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Presentation number: 1.1

Topic: Invited Talk

The Desmosome Comes into Focus

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Desmosomes are calcium-dependent intercellular junctions that are critical for maintaining epithelial tissue architecture and for resisting mechanical stress in tissues such as the skin and heart. These intercellular junctions were first described in 1864 by Italian histologist Giulio Bizzozero and subsequently termed “desmosomes” by Josef Schaffer to describe their role in binding adjacent cells. In subsequent years, desmosomes drew the attention of pioneers in electron microscopy, including Farquhar and Palade, as well as Selby, Kelly, and Porter. More recently, desmosomes emerged as key structures that are compromised in various skin blistering disorders and cardiomyopathies. Advances in microscopy, including volume electron microscopy techniques such as focused ion beam scanning electron microscopy (FIB SEM), are continuing to deepen our understanding of desmosome structure and function. Using FIB SEM in parallel with optical imaging approaches, our lab made the surprising observation that the endoplasmic reticulum (ER) forms frequent associations with desmosomes. We find that ER tubules are stably anchored at desmosomes through ER associations with both keratin filaments and the desmosome plaque. Interestingly, adherens junctions initially recruit ER to nascent cell-to-cell contacts followed by stabilization of ER tubules at desmosomes. Further, ER tubules form contacts with the plasma membrane adjacent to desmosomes and adherens junctions. ER-plasma membrane contacts are known to regulate both calcium homeostasis and non-vesicular lipid transport at the plasma membrane. Indeed, we observe that disruption of intercellular junctions causes loss of peripheral ER organization and alterations in membrane lipid content. The structural and functional integration of cell junctions and the ER is likely to play key roles in heart and skin diseases characterized by loss of desmosome adhesion.

Presentation number: 2.1

Topic: Invited Talk

Regulation of Planar Cell Polarity by Atypical Cadherin CELSR1

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Planar cell polarity (PCP), the collective polarization of cells along a tissue plane, is essential for embryonic development and tissue patterning. Disruptions in the PCP pathway result in developmental disorders ranging from spina bifida and cardiomyopathies to tissue patterning defects of the inner ear and skin. A hallmark feature of PCP is the asymmetric localization of core PCP proteins Fz6 and Vangl2 at an intercellular junctional complex organized by cadherin family member Celsr1. Our studies of Celsr1 in mouse revealed that Celsr1 functions not only as a trans-adhesive molecular bridge, but also as an organization of Fz6 and Vangl2 asymmetry at cell junctions through lateral, cis-interactions and dimerization. These studies reveal key roles for Celsr1 adhesion in vertebrate development. Furthermore, Celsr1 mutations occur in patients with developmental defects such as congenital heart defects and neural tube defects, and in patients with epidermal-derived tumors such as carcinomas and melanoma. We hypothesized that these human disease-associated Celsr1 mutations perturb PCP establishment and function by impairing Celsr1 adhesion. To test this possibility, the function of WT Celsr1 and a panel of Celsr1 mutants were assessed using a combination of cell adhesion assays, advanced optical imaging, and in vivo murine genetic approaches. We identified mutations in the Celsr1 cadherin repeats that were defective in cell adhesion as determined by the ability to accumulate at cell-cell borders and to form stable adhesive interactions as assessed by fluorescent recovery after photobleaching. Interestingly, mutations identified in malignant melanoma result in Celsr1 variants that display significantly reduced adhesive function and disrupt PCP in vivo. In addition to loss-of-function mutants, we also identified human Celsr1 variants with gain-of-function activity. Overall, our findings indicate that Celsr1 adhesive interactions coordinate tissue polarity and suggest that Celsr1 adhesion and PCP are altered in both human developmental disorders and skin cancers.

Presentation number: 2.2

Topic: Varia

The Microscopic Anatomy of the Placental Villous Tree in Health and Disease

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Introduction: The gross anatomy of the placenta and the morphology of the villous tree have been described adequately in the past. It is well established that the weight of the placenta plays a crucial role in the development of the fetus in-utero and after birth through prenatal programming. The pregnancy-related disorders like fetal growth restriction (FGR), preeclampsia (PE) and gestational diabetes mellitus (GDM) have a dysfunctional placenta. Though the pathogenesis of these diseases is well understood, the change in the microscopic anatomy of the placenta has not been researched well and unique histopathological features have not been identified.

METHODS: Over past 10 years, we have investigated placentas from healthy and compromised pregnancies. With help of 3D-Microscopy and unbiased Stereology we have analyzed the villous tree and the feto-maternal (trophoblast) barrier quantitatively.

RESULTS: In our studies, the density of the proliferative and non-proliferative trophoblast nuclei has been identified as a unique, discriminatory parameter between FGR and PE. In FGR, the density of non-proliferative nuclei is higher and the diffusion distance is greater. In PE, the density of proliferative nuclei is higher, whereas the density of non-proliferative nuclei is reduced. The partial volumes of contractile and non-contractile parts of the villous tree show a differential change across the pathologies. In GDM, the branching index of the villous tree was reduced significantly.

Discussion: The FGR and PE are often considered to share a common pathology, that is a poor placental perfusion. We show that these diseases have unique histopathological features.

Presentation number: 2.3

Topic: Embryology and Cell Biology

On the Slow Lane: Mechanisms Underlying the Axonal Transport of the Cytoskeletal Protein Spectrin

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Introduction:

Neurons rely on a continuous delivery of newly synthesized proteins from the cell body to function throughout life. Most proteins, including all cytoskeletal proteins, are conveyed by a very slow transport mechanism termed slow axonal transport. Although this transport mechanism has been discovered over 60 years ago by radio labeling experiments, it remains poorly understood because the high abundance of its cargos and its slow transport rate prevent the use of conventional labeling approaches to study it. Consequently, the molecular mechanisms that underly slow axonal transport as well as its physiological regulation remain largely unknown.

Here we developed a temporally controlled labeling approach to visualize the slow axonal transport of the cytoskeletal protein spectrin for the first time at endogenous, single neuron resolution in a living nematode.

Methods:

We combine temporally controlled labeling with super-resolution microscopy, genetics and biochemistry to identify the molecular mechanisms that underlies the slow axonal transport of spectrin in C. elegans.

Results and Discussion:

Surprisingly slow axonal transport of spectrin is bimodal, comprising fast runs and movements that are 100-fold slower than previously reported. Modeling and genetic analysis suggest that the two rates are independent, but both require kinesin-1 and the coiled-coil proteins UNC-76/FEZ1 and UNC-69/SCOC, which we identify as spectrin-kinesin adaptors. Whereas reduced transport resulted in a proximal spectrin accumulation, impairment of the axonal spectrin cytoskeleton resulted in excessive spectrin transport. This suggests a balance between the slow axonal transport of spectrin and its subsequent assembly into the axonal cytoskeleton.

Presentation number: 2.4

Topic: Varia

LGR-Receptor Expression in Enteric Nervous System Progenitor Cells - Fate Decision between Neural Proliferation and Neuronal Differentiation

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Introduction: Enteric neuropathies, such as Hirschsprung's disease, are life-threatening conditions with massive impact on the quality of life of patients and their families. However, the molecular mechanisms causing the underlying failure of development and maturation of the enteric nervous system (ENS) are still poorly characterized. In previous studies, we found a central involvement of Wnt signaling in the regulation of ENS-progenitor proliferation. Here, we hypothesize that the Wnt-regulator R-Spondin1 drives enteric neuron maturation via LGR4/5/6-receptors, extending the functions of the Wnt-regulatory-network in the ENS.

Methods: We used BrdU-incorporation, immunohistochemistry, Western blot, qRT-PCR, and spatial gene expression profiling to assess the influence of R-Spondin1 on murine and human ENS-progenitors. We employed FACS-analysis and mechanistically probed LGR-signaling human ENS-progenitors.

Results: R-Spondin1 stimulation significantly increased neurogenesis in murine and human ENS-progenitors. Surprisingly, this was paralleled by a reduced rate of proliferation in ENS cells expressing the R-Spondin-receptor LGR5. Instead LGR5 and LGR6 were increasingly expressed during of neuronal differentiation *in vitro* and *in vivo*, while LGR4 was upregulated in proliferative ENS-progenitor cells. This was underpinned by FACS-experiments in human ENS-progenitors and marks a receptor-dependent function of R-Spondin-signaling.

Conclusion: R-Spondins play a dual role and drive receptor-dependent fate-decision in ENS-progenitors. This marks a mechanistic distinction to other stem cell niches, such the intestinal crypt, and deepens our understanding of the involvement of the Wnt-regulatory-network in the cellular homeostasis of the ENS. Our results may therefore pave the way to unleash the regenerative capacity of the developing and mature ENS for future therapies of enteric neuropathies.

Presentation number: 2.5

Topic: Embryology and Cell Biology

Desmosomal Adhesion and Protective Effects of Apremilast in Pemphigus are Dependent on Plakoglobin Phosphorylation at Serine 665

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Introduction:

In the bullous autoimmune disease pemphigus, autoantibodies against the desmosomal cadherins desmoglein (Dsg)1 and Dsg3 cause loss of keratinocyte cohesion clinically represented by intraepidermal blistering. Recently, we found that cAMP increase by the phosphodiesterase-4-inhibitor apremilast represents a novel therapeutic strategy in pemphigus by stabilizing keratinocyte cohesion. This effect was paralleled by phosphorylation of the desmosomal plaque protein plakoglobin (Pg) at serine 665 (S665). Here, we investigate the mechanisms by which Pg phosphorylation at S665 is capable of stabilizing keratinocyte cohesion.

Methods:

In vivo pemphigus mouse model, *ex vivo* skin model, immunostaining, STED, AFM, electron microscopy

Results:

We recently established a phospho-deficient mouse model for Pg at S665 (Pg-S665A) which presented an altered expression of desmosomal proteins. In these mice, ultrastructural analysis showed a reduced number of desmosomes accompanied by diminished keratin insertion. Accordingly, the protective effect of apremilast against pemphigus autoantibody-induced skin blistering *in vivo* was diminished and apremilast failed to restore alterations of the keratin cytoskeleton in Pg-S665A-mice. Keratinocytes derived from Pg-S665A-mice revealed a disrupted keratin filament cytoskeleton, impaired intercellular adhesion and reduced single molecule binding strength of Dsg3. The impact of protective cAMP signaling was further confirmed in *ex vivo* human skin where cAMP increase augmented keratin insertion. Additionally, pPg(S665) was found to co-localize to desmoplakin and keratin filaments anchoring to desmosomes where cAMP increase accelerated assembly of desmosomes.

Discussion:

Phosphorylation of Pg at S665 is crucial for protective effects of apremilast in pemphigus and for maintenance of stable keratin filament anchorage to desmosomes.

Presentation number: 2.6

Topic: Varia

Elucidating the Mechanisms of GPR124/RECK/WNT7 Signaling

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Introduction: Developmental CNS angiogenesis and blood-brain barrier formation critically rely on WNT7 signaling within brain endothelial cells. This signaling pathway requires the cell-surface proteins GPR124 and RECK alongside classical WNT receptors of the FZD and LRP families. Although formation of a ternary GPR124/RECK/WNT7 complex has been shown, its interaction dynamics with classical WNT receptors or other cell-surface proteins remain unclear. This study was designed to elucidate these interactions using a combined chemical crosslinking/affinity chromatography approach.

Methods: bEnd.3 brain endothelial cells were genetically modified to express biotinylated RECK (bRECK) instead of the endogenous protein. Next, bEnd.3 bRECK cells with and without *Gpr124* knockout were generated using the CRISPR/Cas9 system. These cells were either stimulated or not with WNT7 by co-culturing with WNT7-expressing or parental HEK293 cells. Protein-protein interactions were stabilized *in situ* using the chemical crosslinker DSP. Crosslinked bRECK protein complexes were isolated by streptavidin agarose and eluted proteins identified by mass spectrometry.

Results: Mass spectrometry analysis confirmed GPR124 and WNT7 as predominant RECK binding partners. Interestingly, the RECK/WNT7 complex independently recruited classical WNT receptors, without requiring GPR124. Additionally, several cell surface proteins involved in cellular adhesion and motility were identified.

Discussion: Our data suggest that binding of WNT7 to RECK results in recruitment of classical WNT receptors with GPR124 potentially playing a role in receptor activation rather than recruitment. Ongoing investigations aim to clarify the role of GPR124 role in WNT7 signaling and confirm direct binding of RECK/WNT7 to classical WNT receptors in a cell-free system.

Presentation number: 3.1

Topic: Neuroanatomy

Repetitive Transcranial Magnetic Stimulation (Rtms) induces Plasticity of Excitatory Synapses in Acute Human Neocortical Slices

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Introduction: Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that modulates cortical excitability through the intact skin and skull. Widely used in clinical settings for diagnostic and therapeutic purposes, the cellular and molecular mechanisms underlying rTMS-induced plasticity in the human brain remain largely unknown. Most mechanistic data on rTMS-induced plasticity come from animal models. Here, we investigated the effects of rTMS on living human neocortical brain tissue.

Methods: We used cortical access tissue obtained during routine neurosurgical procedures, which is typically discarded. Acute neocortical slices were prepared within 15 minutes after tissue extraction. Using whole-cell patch-clamp recordings, light and electron microscopy, and molecular biology techniques, we assessed the effects of rTMS parameters on the plasticity of excitatory synapses onto layer 2/3 pyramidal neurons.

Results: Our findings provide the first experimental evidence that an intermittent theta burst stimulation protocol induces long-term potentiation of excitatory neurotransmission in human cortical tissue. These functional changes were accompanied by structural reorganization and changes in methylated mRNA transcripts.

Discussion: Our results support the development of more effective rTMS protocols tailored to individual treatments, thereby enhancing the therapeutic potential of rTMS in clinical settings.

Presentation number: 3.2

Topic: Neuroanatomy

Regional Heterogeneity of Morphology and Immune Cell Accumulation in the Leptomeninges

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Introduction

Three layers of meninges surround the central nervous system: the dura mater, the arachnoid mater, and the pia mater. The arachnoid mater contains the subarachnoid space, interwoven with numerous blood vessels. Recent studies have highlighted the leptomeninges' significant role in recruiting immune cells. Due to region-specific pathological alterations of the leptomeninges in multiple sclerosis, we propose a regional heterogeneity in leptomeningeal morphology and immune cell distribution in both human and murine brain tissues.

Methods

The morphology and immune cell distribution of human meninges from various CNS regions were examined using (immuno)histochemical analysis in *post-mortem* tissues. Regional gene expression patterns were compared with next-generation bulk RNA and single-nucleus sequencing analyses. Immune cell distribution and meningeal morphology under neuroinflammatory conditions were analyzed in a murine multiple sclerosis model by (immuno)histochemical analyses.

Results

Meningeal morphology and blood vessel distribution showed significant region-specific heterogeneity in humans. This pattern was also noted, though to a lesser extent, in murine leptomeningeal tissues, particularly in overall meningeal morphology. Next-generation sequencing analyses of gene expression levels revealed significant differences between the basal cistern and other regions. Both human and murine tissues exhibited heterogeneous immune cell distribution patterns. Under inflammatory conditions, a distinct pattern of immune cell accumulation was observed in the meninges at the CNS base and around the quadrigeminal plate.

Discussion

Our studies show that the leptomeninges are a highly specialized, heterogeneous CNS envelope with region-specific characteristics, potentially playing an important role in the development and progression of neuroinflammatory disorders.

Presentation number: 3.3

Topic: Neuroanatomy

Identification of Different Response Types to Entorhinal Denervation by Means of Repeated Time Lapse Imaging of Single Dentate Granule Cells In Vitro

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Introduction:

The reorganization of synaptic connections is an important mechanism contributing to the recovery of neuronal networks from brain injury. In recent years, we established an in vitro denervation model using organotypic slice cultures to visualize structural changes of dentate granule cells (GCs) following entorhinal denervation. Here we used this model to analyze spine density changes of denervated and non-denervated dendritic segments within the same individual GCs.

Methods:

We transduced neurons using localized AAV-injections to express tdTomato in GCs and eGFP in entorhinal projection neurons. This allowed us to visualize both the innervating entorhinal fibers and their target neurons. Furthermore, we could readily distinguish segments innervated by entorhinal fibers in the medial molecular layer (MML) from those receiving other afferents in the inner molecular layer (IML). Time-lapse confocal imaging was used to visualize multiple dendritic segments of single neurons in denervated and non-denervated control cultures.

Results:

Two days post entorhinal lesion, average spine loss in the denervated MML was 14% of all spines while spine density increased by 20% in the non-denervated IML. However, individual neurons but also individual segments within single neurons showed a broad variability in spine density changes in both layers. Different response types to denervation were identified and distinguished.

Conclusions:

Granule cells show variable and layer-specific spine density changes after entorhinal denervation. These changes are mostly contrary and counterbalancing each other in the IML and MML, suggesting a quick and short-lasting response in the IML compensating for the denervation-induced loss of spines in the MML.

Presentation number: 3.4

Topic: Neuroanatomy

Older Pigeons Show Higher Neuron Numbers than Younger Pigeons

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Many data from the literature assume a decreasing cell number in the aged mammalian brain and associate this with a decline of (cognitive) brain functions. But this has not yet been conclusively proven and it is also not clear whether such morphological age-related changes are the same in all vertebrates or whether there are special features in e.g., birds.

Here we analyzed cell and neurons numbers of pallium, subpallium and cerebellum in groups of young adults (10 months) and senescent (>10 years) pigeons using the isotropic fractionator method (i.e., cell counts based on tissue homogenates).

Overall cell numbers within the pallium and subpallium but not the cerebellum differed significantly between groups and were on average 46% and 28% higher in old as compared to young animals. Overall cell density was also significantly higher in the old age group. Specifically, neuron number as well as neuron density of pallium and subpallium were significantly higher in old animals, with an average increase of 80% and 45%, or 86% and 31%, respectively. Again, no such differences were found for the cerebellum. Comparing neuronal to non-neuronal cell ratios, we only found a significant difference for the pallium with an average increase of 23% in older pigeons.

Our results hint at a distinct life-long neurogenesis across the whole cerebrum what lies in contrast with aging of the mammalian brain. It might be worthwhile to further investigate age-related structural and especially functional changes in non-mammalian species like birds to deepen our knowledge of the underlying processes.

Presentation number: 3.5

Topic: Neuroanatomy

Maintenance of a Central High frequency Synapse in the Absence of Synaptic Activity

Sascha Lessle, [1]

Lena Ebbers, [2], Yvette Dörflinger, [1], Simone Hoppe, [1], Michaela Kaiser, [1], Hans Gerd Nothwang, [2, 3], Christoph Körber, [1]

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Neural circuit formation and maintenance has long been considered to be mostly activity-dependent. Here, we explore whether the absence of neurotransmission influences the maintenance of the calyx of Held synapse, a giant auditory brainstem synapse known for its high fidelity, high frequency neurotransmission. We investigated this potential activity-dependency by inhibiting synapse activity by cell specific expression of the tetanus toxin light chain (TeNT).

Globular bushy cells of the ventral cochlear nucleus, which give rise to the calyces, were specifically targeted by usage of juvenile mice expressing cre-recombinase under the Math5-promotor. Using a cre-dependent adeno-associated viral vector (AAV), we delivered the genetic construct for TeNT-EGFP to the VCN by stereotaxic injection. Synaptic silence was determined by electrophysiology after 14 days of TeNT expression. After 21 days of TeNT expression and 10 days of synaptic silence, calyx structure was examined by immunofluorescence and correlative light and electron microscopy.

Evoked neurotransmission was abolished after two weeks of TeNT expression. The expression of TeNT did not alter the general structure (incl. fenestration) of calyces. TeNT did not affect the number of active zones or the composition of postsynaptic AMPA-type glutamate receptors. Electron micrographs showed a loss of synaptic vesicles near actives zones whereby remaining vesicles tended to be bigger.

Our results indicate that synaptic connectivity in the auditory brainstem is mostly genetically hardwired and does not rely on activity.

Presentation number: 3.6

Topic: Neuroanatomy

Singe-nucleus RNA-sequencing of the Motor Cortex in Huntington's Disease Mice Reveals Mechanisms of Neuronal Vulnerability to Degeneration

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Introduction: A common feature of neurodegenerative disorders is selective vulnerability, where certain neurons succumb to disease early, while others remain spared. Huntington's disease (HD) is an incurable hereditary movement disorder caused by a CAG repeat expansion in the Huntingtin gene, which causes degeneration of the striatum and neocortex. In the cortex, glutamatergic projection neurons are highly susceptible to HD, while GABAergic interneurons are more resistant. The molecular underpinnings of these differences are not well understood.

Methods: Here, we have performed single-nucleus RNA-sequencing (snRNA-seq) analysis of the primary motor cortex from the R6/2 mouse model of HD at different disease stages.

Results: Strikingly, snRNA-seq revealed a pronounced disease-related transcriptomic shift within the glutamatergic, but not GABAergic or non-neuronal cell clusters. Tissue sampling at different time points allowed us to delineate a two-stage disease trajectory with distinct changes at early and late stages. Analysis of differentially expressed genes and pathways demonstrated progressive dysregulation of neuronal cell-type identity in the HD cortex. Among the top dysregulated gene categories, we also found genes related to protein homeostasis and ER stress. Interestingly, several receptors for autophagy of the ER (ER-phagy) were upregulated in HD mice. In agreement with these results, we observed increased ER-phagy in cellular models of HD.

Discussion: Taken together, these findings advance our understanding of neuronal vulnerability to degeneration, and point to ER-phagy as an important new mechanism in the pathogenesis of HD.

Presentation number: 4.1

Topic: Method Session of the Young Anatomists Mentoring Program

FLIM-FRET a Powerful Tool to Study Protein-Protein Interactions in Living Cells

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Various cellular and molecular processes carried out by proteins are orchestrated by protein-protein interactions (PPIs). The extent of these interactions varies according to protein composition, type of molecular interaction, affinity and whether the associations are stable or transient. In general, it is of particular importance to study how PPIs modulate structure-function-relationships of macromolecules. FLIM-FRET, or Fluorescence Lifetime Imaging Microscopy-Förster Resonance Energy Transfer, is an excellent approach to monitor dynamic PPIs and visualise their localisation in living cells with high tempo-spatial resolution. FRET is a physical, non-radiative process that occurs between an excited fluorophore (donor) and an acceptor fluorophore, while FLIM provides a sensitive approach to measure and quantify FRET. Once the acceptor is in close proximity (<10 nm) to the fluorescent donor, FRET energy transfer occurs. Due to this distance dependency, the two fluorophore labelled proteins undergoing FRET must physically interact. FLIM-FRET is a unique tool for the investigation of living cellular systems and intracellular signaling processes. In addition, this technique has great potential for investigating the role of PPIs to understand molecular characteristics of biological systems and changes due to disease processes or drug treatment.

Presentation number: 4.2

Topic: Method Session of the Young Anatomists Mentoring Program

Electrophysiological Whole-Cell Patch-Clamp Recordings of Neurons

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Introduction: The function of neuronal networks is facilitated by its abundance of complex neurons that form connections with each other via electro-chemical synapses. The signal transmission and propagation relies on the influx and efflux of ions across the neuronal cell membrane that result in measurable currents and changes of membrane potential.

Methods: The whole-cell patch-clamp technique is a method that enables the detailed investigation of these ionic currents and membrane potentials in individual neurons. By forming a tight seal with the cell membrane and subsequently rupturing a small patch to access the intracellular compartment, this technique allows precise measurement of the electrical properties of neurons in real-time resolution. Thereby, synaptic transmission, plastic adaptions, and e.g., the influence of pharmacological interventions on neuronal function can be investigated. By performing paired recordings of connected neurons, it is furthermore possible to examine specific synapses and microcircuits, thus, gaining insights into local connectivity and its plasticity.

Discussion: Despite its unequivocal benefits in neuroscientific research, the whole-cell patch-clamp technique poses some limitations. It requires technical skill and is time consuming, making it difficult to manage high throughput experiments. Additionally, the local assignment of recorded events to their dendritic origin is not possible and due to leaky membranes, the strength of distal synapses can be underestimated as compared to proximal once. Nevertheless, the whole-cell patch-clamp technique is a crucial method in basic neuroscience, enabling the investigation of functional properties and changes in neuronal networks.

Presentation number: 4.3

Topic: Method Session of the Young Anatomists Mentoring Program

Unbiased Stereology – Quantifying Variables in Whole Organ by Studying Thin Sections

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Thin sections of the organ of interest are studied routinely under a microscope. Often comparisons are drawn between groups based on the subjective, qualitative findings from the study of the thin sections and / or the findings are thought to be representative of the whole organ. For example, if a section from the entorhinal cortex is being studied under the microscope, how can one be sure that the thickness of the layer II, or the density of the neurons in layer III, as measured in the section, is representative of the whole entorhinal cortex. Can these variables be reliably compared between control and Alzheimer's samples?

Unbiased Stereology provides a statistically robust framework for quantifying variables like number, volume, length, and surface in an unbiased, efficient and accurate manner. The backbone of this method is the systematic random sampling. Just like in opinion polls, where a representative section of the population is sampled at random, the sampling of the tissue block from the whole organ must be at random. The rules of selection of the sections are determined a priori without making any assumptions about the shape, the size, the orientation, and the distribution of the feature that is being quantified. In this talk, I'll take you through the step-by-step process of unbiased stereology, right from sample collection to the final data analysis, with placenta as the surrogate organ.

Presentation number: 4.4

Topic: Method Session of the Young Anatomists Mentoring Program

Chromatin Immunoprecipitation Sequencing (ChIPseq)

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Dysregulated gene expression can lead to improper cell functions and is implicated in numerous diseases and developmental disorders. Consequently, regulation of gene expression is an important and complex mechanism in all cells and organisms to ensure that genes are expressed only at appropriate times and locations. To achieve this, cells utilize a comprehensive set of regulatory tools, including the modulation of chromatin accessibility via histone modifications and the control of transcription rates by transcription factors.

Investigation into transcriptional regulation, both in pathological conditions and in normal physiology, is very important to understand the underlying mechanisms and identifying potential therapeutic targets. One prominent method for examining differences in transcriptional regulation involves the analysis of transcription factor binding sites and site-specific histone marks, which are associated with transcriptional regulation. This is achieved through the immunoprecipitation of these factors or histones along with the chromatin fragments to which they bind (ChIP). Subsequent sequencing of these fragments using next-generation sequencing technologies, followed by comprehensive bioinformatics analysis, delineates the regulatory landscape of the analyzed cells or tissues.

Thus, this approach, called Chromatin Immunoprecipitation Sequencing (ChIPseq), facilitates a deeper understanding of the molecular mechanisms underlying gene regulation in both normal and disease states. Additionally, it enables the correlation of phenotypic outcomes with specific dysregulations, the identification of novel therapeutic targets, and the development of innovative therapeutic strategies.

Presentation number: 4.5

Topic: Method Session of the Young Anatomists Mentoring Program

In Utero Electroporation Technique for Brain Development Studies in Mice

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Understanding the complex development of the mammalian brain and its specific neuronal subtypes is facilitated by the targeted manipulation of constituent cells and their extracellular environment in a spatio-temporal manner. This is particularly true in the mammalian cerebral cortex, where neurogenesis, neuronal migration and maturation are precisely regulated, and manipulations targeting subpopulations or small groups of cells have provided valuable insights into the mechanisms underlying these events. The *in utero* electroporation (IUE) technique allows the manipulation of gene expression in subsets of neuronal cells during different stages of brain development. This approach has several advantages over other methods for studying specific steps of brain development *in vivo*, from proliferation to migration and synaptic integration. Once electroporated, the cells can be tracked. In addition, their morphological, transcriptomic and physiological properties can be analysed. Unlike genetic approaches such as knockout mice, whose disadvantages include severe abnormalities that may be masked by functional compensation or lethality before cortical development, IUE may circumvent these particular issues. Acute overexpression, knockdown or reintroduction of a particular gene by IUE may reveal a function of the gene product otherwise veiled. As such, it offers a wide range of applications and is a powerful tool for transfecting and manipulating neural precursor cells of the rodent brain *in vivo*.

Presentation number: 4.6

Topic: Method Session of the Young Anatomists Mentoring Program

Coursing and Terminal Ramification of Peripheral Nerves in Gross Anatomical Specimens – Application of the Modified Sihler-Technique in Clinical Morphology

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Visualizing and examining peripheral nerves in their intramuscular or intramural and highly ramified terminal course has always been a challenge for morphological disciplines. In addition to the classic methods of anatomical dissection and reconstruction using histological section series, it is possible to stain peripheral nerves in large anatomical specimens accompanied by creating a transluminescence for better visibility and subsequent examination. One such technique is the modified Sihler technique, which is becoming increasingly popular in clinical anatomy. Originally developed at the end of the 19th century by Christian Sihler for fast staining of peripheral nerves in fresh muscle fibers, this technique was changed by many modifications in the 20th century, resulting in a time-consuming but effective and valuable staining of peripheral nerves in gross anatomical specimens. After collecting samples, an eight-step process is used involving various solutions for fixation, maceration, and staining. The actual analysis of the nerve course, using transillumination and optical magnification, occurs after creating transparency. Throughout these steps and in the laboratory's technical equipment, there are potential challenges that we aim to highlight while also offering solutions. Additionally, we present insights into potential application areas, technical tips, and a careful evaluation of the advantages and disadvantages of this technique.

Presentation number: 4.7

Topic: Method Session of the Young Anatomists Mentoring Program

Organotypic Slice Cultures of the Hypothalamic Arcuate Nucleus as a Platform to Study the Impact of Alimentary Substances on Neurons and Glia

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Introduction: Through nutrition, we are constantly exposed to a plethora of natural and artificial substances - some are beneficial, some are harmful, many are both - depending on the amount we take in. Neurons in the arcuate nucleus, together with local glia cells, sense blood-borne signals like insulin and leptin through a less strict blood-brain barrier to gain information about the current supply of energy and nutrients. However, the permissive barrier may make cells in this region vulnerable to harmful substances.

Methods: We are establishing organotypic slice cultures (OSC) as a platform to study neuroprotection, neuromodulation, and neurotoxicity of alimentary substances in the hypothalamic arcuate nucleus. We will examine whether arcuate nucleus OSCs serve as a suitable system to bridge the gap between cell culture models and in vivo experiments.

Results & Discussion: In this talk I will present our preliminary work on establishing arcuate nucleus OSCs from adult animals and discuss potential applications and limitations.

Presentation number: 5.1

Topic: Embryology and Cell Biology

The Molecular Logic of Cell Fate Control

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We address fundamental questions in developmental biology: How are cell identities defined and maintained to provide the right cell type at the right time for proper embryonic development? What are the central molecular players in cell-fate choice? How is their function orchestrated to facilitate proper development?

We tackle these questions by focusing on some of the first differentiation decisions taken during embryonic stem cell commitment, when cells of the naïve pre-implantation epiblast transition to a post-implantation epiblast fate upon implantation into the uterus. This latter cell state is termed formative pluripotency. The transition from naïve to formative pluripotency can be modelled in embryonic stem cells, providing a valuable system to study these processes.

Naïve pluripotency is sustained by a self-reinforcing gene regulatory network (GRN) comprising core and naïve pluripotency-specific transcription factors (TFs). Transitioning from the naïve state to a formative pluripotent state represents a critical cellular fate decision crucial for generating an entire organism from a few pluripotent cells. Our large-scale systems biology approaches have revealed that the exit from naïve pluripotency is directed by a core set of signaling pathways. However, the mechanisms by which changes in pathway activities translate into the decommissioning of the naïve GRN and the initiation of the formative GRN remain largely unknown.

Our recent research identifies a critical and previously unexplored function of AKT signaling in controlling the nuclear localization of FoxO transcription factors to establish formative cell identity. Although FoxO-TFs are well-known regulators of longevity and metabolism, their involvement in cell-fate transition has been less examined.

In naïve ESCs and in the naïve E4.5 epiblast *in vivo*, phosphorylated AKT prevents FoxO-TFs from entering the nucleus. At the onset of differentiation, PTEN-induced reduction of AKT activity enables shuttling of FoxO-TFs into the nucleus, both *in vitro* and in the rosette-stage of the E4.75 epiblast. Inside the nucleus, FoxO-TFs enforce the transition from naïve to formative pluripotency by activating formative-specific enhancers and repressing naïve-specific ones, suggesting a dual role for FoxO-TFs in decommissioning the naïve state while establishing the formative gene expression program.

We discovered that FoxO1 binds to around 2000 target enhancers and significantly overlaps with key pluripotency factors such as NANOG, OCT4, and OTX2 on chromatin. Remarkably, FoxO1 binding is a more reliable indicator of gene expression changes during differentiation than other pluripotency TFs, both *in vitro* and *in vivo*.

Together, these findings highlight FoxO1 as a novel pluripotency transcription factor with a crucial role in instructing early embryonic cell fate transitions. Furthermore, we provide a mechanistic explanation for the role of AKT signaling during peri-implantation development.

Presentation number: 5.2

Topic: Embryology and Cell Biology

Prenatal Stress Affects CXCR4/SDF1 Signaling in Abdominal Wall Development

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Introduction

In contrast to the formation of muscles of the limb girdles, limbs and intrinsic tongue muscles all of which originate from long-range migrating progenitors, the lateral body wall muscles develop by direct outgrowth of the dermomyotomes, which add to the extension of the hypaxial myotomes. The G-protein-coupled receptor, CXCR4, and its ligand, stromal derived factor 1 (SDF-1), have been shown to be implicated in various progenitor cell migration events during embryonic development.

Methods

In this study, CXCR4 has been observed to be expressed in the ventrolateral lips of the dermomyotomes in the interlimb region, in a similar domain to that of MyoR and Pax3. Loss-of-function and gain-of-function experiments could demonstrate the importance of CXCR4/SDF-1 signaling pathway in lateral body wall formation. Using the avian model, we investigated the influence of Dexamethasone, a synthetic glucocorticoid hormone, on the CXCR4/SDF-1 axis and its consequences for the development of the ventral midline of the trunk.

Results

Prenatal stress can impair normal embryonic development and depending on the exposure to stress factors, can result in multiple malformations. Treated embryos regularly showed abdominal wall defects comparable to gastroschisis or omphalocele in humans. Our preliminary data indicate that markers of the ventrolateral lip of the dermomyotomes and for the lateral plate mesoderm along with cytoskeletal proteins, are significantly altered under the influence of Dexamethasone.

Discussion

This study demonstrates the vulnerability of body wall closure to prenatal stress conditions and points to an involvement of the CXCR4/SDF-1 signaling pathway in this complex process.

Presentation number: 5.3

Topic: Embryology and Cell Biology

Allergens Activate Tracheal and Olfactory Tuft Cells Leading to Production of Eicosanoids and Acetylcholine, Eicosanoids Subsequently Direct Stem Cell Proliferation in the Olfactory Epithelium

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Objectives: Tuft cells (TC) are rare epithelial cells in the nasal respiratory and tracheal epithelium of mice and humans, but abundant in the olfactory epithelium. TC produce a unique cassette of mediators including Prostaglandins, Cysteinyl leukotrienes (CysLTs) and Acetylcholine. Whether allergens are recognized directly by TC, the full panoply of allergen-elicited TC mediators and the consequences of TC activation are remaining questions. **Methods:** Whole mount Ca^{2+} imaging of noses and tracheas from $Chat^{cre}$-GCaMP6f was employed to define ligands of TC. Nasal and tracheal whole mounts of WT- and TC-deficient mice ($Pou2f3^{-/-}$) were used to assess TC-specific allergen-elicited mediators by ELISA, Lipidomics and HPLC. Allergen-elicited compositional olfactory changes were assessed by FACS, Bulk/single cell sequencing or immunofluorescence in *Pou2f3*$^{-/-}$, *Chat*^{cre}-*Ltc4s*$^{fl/fl}$ (with specific deletion of CysLTs in TC) mice. **Results:** The protease-rich allergen *Dermatophagoides pteronyssinus* (*DerP*, house dust mite), the mold allergen *Alternaria*, the protease papain, a protease receptor 2 (Par2) agonist and ATP trigger acute increases of intracellular Ca^{2+} concentrations in olfactory and tracheal TC. The allergens *DerP* and *Alternaria* induce a TC-dependent generation of CysLTs and PGD_2 in the nose and trachea. In the trachea *Alternaria* induces a TC-dependent release of Acetylcholine. Inhalation of *Alternaria* and ATP induces a TC-dependent proliferation of horizontal basal stem cells in the olfactory epithelium, which is diminished in mice lacking the CysLT producing enzyme specifically in TC. **Conclusions:** Allergens activate airway TC, leading to a release of different effector molecules (CysLTs, Prostaglandins, Acetylcholine) and subsequently to proliferation of stem cells in the olfactory epithelium.

Presentation number: 5.4

Topic: Embryology and Cell Biology

Role of Bcl11a Transcription Factor in Cerebellar Development

Franziska Anna Seigfried, [1]

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Objective:

Bcl11a was previously demonstrated to be essential for the development of the murine neocortex and the dorsal spinal cord (Simon et al., 2020). During development, Bcl11a is also expressed in other brain regions and neuron types, including cerebellar Purkinje cells. Recently, variations of BCL11A in humans have been reported to be associated with cerebellar hypoplasia suggesting this factor to be involved in cerebellar development.

Methods:

To determine functions of Bcl11a during cerebellar development we generated mice with a hindbrain-specific mutation of the Bcl11a gene ($Bcl11a^{flox/flox}$; engrailed1-Cre) Using these mice we determined functions of Bcl11a on a molecular, cellular, and morphological level.

Results:

Hindbrain-specific loss of Bcl11a resulted in a 53% decrease in cerebellar size, abnormal foliation, and impaired development of Purkinje cells at P30. We observed massively reduced survival as well as spatial misdistribution of Bcl11a mutant Purkinje cells. This was followed by decreased postnatal proliferation of granule cells. To identify putative target genes, through which Bcl11a exerts its functions during cerebellar development we selectively isolated Bcl11a mutant Purkinje cells and compared their transcriptomes to wildtype controls.

Conclusions:

Our current data suggest Bcl11a to be essential for cerebellar development. Phenotypes observed in Bcl11a mutant mice display remarkable similarities to the neuroradiological findings observed in humans with a mutation of the BCL11A gene. Thus, hindbrain-specific conditional deletion of Bcl11a in mice might serve an excellent experimental model for the experimental analysis of the pathogenesis of the corresponding neurodevelopmental disorders in humans.

Presentation number: 5.5

Topic: Neuroanatomy

Generation of a human peripheral nerve model from induced pluripotent stem cells using organoids, assembloids and organ-on-a-chip technology

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Objective: The peripheral nervous system (PNS) transmits sensory information to the brain and motor signals to muscles and organs, enabling movement and perception. PNS diseases cause symptoms like paraesthesia, neuropathic pain, and movement disorders. These conditions are poorly understood, and current models lack the complexity of human peripheral nerves.

Methods: Neural and mesodermal organoids are generated from human iPSCs and combined as assembloids to create peripheral nerve-like structures. Their use in a nerve-on-a-chip platform is explored. Cultures are analyzed using immunofluorescence, single-cell RNA sequencing, transmission electron microscopy, and live cell imaging.

Results: We developed two types of organoids to model the peripheral nervous system. "Nerve seeds" were created by modulating WNT, TGFβ, and SHH pathways. These contain both CNS cells and neural crest cells (NCCs). NCCs form sensory ganglia and Schwann cells, while CNS tissue contains OLIG2-positive motoneuron precursors. Blood vessel organoids were generated by modulating WNT, BMP4, and VEGF signaling, resulting in connective tissue with a vascular network and hematopoietic cells upon stimulation. Co-culturing these organoids as assembloids led to neural vascularization, microglia infiltration, and peripheral nerve fiber sprouting. Combining both organoids in an organ-on-a-chip platform could create peripheral nerve models with directed nerve outgrowth toward target tissues.

Conclusions: We established all prerequisites to develop a human peripheral nerve-on-a-chip platform. It will contain all components of the peripheral nerve and allow directed nerve growth towards a separate target tissues. It will offer an in vitro platform for disease modeling, drug testing, and infection biology.

Presentation number: 5.6

Topic: Embryology and Cell Biology

Expression of SOD1 and SOD2 antioxidant enzymes in rat preimplantation embryos

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Introduction. Superoxide dismutase 1 (SOD1) and 2 (SOD2) are antioxidant enzymes which transform the toxic superoxide radical into oxygen and less toxic hydrogen peroxide. The aim of our work was to map the possible occurrence of both SOD1 and SOD2 in rat preimplantation embryos by immunofluorescence method.

Methods. Adult Sprague-Dawley females were mated with males of the same strain. The presence of a vaginal plug was considered as the evidence of successful mating. Females were euthanized with a lethal dose of anesthetic on the first (D1), third (D3) and fifth days of pregnancy (D5). Embryos were obtained by flushing out the fallopian tubes and uterine horns. Embryos were fixed in 1% paraformaldehyde and permeabilized in 0.5% TRITON X-100. Individual superoxide dismutases were stained with the corresponding antibodies diluted 1:100 (anti-SOD1, #bs-10216R-A488, Bioss, USA, and anti-SOD2, #bs-1080R-Cy3, Bioss, USA). Cell nuclei were counterstained with DAPI (4', 6-diamidino-2-phenylindole) and embryos were observed under a confocal microscope.

Results. Both investigated enzymes were present in rat during the preimplantation phase of pregnancy from the unfertilized egg to the blastocyst, but never in the nuclei. SOD1 was observed diffusely in the whole cytoplasm, while SOD2 formed small clusters in the cytoplasm.

Discussion. The fact that both antioxidant enzymes are present in the early embryo during the entire preimplantation phase of pregnancy indicates their great importance in protecting the new individual against oxidative stress.

Presentation number: 6.1

Topic: Clinical and Gross Anatomy

Exploring Feasibility of Nerve Transfer Techniques in the Leg: A Translational Approach to Clinical Anatomy Research

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Nerve transfer techniques have gained significant attention as a means of restoring motor and sensory function in patients with peripheral nerve injuries. While extensive research has been conducted on nerve transfers in the upper extremities, their application in the lower extremities, particularly the leg, remains relatively unexplored. This study investigates the feasibility of nerve transfer techniques targeting the tibial nerve, deep fibular nerve, and superficial fibular nerve, with a translational approach that integrates anatomical research and clinical implications. Previous studies have highlighted the potential of the tibial nerve as a donor nerve due to its robust motor fibers and proximity to key muscle groups in the lower leg. In contrast, the deep and superficial fibular nerves, which innervate the anterior and lateral compartments of the leg, respectively, have been identified as critical targets for reinnervation in cases of nerve injury. This research reviews the cadaveric studies and imaging analyses to demonstrate the anatomical courses, nerve diameters, and branching patterns of the motor nerves of the lower limb, providing a comprehensive map for potential nerve transfer procedures. Building on the foundational works which demonstrated successful tibial-to-deep fibular nerve transfers in a limited series of clinical cases, this study aimed to further explore the anatomical compatibility and functional outcomes of these transfers on cadavers. The nerve transfers underscores the need for precise donor-recipient nerve matching to optimize recovery. Our findings corroborate these studies, suggesting that nerve transfers involving the tibial, deep fibular, and superficial fibular nerves are not only feasible but also hold significant promise for improving lower limb function, particularly in cases where direct nerve repair is not viable. The outcomes of this work bridges the gap between anatomical theory and clinical practice, emphasizing the need for individualized surgical planning based on detailed anatomical understanding. The study provides a solid foundation for future clinical trials aimed at optimizing nerve transfer techniques in the leg, potentially revolutionizing treatment protocols for lower extremity nerve injuries.

Presentation number: 6.2

Topic: Clinical and Gross Anatomy

The effect of functional hemimandibular overload on the inner structure of the mandibular condyle: Exploring a cause of condyle hyperplasia

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Introduction: An altered distribution of mandibular loading has been proposed as a possible cause of condyle hyperplasia (CH), a condition where one of the condyle processes (CPs) grows more than its counterpart, leading to mandibular asymmetry. An altered distribution of functional loading has been proposed as a cause. Using a mouse model of asymmetric masticatory load, we assessed the association between morphometric parameters of the trabecular bone (TB) of the CPs and the mandibular load regime.

Methods: Micro-CT images of adult mouse hemimandibles were used. Fourteen (8 males, 6 females) were underloaded (UL) due to unilateral masseter muscle paralysis; 11 were the contralateral, overloaded (OL) hemimandibles (6 males, 5 females); 14 were not-intervened (NI), control, hemimandibles (6 males, 8 females). Using Dragonfly™ and ad-hoc statistics, different TB parameters were calculated and compared.

Results: Principal component analysis showed that the main differences were found between UL and OL-NI CPs; between these two, main differences were found between sexes and, secondarily, between load types. Overall, OL were more isotropic, had more trabeculae, lower connectivity density, and larger bone volume fraction than NI; overall, robusticity values were larger in females than males.

Discussion: An increase in mandibular loading is associated with changes in the TB structure of the CP, which affects males and females differently. Changes suggest an increased remodeling activity in the OL group, with more robust features in females. Since women are comparatively more affected by CH, further studies are needed to confirm a link between load, sex and CH.

Presentation number: 6.3

Topic: Clinical and Gross Anatomy

Proportional Localisation of the Peroneal Nerve Along the Fibula

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Purpose: The aim of this study was to project the division point of the common peroneal nerve (CPN) into its deep and superficial branch (SPN) and the exit point of the SPN through the crural fascia proportionally along the fibular length.

Materials and Methods: 101 lower extremities were included in the study. The distance between the apex of the fibular head and the distal tip of the lateral malleolus was defined as the fibular length (FL). The interval between the apex of the fibular head and the division side of the CPN and between the tip of the lateral malleolus and the perforation point of the SPN were evaluated.

Data were projected proportionally along the FL and analysed using Dirichlet regression models.

Results: The mean FL was 37.2 cm (SD: 2.8; median: 36.9; range: 32.4-45.6; IQR: 3.6). The CPN's division point was located at a mean of 3.3 cm (SD: 1.2; median: 3.2; range: 1.6 cm proximal to 8.2 cm distal to the tip; IQR: 1.3) distal to the apex of the fibular head, which corresponds to a mean proportion of 9% (range: 2.4%-21.5%), starting from the same landmark. The exit point of the SPN was at an average height of 17.1 cm (SD: 4.5; median: 17.1; range: 7-23.7; IQR: 7.9) proximal to the tip of the lateral malleolus, matching a mean proportion of 46.1% (range: 19.7-65.8) of the FL.

Conclusion: The current results represent easily applicable data for intraoperative localisation of the peroneal nerve's main portions at risk.

Presentation number: 6.4

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 layer-by-layer dissection in the temporal region to identify piercing points within the deep and superficial temporal fascia, 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 of the zygomatic bone 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 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: 6.5

Topic: Clinical and Gross Anatomy

Developmental organization of the median nerve in fetal period

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Introduction: The aim of this study is to examine the developmental process of the micro-anatomical structure of the median nerve in the fetal period.

Methods: This study was performed on 20 aborted human fetuses fixed in 10% formalin. The median nerve samples were taken bilaterally from the middle of the arm and forearm. Tissue samples were embedded in paraffin after using an automated tissue processor. 5 µm sections were taken from each sample and stained with hematoxylin-eosin. Images of the samples were taken using a digital microscopy camera system. The diameters of the median nerves, fascicles and axons were measured. The number of fascicles in each median nerve and the axon numbers for the unit area were counted. The ratio of parenchyma and stroma of the nerve was evaluated.

Results: The median nerve diameter, fascicle number and fascicle diameter were not statistically different between the proximal and distal levels on both sides. In addition, when comparing the sides, there were statistically significant differences in nerve diameter, fascicle number, and fascicle diameter at both levels. The axon number was not statistically significantly different on both sides and levels. The ratio of parenchyma-stroma at proximal and distal levels of the right median nerve was not statistically different, but was different on the left. The parenchyma-stroma ratio at the proximal level was statistically different, but no significant difference was found on the distal level.

Discussion: The differences between the sides suggest lateralisation may have started during the fetal period.

Presentation number: 6.6

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: 7.1

Topic: Clinical and Gross Anatomy

The newborn infant is not a miniature adult; form and function

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The first two years of life is an important period of rapid skeletal muscle growth and development where the rates of muscle growth are higher than at any other stage of postnatal life. The growth rate of skeletal muscle during infancy is essential for achieving key motor milestones, such as crawling, standing, and walking and is also an important determinant of future functional capacity, neurodevelopmental, and health outcomes, as well as quality of life. Despite this paramount importance, we know very little about the response of muscle and bone to physical activity during the first 24 months of life. Our 5 years longitudinal research on typical and non-typical (premature babies) infants' triceps surae revealed the infant musculoskeletal form in rich detail using Magnetic Resonance Imaging (MRI), freehand 3D motion capture ultrasound and microscribe 3D digitiser. Complementing this is our motion analysis work of autonomous infant walking. These works in concert pose the question: **What role does postnatal physical activity before and after weight bearing lay in the formation of our foundational musculoskeletal structures?** This project explains basic understanding of crucial changes in the formation of growing human musculoskeletal architecture during the first two years of life before and after weight bearing.

Presentation number: 7.2

Topic: Form-Function Relationship

Macromechanical Characterization of The Broad Ligament in Young and Aged Women

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Introduction

Until 2050, the number of women affected by pelvic organ prolapse is expected to increase by 50%. Nevertheless, mechanical properties of uterine support structures remain understudied. The broad ligament of the uterus is often disregarded as a load-bearing structure although it connects the uterus laterally to the pelvic wall. Previously, we showed that the broad ligament displays two perpendicular collagen fiber families. This project aimed to determine the resulting biaxial mechanical properties of the broad ligament and possible age-influences.

Methods

Broad ligaments (young n=3, 18-19 years; aged n=7, 74-89 years) were procured according to ethics guidelines from deceased body donors. From each ligament, two samples were used for A) cyclic biaxial testing (5-40% deformation) using a customized sample holder and a fixed pre-load and B) histology to analyze the extracellular matrix.

Results

While tissue from aged women appeared to be stiffer, all mechanical parameters from biaxial tensile tests showed no significant differences between broad ligament samples from young and aged women. The broad ligament displayed a non-linear, anisotropic mechanical behavior with low energy dissipation. Masson-Goldner trichrome staining showed a highly variable amount of muscle fibers in the broad ligament both for the young and aged group.

Discussion

While the variability of broad ligament biomechanics was high within both age groups, no clear age-related differences could be found. Understanding the role of the broad ligament for uterine support may improve computational models of the uterine support structures and aid surgeons planning native tissue repair of uterine prolapse.

Presentation number: 7.3

Topic: Clinical and Gross Anatomy

Biomechanically Testing External Fixators for the Treatment of Pelvic Injury Type AO 61 C1.3a

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Purpose

The objective of this research was to examine the load-deformation behaviour of post-mortem human pelves treated with external fixation for AO61 C1.3a injury.

Methods

The load-bearing capacity of two, three and four external fixator pins was systematically evaluated using a biomechanical test setup. Human post-mortem pelves were carefully dissected. Muscular, vascular and neural tissues, as well as the viscera, were removed, while the ligaments associated with the pelvic ring were preserved. Mechanical characteristics such as stiffness, peak-to-peak, valley-to-valley, fracture line, total displacement, deformation, and maximum load were calculated to measure the stability of the pelvis under different pin configurations.

Results

Surgical treatment by means of external fixation with two pins on the injured side and one on the stable hemipelvis demonstrated optimal biomechanical resistance to C1.3a pelvic fracture. This 3-pin configuration exhibits superior biomechanical stability as evidenced by the least amount of displacement, emphasising its potential benefits for reducing C1.3a pelvic injury.

Conclusion

Only the 3-pin configuration remained below the 15 mm displacement, which is clinically considered the threshold for insufficient stability and thus expected to result in a lower complication rate and better post-operative outcomes when compared to other configurations. Addressing the objectives necessitates a comprehensive understanding of the biomechanical intricacies involved to develop more effective strategies that can contribute to minimizing displacement and fostering favourable outcomes during the recovery trajectory.

Presentation number: 7.4

Topic: Form-Function Relationship

Region- and Direction-Specific Mechanical Tensile Properties of the Human Oral Mucosa

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Introduction: The human oral mucosa is a cell-rich soft layer lining the oral cavity. It protects the underlying tissues against physiological and pathogenic stresses caused by mechanical, chemical, and biological stimuli during daily activities, such as mastication, drinking, speaking, etc. However, in certain situations (trauma, chronic infection, or tumor resection), the mucosa's growth and remodeling mechanisms fail. Hence, investigating the mechanical behavior of the intact mucosa and its structural composition provides crucial insights into the healthy tissue response and helps to understand pathological changes.

Methods: Uniaxial tensile tests were conducted to study the mucosa's region- and direction-dependent stress-stretch response until failure on 78 dog-bone shaped samples punched out from different anatomical regions: hard palate, alveolar mucosa, and attached gingiva (maxillary) as well as attached gingiva, and alveolar mucosa (mandibular). All specimens were harvested from 16 body donors within 48h postmortem and stored at - 80°C until testing. In addition, we performed histological investigations to quantify cellular and non-cellular components.

Results and Discussion: Statistical analyses of the tissue stiffness, Cauchy stress, and stretch at rupture have shown no pronounced direction-specific differences within the different regions. However, the attached gingiva seems to be significantly stiffer than the alveolar mucosa, and it reveals higher Cauchy failure stresses compared to the alveolar mucosa and the hard palate, which correlates with our histological findings and is in line with previous experiments on Thiel-embalmed oral mucosa. This knowledge provides a solid foundation for developing function-preserving therapeutic approaches, such as tissue replacement using tissue-engineered oral mucosa.

Presentation number: 7.5

Topic: Clinical and Gross Anatomy

Changes to the Subtalar Joint Space in Maximum Positions of the Ankle Joint

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Introduction. In minimally invasive surgical interventions of the ankle joint and the subtalar joint, information on the accessible area and the available space is detrimental for the proceedings. For the ankle joint, information is readily available on the changes to the joint space when moving the ankle in maximum plantarflexion or dorsiflexion or applying non-invasive distraction. Whether these manipulations of the ankle joint are also able to provide more space to the subtalar joint are hitherto unknown. The purpose of the study was therefor to evaluate the changes in subtalar joint space in these ankle joint positions.

Methods. Twenty matched pairs (n=40) of anatomical ankle specimen were used. All specimens were be mounted in a standardized fashion, 3D radiography was performed in all four defined positions (maximal plantarflexion, maximal dorsiflexion, neutral position and non-invasive distraction) and all radiographs analyzed and statistically compared.

Results. Non-invasive distraction led to maximum expansion in the joint gap of the subtalar joint with an average increase of 1.03-1.05 mm compared to the other joint positions. Likewise, there was an increase of 0.72-0.85 mm on average in talonavicular part with non-invasive distraction. In the talocalcaneal part of the lower ankle joint, plantarflexion led to maximum expansion with an increase in distance of on average 0.98-1.09 mm ($p<.001$).

Discussion. Non-invasive distraction as well as plantarflexion led to a maximum increase in distances in the joint gaps. Clinically, this may enable better arthroscopic accessibility and insight into the subtalar joint.

Presentation number: 7.6

Topic: From Bench to Bedside

Impact of Cementless "Zweymüller“ Stem Anteversion on Primary Stability and Periprostetic Fracture Predilection in Total Hip Arthroplasty- Biomechanical Study on Artificial Bone Model

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Introduction

Total hip arthroplasty implies the proper orientation of both, the acetabular and femoral component with range of 25-40° of combined anteversion. The aim of the study was to examine the resistance to periprosthetic fracture of the axially loaded cross section rectangular femoral stem (Zweymüller) with respect to the different degree of anteversion, implanted in the artificial bone model, in the laboratory conditions.

Materials and methods

Femoral bone models with implanted femoral stems were divided into 3 groups depending on degree of stem anteversion (A - control group 13-17°, B - stem retroverted 0-4°, C - stem anteverted 26-30°). The amount of axial load leading to the periprosthetic fracture (PPFx) of the artificial bone model was determined by computer simulation experimentally for each construct.

Results

Biggest anteversion sample (26-30°) was found strongest and most stable in conducted mechanical experiments (static and cyclic) and computer simulations. The results show that the load at which the PPFx occurs significantly increases with the increase of the endoprosthesis anteversion angle.

Conclusions

In our clinical practice for intraoperatively determined reasons, we are often unable to place the acetabular component in an ideal grade of anteversion. The results of this experimental study suggest that increasing rectangular femoral (Zweymüller) stem anteversion lowers the risk of PPFx. This study was limited by experimental design (laboratory conditions, artificial bone) and should be clinically verified.

Presentation number: 11.1

Topic: Embryology and Cell Biology

A Tale of Two Losses: Congenital Oligodactyly and the Evolutionary Diversification of Digit Patterns

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Introduction: The cellular mechanisms governing digit numbers and identities in tetrapods and in human limb congenital malformations have remained elusive.

Methods: We have engineered mutations in the BMP antagonist Gremlin1 (*Grem1*) locus that result in the loss of one digit (i.e., tetradactyl mutants) caused by the spatial reduction of the *Grem1* expression domain. Using single cell transcriptomics in limb buds in combination with whole mount RNA-FISH, we have compared wild type (pentadactyl) to tetradactyl limb buds to identify changes in cell populations.

Results: We identified two spatially complementary limb mesenchymal progenitor populations (LMP) altered from early stages onwards in tetradactyl limb buds. The number of peripheral LMPs (pLMPs) is increased, with a distal-posterior expansion of their distribution, whereas the distal LMP (dLMP) population size is decreased. Using signature genes for both populations, we establish that in mouse mutants with either oligo- or polydactyly, pLMPs and dLMPs are changed in a manner consistent with the spatial alterations of *Grem1*-mediated BMP antagonism. The asymmetric distribution of pLMPs is critical for establishing middle digit identities, while the spatial domain and size of the dLMPs population prefigures digit numbers. Tetradactyl pig limbs closely resemble *Grem1* tetradactyl limbs and in pig limb buds both LMP populations retain their *Grem1*-dependent proportionality.

Discussion: These findings establish Grem1-mediated BMP antagonism as an essential instructive mechanism for digit progenitors in mice and illuminate a cellular mechanism for digit reduction, digit loss and the molecular and cellular alterations underlying establishment of the paraxonic axis in Artiodactyl limbs during evolutionary diversification.

Presentation number: 11.2

Topic: Embryology and Cell Biology

Prenatal Glucocorticoid Exposure Compromises Second Heart Field Formation and Further Cardiac Development

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Prenatal stress, including glucocorticoid exposure, has been implicated in various developmental abnormalities. This study investigates the impact of prenatal dexamethasone exposure on the formation of the second heart field (SHF) and subsequent cardiac development, using the chicken embryo as a model organism. This research aims to further elucidate the potential links between prenatal stress and congenital heart defects.

Fertilized chicken eggs were injected with dexamethasone after one day of incubation to simulate prenatal stress. The development of the SHF and overall cardiac formation were monitored through a combination of in-situ hybridization and histological/immunohistochemical methods to analyze the expression of key markers (Nkx2.5, Isl1, FGF8, Sox10 and GATA3). Morphological assessments focused on cardiac looping and structural integrity. Quail-chick chimeras were used to study the migration of cells from the SHF to the outflow tract. Cardiac function was evaluated by measuring heart rate and heart weight.

The results indicated that prenatal dexamethasone exposure altered the expression of Nkx2.5, Isl1, FGF8, Sox10 and GATA3. Morphological analyses revealed impaired cardiac looping and structural deficits, including delayed septation. Quail-chick chimera experiments demonstrated reduced cell migration to the outflow tract in treated embryos. Functionally, these embryos exhibited a decreased heart rate and reduced heart weight, indicating compromised cardiac physiology.

These findings suggest that prenatal glucocorticoid exposure impairs SHF formation and subsequent cardiac development. The altered gene expression and morphological changes observed provide insights into how prenatal stress might contribute to congenital heart defects.

Presentation number: 11.3

Topic: Embryology and Cell Biology

Self-organising Human Pluripotent Stem Cell Derivatives Model the Developmental Interactions between the Heart and Cranial Peripheral Nervous System

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While several mechanisms of early development are conserved in vertebrate and common transitory populations are defined, the validation for the cell fates and trajectories in human embryos needs further investigation. Our research addresses the unexplored crosstalk between the human heart and cranial nervous system during development, which we aim to model in vitro by directed pluripotent stem cell differentiation, followed by tissue self-organisation.

We recorded the cell and tissue morphology changes up to 70 days after the initial WNT modulation in 2D and 3D pluripotent cell cultures, roughly corresponding to 11 weeks in human development. We dynamically phenotyped the cells by immunocytochemistry and in situ hybridisation, implementing a battery of conserved markers validated in human embryonic and foetal tissue samples.

We characterized the earliest cranial mesodermal and ectodermal progenitors, which further generated cardiac plate and tube cells, pharyngeal arches and somite cell clusters, pre-placode and placode cell clusters, and pre-migratory and migratory neural crest cells. We gradually recorded beating cardiomyocytes, sensory and autonomic neuronal cells organised in ganglia nearby the beating cells, compacted cell clusters corresponding to otic and optic placodes, and pigmented cells corresponding to melanocytes and retinal pigmented epithelium.

Our human model helped us identify several cell signatures and trajectories in the development of the heart, sensory and autonomic neurons, skin, ear and eye, but further cell tracing and multiomics approaches are necessary for defining other cell trajectories. This system can be also implemented for disease models and toxicity tests.

Presentation number: 11.4

Topic: Spatial Transcriptomics and Metabolomics

Combining Single-Cell and Spatial Transcriptomics Identifies the Cellular Niche Component Impeding Brain Regeneration

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Introduction

Brain pathologies prompt a coordinated response from immune and glial cells, leading to the formation of a pathology-associated niche. This niche contributes to long-lasting disabilities and the development of secondary conditions such as neurodegeneration and cancer. To develop effective regeneration strategies, a thorough understanding of the mechanisms controlling specific cell types' responses and their interactions within the spatial context of this pathology-induced niche is crucial.

Methods

We integrated single-cell transcriptomics with spatial transcriptomics to chart the similarities and differences in the transcriptomic signatures of the pathology-induced niches caused by neurodegenerative diseases, brain injuries, neuroinflammatory multiple sclerosis, and glioblastoma.

Results

Our analysis identified specific states of various glial and immune cells residing near the pathology border (border niche), common to different brain pathologies. These newly identified populations are present in all analyzed pathologies, and their abundance correlates with the severity of the brain pathology. In the border niche, distinct glial cells share a significant fraction of pathology-regulated genes, including inflammatory programs downstream of the innate immune-associated pathways CXCR3 and TLR1/2. Systemic manipulation of these pathways reduces the reactivity state of glial cells and enhances regenerative processes in the pathology.

Conclusion

The functional relevance of the shared signature of glial cells, identified through a combination of spatial and single-cell analyses, underscores the value of our resource for comprehensively studying early events in various brain pathologies. Inactivating these pathways promotes functional brain regeneration.

Presentation number: 11.5

Topic: Embryology and Cell Biology

Mediolateral Polarity of the Neural Plate Precedes the Dorsoventral Neural Patterning

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Introduction: dorsoventral polarity of the neural tube derivatives is based on molecular patterning established during neurulation and is believed to be induced by two opposing gradients. Pattern formation begins with the induction of the floor plate in the neural tube by Sonic hedgehog (Shh), which is synthesised in the underlying notochord and activates its own expression in the so-called floor plate. Shh generates a ventral to dorsal gradient in the neural tube. At the same time the roof plate generates an opposite, dorsal to ventral gradient of BMP and Wnt. Our previous results revealed expression of Shh in the prospective neural plate of the chicken embryo prior to the formation of the notochord.

Methods: we studied spatiotemporal expression of key components of pattern formation and performed inhibition and activation of the corresponding signalling.

Results: transcription factors Pax7, Pax3 and Nkx6.2 already form a mediolateral pattern during gastrulation, while Nkx6.1 is expressed immediately after the onset of notochord formation while experimental modulation of the signalling revealed permissive role of hedgehog signalling in mediolateral patterning and hedgehog independent floor plate induction.

Conclusion: our data challenges the current view of dorsoventral pattern formation in the neural tube and floor plate induction. We discuss presented results in context of theories of symmetry breaking and gradient based pattern formation and propose an extended model of initial neural patterning during gastrulation.

Presentation number: 11.6

Topic: Embryology and Cell Biology

Development of an In Vitro Culture Model of Astrocytes from Human Brain Biopsies to Study Astrocyte Cell Biology

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Introduction

Astrocytes are a major contributor to the development and progression of neuroinflammatory and neurodegenerative disorders. The need for a robust model is imperative for better understanding of the multiple context-dependent roles that this cell population play, either detrimental or beneficial. However, most *in vitro* studies focus on astrocytes either isolated from murine and/or other non-human animal species. We have obtained and characterized astrocytes from adult human brain biopsies which can be used as a tool to study genotypic/phenotypic characteristics of human astrocytes under different conditions.

Methods

Single-cell suspensions were obtained from brain tissue resection following which astrocytes were separated by magnetic sorting from the rest of the CNS cells based on their expression of the glutamate/aspartate transporter (GLAST). The purity of the astrocyte culture after every isolation was tested by flow cytometry. Further characterization was done by PCR as well as immunocytochemistry.

Results

Human astrocytes from brain biopsies were successfully isolated with high purity and grown in serum-containing media. Cells could subsequently be cultured and maintained for at least 8 passages. Further characterization of the cells revealed astrocyte-like properties.

Discussion

The complexity and heterogeneity of human astrocytes compared to murine astrocytes requires an *in vitro* model which can be used as an alternative to mouse cultures to study human diseases. Moreover, cellular complexity in the mature human brain and interindividual differences are difficult to study by commonly used *in vitro* differentiation protocols, giving additional value to primary human astrocytes obtained from human brain biopsies.

Presentation number: 12.1

Topic: Imaging

S-HREM for Imaging Organoids

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Introduction: Organoids are an important alternative to animal models for studying basic morphogenetic and regenerative events. Optimisation of organoid production and analysis of experimental outcomes heavily rely on highly detailed three-dimensional (3D) visualisation of the organoid morphology and tissue architecture. Here we use Scanning High-Resolution Episcopic Microscopy (S-HREM) to image cardiac organoids.

Methods: Native and experimentally challenged organoids were fixed after 10 and 14 days of development and processed and embedded in resin-blocks for S-HREM. Multiple images of subsequently exposed block surfaces were captured and automatically stitched to generate large volume data sets with voxels sizes below 1 μm^3.

Results: Based on S-HREM data, exact analysis of the microscopic 3D tissue architecture and mapping of various cell types to their precise spatial context could be performed. After (semi-)automatic segmentation we carried out volumetric assessment of single organoid-components at different stages of development and conducted exemplary counts of cell nuclei. In experimentally challenged samples the size of injured areas was determined.

Discussion: The results of our study show the great potential of S-HREM for holistic 3D visualisation and exact volumetric examination of the morphology and tissue architecture of complex organoids. Thus, S-HREM constitutes a crucial tool for evaluating the generation process of organoids and for analysing and interpreting their responses in experimental settings.

Presentation number: 12.2

Topic: Neuroanatomy

The Influence of Exosomes on Nrf2 Activity after Spinal Cord Injury

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Introduction: Spinal cord injury (SCI) is an acute damage associated with inflammation and gliosis. The transcription factors Nrf2 and NF-κB play a decisive role in regulating these processes. Exosomes are released by cells as mediators of intercellular communication, carrying various bioactive molecules. They have become increasingly important in understanding inflammatory diseases.

Methods: Contusion-induced SCI in ARE-Luc reporter mice was followed by *in vivo* Nrf2-imaging. Exosomes from control and LPS-stimulated BV-2 cells were isolated via ultracentrifugation and characterized via nanoparticle tracking analysis. NF-κB and Nrf2 activity in response to exosomal stimulation of primary murine astrocytes was measured by NF-κB and ARE-driven luciferase reporter gene assay combined with qRT-PCR. miRNAs isolated from exosomes were identified by qRT-PCR.

Results: *In vivo* Nrf2-imaging revealed increased activity in the spinal cord but also the brain of mice after SCI. To investigate how this activity is transmitted from the site of injury to the brain, *in vitro* experiments were conducted. Luminometer assay and qRT-PCR data showed increased activity of NF-κB and Nrf2 in astrocytes treated with exosomes from LPS-stimulated BV-2 cells. Furthermore, miRNAs involved in the regulation of both transcription factors were identified as exosomal cargo.

Discussion: We hypothesize that microglia-derived exosomes lead to increased Nrf2 activity in astrocytes, causing the observed elevated activity in the brain of mice after SCI. We further hypothesize, that this mechanism is mediated by miRNAs delivered by exosomes. It remains to be explored whether increased activities serve as priming mechanism, protecting astrocytes in the brain from upcoming inflammatory insults.

Presentation number: 12.3

Topic: Neuroanatomy

Three-dimensional Organization of Connexin Clusters Along Axonal Cisternal Organelle Networks in Human Pyramidal Neurons

Jan Maximilian Janssen, [1, 2, 3]

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High-frequency oscillations have been observed to be particularly prominent in brain regions responsible for seizure initiation and propagation. Connexins play a crucial role in fast intercellular communication within the brain, as they are integral components of gap junctions, which facilitate direct cytoplasmic connections between neighboring cells. Recent studies identified clusters of connexins within the rodent CNS, specifically along the axon initial segment (AIS), a critical neuronal microdomain responsible for the initiation of action potentials. However, details about the subcellular organization of these clusters are still to be uncovered.

Access path tissue from temporal lobe low-grade-glioma removal was used to investigate human temporal lobe pyramidal neurons. Multi-channel immunofluorescence, confocal microscopy and volumetric reconstruction were employed to visualize connexin clusters in AIS microdomains. Super-resolution microscopy techniques, including 3D-STED, protein expansion microscopy and 3D-PAINT were applied to investigate structural relationships between synaptopodin-positive COs and axonal structures immunoreactive for Cx36, Cx43 and Cx45.

Connexin clusters were predominantly found in specific AIS microdomains, aligning with intra-axonal calcium stores (CO). 86% of pyramidal neurons in the primary motor cortex expressed Cx43 at the AIS, closely associated with synaptopodin, a structural component of COs. Super-resolution microscopy facilitated new insights into the 3D arrangement of synaptopodin-positive COs and connexin clusters immunoreactive for Cx36, Cx43, and Cx45.

Ongoing research aims to confirm if these clusters form bona fide gap junctions and elucidate their function within the axonal microdomain.

Presentation number: 12.4

Topic: Imaging

Visualizing Wall Movements of The Seminiferous Tubules in the Testis – Differential Patterns and Relaxing Effects

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Peritubular smooth muscle cells (PTC) surround the germinal epithelium of seminiferous tubules (STs) in the testis. Their contractile function contributes to maintaining male fertility. Upon spermiation, spermatozoa are released from the epithelium, but are still immobile and require PTC contractions to propel them towards the rete testis. The gaseous signaling molecule nitric oxide (NO) relaxes smooth muscle cells and may affect the contractile function of PTCs.

An ex vivo approach allowed live imaging of isolated rat and human seminiferous tubules. To analyze wall movements in rat ST, we developed a custom Fiji-based code to characterize those before and after spermiation and in response to NO treatment. Isolated human PTCs were investigated for NO-induced effects by calcium imaging.

Spontaneous contractions of the rat ST wall were most prominent along the tubule surface and showed an undulating, irregular pattern that differed significantly before and after spermiation. In response to NO donors wall contractions were significantly reduced irrespective of the spermatogenic stage. Human STs also displayed spontaneous contractions and NO-induced relaxation. In agreement, NO effects blunted the calcium increase in PTCs in response to noradrenaline.

Different spontaneous contraction patterns could be detected and visualized in STs. Their association with different spermatogenic stages (before and after spermiation) points towards region-specific, localized functions of PTCs. NO-induced signals affected both spontaneous and noradrenaline-induced contractions, thereby illustrating a yet underexplored role of relaxing factors in the regulation of PTC contractile activity.

Presentation number: 13.1

Topic: Invited Talk

Mechanisms and Translational Approaches to overcome Endothelial Barrier Dysfunction in Inflammation

Nicolas Schlegel, [1]

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Loss of endothelial barrier function is one of the most critical steps that induces organ failure in systemic inflammation. Despite the clinical relevance, specific therapeutic approaches to target endothelial barrier dysfunction remain absent.

Under inflammatory conditions, increased paracellular permeability is caused by disruption of tight junctions (TJ) and adherens junctions (AJ) connecting neighboring endothelial cells. Loss of intercellular adhesion and degradation of vascular endothelial (VE)-cadherin that connects endothelial is regarded as a hallmark for increased microvascular permeability. The integrity of endothelial barrier function is strictly dependent on the interaction between VE-cadherin and VE-protein tyrosin phosphatase (VE-PTP). Furthermore, mechanisms that reduce second messenger cAMP and consecutively modulate activities of RhoGTPases RhoA and Rac1 affect cytoskeletal dynamics that in turn modulate VE-cadherin function. In addition, these signaling pathways are directly and indirectly affected by Tie2-signalling. Obstacles for therapeutic intervention are the complexity of inflammatory responses and the lack of diagnostic means to recognize endothelial barrier dysfunction in patients early.

Based on this, I will discuss the increased knowledge on cellular mechanisms of endothelial barrier regulation and highlight novel therapeutic options that could bring cell biology research into clinical application.

Presentation number: 13.2

Topic: Cardiovascular

Apremilast Enhances Cardiomyocyte Cohesion in a Plakoglobin-Dependent Manner and May Have Therapeutic Potential to Treat Arrhythmogenic Cardiomyopathy

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Background:

Arrhythmogenic cardiomyopathy (ACM) is a heart disease, leading to life-threatening arrhythmias and sudden cardiac death. Currently, treatment options in ACM are targeted exclusively at symptomatic relief. Apremilast was shown to stabilize keratinocyte adhesion in the desmosomal disease pemphigus vulgaris. Therefore, we investigated whether apremilast can be a therapeutic option for ACM.

Methods:

Human induced pluripotent stem cells (hiPSCs) from an ACM patient carrying heterozygous desmoplakin (*DSP*) gene mutation (c.2854G>T) were established. Cyclic-AMP ELISA, dissociation assay, immunostaining, Western blotting analyses, Microelectrode array (MEA) and Langendorff heart perfusion were performed in either hiPSC-derived cardiomyocytes (hiPSC-CM), HL-1 cells, or cardiac slices derived from wild-type (WT) mice, plakoglobin (PG) knockout (KO) (murine AC model) or PG Serine 665 phosphodeficient (PG-S665A) mice.

Results:

ACM hiPSC-CM displayed a significant loss of cohesion, which annihilated upon treatment with apremilast. In addition, in healthy hiPSC-CM, HL-1 cells and WT murine cardiac slices, apremilast strengthened basal cardiomyocyte cohesion. Apremilast enhanced phosphorylation of PG-Serine 665 and colocalization of phosphoS665-PG and desmoglein 2 in ACM hiPSC-CM. In HL-1 cells, apremilast, parallel to PG phosphorylation at serine 665, activated ERK1/2, inhibition of which abolished apremilast-enhanced cardiomyocyte cohesion. Slice cultures from PG-S665A and PG KO mice revealed that PG is crucial for apremilast-enhanced cardiomyocyte cohesion. Finally, apremilast ameliorated heart rate variability and arrhythmia in WT and PG KO mice after apremilast.

Conclusions:

Apremilast rescued the loss of cardiomyocyte cohesion in ACM hiPSC-CM and reduced arrhythmia in PG-KO mice-hearts. Therefore, we propose that apremilast could be developed as a therapeutic option for ACM.

Presentation number: 13.3

Topic: Cardiovascular

Mechanical Characterization of Diseased Blood Vessel Walls by Using Pipette Aspiration Test and Pressure-Imposed Test

Toshiro Ohashi, [1]

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Introduction

There is an increasing demand for medical prevention and treatments of ageing-associated diseases such as atherosclerosis, hypertension, etc. In fact, academic researchers are needed to clarify the cause of the diseases from the viewpoint of biomechanics. The aim of this study is to mechanically characterize atherosclerotic blood vessel walls by using a pipette aspiration test and a pressure-imposed test.

Methods

Regarding the pipette aspiration test, a glass-pipette with a diameter of 1 mm was applied to aspirate atherosclerotic lesions in thoracic aortas of rabbits fed a cholesterol diet for 8, 16, 24 and 28 weeks and to determine local elastic moduli. As for the pressure-imposed test, human thoracic aortic aneurysms (TAAs) and porcine thoracic aortas (PTAs) were pressurized to determine rupture properties by using a custom-built pressure-imposed setup.

Results and Discussion

In the pipette aspiration test, the local Young's moduli decreased from that of the normal tissue in 8 weeks and then increased during the cholesterol feeding period. Histological observation revealed that the initial soft lesion was mainly composed of foam cells, and the stiffening accompanied first the appearance of smooth muscle cells in the hyperplastic intima and then calcification in its bottom. These results suggest that change in mechanical properties of atherosclerotic lesion has a close correlation with its histology. To investigate the mechanism of aneurysm rupture, the pressure-imposed test was performed. The yielding parameter was significantly lower in TAAs than PTAs. This result may indicate that the yielding parameter would be candidate indices for rupture risk estimation.

Presentation number: 13.4

Topic: Varia

Identification of Molecular Drivers of Prostate Cancer Bone Metastasis In Vivo

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Introduction: Patients with advanced prostate cancer (PCa) frequently develop incurable bone metastases (BM). The underlying molecular mechanisms are poorly understood and further identification of the molecular drivers of PCa-BM formation is urgently required.

Methods: Human PCa PC-3 cells were subcutaneously (s.c.) injected into immunodeficient mice to form xenograft primary tumors (PT), spontaneous lung metastases (LM) and BM. From all three sites, tumor cells were recovered, expanded *in vitro* and s.c. re-injected into new recipient mice (four passages). Finally, the spontaneous metastatic capacity of the sublines (PT vs. LM vs. BM) was assessed. The sublines' clonal heterogeneity was assessed using RGB-marking and subline-specific cell clusters were identified using scRNA-sequencing.

Results: The incidence of BM was significantly higher in mice injected with the BM-subline (BM: 88% vs. PT: 30% vs LM: 25%) which additionally formed significantly larger BM ($p<0.05$). Instead, mainly single tumor cells or micro-metastases were found in the bones of the LM- and PT-subline group. The PT- and LM-subline showed a heterogeneous clonality (RGB-marking) but a nearly monoclonal composition of the BM-subline was observed. According to their gene expression profile the s.c. xenograft tumors of the BM-subline were characterized by a cell cluster which was nearly absent in the other sublines (BM: 62.33% vs. LM: 0.19% vs. PT: 0.66%). This cluster contained 37 up-regulated genes with ten of them indicating poor outcome in PCa patients (HR: 3.1, $p<0.001$).

Discussion: We generated a bone metastatic PC-3 subline and thereby identified a gene cluster that might be involved in PCa BM formation.

Presentation number: 13.5

Topic: Embryology and Cell Biology

KRASG12D-driven Early Pancreatic Carcinogenesis and associated Natural Killer Cell Impairment are Influenced by Sex

Elise Arlt, [1]

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Introduction

Pancreatic ductal adenocarcinoma (PDAC) is associated with dysfunctional natural killer (NK) cells, particularly in advanced tumour stages. Although PDAC appears to have higher incidences in men than in women, there is limited knowledge about sex-dependent differences of the immune reaction. The present study investigates an early precancerous stage of PDAC and its impact on NK cells considering males and females.

Methods

Since the $KRAS^{G12D}$ (KC)-mouse model develops an early PDAC, male and female KC mice were compared to their mutation-free littermates (CRE). Histological investigation and NK cell immunolabeling of the pancreas were performed. Additionally, NK cell receptors were analysed in the peripheral blood and in the pancreatic tissue.

Results

The percentage of remodelled pancreatic tissue was significantly higher in female KC mice than in males. A decrease of the activating NK cell receptor densities in KC mice compared to CRE mice was observed in the peripheral blood. A downregulation of these receptors was also revealed in the pancreatic tissue, although precancerous lesions were infiltrated by NK cells. The differences between KC and CRE mice were more prominent in females than in males. Sex-dependent differences of NK cell receptors were confirmed with healthy BL6 mice.

Discussion

The study reveals sex-dependent alterations of NK cell receptors in early PDAC. Most of the observed NK cell damages are more prominent in females than in males, implying that females are more prone to tumor progression and that female NK cells react more intensely to the early tumour cell’s immune escape mechanisms.

Presentation number: 13.6

Topic: Cardiovascular

Identification of Pro-adhesive Drugs and Implications for Arrhythmogenic Cardiomyopathy

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Introduction:

Arrhythmogenic Cardiomyopathy (ACM) is one of the major causes of sudden cardiac death in young adults. With the underlying pathomechanisms not well understood, current therapeutic approaches for this genetic disease are solely symptomatic. A recently developed mouse model demonstrates that loss of cell-cell adhesion is an important initial step leading to ACM. Derived from this central role of defective cohesion, we here aim to identify new compounds from a drug library, which restore intercellular adhesion and can potentially serve as therapeutics for ACM.

Methods and Results:

We established and validated a cell adhesion-based high-throughput assay and screened a FDA-approved drug library containing 1’822 compounds in adhesion-impaired cells (Dsg2 KO). The pro-adhesive effect of selected candidates was validated for different ACM patient mutations presenting with defective cell cohesion and revealed a set of promising drugs. Importantly, in vivo administration of the identified adhesion-strengthening compound dexamethasone abrogated impaired right ventricular function and ECG changes in an ACM mouse model (Dsg2 iKO). Transcriptomics and phospho-proteomics were applied to investigate the protective drug mechanisms and identified cell contractility as relevant factor contributing to the pro-adhesive effect of dexamethasone.

Discussion:

In summary, we developed a high-throughput approach capable of identifying pro-adhesive compounds and applied this to determine a novel potential therapeutic approach for ACM.

Presentation number: 14.1

Topic: Latest developments in undergraduate and postgraduate training

Advances in Undergraduate and Postgraduate Training – An Overview on Traditional and Innovative Teaching in Modern Medical Curricula from a National and International View

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Introduction: The trend of worldwide medical curriculum modernization has shifted the focus from knowledge- and teacher-centred to student-centred problem- and research-based learning concepts, as well as to early vertical integration of clinical and scientific skills.

Methods: In this lecture, advances in undergraduate medical training will be reviewed with special emphasis on traditional and innovative teaching methods in modern medical curricula, both on a national level in Switzerland and internationally. Further, postgraduate education approaches will be highlighted.

Results: Despite curricular restructures over the past 25 years, gross anatomy teaching generally remained at the early stage in medical curricula. Since the COVID-19 pandemic, anatomy teaching underwent dramatic changes in the use of digital technology-based teaching and learning. Nevertheless, practical anatomy teaching by dissection has been demonstrated to be highest appreciated by the students and may be complemented by innovative teaching methods. With regard to postgraduate medical training, the Swiss Clinical Anatomy Network emphasizes the importance of anatomy by organization of anatomical-surgical courses, promotion of modern digital teaching modules and integration of gross anatomy with clinical disciplines.

Discussion: The present lecture will give an overview on international and national teaching in anatomy and discuss future advances in light of modern pedagogical concepts. The positive attitude toward in-person teaching by dissection following the pandemic as observed in medical students aligns with constructivist learning theories that students learn best engaged in learning experiences rather than as passive recipients of information. Further, some aspects of constructive alignment will be highlighted for practical education and examination implications.

Presentation number: 14.2

Topic: Clinical and Gross Anatomy

Novel Fixatives for Anatomical Embalming – A Study on Morphological and Antimicrobial Preservation Effects Based on Low-Toxic Food Preservatives

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Formaldehyde (FA), widely used for embalming due to its preservative qualities, poses cancerogenic and teratogenic risks, necessitating safer substitutes. This study explores low-toxic alternatives to FA for embalming, focusing on common food preservatives, i.e., lactic acid (LA), citric acid (CA) and sodium nitrite (SN).

Embalmments with solutions of LA, CA and SN were compared to FA and phosphate buffered saline (PBS) controls. Murine cadavers were perfused and stored under conditions simulating anatomical dissection courses including repetitive room air exposure over 10 weeks. For microbiological analyses, tissue samples were taken during storage, and microbial load was assessed qualitatively and quantitatively, respectively. To assess microscopic preservation, histological samples were taken at specific storage times. Alterations in organ morphology and coloration, tissue hardness and stiffness were assessed.

Embalming with FA yielded sterile tissues. In comparison, LA and CA preserved microscopic and macroscopic tissue integrity without denaturation effects (i.e., increased tissue stiffness). LA and CA provided good short and long-term antimicrobial effects with microbial loads significantly lower than in the PBS control and comprised only few spore-forming bacteria. LA and CA-treated cadavers, however, exhibited time-dependent tissue softening, bone decalcification and surface precipitates, indicating limitations for anatomical teaching. Embalming with SN had only a moderate antimicrobial effect and resulted in strong brownish organ coloration and poor histological preservation.

Solutions combining LA and SN (LA-SN) showed good antimicrobial and promising macroscopic preservation effects. Future studies on human corpses will elucidate the suitability of LA-SN as a substitute to FA in embalmment.

Presentation number: 14.3

Topic: Latest developments in undergraduate and postgraduate training

Clay Brain Modelling; A Bridge Between 2D Neuroanatomical Atlases and 3D Human Brain Dissection?

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Introduction

Translating two-dimensional (2D) neuroanatomical images from atlases into three-dimensional (3D) brain specimen is challenging for medical students, however they need this skill to interpret medical imaging in their future career. Therefore, our study aimed to more effectively bridge the transition from 2D towards 3D neuroanatomy understanding using clay modelling.

Methods

Two groups (n=40 per group) of Technical Medicine students followed a neuroanatomy practical consisting of two parts:

1) Modelling the human brain using clay adapted from Kooloos et al. (2014).

2) Studying prosected brains and performing brain dissection themselves.

The first group started with clay modelling, the second group started with brain pro- and dissection. Students prepared with an assignment, were guided by a 3D-instruction-website when claying and used a written manual during the dissection. The practical was evaluated by asking student's opinion and feedback using a Woo-clap questionnaire.

Results

Students (response rate 50%) graded the practical with an 8.8 (scale 1-10). They agreed for 88.6% with the statement that their neuroanatomical 3D perception improved after the practical. 3D clay modelling beneficially supported the dissection of a brain specimen according to 85.7% of the students. The students unanimously preferred clay modelling before the dissection part of the practical. Finally, students who started with clay modelling performed better during the brain dissection.

Discussion

These findings emphasize that clay modelling before dissecting a brain is preferred, and that this task is an effective, appreciated and interactive method to bridge the gap between 2D neuroanatomical images and 3D brain dissection.

Presentation number: 14.4

Topic: Clinical and Gross Anatomy

Improving Injection Efficiency in Cadaveric Donors: A Preliminary Study Using Ultrasound for the Carotid Artery Approach

Zygmunt Domagała, [1]

Mateusz Mazurek, [1], Victoria Tarkowski, [1], Agnieszka Pinkowska, [1], Malgorzata Suchanecka, [1], Dominika Domagała, [1], Mateusz Drazyk, [1], Oliwier Pioterek, [1], Slawomir Wozniak, [1]

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Abstract:

Introduction:

The demand for high-quality anatomical specimens is increasing, however, the donation program is facing a challenge due to a small number of cadavers. Moreover, the number of cadavers is fluctuant and can drop in future. Improper injection techniques can risk damaging these valuable specimens. This preliminary experimental study aims to evaluate the use of an ultrasound device to increase the efficiency and accuracy of injecting cadaveric donors through the carotid artery.

Material and Methods:

Three deceased donor bodies were used for this study. A non-invasive initial evaluation of the carotid artery triangle anatomy was conducted using an ultrasound device. Vascular access was obtained through surgical techniques following previously published standards. The flow dynamics and catheter localization were confirmed using the ultrasound device.

Results:

The study confirmed the limited effectiveness of the ultrasound device in assessing the anatomy of the carotid artery triangle in deceased patients. However, it demonstrated the effectiveness of Doppler techniques in assessing flow dynamics. The team observed several technical limitations and difficulties related to the software.

Discussion:

The study showed that using an ultrasound device for this particular purpose was effective; however, it had some limitations (among others the lack of experience in conducting the procedure). Further research with a larger group of participants is needed to improve the methodology and confirm these results.

Presentation number: 14.5

Topic: Clinical and Gross Anatomy

Risk of Body Donor Colonization by Microorganisms after Reduction of Formaldehyde

Christina Nassenstein, [1]

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Formaldehyde (FA) was classified as group 1 carcinogen (carcinogenic to humans) by the International Agency for Research on Cancer (IARC) with an occupational exposure limit (OEL) of 0.37 mg/m^3 (0.3 ppm). In order to comply with the OEL, the FA concentration of the fixative used for embalming body donors was reduced and a post-embalming treatment established by injecting a FA-binding solution (InfuTrace™). Furthermore, the room ventilation system was optimized.

Aim of this study was to analyze the effect of reduced FA tissue-concentrations of donors on the colonization by microorganisms. Swab samples were obtained from defined areas of two body donors at 13 dates within 16 months, from the arrival of the bodies in the anatomy to the end of the dissection course after two semesters. Additionally, fluid samples of Infutrace™ and disinfectants as well as air samples from the dissection hall and the ventilation system were investigated. Quantitative analyses for bacteria, yeasts and fungi were performed by cultivation, followed by qualitative analyses by MALDI-TOF MS and/or sequencing.

Growth of microorganisms was detected sporadically in a limited number of analyzed samples until mid of the 2nd semester. Then, growth of bacteria was consistently observed in almost all samples obtained from the body donor surface. Further analysis revealed different bacterial strains, including individual antibiotic-resistant strains belonging to risk group 2 according to TRBA 466 "Classification of prokaryotes (bacteria and archaea) into risk groups".

Conclusion: Reducing the concentrations of formaldehyde for embalming body donors may increase the risk of their colonization with infectious bacteria.

Presentation number: 14.6

Topic: Clinical and Gross Anatomy

Aminolipin®-Update: Current Status & Future Plans

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New guidelines for occupational safety concerning chemical fixatives for biological materials are about to maximally restrict its use in anatomical science and education. As there are no known authorized alternative substances to formaldehyde, this will dramatically impact medical curricula and surgical training programs. Recently, we introduced Aminolipin® (3-N´-n-Dodecyl-(1-N-α-amido-pyroglutaminyl)-1,3-diamino pro pane) as a novel embalming agent that enables tissue fixation with *in vivo*-like haptics, anti-microbial effects (bactericidal, viricidal, levurocidal), and minimizes user exposure due to its low toxicity and non-volatile nature.

Current Status: We describe the synthesis, chemical characterization and elucidation of the biochemical mechanism underlying the preserving, anti-autolytic effect. As Aminolipin® is currently undergoing the complex, strict, and time-consuming biocide approval process (Regulation (EU) No 528/2012), we can now provide an update on the research and present data on effectiveness and application.

Future Plans: Our results are important for the future of medical education as they indicate that the widespread adoption of Aminolipin® has the power to avert the impending ban of dissection courses from medical curricula and offer an ideal chemical fixative for surgical training. We are now able to provide an overview over the next steps and future procedures.

Presentation number: 16.1

Topic: Neuroanatomy

SMAD4 is Essential for Microglia Homeostasis and Activation

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Microglia undergo postnatal maturation characterized by establishment of a microglia-specific gene expression pattern which is indispensable for their homeostasis-associated physiological functions. Furthermore, expression of activation markers decreases during this postnatal maturation process.

Here, we demonstrate that the intracellular TGF-beta signalling mediator SMAD4 is essential to induce expression of these microglia homeostatic markers and further repress expression of inflammatory activation markers. Using inducible microglia-specific Smad4-KO mice (Cre/LoxP), we demonstrate that loss of SMAD-driven postnatal microglia maturation results in a dyshomeostatic and reactive microglia phenotype accompanied by impaired myelination of white matter tracts, loss of cortical inhibitory neurons, astrocyte reactivity, and a hyperactive motor phenotype. Moreover, deletion of SMAD4 in adult mice triggers the loss of postnatally established homeostatic microglia marker expression and fosters a microglia reactive state reminiscent of disease-associated microglia (DAM) found in a plethora of neurodegenerative diseases.

Together, our results underline the importance of microglial TGF-beta signalling and identify SMAD4 as a key molecule regulating microglial homeostasis and reactivity.

Presentation number: 16.2

Topic: Neuroanatomy

Microglia Induce Changes in Myelin Composition of the Perforant Path during Neuroinflammation

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Introduction: Neuroinflammation is a common feature of various neurological and psychiatric diseases and can lead to different symptoms like fatigue, depression or memory deficits. One morphological feature that has been associated with neuroinflammatory reactions are changes in the myelination of certain brain regions. Hereby, the intercellular communication between different cell types like microglia – the resident immune cells of the brain – and oligodendrocytes seems to play an essential role. However, the complex cellular and molecular mechanisms mediating microglia-oligodendrocyte interactions remain not well understood.

Methods: To investigate microglia-oligodendrocyte communication during neuroinflammatory processes, microglia was depleted from organotypic entorhino-hippocampal tissue cultures with BLZ945 and neuroinflammation was induced using lipopolysaccharide. The myelination and myelin composition of axons was analyzed in microglia-depleted cultures and non-depleted control cultures using immunohistochemical stainings, RNA-analysis and fluorescence in-situ hybridization (FisH). Signal transduction of the perforant path was functionally assessed using whole-cell patch-clamp recordings.

Results: The experiments of this study show changes in the expression of myelin basic protein (MBP) and myelin associated glycoprotein (MAG) of the perforant path on transcriptomic and protein level induced by prolonged neuroinflammation (7-day treatment with lipopolysaccharide), whereas a short inflammatory stimulus (3 days) does not change myelin composition. In microglia-depleted cultures, these effects could not be observed, indicating the crucial role of microglia in mediating neuroinflammation-induced changes in myelin composition.

Discussion: This study shows the central role of microglia in changing myelin composition during neuroinflammation.

Presentation number: 16.3

Topic: Varia

EGFL7, an Angiogenic Protein, Acts as an Immunosuppressive Factor in Glioma Development

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Glioblastoma (GBM) is the most aggressive form of primary brain tumor, characterized by immune evasion, rapid growth, extensive angiogenesis and peritumoral invasion into the brain parenchyma. Recent evidence indicates that epidermal growth factor-like protein 7 (EGFL7), a non-canonical regulator of NOTCH signalling and known angiogenic factor, is highly expressed in GBM microenvironment (GME).

We have observed that EGFL7 alters immune cells infiltrating the tumor mass, but the molecular mechanism remains elusive in GBM. Thus, in vivo studies in GBM mouse models followed by flow cytometry, single cell RNA-sequencing (scRNA-seq) and mass spectrometry were employed to uncover the type of cells and molecular mechanism by which EGFL7 regulates immune evasion. Our findings demonstrate that EGFL7 expression is detrimental for survival of glioma bearing mice while its elimination prolongs survival. We further identified specific immunosuppressive pro-tumorigenic immune cells: namely, regulatory T cells and myeloid-derived suppressor cells (MDSCs), showing a greater infiltration into the GME, in the presence of EGFL7. Concurrently, a reduction in cytotoxic T cells was observed. Using co-immunoprecipitation, we uncovered an interaction between EGFL7 and integrin β2 (present on immune cells). Further, scRNA-seq results provide a deeper understanding into the effect of EGFL7 on immune cell signaling. We believe this interaction is potentially responsible for inducing an immunosuppressive environment and places EGFL7 and integrin β2 at the center of glioma immunotherapy.

In conclusion, EGFL7 protein induces an immunosuppressive environment, possibly through its interaction with integrin β2 and this serves as a key step in developing treatment regimens against GBM.

Presentation number: 17.1

Topic: From Bench to Bedside

Microbeam Technology: How Anatomists Can Contribute to the Fight against Cancer

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Introduction

Microbeam Radiation Therapy (MRT) is an innovative form of spatially fractionated radiation therapy. It delivers radiation dose on a micrometer scale, making it highly effective in treating even radioresistant tumours.

Methodology

Departing from standard radiotherapy, MRT administers an array of ultra-narrow, high-dose beams, as thin as a hair. These beams deliver precise high-doses to the tumor, while the space between them receives a lower dose, similar to a barcode, resulting in MRT's unique benefits.

Results

MRT demonstrated significant results in murine B16-F10 melanoma and mouse glioblastoma models. Temporally fractionated MRT entirely eliminated 50% of tumours and prevented metastases and recurrences for 18 months. Combined with cisplatin, MRT reduced tumour volume dramatically compared to cisplatin alone or no treatment.

The radiation biology underlying the "MRT effect" include novel radiobiological mechanisms: (1) Induction of selective vascular disruption of immature tumor vasculature or transient vascular permeability in a dose-dependent manner (2) Direct cellular damage in the microbeam path that elicits tissue-specific responses. (3) Induction of a unique, tumor-targeted immune response leading to local and systemic anti-tumor immune responses including infiltration of cytotoxic lymphocytes.

Discussion

MRT has exhibited some of the most successful treatment outcomes in preclinical models. MRT not only offers a unique mechanism for drug delivery by increasing vascular permeability while preserving vessel integrity, but it also strengthens the anti-tumor immune response. MRT's unique features make it a promising therapeutic approach for inoperable, radio-resistant lesions and recent tests have shown its safety in initial human applications.

Presentation number: 17.2

Topic: From Bench to Bedside

Targeted Proteomics upon Tofersen Identifies Candidate Response Markers for SOD1-ALS

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Introduction

The antisense oligonucleotide (ASO) tofersen is the first effective and approved therapy for familial amyotrophic lateral sclerosis (ALS) caused by pathogenic variants in the *SOD1* gene. Following treatment with tofersen, neurofilaments in patients´ CSF and serum display a faster response than clinical parameters, underlining their importance as a biomarker for treatment response in clinical trials.

Methods

We hypothesized that tofersen might represent the first opportunity to identify additional therapy-responsive biomarkers for ALS. We chose the commercial NUcleic acid Linked Immuno-Sandwich Assay (NULISA™), to investigate a predefined panel of 120 neural, glial and inflammatory markers in CSF and serum samples longitudinally collected from SOD1-ALS patients at baseline and three months after tofersen treatment.

Results

We identified a group of markers, namely Aβ42, NfH, NfL, NPY, UCHL1 and GOT1, which not only discriminated SOD1-ALS from controls, but whose levels were also partially “corrected” by the ASO, thus potentially qualifying them as dual diagnostic and therapeutic markers for SOD1-ALS (and possibly also for ALS in general).

Discussion

Our findings suggest that a panel of biomarkers may yield an increased informative value on whether and how robustly a drug influences different aspects of disease pathology (e.g., neurodegeneration, gliosis, inflammation). Even though analysis of larger cohorts and additional time points is required to understand how tofersen ultimately influences the disease in SOD1-ALS, we highlighted novel and essential features of neuroprotection achieved in ALS patients. Given validation and refinement, such a panel could represent a valuable readout for future clinical trials.

Presentation number: 17.3

Topic: From Bench to Bedside

Loss of Intestinal Epithelial Plakoglobin Activates Innate Immune Response by P38mapk-Dependent Activation of the Inflammasome

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Introduction:

The contribution of desmosomes to intestinal epithelial homeostasis is poorly understood. Here we provide evidence for new functional role of desmosomal plaque protein plakoglobin (JUP) to control activation of the innate immune response in the context of intestinal inflammation.

Methods

Patient samples from patients with Crohn`s Disease (CD) were collected. Inducible intestinal epithelial knockout model of JUP in mice (ivil-cre $JUP^{fl/fl}$) was generated followed by single-cell RNAseq, functional and structural characterization.

Results and Discussion

In inflamed tissue samples of patients with CD and in acute dextran-sodium sulfate (DSS)-induced colitis loss of JUP was observed. Inducible intestinal epithelial knockout of JUP in mice (ivil-cre $JUP^{fl/fl}$) resulted in augmented submucosal infiltration of macrophages and neutrophils in the absence of functional barrier changes under basal conditions. When animals were subjected to DSS to induce intestinal inflammation JUP-deficiency led to increased disease activity and strong activation of interleukin23/IL17-signalling pathway compared to wildtype littermate controls. On a mechanistic level, intestinal epithelial organoids from ivil-cre $JUP^{fl/fl}$ revealed a strong activation of the NLRP1 inflammasome with augmented interleukin1b (IL1b) secretion following tamoxifen-induced knockout of JUP. NLRP1 activation and IL1b secretion were caused by a p38MAPK hyperphosphorylation in JUP-deficient organoids which were blunted by pharmacological inhibition of p38MAPK.

In summary, these data point to a novel role of the desmosomal protein JUP to be causally involved in the onset of intestinal inflammation. The loss of JUP in a cohort of patients with CD suggests a disease-relevant role of this observation.

Presentation number: 17.4

Topic: Embryology and Cell Biology

Epac1 Regulates Keratinocyte Adhesion and is Involved in Apremilast-Mediated Protective Effects in Pemphigus.

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Introduction In the bullous autoimmune dermatosis pemphigus vulgaris (PV) autoantibodies against the desmosomal cadherins desmoglein (Dsg)1 and Dsg3 cause loss of intercellular adhesion leading to blistering of the skin. We recently showed that the phosphodiesterase 4 inhibitor apremilast was protective in several model systems for PV, which was paralleled by PKA-mediated plakoglobin (Pg) phosphorylation at S665. To further investigate the underlying mechanism, we analyzed the involvement of the cAMP effector cAMP-regulated exchange factor Epac1.

Methods Epac1-deficient mice, pemphigus mouse model, immunostaining, keratinocyte dissociation assay, Western blot, Rap1-pulldown

Results The Epac1 inhibitor Esi09 protected keratinocytes from pemphigus antibody-induced loss of adhesion similar to apremilast. This effect was not affected by additional treatment of apremilast. Therefore, we next analyzed Epac1-deficient ko mice.

While the epidermis of Epac1-deficient mice did not show any significant alterations of desmosomal components, keratinocytes from these mice revealed an enhanced expression of some desmosomal proteins including Dsg1 and Dsg3. This was paralleled by stronger intercellular adhesion under basal conditions but also in response to PV-IgG. Similarly, PV-IgG-induced blistering in the pemphigus mouse model *in vivo* was ameliorated in Epac1 ko mice so that apremilast had no additional effect. However, in Epac1-deficient keratinocytes apremilast-induced Rap1 activation and phosphorylation of Pg were attenuated similar to the protective effect against loss of cell adhesion in response to the Dsg3-specific PV antibody AK23.

Discussion Taken together, these data indicate that Epac1 is involved in cAMP-mediated stabilization of keratinocyte adhesion. However, Epac1 loss of function is compensated by enhanced Dsg levels which stabilizes keratinocyte cohesion.

Presentation number: 17.5

Topic: From Bench to Bedside

New Translational Research Tools to Target B-Glucocerebrosidase in Parkinson's Disease

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β-glucocerebrosidase (GCase) is a lysosomal glycosidase that requires transport through LIMP-2 and represents the biggest genetic risk factor to develop Parkinson's disease (PD). GCase activating compounds are currently undergoing numerous clinical trials and we use biochemistry, cell biology and structural biology to develop and test new and existing GCase activating compounds.

We genetically engineered different LIMP-2 proteins (e.g., secreted, non-binding) to analyze PD associated GCase variants with regard to lysosomal transport and activity. We developed a LIMP-2 mimicking peptide and show delivery to lysosomes in patient fibroblasts using imaging and proteomics methods. We purified quantitative amounts of GCase/LIMP-2 protein complex utilizing affinity-tag and size exclusion chromatography and applied cryo-TEM and single particle reconstruction for structure determination to near atomic resolution.

We observed increased lysosomal GCase activity in patient fibroblasts (genetic GCase variant) after feeding cells with the LIMP-2 mimicking peptide. Using a fluorescently labeled variant of the peptide reveals directed delivery to the lysosome. We show an increase of the lysosomal enzymatic activity of GCase in patient fibroblasts to healthy control levels after addition of the peptide. As we resolved the structure of the GCase/LIMP-2 to 3.7Å resolution we can now describe the molecular interaction to molecular detail. We found a hydrophobic core shielded by a polar/charged rim and two salt bridges between GCase and LIMP-2.

The cellular and structural tools are valuable contributions for translational PD research. They have and will find entry in clinical PD research and might contribute to a first line of disease modifying drugs.

Presentation number: 17.6

Topic: Embryology and Cell Biology

Deciphering the Dark Side of Autophagy to Provide Neuroprotection in Perinatal Brain Injuries

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Introduction: Compiling evidence has shown that autophagy, a physiological intracellular process of lysosomal degradation, is deregulated and excessively activated in dying neurons both *in vitro* and in *in vivo* rodent models of perinatal cerebral hypoxia-ischemia (HI). In these models, genetical and pharmacological modulation of neuronal autophagy revealed that HI-enhanced autophagy is deleterious by, depending on the conditions, mediating apoptosis or being a death-promoting pathway by itself (independent of apoptosis and necrosis). Finally, and more clinically relevant, high neuronal autophagic activity is also observed in dying neurons in autoptic brains of human asphyxiated babies with severe hypoxic-ischemic encephalopathy (HIE).

Methods: We are now investigating the molecular mechanisms by which autophagy could be involved in neuronal death in *in vitro* and *in vivo* HI preclinical models and autoptic human newborns brains with HIE.

Results: We showed that neuronal apoptosis is associated with enhanced autophagy. Genetic inhibition of autophagy is importantly reducing the apoptotic response, including cytochrome c release, caspase-3 activation etc., induced by pro-apoptotic treatments. Using the autophagy-inducing peptide Tat-BECN1 and in HI conditions, we also demonstrated that enhanced autophagy could kill primary cortical neurons without the involvement of other cell death pathways. Autophagic neuronal death (autosis) is dependent on the alpha 3 subunit of the NaK ATPase (ATP1A3) and mediated by ATP1A3-BECN1 interaction.

Discussion: Altogether, these results cast light on a new mechanistic pathway in the pathophysiology of HIE and suggest that experimental neuroprotective strategies targeting autophagy should be considered for the development of future therapeutic approaches for perinatal brain injuries.

Presentation number: 20.1

Topic: Neuroanatomy

Mesoscale visualization of the nervous system: from brain to body

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The nervous system consists of myriad interconnected neurons that form intricate networks spanning the entire brain and the whole organism. The coordinated neuronal activity across networks in the brain generates perception, emotion, learning, and consciousness. From the brain, the nervous system extends to the periphery, interacting with other systems and regulating body physiology. The ultimate understanding of cognition and physiological regulation and related diseases requires mapping of its system-wide network architecture at cellular resolution.

We have developed a high-speed, large-scale, volumetric fluorescence microscopy technique VISoR capable of imaging a whole mouse brain at micron resolution within 0.5 hour and a rhesus monkey brain within 100 hours. Together with a pipeline of efficient sample embedding, sectioning, clearing and semi-automatic data processing, VISoR enables efficient mesoscale connectomic mapping of the primate brain, revealing unexpected trajectories and complex arborization patterns of individual thalamocortical axons. Beyond the brain, we have recently developed a blockface-VISoR system with a new pipeline of labeling, clearing, imaging and 3D reconstruction to enable micron-resolution imaging and single axon tracing of the central and peripheral nervous system across the entire mouse body.

The rapidly developing imaging and related technologies is poised to facilitate large-scale data collection for mesoscopic reconstruction of the nervous system and the entire organism. Such efforts will help unveil unprecedented insights regarding how neurons and other cells organize into holistic systems, and eventually lead to a new data-driven paradigm for life science research and biomedicine.

Presentation number: 20.2

Topic: Clinical and Gross Anatomy

Mesoscopic Anatomy of the Human Deep Fascia and its Surgical Applications

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Introduction: Mesoscopic anatomy provides morphological insight into scales from micrometer to the whole body, particularly including a scale of hundreds micrometers between macroscopy and microscopy. Anatomical definition of 'deep fascia' varies widely. At the macroscopic level, 'dissectible' or 'visible' has been used to define the deep fascia. The ambiguous definition around the true nature of the deep fascia remains the same as it was in the 1st edition of Gray's Anatomy. The objective of this presentation is to comprehensively demonstrate the direct mesoscopic evidence for the nature, origin and architecture of the human deep fascia in the head, neck, torso and limbs.

Methods: Using a combination of epoxy sheet plastination and confocal microscopy methods, the mesoscopic anatomical features of the fascia-like structures were systematically examined in the cadaveric head, neck, torso and limbs.

Results: Three basic types of the fascia-like structural configuration were identified. Their localization and distribution in the human body are regional-dependent at a scale of hundreds of micrometers.

Discussion: Mesoscopic anatomy of the deep fascia highlights both challenges and opportunities that are brought forth by studies at a scale of hundreds of micrometers and strongly indicates that some classic anatomical concepts based on macroscopic observations need to revisit at a mesoscopic scale. Mesoscopic anatomy will foster a closer collaboration between the cadaver-based structural study and its translation into various practical disciplines, e.g., contemporary medical imaging, endoscopic and robotic surgeries.

Presentation number: 20.3

Topic: Clinical and Gross Anatomy

Retrocolic Fascia - an MDCTA Morphometric Analysis in Patients with Right Colon Cancer

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Introduction. The introduction of the complete mesocolic excision (CME) for cancer has highlighted visceral planes and fascia of the retrocolic region. The aim of the study was to delineate these anatomical landmarks through a multimodal approach, including a large scan series from a clinical trial of radical hemicolectomy. **Methods.** The methods applied were stratigraphic pilot dissection on an embalmed cadaver, Mimics segmentation and 3D reconstruction of the Gerota fascia, and a retrospective analysis of multidetector computed tomographic angiography (MDTCA) scans from 196 patients (mean age 65.7 yrs, 118F/ 78M). Systematic measurements of fascial thickness at key renal levels — upper pole, hilum, lower pole, and infra-renal — were taken bilaterally to assess the impact of right-sided colon cancer. Covariates analyzed included Body Mass Index, age, and gender. **Results.** The pilot dissection revealed that the only true retrocolic compact connective tissue formation is the renal fascia of Gerota, and the fusion fascia of Toldt is a mesh of strands of loose connective tissue and fat lobules. MDCTA showed clearer visualization of Gerota's fascia at the hilum and inferior renal pole, with greater visibility on the left side. Statistical analysis revealed significant differences in fascial thickness between sides (1.3 mm on the right and 1.34 mm on the left) and a positive correlation with BMI, whereas age and gender showed no significant effects. **Discussion.** Gerota’s fascia is a critical anatomical landmark in CME for right colon cancer. The study highlights the fascia's structural integrity, unaffected by the tumor, underscoring its importance in surgical navigation.

Presentation number: 20.4

Topic: Clinical and Gross Anatomy

The Connectives Surrounding the Median Nerve Should be more than an Unstructured Filler. We Describe Spaces, and Subspaces, Divided and Both Connected by Describable Structures

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For the median nerve, there is increasing evidence that its surrounding connective tissue plays a role for pathogenesis for diseases as carpal tunnel syndrome (CTS) or the Raynaud's syndrome (RS). We describe a system of connective tissue for the median nerve, distal from the pronator teres, to the carpal tunnel. After dissection, injection, plastination, and MRI we have seen these connectives building plates, as to the ulnar nerve (Martin-Gruber anastomosis). It creates and separates internal subspaces. It houses the median nerve like an encampment (in German: *Lager*). It serves the nerve containing vessels and probably autonomic innervation (A. commitans n. median) like a repository or reservoir (in German: Lager). This “Lager" further connects to flexor muscles of the forearm, and to the radius bone, thus to the known innervation field of the nerve. In the Canalis carpi, it also acts as the outermost internal layer enveloping flexor tendons.

Our description does not negate the existence of described connectives, like fascia, subsynovial connective tissue, endo-, epi- or perineuria, epimysia, periostea, or peritendinea, in this region. However, it tries to bring them to topographical “fascial” hierarchy. This may relate to the median nerve branching (which here is not dissected). Knowing this connective anatomy of the forearm allows researching any morphologically changed “Medianuslager” related to pathological conditions like CTS, or RS.

Bias gives the palmar approach: If the Ramus palmaris and its connectives, or the Ligamentum palmare, or the M. palmaris longus belong to a subspace of such a “Medianuslager” remains open.

Presentation number: 20.5

Topic: Form-Function Relationship

Sacroiliac Joint Motion Focused on Articular Surface Morphology: Healthy and Dysfunctional Joints

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Introduction: The sacroiliac joints (SIJs) in the pelvis consist of a synovial joint anteriorly and tough ligaments posteriorly. Due to these strong ligaments, SIJs have low mobility. Unexpected or repeated impact can cause misalignment and pain in SIJs. Preventing excessive motion is effective in relieving the pain. The articular surface in the synovial joint area has fine irregularities that may restrict joint motion. This study aims to clarify the effect of the SIJ surface on movement resistance, comparing healthy and dysfunctional joints.

Methods: Articular surface models of healthy and dysfunctional SIJs were created from X-ray CT data of three patients with unilateral SIJ dysfunction. The articular surfaces were analyzed on the bony morphology and joint gaps. Using a homemade device, the sliding resistance and repositionability were measured in four directions and three combined positions with the 3D-printed surface models.

Results: The sacral morphology was similar in both models, however the joint gap distribution differed in dysfunctional models compared to healthy ones. In the rotated combination, the gap distribution in dysfunctional models approached that of healthy models. Joint sliding resistance and repositionability were lower in dysfunctional models compared to healthy ones, however in the rotated combination, dysfunctional models approached the healthy models.

Discussion: The decrease in joint repositionability indicates the risk of subluxation under small loads, impairing joint function. The surface morphology and sliding test results showed that rotated combinations in dysfunctional sides approached healthy sides, suggesting that adjusting joint combination positions could be a potential treatment.

Presentation number: 20.6

Topic: Clinical and Gross Anatomy

Source and Course of the Iliohypogastric, Ilioinguinal and Lateral Femoral Cutaneous Nerves in Relation to Surgical Approaches to the Vertebral Column and Hip Joint

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Introduction

This study aimed to re-evaluate the course and source of branches of the lumbar plexus by qualifying and quantifying their origin and possible trunk formations.

Material and Methods

A careful stratigraphic macroscopic dissection was carried out in 39 anatomical specimens. In these specimens, the entrance of the lateral femoral cutaneous nerve into the subcutaneous layer was measured and the relation between the course of the nerve and the different approaches to the hip joints was visualized. In 29 specimens, the course and trunk formation of the iliohypogastric, ilioinguinal and lateral femoral cutaneous nerves was studied. In 13 specimens, the origin of these nerves from the spinal nerves was visualized.

Results

The lateral femoral cutaneous nerve emerged from the subfascial layer 55.64±16.30 mm distal to the anterior superior iliac spine, mostly (69.6%) lateral to a vertical line perpendicular to the linea interspinalis passing through the anterior superior iliac spine. Its branches overlapped with the incision of the direct anterior approach in 84.1%, the anterolateral approach in 89.9% and the lateral approach in 84.1%.

Trunk formations of the iliohypogastric, ilioinguinal and lateral femoral cutaneous nerve were present in 51.7% of lumbar plexus. Regarding the segmental origin of the nerves examined, only one male and one female showed bilateral identical origins for all nerves.

Discussion

Metric data on the exit point of the lateral femoral cutaneous nerve as well as several other details on the formation of the nerves arising from the lumbar plexus are presented for the first time.

Presentation number: 21.1

Topic: Imaging

Nanomotion Imaging as a Diagnostic Tool

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Introduction

A few years ago, our team discovered that all living organisms oscillate at a nanometric scale as long as they are alive, and these oscillations cease upon the organism's death. These oscillations, known as nanomotion, appear to be a universal characteristic of all living organisms on Earth. Initially detected using atomic force microscopy, we have recently demonstrated that classical optical microscopes can also reveal these nanometric vibrations.

Methods

Detection involves recording short, 10-30-second-long movies of the sample by using a traditional optical microscope equipped with a 40x objective. The movies are eventually analyzed with dedicated sub-pixel resolution displacement detecting software.

Results

Results obtained on bacteria, yeast, mitochondria and cancer cells will be presented. They demonstrate the potential of the method in detecting in a label free manner life-death transitions and in monitoring cellular metabolism and its changes in response to chemical or physical stimuli.

Discussion

Various potential applications of this technique will be presented in the fields of clinical microbiology, drug discovery, and oncology.

Presentation number: 21.2

Topic: Embryology and Cell Biology

Unraveling the Intrinsic Regeneration Mechanisms of Lacrimal Gland Acinar Epithelial Cells for Therapeutic Applications in Aqueous-Deficient Dry Eye

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Dry eye affects the ocular surface and tear film, impacting over 344 million people globally. Symptoms include itching, foreign body sensation, recurrent conjunctivitis, and visual impairments, with severe cases potentially leading to blindness. Hypovolemic dry eye, linked to lacrimal gland insufficiency, shows the most severe progression. While animal models reveal the lacrimal gland's ability to regenerate after damage, the underlying mechanisms are unclear. This study aims to uncover these mechanisms, with potential therapeutic implications for aqueous-deficient dry eye (ADDE) patients.

Primary lacrimal gland acinar epithelial cells (LGEC) were obtained from neonatal mice explants. The cells were characterized to confirm lacrimal gland-specific markers and exclude fibroblastic and myoepithelial markers using PCR, immunocytochemistry, and transcriptome analysis. The secretory capacity of murine LGECs (mLGEC) was assessed via a β hexosaminidase assay. Transcriptome analysis identified intrinsic regeneration mechanisms, analyzing pathways and investigating promising proteins.

mLGECs maintained LGEC markers (FOXC1, PAX6, LTF) and acinar cell markers (AQP5, SOX10), with fibroblast and myoepithelial markers at levels similar to native tissue. Stimulation with carbachol and dbcamp demonstrated the secretory potential of mLGECs. Regeneration signs appeared within one hour post-injury. Transcriptome analysis highlighted the TNF, IL-17, and MAPK signaling pathways, with upregulated growth factors.

This study established an *in vitro* lacrimal gland injury model showing spontaneous regeneration. Key pathways involved in LGECs' intrinsic regenerative mechanisms were identified. Future experiments will explore the impact of identified growth factors on lacrimal gland regeneration, potentially guiding new treatments for ADDE patients.

Supported by Ernst and Berta Grimmke Foundation.

Presentation number: 21.3

Topic: Clinical and Gross Anatomy

The Thyroarytenoid Muscle as a Distinctive Morphofunctional Entity in the Context of Voice Research

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Introduction

The study of vocal fold anatomy is a niche but ongoing topic, despite voice being an important component of human society. Previous research has shown that some features of the macro- and microanatomy of the vocal folds have adaptive morphological characteristics. Our study aims to evaluate these features on the human thyroarytenoid neuromuscular system and integrate them into a functional context.

Methods

We performed double antibody immunofluorescence and TEM on human cadaveric tissue from 10 body donors. The larynxes of 5 body donors were analyzed in histological whole larynx sections. At the same time, a functional electromyographic study was performed on 26 fresh porcine larynxes.

Results

We encounter morphological features that allow the classification of thyroarytenoid muscle tissue as a unique form of striated muscle tissue. We also describe the presence and characteristics of three types of laryngeal synapses with unique morphology and distribution within the tissue. We then analyze the possible presence of scattered intramuscular neurons and their relationship to thyroarytenoid musculature. Finally, electromyography results show a coordinated coactivation of thyroarytenoid and cricothyroid muscles.

Discussion

The discussed findings justify the classification of the thyroarytenoid muscle in particular as an independent muscle type, similar to the extraocular muscles. The results imply that integration into the currently discussed vocal oscillation models can explain some functional features whose correlation with the aforementioned models is only partial. Finally, this opens up new research opportunities such as the assessment of myosin heavy chain composition, synaptic protein profile and clinical effects of muscular coactivation.

Presentation number: 21.4

Topic: Varia

Host Brain Initiates Rapid Bacterial Adaptive Response with Capsular Thickening and Better Immune Resistance

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Introduction. Bacterial infections of the brain such as pneumococcal meningitis lead to strong damage of the host structures such as synapses, and life-threating excessive neuroinflammation. Antibiotic resistance starts increasingly threaten therapy of such disease. Thus, understanding the approaches bacteria utilize to fight hosts is of paramount importance.

Methods. We used primary cells and animal model systems of meningitis, combined with genetic screens and next-generation screens for key gene identification.

Results. Using clinical isolates of patients with Streptococcus pneumoniae meningitis, we identified specific pathogenicity modulation of the bacterium once in contact specifically with the brain of the host. Sensing the presence of brain, pneumococci start thickening their capsule, which makes them more resistant to immune cell elimination. This process was activated within 12-14 h after entering the brain and succeeded the initial bacteria multiplication. Using transposon-based random gene knockout screen and NGS, we identified the critical genes involved in this process.

Discussion. Until now, it was suggested that such changes happen only randomly in bacteria. Using capsule thickening versus non-thickening bacteria, we observed that capsule-thickening capacity contributes to better host colonization. Thus, we show that pathogens such as bacteria adapt actively to the host within short period of time. Further, we suggest that the brain can be a possible pathogen-modulating intermediate stop, allowing bacteria better colonization of the host.

Presentation number: 21.5

Topic: Embryology and Cell Biology

Respiratory skeletal muscle degeneration in Covid-19 patients

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Introduction

Dyspnea and whole-body sarcopenia are specific symptoms of acute and post Covid-19 infection (CI). To which extent respiratory muscle degeneration (RMD) is attributed to direct effects of CI, immobility, or mechanical ventilation in intensive care unit remains unknown. Therefore, RMD was studied in CI-positive patients and controls.

Methods

Pseudonymized pathological routine sections of diaphragm and intercostal muscle of 61 deceased in-patients of University Hospital Augsburg were collected. Reports of CI-status, lung-associated comorbidities, duration of hospitalization, mechanical ventilation and biographical data were conceived. Immunohistochemical markers for myofiber type, stem cell (SC) status, inflammation, and oxidative stress (OS) were applied. Immunohistochemistry was quantified and statistically correlated with clinical data.

Results

CI-positive patients showed RMD, since infected elder subjects showed increased muscle-regenerating active SCs (Pax7; $p=0.048$). Further, immobility ($p=0.034$) or duration of CI ($p<0.001$) was positively correlated with muscle fibre type remodelling from myosin slow to fast twitch. Elder patients demonstrated raised markers for OS (ALDH1A1, ALDH1A3, SelK; $p=0.001$) and cell senescence (GLB1; $p=0.027$) with a non-CI-related significance when compared to controls ($p>0.05$). Intercostal muscle of patients with high BMI positively correlated with SCs activation (CD56; p=0.0.024), inflammation (IL-6; $p=0.035$) and OS (ALDH1A1; $p=0.044$). No significant impact of mechanical ventilation and lung-associated comorbidities was observed.

Discussion

CI-positive patients displayed signs of increased RMD correlated with either the duration of CI or age. Interestingly, RMD was not correlated with mechanical ventilation. Future studies need to evaluate the underlying molecular and cellular mechanisms of CI-dependent RMD to further improve therapeutic options of CI-suffering patients.

Presentation number: 21.6

Topic: Varia

Role of Peroxisomes in Type 2 Alveolar Epithelial Cells and Surfactant Synthesis in the Lung

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Pulmonary surfactants play important roles in lung biology by preventing alveolar collapse during normal and forced respiration. Peroxisomes may play a significant role in this process since they can contribute to general phospholipid synthesis via the DHAP pathway. However, the peroxisomal functions in surfactant synthesis in alveolar epithelial type II cells (AECII) remain poorly understood. This study aimed to explore the role of peroxisomes in the synthesis and production of pulmonary surfactants in AECII. Due to the difficulty in isolating AECII, the T7 AECII cell line, derived from H-2kb-tsA58 transgenic immorto-mouse, was used in this study. These cells were transfected with Pex13 siRNA to knock down the peroxisomes. Additionally, a mouse model with AECII-specific peroxisome deficiency was created by disrupting the Pex13 gene using Cre-LoxP technology. The results showed significant downregulation of Pex13 in Pex13 siRNA-transfected T7 AECII and complete deletion of Pex13 in Pex13 knockout mice, confirming the successful depletion/deletion of peroxisomes. Immunofluorescence, qRT-PCR, and Western blotting revealed a substantial decrease in the mRNA and protein levels of the AECII marker protein SP-C and other surfactant proteins such as SP-A, SP-B and SP-D compared to wild-type. Quantitative lipidome analysis demonstrated a significant reduction in various classes of phospholipids including Phosphatidylcholine (PC), Phosphatidylethanolamine (PE), Phosphatidylglycerol (PG), Phosphatidylinositol (PI), Phosphatidylserine (PS), and Cholesterol, along with individual lipid molecular species (LPC 16:1, LPC 16:0, LPC 18:0, etc.) following peroxisomes knockdown. Taken together, this study provides a comprehensive analysis of the involvement of peroxisomes in surfactant synthesis.

Presentation number: 22.1

Topic: Neuroanatomy

Deciphering Amyotrophic Lateral Sclerosis Linked to NEK1 Mutations

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Introduction

Loss-of-function (LoF) mutations in the *NEK1* gene represent the third and fifth most frequent genetic cause of sporadic and familial forms of ALS, respectively. Beside the proven pathogenic LoF mutations, *NEK1* missense variants are also found in a restricted number of ALS patients, suggesting potential pathogenicity also in this case. While NEK1 protein expression of missense variants can be readily examined, functional evaluation of uncertain variants is not available owing to a lack of knowledge of the molecular pathomechanisms underlying NEK1-ALS.

Methods

The aim of this project was to clarify whether missense variants of *NEK1* might trigger pathological phenotypes and lead to neuronal sufferance. To do this, we used CRISPR-Cas9 to generate isogenic hiPSC lines carrying a putative pathogenic missense mutation or a LoF variant. These lines, together with the parental control hiPSCs, were differentiated into spinal motor neurons (MNs) to perform a combinatorial multi-omics evaluation of abnormalities occurring in the presence of *NEK1* mutations.

Results

Similarly to the LoF, mutant MNs carrying the missense variant are characterized by increased apoptosis, reduced DNA damage repair capacity, and impaired protein homeostasis, suggesting potential pathogenicity. The pathological similarities between the two mutations were further confirmed by a NEK1-ALS fingerprint generated by RNAseq and phospho-proteomics approaches and were also recapitulated by MNs differentiated from patients´ hiPSCs.

Discussion

Our data provide the first evidence for pathological alterations triggered by missense mutations in *NEK1* and support a pathogenic role of these variants in ALS.

Presentation number: 22.2

Topic: Embryology and Cell Biology

P38mapk-Mediated Signaling Contributes to Early Pathogenic Effects of Autoantibodies in Pemphigus Vulgaris

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Introduction:

Pemphigus vulgaris (PV) is an autoimmune disease impairing desmosomal adhesion. Altered signaling pathways have been demonstrated to contribute to loss of cell adhesion which is the main pathophysiologic event leading to blister formation. In this work, we investigated whether p38MAPK-mediated signaling contributes to early pathogenic effect of autoantibodies.

Methods:

STED-microscopy, AFM, STED/AFM-SMFS, Triton X-100 protein fractionation, Dispase fragmentation assay

Results:

Autoantibodies from PV patients (PV-IgG) or the monoclonal anti-Dsg3 mouse antibody AK23 were applied on human keratinocyte (HaCaT) cells with incubation times ranging from 5 to 30 min. PV-IgG caused loss of intercellular adhesion after 15 min, whereas AK23 reduced cellular adhesion as soon as after 5 min. Inhibition of p38MAPK rescued intercellular adhesion for both incubation times, indicating that signaling is important. Accordingly, protein fractionation showed that AK23 is present within the desmosome 5 min after application. STED/AFM-SMFS measurements showed a decrease in binding frequency after 5 and 15 min of AK23 incubation. However, the amount of tether bonds, indicating weakly anchored cadherins, was increased after 15 min but not after 5 min of AK23 incubation. PV-IgG together with activated p38MAPK accumulated within desmosomes after 15 min. In line with that, keratin filament retraction occurred 15 min after PV-IgG incubation, whereas first ultrastructural changes of desmosome morphology were observed after 30 min of PV-IgG incubation only.

Discussion:

p38MAPK accumulates with pemphigus autoantibodies within desmosomes and contributes to early loss of cell adhesion in PV.

Presentation number: 22.3

Topic: Embryology and Cell Biology

Hyalocytes are Yolk Sac Derived Tissue Resident Macrophages of the Vitreous

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Introduction

Hyalocytes are tissue resident macrophages of the vitreous body of the eye. They are involved in multiple vitreoretinal diseases with a large impact on society such as diabetic retinopathy. However, their ontogeny and fate are still largely unknown. The aim of this study was to characterize hyalocytes in comparison to other macrophages focusing on their marker profile, their embryonic origin and turnover during homeostasis.

Methods

Transgenic reporter mice, fate mapping and parabiosis experiments were combined with immunofluorescent imaging to study these cells in the eye.

Results

We identified a distinct signature of hyalocytes as $CX_3CR1^+IBA1^+F4/80^+CD163^+CD206^+LYVE1^+MHCII^-HEXB^-TMEM119^-$ cells separating them clearly from retinal microglia. Furthermore, murine hyalocytes originate from the yolk sac and seed the developing eye prenatally, like microglia. In sharp contrast to the existing body of literature, they don't show a contribution of blood-derived monocytes under homeostatic conditions but are a long-lived self-maintaining population.

Discussion

Our study is the first to show a yolk sac-derived origin of hyalocytes while excluding a long-thought contribution of peripheral blood monocytes with several transgenic mouse lines and models. Our findings not only clarify the source of hyalocytes but also provide an important resource for future studies of hyalocytes in terms of marker selection, in line with previous eye macrophage studies. Importantly, the senescence of hyalocytes as a long-lived, self-maintaining cell population, might be contributing directly to the development of vitreoretinal diseases. This insight provides a better understanding of disease mechanisms and with this, new therapeutic avenues for patient treatment in the future.

Presentation number: 22.4

Topic: Embryology and Cell Biology

SERPINB5-TGF-β Signalling Modulates Desmosomal Adhesion and Ameliorates Skin Blistering Phenotypes

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Impairment of desmosomal cell-cell adhesion leads to several life-threatening diseases such as the autoimmune skin blistering disorder pemphigus vulgaris (PV). Strategies which directly stabilize intercellular adhesion, in combination to the existing immunosuppression therapy, may provide ways to improve clinical outcomes. Previous findings showed that SERPINB5 promotes intercellular adhesion by binding to and regulating the localization of the desmosomal adapter molecule desmoplakin (DSP) at the plasma membrane. SERPINB5 overexpression abrogated PV-IgG mediated loss of cell-cell adhesion and prevents the loss of DSP from the cell membrane. SERPINB5 negatively regulates TGF-β signaling, a known regulator of DSP in keratinocytes. TGF-β signaling was activated in skin biopsies of PV patients and keratinocytes treated with PV-IgG or PX4_3, suggesting a contribution to disease. Inhibition of TGF-β activation, ameliorated the PV-IgG mediated loss of cell-cell adhesion, increased DSP membrane expression and prevented PV-IgG-induced blister formation in human *ex-vivo* skin model. Thus, SERPINB5 modulates DSP and intercellular adhesion through regulation of TGF-β signaling. Further, TGF-β inhibition was identified as potential target for pemphigus treatment.

Presentation number: 22.5

Topic: Neuroanatomy

The Influence of Bilingualism on Gray Matter Volume within Subregions of the Hippocampal Formation

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The hippocampal formation (HF) shows age-related structural atrophy associated with memory decline. “Brain reserve” may help preserve memory function during aging. Bilingualism is related to higher gray matter volume (GMV) as one form of brain reserve in the HF. However, the differential influence of bilingualism on HF subregions remains unclear. Thus, we investigated GMV differences and differences in age-GMV-relationships between mono- and bilinguals in the HF and two HF subregions, hippocampus proper (HPr) and subicular complex (SubC).

GMV differences in mono- vs. bilinguals were assessed in 661 adults (257 monolinguals) from the 1000BRAINS study for six regions of interest (left/right HF, left/right HPr and left/right SubC) using ANCOVAs. Effects of bilingualism on age-GMV-relationships were investigated via moderation analyses.

We found higher GMV in bilinguals in the bilateral HF and SubC. Moderation analyses revealed similar age-GMV-relationships between mono- and bilinguals in the bilateral SubC, left HF, and left HPr, but a steeper negative relationship for monolinguals in the right HF and HPr.

We confirmed higher GMV in bilinguals’ HF. With the bilateral HPr showing no effect of language group, bilingualism appears to specifically add brain reserve to regions putatively subserving memory retrieval (SubC) rather than encoding. With similar age-GMV-relationships for mono- and bilinguals, bilingual brain reserve in the SubC may persist over time. For the right HPr, the rate of GMV decline with age was higher for monolinguals, indicating better local brain structure maintenance in bilinguals. Altogether, our results provide new insights into structural adaptations to bilingualism in the human HF.

Presentation number: 22.6

Topic: Neuroanatomy

Chronic Blockade and Optogenetic Stimulation of Synaptic Activity Alters Dendritic Dynamics and Spinogenesis in Postnatally Born Hippocampal Granule Cells

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Neurogenesis of hippocampal granule cells (GCs) starts in the late embryonic phase, peaks postnatally and continues during adulthood. Increasing evidence points to functionally relevant hippocampal adult neurogenesis in mammals including humans. Postnatally born GCs (pbGCs) serve as a valuable tool to study mechanisms of adult neurogenesis in entorhino-hippocampal organotypic slice cultures (OTCs) under live-imaging conditions.

Timelapse imaging of postnatally born and maturated granule cells was performed after viral injections in rat-OTCs. A GFP-Retrovirus was used to label pbGCs whereas an AAV-hSyn-tdTomato-virus served to label developmentally born mature GCs (mGCs). Postnatally born granule cells showed an unexpected rate of dendritic elongation and pruning of individual segments and branches at the time scale of days and even hours during the first three weeks of maturation, whereas the dendritic tree of mGCs remained relatively constant over time. A computer-aided structural analysis of these *in vitro* findings with *in vivo* datasets from adult born and mature GCs revealed a strikingly similar time course and characteristics of dendritic structural maturation.

Local synaptic activity in the dentate gyrus was either chronically enhanced by optogenetic stimulation after local injection of an AAV-hSyn-tdTomato-Channelrhodopsin-2-virus or blocked by tetrodotoxin (TTX) bath application. Optogenetic stimulation enhanced spinogenesis, whereas chronic blockade of synaptic activity with TTX prolonged the phase of high dendritic dynamics which is characteristic for immature GCs.

We conclude that a phase of enhanced dendritic dynamics is a prerequisite for a successful synaptic integration of newly born neurons in a functional mature network.

Supported by Deutsche Forschungsgemeinschaft (DFG).

Presentation number: 22.7

Topic: Cardiovascular

CEACAM1 – Novel Mediator of Atherosclerotic Plaque Progression

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Introduction

Cardiovascular diseases like myocardial infarction and stroke are the leading cause of death worldwide and atherosclerosis is the main underlying pro-inflammatory process.

The carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) has a dual function in the vasculature. Initially, CEACAM1 promotes vascular development and maturation. In contrast progressive age leads to a mutual upregulation of vascular CEACAM1 and TNF-α thereby creating a chronic pro-inflammatory milieu that is suggested to initiate atherosclerotic plaque formation. Therefore, we aimed to investigate the impact of CEACAM1 on atherogenesis.

Methods

For *in vivo* analyses, we used LDL receptor knockout mice (*Ldlr*$^{-/-}$) and double knockout mice (*Ldlr*$^{-/-}$/*Ceacam1*$^{-/-}$) with additional CEACAM1 deficiency. Mechanistic *in vitro* analyses were conducted using the human endothelial cell line EA.hy926 (WT) and a CEACAM1-deficient derivative (*CEACAM1*$^{-/-}$).

Results

Ldlr$^{-/-}$/*Ceacam1*$^{-/-}$ mice showed drastically reduced atherosclerotic plaque size compared to *Ldlr*-/- mice. RNA sequencing of aortic arches from these animals unveiled that CEACAM1 promotes TNF-α signaling, oxidative stress, monocyte recruitment as well as LDL accumulation. These *in vivo* data were confirmed by comparative analysis of WT and *CEACAM1*$^{-/-}$ EA.hy926 cells showing that CEACAM1 augments proinflammatory TNF-α-NF-κB signaling and promotes endothelial-monocyte interaction via enhanced adhesion molecule expression as well as endothelial permeability and LDL transport across endothelial cells.

Discussion

We identified CEACAM1 as a novel central mediator of atherosclerotic plaque formation. CEACAM1 promotes crucial pro-atherosclerotic signaling pathways like inflammation, monocyte recruitment and vascular LDL deposition. Therefore, CEACAM1 is a promising candidate to target atherosclerotic plaque formation and subsequent cardiovascular diseases.

Presentation number: 22.8

Topic: Varia

Regional Differences of (Induced) Vas Deferens Contractility and Its Implications for Sperm Propulsion

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Introduction:

Mature spermatozoa, stored in the most distal part of the epididymis (dEpi) are transported to the urethra during emission (in textbooks). This process is often described as “by noradrenaline-induced powerful contractions of the vas deferens (VasD)” but not detailed further and not fully understood. In our already published results with dEpi we could show equally strong emission-like contractions induced by either noradrenaline or oxytocin.

Methods:

For the first time, we have investigated the VasD in its entirety in toto and in longitudinal pieces of 3 mm each to find and define regional differences in contractility and substance responses using live-imaging combined with a novel analysis method + organ bath studies. From morphology and responsiveness, we grouped the results from the rat VasD into distinct comprehensive regions: 1st loop, pars epididymica (PE), pars libera and pars prostatica. In addition, we investigated regional histological differences.

Results:

In all VasD pieces, contractions were observed predominantly longitudinally while effects of the circular layers were nearly absent.

Only in PE the response was similarly strong to dEpi while the rest of VasD, despite thicker and more intertwined smooth muscle layers, showed little responsiveness.

Especially in toto data indicated that the strong contractions of dEpi and PE drive pump-like the expulsion of spermatozoa.

In these two “emission-relevant” tissues (dEpi and PE) oxytocin induced very strong contractions, equally strong to noradrenaline in dEpi.

Discussion:

This confirms a role for oxytocin during ejaculation and opens up a new alternative therapeutic tool for ejaculatory disorders, including paraplegic patients.

Presentation number: 23.1

Topic: Latest developments in undergraduate and postgraduate training

Behind the Scenes: Nine Years of Mastering Cinematic Rendering in the Classroom

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Introduction

Virtual anatomy is becoming increasingly popular and is implemented by a number of universities to complement traditional anatomy teaching. Cinematic Rendering (CR), provided by Siemens Healthineers, is a post-processing software which transforms clinical datasets into photorealistic three-dimensional visualizations using Monte Carlo integration to simulate natural light diffusion.

Methods

Since 2015, CR presentations have been held at the Deep Space of Ars Electronica Museum Linz. Viewers use active shutter glasses to observe 3D projections on a wall-filling 8k screen, and presenters navigate the visualizations using a commercial controller. Initially, presentations were held for the public, later expanding to doctors, medical students, and other healthcare students.

Results

In 2021, a spin-off facility called medSPACE was opened at the Medical Faculty, Johannes Kepler University Linz. It has since been used for CR presentations for medical students and doctors.

The software ‘Cinematic Anatomy x Deep Space’, created in collaboration with the JKU, Siemens Healthineers and Ars Electronica Futurelab, received the E&T Innovation Award for ‘Best Emerging Technology of the Year’ and the silver medal for ‘Most Innovative Solution in Digital Health and Social Care’ in 2022. It also won a silver medal for ‘Innovation and Entrepreneurship Team of the Year” at the Triple E Awards in 2023’.

Discussion

This infrastructure and software, along with cooperation from the Medical University of Graz, enable contemporary blended anatomy teaching, combining anatomy presentations in dissection courses and in the medSPACE.

Presentation number: 23.2

Topic: Latest developments in undergraduate and postgraduate training

Cinematic Rendering-Aided Virtual Anatomy Teaching Improves Students' Knowledge of Radiological Anatomy

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Introduction

Blended learning approaches integrating virtual anatomy such as radiologic imaging and spatial visualization techniques are becoming increasingly prevalent in medical schools. Previous studies demonstrated that an early integration of radiology stimulates students' interest in anatomy and thus helps create a connection between basic and clinical science. Furthermore, it can demonstrate anatomy *in vivo*, while specimen-based anatomy presents a postmortem state that offers the benefit of a haptic experience. This study aims to substantiate the effect of virtual anatomy education on student's anatomy knowledge in radiological, especially cross-sectional, imaging.

Material and Methods

After completing a four-week dissection course in the first year of their undergraduate medical training, students at the Johannes Kepler University Linz participated in a blended anatomy class including an advanced Volume Rendering-based ("Cinematic Rendering") virtual anatomy course held in the second year. At the beginning and at the end of the semester of virtual anatomy teaching on musculoskeletal and neuroanatomy, seventy-two students were surveyed in short answer tag examinations assessing anatomical knowledge in CT and MR images.

Results

Virtual anatomy lectures helped students improve their knowledge on radiologic anatomy significantly. In neuroanatomy an increase of 42.9% and in musculoskeletal anatomy an increase of 36.2% could be observed.

Discussion

A previous study demonstrated that Cinematic Rendering-based virtual anatomy teaching has minor effects on prosection-based knowledge. Different learning domains appear to be addressed by dissection and virtual anatomy. This given study provides evidence that virtual anatomy teaching promotes knowledge translation for radiological anatomy.

Presentation number: 23.3

Topic: Digital and AI Tools in Teaching

Innovative Learning Applications in Anatomy

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Introduction

Innovative Extended Reality technology has attracted attention in anatomy education due to its high potential for self-directed collaborative learning. Medical students in New Zealand rated the Human Muscular Arm Avatar Augmented Reality application beneficial for their anatomy learning. It is not known, whether this application improves anatomy knowledge of the arm and hand muscles measured by knowledge questions. We aim to assess knowledge gain in medical students in Graz in a before-after design.

Material and Methods

Students completed three learning tasks using the application for 15 minutes in groups of five to six people. Before and after the learning intervention students completed knowledge tests containing true/false questions and questionnaires about their learning experience.

Results

Students (n = eleven) learning via the Human Muscular Arm Avatar showed an increase of knowledge. The mean pre-test score increased from 8.8 (± 1.079) to a mean post-test score of 10.3 (± 1.489) out of 15. Statistical testing via Wilcoxon test for dependent variables showed a statistical difference ($p = 0.011$, significance level $p < 0.05$). Nine out of eleven students totally agreed learning with the Human Muscular Arm Avatar is useful for learning functional anatomy; the remaining two students agreed this to be rather useful.

Discussion

Studying specific learning tasks in groups with this Augmented Reality application seems effective for anatomy knowledge gain. Students perceive this application as useful, which confirms previous results. Next steps include testing more students and using a prosected arm as comparative learning intervention.

Presentation number: 23.4

Topic: Digital and AI Tools in Teaching

Post-Mortem Imaging and 3D Printing as Complementary Tools for the Teaching of Morphology at the Faculty Unit of Anatomy and Morphology in Lausanne

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At the Faculty Unit of Anatomy and Morphology (UFAM) of CURML, one of the priorities is the implementation of new pedagogical tools to complement the teaching of morphology. In this work, we present an overview of our developments concerning these digital tools.

We have recently modernized our website, providing students with access to annotated images of various anatomical structures (musculoskeletal system, nervous system, etc.). Furthermore, we undertook 3D surface scans on human skeletons with a high-resolution colorless 3D scanner. High-resolution 3D prints of some bones were performed as well. We made them available for first year Bachelor medical students. This allowed many students to manipulate them without damaging the originals bones as they are fragile. Moreover, we digitized some neuroanatomical pieces, such as cerebral hemispheres and genital organs in 3D and in color by means of photogrammetry. As time allocated to practicals has been reduced over the years, we introduced these 3D models to help students in their learning process and to optimize the time spent in practicals.

Besides, we perform a native total body CT-scan of every anatomy body, before the fixation process. This exam allows a quick and complete documentation of the body, helping in selection of bodies according to the teaching needs (undergraduate or postgraduate), and providing data to research projects, or external collaborations.

Post-mortem imaging and 3D printing techniques have an undeniable potential to complement the teaching of morphology, helping students to understand the spatial representation of certain structures, integrate clinical aspects and prepare for exams.

Presentation number: 23.5

Topic: Varia

Decline in Anatomy Grades: Analysis of Trends for Different Exam Components Over the Last Decade

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Introduction: Anatomy assessment in Split includes written, practical and oral components, as well as daily written mini-exams. The final grade is a sum of differently pondered exam components. Students can attempt assessments five times within one academic year.

A decline in scores in both final grades and in individual exam components was noticed over the last decade. Mean scores for each exam component in the first sitting, and cumulative results for all five attempts within one academic year, are presented, as well as trends over the last decade.

Methods: Grades for 10 generations of medical students were extracted from exam reports. Overall performance and presentation of different exam components was plotted, trends and trendlines were established, evaluated and compared with the aim of finding which component(s) affected the decline most/least.

Results:

A continuous decline in performance on almost all components of the exam was noted. The declining trend in the written component was between 1% and 1.7% per year, with a declining probability around seven times greater than non-declining. The only exception was the practical component, and only in the first sitting. However, overall performance in the practical component showed the smallest decline (-0.05%).

The most prominent steady decline was noticed in daily tests (-1.6% per year).

Both oral and written components showed slightly sharper declines in the first sitting when compared to overall performance.

Conclusion:

The decline in exam performance is highest for daily tests, smallest for the practical component, with written and oral components being in-between.

Presentation number: 23.6

Topic: Digital and AI Tools in Teaching

Knowledge Retention of Undergraduate Medical Students in Regional Anatomy Following a One-Month Gross Anatomy Course Setting

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Introduction: Knowledge retention presents a major concern for medical students and educators to achieve optimal learning outcomes. Practical dissection courses facilitate the consolidation of anatomy knowledge. Previously, it was shown that a regional anatomy dissection course is more beneficial over a 3-month than a 1-month duration regarding pre-examination knowledge. This study aimed to assess if follow-up anatomy interventions help consolidate regional anatomy knowledge and facilitate knowledge retention of undergraduate medical students. It was hypothesized that knowledge retention could be enhanced using post-dissection teaching interventions. Methods: Upon completion of the dissection course, Objective Structured Practical Examinations (OSPEs) were performed for the neck, thorax and abdomen immediately before the start of the oral examinations, with follow-ups at 6 and 12 months. Between each of the examinations, virtual and in person lectures and seminars on (radiologic) anatomy and pathology were held, including Cinematic Rendering but without additional teaching on human tissues. Results: Significant improvements were observed for the neck and abdomen region in the 6- and 12-month follow-up OSPEs. The effects of knowledge gain were less marked in ethanol-glycerin than in Thiel-embalmed tissues. Student perceptions regarding tissue quality correlated positively with their assessment of tissue suitability for examination preparation. In conclusion, even anatomy teaching interventions not utilizing human tissues may help consolidate and improve regional anatomy knowledge over a one-year term. Discussion: Knowledge retention can be enhanced by accompanying virtual with physical teaching interventions.

Presentation number: 24.1

Topic: Neuroanatomy

Diversity of Proximal Axon Geometry in the Mouse and Human Hippocampus

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Introduction

The axon initial segment (AIS) is integral to neuronal excitability, yet its geometrical diversity within the hippocampus is poorly understood. In particular, dendritic axon origins give rise to privileged input channels that bridge both hemispheres and are resilient to perisomatic inhibition during network states associated with memory formation. Our research focuses on the geometric variability of axons and the AIS in murine and human hippocampal neurons.

Methods

We analyzed AIS length and position, dendrite shape, and sizes of soma and apical dendrites across various hippocampal regions in male mice, using Thy1-GFP labeling for morphology and βIV-spectrin immunolabeling for AIS visualization. Additionally, human hippocampal tissue from post-mortem autopsies and surgeries was examined. Computational simulations were conducted using NEURON simulation environment to explore form-function relationships.

Results

Significant differences were found in AIS characteristics, with CA3 neurons exhibiting longer AIS and more distal origins compared to CA1 and subicular neurons. Neurons with dendritic axon origins showed specific regional prevalence and minimal correlation with general cell morphology. Simulation of 3326 cells indicated that AIS diversity impacts neuronal function and hippocampal network dynamics. Similar findings were observed in human hippocampus, suggesting a shared structural-functional paradigm across species.

Discussion

These results underline the complex interplay between neuronal structure and function, urging further exploration of AIS variability's role in excitability and neuronal circuit behavior.

Presentation number: 24.2

Topic: Neuroanatomy

Morphology of Perforant Path-Granule Cell Synapses in the Murine Hippocampus Across Developmental Stages

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Introduction:

The dentate gyrus, a component of the hippocampal formation, plays a crucial role in cognitive functions such as learning and memory and is implicated in neurological and psychiatric disorders, including temporal lobe epilepsy and depression. Understanding the development of hippocampal neural networks is essential to elucidate their physiological and pathological dynamics. This study investigates the perforant path-granule cell synapses in the outer molecular layer (OML), the primary cortical input to the hippocampus.

Methods:

Using advanced volume electron microscopy (focused ion beam scanning electron microscopy, FIB SEM), we generated nanoscale image stacks from C57BL/6 mice at three developmental stages: juvenile (2 weeks), adolescent (8 weeks), and fully mature (16 weeks). These image stacks enabled us to characterize the ultrastructure of presynaptic (perforant path axons) and postsynaptic (granule cell dendrites) structures. Our three-dimensional reconstructions provided detailed insights into dendritic branch and spine morphometrics.

Results:

Our findings reveal that overall dendritic spine volume decreases significantly during development, while spine length remains constant, indicating a change in spine shape. Further analysis showed notable developmental changes in spine morphology, correlated with metrics such as the areal size of the postsynaptic density, which houses neurotransmitter receptors. Interestingly, heterogeneity in these structures increased with age. Furthermore, the correlation between different morphological metrics of spine synapses becomes significant only at later developmental stages.

Discussion:

These developmental changes in the hippocampal network's fundamental units suggest a newly discovered mechanism for enhanced synaptic plasticity efficiency, potentially contributing to improved memory formation as the hippocampal formation matures.

Presentation number: 24.3

Topic: Neuroanatomy

Influence of Clinical Parameters on the Structure and Function of Superficial Pyramidal Neurons in the Adult Human Neocortex

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Introduction: The dynamic nature of neuronal networks is driven by the interplay of cellular structure and function. Despite extensive research in animal models, the structure-function relationships in the human neocortex are still not well understood. Recent methodological advances now allow functional analysis of individual human neurons, offering new insights into fundamental brain processes. In this study, we investigated the structural and functional variability of superficial pyramidal neurons in the human neocortex.

Methods: We employed whole-cell patch-clamp recordings of neurons from acute neocortical slices obtained from seven neurosurgical resections to analyze excitatory neurotransmission and intrinsic membrane properties in superficial pyramidal neurons. For structural analysis, we used confocal microscopy to perform *post hoc* analysis of dendritic spine morphology in the recorded cells.

Results: We identified significant inter-individual differences in the analyzed neurons of seven patients. Our findings reveal age and potential disease/treatment effects – such as epilepsy/antiepileptic drugs and tumor/steroids – on excitatory neurotransmission, membrane properties, and dendritic spine morphologies.

Discussion: These results identify both endogenous and external factors that may affect the structural and functional properties of superficial pyramidal neurons. The observed inter-individual differences highlight the importance of considering these variations when working with human cortical resection material.

Supported by Deutsche Forschungsgemeinschaft (DFG; CRC/TRR 384).

Presentation number: 24.4

Topic: Neuroanatomy

Uniform Intralaminar but Specific Translaminar Disinhibitory Circuit Motifs of L5 SST Neurons in Mouse Barrel Cortex

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Layer (L) 5 is a hub in the cortical column in which a multitude of feedforward and feedback pathways converge. These inputs are then transmitted to distant sites by resident pyramidal cells. L5 pyramidal cells are under the strong influence of local somatostatin (SST)-expressing Martinotti cells (MC), while preferentially L4 excitatory cells are controlled by L5 non-Martinotti cells (nMC). To better understand the inhibitory control of L5 SST cells, which leads to disinhibition of excitatory cells, we used paired whole cell recordings. We investigated whether they receive intra- and translaminar inputs by parvalbumin (PV) and vasoactive intestinal peptide (VIP) neurons and what type of short-term synaptic plasticity these inputs display. In transgenic mice, we found that intralaminarly both PV and VIP showed a high (and also reciprocal) connection probability with L5 SST cells. PV to SST connections were depressing at all tested frequencies while VIP to SST connections were facilitating at high-frequency VIP cell stimulation. Interestingly, the translaminar inputs from L2/3 VIP to L5 SST cells showed similar connection probability (30%) and short-term plasticity in comparison to their L5 counterparts. However, L2/3 PV cells, despite numerous descending axon collaterals, showed hardly any connection (1/48). Thus, we show that intralaminar disinhibitory circuit motifs of L5 SST cells resemble those previously studied in L2/3. Furthermore, we demonstrate a selectivity in translaminar disinhibitory targeting by presynaptic PV and VIP neurons. These results shine new light on the circuit layout that enables intra- and translaminar dis/inhibitory processing in the cortical column.

Presentation number: 24.5

Topic: Neuroanatomy

The Tail of the Ventral Tegmental rea (tVTA)/Rostromedial tegmental nucleus (RMTg)

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INTRODUCTION

The tail of the ventral tegmental area/rostromedial tegmental nucleus (tVTA/RMTg), is a bilateral cluster of GABAergic neurons located in the most caudal part of the ventral tegmental area (VTA).

The tVTA/RMTg receives dense projections from the lateral habenula (LHb) and sends projections to the midbrain dopamine system (VTA, SNC) to the dorsal raphe (DR), to the extrapyramidal neurons, and the reticular formation in the midbrain.

METHODS

We performed a stereotactic injection in the tVTA/RMTg, in the globus pallidus (GP), nucleus accumbens (Acb) and ventral pallidum (VP) of adult male rats using dextrane biotin amine (BDA) as an anterograde tracer and Fluorogold as a retrograde tracer.

RESULTS

We identified several brain regions, in the telencephalon, diencephalon and mesencephalon, that may play a role as relay centers between the tVTA/RMTG, the GP, AcbSh, AcbC and the VP.

DISCUSSION

The LHb activity is modulated by the excitatory and inhibitory inputs arising from the GP, the VP and indirectly from the Acb. The VP, together with the LHb, the VTA and the SNC, modulates the limbic and cognitive stimuli integrating motivation and action. The relationship between the tVTA/RMTg and the basal ganglia leads us to better define the role of this pathway in modulating the midbrain dopamine system activity in relation to the aversive responses, the reward system and the locomotor activity.

Presentation number: 24.6

Topic: Neuroanatomy

Fecal Microbiota Transplantation of Patients with Anorexia Nervosa in an Activity-Based Anorexia Animal Model

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Introduction: Anorexia nervosa (AN) is an eating disorder characterized by extreme weight loss through self-starvation and hyperactivity. Research focusses on the gut-brain axis in relation to disease specific properties. The present study examines the combination of fecal microbiota transplants (FMT) and starvation on body weight loss, hyperactivity, and glia cells in the brain.

Methods: The activity-based anorexia (ABA) model mimics symptoms of AN such as weight loss, hyperactivity, and brain volume reduction. The experimental design included four groups: Two control groups (with and without starvation) received no FMT, while two ABA groups received FMT either from patients with AN (P) or healthy controls (HC). Body weight, food intake, and wheel activity were documented daily. Additionally, immunohistological stainings of the brain with GFAP and its mRNA expression in the cerebral cortex were analysed.

Results: Starvation in combination with FMT from one patient with AN led to a greater weight loss during starvation due to a lower food utilization efficiency in the ABA animals, effects that were not observed without starvation. Less $GFAP^+$ cells in corpus callosum of the HC group compared to P and a downregulated gene expression in the cerebral cortex in the P group were observed.

Discussion: Based on our findings we assume that the combination of food restriction in combination with microbiota alterations contribute to the development of AN.