitter hydrogen sulfide in the human choroid: first results

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Introduction: The choroid is an important mediator in myopia development and is densely innervated. While the gaseous transmitter nitric oxide contributes to choroidal innervation, it is also discussed in regulation of ocular growth. Since the presence of other gaseous transmitters is not clear, we here investigate the presence of hydrogen sulfide (H_2S) in human choroid.

Methods: Human choroids were prepared for immunohistochemistry of CBS (cystathionine-beta-synthase) or CTH (cystathionine-γ-lyase), the key enzymes in H_2S-synthesis, and combined with neurofilaments 160/200 (NF), α-smooth–muscle actin (SMA), TH (tyrosine-hydroxilase), and CGRP (calcitonin gene-related peptide). Confocal laser-scanning microscopy was used for documentation.

Results: CTH was detected in stromal and perivascular nerve fibres, in vessel walls, in small cells (10 microns diameter) and intrinsic choroidal neurons (ICN). CBS revealed a similar staining pattern. When combining CBS with NF for ICN-identification, 132/132 ICN were CBS+; CBS/CTH co-localized in ICN. Stromal nerve fibres co-localized for CBS and CGRP, but not TH. CBS and SMA revealed an overlap in vessel walls.

Discussion: CTH and CBS were detected in neuronal structures with same appearance, thus an involvement of H2S in choroidal neurotransmission is likely. ICN represent an intrinsic source while co-localization with CGRP suggests trigeminal origin; sympathetic fibres (TH) do not utilize H_2S. The role of H_2S in the vascular wall is not clear, but has been reported in other non-ocular systems. Further studies will clarify the role of H_2S in choroidal homeostasis and ocular growth.

Grant support: OeNB-Jubilaeumsfonds #18192, PMU-FFF E-19/29/154-SKP, European Union (EU) GAno. 101119501 (MSCA DN MyoTreat)

Presentation number: P1.27

Topic: Neuroanatomy

Immunohistochemical studies on dopamine in the human choroid

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Introduction: The choroid supplies the retinal photoreceptors but is also a growth factor source for the sclera and therefore the key tissue for emmetropization. In both cases, the autonomic nervous system plays an important role while the interplay of visual input and choroidal response is not understood. Since dopamine (DA) is a key player in retinal response upon visual stimuli, data in the choroid are lacking, and filling this gap is aim of this study.

Methods: Human choroids were prepared for immunohistochemistry of DA, TH (tyrosine-hydroxylase), DBH (dopamine-b-hydroxylase), neurofilament 160/210 (NF), and protein-gene product 9.5 (PGP9.5). For documentation, fluorescence- and confocal laser-scanning-microscopy was used.

Results: DA-immunoreactivity was detected in a minority of fibres in PGP9.5+ nerve-strands and in bouton-forming fibres in the choroidal stroma. Double-immunohistochemistry with DA and DBH lacked co-localization in stromal nerves, and thus discriminated between noradrenergic and dopaminergic fibres. TH and DBH were co-localized in some fibres, as was TH and DA, while single fibres showed immunoreactivity for DBH or DA only and lacking TH, indicating that TH apparently is not a robust marker. Some intrinsic choroidal neurons (ICN) identified with PGP9.5/NF were DA+, but were DBH/TH-, and also other small cells in the choroidal stroma not representing ICN were DA+.

Discussion: Indeed, DA is relevant in catecholaminergic choroidal innervation, with hitherto unknown functional significance. ICN and choroidal small cells represent a source of choroidal DA, possible extrinsic origins need to be established.

Grant support: OeNB-Jubilaeumsfonds #18192, PMU-FFF E-19/29/154-SKP, European Union (EU) GAno. 101119501 (MSCA DN MyoTreat)

Presentation number: P1.28

Topic: Neuroanatomy

Comprehensive Analysis of Brain Tissue Using Focused Ion Beam Scanning Electron Microscopy (FIB-SEM): A Methodological Approach

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Introduction:

Developed in the 1980s, focused ion beam scanning electron microscopy (FIB-SEM) technology has traditionally been utilised in materials science. Recently, however, it has gained significant traction in the life sciences, particularly for the examination of a diverse array of organ tissues. This method enables the recording of several thousand serial sections at nanometer resolution, thus enabling three-dimensional (3D) reconstructions and enhancing our understanding of cellular and subcellular structures. Acquisition and analysis processes, however, have to be optimised and partial developed from scratch.

Methods:

In our research group, we employ the FIB-SEM technique to gain detailed insights into the morphology of neuronal networks in the murine hippocampal formation. To develop and validate new methodological approaches in sample preparation, acquisition, post-processing analysis and statistics, we generate image stack from the Stratum Radiatum (SR) in CA1 and the outer molecular layer (OML) of the dentate gyrus.

Results:

Initially, we optimised all phases necessary for generating the corresponding data sets including sample preparation, acquisition settings, and 3D reconstruction setup. These methodological optimisations allow the investigation of the data sets in a manner that directly addresses specific research questions, such as (I) dendritic and spine 3D-morphology, (II) axonal 3D-morphology, (III) the number and size of subcellular structures, such as synaptic vesicles, postsynaptic densities and mitochondria.

Discussion:

This approach provides the opportunity to explore additional scientific topics, including developmental changes or comparisons of different brain regions. Furthermore, it enables, in the future, the comparison of our data with those from disease models with neurological dysfunctions.

Presentation number: P1.29

Topic: Neuroanatomy

The oligomer modulator molecule anle138b ameliorates Huntington's disease phenotypes in vivo

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Introduction:

Huntington's disease (HD) is a devastating neurodegenerative disorder characterized by the progressive loss of motor function and cognitive decline. HD is caused by the expansion of the CAG tract in the Huntingtin gene (HTT) above a threshold of 35 repeats. Currently there are no disease-modifying therapies available for HD, making the search for effective treatments a critical enterprise.

Methods:

Here we show that administration of the small oligomer modifying molecule anle138b, ameliorates disease phenotypes in cellular and mouse models of HD.

Results:

anle138b reduced mutant HTT aggregate formation and ameliorated toxicity in human induced pluripotent stem cells and mouse primary neurons. Moreover, R6/2 HD model mice treated with anle138b performed significantly better in a battery of motor assays (rotarod, grip strength, open field and hindlimb clasping test) when compared to littermate R6/2 mice treated with placebo. In addition, anle138b-treated R6/2 mice had reduced brain atrophy and increased lifespan. No adverse effects of anle138b administration were observed in wildtype littermates. Further investigation into the possible mechanisms underlying these improvements revealed that anle138b decreases intranuclear mutant HTT aggregate load, rescues neurochemical imbalances, mitigates dendritic spine loss in striatal spiny projection neurons and reduces neuroinflammation. Altogether these results suggest that oligomer modulators may represent an effective approach in the treatment of HD.

Presentation number: P1.30

Topic: Neuroanatomy

Modulation of hippocampal fear memory circuits by orexin

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Introduction: Cognitive function and memory are coupled to the circadian rhythm and circadian strains such as sleep deprivation, shift work or jet lag impair cognitive performance by disturbing prefrontal-hippocampal information flow. Orexinergic neurons of the hypothalamus are a central component of the wake-promoting system and ideally suited to stimulate cognitive performance under circadian strain.

Methods: Using RNAScope, high-resolution quantitative PCR and viral tracing techniques we determined the susceptibility of hippocampal networks to orexinergic modulation in C57Bl6J mice. The activity of these circuit components as well as of orexinergic neurons of the lateral hypothalamus were assessed during contextual fear memory retrieval under a “jet-lag”-like acute circadian shift and under external application of orexin by immunohistochemistry for cFos and a viral Robust Activity Marker (RAM) for engram cells.

Results: Orexin receptors were expressed in a network comprising the medial prefrontal cortex (mPFC), the supramammillary nucleus (SUM) and the dorsal hippocampus (dHipp) with a high level of regional differentiation and in specific cell-types. Hippocampus-dependent contextual fear memory was impaired under circadian strain induced by acute phase shift. This was associated with a reduced re-activation of fear memory engram cells within the dentate gyrus. Acute phase shift as well as a pharmacological orexinergic modulation altered the activity of intra- and extrahippocampal network structures.

Discussion: Together, our project provides insights into hippocampus-dependent neurocognitive circuits regulating contextual fear memory strength and their modulation by orexin. Identifying the relevant neurocircuits may help to develop new therapeutic access points for cognitive impairments during aging or stress.

Presentation number: P1.31

Topic: Neuroanatomy

Lysophosphatidic Acid selectively modulates excitatory Transmission in hippocampal Neurons

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Proper signalling and synaptic transmission are fundamental for normal brain function. Besides the development of the nervous system, bioactive lipids such as LPA are involved in the modulation of neuronal transmission. A potential interaction of plasticity-related gene 1 (PRG-1) with LPA has recently been shown at the synapse. PRG-1 influences excitatory transmission on glutamatergic neurons from the postsynaptic side, by controlling LPA in the synaptic cleft, probably acting via the presynaptic LPA_2 receptors (LPA_2R). Little is known about how LPA triggers specific LPAR-mediated cellular events in neurons. As LPA_2Rs are expressed in glutamatergic presynaptic terminals, we aimed to clarify LPA-induced signalling and the impact of LPA on neuronal transmission and neurotransmitter vesicle release following this pathway.

We examined the effect of LPA on neuronal transmission in primary hippocampal neurons by using live cell calcium imaging with pharmacological and genetical approaches ($LPA_2R^{-/-}$ mice), immunohistochemistry and electrophysiological recordings.

We provide evidence that, in primary cultured hippocampal neurons, LPA elicited somatic $[Ca^{2+}]_i$ transients mainly via LPA_2Rs, G_i-coupling, PLC activation, inositol (1,4,5) trisphosphate (IP_3)-induced Ca^{2+} release, and voltage-gated Ca^{2+} channels. LPA induced $[Ca^{2+}]_i$ transients in presynaptic terminals and consequentially altered the frequency of spontaneous vesicle release in excitatory - but not inhibitory - synapses. The LPA-induced reduction of miniature excitatory postsynaptic current frequency was due to a depletion of releasable vesicles. This loss resulted from a slowed recycling, as synapto-pHluorins indicated a transient augmentation of release followed by prolonged persistence in the membrane. Our data endorse membrane derived phospholipids as modulators of synaptic transmission.

Presentation number: P1.32

Topic: Neuroanatomy

Cajal-Retzius cell stimulation influences hippocampal network activity

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Cajal-Retzius (CR) cells, crucial for proper structural brain development, are rarely found in the postnatal brain. However, in the postnatal hippocampus, they are integral to a powerful neuronal circuit.

To investigate the impact of CR cell activity on hippocampal circuits, we developed a mouse line with conditional expression of the DREADD (Designer Receptor Exclusively Activated by Designer Drugs) hM3Dq in CR cells. This DREADD is activated by Clozapine-N-Oxide (CNO), which increases the excitability of CR cells via a G-protein coupled receptor pathway. Patch-clamp electrophysiological measurements were taken from acute tissue slices, focusing on the frequency of action potentials in CR cells, EPSCs (excitatory post synaptic currents) in GABAergic interneurons, and IPSCs (inhibitory post synaptic currents) in granule cells of the dentate gyrus before and after CNO application. CR cells were identified by the presence of mCitrine, while GABAergic interneurons and dentate gyrus granule cells were confirmed through confocal imaging of filled cells.

Our measurements show significant alterations in circuit activity among distinct, morphologically identified cell types. This includes increased direct excitatory input to local GABAergic interneurons and semilunar cells, as well as di-synaptic inhibitory activity on dentate gyrus granule cells. Subsequent electrophysiological field recordings reveal that stimulating CR cells generates suprathreshold network activity across the hippocampal formation.

These results confirm the successful expression and functionality of DREADDs in CR cells, making them a valuable tool for studying hippocampal networks. Future experiments will further investigate the influence of CR cell activity on hippocampal physiology and behavior.

Presentation number: P1.33

Topic: Neuroanatomy

Siponimod supports remyelination in the non-supportive environment

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Introduction

Remyelination is believed to protect axons, but in many multiple sclerosis patients this endogenous-regenerative process fails. This study explores whether siponimod, known for its protective benefits in active multiple sclerosis, also guards against recurrent demyelination, thus allowing remyelination in the non-supportive environment.

Methods

We used the cuprizone model in which administration of “cuprizone” leads to immune cell independent oligodendrocyte degeneration, followed by endogenous remyelination after cessation of the intoxication. However, despite the recruitment of oligodendrocyte progenitor cells (OPCs), remyelination fails under continuous cuprizone-intoxication. Here, mice were subjected to a cuprizone diet for seven weeks and treated with siponimod starting at week five, the time point associated with intrinsic remyelination in this model. Brain sections were analyse by histochemical Luxol-Fast-Blue, immunohistochemical and immunofluorescence stains. To assess myelin status the density of proteolipo-, myelin basic and myelin-associated glycoprotein was determined. Ionised calcium-binding adaptor molecule 1 was chosen to identify microglia cells while oligodendrocyte transcription factor 2 (OLIG-2) was utilised to mark non-proliferating oligodendrocytes. OLIG-2/Ki67-double staining was performed to label proliferating OPCs.

Results

After week seven, all myelin stains showed higher expression levels in siponimod vs. vehicle treated mice. The degree of microgliosis was comparable between groups. The oligodendrocyte cell density was found to be higher in the siponimod group. The double staining indicated that this finding is due to the protection of mature oligodendrocytes rather than the induction of OPC proliferation.

Discussion

Siponimod-treatment supports myelin repair in the non-supportive environment. Newly forming oligodendrocytes are just moderately responsive for siponimod-mediated protective pathways.

Presentation number: P1.34

Topic: Neuroanatomy

Hypermyelination of peripheral axons caused by gut microbiota depletion cannot be rescued by simple recolonization with a complex gut microbiome

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Introduction: The definition of a variety of “gut-organ axes” describes an effect gut microbiota (GM) composition and diverse organ systems. We have recently demonstrated that also the peripheral nervous system and the neuromuscular compartment depend in their proper postnatal development on the presence of a well-composed GM [1]. Here we demonstrate pre-liminary result of our follow-up analysis of peripheral nervous system myelination after colonizing mice born in a germ-free condition with a complex GM at weaning.

Methods: Data from stereological and morphometrical analysis performed on median nerves derived from young adult germ free (GF) mice, gnotobiotic mice, selectively colonized with oligo-mouse microbiota 12 (OMM12, 12 specific gut bacterial strains) and mice colonized with specific-pathogen free complex gut microbiota (CGM) were derived from our previous study [1]. New data were derived from median nerve samples of GF-mice colonized with a CGM at weaning (ex-GF), collected at 63-67 days of age.

Results: Young adult ex-GF mice demonstrate a less reduced peripheral axon diameter than GF mice but a significantly thicker myelin sheath in comparison to all other groups. Additional analysis of the neuromuscular system and gene expression analysis for nerves and dorsal root ganglia are ongoing.

Discussion: Colonization of GF mice at weaning seems to result in an over compensatory response in the myelination of peripheral axons. Further comprehensive analysis is needed for understanding which GM metabolites modify peripheral myelination and if GM composition can also modulate peripheral nerve function and regeneration.

Reference: [1] Cescon *et al., Gut Microbes*, *16*(1), doi:10.1080/19490976.2024.2363015

Presentation number: P1.35

Topic: Neuroanatomy

Linking Reelin and Epigenetics: New Perspectives on the Effect of Reelin on Neuronal Signaling

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The extracellular matrix protein reelin, named after the reeler-mutant mouse, exerts a multitude of key functions in both the developing and adult brains of mammals. In addition to the well-studied effect of reelin on the migration of neuronal cells during embryonic development, several studies have demonstrated an effect of reelin on neuronal signaling in the mature brain. By modulating both excitatory glutamatergic and inhibitory GABAergic neuronal signaling, reelin affects central neurophysiological processes such as learning and memory formation.

We aim to further investigate reelin-induced changes of the neuronal signal transmission focusing on the cholinergic system. Although cholinergic projections modulate neurons in various brain regions, the impact of reelin on the cholinergic system has so far not been examined. By using the calcium imaging technique on primary neurons, cell lines and rodent brain slices we investigated the effect of reelin on neuronal acetylcholine-induced calcium signals. Furthermore, we analyzed the underlying molecular mechanisms of action in more detail by using mass spectroscopy, epigenetic profiling, western blotting and immunofluorescent staining.

Our preliminary results show that reelin reduces acetylcholine-induced calcium signals in a receptor-specific manner. Furthermore, reelin increases the nuclear distribution of specific transcription factors, alters the level of different epigenetic protein and histone modifications and modulates the whole proteome of neurons.

Identifying all underlying molecular mechanisms will complement our knowledge of reelin's action in both the developing and the mature brain and contribute to a better understanding of the interplay between posttranslational protein modifications, their intracellular pathways and neuronal signaling processes

Presentation number: P1.36

Topic: Neuroanatomy

Distribution and Expression Patterns of Mas-related G-protein Coupled Receptor D (MrgD) in the Mouse Brain

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Introduction:

Recent research has uncovered a local renin-angiotensin system (RAS) in the central nervous system (CNS), with widespread components such as Ang II and Ang IV, revealing its complex roles in brain function. The ACE2/Ang-(1-7)/Mas receptor pathway is crucial for influencing neuronal activity and memory. Mas-related G-protein coupled receptors (Mrg) are involved in pain and itch sensation. The novel receptor MrgD, activated by Ala1-Ang-(1-7) and Ang-(1-7), has been identified, though its biological significance remains unclear.

Methods:

To explore MrgD's role in the CNS, we utilized a MrgD IRES-EGFPf mouse model. Brain sections were stained with GFP and Cy3 antibodies, then analyzed using fluorescence microscopy. The fluorescence intensity was quantified and corrected with the CTCF method, and results were presented as the mean number of cells per brain area (±SEM).

Results:

MrgD-positive cells were observed in various forebrain regions, including the cortex, hippocampus, amygdala, hypothalamus, habenular nuclei, striatum, and pallidum. Additionally, MrgD-positive cells were detected in specific mid-brain nuclei.

Conclusion:

This study reveals that the MrgD receptor is sparsely expressed in the murine forebrain, notably in cortical, subcortical, and limbic regions associated with reward and motor functions, beyond its role in nociception. MrgD also contributes to cardiovascular regulation and neuropathic pain modulation. Despite its lower expression compared to Mas, MrgD's presence in pain-related and reward circuits indicates a potential role in pain perception, synaptic plasticity, and cognition. Further research is needed to clarify the functions of the Ang-(1-7)/MrgD system in the brain.

Keywords: MrgD, Brain, Mouse

Presentation number: P1.37

Topic: Neuroanatomy

The Influence of Longitudinal Gait Analyses on the Gait Pattern of Healthy Mice

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Introduction

Gait pattern analyses of small rodents are commonly used in neuroinflammatory and neurodegenerative research to depict histopathological changes functionally. In multiple sclerosis (MS) models and patient assessments, gait disturbances are significant. These changes may result not only from histopathological alterations but also from learning processes and age-related changes, especially during repetitive measurements. This study aimed to quantify the influence of these latter two factors on gait pattern changes.

Methods

The gait pattern of healthy C57BL6 mice was analyzed over 15 weeks using high-speed ventral plane videography with the DigiGait system. Motor coordination was also assessed using the RotaRod setup for comparative analysis.

Results

During the fifteen-week analysis, significant changes were observed in gait parameters, including stride width, paw placement dynamics, and push-off phase dynamics. These changes were most noticeable in the first two weeks and towards the end of the period. Motor coordination, measured using the Rotarod, changed primarily in the final weeks, with no direct correlation between the two paradigms (DigiGait vs. Rotarod).

Discussion

Our results demonstrate that repeated testing in mice leads to significant changes in gait parameters. Therefore, when using gait patterns to assess histopathological changes in preclinical studies, an additional control group of the same age should be analyzed throughout the experiment.

Presentation number: P1.38

Topic: Neuroanatomy

Unveiling Gephyrin's Role in Endocytic Pathways and Vesicular Traffic in Neuronal and Non-Neuronal Cells

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At inhibitory postsynaptic membranes the scaffolding protein gephyrin is well-studied and performs several tasks associated with structural and functional processes. As various as its functions is the set of interaction partners including neurotransmitter receptors, synaptic proteins and cytoskeletal elements.

Recently, transport processes of gephyrin molecules marked for early endosomes have been observed in live cell imaging of inhibitory postsynapses. Endosomes are key players in maintaining the homeostasis of membrane components in eukaryotic cells. They participate in diverse fundamental cellular processes such as the uptake of extracellular substances, intracellular transport, and recycling. The role of gephyrin in endosomal transport is poorly understood. In mass spectrometry datasets from broad-range protein interaction studies, several promising candidates for gephyrin interaction partners associated with endosomal transport and sorting processes have been identified. Representative proteins for various steps of the endocytic pathway and vesicle traffic among these potential interaction partners will now be analyzed for colocalization and cotransport with gephyrin. Additionally, it will be examined whether the colocalization of gephyrin and early endosomes is specific to neurons or can also be found in other cultured cell types.

Presentation number: P1.39

Topic: Neuroanatomy

Urethral tuft cells trigger neuropeptide release from sensory nerve fibres through nicotinic signalling

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Introduction: Urethral tuft cells (UTC; aka cholinergic chemosensory cells) monitor for luminal hazardous substances. Upon stimulation, they promote micturition ("flushing response") through a reflex initiated by release of acetylcholine, which then excites nearby sensory nerve fibres. We hypothesized, that they also might induced substance P (SP) release from sensory fibres, the initial step in neurogenic inflammation, as reported for nose and trachea, and addressed this in an optogenetic model.

Methods: Species: *Mus musculus*, strains: C57BL/6J, *Chat*-ChR2-EYFP (expresses the light-sensitive channelrhodopsin-2 controlled by the choline acetyltransferase promotor), *Chat*-GFP, *Chrna3*-GFP (reporter for the nicotinic receptor α3-subunit), *Pou2f3*$^{-/-}$ (lacks UTC); immunofluorescence of tissue sections and cleared urethral whole-mounts; ELISA for neuropeptides in supernatant of explanted and stimulated urethrae.

Results: UTC were closely approached by various neurochemical types of nerve fibres, including peptidergic fibres with and without expression of the nicotinic receptor α3-subunit. Denatonium induced neuropeptide release from both wildtype and *Pou2f3*$^{-/-}$-urethrae, indicating action upon more than just brush cells. The expression of the transgene in *Chat*-ChR2-EYFP mice was validated by immunofluorescence with antibodies against the brush cell marker DCLK1 (Double-cortin like kinase 1), showing extensive colocalization (90%, 47/52 cells, from 5 animals). Stimulation of such urethrae with LED induced release of SP, which was fully blocked by the general nicotinic receptor blocker mecamylamine (20 mM).

Discussion: The optogenetic model established that urethral bush cells can evoke neuropeptide release from sensory nerve fibres through nicotinic cholinergic transmission. A selective natural stimulus still needs to be identified.

Presentation number: P1.40

Topic: Neuroanatomy

The effect of dihydropyridines on gene expression patterns and mitochondrial stress in human neurons, oligodendrocytes and astrocytes.

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Multiple sclerosis (MS) is a chronic neuroinflammatory disease caused by an autoimmune response against central nervous system (CNS) antigens. Mitochondrial damage can be linked to myelin loss and neurodegeneration in late disease stages for which there is currently only insufficient treatment. The dihydropyridine (DHP) nimodipine has been shown to promote remyelination in a mouse model of MS, but the cellular mechanisms need further investigation.

We explored the effects of four structurally distinct DHPs (nimodipine, nifedipine, amlodipine, cilnidipine) on different CNS cell types *in vitro*. To this end, we pharmacologically induced mitochondrial stress in human oligodendrocytes, neurons and astrocytes and treated the cells with the different DHPs. We analyzed cell type-specific differentiation and/or pathology-associated gene expression patterns by principal component analysis, compared mitochondrial structural parameters by immunofluorescence, and measured the mitophagy marker PTEN-induced kinase 1 (PINK1) by Western blot.

We found that DHP treatment induced alterations in gene expression after mitochondrial stress induction, which were associated with myelin production, oxidative stress, and calcium signaling. Interestingly, the different DHPs were associated with distinct transcriptional response patterns and exhibit molecule- and cell type-specific effects on gene expression patterns and on PINK1 protein levels.

Our data show that in human oligodendrocytic, neuronal, and astrocytic cell lines, DHPs exhibit previously unknown and potentially beneficial effects by modulating pathology-associated gene expression patterns and mitochondrial proteins. Based on our observations, nimodipine and other DHPs may be considered as future therapeutic options to alleviate myelin loss and neurodegeneration in progressive MS.

Presentation number: P1.41

Topic: Neuroanatomy

Interactions of an antiserum to Treponema pallidum with synapsin Syn1 and the collapsin response mediating protein CRMP1 - functional effects in SiMa neuroblastoma cells

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Syphilitic infections by the Gram negative spirochaete *Treponema pallidum* (*Tpa*), are on the rise again all over the world. If syphilis is not successfully cured, it later may affect the central nervous system, leading to personality changes like mania, depression and psychosis (Friedrich et al., Psychopathology 2014, 47:3-9). Hypothesizing an immune mediated mechanism, the present study demonstrates that an antiserum to *Tpa* (α-TPa) on a human brain multiprotein array (HexSelect, Engine, Berlin, Germany), interacts with 60 different proteins, including the exocytosis regulator synapsin1 (Syn1) and the collapsin response mediating protein 1 (CRMP1). Interaction of these proteins with α-*TPa* was confirmed by Western blot with HEK293 transient overexpression lysates. Furthermore expression of CRMP1 but not Syn1 could be demonstrated by two-dimensional Western blot analysis in SiMa human neuroblastoma cells, an established *in vitro* model for neuronal differentiation. On the functional level, preincubation of these cells with 10µg/ml α-*Tpa* resulted in a significant reduction in neurite length. These results demonstrate for the first time immunological crossreactivity and also functional interference of α-*Tpa* with Syn1 and CRMP1 by molecular mimicry. Although highly speculative, together with previous reports on changes in expression of Syn1 and CRMP1 in brains of schizophrenic patients, the present results could be of importance for a better understanding of at least some aspects of this disorder.

Presentation number: P1.42

Topic: Neuroanatomy

CXCL16 and CXCR6 expression in the aged human brain

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Introduction: Chemokines navigate migration processes, e.g. of immune cells or during tissue development. The chemokine CXCL16 and its receptor CXCR6 have recently been identified as critical modulators in Alzheimer's disease (AD). However, a comprehensive study on the expression and distribution of CXCL16 and CXCR6 in the aged human brain is still missing.

Methods: Brain tissue samples from 8 human body donors (age: 61-95y) were analysed by quantitative PCR for mRNA expression of *CXCL16* and *CXCR6*, alongside with *Tumor necrosis factor-alpha*, *Aquaporin-4*, *Galectin-3* and *Vimentin*. By fluorescence-immunohistochemistry, CXCL16 and CXCR6 were detected, and cellular identity was investigated using cell type specific markers. Furthermore, regulation of *CXCL16* and *CXCR6* mRNA by different stimuli (e.g. lipopolysaccharide, LPS) was investigated in immortalized human astrocytes and microglia.

Results: We could show that CXCL16 was expressed by endothelial cells, and sporadically by tissue-resident microglia/macrophages and subsets of astrocytes in the aged human brain *in situ*, while the receptor CXCR6 was less abundantly found on subsets of immune cells, but also neural cells. *CXCL16* mRNA was in trend, but not significantly upregulated by Tumor necrosis factor-alpha and Interferon-gamma in cultured microglia, but not in astrocytes.

Discussion: Apart from myeloid cells, a well-accepted source for CXCL16, we could show that endothelial cells and astrocytes also express CXCL16, and that CXCR6 in the aged human brain is not restricted to invading immune cells. Our findings indicate that the CXCL16-CXCR6-axis may contribute to immune surveillance in complex ways, being a potential target for therapeutic strategies to ease cognitive impairment.

Presentation number: P1.43

Topic: Neuroanatomy

IL-11 regulates VGAT protein levels in hippocampal neurons

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Introduction: Interleukin (IL-)11 is a cytokine of the IL-6 family that is involved in autoimmune disease, fibrosis and cancer. The IL-11 receptor complex activates important signaling pathways, including the JAK/STAT pathway. Thus, IL-11 has the potential to regulate the expression of proteins relevant for synaptic plasticity. IL-11 and its receptor complex is expressed in the hippocampal neurons, but their functional role is not known yet.

Methods: Primary neuronal cell cultures and organotypic slice cultures of the mouse hippocampus were stimulated with recombinant IL-11 peptide for different time points. By using immunofluorescence staining, western blot and qPCR analysis as well as synaptosome preparations the impact of IL-11 on the expression of proteins relevant for synaptic plasticity were investigated.

Results: In hippocampal neurons the JAK/STAT pathway was activated after stimulation with IL-11. A screen for the expression regulation of synaptic proteins identified a downregulation of VGAT (vesicular GABA transporter) in neurons upon 24h of IL-11 stimulation at the protein, but not the mRNA level. Either reduced translation rates or elevated ubiquitination rates of proteins could be a reason for this effect. Therefore, experiments using fluorescent non-canonical amino acid tagging (FUNCAT) or evaluation of ubiquitination rates of total proteins are planned.

Discussion: Unraveling the neuronal impact of proinflammatory IL-11 may support the development of new therapeutic strategies for neuropsychiatric disorders associated with (micro-)inflammation such as neurodegeneration during aging and/or depression. IL-11 based treatments may support individualized therapeutic approaches.

Presentation number: P1.44

Topic: Neuroanatomy

Microglia-neuron contacts demonstrated by correlative live confocal and serial block-face scanning electron microscopy

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Contact-dependent, direct interaction between microglia and neurons is a key moment in processes of development, inflammation, ischemia, and neurodegeneration. Microglia actively monitors neuronal function and intimately interacts with neurons. Despite certain advancements, this cell-cell interaction is not yet completely understood, with delicate details remaining elusive, where high-resolution microscopy has its place.

We were able to develop a simple pipeline for studying microglia-neuron contacts in a primary cell culture model by live cell confocal laser scanning imaging, followed by serial block-face scanning electron microscopy.

Using this technique, we successfully generated high-resolution confocal images and correlated them to serial block face electron microscopy volumes. This method provides a highly detailed imagery of microglia-neuron interaction, allowing assessment of cellular contacts and subcellular structures.

Microglia priming by bacterial products in the context of infection-triggered neuroinflammation was used as a model setting to verify the usability of the system. We demonstrated alterations of interaction patterns by activating microglial TLRs.

Presentation number: P2.01

Topic: Cardiovascular

Anatomy of the Aortic Segmental Arteries

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Introduction: Spinal cord ischemia (SCI) resulting from occlusion or damage to the aortic segmental arteries (ASA) is a serious side effect of open and minimal invasive aortic repair. This study aims to provide detailed information on the topology of the proximal ASAs and descriptive and metric information on their orifices.

Methods: 200 randomly selected, embalmed cadavers of human body donors were anatomically dissected and examined. 47 cadavers with macroscopically visible pathologies were excluded.

Results: In all specimens, posterior intercostal and lumbar arteries were bilaterally observed. However, the aorta showed a mere 19 to 30 ASAs endoluminal orifices and in only 6.5% of the specimens, all ASAs (14 pairs) branched directly and bilaterally from the aorta. In 74% of the specimens, at least one segmental artery was a direct branch of a cranially or caudally located ipsilateral ASA. In 56% of the specimens, in at least one body segment, a single blood vessel exited from the aorta and split into the left and right ASA.

Discussion: Our large-scale study, provides detail descriptive and metric information on the origin and branching patterns of the proximal segments of ASAs. A large spectrum of variations was identified and information on their frequency is provided. The data will thus form the fundament for understanding the effect of aorta pathologies and for designing and planning their therapy.

Presentation number: P2.02

Topic: Cardiovascular

Arteriovenous Anastomoses of the Sucquet-Hoyer Type; Complexity and Distribution in the Human Finger

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Introduction: Sucquet-Hoyer canals (SHCs) are arteriovenous anastomoses, which are key elements of Hoyer Grosser Organs (HGOs) and are considered to regulate blood flow in the skin. This study aims to pave the way to understanding the function of SHCs located in the dermis of the fingers by defining their frequency, topology, and complexity.

Methods: Digital volume data from 24 samples harvested from the subungual region, nail fold corner, and thumb pad of embalmed human body donors were generated with the High-resolution episcopic microscopy (HREM) technique. Virtual 3D models of dermal SHCs were created and morphologically characterized using the Amira software. Then the numbers of SHCs in comparable regions of 2mm x 2mm x thickness of the dermis were counted.

Results: A total of 66 dermal SHCs were identified in the analyzed volumes. On average, 4 SHCs were found in the subungual area, 3 in the thumb pad, and 1 in the nail fold corner. 54.2% of the subungual region, 64% of the thumb pad, and 74% of the nail fold corner specimens were located in the profound half of the dermis. Tortuosity values ranged from 1.11 to 10. They permitted the design of an objective classification system, which distinguishes four SHC classes.

Discussion: Our results show that in human fingers, dermal SHCs are most frequent in the subungual region and finger pad. Together with the novel, objective, morphology-based classification system, this information provides the basis for researching the function of SHCs in humans.

Presentation number: P2.03

Topic: Cardiovascular

Cutaneous Microcirculation of the Human Thumb; Deciphering Hidden Features by 3D Visualization

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Introduction: Understanding the architecture of cutaneous microcirculation is vital for diagnosing and treating skin pathologies. This study aims to examine the three-dimensional (3D) morphology and topology of the dermal arteries, arterio-arterial anastomoses (AAA), and dermal arterio-venous anastomoses (SHC) in the human thumb and to compare pad and tip.

Methods: 24 biopsy samples (diameter 4mm) were harvested from the pad (n=12) and tip (n=12) of the thumb of embalmed human body donors. They were prepared for and subjected to creating digital volume data using the high-resolution episcopic microscopy (HREM) method. HREM data were then processed and visualized in the Amira software and SHC counts were performed in volumes of 2mm x 2mm x thickness of the dermis.

Results: 67 SHCs and 16 AAAs were identified in the reference volumes of the tips and 30 SHCs and 19 AAAs in the pads. 82.5% of the SHCs were located in the profound half of the dermis. 100% of the AAAs were located in the superficial dermis. 36 dermal arterial units were counted in the tip and 31 in the pad. The epidermal surface area supplied by these units was significantly greater in the pad.

Discussion: Microcirculation differs significantly between the thumb pad and tip. The large number of SHCs in the tip seems to reflect the role of SHCs in thermoregulation. Since dermal nerves usually accompany arteries, the smaller dermal arterial units in the tip may reflect superior sensory discrimination in the tip compared to the pad.

Presentation number: P2.04

Topic: Cardiovascular

Is the tricuspid valve tricuspid?

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Introduction:

Quite recently, echocardiography was used to propose a system for classifying tricuspid valve morphology. We aim at evaluating the accuracy of this classification system by *post mortem* inspection of body donor material and to provide statistics on the frequency of the different types of tricuspid valves.

Material and Methods:

The hearts of 60 non-embalmed human body donors without a medical history of cardiac diseases or macroscopically visible heart pathologies were extracted. The chambers were opened, the right sided papillary muscles were cut and the tricuspid valves were resected along the outer rim of the anulus. Finally, the annuli were transected and the valves were straightly mounted on cork sheets for examination. Valve arrangement was categorized according to the classification system proposed by Hahn et al. (2022).

Results:

10 (16,7%) valves could not be assigned to any of Hahn's types. 19 (31,7%) had a configuration with three distinct leaflets and were classified as type I. 5 (8.3%) had a bicuspid configuration and were classified as type II. 19 (31,7%) had one split leaflet and were classified as type III, with 6.7% having a split anterior (IIIa), 16,7% a split posterior (IIIb) and 8,3% a split septal leaflet (IIIc). 11,7% had several split leaflets and were classified as type IV.

Conclusion:

Our results show that anatomic examination of tricuspid valve morphology provides information not visible in echocardiographic images. Thus, a novel classification system, based on visual inspection and planimetric analysis is required for comprehensively and correctly describing tricuspid valve anatomy.

Presentation number: P2.05

Topic: Cardiovascular

Morphological Characterization of Cardiomyocyte Subtypes in Arrhythmogenic Cardiomyopathy

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Introduction:

Arrhythmogenic Cardiomyopathy (ACM) is a genetic cardiac disorder presenting with arrhythmia and cardiac fibrosis which can lead to heart failure and sudden cardiac death. In this study, we aim to establish an imaging technique to characterize different cardiomyocyte subtypes observed during development of the disease phenotype to lay the basis for more detailed studies on their functional relevance in ACM.

Methods:

To evaluate the occurrence of cardiomyocyte subtypes during disease progression, hearts from an inducible ACM mouse model (iDsg2-W2A) were collected at different disease stages and prepared for FFPE sections. To analyze the cell subtypes in entire heart sections, we designed an immunostaining and imaging analysis pipeline via QuPath.

Results:

We established and validated the semi-automated analysis pipeline to detect cardiomyocytes via PCM1/WGA staining and combined this with Ki67 or PCNA to mark cycling cardiomyocytes or alpha smooth muscle actin to identify dedifferentiating cells. With this method, we are going to characterize these cell types with respect to the localization within the heart and occurrence frequency during development of the ACM phenotype. In addition, we will analyze the ultrastructure of these cells using correlative Transmission Electron Microscopy.

Discussion:

Together, this will lay the basis for a better understanding of the processes leading to ACM. This will not only contribute to the goal of finding a causal therapy option for ACM but also to a general understanding of pathologies concerning cardiac function such as fibrosis and arrhythmia and the role of cycling or dedifferentiating cardiomyocyte subtypes.

Presentation number: P2.07

Topic: Clinical and Gross Anatomy

222 years later - preparation of the second situs inversus totalis for the anatomical Meckel Collection

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Introduction

The Meckel Collection in Halle (Saale) is considered one of the largest anatomical collections in Europe. It originates from the second half of the 18th century. Since then, the collection flourished under the influence of the Meckel family and their successors. It contains the preparation of a situs inversus totalis, which was first described by the anatomist J. F. Meckel Jr. in the year 1802.

222 years later, a second preparation of a situs inversus totalis is added to the Meckel Collection.

Methods

The body of a 61-year old Caucasian male was dissected after fixation in

formaldehyde-solution. Afterwards, final fixation was attained using polyethylene glycol.

Results

The complete dissection of the thoracic and abdominal cavity confirmed the presence of a situs inversus totalis with dextrocardia and inversed location of the inner organs and their vascular supply. Thus, the abdominal aorta runs on the right side of the inferior vena cava.

Discussion

With a prevalence of 1:10 000, it is not unlikely that medical professionals come across a patient with this condition. In 25% of all cases, a situs inversus totalis is associated with Kartagener's syndrome. To find out whether this is the case for the present situs inversus, we will focus on the histological analysis of respiratory epithelia and the donor's medical history, since the informed consent states that no DNA analysis is allowed for tissue from body donors.

The study highlights the relevance of preparing body donors for teaching, continous medical education and anatomical collections.

Presentation number: P2.08

Topic: Clinical and Gross Anatomy

Palmaris accessorius profundus muscle - a rare variation

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Introduction

The palmaris accessorius profundus muscle (PAPM) is considered to be a rare anatomical variation of the palmaris longus muscle (PLM), which is blamed to cause carpal tunnel syndrome. Given its significance in hand surgery, our study aimed to describe the morphology of an accidentally discovered PAPM.

Materials & Methods

During a student dissection course, the right arms of 120 human cadavers, fixed in a formaldehyde/carbol solution were dissected. While dissecting the right forearms, a PAPM was identified by one of the instructors. The contralateral arm of this specimen was then anatomically dissected by the authors.

Results

One out of 120 body donors bilaterally featured a PAPM and a PLM. Origin, insertion, and topography of both were almost identical on both sides. PAPM had a tendinous origin from the anterior surface of the proximal radius and formed a fusiform belly. From the tendon the radial head of the flexor digitorum superficialis muscle (FDSM) originated. The PAPM inserted in the palmar aponeurosis.

The origin was covered by pronator teres muscle (PT). In the middle of the forearm muscle belly of PAPM was sandwiched between the flexor pollicis longus muscle (FPLM) and the flexor carpi radialis muscle. It entered the carpal tunnel between the FDSM tendon and the median nerve. Then it passed the tunnel running through an isolated compartment to its insertion.

Discussion

Our result confirms that the PAPM is rare variation, which narrows the carpal tunnel space. Its origin suggests that PAPM and PLM are separate entities.

Presentation number: P2.09

Topic: Clinical and Gross Anatomy

Assessment of the influence of changing dietary habits on the state of the human dento-mandibular system in the age aspect.

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Introduction. Eating more plant-based and liquid foods can change the type of mastication, reducing the load on the dento-mandibular system. Therefore, it is important to carry out preventive measures that familiarize all segments of the population with a culture of balanced food consumption.

Methods. Questionnaire data containing 9 questions regarding dietary patterns, age, dento-mandibular system status, patient's gender and region of residence were taken for the study. A total of 300 patients' data were included in the study.

Results: In our study, 39.3% of the patients had no dentoalveolar anomalies and 61.7% of the patients interviewed had dentoalveolar and dentoalveolar anomalies. Anomalies in the position of individual teeth were found in 37.3% and in the ratio of dental arches in 21.3%. At the same time, anomalies of the shape of the dental arches amounted to 10.7 %, anomalies of the position - 8.3 %, and jaw size - 9 %. We found that dento-mandibular anomalies depend on the food consumed by the respondents: 66.3 % of the respondents indicated a balanced diet, 21 % indicated a predominance of soft foods in the diet, the remaining 12.7 % of the respondents indicated other types of food.

Discussion. Based on the findings of the pilot study, a trend of adaptive effects on the health of the dento-mandibular system in the form of orthodontic anomalies and changes in the pattern of tooth hard tissue erasability has been identified.

Presentation number: P2.10

Topic: Clinical and Gross Anatomy

An interesting variation, severe kinking in a post-ileal vermiform appendix and a suspensory ligament

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Introduction: Appendicitis is a common condition in society. From time to time, there may be problems in diagnosis and the patient may have to struggle with serious complications due to delayed treatment. While the vermiform appendix is often found retrocecal, there are also types such as pre-ileal, post-ileal, and pelvic, albeit with decreasing frequency. The positions of the vermiform appendix; there is the possibility of changing the type, mode of presentation, and duration of appendicitis symptoms.

Methods: During a dissection performed for educational purposes, a post-ileal (splenic) vermiform appendix was identified in male cadaver.

Results: The difference of this appendix was that as it moved towards the splenium, it suddenly kinked at a sharp angle and turned towards the pelvis and extended vertically downward. Vermiform appendix was found to be 6.87 cm in length, 6.56 mm in width. Contrary to what was expected in the structure of the vermiform appendix, unlike the horizontal course of the last 2.33 cm, it changed direction towards the pelvis by making a serious kinking and then followed a short vertical course. The angle between the horizontal and vertical sections was measured as 26 degrees. In addition, the vermiform appendix was attached to the posterior abdominal wall by a suspensory ligament.

Discussion: We believe that this variational situation, which we have not encountered in the literature will be beneficial for surgeons in the evaluation of patients, interpreting unexpected symptoms in terms of appendicitis, and reducing complications such as perforation and rupture during the surgical procedure.

Presentation number: P2.11

Topic: Clinical and Gross Anatomy

Macroscopical and histological characterization of the perineal membrane and the deep perineal space

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Introduction: Although the deep transverse perineal muscle is described in many textbooks, studies on it are rare. In addition to the question of its existence, its histological composition is also discussed.

The aim of the study was to find out whether the macroscopically visualizable plate consists of connective tissue or striated respectively smooth muscle.

Methods: Investigations were performed on embalmed human body donors (n=10, mean age of death: 80.1 years). After preparation of the superficial and deep perineal space, the perineal membrane including transverse structures between the ischial branches were removed. For light microscopic analysis, 4µm thick transversal sections were made in caudocranial direction at 40µm intervals. Sections were stained with Azan and were analyzed stereologically. We determined the volume densities (V_V) of connective tissue (V_V(ct/dps)), smooth muscle (V_V(gm/dps)) and striated muscle (V_V(stm/dps)).

Results: A transverse muscle belly was macroscopically neither seen in females or in males clearly. Both sexes showed an increase in V_V(ct/dps) and a decrease in V_V(gm/dps) and V_V(stm/dps) within the deep perineal space with aging. While males showed a rather balanced distribution between V_V(gm/dps) and V_V(stm/dps), in females striated muscle was not observed. In addition, females exhibited a significantly higher V_V(gm/dps) than males.

Discussion:A deep transverse muscle was not clearly seen in the investigated corpses. Tissue samples showed predominantly connective tissue. However, some transverse muscle fibers corresponding to the deep transverse muscle were visible, which decreased with increased age. It not excluded that in younger people a uniform transverse muscle plate exists.

Presentation number: P2.12

Topic: Clinical and Gross Anatomy

Variant anatomy of the relations between the facial nerve and the buccal fat pad in the maxillofacial region.

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Introduction

The question about the variants of the relations between the facial nerve (FN) and the buccal fat pad (BFP) is open. And the purpose of our research is to study the variant anatomy of the syntopy of the branches of the FN and the BFP.

Materials and methods

The material for this study was the frozen heads of adult males and females aged 46 to 94 years. Number of observations was 163. As method we used standard layer by layer dissection.

Results

Three variants of the relations between the FN and the BFP were described. The variant of syntopy between the BFP and the FN were the branches of the FN passed directly along the surface of the BFP was indicated as the 1 variant (37,42%; n=61). The 2nd variant of syntopy of the considered anatomical structures (33.74% n=55), in which the branches of the FN passed along the upper and lower edges of the BFP. The last 3rd variant of syntopy occurred in 28.83% (n=47) of observations, characterized by the fact that one or more branches of the FN passed directly through the thickness of the BFP.

Discussion

It can be considered that the risk of damage to the branches of the facial nerve with percutaneous approaches to the buccal region is high due to their superficial location, however, with 3rd type, through the thickness of the BFP, even performing intraoral approach, there is a high risk of damage to the FN.

Presentation number: P2.13

Topic: Clinical and Gross Anatomy

Systematic Review of Arterial Vascularization of the Forehead in Aesthetic Dermatology

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Introduction

The increase in facial aesthetic procedures has raised safety concerns, especially in the highly vascularized forehead area. This review identifies risk zones for procedures by examining the local arterial vascularization.

Methods

A systematic search was conducted. Titles and abstracts were screened, followed by full-text evaluation.

Results

The search identified 714 articles, with 25 included in the review. Studies using cadaveric dissection, CT on cadavers, and ultrasonography on volunteers were included. In total, 1714 cases were analyzed. Artery locations varied: central artery (CA), paracentral artery (PCA) in cadaver studies ranged from 0.2 to 10.8 mm and 0.8 to 16.2 mm respectively, from the glabellar point to the frontal prominence. Midline distances ranged from 0.6 to 28.0 mm for the superficial branch of the supratrochlear artery (STrA) and 13.6 to 40.7 mm for the deep branch. For the supraorbital artery (SOA), the midline distance ranged from 23 to 32 mm. Doppler studies showed distances of 0 to 23 mm for STrA and 10 to 50 mm for SOA. CT showed STrA at 11 to 21 mm and SOA at 21 to 32 mm from midline.

Discussion

The review highlights significant arteries like the STrA, SOA, and PCA, which can pose risks of ophthalmic complications due to their connections with the ophthalmic artery. The frontal branch of the superficial temporal artery, although less risky, still requires caution. The variability and extensive distribution of forehead arteries underscore the importance of identifying high-risk zones, particularly the glabella, to enhance the safety of dermatologic procedures.

Presentation number: P2.14

Topic: Clinical and Gross Anatomy

Investigation of an ethanolic citric acid solution for embalmment as a low-toxic alternative to formalin-based fixatives

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Anatomical dissection courses with embalmed body donations are an essential part of medical education. Common embalming procedures often use formaldehyde for preservation, which, however, is toxic and teratogenic and therefore should be replaced.

In this study, the substitution of formaldehyde with citric acid, a common food preservative, was investigated by means of murine cadavers. Cadavers were perfused with different ethanolic fixative solutions including an ethanolic citric acid solution (CA-EtOH) and an ethanolic formaldehyde solution (FA-EtOH) commonly used in our institute for embalmment of body donations and phosphate buffered saline (PBS) as control groups. To compare preservation effects between different concentrations of CA-EtOH and the control solutions, cadavers were stored and regularly exposed to room air over a 12-week period simulating the conditions of an anatomical dissection course. For evaluation, microbial load, tissue hardness and stiffness, color, odor, and macroscopic and microscopic preservation were regularly assessed. Possible bone decalcifications were measured with radiography and micro computed tomography (mCT).

Colonic tissue samples from cadavers perfused with CA-EtOH showed a low concentration of colony forming units (CFU). It was significantly lower compared to the PBS control group and stayed on a low level during the experiment. Cadavers embalmed with FA-EtOH were sterile. The CA-EtOH-perfused cadavers showed time-dependent bone softening, decalcification and surface precipitates during room-air exposure, limiting the suitability of CA-EtOH for embalmment for anatomical teaching. However, internal organs of cadavers perfused with CA-EtOH showed a macroscopic appearance comparable to the FA-EtOH group, i.e. with good preservation and differentiability.

Presentation number: P2.15

Topic: Clinical and Gross Anatomy

Embroidered silk fibroin scaffolds for ACL tissue engineering

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Objective

Silk could be an interesting material for anterior cruciate ligament (ACL) reconstruction. Sericin is usually removed to reduce immunogenicity and improve processability of Bombyx (B.) mori derived silk. Based on selected patterns, embroidering allows adaption of biomechanical properties. This project aims to identify an embroidered silk fibroin-based scaffold variant facilitating ACL tissue engineering.

Methods

For removal of sericin, two different procedures were applied to the silk threads: a standard ("raw silk") and a novel ("purified silk") technique. Both types of silk fibroin threads were used to embroider pure silk scaffolds or were combined with PLA-co-caprolactone (P(LA-CL)) fibers. Hence, four groups ("raw silk","raw silk/P(LA-CL)", "purified silk", "purified silk/P(LA-CL)") were seeded with lapine cruciate ligament fibroblasts (LCL-Fb). Cytotoxicity was measured with scaffold extracts (MTS assay) and LCL and L929 fibroblasts (Fbs). Cell adherence, vitality, cytoskeletal and extracellular matrix proteins were monitored.

Results

Scaffolds showed no cytotoxicity. LCL-Fb adherence on scaffolds differed, being low on raw silk and higher on raw silk/P(LA-CL) and highest on the purified silk and purified silk/P(LA-CL) scaffolds. Interestingly, the P(LA-CL) integration into the scaffold increased also the cytocompatibility of raw silk fibers. Cell survival on the scaffolds was high for the whole observation period (14 days). The focal adhesion component paxillin was abundantly expressed in cells on purified silk scaffolds underlining intimate cell material interaction and also typical ECM could be detected.

Conclusions

Purified silk fibroin threads are highly cytocompatible and represent a versatile material, suitable to prepare embroidered LCL-Fb carriers without the necessity of further functionalization.

Presentation number: P2.16

Topic: Clinical and Gross Anatomy

Anatomical dissection of the clitoris in teaching and research: Detailed examples of neglected topographical relationships

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The anatomy of the human bulbo-clitoral organ has been examined and described by the morphological disciplines in detail for more than 150 years. Nevertheless, often it is not part of the dissection course in the anatomical curriculum at universities and medical schools. This is partly explained by the supposed technical difficulty and time-consuming dissection, and partly due to a cultural taboo on female sexual anatomy, physiology, and arousal. Additionally, when comparing information on clitoral anatomy to penile anatomy, modern anatomical textbooks lack information and details about the clitoris and surrounding structures. Due to the expanding range of surgical procedures that can be performed on the external female genitalia (e.g. surgical reconstruction after female genital mutilation/cutting, clitorido- and labioplasties, surgical repair of urogenital anomalies), it is expected that detailed knowledge of clitoral anatomy will gain clinical relevance and become increasingly necessary in gynecology, urology, and plastic surgery. Therefore, integrating detailed anatomical knowledge into the anatomical curriculum is of increasing importance. Our inter-institutional collaboration aims to demonstrate that a detailed dissection of the bulbo-clitoral organ is also possible in the dissection course of macroscopic anatomy. To this end, we provide insights into preparation results relating to the clitoris and encourage the integration of these preparations into anatomy teaching at different anatomy institutes. To support this, we additionally provide different strategies for the preparation of the clitoris, to be adapted to the existing curricula with a focus on troubleshooting for the most common pitfalls.

Presentation number: P2.17

Topic: Clinical and Gross Anatomy

Tissue-fixation of neuronal and glial structures for immunohistochemistry using a non-toxic food preservative

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Introduction

Neutral buffered formaldehyde (NBFA) is widely used for tissue fixation in histopathology and research although its health risks, i.e. toxicity and mutagenicity, are well known. Due to the lack of less toxic alternatives, we tested lactic acid (LA), a commonly used food preservative, for histological fixation.

Methods

Immersion fixation and transcardial perfusion with subsequent immersion postfixation of healthy murine brains was carried out using NBFA, LA, and phosphate-buffered saline (PBS). Paraffin sections of the fixed brains were stained against immunohistochemical markers of different cell compartments, using the DAB precipitation method and immunofluorescence. Antigen preservations of the different fixatives were quantified via cell counting and densitometry. The impact of acidity in LA-based fixation was tested in parallel.

Results

Staining against GFAP, an astrocyte marker, resulted in similar signal densities comparing LA-fixed and NBFA-fixed tissue. MBP staining of LA-fixed tissue yielded staining of myelinated fiber tracts with unspecific nuclear staining of various cell populations. Staining against OLIG2 and IBA1, used as markers for oligodendrocytes and microglia, respectively, was inadequate in LA-fixed tissues. When using pH-neutral LA, OLIG2 staining was enhanced compared to acidic LA and similar to NBFA fixation. With acidic PBS staining results worsened and were similar to samples fixed with acidic LA. Staining against MBP, IBA1, and GFAP showed less pH-dependent effects.

Discussion

The tested LA-based fixatives did not preserve the studied antigens appropriately. This might be overcome by direct pH optimization or addition of supplemental preservatives with buffering effects.

Presentation number: P2.18

Topic: Clinical and Gross Anatomy

Food preservatives as potential formaldehyde substitutes: effects of lactic acid on the microscopic scale

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Neutral buffered formaldehyde (NBFA) is the gold standard for tissue fixation due to its effective preservation of tissue morphology and subcellular structures. However, formaldehyde-associated health risks necessitate safer alternatives. Our group aims to develop novel tissue fixatives based on food preservatives. In this study, lactic acid (LA), a commonly used food preservative, was tested as a novel, non-toxic tissue fixative. Its suitability for common histochemical staining of neuronal and glial structures was evaluated.

Murine brain specimens were fixed by immersion or transcardial perfusion with differently composed LA solutions and, as controls, NBFA and phosphate buffered saline (PBS). Specimens underwent different post-fixation immersion times. Paraffin-embedded brain sections were stained (HE, LFB-PAS, Nissl) and blindly evaluated using an in-house developed numerical histological scoring system. In addition, quantitative densitometrical measurements were conducted for distinct parameters.

As expected, NBFA fixation resulted in well preserved brain tissues with an intact white matter integrity, sharply demarcated nuclear borders, easily distinguishable hetero- and euchromatin, and an intact neuropil. All these histological quality criteria were not met in PBS-treated tissue. Tissue samples incubated in the different LA solutions showed intermediate histological preservation with particularly good effects on neuronal preservation but limitations concerning white matter integrities and crack artifacts.

Among other food preservatives, LA shows promising tissue preservation effects on both, the macroscopic and microscopic scale. Future experiments need to be conducted to optimize preservative effects of LA to be used as an alternative for NBFA in anatomy, pathology and research.

Presentation number: P2.20

Topic: Clinical and Gross Anatomy

Morphometry and variations of foramens in maxilla, mandible and zygomatic bones

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Introduction: The anatomy of the zygomatic bone, maxilla, periorbital and mental region are important due to the important vessels and nerves passing through that regions. Zygomaticofacial nerve can be injured during facial surgeries, especially zygomatic implant surgeries. Infraorbital and mental nerves are among the nerves blocked during local anesthesia in dentistry. Knowing the location of the mental foramen and mental nerve in complex intraoral surgical interventions is important to prevent possible complications. Variations of the foramens affect the risk of possible complications in facial surgery.

Methods: 30 dry human skull bones were examined. The distance of the zygomaticofacial foramen to the edge of the orbit, the distance to the zygomaticomaxillary suture, the distance to the zygomaticatemporal suture, and the distance to the infraorbitalis foramen were measured. The distance of the foramen infraorbitalis to the edge of the orbit and the lower end of the suture zygomaticomaxillaris was measured. Morphometric measurements of the foramen mentale variations were examined.

Results: Distance between infraorbital foramen and zygomaticomaxillary suture found 24,42 mm on the right; 25.21 mm on the left. It was statistically significant (p= 0.030). The most common location of the zygomaticofacial foramen was A, both on the right and left.

Discussion: Determining the area where the zygomaticofacial foramen is most commonly seen will be a guide in preventing nerve injuries in facial surgeries. It is important that there is no significant difference between the distances of the foramens on the right and left to facilitate surgical interventions.

Presentation number: P2.21

Topic: Clinical and Gross Anatomy

Combined anatomical and sonographic evaluation of the myotendinous junction of the long head of the humeral biceps tendon: The horse shoe sign

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Introduction

Injuries of the long head of the biceps tendon (LHBT) are a typical cause for anterior shoulder pain. Usually, tears of the LHBT are well assessable with sonography. In some cases, like tendon remnants in the bicipital groove or autotenodesis, the diagnosis may be a challenge. To improve the sonographic diagnosis and therefore an adequate treatment, the morphology of the myotendinous junction (MTJ) of the LHBT was investigated.

Methods

Thiel-fixated human cadaveric material obtained from the institutional body donation program was dissected to analyze the morphology of the MTJ of the LHBT for future correlation with ultrasound findings.

Results

The MTJ was found to be asymmetrical: on its medial side, the tendon-muscle transition is more cranial than on the lateral side, where the transition has fringe-like tendon fibers. In a cross-section, the MTJ resembles a horseshoe, which is open medially and where the tendinous part decreases and the muscular part increases towards distal. The height of the MTJ was approximately 8 cm and situated between 3-4 cm above and 4-5 cm below of the lower pectoralis major tendon.

Discussion

To the best of our knowledge, this is the first anatomical description of the morphology of the MTJ, which, because of its resembling morphology, was termed “horseshoe sign”. For clinicians, the knowledge of the morphology and position of the MTJ will be helpful for sonographic diagnosis of LHBT rupture, reduce additional examinations and improve the adequate therapy.

Presentation number: P2.22

Topic: Clinical and Gross Anatomy

Go with the Flow – The Rheology of Fixation Solutions in the Abdomen During Fixation

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Introduction

Effective fixation of cadavers is crucial for anatomical teaching and training. Current protocols are often location-specific, mostly relying on intra-arterial infusion or perfusion of fixative solutions. Most protocols, however, derived from the experience of local staff rather than from evidence-based knowledge of the rheology and distribution of fixatives within the cadavers. Here, we aimed to elucidate how fixative solutions are penetrating vessels and tissues in the abdominal cavity during infusion via the femoral artery using an unprecedented peri-fixation laparoscopy.

Material & Methods

The cadavers, donated to our institute, were fixed by an intra-arterial infusion of an Aminolipin-containing solution. The in-body distribution of the fixative was monitored with a rigid endoscope via a laparoscopy using photo- and video documentation.

Results

Here, we present novel insights into the perfusion-dynamics of intraabdominal organs, including intestines, stomach, liver, and the abdominal wall during intra-arterial infusion. We found considerable swelling of organs and tissues correlating with infusion time. Moreover, infusion led to a visible filling of vessels on the organ surface followed by partial whitening of tissues arguably due to imbibition of fixative. Most cases formed ascites after approximately 20 minutes after starting the injection. It is noteworthy that we also detected interindividual differences indicating confounding effects of vascular conditions or previous operations.

Discussion

Using peri-fixation laparoscopy, we were able to document changes of intraabdominal organs throughout intra-arterial infusion. Our results demonstrate the perfusion and tissue-imbibing by fixative solution in real-time providing unprecedented insights into the dynamics of anatomical cadaver fixation.

Presentation number: P2.23

Topic: Clinical and Gross Anatomy

Left Common Carotid Artery Arising from Brachiocephalic Trunk: A Rare Case Report

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Introduction: The aortic arch typically gives rise to three branches: the brachiocephalic trunk, the left common carotid artery, and the left subclavian artery. The left common carotid artery is the second branch arising from the aortic arch. However, various anatomical variations of the aortic arch exist. One rare vascular variation is the left common carotid artery arising from the brachiocephalic trunk instead of the aortic arch. This case report examines the imaging findings of a left common carotid artery variation in a 20-year-old female patient diagnosed with osteosarcoma.

Case report: A 20-year-old female patient, followed by the Department of Medical Oncology at Selçuk University Faculty of Medicine with a diagnosis of osteoblastic osteosarcoma, underwent thoracic aorta magnetic resonance angiography (MR angiography) due to suspected recurrent metastasis. The thoracic MR angiography revealed that the ascending aorta, aortic arch, and descending aorta were of normal caliber and had patent lumens. However, the left carotid artery was seen to originate from the brachiocephalic trunk rather than the aortic arch. The lumens of the arteries were observed to be patent.

Discussion: This variation is usually asymptomatic and is often discovered incidentally during radiological imaging (especially MR angiography), surgeries, or cadaver dissections. Early detection of these vascular pathologies is crucial for surgeries and endovascular procedures. This case presents an example of the incidental finding of a left common carotid artery variation and emphasizes the importance of preoperative evaluation and caution in such rare conditions.

Presentation number: P2.24

Topic: Clinical and Gross Anatomy

Analysis of morphometric properties maxilla and palatine bone in dry bones

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Introduction: The maxilla participates in or restricts the structure of many important anatomical regions, including the oral cavity, nasal cavity, orbit, sinus maxillaris, fossa infratemporalis, fossa pterygopalatina. The hard palate forms the maxilla and palatine bones. Our aim is to investigate the morphological properties of maxilla and palatine bone in terms of their pathologies, surgical procedures and dental implant applications, which are important for compliance.

Methods Thirty-five maxilla and palatine bones were evaluated. The distance between the intermaxillary suture and nasal spine was measured, and the distance between the intermaxillary suture and the frontomaxillary suture. The distance between the frontomaxillary suture and the midpoint of the zygomaticomaxillary suture was evaluated. The distance the intermaxillary suture to the midpoint of the zygomaticomaxillary suture was measured. The furthest distance between the greater palatine foramen was evaluated. The distance of the posterior nasal spine to the right and left lesser palatine foramen was measured. The distance of the foramen incisivum to the spina nasalis posterior and to the foramen palatinum minus was examed.

Results The distance between frontomaxillary suture and zygomaticomaxillary suture was found to be 61.92 mm on the right, 61.31 mm on the left, this difference was significant ($p=0.027$). Other parameters were not found to be significant from the point of view of the side ($p>0.05$).

Discussion The morphometry of this region is important in trauma, tumor surgery or congenital deformities.

Presentation number: P2.25

Topic: Clinical and Gross Anatomy

Arthroscopic accessibility to the subtalar joint in inversion/eversion and non-invasive distraction

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Introduction: Subtalar arthroscopy is used to address soft tissue impingement, synovitis, osteochondral defects or other degenerative arthropathies. Especially in cases of osteochondral defects, knowledge on the amount of reachable cartilage is of importance for treatment planning. Thus, the aim of this study was to evaluate and compare the accessibility of the subtalar joint between inversion/eversion and non-invasive distraction.

Methods:40 paired fresh-frozen foot and ankle specimens were used. Two groups were created (inversion/eversion-group, non-invasive distraction group) by randomly assigning one side of each pair to a respective group. Standard anterior, middle and posterior lateral portals were placed for subtalar arthroscopy. Maximum joint accessibility to the posterior talar articular facet of the calcaneus was tested arthroscopically through markings by a chondropick. Afterwards, the subtalar joint was dissected, the location of the markings on the posterior talar articular facet evaluated and compared between the groups.

Results: Medialmost accessible point was 20.31+/-3.55mm in the inversion/eversion group and 20.28+/-4.75mm in the non-invasive distraction group. Posteriormost accessible point was 21.27+/-3.86mm in the inversion/eversion group and 20.64+/-4.68mm in the non-invasive distraction group. 428.70+/-89.50mm2 (75.08+/20.75%) of the posterior talar articular facet were accessible in the inversion/eversion group and 422.85+/-135.87mm2 (68.02+/-21.56%) in the non-invasive distraction group. No statistical difference was identified between the two groups ($p>0.05$).

Discussion: Neither the use of the non-invasive distraction strap nor positioning the foot in inversion/eversion showed superior joint accessibility. However, a specific distraction-setup is not necessarily needed to maximize joint access to the subtalar joint, as physiological maximum joint positioning would suffice.

Presentation number: P2.26

Topic: Clinical and Gross Anatomy

Intestine in a post-corrosive burns oesophageal reconstructions

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Introduction

Corrosive substances intake, both accidental or intentional, cause upper gastrointestinal tract burns followed by stenoses which have to treated with oesophageal reconstructions. The oesophageal reconstruction surgical treatment is concerned with extensive anatomical changes in the abdominal cavity, thoracic cavity and on the neck.

Methods

The patients with surgically reconstructed oesophageal passage with pedicled intestinal segments were enroled. Surgical reconstructions were performed in patients when the endoscopic dilatations failed to restore oral feeding. Among 335 surgically treated subjects in years 1954 – 2022 252 patients (58 Females, 194 Males) were analysed.

Results

in 19 Females (F) and 57 Males (M) the small intestine was used for reconstructions (p=0.6); in 20 Fs and 63 Ms the large intestine (p=0.8) and in 19 Fs and 74 Ms combined (large with small intestine) (p=0.45) were used.

Discussion

Our analysed Females were younger than Males – mean age was smaller by more than 9 years (we think is was caused by a small female group), but the waiting time for reconstruction was similar - circa 2 years. There are many types of intestinal oesophageal reconstructions, none of them is universal, because of different vascular patterns in patients. we strogly support to perform the reconstructions from the jejunum. We observed the best function of the pedicled substitute performed form the small intestine.

Presentation number: P2.27

Topic: Clinical and Gross Anatomy

IMMUNOHISTOCHEMICAL EVALUATION OF MECHANORECEPTORS IN THE ANTERIOR CRUCIATE LIGAMENT OF THE HUMAN KNEE JOINT

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IMMUNOHISTOCHEMICAL EVALUATION OF MECHANORECEPTORS IN THE ANTERIOR CRUCIATE LIGAMENT OF THE HUMAN KNEE JOINT

Introduction: Mechanoreceptors are specialised sensory nerve endings. There are four major groups of mechanoreceptors based on their morphological specialization, according to Freeman and Wyke classification. They are primarily located in the skin, but are also found in muscles, tendons, joints, blood vessels and attached to hair follicles. Mechanoreceptors play vital role in proprioception and dynamic stability in the knee joint. Various previous studies suggest the presence of different types of mechanoreceptors in anterior cruciate ligament (ACL), including Ruffini corpuscles.

Methods: The purpose of the study was to find a panel of immune markers for mechanoreceptors based on the morphology specifications. Seven human anterior cruciate ligaments from fresh frozen cadaveric knees were used for the study. In single and double immune histochemical (IHC) staining of ACL specimens

SMI 31 and S100 markers were explored.

Results and conclusion: The anterior cruciate ligaments were highly innervated with bundles of nerve fibres in both HE and IHC staining. These nerve bundles are located more towards bony attachments of ACL and distributed in the loose connective tissues, closer to the blood vessels and between the collagen fibre bundles. In our study, no Ruffini corpuscles were identified by morphology with these two markers. In conclusion, more markers have to be tested to specifically identify Ruffini corpuscles or other mechanoreceptors in the ACL.

Presentation number: P2.28

Topic: Clinical and Gross Anatomy

Extensor indicis proprius and extensor digiti medii muscles – three examples of frequent subtypes of the extensor brevis digitorum manus muscle in humans

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Introduction

Muscle variants in the dorsum of the hand, such as the Musculus Extensor Digitorum Brevis Manus (EDBM), can cause pain and restricted movement, often being mistaken for wrist ganglia in clinical practice. Accurate diagnosis is typically achieved during surgical exploration.

Materials and Methods

These muscle variants have been detected in three individuals during a student dissection course case held at the Division of macroscopic and clinical anatomy of the Medical University of Graz. The origin, course and insertion of the muscles were determined by precise macroscopic dissection. In addition, a comprehensive narrative literature review has been carried out.

Results

The first variant was identified as Musculus Extensor Indicis Proprius, while in the two other individuals, a Musculus Extensor Medii Digiti was found to be present.

Discussion

These variants, although frequently overlooked, are significant in clinical practice due to their potential to mimic other pathologies and cause symptoms by compressing adjacent structures.

Presentation number: P2.29

Topic: Clinical and Gross Anatomy

Graz Anatomy on the move: a bit of history

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Introduction

A glance at the city map of Graz will show the path anatomy has taken since its beginnings.

Materials and Methods

The historic background of the Anatomy in Graz has been researched on the basis of existing documents and monographs.

Results

It has presumably started around 1580 in the Deutschordenshaus in nowadays Zinzendorfgasse. The Mur was then crossed and around 1730, anatomical acts have been performed at Saint Georg's cemetary, now replaced by the Orpheum. Back to the opposite bank of the Mur, between 1788 and 1869, anatomy has been part of the Landeskrankenhaus at the Paulustorgasse. From 1870, Anatomy was housed in its own building in Harrachgasse, together with Physiology. It was replaced by a new building between 1970 and 1977. During the construction, anatomy was housed in the Sankt Anna Kinderspital and thus has to move again. When in 2004 the medical faculty was separated from the Karl Franzens University thereby founding the Medical University of Graz, a new university campus was erected close to the university hospital. And as a great chance, anatomy was given a new building combining art nouveaux with modern style and offering everything needed.

Discussion

Apparently until now, the Grazer anatomists were always on the pulse of time and knew how to use the opportunities that presented themselves.

Presentation number: P2.30

Topic: Clinical and Gross Anatomy

Clinical-Applied Anatomy of the Carpal Tunnel regarding mini-invasive Carpal Tunnel Release

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INTRODUCTION

Carpal tunnel release is a widely performed procedure. Despite a high success rate, iatrogenic neurovascular injuries can occur which lead to a painful and unsatisfying outcome. This study conducted a detailed examination of the proximity of neurovascular structures that are particularly susceptible to injury.

METHODS

The anatomy of carpal tunnel of 104 wrists of 52 body donors was examined. The distance between median nerve, ulnar artery, ulnar nerve, and Berrettini branch was measured in a proximo-distal and radio-ulnar direction in relation to the distal ulnar end of the flexor retinaculum.

RESULTS

There are four main dangerous anatomical situations presented. 1. proximal separation of the Long-Finger/Ring-Finger branch of the median nerve together with a narrow safe-zone; 2. ulnar take-off of the recurrent muscle branch of median nerve with a close radio-ulnar distance to the distal ulnar end of carpal tunnel; 3. ulnar arterial arch lying close to the transverse carpal ligament; and 4. proximal Berrettini branch lying close to the latter. All situations are illustrated by photographs. A sonographic carpal tunnel assessment protocol is presented to reduce the risk of injury of any neurovascular structure in proximity of the carpal tunnel.

DISCUSSION

Certain patients face an elevated risk of neurovascular injuries during minimally invasive carpal tunnel releases due to their anatomical variations. Consequently, it is strongly recommended to conduct a preoperative ultrasound assessment of neurovascular structures at risk before any surgical intervention. In high-risk patients, open surgery might be a preferable choice over endoscopic or ultrasound-guided tunnel releases.

Presentation number: P2.31

Topic: Clinical and Gross Anatomy

Forearm Tendon Variations – A clinical-anatomical mapping for daily clinical practice

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Introduction

The palmaris longus (PL) and flexor carpi radialis (FCR) tendons are often used for tendon transplants. Due to many anatomical variations, the purpose of this study was to describe the prevalence and possible variations of the PL and FCR muscles.

Methods

A dissection of the flexor compartment of the forearm was conducted on 31 bodies. Both muscles were examined to outline the length and the width of the tendons and anatomical variations.

Results

PL was found in 74 % of all specimens and FCR in 100%, respectively. 64 % had a bilateral, 10 % a unilateral and 26 % had an agenesis of PL. The tendon length was approximately 13 cm long (SD 3 cm, range 4 -19 cm). The PL tendon had a round structure in 71% of all donors and a flat, aponeurotic structure (with a width of more than 1 cm) in 3% of all donors. The PL tendon showed a bifid variation in 10% of all donors. One case showed a central muscle belly, a proximal tendon and a distal bifurcated tendon. In one case the ulnar artery overcrossed the PL.

The distance between the most distal FCR muscle fibers and the transverse carpal ligament was 8.3 cm (SD 1.5 cm, range 5.5-11.5 cm). The shape of FCR was constant, variations showing solely in tendon length.

Discussion

Different tendon variations might lead to a poor tendon harvesting, neurovascular structures might be endangered due to the variability around the PL and FRC tendon.

Presentation number: P2.32

Topic: Clinical and Gross Anatomy

Exploring Clinical Anatomy of Temporal Migraine: New Insights from Zygomaticotemporal Nerve Mapping

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Introduction

In recent years, surgical interventions targeting irritated craniofacial nerves have emerged in the management of pharmaco-refractive migraine headaches. For temporal migraine, the zygomaticotemporal nerve (ZTN) has been identified, but its anatomical variations remain underrepresented in literature. Despite high success rates, incomplete depiction of all trigger points may be considered a cause for surgical failure in up to 20 %.

Methods

We conducted a macroscopic, stratigraphic layer-by-layer-dissection in the temporal region while tracing the ZTN to identify and locate piercing points within the fascial layers, as well as potential vascular, muscular and osseus compression points.

Results

Sixty-four hemifaces underwent dissection. Based on the anatomical relation to the marginal process and the presence of an accessory branch, we described four main patterns of the ZTN's anatomy. We found an accessory branch in 58 %, piercing the deep layer of the temporal fascia with a mean distance of 3 mm nasal to the marginal process and 25 mm cranial to the Frankfurt plane. An intramuscular course within the temporalis muscle was seen in 16 %. Furthermore, we identified a cross section with the zygomatico-orbital and/or the superficial temporal artery in 31 %. No statistical difference was noted between sexes or sides.

Discussion

The patterns of the ZTN's anatomy may be utilized as guidance for the surgical approach of temporal migraines. Our findings further emphasize the importance of targeting accessory branches to achieve optimal results in migraine patients. Additionally, a novel vascular compression point may be considered in preoperative diagnostics and surgical procedures.

Presentation number: P2.33

Topic: Clinical and Gross Anatomy

Ossification of the pterygospinous and pterygoalar ligaments – Prevalence, degree of ossification, and relevance of these anatomical variations

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Objective

In the infratemporal fossa close to the foramen ovale, two accessory ligaments can occur: the so-called pterygospinous and pterygoalar ligaments. These ligaments can be completely or partially ossified. The existence of these structures could lead to entrapment of the mandibular nerve or one of its branches, which could be considered as a possible cause of trigeminal neuralgia. Additionally, during invasive procedures, such as the treatment of trigeminal neuralgia, these structures may represent an anatomical obstacle.

Methods

564 macerated skulls were examined for ossification of these ligaments. Additionally, the visibility on CT scans was evaluated. 64 infratemporal fossae of ethanol-embalmed heads were dissected layer-by-layer to document the ligaments' presence and their relationship to the mandibular nerve and its branches.

Results

In macerated skulls, partial or complete ossification of the pterygospinous ligament was found in 33.5% (left) and 33.8% (right). Partial or complete ossification of the pterygoalar ligament was found in 18.6% (left) and 18.1% (right). Complete ossification of the pterygospinous ligament occurred in 2.7% (left) and 1.8% (right). Complete ossification of the pterygoalar ligament occurred in 1.8% (left) and 0.7% (right). Overall, in ethanol-embalmed heads, the pterygospinous ligament was found in 54% and the pterygoalar ligament in 18% of cases.

Conclusion

The high prevalence of these ligaments and their (partial) ossification highlights the importance of awareness of their existence, location, and relevance in clinical practice.

Presentation number: P2.34

Topic: Clinical and Gross Anatomy

Changes of the Intercondylar Notch and their impact on the morphology of the cruciate ligaments in osteoarthritis.

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Introduction. The anterior cruciate ligament (ACL) is not only impinged against the roof but also against the lateral wall of the intercondylar notch (IN), thus information of changes during the progression of osteoarthritis could be relevant in predicting the risk for ACL-rupture and -degeneration. The purpose of this study is to evaluate the influence of osteoarthritis on notch morphology and on the envased ligaments.

Material and Methods. Image data was retrieved from the osteoarthritis initiative. At the level of the popliteal sulcus and on the level of the joint line, the width of the lateral and medial femoral condyle, the notch width (NW) as well as the total width of the distal femur were measured and the shape of the IN was evaluated (A-shape, Inverse-U-shape, Ω-shape). The notch width index (NWI) was calculated. The morphology of the ACL, the posterior cruciate ligament (PCL) and the meniscofemoral ligaments were assessed.

Results. The morphology of the IN is directly influenced by the development of osteoarthritis. Especially the Ω-shape is directly correlated with rupture of the ACL. Changes to the IN also significantly influence the morphology of the other ligamentous structures.

Conclusion. The intercondylar space is not a static area but undergoes continuous changes throughout ongoing osteoarthritis. At the level of the joint line a NWI<0.17 and a NW<14mm should be interpreted as notch stenosis and are definite risk factors for ACL rupture. Measurements combined with the evaluation of the shape of the IN improve risk estimation for ligament pathologies through semiquantitative assessment.

Presentation number: P2.35

Topic: Clinical and Gross Anatomy

Successful osseointegration of Zweymlüller® hip stems – Correlation of histology and imaging.

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Background: The increasing life expectancy leads to a rise in endoprosthetic operations, especially at the hip joint. Diagnosing prosthetic loosening is possible but remains challenging. The aim of the study was to histologically examine the osseointegration of Zweymüller®stems and to compare the results with imaging.

Methods: Eleven specimens with implanted Zweympller®stems were included. X-rays and dual-energy-CT scans were evaluated by calculating the Canal fill ratio (CRF). For histology transverse thin-ground sections were produced. Then the Appositional bone index (ABI) and the CFR was calculated to examine the attachment behavior of the bone to the prosthetic surface.

Results: Osseointegration was observed in all specimens differ along the prothesis, with limited ingrowth in the proximal and intermediate thin sections, while the distal areas exhibited better bone-implant-contact. The corners ($p = 0,001$) and the medial and lateral surfaces ($p = 0,04$) in relation to the total surface area showed statistically significant results in the quantitative analysis. The correlation analysis of the CFR showed a statistically significant strong correlation ($p = < 0,001$) between all three examination modalities.

Conclusions: Existing osseointegration and stable bone-implant-contact was present in all heights of the implant even after several years of service. The typical 3-point anchorage and 4-point rotational stability of Zweymüller® hip prosthesis stems could be well demonstrated by calculating the ABI. In the CT scans significant streak artefacts, especially at the corners, where noticeable, masking any bone-implant-contact that may be present. A statistically significant strong correlation of the three examination modalities has been proven.

Presentation number: P2.36

Topic: Clinical and Gross Anatomy

Neuronal Supply of Cranial Sutures

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Introduction

Cranial sutures are fibrous joints crucial for skull integrity. They are key in craniofacial biomechanics and interventional techniques like sutural distraction osteogenesis. Neuronal supply is essential for bone development, homeostasis, and remodeling and may be involved in conditions like craniosynostosis and headaches, including migraines and tension-type headaches. We assumed an additional role in registering minimal movements to maintain cranial bone homeostasis.

Material and Methods

Bregmas, Asterions, and squamosal sutures of 12 heads were collected, decalcified, histochemically, and immunohistochemically processed, digitized, and analyzed. Basic statistics focused on sensory innervation concerning gender, side, grade of suture closure, and associated vessels.

Results

We found Ruffini corpuscles, mainly associated with lymphatic vessels. No other corpuscular structures have been detected.

Longer open sutures had more intense innervation ($R=0,355$, $p<0,001$). No significant differences in gender, age, side, or internal versus external side were found. However, Asterion contains fewer corpuscles than the squamosal suture ($p=0,09$).

Discussion

Ruffini corpuscles detect shifts between movable tissues and are sensory and sympathetically innervated. They likely regulate muscle forces, such as during chewing, and are involved in pain sensation. This could potentially impact the effectiveness of Botulinum neurotoxin injection sites along cranial sutures. The association with lymphatic vessels in cranial sutures may be significant for clearing cerebrospinal fluid by registering their filing status.

Presentation number: P5.31

Topic: Embryology and Cell Biology

Investigation of Mechanically Stretched Podocytes Reveals Podocyte-Specific Alternative Spliced Isoforms of Myl6 and Shroom3

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Introduction

Alterations in pre-mRNA splicing play an important role in disease pathophysiology. However, the role of alternative splicing (AS) in hypertensive nephropathy (HN) has not been investigated. The purpose of the Sys_CARE project was to identify AS events that play a role in the development and progression of HN.

Methods

Murine podocytes were exposed to mechanical stretch under low and high stretch conditions for three days. RNA-Seq was used to analyze mRNA. Bioinformatic tools were used to evaluate splicing and transcript expression.

Results

Mechanically stretched podocytes showed over 1000 differentially expressed genes compared to unstretched podocytes. We identified 17 genes that showed an AS event in four different splicing analysis tools. We focused on Myl6, a component of the myosin protein complex, and Shroom3, an actin-binding protein crucial for podocyte function. We found two Shroom3 isoforms that showed significant changes in expression upon mechanical stretch. Isoform-2 was significantly decreased and the shorter isoform-X1 was significantly upregulated after mechanical stretch. Both were verified by qRT-PCR and *in-situ* hybridization. Furthermore, we observed an expression switch from two Myl6 isoforms after mechanical stretch. This switch is accompanied by a change in a C-terminally located amino acid sequence. Protein structure analysis indicates that this amino acid change could impair the binding of Myl6 to actin.

Discussion

Mechanical stretch of cultured podocytes is an excellent model to simulate hypertensive nephropathy. Additionally, RNA-Seq analysis identified alternative splicing events, such as Shroom 3 and Myl6, which may play a crucial role in the pathophysiology of hypertension-induced nephropathy.

Presentation number: P3.01

Topic: Imaging

"GENUINE" SEXUAL DIMORPHISM OF RADIOGRAPHIC JOINT SPACE WIDTH AND QUANTITATIVE CARTILAGE METRICS

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OBJECTIVE: For radiographic and cartilage endpoints commonly used in clinical osteoarthritis trials it is unclear whether sex-differences are genuine (independent of sex-differences in anthropometrics variables). We therefore studied whether radiographic joint space width (JSW) depends on sex in healthy participants and those with radiographic knee osteoarthritis. We further explored sex-differences after close matching for anthropometrics variables.

METHODS: Minimum medial JSW and joint space narrowing (JSN) grades were obtained from weight-bearing X-ray. Healthy (35M, 50W) and osteoarthritic knees with medial JSN0 (50M, 124W), JSN1 (98M, 160W), JSN2 (154M, 169W), and JSN3 (44M, 28W) and quantitative femorotibial cartilage measurement from MRI were studied (n=912). Next, participants with similar body height (±1cm), BMI (±2kg/m2), and age (±5y) without radiographic osteoarthritis were matched (1:1) between men and women (n=63).

RESULTS: There was a significant 18% (0.8mm; $p<0.001$) JSW difference between men and women in healthy knees. Sex-differences became less with increasing medial JSN, and these were completely absent in JSN3 knees. After matching for anthropometric factors, men still exhibited 17% greater JSW, 11% greater femorotibial cartilage thickness, and 10% greater joint surface areas ($p<0.01$).

CONCLUSION: Radiographic JSW is greater in men than women prior to the onset of knee osteoarthritis. Hence, sex-differences at early disease stages must be taken into account when using JSW diagnostically or for trial inclusion. JSW and cartilage metrics were genuinely greater in men than in women, independent of height, weight/BMI, and age. This provides clues to potentially greater structural vulnerability of the female knee.

Presentation number: P3.02

Topic: Imaging

Detection, morphological characterization, and verification of expression pattern of TMEM119-positive cells in the postnatal and adult murine cochlea

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Microglia are a subset of neural glia in the central nervous system. They play an essential role in brain homeostasis, inflammation, and aging. Transmembrane protein 119 (TMEM119) is a specific microglial marker expressed in a subset of resident brain macrophage cells. This study demonstrates that the TMEM119 protein is present in the cochlea of healthy and noise-exposed C57BL/6 mice.

Using immunofluorescent staining on the cryosections, we detected TMEM119 protein in the spiral limbus fibrocytes and the developing stria vascularis (SV) on postnatal day 3. Double immunostaining with macrophage marker Iba1 revealed that TMEM119 is not a marker of cochlear macrophages or their subsets. In the adult murine cochlea (30 days), TMEM119 protein was detected in the basal cells of the SV and the dark mesenchymal cells of the supralimbal zone. Experimental exposure to noise was not associated with a qualitative change in the types or distributions of the TMEM119-expressing cells of the adult cochlea. Western blot analysis showed similar levels of TMEM119 protein in the postnatal cochlea and brain tissues. While the results do not confirm the presence of TMEM119 as a specific microglial or macrophage marker in the cochlea, they do hint at a potential role of TMEM119 in the cochlear response to toxicity and inflammation in the stria vascularis. This could have significant implications for our understanding of cochlear health and disease.

Presentation number: P3.03

Topic: Imaging

Is there a fallopian tube sphincter that causes tubal spasm? An anatomic pilot study in transmen.

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Introduction: Tubal factor is the primary reason for subfertility. Women diagnosed with proximal tubal blockage often show open tubes in subsequent examinations. A variety of etiologies, including previous tubal spasm, displacement of intraluminal tubal debris, and elevated pressure of contrast injection, could explain the discordant results. Many studies on the interstitial part of the fallopian tube have dealt with its gross anatomy only and there has been controversy about the presence of a sphincteric mechanism. In this study high-resolution episcopic microscopy (HREM) was used to evaluate the structure of the interstitial fallopian tube in detail.

Methods: Ten transgender men undergoing gender reassignment surgery volunteered their normal uteri for HREM analysis. Three-dimensional volume models of the samples were created, and the virtual surface-rendered models were visualized and metrically analyzed using Amira™ software.

Results: In the HREM analysis of all samples, a uniquely identifiable spiral muscular ring, surrounding the intramural part of the fallopian tube, was found. It appears contiguous with the adjacent myometrium. The thickness of the muscular ring increased steadily (uterotubal junction: 347 µm up to uterotubal ostium: 1120 µm).

Discussion: The spiral muscular ring appears contiguous with the adjacent myometrium and surrounded the intramural part of the fallopian tube. This seems reasonable because they derived from the same embryonic structure. This relation may explain why increased pressure of contrast injection and uterine manipulation can affect fallopian tube function by induction of proximal tubal spasm.

Presentation number: P3.04

Topic: Imaging

Visualisation of plasticity-related gene 5 multimerization at plasma membrane using FLIM-FRET

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Introduction:

Plasticity-related gene 5 (PRG5) is a membrane protein predominantly found in neurons which is involved in cellular processes such as growth cone guidance, migration and spine formation. Overexpression of PRG5 induces filopodia in non-neuronal cell lines, contributes to the induction of spines in immature neurons, and regulates spine density and morphology in mature neurons. Understanding the formation of spines is pivotal, as spine disruptions are associated with numerous neurological disorders. Although the importance of PRG5 in neuronal function is inevitable, the precise mechanisms how it exactly induces membrane protrusions and orchestrates cellular responses remain unresolved. We hypothesise that multimerization of PRG5 is required for its functionality.

Methods:

To investigate this, we used *in vitro* biochemical assays and Fluorescence Lifetime Imaging using Förster Resonance Energy Transfer (FLIM-FRET), a powerful technique that uses fluorescence lifetimes to detect protein-protein interactions.

Results and Discussion:

Using Co-immunoprecipitation, we show that PRG5 forms homodimers. This was further confirmed in living cells, where we used FLIM-FRET to detect PRG5 multimerization at the plasma membrane, particularly at the tips of filopodial protrusions. Notably, these results are further confirmed in primary hippocampal neurons, where PRG5 multimers are predominantly localised within neuronal protrusions. The exciting current results indicate a functional role for PRG5 multimers. Deciphering the mechanisms of PRG5 in the formation of membrane protrusions is crucial to improve our understanding of neuronal development and it opens the venue to manipulate this pathway therapeutically.

Presentation number: P3.05

Topic: Imaging

Effect of polyethylen terephthalate (PET) nanoparticles on human macrophages

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Objective: Due to the wide spread plastic pollution, micro- & nanoplastics (MNPs) can be found in human blood. Plastic in vascular plaques is associated with a higher risk of myocardial infarction, stroke, or death. A better understanding of entering-, transporting and leaving processes of MNPs in human bodies can help taking preventive steps. As macrophages (MPHs) take up and react to ingested particles, a human primary cell macrophage model was established to study the MPHs' behaviour towards different kinds of plastic. As polyethylene terephthalate (PET) is used in drinking bottles, clothes or food packaging, it affects humans every day. The phagocytosis behaviour and potential cytotoxic effects of PET nanoparticles on human MPHs were therefore investigated in our novel *in vitro* model.

Methods: MPHs were obtained by differentiating monocytes isolated from human peripheral blood mononuclear cells and stimulated with PET nanoparticles. The uptake was studied with transmission electron microscopy (TEM) and live cell imaging (LCI). Activation, polarization, cell viability and ROS production of MPHs were analyzed by flowcytometry.

Results: TEM and LCI showed a dose-dependent uptake of PET in vacuoles. Polarization and ROS production were not affected. High PET nanoparticle doses caused significantly increased necrosis and apoptosis.

Conclusions: PET is taken up by MPHs. Although there are no clear effects on the polarization and ROS production, PET leads to increased necrosis and apoptosis. These findings are in line with our previous findings using polystyrene, even though the uptake of PET into vacuoles differs from the uptake of polystyrene in the cytosol.

Presentation number: P3.06

Topic: Imaging

Hierarchical phase-contrast tomography and Cinematic Rendering – a powerful combination for a high resolution visualization of the human heart

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Introduction

One of the most promising approaches in biomedical imaging is the recently developed hierarchical phase-contrast tomography (HIP-CT), which is an X-ray phase propagation technique based at the European Synchrotron Radiation Facility (ESRF-EBS) in Grenoble, France. Thus, it is possible to gain 3D scans of fixated organs with a hierarchically increasing resolution down to the cellular level at any spot within the whole organ.

Methods

Cinematic Rendering technology (CR) using a physically based volume rendering algorithm (Volumetric Monte-Carlo Path Tracing) simulates the complex interaction of photons (emission, absorption, scattering) within the scanned body of a patient/body donor. To define the lighting environment, high dynamic range light maps are used to create a natural lighting situation. To make anatomical structures visible, colors and transparencies can be varied using a transfer function. HIP-CT scanning allows a high-resolution volume rendering down to a current maximum scale of approximately 10 µm. This indicates that the boundary between macroscopic and microscopic anatomy in medical imaging may more and more dissolve to further improve digital data reconstruction for medical education.

Results

Here we show the macroscopic structures of the heart (e.g. myocardium, semilunar valves, coronary vessel course) in previously unattained quality and resolution through visualization with CR.

Discussion

HIP-CT scans in combination with a CR based visualization of 3D volumes offer a major advantage for future image analyses displaying a more precise volume representation of the inner organ tissues.

Presentation number: P3.07

Topic: Imaging

Interactive 3-Dimensional Anatomy Visualization using Cinematic Rendering of Computed Tomography in Orofacial Clefts

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Introduction

Orofacial clefts present with a complex bony and dental anatomy, often necessitating cross-sectional imaging for consecutive orthodontic treatment and surgical cleft repair. Cinematic rendering (CR) was used to create 3D images from DICOM data. The aim of this study was to tailor previously developed CR settings for midface and dental anatomy to the specific needs of 3D visualization in orofacial clefts.

Methods

CR was used for volumetric image visualization in two selected patient cases with right-sided cleft lip, alveolus and palate (RCLP) and a bilateral cleft lip, alveolus and palate (BCLP). We used previously established custom-made presets for these specific cases to visualize the dental and bony anatomy of the upper and lower jaw.

Results

This study is the first to apply CR for the visualization of the hard palate, the cleft area and adjacent dentition in patients' orofacial clefts. We employed the soft kernel for this used case to achieve a natural image impression in the context of CR. Reconstructing the soft kernel leads to blurring of anatomic landmarks in close proximity, therefore the additional usage of hard kernel reconstruction is advisable in order to display anatomic details.

Discussion

CR is suitable for visualizing orofacial clefts, adds diagnostic value and improves decision making for orthodontist and maxillofacial surgeons.

Presentation number: P3.08

Topic: Imaging

Introduction of HistoDigital (HiD®) as a new technique for volumetric tissue reconstruction

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Introduction

Today, still the most common way to gain more knowledge about the morphology of tissues in the sub-millimeter range is the microscopic investigation of histological tissue slices. A much better understanding of the specific tissue situation could be reached, when the volumetric data of histological serial sections would be analyzed. An important requirement is, however, that the final reconstruction should restore the anatomy in a way that ideally matches to the original in vivo tissue situation before it was histologically processed. HistoDigital (HiD®) is a powerful tool to deal with these requirements and to obtain best fit volumetric reconstructions out of histological serial sections.

Methods

Tissue artifacts are actual physical defects or anomalies of the tissue slices - like folds, tears and color offsets. HiD® combines a specific digital preprocessing as well as rigid and non-rigid registration of digital histological slice data applying an iterative use of the Gauss-Seidel algorithm to minimize artificial tissue deformations but to keep the natural curvature of the original tissue, simultaneously. Thus, it is possible to 3D visualize and investigate the original anatomical morphology.

Results

Here we show the 3D tissue reconstruction using HiD® on fetal tissue slices to demonstrate the high quality and the far-reaching possibilities of modern visualization techniques.

Discussion

We expect a broad range of interest arising for 3-D tissue reconstruction out of histological serial sections not only for the purpose of biomedical research, but also as a powerful tool for teaching microscopic and macroscopic anatomy and embryology.

Presentation number: P3.09

Topic: Imaging

Epithelial cell specifications in the rat common bile duct

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Introduction: Besides canonical cholangiocytes, extrahepatic bile ducts harbour rare cell types with ill-defined function. We hypothesize their involvement in the host response to parasitic worms and, as a basis for further studies, set out to characterise them in the common bile duct (CBD) of the rat, a common animal model for fascioliasis, a parasitic worm disease.

Methods: Cell isolation and single cell-RNA sequencing (scRNA-seq); RT-PCR; immunofluorescence of tissue sections and CBD whole-mounts; species: rat

Results: Unbiased scRNA-seq data analysis revealed 14 distinct cell clusters, among them 4 epithelial (*Epcam*$^{+}$) clusters, including secretory (pancreatic enzymes) and absorptive cells. Cells with the signature of endocrine cells of the closed type with glucagon as the dominating hormone built up the smallest cluster. Cells with canonical markers of chemosensory tuft cells (*Trpm5*, *Pou2f3*) were encountered at low frequency in cluster #4. RT-PCR of whole CBD validated their expression. Immunolabelling revealed DCLK1- (double-cortin like kinase-1) and TRPM5-double and single positive cells primarily in peribiliary glands; they were distinct from cells positive for fatty acid binding protein-1.

Discussion: Peribiliary glands of the rat CBD contain a heterogeneous lining with cells sharing key features with endocrine and exocrine secretory pancreatic cells, and cells resembling absorptive epithelial cells of the gallbladder (which the rat has not) in other species. While the previously described protein repertoire of “brush cells” in the rat CBD is more characteristic for ionocytes described in other organs, we here identified an independent rare cell population with characteristic of chemosensory tuft cells.

Presentation number: P3.10

Topic: Imaging

Ultrasound Scanning Technique of Subclavian Vessels from Anatomical Point of View

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Knowledge of ultrasound scanning technique of subclavian vessels is important for diagnostic process of vascular pathology as well as for visualizing vessels for vascular access. Central venous catheters can help with diagnosis and treatment of the critically ill adult and paediatric patients. Whilst this is beneficial overall, inserting the catheter risks arterial puncture and other complications. Ultrasound imaging allows to perform this procedure without a significant risk of endangering the patient.

When visualising both vessels, a linear probe is positioned just below the clavicle in the direction of the transverse plane. In the ultrasound image, both vessels can be distinguished. The subclavian a. runs deeper, pulsates, and is only slightly compressible. The subclavian v. lies superficially and is more (easily) compressible. Vein pulsation reflects the adjacent artery's pulsation. By positioning the linear probe just below the clavicle in the sagittal plane, it is possible to visualise the vessels on a cross section. The upper edge of the probe touches or is placed just below the clavicle. In the ultrasound image the subclavian v. is always placed more caudally and subclavian a. more cranially, to a greater extent disappearing under the clavicle.

Detailed knowledge of the human anatomy is an integral part of every surgical procedure. Therefore, ultrasound knowledge of the vascular anatomy in the region of the neck and upper thorax is fundamental and a prerequisite to having a favourable quality of patient care.

This study was supported by the grants KEGA 018UPJŠ-4/2021 and KEGA 006UPJŠ-4/2024

Presentation number: P4.01

Topic: Cardiovascular

PKC activation enhances cardiomyocyte cohesion in induced pluripotent stem cell-derived cardiomyocytes of an arrhythmogenic cardiomyopathy patient

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Background:

Arrhythmogenic cardiomyopathy (AC) is an inherited heart disease known as the disease of desmosome, as more than 50% of these patients carry mutations in desmosomal protein-coding genes. Protein kinase C (PKC) alpha, a member of serine/threonine family kinases, was found to be downregulated in the myocardium of AC patients and murine AC models. We recently established that PKC activation led to strengthened cardiomyocyte cohesion in the murine AC model. Further unraveling the molecular mechanisms would enhance PKC as a new therapeutic target to treat AC.

Methods

Human induced pluripotent stem cell-derived cardiomyocytes from an AC patient (AC iPSC-CMs) carrying heterozygous desmoplakin (*DSP*) gene mutation (c.2854G>T, pGlu952Ter) were established. Dissociation assay and Western blotting analyses were performed in AC iPSC-CM and murine atrial cell line, HL-1.

Results:

Activation of PKC in AC iPSC-CM and HL-1 cells for 1 and 24 hours strengthened cardiomyocyte cohesion and increased phosphorylation of desmoplakin (DP) serine(S)165/166 and ERK1/2 after 1 hour, which returned to basal levels after 24 hours. In AC iPSC-CM, PKC activation for 1 hour reduced Cx43 expression, whereas, after 24 hours, Cx43 expression was increased. Since we previously observed reduced conduction velocity in PKC-activated murine cardiomyocytes, further studies are underway in AC iPSC-CM. Finally, ERK1/2 inhibition led to the abrogation of PKC activation-enhanced cardiomyocyte cohesion in HL-1 cells.

Conclusion:

Our data show that PKC activation in AC iPSC-CM and HL-1 cells enhances cardiomyocyte cohesion paralleled by phosphorylation of DP-S165/166 and ERK1/2, and early activation of ERK1/2 is necessary for PKC-enhanced cardiomyocyte cohesion.

Presentation number: P4.02

Topic: Cardiovascular

Allometric scaling of cardiomyocyte number, mitochondria and myofibril volume in mammals of different size

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Introduction:

Compared to body weight (bw), small mammals have higher heart (HR) and metabolic rate (MR) than large mammals, whereas heart weight and stroke volume scale linearly with bw. Mitochondria (Mit) fill nearly 50% of a cardiomyocyte (Cm) of shrews and volume density of mitochondria (V_v(Mit/Cm)) declines with bw. How do small mammals provide enough myofibrils (Mf) to keep up their high HR, if that much space is occupied by mitochondria? We hypothesized that more cardiomyocytes compensate for less myofibrils per cardiomyocyte.

Methods:

Literature was reviewed for stereologic data of healthy, adult mammals of different species. Number of cardiomyocytes, V_v(Mit/Cm) and V_v(Mf/Cm) were analysed. Major axis regression analysis was performed to examine allometric relationships between these quantities and bw, described by equation $Y = a(\text{bw})^b$, where Y denotes quantity of interest and b its scaling exponent.

Results:

25 studies with 20 species (bw 0.0022-920kg) were included. Number of cardiomyocytes in the left ventricle increases linearly with bw ($b=1.04$, $p=0.29$), whereas V_v(Mit/Cm) decrease ($b=-0.05$, $p<0.0001$) and V_v(Mf/Cm) increase ($b=0.024$, $p<0.0001$) allometrically.

Discussion:

Correlation between HR, oxygen consumption and V_v(Mit/Cm) is known as smaller mammals with higher MR per bw have higher HR. They need more mitochondria per bw, which leads to higher oxygen consumption per bw. A slight blood pressure increase in large mammals demands higher forces needing more myofibrils per bw. As we consider mitochondria the fuel and myofibrils the engine of pumping heart, small mammals seem to need less myofibrils per bw compared to cardiomyocytes of large mammals.

Presentation number: P4.03

Topic: Cardiovascular

Deciphering prostate cancer bone metastasis formation by characterizing the interaction of prostate cancer sublines with the bone microenvironment

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Introduction: Prostate cancer (PCa)-related death is largely linked to bone metastasis (BM). We have generated PCa sublines from primary tumours (PT), spontaneous lung metastases (LM) and BM using spontaneous metastasis PCa xenograft models. To better understand the bone metastatic capacity of the BM subline, we compared the *in vitro* phenotype of our PCa sublines at the functional level.

Methods: Tumour cell proliferation, migration and 3D spheroid formation were assessed using XTT, transwell migration assays and live cell imaging. Experiments were performed in control- (CTRL) and osteoblast-conditioned media (ObCM) and partially also under normoxic and hypoxic conditions. Dynamic adhesion assays were used to investigate the interaction of the sublines with human umbilical vein endothelial cells (HUVECs).

Results: Under normoxic conditions no differences in tumour cell proliferation were observed while the LM and BM subline migrated faster in ObCM compared to CTRL (LM: $p=0.0087$ BM: $p=0.0071$). Preliminary data suggest improved proliferation of the metastatic sublines in ObCM when cultured under hypoxic conditions (LM: $p=0.0247$, BM: $p=0.0006$). In hypoxia, all PCa sublines formed smaller and more compact 3D sphero in ObCM when compared to CTRL. The BM subline showed a ~1.7-fold higher number of E-selectin-dependent, dynamic adhesions on HUVECs than the PT subline.

Discussion: Our preliminary data indicate that mimicking a more bone-specific environment, i.e. hypoxia and osteoblast-derived soluble factors, is necessary to recapitulate a more bone-metastasis-prone phenotype *in vitro*. Additionally, an altered adhesive behaviour of the BM subline might account for its metastatic capacity, which should be confirmed by future experiments.

Presentation number: P5.01

Topic: Embryology and Cell Biology

Inhibition of EGFR prevents PV-IgG induced acantholysis and averts ultrastructural alterations in human skin.

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Inhibition of EGFR prevents PV-IgG induced acantholysis and averts ultrastructural alterations in human skin.

Introduction Pemphigus is a severe blistering disease caused by autoantibodies that primarily engage the desmosomal cadherins desmoglein (DSG)1 and DSG3 resulting in impaired desmosome function. Currently, various treatment paradigms are in place, and especially for the acute phase, additional treatment options allowing to reduce corticosteroids would fulfill an unmet medical need.

Methods Cell culture, *ex vivo* human skin model, STED microscopy, FRAP, Atomic force microscopy, GLISA, STRING analysis, PamGene

Results Epidermal growth factor receptor (EGFR) inhibition by erlotinib ameliorates pemphigus vulgaris immunoglobulin G (PV-IgG) -induced acantholysis in intact human epidermis. PV-IgG caused phosphorylation of EGFR (Y845) and SRC in human epidermis. In line with this, a phosphotyrosine kinome analysis revealed a robust response associated with EGFR and SRC family kinase signaling in response to PV-IgG but not pemphigus foliaceus autoantibodies. Erlotinib inhibited PV-IgG-induced epidermal blistering and EGFR phosphorylation, loss of desmosomes as well as ultrastructural alterations of desmosome size, plaque symmetry, keratin filament insertion and restored the desmosome midline considered as hallmark of mature desmosomes. Erlotinib enhanced both single molecule DSG3 binding frequency and strength and delayed DSG3 fluorescence recovery.

Discussion EGFR inhibition rescued desmosome and keratin dysregulation. This enhanced cell adhesion and increased DSG3 availability as well as cytoskeletal anchorage. Therefore, our data indicate that EGFR is a promising target for pemphigus therapy due to its link to several signaling pathways known to be involved in pemphigus pathogenesis.

Key words: EGFR signaling; Pemphigus; desmogleins; erlotinib

Presentation number: P5.02

Topic: Embryology and Cell Biology

The Interplay of Proliferation and Migration in Glioblastoma

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Introduction: Glioblastoma is the most aggressive primary brain tumor, characterized by high proliferation rates and infiltrative migration. Recently, evidence was gathered that cell density and mitosis events influence cell migration. During mitotic rounding and subsequent post-division spreading, cells exert forces on their surroundings, influencing shape and movement of neighboring cells. Yet, this effect has almost exclusively been studied in healthy epithelial cell populations.

Method: Here, we studied the effect of approximately 134,000 cell division events on the local velocity of four different glioblastoma lines under confinement, using live cell imaging, particle image velocimetry and AI systems. Cell density dependent mechanical properties of cell sheets were measured via AFM.

Results and Discussion: Pre-mitotic contraction and post-mitotic expansion increased the migration of cells next to the dividing cell and their subsequent neighbors. No such effect was observed during cytokinesis. On average the velocities of 20-30% of all cells were affected by proliferation events. Furthermore, the region affected by proliferation events decreased with increasing cell density, but the average number of affected cells increases. Interestingly, the time at which the maximal effect of contraction or expansion on migration is reached negatively correlated with cell density, implying that cells react quicker to fluctuations in their vicinity for high cell densities, suggesting density dependent biomechanical properties. Nonetheless, no changes in bulk-biomechanical properties were found when comparing different cell densities. In summary, we demonstrated that proliferation and migration are coupled in GBM, in a cell density dependent manner, which might be important in vivo too.

Presentation number: P5.04

Topic: Embryology and Cell Biology

Diversity of mucins in labial glands of infants

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Introduction

Mucins as components of the saliva exhibit multiple functions like protection, homeostasis, immune defense, cell signaling. MUC1, MUC3, and MUC4 comprise transmembrane proteins, while the secretory pathway is characteristic for MUC2, MUC5AC, MUC5B, and MUC7. Labial salivary glands in the mucosa of the upper and lower lip belong to the minor salivary glands and are predominantly of mucous character. The aim of the study was to examine the occurrence and localization of specific mucins in infantile labial glands.

Methods

For differentiation of serous and mucous endpieces, sections were treated with Periodic acid-Schiff (PAS) reagent for neutral carbohydrates and Alcian-blue (pH 2.5) for polyanions. The localization and distribution of mucins were studied by immunohistochemical methods.

Results

MUC1 and MUC4 were detected in serous and ductal glandular cells, partially intensified at the apical plasma membrane. MUC3 was found in ductal glandular cells and myoepithelial cells. MUC5B exhibited a mosaic expression pattern in mucous glandular endpieces. MUC2 and MUC7 were abundant in serous acini. Glandular structures were negative for MUC5AC.

Discussion

The occurrence and localization of different mucins vary within the three major salivary glands and between major and minor salivary glands due to the anatomical location of the glands, physiological aspects like unstimulated and stimulated state or methodological approaches.

Conclusion

The distribution of a broad spectrum of mucins in infantile labial glands indicates their importance early in human development to sustain oral health.

Presentation number: P5.05

Topic: Embryology and Cell Biology

The importance of FOXO1 and microRNA-21 in the angiogenesis of distal cholangiocellular carcinoma and pancreatic cancer

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) and distal cholangiocellular carcinoma (dCCA) share aggressiveness, short survival time and resistance to chemotherapy. The functions of FOXO1 and microRNA-21 are respectively tumor suppressor and oncogene in PDAC. Moreover, FOXO1 has an important role in vascular homeostasis because it is a fundamental modulator of the formation and maturation of blood vessels.

Methods:

The cell line with the lowest FOXO1 expression will be selected for transfection with the goal of overexpressing FOXO1. The clone will be then inoculated onto CAM. Then, the IKOSA platform will be used to study the angiogenesis in the CAM thanks to an algorithm that detects blood vessels. Part of the explanted cell pellets will be used to analyse the expression of angiogenic factors and for immunohistochemistry for the staining of FOXO1 and phospho FOXO1^{Ser256} (phosphorylated FOXO1).

Results:

As part of preliminary work, the protein expression of FOXO1 was detected using Western blotting in different PDAC and CCA cell lines. The expression of FOXO1 was significantly higher in BxPC-3 than in MiaPaCa2. Therefore, MiaPaCa2 is a good candidate for overexpression of the gene, while BxPC-3 is a good candidate for knockdown experiments. In addition, extrahepatic cholangiocellular carcinoma tissue was cultured on the CAM model for the first time and the tissue was monitored macroscopically by taking daily photos.

Discussion:

The future aims are to investigate the role of FOXO1 and microRNA-21 in angiogenesis of PDAC and dCCA and to cultivate dCCA tumor tissue on the CAM for testing chemotherapeutic drugs.

Presentation number: P5.06

Topic: Embryology and Cell Biology

3D cultivation of the recently established human lacrimal gland cell line serves as a simplified lacrimal gland model

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The utilisation of three-dimensional (3D) models in research is becoming increasingly prevalent, as they facilitate the replication of in vivo conditions within cells. This project creates a simplified 3D model of the lacrimal gland using the recently established human lacrimal gland cell line.

Two distinct 3D cell culture approaches were examined, including culturing spheroids in ultra-low attachment (ULA) plates and within extracellular matrix (ECM). Spheroids cultured in ULA plates were observed for four weeks. After seven days some spheroids were harvested for staining (utilizing DAPI for immunofluorescence, Azan, and hematoxylin-eosin (HE)) and transmission electron microscopy (TEM). Spheroids were seeded in ECM and cultured with and without growth factors (e.g., EGF, FGF10) and observed for two days. RT-PCR was conducted to validate the continuous gene expression of ocular epithelial cells observed in 2D cell culture.

Spheroids cultivated on ULA plates exhibited compaction and reduced translucency over time. Immunofluorescence demonstrated DAPI staining throughout the spheroids, while HE staining indicated higher density in the outer layers, signifying epithelial barrier formation. Budding was observed in spheroids grown in ECM with and without growth factors after two days, suggesting a potential for organoid cultivation. RT-PCR confirmed continuous expression of ocular epithelial genes. TEM revealed the presence of secretory vesicles in the inner cells.

This study proposes straightforward methods for generating a 3D in vitro model using the newly established human lacrimal gland cell line. These spheroids serve as valuable tools for comprehending processes in the human lacrimal gland, facilitating drug testing, and simulating pathological conditions.

Presentation number: P5.07

Topic: Embryology and Cell Biology

Cyclic stretching enhances lapine Achilles tenocytes and human mesenchymal stem cell proliferation and cytoskeleton organization structure in 2D culture

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Objective

Mobility can be severely impaired after tendon injuries. The self-healing and regenerative capacities of tendons are generally low. Therefore, the effect of different protocols of cyclic stretching on both tenocytes and human mesenchymal stem cells (hMSCs) after 2D stimulation will be investigated in detail.

Methods

Silicone chambers were seeded with Lapine Achilles Tenocytes (LAT) on the one hand and hMSCs on the other. After 24 hours of adherence, the stimulated chambers were exposed to either moderate or strenuous exercise, while the control chambers were not exposed to stimulation. At the end of each training session, viability was qualitatively assessed with a viability assay and DNA and sulfated glycosaminoglycan (sGAG) contents were quantitatively measured. Immunocytochemical staining of actin, paxillin, collagen type I and alpha smooth muscle actin were performed.

Results

The viability showed that both LAT and hMSCs predominantly survived not only the moderate but also the strenuous training. The stronger training led to enhanced cell orientation against the stretch direction. Cyclic stretching reorganized the cytoskeleton. Both cell types express paxillin, collagen type I and alpha smooth muscle actin. The expression can be upregulated by stretching, especially by the strenuous exercise. Quantitative analyses confirmed that moderate stretching has a greater influence on the sGAG synthesis and proliferation of hMSCs than on LAT.

Conclusions

Differences in cell viability have already been observed, not only between LAT and hMSCs, but also between depending on the training programs. The effects of strenuous exercise on cell behavior were greater than those of moderate stimulation.

Presentation number: P5.08

Topic: Embryology and Cell Biology

PKC subtypes play a major role in signaling-mediated loss of adhesion in pemphigus

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Aim:

Autoantibodies in the skin diseases pemphigus vulgaris (PV-IgG) and pemphigus foliaceus (PF-IgG) primarily target the desmosomal cadherins, desmoglein (Dsg) 1 and Dsg3 and cause loss of keratinocyte adhesion and epidermal blistering via signaling events. In previous studies, protein kinase C (PKC) inhibition was protective in murine but not human epidermis. This study investigates the roles of PKC subtypes for pemphigus pathogenesis.

Methods:

ex vivo human skin model, dispase-based dissociation assay, confocal and STED microscopy, membrane fractionation, Western blot

Results:

We investigated the role of PKC subtypes for PV-IgG-induced blistering in human epidermis. The inhibitor of atypical PKCs (aPKC) CRT0066854 (CRT) completely abolished acantholysis whereas the conventional PKC (cPKC) inhibitior Gö6976 (Gö) did not. In cultured keratinocytes, both CRT and Gö effectively inhibited loss of cell adhesion, keratin filament retraction and Dsg3 depletion in response to PV-IgG as well the pathogenic anti-Dsg3-IgGs AK23 and 2G4. Further inhibitors of aPKC, cPKC or all PKCs confirmed their effectiveness in inhibiting PV-IgG-induced loss of adhesion *in vitro*. In contrast, reduced cell adhesion, keratin filament retraction and translocation of PKCα to the cell membrane, induced by the PKC activator phorbol-12-myristate-13-acetate (PMA) and PF-IgG, were blocked by inhibition of cPKC but not of aPKC. Mechanistically, both cPKC and aPKC were required for PV-IgG-induced translocation of PKCα towards peripheral keratin filaments and desmosomal plaque disassembly as revealed by STED microscopy.

Conclusion:

These findings demonstrate that aPKC is critical for blistering in human epidermis in PV dependent on the autoantibody profile.

Presentation number: P5.09

Topic: Embryology and Cell Biology

Role of Complement 1q tumour necrosis factor-related proteins in the Lipid Metabolism of Meibomian Glands

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Purpose

The human Meibomian glands are essential for producing the tear film that protects and nourishes the ocular surface. Their lipid-rich secretion prevents the evaporation of the aqueous layer of the tear film. Dysfunction of these glands is the most common cause of dry eye disease, affecting 15-17% of the population in Germany, leading to impaired vision, pain, and inflammation of the ocular surface. CTRPs are secretory proteins known to influence lipid metabolism. In the present study, we investigated the impact of CTRP1, CTRP6, and CTRP8 on the lipogenesis of the Meibomian gland.

Methods

Expression of CTRP1, CTRP6, and CTRP8 was examined in immortalized human Meibomian gland epithelial cells (HMGECs) and human Meibomian gland tissue. Impact of CTRPs on lipid production and the expression of key lipogenesis markers were studied in HMGECs and organotypic *ex vivo* slice cultures of murine Meibomian glands.

Results

RT-PCR analysis detected the gene expression of CTRP1 and CTRP6 in HMGECs and CTRP1 in human Meibomian gland tissue. Stimulation with CTRP1 and CTRP6 resulted in increased lipid levels in cultured HMGECs. Similarly, CTRP1 stimulation increased lipid levels in organotypic *ex vivo* slice cultures of murine Meibomian glands. Additionally, the expression of lipogenesis markers PPARγ, SCD, and FABP4 in HMGECs was modulated by stimulation with analysed CTRPs.

Conclusion

These findings reveal the influence of the investigated CTRPs on lipogenesis in the Meibomian gland. This provides a basis for further studies on the physiology of tear film formation and opens new intervention strategies to treat Meibomian gland dysfunction.

Presentation number: P5.10

Topic: Embryology and Cell Biology

Dsg2 truncation in inflammatory bowel disease causes lethal barrier breakdown and skewed Interleukin 17 response in mice

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Objective: Inflammatory bowel diseases (IBD) such as Crohn's disease (CD) have a complex aetiology with alterations of both the intestinal epithelial barrier and the IL23/IL17 immune response. The desmosmal cadherin Desmoglein 2 (DSG2) is known to regulate intestinal epithelial barrier integrity. Here we investigated the role of a mutation in the desmoglein 2 gene (*DSG2*), which was identified in an IBD patient.

Methods: Genetic analysis of an IBD patient revealed a novel likely pathogenic *DSG2* mutation leading to a truncated protein lacking part of the intracellular domain. We generated an enterocyte-specific mouse model, recapitulating the human mutation to study how the cytoplasmic truncation of *Dsg2* affects intestinal barrier properties systemically.

Results: Here, we describe a first CD patient with a nonsense mutation in the *DSG2* gene. We analysed the intestinal genetic profile in the enterocyte-specific Dsg2 truncation mouse model and compared it to IBD patients. The mice suffered from a lethal intestinal barrier defect and presented a skewed IL17 response similar to CD patients.

Conclusion: We identified the desmosomal cadherin Dsg2 as a regulator of the skewed IL17 response. The data indicate that desmosomes regulate inflammation similar to psoriasis which explains why the same novel immune therapies are effective for both diseases.

Presentation number: P5.11

Topic: Embryology and Cell Biology

Microglia in the Spotlight: Deciphering Phenotypes in a Fucosidosis Mouse Model

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Introduction

Fucosidosis, a human lysosomal storage disorder (LSD), results from a deficiency in lysosomal hydrolase α-L-fucosidase, leading to impaired degradation of fucosylated glycoproteins and glycolipids within lysosomes. Patients exhibit a wide range of symptoms such as progressing motor and cognitive impairments. Using a mouse model lacking the *Fuca1* (lysosomal α-L-fucosidase), which exhibits a severe neuropathological phenotype at six months of age, we conducted an in-depth analysis of microglial reactivity during the neurodegenerative processes in this disease.

Methods

Neurodegeneration as well as microglia activation were characterized using immunohistochemical stainings and Western blots in 1-month-old animals as well as in 6-7-month-old phenotypic *Fuca1*-deficient mice. Additionally, transcriptomic profiling was conducted to quantify microglial gene expression. For this purpose, a microglia-specific custom panel comprising 178 genes was used to analyze *ex vivo* isolated microglia from *Fuca1*-deficient mice.

Results

Microglia in phenotypic *Fuca1* deficient mice displayed loss of homeostatic marker expression and a significant increase in microglial activation markers (*Cd68, ApoE, MHCII*) along with an amoeboid morphology and increased numbers of Iba1$^+$ cells. Enhanced levels of the lysosomal marker Lamp1 in microglia indicates lysosomal dysregulation. Interestingly, transcriptome profiling of young microglia revealed reactive microglia state prior to the onset of the neurodegenerative process.

Discussion

Our study offers novel insights into the neuropathological aspects of human LSD fucosidosis. We observe pronounced microglial activation in the phenotypic model, even preceding neurodegeneration. This suggests that lysosomal transport dysfunction significantly influences microglial biology resulting in microglial reactivity. Together, our findings contribute to the understanding of microglial functions in LSD.

Presentation number: P5.12

Topic: Embryology and Cell Biology

Regulation of HspB5/alphaB-crystallin by microRNAs

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Introduction

The small heat shock protein HspB5/alphaB-crystallin is a chaperone known to be cyto- and especially neuroprotective. On the other hand, HspB5 can also promote tumorigenesis in several cancers. We previously investigated whether HspB5 can be post-transcriptionally regulated and identified four microRNAs which can either upregulate the amount of endogenous rat HspB5 (miR-140-5p, miR-330-5p) or downregulate it (miR-101a-3p, miR-376b-3p). As all four microRNAs have distinct binding sites on the HspB5 mRNA the question arose whether a combination of the microRNAs affecting HspB5 amount in the same direction would have an additive effect.

Methods

C6 rat glioma cells were transfected with microRNA mimics or respective controls alone or in combination. One day after transfection the cells were stressed by addition of 100 µM sodium arsenite for 30 minutes to induce HspB5 expression. 48h after transfection cells were lysed and HspB5 protein amount was detected by western blot.

Results

While the transfection of miR-140-5p and miR-330-5p alone increased the HspB5 protein amount in C6 cells after sodium arsenite stress as expected, the combination of both did not further enhance it significantly. In contrast, co-transfection of miR-101a-3p and miR-376b-3p clearly led to an additive effect, namely a stronger reduction of the HspB5 amount compared to the respective single transfections.

Discussion

Upregulation of HspB5 was shown to be beneficial in several neurodegenerative diseases while downregulation of HspB5 is thought to be a promising therapeutic option in many cancers. The targeted regulation of HspB5 protein amount with microRNA mimics could therefore open new therapeutic avenues.

Presentation number: P5.13

Topic: Embryology and Cell Biology

The IGF1 signaling in the aging Enteric Nervous System

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Introduction:

Insulin growth factor 1 (IGF1) serum levels change throughout life peaking in puberty. The dropping level of IGF1 in elderly is currently thought to be a risk factor for age associated functional gastrointestinal disorders, including motility dysfunctions. Thus, we hypothesized that IGF1 and its the corresponding receptor IGF1R regulates the cellular homeostasis of the enteric nervous system (ENS) throughout postnatal life.

Methods:

Therefore, we mapped the *in vivo* expression of IGF1 and IGF1R in the human ENS by immunhistochemistry from 3 weeks to 82 years of age. Moreover, we analyzed the cell biological function of IGF1/IGFR1 signaling on isolated murine ENS progenitor cells by proliferation assays and immuncytochemical analyis of established differentiation markers.

Results:

We found, that IGF1 and IGF1R were expressed in enteric neurons, but less in enteric glia cells of submucosal and myenteric ganglia of human small and large intestine. In addition, IGF1/IGF1R is less expressed in the gut samples of the elderly patients. Further, if applied *in vitro*, IGF1 led to changes in the proliferative capacity, and neurite outgrowth of ENS progenitor cells in comparison to the unstimulated control group.

Discussion:

Our results indicate, that IGF1-mediated signaling plays an important role in enteric neuronal differentiation *in vitro*. However, the observed decline in IGF1 and IGF1R expression in enteric neurons *in vivo* raises the question, if age-associated changes in IGF1-mediated signaling are associated with the increasing risk for gastrointestinal disorders in the elderly, that needs to be elucidated in the future.

Presentation number: P5.14

Topic: Embryology and Cell Biology

Development of 3D organoids from human meibomian gland cells to investigate the effects of endocannabinoids on exocrine secretion

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Introduction

The meibomian glands in the eyelids produce meibum, a lipid-rich secretion that forms the outer layer of the tear film, preventing excessive evaporation. Dysfunction of these glands is the primary cause of dry eye disease (DED), an increasing public health issue. Recently, there has been significant interest in 3D cell culture systems as they better reflect the tissue microenvironment and biological processes occurring *in vivo*. Therefore, this study aims to create 3D organoids derived from primary human meibomian gland epithelial cells and investigate the effects of endocannabinoids on exocrine secretion.

Methods

Primary human meibomian gland cells were obtained from thoroughly dissected acini explants of body donos. To ensure cell viability, a ROCK inhibitor and collagen I were utilized. Characterization involved confirming meibomian gland-specific markers and excluding fibroblastic markers through qPCR and immunocytochemistry. Organoids derived from the primary human meibomian gland cells were formed with Matrigel, subjected to the endocannabinoids anandamide and 2-arachidonoylglycerol, then analysed for lipid content and acini size.

Results

Primary human meibomian gland cells were successfully isolated and cultured up to at least passage 5. When embedded in Matrigel, they formed acinar structures within 2 weeks. Expression of cannabinoid receptors, which are activated by endocannabinoids, was confirmed in human meibomian glands.

Discussion

We successfully established organoids derived from human meibomian gland epithelial cells. This cell culture model has the potential to accelerate the search for new treatment options for DED, as it better reflects the *in vivo* situation of meibomian compared to the standardly used cell lines.

Presentation number: P5.15

Topic: Embryology and Cell Biology

PRGF induces the antimicrobial peptides HBD-2 and HBD-3 in an NRF2-dependent manner in primary human keratinocytes

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Methods: An in-vitro keratinocyte model was used to investigate Platelet-Released Growth Factor's (PRGF's) stimulatory activities. Treated cells were assayed in cell viability/proliferation experiments alongside target protein expression (NQO1) using Western blot. Moreover, luciferase-based reporter gene assays for NRF2-ARE activity and NFκB-Luc response were applied to visualize NRF2 involvement under NRF2-inhibited conditions. To visualize the PRGF effect more clinically, a human 3D full-thickness laser skin model was used. ELISA and immunohistochemistry were used to analyze Ki-67, HBD-2, and HBD-3 response upon PRGF stimulation.

Results: PRGF activates NRF2 directly. These findings were validated by Western blot and ARE-reporter gene assays that show significant ARE and NFκB response and are at least partly dependent on NRF2 availability. TNF-α pre-stressed cells showed total rescue by PRGF treatment upon NRF2 availability. In addition, SFN and PRGF influence HBD-2 and HBD-3 secretion in an NRF2-dependent manner.

Conclusion: PRGF treatment activates the NRF2/ARE pathway and alleviates TNF-α/NFκB-associated inflammatory responses to a total rescue, proposing clinical relevance of PRGF as a treatment for locally inflamed and AMP-depleted skin conditions such as atopic dermatitis.

Presentation number: P5.16

Topic: Embryology and Cell Biology

The impact of signalling pathways on the desmosome ultrastructure in pemphigus

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Introduction:

The autoantibody-driven disease pemphigus vulgaris (PV) impairs the adhesive function of desmosomes in the epidermis and mucosa. In desmosomes, desmogleins (DSGs) link adjacent cells. They are clustered by the plaque proteins and linked to the keratin cytoskeleton by linker proteins, including desmoplakin (DP). The aim of this study was to identify the impact of multiple signalling pathways involved in PV pathogenesis on desmosome ultrastructure.

Methods:

STED microscopy, dispase dissociation assay

Results:

Pemphigus autoantibodies (PV-IgG) reduced desmosome number, decreased desmosome size, and increased desmosomal plaque distance and thickness. Decreased desmosome number, increased plaque distance and thickness correlate features found for newly assembled immature desmosomes as observed after Ca2+ depletion and repletion. This was paralleled by plaque asymmetry, keratin filament retraction and fragmentation of Dsg1 and Dsg3 immunostaining. Inhibition of each individual signalling pathway investigated prevented the loss of adhesion and ameliorated keratin retraction. In addition, inhibition of p38MAPK or PLC completely rescued all parameters and increased desmosome number under basal conditions. In contrast. inhibition of MEK1/2 was only partially protective for desmosome size and plaque thickness whereas inhibition of SRC or increased cAMP decreased desmosome size but strongly increased the desmosome number in presence of PV-IgG.

Discussion:

Alterations of the desmosome plaque ultrastructure are closely related to loss of adhesion and regulated differently by various signalling pathways involved in pemphigus pathogenesis. This insight may allow treatment options targeting specific steps of desmosome turn-over in the future.

Presentation number: P5.17

Topic: Embryology and Cell Biology

Deletion of the neonatal Fc-Receptor and its consequences on the renal endothelium

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Diabetic microangiopathy/ Diabetic nephropathy (DN) is a long term consequence of diabetes mellitus (DM) and is the most common reason for chronic kidney disease (CKD) and reduced renal function. It was shown that elevated glucose levels lead to a reduction of the neonatal Fc-Receptor (FcRn). The correlation between FcRn and the progression of CKD remains unknown.

3- month and 15- month old FcRn knockout mice (FcRn -/-) were compared with wildtyp mice and analyzed regarding to morphological and functional alterations on the vascular endothelium of the kidney. The endothelium was examined through immunohistological staining and western blots of Ki67, ATG5 and collagen 3a1, respectively. The thickening of connective tissue between the basal membrane of the endothelium and the proximal tubule was also determined by electron microscopy. Protein samples of diabetes type 2 mice were used for western blotting.

In endothelial cells, the expression of ATG5 showed no difference between FcRn-/- and wildtype mice neither in 3- nor in 15-month old mice. The number of Ki67-positive endothelial cells were significantly reduced in 3-month old FcRn -/- mice. Moreover, the amount of connective tissue and collagen 3a1 was elevated in 15-month old FcRn -/- mice, whereas in mice suffering from type 2 diabetes no difference was observed.

In summary, the loss of FcRn leads to an accumulation of connective tissue and reduces the proliferation rate of endothelial cells. This shows a possible impact of FcRn on declining renal function and therefore on progression towards CKD.

Presentation number: P5.18

Topic: Embryology and Cell Biology

The role of Nrf2/Keap1 in chondral ossification and bone growth.

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Introduction: The transcription factor Nrf2 plays an important role in bone homeostasis. Deficiency of Nrf2 results in impaired bone and cartilage quality, increasing the risk of osteoarthritis and osteoprosis. The novel mechanisms of Nrf2 on bone are not yet fully elucidated.

The present study hypothesizes that a permanent activation of Nrf2 in cartilage tissue may improve bone growth during chondral ossification.

Methods: We used the Postnatal and young Col2-Cre::Keap1loxP/loxP animals to test this hypothesis. The analysis involved using alcian blue/Alizarin red for skeletal staining, µCT, histological, and immunohistochemical analysis to examine bone growth.

Results: It was demonstrated that the bone length in Keap1 cre+ animals ((overactivation of Nrf2) was shorter than in cre- animals. Immunohistochemical analysis against I*ndian hedgehog* (*Ihh*) and parathyroid hormone-related peptide (PHrP) revealed distinct expression patterns of these factors in the hypertrophic zone and periarticular cartilage, respectively.

Discussion: Our findings suggest that Nrf2/Keap1 may influence chondral ossification by modulating Hedgehog Signaling. Mderate Nrf2 activation is necessary for bone hemostasis and growth.

Presentation number: P5.19

Topic: Embryology and Cell Biology

Molecular markers for M cells in porcine Peyer's patches

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Introduction:

M cells of Peyer's patches (PP) provide a basis for immune surveillance in capturing luminal antigens followed by transcytosis to the underlaying lymphatic tissue. The follicle-associated epithelium (FAE) has no goblet cells, except at the base of the follicle-associated intestinal crypts (FAIC), where M cells are also generated.

Methods:

PP containing tissue samples of the jejunum and ileum and from the colon were taken from 3 piglets aged 42 days and 56 days. Cryostat sections (5 µm) were used for immunofluorescence dual stain. Glycoprotein (GP2) and cytokeratin 18 (CK18, specific in porcine M cells) antibodies were used markers, as well as a single with annexin A5 (direct stain).

Results:

The number of M-cells is very limited. Porcine M-cells express GP2 and are CK18 positive. GP2 is present apical on the cell, whereas CK18 is located within the cells as intracellular structural protein. Colonic and FAIC associated goblet cells are also CK18 positive. The base of the follicle-associated intestinal crypts above the basal membrane expresses intense apical and lateral annexin A5 positivity.

Discussion:

GP2 serves as an uptake receptor for commensal and pathogenic bacteria, which explains the specific expression on M-cells. The requirement for enhanced structural cellular integrity rationalizes the expression of CK18 by both M-cells and goblet cells either for stabilization of transcytotic vesicles or mucin vesicles, respectively. Differentiation of M-cells requires annexin A5, a self-assembling Ca^{2+}- and phospholipid-binding protein, that endorses reseal of damaged membranes after transcytosis.

Presentation number: P5.20

Topic: Embryology and Cell Biology

Sprouty2 regulates degradation and signaling of fibroblast growth factor receptor 1 in glioblastoma cells

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Endocytic trafficking of receptor tyrosine kinases (RTKs) regulates spatio-temporal intracellular signaling, and aberrant RTK signaling is a common phenomenon observed in glioblastoma (GBM). The Sprouty (SPRY) proteins are evolutionary conserved modulators of RTK signaling. SPRY2 inhibits fibroblast growth factor (FGF) signaling, whereas it enhances epidermal growth factor (EGF) signaling through inhibition of EGF receptor (EGFR) endocytosis and degradation. In this study, we analyzed the effects of SPRY2 on degradation and signaling of FGF receptor 1 (FGFR1) compared to EGFR using two human GBM cell lines with different endogenous SPRY2 levels. In U251 cells with low endogenous SPRY2 levels, SPRY2 was overexpressed, while in SF126 cells with high endogenous SPRY2 content, SPRY2 was downregulated using short hairpin (sh)RNA. SPRY2 inhibited clathrin- and caveolae-mediated endocytosis of FGFR1, reduced the number of caveolin-1 vesicles and the uptake of transferrin. Furthermore, FGFR1 protein was decreased by SPRY2 whereas EGFR protein was increased. SPRY2 enhanced FGFR1 degradation by increased c-casitas b-lineage lymphoma (c-CBL)-mediated ubiquitination but it diminished binding of phospholipase Cγ1 (PLCγ1) to FGFR1. Consequently, SPRY2 inhibited FGF2-induced activation of PLCγ1, whereas it enhanced EGF-induced PLCγ1 activation. These results demonstrate that the inhibitory effect of SPRY2 on FGF signaling is at least in part due to the reduction of FGFR1 levels and the decreased binding of PLCγ1 to the receptor.

Funding: Austrian Science Fund (FWF) P 28909

Presentation number: P5.21

Topic: Embryology and Cell Biology

Monocyte-Derived Microglia Like Cells - An Opportunity for Patient-Specific Models?

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Introduction

Due to the inaccessibility of human microglia, there is a lack of species-specific models for these resident immune cells of the central nervous system (CNS). Until now, mouse models were considered as the standard in this research field.The attempt to differentiate blood derived monocytes into monocyte-derived-microglia cells (MDMi) using a standardized in vitro protocol is intended to create a novel model system that could be used in everyday clinical use.

Methods

Various media additives such as supplements and cytokines, as well as the combination of these, were tested to improve the differentiation of monocytes into MDMi. After a fourteen-day differentiation period, MDMi maturation was assessed by analysis of expression of 144 selected genes via a new custom nCounter® human microglia profiling panel by NanoString®. Furthermore, immunocytochemical stainings to validate P2RY12 and TMEM119 expression as well as different functional microglia characteristics such as phagocytosis and migration were performed.

Results

Together, our results demonstrate that the addition of M-CSF, IL-3, B27 and N2 led to an increase in microglia-enriched markers at the transcriptional and protein levels. The combination of the tested supplements and cytokines revealed the highest increase of microglia- enriched genes and proteins.

Discussion

MDMi could serve as an accessible and easy approach to provide insights into the biology and/or pathology of human microglia. Moreover, we have established and improved the differentiation protocol to obtain MDMis from peripheral blood monocytes as a prerequisite to conduct future studies involving patients with neurological and/or neurodegenerative diseases.

Presentation number: P5.22

Topic: Embryology and Cell Biology

CXCL13 is constitutively expressed in the parafollicular cells of the thyroid gland

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Introduction:

The thyroid gland contains two distinct types of cells: follicular cells and parafollicular cells. Follicular cells are responsible for producing the primary thyroid hormones triiodothyronine (T3) and thyroxine (T4). Parafollicular cells produce calcitonin, a hormone that reduces serum calcium levels. Parafollicular cells are members of the APUD cells (amine precursors uptake and decarboxylation) due to their ability to selectively uptake amine precursors. They can give rise to medullary thyroid carcinoma. Our previous data identified the homeostatic chemokine CXCL13 as one of the messengers produced by neuroendocrine cells in the murine airway. Given the proximity and similar histochemical characteristics of parafollicular cells and airway neuroendocrine cells, we will assess the expression of CXCL13 in parafollicular cells.

Methods:

We assessed CXCL13 expression in the thyroid glands of C57BL/6J mice by immunohistochemistry, RT-PCR, and immuno-electron microscopy.

Result:

RT-PCR utilizing primers specific for CXCL13 revealed expression of CXCL13 in the whole thyroid tissues. Immunolabeling localized CXCL13-immunoreactivity to parafollicular cells. Relative frequencies of immuno-reactive phenotypes were quantified in sections of the thyroid glands. Double-positive cells ($CGRP^+$/ $CXCL13^+$) made up the majority (89%, 681/768 cells from 5 mice) of parafollicular cells, and $CGRP^+$/ $CXCL13^-$ cells accounted for 10%, and $CGRP^-$/ $CXCL13^+$ cells accounted for 1%. Pre-embedding immuno-electron microscopy validated the neuroendocrine identity of CXCL13-immunoreactive cells.

Conclusion:

We identified that most parafollicular cells in naive mice produce the chemokine CXCL13, suggesting an immunoregulatory role in the neogenesis of secondary lymphoid tissues and modulating immune responses.

Presentation number: P5.23

Topic: Embryology and Cell Biology

Bitter tastants relax the mouse gallbladder smooth muscle independent of signaling through tuft cells and bitter taste receptors

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Introduction: Disorders of gallbladder motility can lead to serious pathology. Bitter tastants acting upon bitter taste receptors (TAS2R family) have been proposed as a novel class of smooth muscle relaxants to combat excessive contraction in the airways and other organs.

Methods: To explore whether this might also emerge as an option for gallbladder diseases, we here tested bitter tastants for relaxant properties and profiled *Tas2r* expression in the mouse gallbladder. The bitter tastants denatonium, quinine, dextromethorphan, and noscapine dose-dependently relaxed the pre-contracted gallbladder in organ bath experiments.

Results: Utilizing gene-deficient mouse strains, neither transient receptor potential family member 5 (TRPM5), nor the *Tas2r143/Tas2r135/Tas2r126* gene cluster, nor tuft cells proved to be required for this relaxation, indicating direct action upon smooth muscle cells (SMC). Accordingly, denatonium, quinine and dextromethorphan increased intracellular calcium concentration preferentially in isolated gallbladder SMC and, again, this effect was independent of TRPM5. RT-PCR revealed transcripts of *Tas2r108*, *Tas2r126*, *Tas2r135*, *Tas2r137*, and *Tas2r143*, and analysis of gallbladders from mice lacking tuft cells revealed preferential expression of *Tas2r108* and *Tas2r137* in tuft cells. A TAS2R143-mCherry reporter mouse labeled tuft cells in the gallbladder epithelium. An *in silico* analysis of a scRNA sequencing data set revealed *Tas2r* expression in only few cells of different identities, and from *in situ* hybridization histochemistry, which did not label distinct cells.

Discussion: Our findings demonstrate profound tuft cell- and TRPM5-independent relaxing effects of bitter tastants on gallbladder smooth muscle, but do not support the concept that bitter receptors mediate these effects.

Presentation number: P5.24

Topic: Embryology and Cell Biology

Age-dependent induction of hypothalamic c-fos activity by noxious stimuli in chick foetuses

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Pain is an unpleasant sensory and emotional experience typically associated with tissue damage. Its perception depends on the brain's structural complexity, which develops at specific embryonic stages. However, the embryonic development of pain perception in chickens remains to be fully understood.

In this study, we examined chicken foetuses from embryonic days (ED) 12-17. Nociceptive stimuli were generated by injecting a 4% paraformaldehyde solution into the sole of one foot. Paraffin sections were analyzed using antibodies against c-fos for neuronal activation and histone H3 for normalisation. Immunofluorescence signals were acquired via confocal microscopy.

Our results show that at ED 14 or older, nociceptive stimulation induced c-fos activation in the paraventricular nucleus (PVN) of the hypothalamus. This activation pattern was always bilateral, regardless of the stimulation side. In contrast, younger embryos rarely exhibited c-fos activation in the same region.

The PVN of the hypothalamus plays a crucial role in the emotional processing of pain through hormone secretion, such as oxytocin. Previous studies have observed c-fos responses to nociceptive stimuli in the PVN of infant rats. Our findings indicate that this capability is acquired prenatally in chick foetuses, which has significant implications in light of recent legal changes regulating the euthanasia of excess chick embryos in the poultry industry.

Presentation number: P5.26

Topic: Embryology and Cell Biology

Investigation of the role of connexins during skin wound healing in a novel 3D-in-vivo-wound healing model

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Skin integrity is regulated by cell-cell contacts and protects against environmental stress. However, skin diseases are on the rise, and our understanding of human skin wound healing mechanisms remains limited.

One molecule-family that influences skin wound healing are connexins, the basic component of Gap junctions. Studies in mice show that, compared to intact skin, expression of Connexin 43 (Cx43) decreases and Connexin 26 (Cx26) increases in wounded skin areas. Their role in human wound healing is not well understood yet, due to the lack of an adequate human model.

To fill the gap of lacking models for monitoring human skin wound healing, we developed an 3D-in-vivo-CAM-model applying skin biopsies after inducing defined cuts. At different time-points, connexin expression was analyzed using Western blots, immunofluorescence staining, qPCR, and mRNAscope. Future approaches include testing modulators and identifying dysregulated pathways in diseased or irradiated skin.

We were able to keep human skin alive on the CAM for seven days, confirming viability histologically. Marking wounds with color allowed precise localization of healing wounds after seven days.

Western blots and immunofluorescence staining for connexins were challenging due to low antibody specificity. mRNAscope showed an Cx26-upregulation at day one on the CAM, with minor changes in Cx43 expression. Differential expression levels were confirmed by qPCR.

A reliable model for analyzing biological processes like proliferation, neoangiogenesis and melanin deposition during wound healing was developed. We aim to develop tests beyond the CAM-model to determine if connexin expression changes are due to CAM effects or wound healing mechanisms.

Presentation number: P5.27

Topic: Embryology and Cell Biology

mTORC1-induced megalin phosphorylation acts as a switch between proliferation and endocytosis

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The importance of proper proximal tubular function in the kidney is shown in Fanconi syndrome. Loss of urinary proteins is counteracted by endocytosis, e.g. by megalin/LRP2, which is one of the main scavenger receptors. Post-translational modifications such as phosphorylation at the c-terminus of megalin regulate endocytic function, but the impact of S4577 phosphorylation is still unknown.

Transient transfection of megalin mini-receptor construct 2 (MMR2) with mutations in S4577 (MMR2 S->A mimics permanent non-phosphorylated state, MMR2 S->D mimics permanent phosphorylated state) were used in MDCK2 or EBNA/HEK cells, followed by functional endocytosis assay, immunocytochemical staining, western blotting, surface expression analysis, and co-immunoprecipitation.

The phosphorylation of MMR2 at S4577 induced by mTORC1 was confirmed and had no impact on MMR2 surface expression level but reduced the endocytosis of albumin. S4577 phosphorylation had minor effects in subcellular distribution of MMR2 in clathrin vesicles and early endosomes and did not change MMR2 distribution in recycling endosome and Rab35-positive vesicles. S4577 phosphorylation led to a stronger binding affinity of MMR2 to the endocytosis adaptor protein ARH. Surprisingly, S4577 phosphorylation reduced the cell proliferation rate and MMR2 was found to be partially co-localized with alpha-tubulin in mitotic spindles.

The phosphorylation S4577 in megalin c-terminus is involved in the cellular switch between cell proliferation and endocytic function.

Presentation number: P5.28

Topic: Embryology and Cell Biology

Spatiotemporal expression analysis of vascularization-related genes in the developing tooth germ.

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Vascularization is essential for embryonic organ development as well as tissue repair in adults, since adequate vasculature is required for supplying nutrients and oxygen to tissues and for excreting metabolized waste. Vascular endothelial cells invade forming dental papilla during the cap stage of tooth development, building vascular networks through angiogenesis. Several types of hematopoietic cells express the angiogenic factors such as vascular endothelial cell growth factor (VEGF) which recruits endothelial cells to the sites of both normal and pathological angiogenesis. However, it remains unknown which cells are responsible for attracting and leading vascular endothelial cells through the dental papilla of developing tooth germ. In this study, we investigated the expression and localization of several markers of hematopoietic cells, and compared with the spatiotemporal distribution of vascular endothelial cells during mandibular molar tooth development of fetal mice from E12.5–18.5, through *in situ* hybridization. We found that cells expressing thrombopoietin receptor c-Mpl, known as a marker for megakaryocytic cells, appeared in several parts of the mouse tooth germ. Finally, at E18.5, c-Mpl expressing cells accumulated at the periphery of the dental papilla along the inner enamel epithelium of the future cusp region and were found to be odontoblasts. The accumulation of c-Mpl-expressing odontoblasts preceded invasion of vascular endothelial cells into the dental papilla. These results suggest that odontoblasts and their precursor cells have functions similar to those of other hematopoietic cells and may be involved in the formation of vascular networks during tooth development.

Presentation number: P5.29

Topic: Embryology and Cell Biology

Piezo1 regulates the maturation of oligodendrocytes and dorsal root ganglion (DRG) cells

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Multiple sclerosis (MS) is a complex, chronic, immune-mediated disease of the central nervous system (CNS), characterized by the development of large demyelinated plaques, oligodendrocyte destruction, and axonal degeneration. Neurons and oligodendrocytes express a wide range of Ca^{2+} channels and receptors, and the excessive influx of Ca^{2+} into these cell types can contribute to MS pathogenesis. Piezo1 is a novel class of ion channels involved in mechanotransduction, expressed mainly by neurons, endothelial cells, and glial cells in the brain. However, the exact role of Piezo1 in glial cells and neurons is not fully understood.

To this end, we downregulated the expression of *piezo1* in zebrafish lines carrying the transgenes Tg(Olig2:eGFP), Tg(mbp:eGFP-caax), and Tg(ngn1:eGFP) using the CRISPR/Cas9 method. Furthermore, we modulated Piezo1 channel using both agonist (Yoda1) and antagonist (GsMTx4) drug treatments. Concurrently, we explored the role of Piezo1 in OPC mouse cell culture by treating the cells with Yoda1 and GsMTx4. Our imaging results demonstrated that downregulating and inhibiting piezo1 led to the early migration and maturation of OPCs, initiating myelination in both zebrafish and primary mouse cell culture. Moreover, this downregulation and inhibition promoted the growth and maturation of DRG in zebrafish. This finding is not only relevant in the context of MS but also in other neurodegenerative diseases, particularly those involving oligodendrocytes and myelination.

Presentation number: P5.30

Topic: Embryology and Cell Biology

In the sake of TIME: Nrf2's impact on the Tumor Immune MicroEnvironment

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Hepatocellular carcinoma (HCC) formation and progression is influenced by the inflammatory status of the tumor immune microenvironment (TIME). It has been proposed that the activity of the nuclear factor-erythroid 2 related factor 2 (Nrf2) can affect TIME, especially with respect to the polarization of tumor-associated macrophages. However, the underlying mechanisms are still unclear. The objective of our study was to provide new insights using our established 3D co-culture model.

Multicellular tumor spheroids (MCTSs) consisting of non-alcoholic steatohepatitis-derived HCC (N-HCC25) cells and bone marrow-derived macrophages (BMDMs) were used. In this 3D model, the Nrf2 influence on both BMDMs and tumor cells was investigated. We analyzed invasive behavior of tumor cells by a longitudinal time-lapse study. The inflammatory status of TIME was determined by ELISA using MCTS supernatant. Macrophage distribution within spheroids and their phenotype were assessed by flow cytometry, histology and spheroid clearing methods.

We were able to show that Nrf2 activity within MCTSs has an effect on the inflammatory status of the TIME. Furthermore, Nrf2 influences invasion behavior of tumor cells. Immunofluorescence studies as well as 3D di-photon microscopy of cleared MCTSs revealed the distribution of macrophages throughout the whole spheroid. The incorporated amount of BMDMs was confirmed by flow cytometry.

Our MCT model represents a promising tool to characterize HCC in vitro, as it precisely simulates many aspects of tumor behavior and its TIME. As the Nrf2 status in HCC cells as well as macrophages affects these processes, pharmacological intervention targeting Nrf2 will be part of our ongoing studies.

Presentation number: P5.32

Topic: Embryology and Cell Biology

Role of Rock for desmosomal adhesion and pemphigus autoantibody-induced effects in cultured keratinocytes

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Introduction

In the life-threatening disease pemphigus vulgaris (PV) autoantibodies directed against desmoglein 1 (Dsg1) and Dsg3 cause blistering of the skin. We reported previously apremilast similar to activation of Rho family GTPases to be protective against PV-IgG-mediated loss of cell adhesion. Nevertheless, the underlying mechanisms are not fully understood.

Methods

PAMGENE multiplex kinase assay, immunostaining, keratinocyte dissociation assay

Results

Activation of Rho family GTPases by CN04 ameliorated loss of adhesion induced by the Dsg3-specific pemphigus autoantibody AK23, which was diminished by inhibition of Rho-associated protein kinase (Rock) using Y-27632. In line with this, the specific RhoA activator CN01 also improved cell adhesion after AK23 treatment. Moreover, Rock inhibition alone impaired keratinocyte adhesion, which was not completely restored by activation of Rho family GTPases. Interestingly, a kinome analysis revealed Rock1 to be activated by increased cAMP in response to both apremilast and forskolin/rolipram. Treatment with apremilast did not restore adhesion after Y-27632 treatment and inhibition of Rock impaired the protective effect of apremilast on AK23-induced loss of adhesion. Finally, immunostaining of cytokeratin revealed attenuation of PV-IgG-induced keratin retraction by apremilast, which was diminished by Y-27632.

DiscussionTaken together, these data indicate an important role of Rock for Rho GTPase- and apremilast-mediated protective effects against PV-IgG-induced loss of keratinocyte adhesion in cultured cells.

Presentation number: P5.33

Topic: Embryology and Cell Biology

Regulation of hyaloid blood vessel regression by GPR124

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Introduction: Hyaloid blood vessels (HBV) transiently supply the developing vitreous body and lens. Normally, these blood vessels regress in late gestation. Failure of HBV regression can lead to a congenital eye disorder associated with impaired vision as well as retinal tears, hemorrhage, and detachment. Genetic studies in mice have shown that WNT7 signaling in hyaloid endothelial cells (hyEC) critically regulates HBV regression. However, the WNT7 receptors and target genes in hyEC are still elusive. The G-protein-coupled receptor 124 (GPR124), also known as TEM5 or ADGRA2, is an essential regulator of WNT7 signaling in brain EC. Here, we tested the hypothesis that GPR124 also mediates WNT7 signaling in hyEC.

Methods: HBV flat-mounts from endothelial-specific *Gpr124* knockout (*Gpr124*$^{\Delta EC/\Delta EC}$) and control mice at various postnatal days (P4-P10) were prepared and vessel density was quantified. To test if GPR124 mediates HBV regression by regulating the WNT signaling pathway, we administered the receptor-independent WNT signaling activator CHIR-99021 to potentially rescue the *Gpr124*$^{\Delta EC/\Delta EC}$ phenotype.

Results: *Gpr124*$^{\Delta EC/\Delta EC}$ mice showed drastically decreased HBV regression compared with control littermates. Pharmacological activation of WNT signaling by CHIR-99021 resulted in complete rescue of the HBV phenotype in *Gpr124*$^{\Delta EC/\Delta EC}$ mice but did not accelerate HBV regression in control littermates.

Conclusion: Our data indicate that GPR124 mediates hyaloid blood vessel regression by regulating WNT signaling in hyEC. GPR124/WNT signaling is necessary, but not sufficient to induce HBV regression. To further elucidate the molecular mechanisms of GPR124-mediated HBV regression, we plan to perform single-cell RNA-Seq analyses on HBV from *Gpr124*$^{\Delta EC/\Delta EC}$ and control mice.

Presentation number: P5.34

Topic: Embryology and Cell Biology

Uptake of Micro- and Nanoplastics in Ocular Surface Cells and Impact on Cell Viability

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Introduction The etiology of dry eye disease (DED) is complex and not yet fully understood. Consequently, treatment is primarily symptomatic, but several risk factors, such as contact lens wear, provide insights into its development. Since contact lenses can release plastic particles into aqueous solution, it raises the question of whether micro- and nanoplastics (MNPs) particles interact with the ocular surface and may contribute to DED.

Methods Immortalized human cell lines from the cornea, conjunctiva, and meibomian gland were stimulated with 0.5 µm, 1.0 µm, 3.0 µm polystyrene microbeads, a widely used plastic. Uptake of MNPs by the different ocular surface cells was detected using transmission electron microscopy. The impact on cell survival was assessed via flow cytometry. Intracellular ATP concentration was determined using a bioluminescence assay.

Results Uptake of polystyrene microbeads was confirmed in human cells from the cornea, conjunctiva, and meibomian gland. At concentrations up to 2*10^6 particles/ml, no significant changes in viability were observed. An increase in ATP concentration in the bioluminescence assay after 48 hours of stimulation with MNPs suggests that the cells are experiencing mechanical and/or oxidative stress.

Discussion While polystyrene microbeads were successfully internalized by ocular surface cells, their presence did not significantly impact cell viability. However, the observed increase in ATP levels indicates a stress response, potentially due to mechanical and oxidative factors. These findings suggest that microplastic exposure may contribute to ocular surface stress, and, thus, DED pathogenesis. Further research is needed to elucidate MNPs potential role in inflammation and DED.

Presentation number: P5.35

Topic: Embryology and Cell Biology

Distribution of IgA-plasma cells on the ocular surface and quantification of IgA concentration in tear fluid of healthy subjects and patients with primary Sjögren syndrome

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Introduction

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease that causes damage to the lacrimal glands due to lymphocytic infiltration, resulting in dryness of the eyes. Recent evidence indicates that B and plasma cells play a multifaceted role in the pathophysiology of pSS and may even have a central role in the development of the disease. The most abundant immunoglobulin in tear fluid is IgA, which is produced by plasma cells. IgA plays a crucial role in immune defence. This study investigates the distribution of IgA-producing plasma cells on the ocular surface and quantifies IgA and subtype concentrations in tear fluid.

Methods

To investigate the distribution of IgA plasma cells on the ocular surface, healthy human lacrimal glands and paraffin-embedded conjunctiva from body donors were analyzed by immunohistochemistry. To quantify IgA concentrations and subtypes, an ELISA was performed with tear fluid from healthy donors and patients with pSS.

Results

Immunolabeling showed no difference in the distribution of IgA1 and IgA2 plasma cells in the lacrimal gland. In contrast, the conjunctiva contains more IgA2 plasma cells than IgA1 cells. The ELISA examination showed an altered IgA and subtype concentration in tear fluid of pSS patients with dry eye compared to the healthy group.

Discussion

This study emphasizes that IgA-producing plasma cells play an important role in the pathophysiology of pSS and could therefore represent an interesting target for therapeutic approaches.

Presentation number: P5.36

Topic: Embryology and Cell Biology

Morphometry and morphology of the Human placenta in mining and non-mining areas in Northwestern Tanzania.

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Introduction: The placenta is an organ of fetal origin providing interchange between the mother and fetus. The morphology and morphometry of the human placenta vary across populations due to different factors such as ethnicity, environmental pollutants e.g., heavy metals and maternal illnesses. However, there is limited information the effect of heavy metal exposure due to mining activities on placenta morphometry and morphology specific to the Tanzanian population.

Methods: This was a comparative cross-sectional study that involved placentas, mothers, and babies from mining and non-mining areas in Northwestern Tanzania. Comparison of the morphometric and morphology variables was done using the independent sample t-test and Chi-square/ Fisher's exact test respectively. A multilevel linear model was used to determine the relationship between placenta morphometry, maternal characteristics, and fetal birth weight.

Results: The mean placenta weight, diameter and cotyledon number were significantly higher in the non-mining area. The mean placenta thickness was higher in the mining area. There were no differences in placenta shape, cord insertion, number of cord vessels and occurrence of placenta abnormalities between the two areas. Increase in maternal pre-pregnancy BMI and maternal age was associated with increase in placenta morphometry and fetal birth weight significantly increased with an increase in placenta morphometry in both areas.

Discussion: Placenta morphometry variables were significantly lower in the mining area compared to the non-mining area in Northwestern Tanzania. This finding suggests that the increased risk of heavy metal exposure due to mining may alter placenta function and thus affect placenta growth.

Presentation number: P5.37

wurde zurückgezogen

Presentation number: P5.38

Topic: Embryology and Cell Biology

Expression and Function of MDR1 in Ocular Surface Inflammation

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Purpose:

The ABC transporter family is crucial for maintaining cellular homeostasis and the efflux of endogenous substances and xenobiotics. Among these transporters, the protein encoded by the ABCB1 gene, known as multi-drug-resistance-protein (MDR1) or P-glycoprotein-1 (P-Gp), is significant due to its variability in interacting with pharmacological substances and its clinical relevance. However, the expression and physiological role of P-Gp in the ocular system during inflammation is not well understood.

Methods:

In this study, P-Gp expression was analyzed in human ocular tissues from body donors and in immortalized human corneal epithelial (HCE) and conjunctival epithelial (HCjE) cell lines using RT-PCR and immunohistochemistry. To investigate MDR1 regulation, cell culture experiments were conducted under stress conditions, including proinflammatory cytokines and different salt concentrations. The regulatory effects on MDR1 were assessed via qPCR, western blot analysis, and immunofluorescence. Additionally, P-Gp functional activity was determined using calcein AM assays.

Results:

RT-PCR and immunohistochemistry indicated aberrant P-Gp expression in the ocular tissues and cell lines examined. MDR1 expression was regulated by the culture medium and various chemical stressors, suggesting that ocular MDR1 expression responds to environmental changes and inflammatory stimuli.

Conclusions:

This study demonstrates that P-Gp is vital for maintaining homeostasis on the ocular surface during inflammation. The regulation of MDR1 expression by different stressors highlights its importance in ocular health and disease, emphasizing the need for further research into its therapeutic implications in ocular inflammation and drug delivery.

Presentation number: P5.39

Topic: Embryology and Cell Biology

Modeling the Kinetics of P-Gp using a common fluorescent probe

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Introduction

P-Gp is a well-known member of the ATP-binding cassette transporter (ABC-transporter), whose physiological function includes the efflux of xenobiotics, which thereby alters the bioavailability of commonly prescribed drugs such as Cyclosporin A and Verapamil. This study presents a detailed approach to modeling the kinetics of P-Gp using differential equations, to provide deeper biological insights.

Methods

We developed a mathematical model using a commonly used fluorescent probe to describe the dynamics of the membrane-bound protein. A numerical solution scheme was applied to solve the differential equations. Sensitivity analysis was conducted to identify key parameters influencing the model's behavior. With P-Gp transfected MDCK-cells were used to gain experimental data for the model.

Results

Our model aligned with the experimental data, effectively capturing the protein's functional dynamics. Sensitivity analysis revealed critical parameters significantly impacting model outcomes, guiding further model refinement.

Discussion

The created mathematical mode improves the understanding of P-GP dynamics and establishes a framework applicable to other biological systems and experimental conditions. Future work will extend the model to incorporate more complex interactions and validate its performance under diverse experimental conditions.

Presentation number: P5.40

Topic: Embryology and Cell Biology

Alterations of Peroxisomes in Differentiated Macrophages Using Human THP-1 Cells as an in Vitro Model

Khaled Mahmoud, [1]

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Introduction:

Peroxisomes are single-membrane-bound cytoplasmic organelles involved in the metabolism of reactive oxygen species, various bioactive and proinflammatory lipids, and other metabolic processes. These metabolic products are crucial in activating nuclear receptor signaling pathways such as PPAR-α, PPAR-β, and PPAR-γ. PPAR-γ modifies macrophage (MΦ) functions, a cell type important to the innate immune system through their role in phagocytosis and antigen-presenting capability.

Methods:

This study uses the promonocytic cell line THP-1 as an in vitro macrophage model to produce cells that resemble classically activated macrophages when treated with IFNγ and LPS. In addition, THP-1 cells exhibit characteristics of alternatively activated macrophages when treated with IL-4, IL-13, or IL-10. We investigated different macrophage-specific markers in differentiated THP-1 cells, analyzing their expression profiles using qPCR and measuring protein concentration using ELISA. Additionally, we investigated the alterations of peroxisomes during macrophage differentiation, focusing on peroxisomal markers involved in lipid metabolism such as ABCD3, ACOX1, thiolase, and PPAR-α, β, and γ using western blot, qPCR, and immunofluorescence techniques.

Results:

Our finding revealed that upon treatment with phorbol 12-myristate-13acetate (PMA), there was a significant induction of PEX14, a peroxisomal membrane protein involved in peroxisomal biogenesis. Furthermore, ABCD3, a long-chain fatty acid transporter, as well as ACOX1, the first enzyme in the peroxisomal β-oxidation pathway, and thiolase, were significantly upregulated.

Conclusion:

These results indicate that lipid metabolism in differentiated THP-1 cells is significantly enhanced. Providing insights into the role of peroxisomes in macrophage differentiation and function, highlighting potential metabolic shifts associated with macrophage activation states.

Presentation number: P5.41

Topic: Embryology and Cell Biology

Alterations of Peroxisomes in Differentiated Macrophages Using Human THP-1 Cells as an in Vitro Model

Khaled Mahmoud, [1]

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Conclusion:

These results indicate that lipid metabolism in differentiated THP-1 cells is significantly enhanced. Providing insights into the role of peroxisomes in macrophage differentiation and function, highlighting potential metabolic shifts associated with macrophage activation states.

Presentation number: P5.42

Topic: Embryology and Cell Biology

CXCL13 is constitutively expressed in the parafollicular cells of the thyroid gland

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Introduction:

The thyroid gland contains two distinct types of cells: follicular cells and parafollicular cells. Follicular cells are responsible for producing the primary thyroid hormones triiodothyronine (T3) and thyroxine (T4). Parafollicular cells produce calcitonin, a hormone that reduces serum calcium levels. Parafollicular cells are members of the APUD cells (amine precursor uptake and decarboxylation) due to their ability to selectively uptake amine precursors. They can give rise to medullary thyroid carcinoma. Our previous data identified the homeostatic chemokine CXCL13 as one of the messengers produced by neuroendocrine cells in the murine airway. Given the proximity and similar histochemical characteristics of parafollicular cells and airway neuroendocrine cells, we will assess the expression of CXCL13 in parafollicular cells.

Methods:

We assessed CXCL13 expression in the thyroid glands of C57BL/6J mice by immunohistochemistry, RT-PCR, and immunoelectron microscopy.

Result:

RT-PCR utilizing primers specific for CXCL13 revealed expression of CXCL13 in the whole thyroid tissues. Immunolabeling localized CXCL13-immunoreactivity to parafollicular cells. Relative frequencies of immuno-reactive phenotypes were quantified in sections of the thyroid glands. Double-positive cells ($CGRP^+$/ $CXCL13^+$) made up the majority (89%, 681/768 cells from 5 mice) of parafollicular cells, and $CGRP^+$/ $CXCL13^-$ cells accounted for 10%, and $CGRP^-$/ $CXCL13^+$ cells accounted for 1%. Pre-embedding immuno-electron microscopy validated the neuroendocrine identity of CXCL13-immunoreactive cells.

Conclusion:

We identified that most parafollicular cells in naive mice produce the chemokine CXCL13, suggesting an immunoregulatory role in the neogenesis of tertiary lymphoid tissues and modulating immune responses.

Presentation number: P6.01

Topic: From Bench to Bedside

Functional and prognostic relevance of CD44 isoforms in PDAC

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Introduction:

Pancreatic cancer (PDAC) represents an aggressive tumor disease drastically limiting the prognosis of patients. CD44 is a multifunctional glycoprotein, for which a potential key role for cancer progression has been described. Here, we focused on the interplay between CD44 isoforms, tumor growth and extracellular matrix (ECM) remodeling in PDAC.

Methods:

CD44 was depleted in human PDAC cell lines (PaCa5061, BxPC3) by shRNA knockdown (KD) and functional consequences were studied in xenograft models. CD44 isoform expression patterns and transcriptome changes upon KD were analyzed by RNA-sequencing. ECM components were detected by IHC. Patient material was analyzed using public databases and a tissue microarray.

Results:

In vivo tumor growth was delayed after CD44-KD in the PaCa5061 model, accompanied by enriched ECM (remodeling) genes. IHCs confirmed remarkable alterations of matrix components upon CD44 KD. PaCa5061 and BxPC3 cell lines and xenografts showed predominant expression of isoforms 1-3. Using TCGA database analyses, CD44 isoforms 1-3, but not isoform 4, were identified as prognostically relevant for PDAC. Instead, isoform 4 was linked to tumor stroma and immune cell infiltration. A TMA of PDAC patients also showed a correlation between CD44v3, CD44v6 and CD44v9, while panCD44 only correlated with CD44v9; CD44v3 and CD44v6 were associated with higher grading.

Discussion:

CD44 is apparently not only a receptor but also a regulator of the ECM in the tumor microenvironment. The association of CD44v3 and CD44v6 with grading might account for the adverse prognostic value of isoforms 1 and 2.

Presentation number: P6.02

Topic: From Bench to Bedside

Engineering antiviral peptides to prevent the cell entry of human cytomegalovirus

Ruben Caspary, [1], Eileen Socher, [1]

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Introduction:

Human cytomegalovirus (HCMV) poses significant developmental risks for infants infected in utero, as well as high risks to immunosuppressed and transplantation patients, due to its ubiquitous prevalence in the human population (up to 80%). In HCMV, the trimer envelope protein gH/gL/gO plays a key role in mediating cell entry. This study aims to elucidate key interactions at the interface between the HCMV trimer gH/gL/gO and the human Platelet Derived Growth Factor Receptor α (PDGFRα) by using methods of structural bioinformatics.

Methods:

Two different cryo-EM structures of the protein complex of the human receptor PDGFRα and the HCMV trimer gH/gL/gO were investigated with in silico analyses. Thereby, we focused on amino acids at the interface between the viral glycoproteins gH/gL/gO and the human PDGFRα to identify interaction hotspots with important contacts for mediating cell entry and thus containing possible target sites for antiviral peptides. Furthermore, we examined the differences between two HCMV strains in order to recognize which interactions are conserved or mutation-induced. Additionally, a receptor-derived peptide proposed by an experimental workgroup was characterized at a structural level.

Results:

Structural analyses of gH/gL/gO trimers of two HCMV strains reveal differences at the interface with the cellular receptor PDGFRα concerning important molecular interactions, surface area and binding energies.

Conclusion:

Disrupting the interface between the HCMV trimer gH/gL/gO and PDGFRα during the viral spread (cell-associated/cell-free) is a promising approach to target HCMV infection. Our structural analyses provide a basis for engineering receptor-derived antiviral peptides preventing the binding of HCMV to PDGFRα.

Presentation number: P6.03

Topic: From Bench to Bedside

Patient-derived xenografts generated from circulating cancer stem cells in a 3d-in-vivo model as a novel concept for research and clinical deci-sion-making in pancreatic cancer

Andreas Ettner-Sitter, [1,2], Benedikt Wagner, [1]

Nicolas Ihlo, [3], Merle Behr, [3], Florian Weber, [4], Bettina Rau, [5], Hans Jürgen Schlitt, [1], Dorothea Schott, [5], Monika Pizon, [5], Katharina Pachmann, [5], Thiha Aung, [6], Christina Hackl, [1], Silke Haerteis, [7]

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[7], Institute for Molecular and Cellular Anatomy, Regensburg, Germany

Background: Despite advancements in pancreatic cancer treatment, prognosis remains dire, with a 5-year survival rate under 10%. Innovative therapies and preclinical models are urgently needed. Circulating epithelial tumor cells (CETCs), particularly the rare subpopulation of circulating cancer stem cells (cCSCs), are crucial for recurrence and metastasis. Patient-derived xenografts (PDXs) are pivotal for personalized oncology. This study explores generating PDXs from cCSCs on the chorioallantoic membrane (CAM).

Methods: CETC and tumorsphere counts were analyzed in 25 pancreatic cancer patients pre-, intra-, and postoperatively. For the identification of cCSCs, cell suspensions from the peripheral blood were cultured in vitro under conditions favoring growth of tumorspheres. Furthermore, we used a rapid and efficient CAM culture system to generate PDXs from tumorspheres.

Result: An innovative in vitro assay was established for identifying cCSCs in peripheral blood. Higher CETC and tumorsphere counts correlated with worse UICC grading post-surgery. Tumorspheres successfully established PDXs within 7 days, closely mimicking primary tumor histology.

Discussion: A subset of circulating tumor cells exhibits stem cell characteristics, qualifying as cCSCs. The CAM model is ideal for xenografts due to its immunodeficiency until day 14 and late lymphatic development. It offers advantages over other models, including easy tissue access and real-time growth and angiogenesis observation.

Conclusion:CETC and tumorsphere counts correlate with clinicopathological parameters. The CAM model is an efficient and cost-effective method for generating PDXs from cCSCs, providing a valuable platform for testing new pancreatic cancer therapies. Further studies are needed to assess the prognostic significance of cCSCs detection.

Presentation number: P7.01

Topic: Form-Function Relationship

Cytoarchitectonic probability maps, co-activation patterns, and functional decoding of the human ventral anterior insula

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Introduction

To allow a study of structure-function relationship we postulate a cytoarchitectonic map of the human ventral anterior insulacortex that accounts for larger interindividual variability (n=10), minimizes human bias, and is available in a public accessible common reference space. We add a quantitative analysis of functional coactivation patterns, and functional decoding, to show a multimodal analysis of the human ventral anterior insula.

Methods

Cell-body stained histological sections were investigated. For the detection of borders between areas, sections were digitized and grey level index (GLI) profiles of the cortex were extracted, depicting the fraction of cell bodies throughout the cortical cross section. Borders were calculated using a sliding-window procedure on blocks of adjacent profiles. Moving along the cortical ribbon enabled systematic comparison of neighboring GLI profiles and detecting maximal difference (cytoarchitectonic borders) between them. Similarities between insular areas were analyzed using a cluster analysis. Overlaying the delineations of all discovered insular areas within the Montreal Neurological Institute reference space, 3D probability maps were generated in JuBrain Cytoarchitectonic Atlas and the Human brain atlas.

Results

Five new areas in the ventral anterior insula were identified. All areas differed in cytoarchitecture, particular their granularity. One area differed also in showing unique cell types, bipolar neurons.

Discussion

Our data suggest that the insular cortex is cytoarchitectonically composed of 16 areas, grouped into six superordinated microstructural domains, with a longitudinal gradient of granularity from in the dorsal portion of the insula from posterior to anterior and a diagonal gradient of granularity from posterior/dorsal to anterior/ventral.

Presentation number: P7.02

Topic: Form-Function Relationship

Molecular Case Studies of GALC Mutations Causing Krabbe Disease

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[1], Friedrich-Alexander University Erlangen-Nürnberg (FAU), Erlangen, Germany

Introduction:

Globoid cell leukodystrophy, also known as Krabbe disease, is a rare lysosomal disorder affecting the white matter of the central and peripheral nervous system. It is characterized by neurodegeneration and the most common form being infantile Krabbe cases, thus is usually diagnosed within the first year of life and with high morbidity and mortality. This autosomal recessive disease is caused by mutations in the *GALC* gene, which encodes the lysosomal enzyme galactocerebrosidase. This study focuses on examining the structural effects of galactocerebrosidase variants found as mutations in the *GALC* gene of patients with Krabbe disease.

Methods:

To investigate the effects of these mutations on protein structure, a structural model of human galactocerebrosidase was build. This model served as the basis for a series of all-atom molecular dynamics (MD) simulations to analyze the structural stability of the wild type and the mutated enzyme variants. Since galactocerebrosidase is subcellularly localized in the lysosome (pH 4.5-5.5), MD simulations were performed with protonation states corresponding to pH 4.5.

Results:

Differences in protein flexibility and intramolecular interactions between the wild type and the mutated enzymes were observed. Similarly, we detected effects of the mutations on the size of the substrate binding pocket, although the mutation site itself is not part of the active site/binding site of the enzyme.

Conclusions:

Overall, our MD simulations shed light on how these mutations affect the structure of human galactocerebrosidase in the lysosome and they offer possible explanations as to why these mutations have an effect on enzyme function.

Presentation number: P8.01

Topic: Digital and AI Tools in Teaching

A virtual microscope web-application with multi-lingual annotations for biomedical teaching

Franck Girard, [1]

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Three complementary pedagogical approaches are used at the University of Fribourg for teaching/learning histology during the first and second year of studies in medicine and biomedicine: 1)Learning with image projection during the theoretical courses (lecture-like presentation); 2)guided learning during the practical sessions (each student is provided with slides and a microscope); 3)virtual microscope web-application (self-directed learning).

Here, we present our virtual microscopy based on the programs OMERO and PathViewer made available on the public domain (https://virtual-microscopy.unifr.ch/index/). It contains 366 tissue sections (mostly human) scanned with the Hamamatsu NanoZoomer, covering a complete collection of organs and physiological systems. All virtual slide images were annotated and described in French, German or English.

Our experience and evaluation by students confirmed the virtual microscope to be a very valuable complementary resource to our traditional histology teaching and learning. It is particularly useful for self-directed learning and revision in the context of exam preparation. The unambiguous annotation of histological structures and the added flexibility provided by an easily accessible web-application were deemed very effective for the learning process.

Presentation number: P8.02

Topic: Digital and AI Tools in Teaching

A Novel Strategy for Practical Courses in Human Neuroanatomy

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Introduction

Human neuroanatomy is highly complex, and its understanding is particularly challenging. We propose a new didactic concept for a practical course in neuroanatomy, which activates medical students through flipped classroom, clinical case studies, peer teaching and the study of a pre-dissected human brain. An e-learning tool tailored to the course expands the learning space and enables individual preparation and follow-up learning.

Methods

The main e-learning tool, a virtual, annotated, three-dimensional rendering of a human brain, was achieved with help of photogrammetry. The gained images were integrated into SketchNote®, a 3D-rendering program. Additionally, the students can visualize neuroanatomical structures using pre-dissected human brains conceptualized as kits, where parts can be disassembled and reassembled following instructions in a script. The 3D-brain as well as further e-learning tools remain available to the students also outside of the course setting.

Results

The proposed course concept was applied as a pilot for medical students belonging to the second year of the two medical faculties in Zurich, Switzerland. Student feedback was very positive: The interactivity, the 3D-brain renderings, the possibility to freely interact with each other and dedicated tutors, and the manipulation of the pre-dissected brains were regarded as important learning assets.

Discussion

Universities promote the use of digital methods for supporting teaching, also for anatomy. The basis of learning clinical anatomy in a practical setting remains the dissection of specimens. However, digital methods, which usefulness should be carefully evaluated, can represent important, additional learning assets, welcomed by students.

Presentation number: P8.03

Topic: Digital and AI Tools in Teaching

Hybrid education in anatomy

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Modern technologies have revolutionized the teaching of anatomy by providing innovative tools and resources that enhance learning experiences. Virtual reality (VR) has become a powerful tool allowing students to explore realistic 3D anatomical structures. With VR, students can manipulate virtual cadavers, dissecting and visualizing anatomical details from different perspectives, encouraging deeper understanding.

iPad apps have also become popular for teaching anatomy, and apps offer interactive and portable platforms for studying anatomy on the go. They provide comprehensive visualizations, quizzes and interactive modules, adapting to different learning styles and preferences. They enable students to study anatomy from all angles.

The Virtual Desk is a top-quality technology that replicates the human anatomy in incredible detail. This interactive table allows students to virtually dissect cadavers, making it a valuable hands-on learning tool without the limitations of traditional dissection labs.

Additionally, the continued use of cadavers in teaching anatomy remains crucial as it provides authentic experiences that cannot be fully replicated by digital means. The combination of VR, iPad apps, virtual desks and traditional cadaver learning complement each other, offering a comprehensive and dynamic approach to anatomy lectures.

The combination of digital tools and traditional cadaver learning is the future of anatomy learning. This modern combination of technologies enriches lectures, encourages student engagement and develops a deep understanding of complex human body. As technology continues to develop, so will the potential for improving education, and teaching a next generation of healthcare professionals through a hybrid learning model.

Presentation number: P8.04

Topic: Digital and AI Tools in Teaching

Less is more – development and assessment of an augmented-reality (AR) clinical case-based teaching format in anatomy/orthopaedics

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Qualitative and in-depth anatomical education is fundamental in training competent medical professionals. The “gold standard” for acquiring anatomical knowledge relies on hands-on experiences in dissection rooms, which is essential for students to develop a profound understanding of anatomy in 3D space. Cadaveric dissection in Oldenburg is currently only possibly in collaboration with the UCM Groningen. Augmented-reality (AR) based learning scenarios using head mounted displays (HMDs) are an interesting teaching modality to complement pro- and dissection classes and offer students the chance to engage with the topographical relations of the human body in a new and engaging manner. Moreover, clinical content and cases can be implemented in the teaching tool enabling students to recapitulate and reactivate anatomical knowledge and concepts. In the present study, we developed a "Virtual Seminar-Anatomy and Orthopaedics" (VS-AaO), a digital AR learning environment developed to teach anatomy using the Hololens1 with relevance for orthopaedic clinical training and patient assessment. The qualitative pilot phase of the concept involves testing in groups from different universities, allowing students to interact in a virtual classroom. The objectives of this pilot study fall in two categories: first, we were interested to investigate the technical feasibility of creating an immersive teaching environment. Second, we also examined the views of students and educators/teachers on the potential and drawbacks of AR technology, particularly in relation to group teaching.

Presentation number: P8.05

Topic: Digital and AI Tools in Teaching

BONAVI: Short online video-clips for learning human bone anatomy

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Alvin Curtis Lin, [1], Nicholas Beger, [1], Christian Platzl, [1], Martin Hudelmaier, [1]

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Introduction: In medical education, the flipped-classroom model of pre-class preparation before in-classroom assignments has improved learning by self-pacing and tailoring content towards students' needs. At Paracelsus Medical University (PMU), students learn anatomical landmarks of human bones, using life-sized plastic models and in-classroom assignments. To enhance learning, students created video-clips of bone anatomy using smartphones. Based on dual channel and cognitive educational theories, segmenting content into short videos with static images and concise language help maximize effective use of both auditory and visual working memory pathways. Expanding upon the student-led initiative, with faculty support, high-quality videography and content-checking were applied to generate a series of BONAVI (Bone Navigation Videos) video-clips for open-source dissemination.

Methods: Plastic-models of human bones of the upper and lower extremity were chosen. A storyboard script was created, based on learning objectives of anatomical terms. Video-clips were recorded for the clavicle, scapula, humerus, radius, ulna, hand bones, hipbone, coccyx, femur, patella, tibia, fibula, talus, calcaneus, foot bones, and skeletal overview. Landmarks were described in Latin and English with Latin-labels. Video-editing was performed using Davinci Software.

Results: A total of 14 QR-coded video-clips were created. Videos varied from two to six minutes in length. Some bones were shown in different planes. All videos are published by PMU and available online.

Discussion: Preliminary informal student and faculty feedback has been positive, in pre-class learning and exam preparation. Future work will include collecting feedback through voluntary surveys. Video-clips of additional bones are planned, along with joints in different axes of movement.

Presentation number: P8.06

Topic: Digital and AI Tools in Teaching

Learning strategy profiles in anatomy: association with media use and performance

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Medical students may employ diverse learning strategies (LS), but research on subgroup-specific LS usage is limited. This study uses latent profile analysis (LPA) to investigate LS subgroups among 689 preclinical medical students from 6 German universities and explores how these patterns relate to learning outcomes.

Using the LIST-K questionnaire, we identified four distinct learning profiles: Active (45%), collaborative (17%), structured (29%), and passive learners (9%). Each profile uniquely combines 13 LS facets for anatomy study. Profiles differ in overall LS usage and specific LS combinations. LS facets show heterogeneous, subgroup-specific correlations with outcome criteria, often diverging from population-level effects.

These findings extend variable-centered research, challenge the linear continuum concept of LS, and highlight learner subgroup heterogeneity. Our analysis offers insights for educators to customize learning experiences to individual student needs.

Presentation number: P8.07

Topic: Digital and AI Tools in Teaching

Evaluation of Digital E-Learning Platform “Complete Anatomy” in first-year medical students

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Introduction: This study evaluates the effectiveness of the "Complete Anatomy" software as a learning tool for medical students. It provides detailed and interactive anatomical models to enhance understanding and retention of complex systems.

Materials and Methods: At the end of the first semester, we surveyed 233 first-year medical students to assess their experiences using "Complete Anatomy" Version 10.4.0 by 3D4Medical Ltd. The evaluation covered various systems, including musculoskeletal, cardiovascular, respiratory, digestive, urogenital, endocrine, nervous, topography, histology, and embryology. The survey also explored visual clarity, intuitiveness, ease of activation, need for tutorials, and overall impact on knowledge, motivation, exam preparation, and dissection readiness.

Results: The results indicated a predominantly positive reception. High levels of agreement were noted in visual clarity (68%), intuitiveness (77%), and ease of use (49%). Many students reported that the software improved their knowledge (66%), increased motivation (62%), and prepared them for exams (69%) and dissections (96%). Areas for improvement included the need for more tutorials (54%) and localization into German (41%).

Discussion: "Complete Anatomy" is a valuable educational tool that effectively enhances anatomical knowledge and preparation for practical exams. Its visual and interactive nature was particularly praised. However, the need for additional tutorials indicates that some students may require more guided learning experiences. Future versions could benefit from multilingual support.

Conclusion: Overall, "Complete Anatomy" is a robust e-learning tool that significantly aids in understanding complex anatomical concepts. Continuous updates and improvements will further enhance its educational impact.

Presentation number: P8.08

Topic: Digital and AI Tools in Teaching

Cyber sickness in virtual reality-based anatomy classes: lessons learnt from first year medical students of the Medical University of Vienna

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Introduction: Cyber sickness is defined as an uncomfortable side effect experienced by users of immersive interfaces commonly used for virtual reality (VR). This study aimed to evaluate the prevalence of cyber sickness during VR teaching approaches in anatomy.

Methods: 760 first semester students of human medicine and dentistry were provided with VR headsets (Oculus/Meta Quest 2) operating Human Anatomy VR software for studying bones and joints during osteology courses (3 x 2 hours). Detailed check-lists of anatomical details were provided and had to be studied in a self-determined setting. After finishing the practical courses, students were encouraged to fill in questionnaires. The response rate was 73.0 % (555 questionnaires were returned).

Results: 32 students (5.8 %) experienced symptoms of cyber sickness, which forced them to quit the practical VR sessions. These participants were offered alternative digital teaching methods. 151 students (27.2 %) claimed to have moderate symptoms, but were able to continue using VR.

Discussion: The present study indicates that 33.0 % of students experience cyber sickness, if working with VR headsets to study human anatomy. To allow all students to be educated in a decent manner, alternatives to VR headsets must be provided.

Presentation number: P8.09

Topic: Latest developments in undergraduate and postgraduate training

Role of examination format, teaching material and methods in anatomical courses for dental students

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Introduction: Changes in medical and dental studies have taken place due to corona pandemic restrictions and new licensing regulations for dentists. Generally, grades of undergraduate students are influenced by factors, such as use of certain teaching materials and methods. We hypothesize that the availability of online lectures and anatomical dissection courses as well as the choice of the exam format affect students' performance.

Methods: We analyzed the exam results of medical and dental students from a 2nd semester course of microscopic anatomy. The results from two consecutive years, one with and one without live lecturing, were compared. Further, grades from anatomical courses and state examinations in anatomy of dental students studying according to old (state examination: free oral exam) and new licensing regulations (state examination: structured oral exam) were examined.

Results: In two runs of a course under the same framework conditions, students achieved better exam results in the year with available live lectures. Additionally, students who were highly affected by corona pandemic restrictions, e.g. including cancelled dissection courses, performed worse in state examinations compared to those who experienced no restrictions. Regarding the examination format, we observed that students performed worse in the structured oral exam compared to the free oral exam.

Discussion: Taken together, our results indicate that live lectures and dissection courses are of essential importance for medical and dental students. The role of the examination format in dependence of teaching conditions must be further pursued and optimized to create a well-balanced education and training of dental students.

Presentation number: P8.10

Topic: Latest developments in undergraduate and postgraduate training

Mnemonic devices in anatomy teaching

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Introduction

Anatomy learning is a key factor for becoming a medical professional. Anatomical features retaining is a challenging matter.

Methods

We grouped the anatomical devices in three clusters – easy, medium and advanced. The base for our division was the complication level. The easy device was used to describe the position of an anatomical features based on relation with the lateral and medial position. We described the conoid tubercle and trapezoid line. The medium complexity was needed for description of a submandibular region – the triangles and theirs content – muscles, nerves and vessels. The advanced method was applied for the branches of maxillary artery.

Results:

The conoid tubercle is medial in relation to the trapezoid line – ct vs lt. C stands for central or medial position, l for lateral. The submandibular region can be described as normal and abnormal sandwiches. Normal sandwich = 2 slices of bread (muscles: hyoglossus and mylohyoid) and a slice of ham (CN XII) between them. In the advanced device we used the first letters of the title: “An adventure with Dima in Moscow – be careful of AIDS” – the first letters stand for the first letters of the branches.

Discussion

We strongly support the opinion that the anatomy learning is extremely important for clinicians, especially surgeons. The mnemonic devices can facilitate memorizing of the anatomical difficulties. Moreover, there are many approaches to anatomy teaching which can be applied. The variety of didactic methods is a key factor in this process.

Presentation number: P9.01

Topic: Spatial Transcriptomics and Metabolomics

Spatial gene expression profiling of WNT-signaling components in the enteric nervous system

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Introduction: Wnt-signaling is a key regulator of stem cell homeostasis, extensively studied in the intestinal crypt and other metazoan tissues. Yet, there is hardly any data available on the presence of Wnt-signaling components in the adult enteric nervous system (ENS) *in vivo*.

Methods: Therefore, we employed RNAscope HiPlex-assay, a novel and more sensitive *in situ* hybridization technology on murine small and large intestine samples. By amplifying target-specific signals, this technique enables the detection of low abundant, tightly regulated RNA content as it is the case for Wnt-signaling components. Additionally, we compared our data to previously published physiological single cell RNA sequencing data using data-mining approaches.

Results: Our descriptive analysis shows that several components of the multidimensional regulatory network of the Wnt-signaling pathway are present in the murine ENS. The transport and secretion protein for Wnt-ligands Wntless as well as canonical (*Wnt3a* and *Wnt2b*) and non-canonical Wnt-ligands (*Wnt5a, Wnt7a, Wnt8b* and *Wnt11*) are detectable within submucosal and myenteric plexus. Further, corresponding Frizzled receptors (*Fzd1, Fzd3, Fzd6,* and *Fzd7*) and regulatory signaling mediators like R-Spondin/Dickkopf ligands are present in the ENS of the small and large intestine.

Discussion: Our high-throughput study demonstrated that, a plethora of canonical and non-canonical Wnt-signaling components are expressed within the adult ENS, indicating a yet to be elucidated functional role of WNTs in cellular homeostasis of the adult ENS. Further, our results substantiate previously published single cell RNA-sequencing analyses of the murine ENS, thereby adding a valuable spatial component to big data gene expression studies.

Presentation number: P9.02

Topic: Spatial Transcriptomics and Metabolomics

Early life dysbiosis exacerbates airway hyperresponsiveness with minor impact of the duration of the dysbiotic state

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Introduction:

Epidemiological studies in humans correlate perinatal dysbiosis with increased long-term asthma severity. However, a correlation between absence or presence of specific taxa and asthma outcomes remains unclear. Given that maternal antibiotic treatment (AbT)-induced dysbiosis in dams increases the risk of newborn bacterial pneumonia in offspring, we hypothesized that early life dysbiosis stimulates long-term immunological effects in the offspring leading to an aggravated asthma phenotype.

Methods:

Pregnant and nursing dams underwent AbT from embryonic day 15 until postnatal day 28 at two institutions. At six weeks of age, experimental allergic asthma (AA) was induced in offspring by four weekly repeated applications of house dust mite extract. 72 h after the last immunization, airway hyperreactivity (AHR), Th2 cytokine secretion and pulmonary cell composition were assessed and correlated with previous microbial imbalance.

Results:

AbT elevated AHR in asthmatic mice site-independently. Contrarily, cellular infiltration of the airways or Th2 cytokine production by isolated lung cells remained unaffected by early life AbT at both institutions. Site-dependent effects were observed regarding diversity of microbial composition in the offspring directly after Abt and during asthma induction as well as persistence of dysbiosis.

Discussion:

These data show that early life dysbiosis has an aggravating impact on AA development later in life. However, they also suggest that this impact is rather related to early life changes in lung and/or immune system development instead of the actual microbial composition at the time point of asthma assessment, emphasizing the importance of early treatment of dysbiosis to prevent long-lasting developmental changes.

Presentation number: P9.03

Topic: Spatial Transcriptomics and Metabolomics

Spatial transcriptomics of repopulating microglia in adult mice

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Microglia are the resident immune cells in the central nervous system (CNS) and play crucial roles during phagocytosis of dying cells and engulfment of cellular debris in the adult brain. The colony-stimulating factor 1 receptor (CSF1R) is essential for microglial differentiation, proliferation and survival.

Using an inducible *Cx3cr1CreERT2/EFYP/Csf1rfl/fl* mouse line we were able to deplete up to 95% of microglia in the adult brain. Interestingly, despite the continued administration of tamoxifen, microglia began to repopulate the brain after 14 days. To identify the gene expression pattern of these repopulating microglia, we conducted spatial transcriptomics using GeoMX platform.

We compared IBA1+ microglia in brains of tamoxifen- and control chow-treated mice at 14 and 28 days post-treatment. At both time points, repopulating cells upregulated a number of markers associated with homeostatic and activated microglia, including *Aif1, P2ry12* and *Tmem119*, as well as *Apoe*, *Axl* and *Tyrobp*. Interestingly, an upregulation of TGFβ signalling-associated genes has been observed in microglia after 14 days.

Taken together, our spatial transcriptomics data from repopulating microglia indicate that microglial TGFβ signalling is an important driver of homeostatic marker expression further highlighting the role of TGFβ during postnatal microglia maturation.

Presentation number: P9.04

Topic: Spatial Transcriptomics and Metabolomics

Histology and single-cell transcriptomics reveal cell type heterogeneity in kidney thick ascending limb

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A single, terminally differentiated cell type with zone-related specificities has so far been defined to line thick ascending limb (TAL), but recent transcriptomic findings report distinct TAL cell clusters with mosaic expression pattern, illustrated by differential expression of ion transporters and junctional components. Histology and single-cell (sc) RNA sequencing are coupled to define mosaic cell features along TAL.

Mammalian kidney samples were used to examine the morphology of medullary (mTAL) and cortical (cTAL) TAL epithelia. Immunohistochemistry was used to assess the expression of ROMK, NKCC2, pNKCC2, Kir4.1, CaSR, Cldn10 and Cldn16 in TAL. Additionally, scRNA-seq datasets from mouse kidney were leveraged to define transcriptomic signatures of TAL cells using Seurat workflow.

NKCC2 was expressed throughout TAL and macula densa. Mosaic expression of ROMK in TAL showed 46 ± 7% ROMK-negative cells in mTAL, decreasing with cTAL. ROMK-negative cells inversely displayed p-NKCC2 signal chiefly in mTAL, suggesting mosaic NaCl transport activity. Cldn10 and ROMK were colocalized in mTAL and cTAL. CaSR and Kir4.1 were mutually exclusive to ROMK, with Cldn 16 coexpressed in outer stripe and cTAL cells. Macula densa expressed exclusively Cldn 10. ScRNA-seq analysis confirmed distinct cell clusters with Cldn 10 coexpressing Stk39, Ptger3, and Cryab, and Cldn16 cells coexpressing Kir4.1, CaSR, Clcnkb, Tmem52b, Wnk1, and Pth1r.

TAL cells exhibit marked heterogeneity in transporter and tight junction protein expression, correlated with distinct cell clusters from scRNA seq. Modeling TAL function with two distinct cell types suggests separate functions within TAL cells serving renal concentrating ability or ion transport homeostasis.

Presentation number: P9.05

Topic: Spatial Transcriptomics and Metabolomics

Exploring Microglial Diversity: Linking Bioinformatic and Experimental Approaches

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Introduction

Microglia, the immune cells of the CNS, play pivotal roles in brain development, maintaining balance, and responding to immune challenges. Their maturation primarily occurs in the early postnatal period. Unraveling the molecular mechanisms governing microglial development is crucial for comprehending their various functions.

Methods

In our study, we performed spatial transcriptomics on sagittal FFPE samples from wild-type mice at three postnatal time points, conducting bioinformatic differential gene expression analysis using an R script specifically developed for this study. Here, region-specific transcriptome analyses were conducted in the corpus callosum, hippocampus, and cortex.

Results

Transcriptome data from different brain regions showed a pattern of microglial maturation over time, while also highlighting distinct, region-specific gene expression profiles for microglia. Notably, the expression of additional glial markers in the microglial transcriptome during early development, such as *Olig2*, *Mbp*, *Plp1*, and *Gfap*, was evident. Subsequently, primary microglial cultures were examined to determine whether these markers were present at both mRNA and protein levels. Interestingly, RT-qPCR results revealed a specific gene expression pattern of oligodendrocyte-associated genes exclusively in primary microglia.

Discussion

This study provides new insights into the postnatal microglial gene expression pattern across different brain regions, elucidating the transcriptomic signatures that influence their maturation and functional diversity.

Presentation number: P10.02

Topic: Varia

The Legal and Ethical Framework Governing Body Donation in Europe – 2nd update on Current Practice

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Background: In 2008, members of the TEPARG provided the first insights into the legal and ethical framework governing body donation in Europe. The first update followed in 2012. This paper is now the second update on this topic and tries to extend the available information to many more European countries.

Methods: For this second update, we asked authors from all European countries to contribute their national perspectives. This inquiry compiled many contributions to this paper. When we did not get a personal contribution, we (EB) searched the Internet for relevant information.

Results: Perspectives on the legal and ethical framework governing body donation in Europe.

Conclusions: A clear and rigorous legal framework is still unavailable in several countries. We found national regulations in 18 out of 39 countries; two others have at least federal laws. Several countries accept not only donated bodies but also utilise unclaimed bodies. These findings can guide policymakers in reviewing and updating existing laws and regulations related to body donation and anatomical studies.