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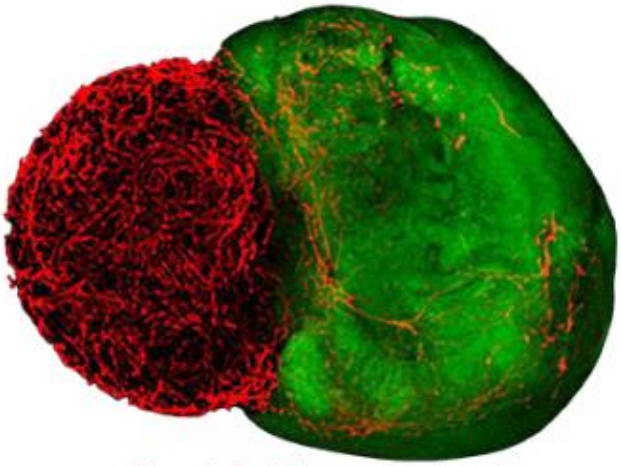

Vascularized Neuro-mesodermal
Assembloid

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am Institut für Anatomie und Zellbiologie
der Universität Würzburg

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an abstract of interest

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Vortrag 1:

Title:
Disentangling a L2/3 VIP cell to L4 SST cell circuit motif across primary somatosensory and visual cortices of mouse

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Abstract:
The mouse brain consists of a plethora of neurons, forming distinct cell-type specific circuits. One such motif is the vasoactive intestinal polypeptide (VIP) cell targeting of somatostatin (SST) cells. L4 SSTs of primary somatosensory (S1) and visual (V1) cortices are morphologically distinct. We aim to study if these morphological differences manifest functionally in the L2/3 VIP to L4 SST motif in S1 and V1 of mouse.
We performed single or paired whole-cell in-vitro patch clamp recordings in transgenic mice. VIPs and SSTs were recorded with standard intracellular solution (IC) or cesium methylsulfonate IC respectively. Both ICs contained 2% biocytin for morphological characterization.
Reconstructions of SSTs revealed that all SSTs in S1 (12/12 cells) were non-Martinotti cells (nMCs) whereas most in V1 (9/10 cells) were Martinotti cells (MCs). VIP-SST connectivity was 47% in S1 and 36% in V1 (S1- 28/61 pairs; V1- 27/74 pairs), and unitary synaptic properties were comparable. Short-term plasticity (STP) was studied by evoking VIPs to spike at 1, 10, and 50 Hz. Some connections in both cortices either showed stable responses (S1- 9/25, V1- 13/27) or short-term facilitation (S1- 9/25, V1- 14/27) during 50Hz stimulation. Strikingly, a distinct population of connections only in S1, exhibited strong short-term depression during 50Hz stimulation (7/25).
Despite morphological differences in L4 SSTs, the VIP – SST motif in S1 and V1 exhibits comparable unitary connectivity properties. However, short-term depression was exhibited only by S1 VIP-nMC motif during 50 Hz stimulation. Therefore, we report cell-type specific inhibitory circuits in sensory cortices of mouse.

Vortrag 2:

Title:
Altered cortical synaptic lipid signaling leads to intermediate phenotypes of mental disorders

Authors:
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Abstract:
Excitation/inhibition (E/I) balance plays an important role in mental disorders. Bioactive phospholipids synthesized by the enzyme autotaxin (ATX) at the cortical synapse modulate glutamatergic transmission, E/I balance and cortical network excitability. Here, we aimed to investigate functional consequences of altered E/I balance in the human brain induced by genetic disruption of the synaptic lipid signaling modifier PRG-1 and to assess potential therapeutic interventions.
EEG combined with TMS in an instructed fear paradigm, neuropsychological analysis and fMRI based episodic memory task. Behavioral and in-vivo cortical measurements in an animal model.
Using EEG combined with TMS in an instructed fear paradigm, neuropsychological analysis and fMRI based episodic memory task we found intermediate phenotypes of mental disorders in human loss-of-function SNP carriers (PRG-1R345T/WT). Cortical network analysis revealed that coherence and phase-amplitude coupling were substantially altered by PRG-1 deficiency in memory related circuits in humans and mice alike.
Dysregulated synaptic lipid signaling alters E/I balance inducing intermediate phenotypes of psychiatric disorders in humans carrying loss-of-function PRG-1R345T/WT mutation and in related animal models. Inhibiting lipid signaling in mice normalized E/I balance indicating interventional potential for mental disorders.

Vortrag 3:

Title:
How does spatial and non-spatial training affect adult neurogenesis in the avian hippocampus?

Authors:
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Abstract:
In the past years, a lot of research has been conducted on adult neurogenesis (AN) but the functional significance of this trait is still ambiguous. In birds, AN is more widespread compared to mammals which allows to study AN in a more comprehensive way.
Here, 29 homing pigeons (Columba livia f.d.) were raised together. 10 of them lived permanently in the loft (Group Box-Training) while the other 19 could fly around the loft. After reaching sexual maturity, all pigeons were treated with 5-bromo-deoxyuridine (BrdU) to label dividing cells. Thereafter, Group Box-Training was trained in a learning task in an operant chamber. Group Flight-Training (n=10) got an individual training with several releases from unknown places. The remaining 9 animals served as control group. After three months, all pigeons were sacrificed, brains were dissected and immunohistochemically processed with several markers to examine newly generated cells in the subregions of the hippocampal formation.
The level of AN differs between groups and hippocampal subregions. Both training groups showed increased number of adult newborn neurons compared to control pigeons. Immature neurons showed a training-task dependent pattern with decreased levels in both training groups but still higher levels in Flight-Training pigeons compared to Box-Training pigeons.
Our findings indicate that learning processes have a positive effect on AN. The different distribution of maturing cells in the hippocampal structures support the idea that there is a functional specialization, respectively, that there is a link between brain-structure and function, species-specific requirements and AN.

Vortrag 4:

Title:
CCN2/CTGF levels affect pathologic angiogenetic processes in oxygen-induced retinopathy

Authors:
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Abstract:
Aberrant vessel growth is a common hallmark of retinal diseases like, retinopathy of prematurity and diabetic retinopathy, leading finally to blindness. Here we investigated whether CCN2/CTGF, a reported target gene and a modifier of VEGF, is involved in vessel loss and neovascularization, and the development of intraretinal capillaries under pathologic conditions.
The BETAB1-CTGF1 mouse-model, with a lens-specific CCN2/CTGF-overexpression and the conditional-inducible knockout CAGCCre-ERTMCTGFCoin/Coin mouse-model (tamoxifen treatment: 5mg/ml; 3x/d for 5d) were analyzed in the oxygen-induced retinopathy mouse-model. Mice were exposed to 75% oxygen from postnatal day (P)7 to P12 and returned to room air until final analysis. Wildtype and CTGFCoin/Coin littermates served as controls. On P17, mice were perfused with FITC-conjugated-dextran, area of vessel loss, area of neovascular tufts and the deep vascular plexus was quantified on retinal flat mounts and plotted as percentage of the total area. Intraretinal capillary development was investigated in the Ndp-deficient mice in combination with a CCN2/CTGF overexpression.
B1-CTGF1 mice showed a significantly smaller area of neovascular tufts, avascular zone and a significantly larger area of the deep vascular plexus compared to wildtypes. In CAGCCre-ERTMCTGFCoin/Coin mice only the avascular area was significantly increased compared to CTGFCoin/Coin controls. Immunohistochemical analysis showed that CCN2/CTGF-overexpression of the BETAB1-CTGF6 mice does not rescue the lack of intraretinal capillaries and the impaired blood-retinal-barrier in Ndp-deficient mice.
We conclude that CCN2/CTGF is an important mediator of vascular integrity in the mouse retina that stabilizes retinal vessels and promotes regrowth of capillaries after oxygen-induced vascular damage.

Vortrag 5:

Title:
Intersectional strategy to study cortical inhibitory parvalbumin-expressing interneurons

Authors:
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Abstract:
The aim of this study was to investigate how much two transgenic mouse lines, (i) the PV-Cre/tdTomato and (ii) the intersectional Vgat-Cre/PV-Flp/tdTomato mouse line are able to fulfill the need of a specific access to inhibitory parvalbumin-expressing (PV) interneurons of the mammalian cerebral cortex.
We assessed the colocalization of the immunoamplified transgene (tdTomato) with the parvalbumin protein (labeled by immunohistochemistry), the colocalization of tdTomato with the Gad1 probe (a conclusive inhibitory cell marker) and the Vglut1 probe (a conclusive excitatory cell marker) and the codistribution of tdTomato with the lectin marker WFA (a marker for perineuronal nets).
In the PV-Cre/tdTomato mouse line, we detected a substantial proportion of layer 5 PV neurons to be excitatory and not inhibitory, whereas in the Vgat-Cre/PV-Flp/tdTomato mouse line, no colocalization of tdTomato with the Vglut1 probe was found.
In conclusion, the Vgat-Cre/PV-Flp/tdTomato mouse line seems to be a more reliable animal model for experiments investigating the connectivity of parvalbumin-expressing GABAergic neurons and future studies using the PV-Cre/tdTomato mouse line have to consider L5 pyramidal cells as a putative confounder.

Vortrag 6:

Title:
GPR124 regulates murine brain developmental angiogenesis and blood-brain barrier formation by an intracellular domain-independent mechanism

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Abstract:
The GPR124/RECK/WNT7 pathway is an essential regulator of central nervous system angiogenesis and blood-brain barrier (BBB) function. GPR124, a brain endothelial adhesion 7-pass transmembrane protein, associates with membrane RECK, which binds and stabilizes newly synthesized WNT7 for transfer to Frizzled (FZD) and canonical beta-catenin signaling. GPR124 function remains enigmatic; while its extracellular domain (ECD) is required, the poorly conserved intracellular domain (ICD) appears to be variably required in mammals versus zebrafish, potentially mediated by intracellular adaptor protein bridging of the GPR124 and FZD ICDs. GPR124 ICD deletion mutants impair zebrafish angiogenesis, but paradoxically still mediate WNT7 signaling upon mammalian cell transfection.
We thus further investigated the functionality of the GPR124 C-terminal ICD by deletion in mice (Gpr124ΔC).
Although GPR124ΔC protein was inefficiently expressed, Gpr124ΔC/ΔC mice could be born and exhibited normal cerebral cortex angiogenesis, in marked contrast to Gpr124-/- embryonic lethality, forebrain avascularity and hemorrhage. The only vascular phenotypes observed in Gpr124ΔC/ΔC mice were sporadic angiogenic defects confined to ganglionic eminences which were attributable to impaired expression of GPR124ΔC protein. Further, GPR124ΔC and recombinant GPR124 ECD both rescued WNT7 signaling following brain endothelial Gpr124 knockdown.
Thus, in mice, the GPR124 essential regulation of WNT7-dependent CNS forebrain angiogenesis and BBB function is exerted by ICD-independent functionality, extending the range of signaling mechanisms used by adhesion 7-pass transmembrane receptors.

Vortrag 7:

Title:
Peripherally derived lysophosphatidic acid controls feeding behavior by modulating glutamatergic transmission at cortical synapses

Authors:
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Abstract:
Lysophosphatidic acid (LPA) has been shown to influence glutamatergic transmission and cortical excitability. The levels of phospholipids like LPA are under the influence of peripheral metabolism. Here we investigated if the peripheral energy metabolism via influencing brain LPA levels can remotely influence cortical excitability and thereby modulate behavior.
We combined electrophysiology with behavioral assays to probe changes in cortical excitability and their functional consequences during fasting of mice and used mass spectrometry to assess lipid levels in blood and cerebrospinal fluid (CSF).
We found an increase of LPA species in blood and CSF after overnight fasting, which coincides with increased excitability. LPA-related cortical excitability increases fasting-induced hyperphagia, and is decreased following inhibition of LPA synthesis. Mice expressing a human mutation (Prg-1R346T) leading to higher synaptic lipid-mediated cortical excitability display increased fasting-induced hyperphagia. Accordingly, human subjects with this mutation have higher body mass index and prevalence of type 2 diabetes. We further show that the peripheral lipid metabolism and consequently LPA levels following fasting are controlled by hypothalamic agouti-related peptide (AgRP) neurons. Depletion of AgRP-neurons decreases fasting-induced elevation of circulating LPAs and hereby reduces cortical excitability, while blunting hyperphagia.
Our findings reveal that, peripheral phospholipid levels may influence cortical excitability. This presents a novel non-neuronal body-to-brain pathway mediating food intake behavior and thereby a potential new target for the treatment of eating disorders.

Vortrag 8:

Title:
Axon morphology and intrinsic cellular properties determine the threshold for plasticity-induction through repetitive transcranial magnetic stimulation

Authors:
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Abstract:
Repetitive transcranial magnetic stimulation (rTMS) is widely used in clinical and research settings, yet its cellular and molecular mechanisms remain unclear. Standardizing stimulus parameters, particularly electric field strength, is essential for meaningful comparisons and clinical translation. The influence of structural and functional properties of stimulated neurons on rTMS outcomes is not well understood.
In this study, we employed a cross-species comparison strategy to investigate the effects of 10 Hz rTMS on entorhino-hippocampal tissue cultures from mice and rats. Through electrophysiology, confocal microscopy, and computer modeling, we examined the influence of the stimulation protocol on comparable neuronal networks in highly standardized experimental conditions.
We observed similar plastic changes in excitatory and inhibitory synapses of CA1 pyramidal neurons in both mouse and rat tissue cultures, consistent with previous reports. However, we identified that higher stimulation intensity was necessary to induce rTMS-induced plasticity in rat cultures. By systematically comparing neuronal properties and employing computational modeling, we determined that axon morphologies play a critical role in rTMS-induced synaptic plasticity. However, morphological parameters alone were insufficient to explain the observed differences. Instead, disparities in intrinsic cellular properties emerged as the primary factor accounting for the 10% higher intensity required for plasticity induction in rat cultures.
These findings underscore the importance of biophysical cellular properties in predicting the impact of rTMS on plasticity. They carry important implications for advancing computer models that aim to predict and standardize the biological effects of rTMS.

Vortrag 9:

Title:
Modeling neural crest cell induction, migration, and peripheral nervous system development in complex human 3D organoid models

Authors:
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Abstract:
Our aim is to develop complex human 3D organoid models that recapitulate key aspects of peripheral nervous system (PNS) development, including neural crest cell (NCC) induction, migration, and the formation of sensory and sympathetic ganglia in the cell culture dish.
Human induced pluripotent stem cells (hiPSCs) are aggregated in 3D suspension culture and directed towards a neural plate identity using a specific differentiation protocol that involves dual-SMAD inhibition and WNT activation. The resulting neural plate organoids (NPOs) are then co-cultured with hiPSC-derived mesodermal organoids to form a neuro-mesodermal assembloid. The assembloids are analyzed using immunofluorescence analyses, tissue clearing, single-cell RNA sequencing as well as calcium imaging. Moreover, a Sox10-GFP reporter hiPSC line is generated to directly trace migrating NCCs in living cultures.
The model recapitulates aspects of PNS development such as NCC induction, migration, and sensory as well as sympathetic ganglion formation. The ganglia send projections to the mesodermal and the neural compartment. Axons are associated with Schwann cells. In addition, peripheral ganglia and nerve fibers interact with a co-developing vascular plexus, forming a neurovascular niche. Finally, developing sensory ganglia show a response to capsaicin indicating their functionality.
The new assembloid model will be useful to gain insights into the mechanisms underlying early human development and to study NCC-related defects. Finally, it may be even possible to study nociception in the dish. Moreover, the model could be used for toxicity screenings and drug testing.

Vortrag 10:

Title:
The lincRNA Pantr1 is a critical mediator of dendritic outgrowth in a murine and human model of FOXG1 syndrome

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Abstract:
Rett- and Rett-spectrum disorders, such as FOXG1 syndrome, arise from disturbances in gene expression programs involving transcriptional and posttranscriptional mechanisms. Although non-coding RNAs are involved in brain development and aberrant expression has been associated with a wide range of neurological diseases, the role of long non-coding RNAs (lincRNAs) in FOXG1 syndrome development remains unexplored yet.
Therefore, we investigated the expression of lincRNAs in the hippocampus and cerebral cortex of adult and developing mice, as well as in human brain organoids. Our findings revealed differential expression of Pantr1 (Pou3f3 adjacent non-coding transcript 1) upon heterozygous loss of FOXG1. Pantr1 localized to the nucleus, cytoplasm, and dendrites, and it exhibited interactions with various proteins. One such protein identified through pulldown experiments and mass spectrometry is PURB. Upon knockdown of FOXG1, Pantr1, or PURB using shRNA in cultured hippocampal neurons and neural progenitor cells, we observed differently expressed shared target genes and altered binding of FOXG1 by RNAseq, ChIPseq, and RT-qPCR. Additionally, Sholl analysis demonstrated changes in neuronal morphology and dendritic outgrowth, while immunoprecipitation assays confirmed interactions between Pantr1, FOXG1, and PURB.
Our study suggests that the expression and function of FOXG1, PURB, and Pantr1 are critical for dendritic outgrowth and neuronal differentiation by establishing an interactive network that regulates gene transcription associated with dendritic complexity during brain development.
Given that aberrant Pantr1 expression contributes to defects in dendritic outgrowth, it holds considerable potential as a therapeutic target for neurodevelopmental disorders such as FOXG1 syndrome.

Vortrag 11:

Title:
Extracellular vesicles may play a role in the brain Nrf2 activation following Spinal Cord Injury, and leading to the induction of oligodendrogenesis in the subventricular zone

Authors:
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Abstract:
Spinal cord injuries (SCI) disturb the communication between the brain and other body parts, resulting in loss of movement and sensation. The initial injury primarily leads to tissue damage at the injury site, but it is followed by secondary events that contribute to the spread of damage. The objective of this study was to assess SCI-induced brain plasticity and its influence on the subventricular zone (SVZ)-derived stem cells.
To induce SCI in mice, an Infinite Horizon Spinal Cord Impactor was employed. Subsequently, the activation of Nrf2/ARE, neuroinflammation, the population of extracellular vesicles, and neurogenesis/gliogenesis were assessed at different time points post-SCI (PSCI).
By utilizing ARE-Luc mice, we confirmed a significant activation of Nrf2 in the brain 24h PSCI along with upregulation of the Nrf2-related genes, and inflammatory markers. However, there were no significant changes observed in the population of GFAP and Iba-1 cells. Intriguingly, neurogenesis and oligodendrogenesis showed a substantial increase in the SVZ 24h PSCI and a high concentration of extracellular vesicles. Conversely, astrogliogenesis significantly increased in the SVZ 7 days PSCI along with, accompanied by a decrease in serotonergic neurons and an increase in cholinergic neurons in the cerebral cortex.
These findings suggest that injury-derived extracellular vesicles play a role in influencing SVZ-derived stem cells after 24h PSCI. This effect is achieved by activating the Nrf2, promoting oligodendrogenesis vs astrogenesis. However, further studies are required to determine the cellular source of these specific vesicles within the injury site and their precise biological cargo that mediates these desired effects.

Vortrag 12:

Title:
Morphological and mechanical mapping of the human dura mater

Authors:
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Abstract:
The dura mater is the outermost layer of the meninges, acting as a protective membrane for the brain and spinal cord. It is composed of collagen and elastin fibers, proteoglycans, and other extracellular matrix components, supporting the stability and integrity of the central nervous system. Despite its importance, computational and physical head models often overlook the dura, especially regarding traumatic brain injuries. Little is known about its anisotropic mechanical behavior and collagen fiber orientation. Hence, this study investigates the mechanical anisotropy of different locations, correlating it with the orientation of collagen fibers.
To achieve this objective, sixty samples from six donors were subjected to uniaxial extension tests until failure in a heated tissue bath, utilizing a Z020 torsion multi-axis testing system (ZwickRoell AG, Ulm, Germany) together with an Aramis image correlation system (GOM, Braunschweig, Germany). Additionally, the collagen microstructure was analyzed using second-harmonic generation imaging.
The data obtained were used to determine the failure stress and strain, E-moduli, and a microstructurally motivated material model was employed to examine local differences in both structure and mechanics. Among others, significant differences in collagen fiber dispersion and main fiber orientation were found. The structural parameters obtained from only four out of six donors yielded good fitting results to the structurally motivated mechanical model for the remaining two donors in all directions.
This study establishes a foundation for further research on the microstructure and mechanical properties of the human dura mater, enabling realistic modeling and prediction of tissue failure.

Vortrag 13:

Title:
Direct exosome transfection with fluorescently labeled small RNAs is a useful tool for exosomal cargo tracking and functional RNAi in cultured podocytes.

Authors:
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Abstract:
Podocytes form the outer aspect of the glomerular filtration barrier. Changes of their complex 3D morphology are the leading cause for 80% of chronic kidney disease (CKD) cases. Exosomal small RNAs are important means of cell-cell communication in CKD pathogenesis. We investigated if isolated exosomes, directly transfected with fluorescently labeled small RNAs, are suitable for exosomal cargo tracking and for functional delivery of small RNAs in cultured podocytes.
We isolated exosomes from cultured, murine podocytes and transfected them directly with Cy3-labeled siRNAs and miRNAs using ExoFect siRNA/miRNA Transfection Kit and co-cultured them with podocytes in vitro. The transfected exosomes were characterized by transmission electron microscopy and Western blot. Isolated exosomes were also transfected with filamin A (FlnA)-siRNAs and pre-miR-21. Exosome-uptake, transfection- and knockdown efficiency were confirmed by RT-qPCR, Western blot and immunofluorescence, respectively.
Exosomes display a typical shape and size of 20 nm and a specific marker expression before and after transfection. Cultured, murine podocytes take up fluorescently labeled exosomal RNAs in a time-dependent manner. Transfection of exosomes with FlnA-siRNAs leads to a decrease of FlnA-expression in podocytes co-cultured with transfected exosomes as revealed by immunofluorescence and Western blot. Podocytes incubated with pre-miR-21-transfected exosomes showed a 338-fold upregulation of miR-21 in RT-qPCR.
Here we show that direct transfection of exosomes with fluorescently labeled small RNAs is a useful tool for exosome cargo tracking and for administration of small RNAs into cultured podocytes. This might be a novel therapeutic strategy for regulating protein and miRNA expression in podocytes.

Vortrag 14:

Title:
Effects of Punicalagin on Osteosarcoma Cell-Lines and Patient Tissue in the 3D-in-vivo-tumor model

Authors:
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Abstract:
Osteosarcomas are the most common primary malignant bone tumors. Patients with metastasis at diagnosis have an especially dismal prognosis that indicates a strong need for new treatment options. One substance that has shown good results in several studies is Punicalagin, an antioxidant ellagitannin found in pomegranate juice. The aim of this study was to examine the effects of Punicalagin on osteosarcomas in a 3D in-vivo-tumor model.
Human osteosarcoma biopsies, SaOs-2 and MG-63 cells were cultivated in the 3D in-vivo chorioallantoic membrane model (CAM). The tumors were treated daily with punicalagin. The IKOSA CAM Assay Application, an automated Artificial Intelligence (AI) based image analysis algorithm was used to analyze the tumors on the CAM, to detect vessel length and branching points. After explantation, HE- and Ki67-stainings were performed. Ki-67-stained MG-63-cell-pellets were used to train a novel application for the quantitative analysis of Ki-67-stainings of Osteosarcoma tissue using IKOSA AI.
The SaOs-2-tumors treated with Punicalagin exhibited a decrease of vessel length and branching points per area. The human tissue also displayed a decrease of vessel length and branching points per area. HE- and Ki-67-stainings indicated lower vitality and proliferation of the treated tumors. The decrease of vessel length and branching points per area in the treated group confirmed the antiangiogenic effects of Punicalagin. The lower vitality and proliferation in the histological stainings support the results of previous cell culture experiments. Punicalagin could be a promising treatment option for osteosarcoma patients and further studies should be conducted.

Vortrag 15:

Title:
Effect of micro- and nanoplastic particles (polystyrene microbeads) on human macrophages

Authors:
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Abstract:
Micro- and nanoplastics (MNPs) are ubiquitously in our environment and even in human blood. Since macrophages (MPHs) are crucial for innate immunity, the question arouse how they take up and react to ingested MNPs. The thermoplastic polymer polystyrene (PS) is frequently used in objects of our daily life like food packaging and is therefore of major interest for this study. The phagocytosis behaviour and potential cytotoxic effects of MNPs on human MPHs were investigated in primary MHPs cells. Preliminary experiments were the first steps towards establishing an in vitro model for MNPs in MHPs
MPHs were obtained by differentiating monocytes isolated from human peripheral blood mononuclear cells and stimulated with PS microbeads. Transmission electron microscopy (TEM) and Nanolive cell imageing video (NLCIV) were used to study the phagocytosis behaviour. Flow cytometry was used to study the activation and polarization of MPHs as well as cell viability, mortality and ROS production.
TEM and NLCIV showed dose-dependent phagocytosis of MNPs with a maximum absorption capacity. Stimulation with plastic had no clear effect on the polarization of MPHs or ROS production. Nevertheless, reduced metabolic activity and significantly increased necrosis were observed with higher MNP doses.
In summary, MNPs are taken up by MPHs in a dose-dependent manner and lead to changes in cell size and shape. Although there are no clear effects on the polarization of ROS production by MPHs, MNPs lead to decreased metabolic activity and necrosis of MPHs. Further studies are needed to fully elucidate the effects of MNPs on MPHs.

Vortrag 16:

Title:
Regulation of hyaloid blood vessel regression by GPR124

Authors:
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Abstract:
Hyaloid blood vessels (HBV) transiently supply the developing eye and usually regress in late gestation. Failure of HBV regression results in persistent hyperplastic primary vitreous, a congenital eye disorder that can lead to retinal tears, hemorrhage, and detachment. Genetic studies in mice have shown that endothelial WNT7B/β-catenin signaling critically regulates HBV regression. However, the receptors and target genes of WNT7B in hyaloid endothelial cells (hyEC) are still elusive. The adhesion G protein-coupled receptor 124 (GPR124) is an essential regulator of WNT7A/7B/β-catenin signaling in brain EC. Here, we tested the hypothesis that GPR124 also mediates WNT7B/β-catenin signaling in hyEC.
Endothelial-specific Gpr124 knockout mice (Gpr124ΔEC/ΔEC) were compared with control littermates (Gpr124fl/fl) and HBV density was quantified in stained flatmounts. To test, if GPR124 mediates HBV regression by regulating WNT/β-catenin signaling, we administered the WNT receptor-independent β-catenin activator CHIR-99021 to potentially rescue the Gpr124ΔEC/ΔEC phenotype.
Analysis of Gpr124ΔEC/ΔEC mice showed persistent HBV at P8, while substantial HBV regression had occurred in control littermates. Pharmacological activation of WNT/β-catenin signaling by CHIR-99021 resulted in complete rescue of the HBV phenotype in Gpr124ΔEC/ΔEC mice, but did not accelerate HBV regression in control littermates.
Our data show that GPR124 mediates hyaloid blood vessel regression by activating the WNT7B/β-catenin signaling pathway in hyEC. GPR124/WNT7B signaling is necessary, but not sufficient to induce HBV regression. To further elucidate the molecular mechanisms of HBV regression and target genes of GPR124/WNT7B signaling in hyEC, we are planning to perform single cell RNA-Seq analyses of HBV/vitreous body cells from Gpr124ΔEC/ΔEC and Gpr124fl/fl mice.

Vortrag 17:

Title:
Protective effect of apremilast on pemphigus autoantibody-induced loss of cell adhesion is dependent on EPAC1

Authors:
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Abstract:
In the life-threatening disease pemphigus vulgaris autoantibodies (PV-IgG) directed against the desmosomal cadherins desmoglein (Dsg) 1 and Dsg3 cause loss of keratinocyte adhesion and thereby blistering of the skin. We recently reported that the phosphodiesterase 4 inhibitor apremilast ameliorates skin blistering as well as loss of keratinocyte adhesion and strengthens keratin network. Nevertheless, for therapeutic use more knowledge about the underlying mechanism is desirable. For this purpose, we analyzed the involvement of the cAMP-regulated exchange factor EPAC1.
EPAC1-deficient mice, immunostaining, keratinocyte dissociation assay, Western blot
While the epidermis of EPAC1-deficient mice did not show any significant alterations of desmosomal components, EPAC1-deficient keratinocytes revealed an enhanced expression of some desmosomal proteins including Dsg1 and Dsg3, which was paralleled by stronger intercellular adhesion. This was also reflected by reduced loss of keratinocyte adhesion in response to the Dsg3-specific pathogenic pemphigus antibody AK23. Interestingly, the effect of apremilast to rescue loss of adhesion after challenge with pemphigus autoantibodies was abrogated in EPAC1-deficient keratinocytes indicating that EPAC1 is involved in mediating this protective effects. In contrast, cAMP increase in response to combined treatment with the phosphodiesterase 4 inhibitor rolipram and the adenylate cyclase activator forskolin, which was drastically more pronounced compared to apremilast treatment, was still effective to ameliorate autoantibody-induced keratin retraction and loss of adhesion in EPAC1-deficient cells.
Taken together, these data indicate that EPAC1 is involved in cAMP-mediated stabilization of keratinocyte adhesion, however, its dysfunction can be compensated in murine epidermis in vivo and by high cAMP levels in vitro.

Vortrag 18:

Title:
FcRn-/- mice display features of chronic kidney disease

Authors:
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Abstract:
Chronic kidney disease (CKD) increases worldwide and is a high social economic burden. Diabetic kidney disease is the leading cause for the development of CKD. GWAS studies presented a strong association between the neonatal Fc receptor (FcRn) and diabetes mellitus. Previous results from our group found a strong FcRn mRNA reduction in STZ-treated type 1 diabetic mice. The role of FcRn decline in the progression towards CKD remain unknown and are the subject of our analysis.
3-, 6- and 15-month-old mice lacking FcRn (FcRn-/-) in comparison to wildtype mice (WT) were analyzed. Renal functional parameters and morphology were analyzed, RNA sequencing analysis was performed, and FcRn-CRISPR knockout in BN16 cells were generated for in vitro analyses. The glomerular filtration rate was significantly reduced in 3-month-old FcRn-/-. After 6 month a significant reduction of renal cortices in FcRn-/- was observed and progressed over time due to shortening of proximal tubules, which was accompanied by reduced endocytosis capacity. The number of Ki-67 positive proximal tubule cells was significantly reduced in FcRn -/- compared to WT mice. RNA sequencing analysis revealed altered genes playing a role in autophagy and ciliogenesis. An elongation of cilia in FcRn-/- was confirmed immunohistologically. FcRn -/- CRISPR/Cas9 knockout cells showed a reduced number of Ki-67 positive cells, an elevation of autophagy markers p62 and LC 3 A/B and a higher oxygen consumption.
In conclusion, loss of FcRn results in a switch of cellular metabolism with enhanced autophagy and respiration combined with proximal tubule reduction and functional impairment. Therefore, loss of FcRn results in a decline in kidney function mirroring some features of CKD.

Vortrag 19:

Title:
HDAC3 and KLF5 are potential targets for treatment of the blistering skin disease pemphigus vulgaris.

Authors:
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Abstract:
Desmosomes are crucial intercellular junctions to enable strong intercellular adhesion. This adhesive function is impaired in severe diseases such as the autoimmune skin disease pemphigus. Using unbiased approaches, we want to identified unknown regulatory pathways that influence desmosomal adhesion.
A CRISPR/Cas9 screen of the whole genome and a promoter screen of the desmosomal gene DSG3 were performed in human keratinocytes to identify unknown endogenous modulators of desmosomal adhesion. The transcription factor Kruppel-like-factor 5 (KLF5) was discovered to be a direct binder of the regulatory region of DSG3 and a pro-adhesive hit. Using newborn mice and ex-vivo skin models of human pemphigus, we investigated the KLF5 regulator HDAC3 as a potential treatment target.
Incubation with autoantibody fractions from pemphigus vulgaris patients (PV-IgG) resulted in a decrease in KLF5 protein levels and an upregulation of histone deacetylase activity, particularly histone deacetylase3 (HDAC3), while abrogating intercellular adhesion in vitro and inducing blister formation in vivo. Overexpression of HDAC3 resulted in decreased intercellular adhesion and mimicked the phenotype induced by PV-IgG. Inhibition of HDAC3 led to induction of the DSG3 promoter and restoration of intercellular adhesion through an overall increase in DSG3 levels and localization in the membrane. Finally, two different HDAC3 inhibitors prevented PV-IgG-induced blister formation and restored KLF5 levels in human epidermis.
KLF5 and HDAC3 have been identified as novel regulators of DSG3 gene expression and intercellular adhesion and are potential targets for the treatment of pemphigus.

Vortrag 20:

Title:
Establishment of pan-glutamatergic subtype diversification in the cortex depends on Bcl11a and Bcl11b

Authors:
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Abstract:
In the neocortex, immature projection neurons acquire neuronal subtype identity in the cortical plate by combinatorial expression of developmentally expressed transcription factors. Despite advances in defining the mechanisms that control subtype diversification, the genetic program that allows subtype identity acquisition in the cortical plate remains to be characterized.
We combine mouse genetics with differential bulk RNA expression and single cell RNA sequencing analyses to identify changes in gene regulatory networks at mid-corticogenesis in Bcl11a/b double knockouts. CUT&RUN followed by sequencing is used to map binding sites of Bcl11a and Bcl11b in cortical neurons.
Bcl11a and Bcl11b cooperatively regulate gene expression in the cortical plate and underlying intermediate zone. On a single cell level, differentiation of Bcl11a/b mutant neurons is arrested at the migratory state, leading to aberrant cell types and a disruption of cortical plate formation. Genetic programs required by immature neurons to progress to a mature state are downregulated upon loss of Bcl11a/b, leading to defects in cortical lamination and absence of major axon tracts. Our data show that Bcl11a and Bcl11b together allow pan-glutamatergic subtype diversification during a critical developmental period marked by the occurrence of the cortical plate.

Vortrag 21:

Title:
Regulation of hippocampal mossy fiber-CA3 synapse function by a Bcl11b/C1ql2/Nrxn3(25b+) pathway

Authors:
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Abstract:
The transcription factor Bcl11b has been linked to neurodevelopmental and neuropsychiatric disorders associated with synaptic dysfunction. Bcl11b is highly expressed in dentate gyrus granule neurons and is required for the structural and functional integrity of mossy fiber-CA3 synapses. The underlying molecular mechanisms, however, remained unclear.
We employ a wide spectrum of state-of-the-art genetic, biochemical, molecular, electrophysiological and ultrastructural approaches including Cre-/loxP system, stereotaxic AAV-mediated gene expression and silencing, transmission electron microscopy, mossy fiber-LTP recordings, and structural protein modelling.
We show that the secreted synaptic organizer molecule C1ql2 is a direct, functional target of the transcription factor Bcl11b in murine dentate granule neurons that regulates synaptic vesicle recruitment and LTP at the mossy fiber- CA3 synapse. Moreover, we demonstrate that C1ql2 exerts its regulatory function through direct interaction with a specific splice variant of neurexin-3, Nrxn3(25b+). Interruption of this protein interaction by expression of a non-binding C1ql2 variant as well as deletion of Nrxn3 in dentate granule neurons perturbs ultrastructural organization of the mossy fiber synapse and recapitulates phenotypes observed upon ablation of both, Bcl11b or C1ql2.
Together, this study identifies a novel C1ql2-Nrxn3(25b+)-dependent signaling pathway through which Bcl11b controls mossy fiber-CA3 synapse function. Our findings contribute to the mechanistic understanding of neurodevelopmental disorders accompanied by synaptic dysfunction.

Vortrag 22:

Title:
Holoprosencephaly with cyclopia or anophthalmia result from alterations in BMP signaling

Authors:
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Abstract:
BMP antagonism is necessary for proper morphogenesis of the optic cup in zebrafish and is involved in the pathogenesis of coloboma. Our current focus is the role of BMP signaling during morphogenesis of the Anterior Neural Plate (ANP). Alterations of ANP development, resulting in Holoprosencephaly (HPE), can also present coloboma.
We use the model system zebrafish, CRISPR/Cas9 injections targeting the locus of Bmp7b, overexpression of bmp4 using a heat-shock inducible transgenic line, qPCR analysis, whole mount in situ hybridization and microscopy.
We show that ANP morphogenesis is sensitive to BMP signaling. We found two distinct but different HPE phenotypes. Induction of bmp4 resulted in a failure of forebrain splitting and anophthalmia, suggesting that antagonists to BMPs (fsta, grem2b, nog2, chrd), found in the ANP, are important to facilitate splitting of the whole ANP. Rx2 positive retinal precursors were specified, however, failed to evaginate from the eye field within the ANP. CRISPR/Cas9 injections, targeting Bmp7b, however, resulted in cyclopia. Here, our data suggest that the telencephalic precursors (emx3) were able to split, while the precursors of the eye field remained condensed at the midline. Our data show that BMP signaling is important during ANP development and that alterations result in HPE. Together, our data show distinct but also different HPE phenotypes, resulting from either an induction of a ligand (bmp4) or a targeted inactivation of another ligand (bmp7b). We are currently trying to better understand the mechanism behind, using transcriptomics and analysis of BMP signaling, canonical as well as non-canonical.

Vortrag 23:

Title:
Postnatal microglial heterogeneity along a spatio-temporal axis

Authors:
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Abstract:
Microglia, the resident immune cells of the central nervous system, play crucial roles in brain development, homeostasis, and immune response. Their development and maturation occur predominantly during the early postnatal period. Understanding the molecular mechanisms underlying microglial development is essential for unraveling their diverse functional roles. In this study we used the GeoMxTM digital spatial profiling to investigate spatial gene expression that drive microglial migration, heterogeneity, and responses to microenvironmental cues.
Spatial transcriptomics was performed using FFPE samples from C57BL/6 wild type mice at three postnatal time points (P0, P5, P15). Immunohistochemistry was performed on sagittal brain slices using the microglial-specific marker Iba1. Additionally, nuclear staining was utilized to identify and select multiple regions of interest (ROI) within the corpus callosum, hippocampus, and cortex. Each ROI was further segmented into Iba1-positive and Iba1-negative segments, and the transcriptome of both areas was analyzed.
In all three brain regions, transcriptome data revealed specific microglial maturation over time. However, microglia exhibited an individual region-specific gene profile. Additionally, gene ontology analysis demonstrated the activation of different signaling pathways, indicating region-specific microglial functionality. Furthermore, analysis of the Iba1-negative signal showed a highly heterogeneous gene signature in different brain regions.
This study provides insight into regional microglial postnatal development and highlights the transcriptomic signatures that contribute to their maturation and functional heterogeneity. Furthermore, our results identify factors in the Iba1-negative areas, which are likely to influence migration and phenotype of postnatal developing microglia.

Vortrag 24:

Title:
Presenilin / y-Secretase – mediated signaling is crucial for cell migration in brain development

Authors:
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Abstract:
Cortical development is a complex process which is subjected to different signals coming from the meninges, Cajal Retzius (CR) cells and the ventricle, controlling the development and differentiation of radial glia and neurons. Thereby, radial glia harbors two important functions: (1) the correct positioning of radial migrating projection neurons on their fibers; (2) providing a neuronal stem cell pool. Presenilin-1 (PS1), the main active side of the □-secretase complex, is essential for cortical development. Its knockout in mice leads to lamination defects and a disruption of the basal lamina underneath the meninges comparable to lissencephaly type 2, with overmigrating cells in the position of rupture. This study aims to find out how PS1 influences radial glia, CR cells and the structure of the basal lamina.
To investigate the phenotype of PS1 deficiency and explore its functions in cortical development, brain tissue of PS1 WT- and KO- mouse embryos were investigated using light and electron microscopy.
Ultrastructurally, our results show two different forms of basal lamina disruption in the PS1 KO. The basal lamina appeared as thinned out and degenerated by external influences, but also mechanically destroyed by a penetrating cell. Furthermore, quantity, localization and morphology of radial glia and CR cells are affected by presenilin 1 deficiency.
PS1 is highly important in the control of cell migration in embryonic cortex development. Its deficiency might prevent the function of cell membrane signal transmission leading to loss of function of radial glia, CR cells and meninges, which are known to be essential in brain development.

Vortrag 25:

Title:
Heterozygous loss of Syt13 reproduces ALS features and induces cellular vulnerability in human motoneurons

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Abstract:
Synaptic alterations represent a common feature shared across the heterogenous pathogenetic spectrum of Amyotrophic Lateral Sclerosis (ALS). In particular, we have recently shown that the presynaptic SNARE machinery is detrimentally impaired in ALS motoneurons (MNs), which indeed display reduced firing properties. In this work, we aimed at identifying specific presynaptic targets actively contributing to neuronal vulnerability and disease progression in ALS.
We combined multi-omics and deep learning strategies with human iPSC-derived MNs to highlight Synaptotagmin 13 (Syt13) as a candidate synaptic protein contributing to neuronal vulnerability in ALS. By using CRISPR-Cas9 technology, we then investigated whether the heterozygous loss of Syt13 is sufficient to resemble an ALS phenotype.
Syt13+/- hiPSC-derived MNs display a progressive manifestation of typical ALS hallmarks such as loss of synaptic contacts and accumulation of aberrant aggregates. By comparing the transcriptome of Syt13-deicificent cells to Syt13+/+ ones, we found a significant impairment in biological mechanisms involved in motoneuron specification and spinal cord differentiation. In addition, we identified an astonishing correlation of the Syt13+/- transcriptome with an ALS fingerprint generated using RNAseq data from human MNs and post mortem spinal cord samples. This significant overlap converged toward a detrimental upregulation of neuronal death and pro-inflammatory response, which was linked to a dysfunctional Akt-GSK axis.
Our data show for the first time that the heterozygous loss of a single presynaptic protein, Syt13, is sufficient to trigger a typical ALS phenotype leading to the death of human MNs, thus revealing novel insights into the selective vulnerability of this cell population.

Vortrag 26:

Title:
Mechanistic insight into vascular inflammaging: TNF-ALPHA mediates CEACAM1 expression in endothelium by NF-κB and BETA-Catenin in a biphasic manner

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Abstract:
Chronic low-grade systemic inflammation with aging (inflammaging) promotes cardiovascular diseases like myocardial infarction and stroke. Previously we have shown that with progressive age mutual upregulation of TNF-ALPHA and the Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) generates a chronic pro-inflammatory milieu within the vasculature. CEACAM1 in turn promotes age-associated vascular alterations. Therefore, CEACAM1 seems to be a main mediator of progressive inflammaging. In this study, we analyzed the underlying mechanism of CEACAM1 induction by TNF-ALPHA.
WT and TNF-ALPHA knockout mice were used to determine age-dependent CEACAM1 expression in vivo. Endothelial cells (EA.hy926) were used as an in vitro model to analyze underling signaling mechanism by chemical and non-chemical approaches. Co-immunoprecipitation of VE-Cadherin with BETA-Catenin was used to determine adherens junction complex disassembly.
Aging studies of WT and TNF-ALPHA knockout mice revealed that TNF-α is responsible for vascular CEACAM1 upregulation with progressive age in vivo. TNF-ALPHA upregulated CEACAM1 in endothelial cells in a biphasic manner, with an early response mediated by NF-κB and a delayed response by β-Catenin. The TNF-α mediated Akt activation promoted adherens junction disassembly by phosphorylation of BETA-Catenin. BETA-Catenin released from adherens junction in turn promoted CEACAM1 expression.
Inhibition of vascular TNF-ALPHA or other pro-inflammatory pathways are not suitable to prevent vascular inflammaging based on potential side effects. In contrast interfering with CEACAM1-dependent signaling is a promising strategy to prevent vascular inflammaging and thereby cardiovascular diseases.

Vortrag 27:

Title:
Apremilast, a PDE4 inhibitor, enhances cardiomyocyte cohesion in a plakoglobin-dependent manner and may have therapeutic potential to treat arrhythmogenic cardiomyopathy.

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Abstract:
Arrhythmogenic cardiomyopathy (AC) is a heart disease majorly associated with desmosomal gene mutations, resulting in sudden cardiac deaths by arrhythmia in young individuals. So far, therapeutic strategies for AC consist solely of symptomatic treatment. Recently, we demonstrated that cAMP increase by apremilast could be utilized to stabilize cell adhesion in the desmosome disease pemphigus vulgaris. Therefore, this study investigated whether apremilast can be applied as a therapeutic in AC.
ELISA, dissociation assays, immunostaining, Western Blots, and microelectrode array (MEA) analysis were performed in either HL-1 cells or murine cardiac slices derived from plakoglobin (PG) wild-type, knockout (murine AC model) and PG Serine 665 phosphodeficient (PG-S665A) mice.
The phosphodiesterase 4-inhibitor, apremilast, enhanced cardiomyocyte cohesion in HL-1 cells and wild-type murine cardiac slices and induced translocation of Desmoglein 2 (DSG2) into the membrane and enhanced its colocalization with Desmoplakin (DP). Further, apremilast led to the phosphorylation of PG-Serine 665 and activation of ERK1/2. However, dissociation assays in slice cultures from PG-S665A mice and PG knockout mice revealed that PG phosphorylation at S665 is not strictly required for apremilast-enhanced cardiomyocyte cohesion, whereas PG is necessary. Further, ERK1/2 inhibition abolished apremilast-enhanced cardiomyocyte cohesion in HL-1 cells. Heartbeat intervals measured by MEA in wild-type and PG KO mice ventricular cardiac slices revealed decreased variability after apremilast treatment.
In conclusion, apremilast treatment enhanced cardiomyocyte cohesion and needs further investigation on whether it will reduce arrhythmia in intact hearts and could be utilized as a therapeutic to treat AC patients.

Vortrag 28:

Title:
The role of peroxisomes in Barth syndrome cardiomyopathy

Authors:
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Abstract:
Barth syndrome (BTHS) is an X-linked inherited disease characterized by cardiomyopathy in the first years of life. It is caused by a mutation in the enzyme tafazzin (gene Taz), which affects cardiolipin (CL) synthesis, leading to mitochondrial dysfunction and increased oxidative stress. Peroxisomes are involved in various metabolic pathways, including ROS defense and plasmalogen biosynthesis, potentially protecting against ROS-induced damage. This study aims to investigate the role of peroxisomes in compensating for mitochondrial dysfunction in Barth syndrome, particularly in terms of ROS defense and plasmalogen biosynthesis.
We used a well-established BTHS-mouse model. Hearts of WT and Taz knockdown at the age of 2 and 11 months were analysed by using immunofluorescence, electron microscopy, qPCR and WB. Additionally, quantitative lipidome profiling was performed with FIA-MS/MS, QQQ triple quadrupole method.
Peroxisome biogenesis protein 14 (PEX14), and peroxisomal proteins involved in maintenance, plasmalogen biosynthesis and ROS defence (FAR1, LONP2, CAT) are upregulated in Taz-KD. Lipidomic analyses demonstrate that tafazzin loss of function results in profound alterations in the myocardial lipidome and affects both the young animals who do not display a cardiomyopathic phenotype, and the older animals who suffer from heart failure.
Catalase may alleviate ROS damage in BTHS, highlighting peroxisome’s compensatory role in BTHS-related heart failure. LONP2 has both beneficial effects on cellular survival and associations with increased oxidative stress and cancer survival, potentially posing contradictory effects on the myocardium. As there is currently no cure for BTHS, this study addresses the need for a treatment by utilizing peroxisomes' compensatory capacity.

Vortrag 29:

Title:
Cell density and tension induce a jamming transition leading to migratory arrest in astrocytes and glioblastoma

Authors:
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Abstract:
Glioblastoma (GBM) is the most aggressive form of primary brain tumors. It infiltrates the adjacent healthy brain, rendering surgical resection ineffective. Infiltration occurs as single cells but also possess collective migration modes correlating with the grading of gliomas. Collective behavior emerges from coordination of cell-cell-interactions and can result in spontaneous, cell density dependent self-organization and phase transition-like phenomena. Here, we analyzed collective migration of glioblastoma and possibilities to induce migratory arrest.
We analyzed collective migration dynamics of astrocytes and GBM, using live cell microscopy. Furthermore, atomic force microscopy, traction force microscopy, spheroid formation assays and staining were used to analyze adhesion, force generation and cell-mechanics.
Astrocytes resided in a non-migratory state and GBM were migratory. Upon inhibition of ROCK and myosin II, a migratory arrest was induced in GBM. The transition from migratory to non-migratory showed properties of a phase transition called jamming transition. Upon ROCK or myosin II inhibition cell adhesion and traction were affected, but migratory arrest occurred only when tension dominated over adhesion. Another route to a migratory arrest via jamming occurred in cell density dependence. While confluence in astrocytes induced jamming, GBM remained migratory. Only at very high cell densities, 4 times higher than initial confluence, migratory arrest occurred in some GBM cell lines.
In conclusion, migratory arrest in a phase transition-like manner was induced in GBM via cell density or increased tension. These findings have implications for understanding the migratory properties of astrocytes and GBM, brain tumor infiltration and may help to develop anti-migratory drugs.

Vortrag 30:

Title:
3D-in-vivo-tumor-model for the investigation of chemosensitivity in pancreatic ductal adenocarcinoma

Authors:
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Abstract:
Pancreatic ductal adenocarcinoma (PDAC) represents the fourth leading cause of cancer-related deaths with a 5-year survival rate of less than 8%. The only current curative treatment option is surgical resection followed by adjuvant chemotherapy and can only be considered in about 15% of patients due to frequent diagnosis at advanced stages of the disease. The aim of this study is to identify the most effective substance for the inhibition of tumor growth and metastasis.
The chorio-allantoic membrane (CAM) is a highly vascularized extraembryonic membrane that develops in fertilized chicken eggs and can be used for the grafting and cultivation of tumor tissue. This model enables the testing of cytostatic drugs with regards to their effects on tumor size, differentiation, and metastasis. Human tumor tissue from PDAC patients was grafted onto the CAM and intravenous injection of different substances was performed. Histopathological evaluation was conducted using HE, Ki-67, Keratin 7, and CD31 staining techniques, and molecular analysis was performed via PCR analysis of the chick embryo's liver, lung, and brain tissue.
Intravenously injected indocyanine green, as well as ultrasound examinations of the tumors cultivated on the CAM, enabled the identification of anastomoses between the tumor vessels and the chicken's circulatory system one day after grafting. Initial experiments with Oxaliplatin showed distinct differences in morphology and tumor tissue differentiation compared to controls.
The CAM model appears to be a valuable methodology for the detection of promising new therapies for each individual patient and could possibly improve the prognosis of PDAC patients in the future.

Vortrag 31:

Title:
The oncogenic functions of CD109

Authors:
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Abstract:
In patient data, we identified the cell surface protein CD109 as a risk factor for patients suffering from lung adenocarcinoma. Based on this, the aim of the present studies was to dissect the oncogenic nature of CD109.
We depleted CD109 in human H460 lung carcinoma cells using CRISPR/Cas9 and single clone selected two CD109 deficient cell lines (H460ΔCD109). To characterize differences between parental and H460ΔCD109 cells, we applied western blot, immunofluorescence staining, transmission and scanning electron microscopy, a transwell assay, a scratch assay, assessed cell proliferation and performed total RNA sequencing. To identify new cell surface interaction partners of CD109 we applied co-immunoprecipitation and mass-spectrometry fingerprinting. Target verification was achieved through co-immunoprecipitation, western blot and immunofluorescence.
We identified drastic cellular changes upon depletion of CD109. The cells reverted to a more epithelial behavior in terms of 2D cell sheet formation and migration as a cellular front. In RNA sequencing experiments, we identified a number of genes involved in in the organization of the extracellular matrix, the expression of which was associated with reduced overall patient survival. We identified the desmosomal protein DSG-2 as a new interaction partner for CD109 at the cell surface. We show that depletion of CD109 reduces DSG-2 protein levels in total and on the cell surface. In contrast, DSG-2 RNA levels are not affected.
We gained initial insights into the oncogenic nature of CD109 and begun to understand its cellular effects at protein and transcriptional level. Future experiments will provide a more detailed understanding and uncover new molecular pathways.

Vortrag 32:

Title:
The retrocolic fascial system revisited – surgical anatomy required for oncologic right hemicolectomy with complete mesocolic excision

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Abstract:
Oncologic hemicolectomy requires not only the removal of the affected colon segment but also its supplying lymphatics within the mesocolon. To achieve complete mesocolic excision (CME) and prevent tumor cell dissemination, it is essential to preserve the fascial integrity of the specimen. This study aimed to determine the optimal dissection plane for right hemicolectomy with CME by macroscopic and microscopic studies.
Cross-section studies, stepwise dissection and histological analysis were performed in formalin-fixed body donors to identify the components of the retrocolic fascial system and its corresponding interfaces. These interfaces were used to define the optimal surgical dissection plane for CME and validated in surgical training courses and patients.
The ventral and dorsal mesocolic visceral peritoneum enveloped the mesocolic lymphovascular pedicles. The dorsal mesocolic leaf was attached to the parietal peritoneal fascia ("fascia of Toldt") forming the parieto-mesocolic interface. In front of the duodenum and pancreatic head this interface blended into the mesocolic-duodeno-pancreatic interface ("space of Fredet"). Dorsally, a distinct separation of the parietal peritoneal fascia and the anterior renal fascia ("fascia of Gerota") was possible by opening the parieto-renal interface. The best fascial integrity of the surgical specimen was achieved by dissecting along this interface towards the duodenum, followed by an incision of the parietal peritoneal fascia and mobilisation of the specimen along the mesocolic-duodenal interface.
Stepwise surgical dissection along the outlined fascial interfaces was considered optimal to prevent mesocolic lacerations and local tumor spillage. Moreover, this concept was successfully applied in surgical workshops and patients thereby confirming technical feasibility.

Vortrag 33:

Title:
Promoting interprofessionalism in anatomy: A pilot study

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Abstract:
The draft of the new licensing regulations for physicians emphasizes the importance of promoting interprofessional attitudes. This parallel development presents novel prospects for integrating interprofessionalism into medical education. Given its foundational nature and role in various health sciences, anatomy emerges as an ideal subject to facilitate early collaboration among diverse health professions. The MILA pilot project aimed to enable students of midwifery and medicine in Münster to engage in interprofessional learning of anatomy.
A total of 24 first-semester midwifery students and 18 second-semester medical students were recruited on a voluntary basis to participate in a four-hour block course. The study employed a one group pre- and post-design approach. To measure the effects on interprofessional attitudes, the validated ISVS questionnaire with a reliability coefficient of $\alpha = .67$ was utilized. Additionally, participants were required to complete an essay.
In a collaborative effort the students formed "interprofessional tandems" and participated in a sequence of eight 15-minute anatomy stations. The theoretical stations included activities such as evaluating a spermiogram using a microscope, engaging in anatomical case discussions, and analyzing the layers of the abdominal wall. The practical tasks were conducted in the dissection room, where the tandems had to identify anatomical structures in the abdomen and pelvic region using donated bodies, sketch and compare longitudinal sections pelvises, and explore sexual dimorphisms in the bony pelvis. Preliminary results from the ISVS indicated a significant pre-post improvement in interprofessional attitudes, with a large effect size (mean difference = .303, $P = .001$, $\eta^2 = .171$)
The initial findings suggest that interprofessional training can be successfully implemented within the anatomical curriculum and is well-received by students.

Vortrag 34:

Title:
On the curricular applicability of Mixed Reality in the dissection course

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Abstract:
Digital anatomic training solutions are developing but are currently largely decoupled from classic dissection teaching. Particularly the combination between hands-on training and 3D digital add-on information might benefit learning, and curricular integrated combined solutions are warranted.
We investigated the usability of interactive Mixed Reality (MR) for learning in peer groups on a lower limb specimen in a large group of first-semester students. The virtual model of the dissected specimen was obtained via vascular CT and MRI and subsequent vector-based surface generation through semi-automated segmentation. Using preexisting vendor software, a teaching setup integrating relevant additional features for an interactive learning experience was established, 12 MR glasses and a 5G environment for delay-free synchronization over distances.
The generated virtual lower limb model was implemented with features including virtual expansion, selective compartment visualization, and interactively adaptable 2D slice views of the imaging data within the 3D model. Selectable structure labeling and information abet learning and mutual quizzing. Overall positive evaluations were accompanied by better response rates in final exams for topography-related questions.
We demonstrated curricular implementation of MR setups in the dissecting course in a group of more than 100 students, enabled via the scalability of the mixed reality setup in groups of up to 12 students. Using the original specimen with the virtual model allowed for optimized direct investigation of the individual 3D topography together with cross-sectional clinical anatomy. Personalized and peer teaching experiences can be realized for the students in one training session.

Vortrag 35:

Title:
A comparison of 1- versus 3-month regional anatomy exposure on learning outcomes of undergraduate medical students

Authors:
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Abstract:
Regional anatomy teaching forms a cornerstone of undergraduate medical education.
Owing an increase in teaching and learning contents throughout the medical curriculum in recent years, contact hours and overall course durations in anatomy are under review worldwide. This given study aimed to assess if the learning gain and the ability to identify anatomical structures is impacted by shortening the duration over which course contents are being delivered.
Undergraduate medical students of the Johannes Kepler University Linz (JKU; n=310) and at Medical University of Graz (MUG; n=156) participating in regional anatomy courses were included. Whole body regional anatomy courses were delivered over a duration of one or three months, including hands-on dissection and accompanying lectures. Course content and examination mode were kept consistent, while the duration of knowledge delivery was one or three months, respectively. Objective structured practical examinations (OSPE) were then carried out on prosections for the neck, thorax and abdomen.
3-month course exposure resulted in significantly higher OSPE scores for the neck (49 vs. 37%), thorax (64 vs. 54%) and abdomen (65 vs. 45%), respectively. Further evaluation on the utility of different embalming types yielded higher 3-month scores in the neck and thorax regions with Thiel-embalmed tissues, and thorax and abdomen regions in ethanol-embalmed tissues.
Course exposure over a more extended period appears to be beneficial. No distinct difference between embalming types appears to exist concerning these observations.

Vortrag 36:

Title:
A transgenic system for sensing mechano- and ligand-dependent adhesion GPCR dissociation

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Abstract:
Adhesion-type G-protein coupled receptors (aGPCRs) constitute a large family of surface molecules that can transduce mechanical stimuli into intracellular metabotropic responses in all major organ systems including the brain. Mechano-dependent receptor dissociation is a main mechanism suspected to initiate the transduction event, but was never observed at cellular resolution and in vivo.
To fill this experimental gap we developed a transgenic sensor design that can assay aGPCR dissociation and tested its functionality in cell culture and in the fruit fly Drosophila melanogaster.
We show that the N-terminal fragment release sensor (NRS) for the neurally expressed aGPCR ADGRL/Latrophilin requires mechanical stimulation, adhesive interaction with its Toll-like receptor ligand Tollo/Toll-8, and consequent shedding of the ectodomain of the receptor. This interaction triggers receptor dissocation at the cortex glia-neuroblast boundary in the developing cortex, and is essential to determine the amount of neuroblasts generated.
We conclude that receptor dissociation is a conserved molecular and physiological property of aGPCRs, which initiates transduction of extracellular mechanical cues across the plasma membrane. Further, we assume that NRS technology will help to characterise the mechanosensitive properties of aGPCRs in more detail and serve as a tool to identify compounds to interfere with their mechanosignaling.

Vortrag 37:

Title:
Microglia involvement in neovascular eye diseases – Temporo-spatial and transcriptional profiling across disease types

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Abstract:
Neovascular eye diseases lead to rapid visual impairment and currently cannot be treated curatively. The molecular mechanisms leading to ocular neovascularization are often not yet conclusively understood. Myeloid cells, such as resident microglia (MG) and infiltrating blood-derived macrophages (MAC), accumulate at neovascularization sites and are discussed as key players in these processes. The aim of this study is to determine the contribution of MG and MAC to neovascularization and to define the transcriptional profile of the dominant cell population.
Three mouse models of retinal and choroidal neovascularization were used: The oxygen-induced retinopathy model (OIR), the laser-induced CNV (choroidal neovascularization) model and the Vldlr-knockout mouse, developing retinal angiomatous proliferation (RAP). These models were combined with the Cx3cr1CreER/+:Rosa26-Tomfl/+ mouse line, allowing discrimination between MG and MAC. We quantified both cell populations accumulating at neovascularization sites and isolated MG via FACS followed by RNA-sequencing.
Quantification of MG and MAC at neovascularization sites showed that MG represent the dominant myeloid cell population in all neovascularization models. RNA-Sequencing revealed that MG massively change their transcriptional profile after disease, including an upregulation of genes, involved in immune activation, chemotaxis, migration, and proliferation. Interestingly, hardly any common pro-angiogenic factors were upregulated in microglia during neovascularization suggesting no direct angiogenic effect of MG on neovascularization.
Our study demonstrates that retinal MG are the dominant myeloid cell population accumulating at neovascularization sites. MG strongly change their transcriptional profile upon disease onset and express a plethora of molecules contributing to immune-associated processes.

Vortrag 38:

Title:
Elaborated gait analysis using high-speed ventral plane videography allows the detection of central nervous lesions in the murine cuprizone-induced multiple sclerosis model.

Authors:
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Abstract:
Multiple sclerosis is a disease of the CNS, characterized by inflammation, demyelination, and neuronal injury, leading to gait deficits. Parts of the pathological spectrum of the disease can be recapitulated in the cuprizone model. While histological readouts are robust and frequently applied in this model, functional deficits such as gait disturbances are usually not used as a biomarker. This study aimed to investigate gait deficits in the cuprizone model and how such deficits correlate with histopathological changes.
In mice, demyelination was induced by cuprizone-intoxication for 5 weeks. Gait analyses were performed twice a week using high-speed ventral plane videography. Histochemical and immunohistochemical methods were used to examine the brains of the animals. The extent of demyelination in motor-related brain regions, among the corpus callosum, striatum, and motor cortex, was performed by digital image analysis.
After Cuprizone-intoxication, demyelination and increased microglial cell densities were demonstrated in the examined brain areas. Gait deficits were most obvious at the hind feet, including a prolongation of the push-off phase by 12 %, an increase in the angle between the hind paws and the medio-sagital axis of the mouse body from 11° to 19° and a reduction of the distance of the hind paws from the mid-horizontal plane of the mouse body by about 37 %.
We demonstrated that high-speed ventral plane videography is an appropriate tool to study gait deficits in a toxin-mediated MS animal model. We propose to use this method in future pre-clinical trials to assess therapeutic efficacy.

Vortrag 39:

Title:
Epigenetic basis of microglia specific gene signature

Authors:
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Abstract:
Microglia are the immune cells of CNS and are critical for its maintenance. Their early postnatal development of microglia is associated with an activated TGFβ signaling which peaks at around post-natal day 7 (P7). Interestingly, microglia specific gene expression was found to be unaffected upon abrogation of TGFβ signalling in mature microglia, while early post-natal deletion leads to a reduction. This begs the question of whether TGFβ1 triggers epigenetic modifications that can induce a permanent expression of microglial genes.
Ex vivo microglia from P5 and P30 mice were analyzed using a microglia panel for Nanostring analysis. Effect of TGFβ on the opening of chromatin was assayed using ATAC-See technique. Post-translational modifications (PTMs) such as methylation of Histone 3 upon TGFβ1 treatment and inhibition were analyzed in primary microglia cultures using western blot.
nCounter analysis revealed that homeostatic markers are up regulated in P30 microglia when compared to that of P5. Opening of chromatin was evident at 2hr post TGFβ1 treatment in primary microglia. Increased H3K27Me1 and H3K4Me3 were observed at this time point while inhibition of TGFβ signalling for 5 days resulted in loss of these methylations.
These data suggest that microglia specific homeostatic signature is increased in P30 when compared to P5 animals in vivo. And In vitro, TGFβ can trigger an opening of chromatin in primary microglia and increase the levels of H3K27Me1 and H3K4Me3 while inhibiting the TGFβ signalling leads to their reduction.

Vortrag 40:

Title:
TDP-43 condensates and lipid droplets regulate the reactivity of microglia and regeneration after traumatic brain injury

Authors:
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Abstract:
Regeneration of the damaged adult mammalian CNS, including that in humans, is largely limited. This response is due to an adverse environment generated by prolonged inflammation and glial scar formation. Therefore, understanding the cellular dynamics and signalling cues underlying the long-lasting neuroinflammation and scar formation provides crucial insights that can be harnessed to promote regeneration in the mammalian CNS in response to traumatic brain injury (TBI) and neurodegenerative diseases.
Here, we sought to investigate the microglial dynamics in the injured adult telencephalon, using single cell and spatial transcriptomics combined with forward genetics.
We identified the transient state of reactive microglia that emerges in a granulin-dependent manner. Furthermore, we demonstrated that granulin-mediated clearance of injury-induced lipid droplets and TDP-43+ condensates in microglia is fundamental for their return to the basal state. We show that the liquid-liquid phase separation of TDP43 and accumulation of solid-like TDP-43 aggregates in microglia leads to permanent microglial activation and generation of glial scar, preventing tissue regeneration. These results highlight TDP-43 phase separation as a target to improve CNS regeneration in response to damage. The translational value of our research is strengthened by our observation that microglial reactivity correlated with the presence of TDP-43+ condensates and lipid droplets in humans with TBI.
Overall, our results provide regulatory mechanisms that prevent long-term inflammation and promote CNS regeneration. We report the crosstalk between granulins and TDP-43 phase separation that could potentially be targeted to develop new approaches for increasing regeneration after TBI or neurodegenerative diseases in humans.

Vortrag 41:

Title:
Towards a light-mediated gene therapy for the eye - retinal transgene expression through photoactivation of caged ethinylestradiol and the inducible Cre/lox system

Authors:
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Abstract:
Increasingly, retinal pathologies are being treated with virus-mediated gene therapies. To be able to target viral transgene expression specifically to the pathological regions of the retina with light, we established an in vivo photoactivated gene expression paradigm for retinal tissue.
Based on the inducible Cre/lox system, we discovered that ethinylestradiol is a suitable alternative to Tamoxifen as ethinylestradiol is more amenable to modification with photosensitive protecting compounds, i.e., ‘caging.’ Identification of ethinylestradiol as a ligand for the mutated human estradiol receptor was supported by in silico binding studies showing the reduced binding of caged ethinylestradiol. Caged ethinylestradiol was injected into the eyes of double transgenic GFAP-CreERT2 mice with a Cre-dependent tdTomato reporter transgene followed by irradiation with light of 450 nm.
Photoactivation of eyes injected with caged ethinylestradiol significantly increased retinal tdTomato expression compared to controls. Successful photoactivation was also achieved in retinal neurovasculature using Tie2-CreERT2 mice.
Photoactivated transgene expression was robust, reproducible, easily implemented, without obvious toxicity, and flexible in different genetic backgrounds. We thus demonstrated a first step towards the development of a targeted, light-mediated gene therapy for the eyes.

Vortrag 42:

Title:
The hormone oxytocin is equipotent to norepinephrine in the sperm-releasing distal part of the epididymis

Authors:
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Abstract:
During ejaculation, sperm is driven forward through the vas deferens by strong contractions of the cauda epididymidis (mainly mediated by sympathetic innervation and norepinephrine). We wanted to investigate how the hormone oxytocin influences contractions of the epididymis and ejaculation.
We used live-imaging in combination with our novel analysis method to quantify and visualize the contractions induced by oxytocin, norepinephrine and selected antagonists in the sperm-storing (most distal) part of the human and rodent epididymis.
Oxytocin was able to induce a strong and complex series of contractions in the distal epididymidis, which visibly expulsed spermatozoa from the duct's lumen. This response was equipotent to the one induced by norepinephrine. The oxytocin-antagonists atosiban and cligosiban but not the arginine-vasopressin antagonist SR 49059 were able to completely block this strong response to oxytocin. While the response of the tissue to norepinephrine (both human and rodent) could reliably be inhibited by pretreatment with the alpha-1-adrenergic-receptor-blocker tamsulosin, the response to oxytocin was unaltered by tamsulosin, indicating an independent oxytocin pathway.
The hormone oxytocin induced the same strong contractions as the sympathetic norepinephrine, which expelled spermatozoa forcefully from the epididymal duct. Therefore, we suggest that the oxytocin pathway is involved in the ejaculatory process and might present as a yet unexplored non-adrenergic treatment target for ejaculatory disorders, e.g. in case of spinal cord injuries. In comparison to other tissues, the distal sperm-storing part of the epididymis is an advantageous model (detecting very low doses of oxytocin) to test the bioactivity of new oxytocin-agonists and -antagonists.

Vortrag 43:

Title:
Human polycystic renal tissue perfusion visualized by high frequency ultrasound in a 3D-in-vivo-model

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Abstract:
Autosomal dominant polycystic kidney disease (ADPKD) is a monogenetic kidney disease characterized by the presence of cysts in both kidneys. According to recent studies human ADPKD kidney tissue can be cultivated on the chorioallantoic membrane (CAM), which bridges the gap between preclinical and clinical research. One central aspect of this innovative model is the vitality of the cystic tissue which strongly depends on adequate levels of perfusion.
Human renal cystic tissue from elective cyst nephrectomies is grafted onto a CAM and incubated for one week. Ultra high frequency ultrasound (UHF) could be a suitable method for monitoring/visualizing of the renal perfusion which makes this model highly interesting as a new drug testing platform. In addition, advanced image processing methods were utilized to perform a 3D-reconstruction from a light sheet microscopy image stack.
Histological results showed numerous chicken erythrocytes within the human cystic tissue at the end of the incubation period of 7 days. Based on the distribution of active blood vessels detected by UHF ultrasound, corresponding functional anastomoses between chicken vessels and human vessels were detected as early as 12 hours after grafting the human renal cystic tissue onto the CAM. These results could be confirmed by 3D reconstructions.
Contrary to the widespread assumption that perfusion of the human cystic tissue on the CAM happens via diffusion, this study shows that vascular perfusion occurs within a very short period of time. This was detected functionally by UHF ultrasound and structurally by 3D reconstructions of the vascular anastomoses.

Vortrag 44:

Title:
Gender Diversity in Anatomy

Authors:
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Abstract:
The worldview of most cultures is strongly heteronormative. This also continues in medicine - we differentiate between men and women and often exclude non-binary or intersex people. We also rarely address trans people, although in 2017 it was enshrined in German law that in addition to male and female trans people and other gender identities exist.
In addition, medicine has been very guilty of non-binary people in the past and immeasurable damage has been done.
In order to continue to act in accordance with the constitution, it is necessary that we expand our worldview to include these categories and treat the topic appropriately. This may mean that we need to reexamine our own images of gender identity. While many students naturally adopt more than two genders due to their school education and contemporary influences, doctors and lecturers in anatomy are often still stuck in a binary worldview.
In order to prevent the same from continuing, a fundamentally revised training of future physicians is necessary, and teaching anatomy can make a significant contribution.

Vortrag 45:

Title:
Asymmetric morphogenesis and hedgehog signaling in left-right patterning.

Authors:
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Abstract:
Leftward fluid flow in vertebrate left-right organizer (LRO) localized on the ventral surface of the amphibian gastrocoel roof plate or equivalent structures was suggested to break the left-right symmetry. Symmetry breaking in LRO is required for asymmetrical gene expression in the lateral plate mesoderm. However, further studies revealed a remarkable variability of LRO and indicated divergent symmetry breaking mechanisms in amniotes.
We aimed to study this divergence with the focus on birds and utilized both descriptive and experimental approach. First we studied morphology and molecular anatomy of left-right organizer using light and electron microscopy as well in-situ hybridisation. Activation and inhibition of signaling pathways were used to clarify the mechanisms of left-right patterning.
Comparative analysis of the left-right organizer and equivalent areas in different vertebrate species reveals symmetrical paraxial nodal domain in organisms with observed ciliary flow and asymmetric left-sided nodal expression in organisms with apparently absent ciliary organizer. Further analysis of the corresponding region in the chick suggests that the symmetry breaking starts with asymmetric morphogenesis of the Hensen' node and involves a shift of the notochord forming area to the right side. As a consequence, the sonic hedgehog expressing floor plate is located above the medial left paraxial mesoderm domain which then starts to express nodal. Furthermore, the modulation of hedgehog-signaling revealed that it is both necessary and sufficient for early paraxial nodal expression.
Based on our findings we propose a model for left-right patterning and symmetry breaking in birds and discuss divergence in amniotes left-right symmetry breaking.

Vortrag 46:

Title:
Nrf2 induces malignant transformation of hepatic progenitor cells by inducing BETA-catenin expression

Authors:
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Abstract:
The Nrf2 signaling pathway prevents cancer initiation, but genetic mutations that activate this pathway are found in various types of cancer. The molecular mechanisms underlying this Janus-headed character are still not understood.
Using aged hepatocyte-specific Keap1-knockout mice, we examined the effects of sustained Nrf2 hyperactivation on the liver. FFPE samples were used for histological, immunohistochemical and –fluorescent staining to characterize liver morphology as well as the expression of specific markers. Luciferase reporter gene assays, EMSA and ChIP-qPCR approaches were performed to confirm the transcriptional control of BETA-Catenin by Nrf2. We established a hepatoblastoma-like neoplasia (HLN) cell line from these mice to intensify our mechanistic analyses on the relationship of Nrf2 and BETA-Catenin. We applied shRNA against Nrf2 as well as BETA-Catenin to examined their influence on proliferation and the expression of tumor markers of these cells.
Sustained Nrf2 activation induced proliferation and dedifferentiation of a Wnt-responsive perivenular hepatic progenitor cell population, transforming them into metastatic cancer cells. The neoplastic lesions displayed many histological features known from human hepatoblastoma. Moreover, we were able to describe an Nrf2-induced upregulation of BETA-catenin expression and activation as the underlying mechanism for the observed malignant transformation.
We identified the Nrf2–BETA-catenin axis promoting proliferation of hepatic stem cells. Activation of this stem cell compartment conferred the observation that unbridled Nrf2 activation may trigger tumorigenesis.

Vortrag 47:

Title:
Dsg3 epitope-specific signalling in pemphigus

Authors:
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Abstract:
Pemphigus is an autoantibody driven disease that impairs the barrier function of the skin and mucosa by disrupting desmosomes and thereby impeding cellular cohesion. It is known that the different clinical phenotypes of pemphigus vulgaris (PV) and pemphigus foliaceus (PF) are dependent on the autoantibody profile and target antigens that, amongst others, are primarily desmoglein (Dsg)1 and/or Dsg3 for PV and Dsg1 for PF. However, it was reported that autoantibodiesagainst different epitopes of Dsg1 and Dsg3 can be pathogenic or not. The underlying mechanisms are very complex and involve both direct inhibition of Dsg interactions and downstream signalling. The aim of this study was to find out whether there is target-epitope-specific Dsg3 signalling by comparing the effects of the two pathogenic murine IgGs, 2G4 and AK23.
Dispase-based dissociation assay, Western Blot analysis, Stimulated emission depletion microscopy, Fura-based Ca2+ flux measurements, Rho/Rac G-Protein-linked immunosorbent assay, Enzyme-linked immunosorbent assay
The IgGs are directed against the EC5 and EC1 domain of Dsg3, respectively. The data show that 2G4 was less effective in causing loss of cell adhesion, compared to AK23. STED imaging revealed that both autoantibodies had similar effects on keratin retraction and reduction of desmosome number whereas only AK23 induced Dsg3 depletion. Moreover, both antibodies induced phosphorylation of p38MAPK and Akt whereas Src was phosphorylated upon treatment with AK23 only. Interestingly, Src and Akt activation were p38MAPK-dependent. All pathogenic effects were rescued by p38MAPK inhibition and AK23-mediated effects were also ameliorated by Src inhibition.
The results give first insights into pemphigus autoantibody-induced Dsg3 epitope-specific signalling which is involved in pathogenic events such as Dsg3 depletion.

Vortrag 48:

Title:
The role of the nonsense-mediated mRNA-decay in polycystic kidney disease

Authors:
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Abstract:
A two-hit mechanism with a germline and a somatic mutation has not only been proposed as an explanation for hereditary types of cancer but also for autosomal-dominant polycystic kidney disease. In order to test whether other mechanisms also contribute to the formation of renal cysts, a premature stop codon was introduced in the Pkd2 gene, one of the two genes mutated in patients. This led to reduced Pkd2 mRNA levels probably by mRNA degradation. The aim of the study was to determine whether Pkd2 mRNA degradation is caused by nonsense-mediated mRNA decay (NMD) and whether the truncated polycystin-2 is still functional.
A compound heterozygous mouse line was generated in which one Pkd2 allele contained a premature stop codon and the second Pkd2 allele contained loxP sites flanking exons 3 and 4. Additionally, the Upf2 gene, an important component of NMD, was inactivated in a collecting duct-specific manner.
When NMD was not disturbed, renal cysts developed rapidly in the collecting ducts and kidneys were markedly enlarged. Upon the inactivation of NMD, cyst formation was almost completely prevented.
This study demonstrated that collecting duct-specific inhibition of an important RNA surveillance pathway prevents renal cyst formation in the investigated Pkd2 mouse model. Accordingly, the truncated polycystin-2 is able to substitute for the full-length protein. In further experiments, the potential therapeutic effect of different drugs on cells with a premature stop codon at the same position in the Pkd2 gene will be analyzed.

Vortrag 49:

Title:
Decoding the functional complexity of the human insula linking intracranial EEG and direct cortical electrical stimulation with cytoarchitecture

Authors:
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Abstract:
The human insula is a complex brain region characterized by a multitude of functions and microstructural variability. While previous studies have localized different functions based on macroscopic landmarks, it is yet to be known how the intricate functionality of the human insula relates to its microstructural organization. This study aims to further decode this relationship by combining direct electrical stimulation, intracranial EEG recordings, and microstructural areas.
We stimulated 142 electrode pairs in the insula of 17 patients and reported induced changes in their conscious experience. Additionally, we recorded intracranial EEG activity in seven subjects performing a salience task to determine the insula's role in the "salience network." Using the cytoarchitectonic Julich-Brain Atlas, we assigned electrodes to microstructural areas in each subject's native anatomical headspace. Responses per area were tested for significance by comparing them to a randomly drawn Null-distribution. 19% of electrodes evoked significant pain/temperature perceptions in areas Ig2/Id2 in the posterior insula. 10% of stimulated electrodes elicited a feeling of touch, significantly associated with posterior area Id3. In the anterior insula, 7% of electrodes significantly induced visceroceptive sensations in area Id6, while salience testing revealed significant neuronal activity in area Id7.
This pioneering study connects experimental task recordings, direct stimulation, and cytoarchitectonic mapping of the insula, demonstrating that sensations from different functional categories can be assigned to specific microstructural areas. These findings lay the groundwork for an integrated structural-functional model of the human insular cortex, which could potentially guide deep brain stimulation targeting in the future.

Vortrag 50:

Title:
The prevalence of IgG antibodies against milk and milk antigens in patients with multiple sclerosis

Authors:
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Abstract:
Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system (CNS). The pathophysiology of MS is complex and is said to be influenced by multiple environmental determinants, including diet. We and others have previously demonstrated how consumption of bovine milk can aggravate disease severity in MS patients, which can be explained by molecular mimicry between milk antigens and those expressed within the CNS. In this study we set out to identify alternatives to drinking cow milk which might be less detrimental to MS patients who have a genetic predisposition towards developing antibody titers against bovine milk antigens that cross-react with CNS antigens.
We screened 35 patients with MS and 20 healthy controls for their IgG reactivity against an array of animal-sourced milk, plant-based alternatives as well as individual antigens from bovine milk.
We demonstrate that MS patients have a significantly higher IgG response to animal-sourced milk, especially cow milk, in comparison to healthy donors. We also show that the reactivity to cow milk in MS patients can be attributed to reactivity against different bovine milk antigens. Finally, our correlation data indicate the co-existence of antibodies to individual bovine milk antigens and their corresponding cross-reactive CNS antigens.
Taken together, we suggest screening of blood from MS patients for antibodies against different types of milk and milk antigens in order to establish a personalized diet regimen.

Vortrag 51:

Title:
A novel High-throughput Adhesion Assay and its Implications for Arrhythmogenic Cardiomyopathy

Authors:
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Abstract:
Defective cell-cell adhesion contributes to the patho-mechanism of various diseases. In line with this, a recently developed mouse model demonstrates that loss of cell-cell adhesion is an important initial step leading to Arrhythmogenic Cardiomyopathy (ACM). Derived from the central role of defective cell-cell adhesion, we here aim to identify new compounds from a drug library, which restore intercellular adhesion and can potentially serve as therapeutics for ACM.
To screen a high number of compounds, we developed an adhesion-based high-throughput screening assay. To model loss of intercellular adhesion, cells deficient for the desmosomal adhesion molecule desmoglein-2 (Dsg2) were employed. Revealed candidates were validated by classical adhesion assays and their in vivo relevance was investigated in an ACM mouse model (Dsg2 KO).
After establishing settings to sensitively detect changes in cell-cell adhesion, the high-throughput approach was applied to screen a library of 1´822 FDA-approved drugs in three concentrations. Several new compounds strengthening intercellular adhesion were identified in addition to known drugs, which confirms the robustness of our assay. The pro-adhesive effect of selected candidates was confirmed in cells expressing various ACM patient mutations. Importantly, in vivo administration of the revealed top drug abrogated the impairment of right ventricular function in the ACM mouse model.
In conclusion, we here developed an adhesion-based high-throughput approach capable of identifying adhesion modulators. The identified compounds have the potential to be used as therapeutics for diseases with defective desmosomal adhesion such as ACM.

Vortrag 52:

Title:
The regional distribution of resident immune cells shapes distinct immunological environments along the murine epididymis

Authors:
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Abstract:
The epididymis faces contrasting immunological challenges (tolerance towards spermatozoa vs. reactivity against pathogens) and thus, healthy organ function depends on a tightly controlled immune balance. We have previously shown that the opposing ends of the epididymal duct react differently upon bacterial infection. While proximal regions remain mostly unaffected, the distal regions are prone for inflammation-associated tissue damage that often leads to persistent duct obstructions and male subfertility.
To understand the reasons for region-specific differences in immune responses, we isolated extravascular immune cells from the four epididymal regions and performed single cell RNA sequencing. High dimensional flow cytometry was conducted to assess immune cell distribution among regions at steady-state and upon infection with uropathogenic Escherichia coli (UPEC). Immune cell infiltrations were correlated with histopathological and transcriptional changes throughout the disease progression.
In total, 12 immune cell populations were identified, ranging from mononuclear phagocytes to lymphocytes. While proximal regions are densely populated by intraepithelial macrophages, the distal regions contain a more heterogeneous network consisting of myeloid (monocytes, macrophages, dendritic cells) and lymphoid cells (T, B and NK cells). Upon UPEC infection, only distal regions showed severe histopathological alterations and upregulation of pro-inflammatory mediators that correlated with the appearance of immune cell infiltrations. High-dimensional flow cytometry analysis revealed a drastic change in the immune landscape towards a pro-inflammatory environment.
Our findings indicate that resident immune cells are strategically positioned along the epididymal duct creating distinct immunological milieus to tightly control tissue integrity, and to adequately tackle invading pathogens ascending from the urogenital tract.

Vortrag 53:

Title:
The role of CEACAM1 in the pathogenesis of atherosclerosis

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Abstract:
Atherosclerosis is a chronic inflammatory disease characterized by endothelial dysfunction and the formation of lipid-rich plaques. In advanced stages, atherosclerosis may provoke myocardial infarction and stroke, which are major causes of death worldwide.
Aging is an independent risk factor for atherosclerosis. We have shown previously that during vascular aging mutual upregulation of carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) and TNF-α within the vasculature creates a chronic pro-inflammatory milieu that in turn might promote atherosclerotic plaques formation. This study aimed to investigate the role of CEACAM1 in atherogenesis in more detail.
In order to study CEACAM1-mediated pro-atherosclerotic mechanisms in vitro and in vivo, we introduced a knockout of Ceacam1 into the endothelial cell line EA.hy926 and generated double knockout mice (Ldlr-/-/Ceacam1-/-) based on the established murine atherosclerosis model of the low density lipoprotein receptor knockout mouse (Ldlr-/-).
Ldlr-/-/Ceacam1-/- mice showed drastically reduced atherosclerotic plaque sizes and decreased vascular accumulation of reactive oxygen species compared to Ldlr-/- mice. RNA sequencing of aortic arches from these animals unveiled downregulation of inflammatory and monocyte-recruiting cytokines, but upregulated lipid metabolism in Ldlr-/-/Ceacam1-/- mice compared to Ldlr-/- mice.
Comparative analysis of endothelial cells with and without CEACAM1 expression demonstrated modulation of cell adhesion molecule and chemokine expression and the contribution of CEACAM1 to TNFα-mediated endothelial permeability and monocyte transmigration.
We proved CEACAM1 to play a crucial role in atherosclerotic plaque formation. Therefore, CEACAM1 might represent a promising target to prevent atherogenesis and subsequent life-threatening cardio-vascular events.

Vortrag 54:

Title:
Activity dependent release of microglial cytokines mediates synaptic plasticity induced by 10 Hz repetitive transcranial magnetic stimulation (rTMS)

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Abstract:
Microglia, the resident immune cells of the brain, can interact with neurons through various mechanisms. Their involvement in essential physiological processes, including the regulation of neural excitability and plasticity, is well recognized. In this study, we investigated the impact of microglia on synaptic plasticity induced by 10 Hz repetitive transcranial magnetic stimulation (rTMS), a non-invasive brain stimulation technique commonly used in clinical settings.
Synaptic plasticity induced by 10 Hz rTMS was investigated in the hippocampal region CA1 of organotypic tissue cultures and acute cortical slices of adult mice. Whole-cell patch-clamp recordings, immunohistochemistry, confocal microscopy, protein and transcriptome analyses were used to assess the role of microglia and microglial cytokines in rTMS induced plasticity.
The presence of microglia plays a vital role in mediating the expression of excitatory synaptic plasticity following 10 Hz rTMS in both in vitro and in vivo settings. Notably, a significant upregulation of microglial cytokines was observed 3 h after stimulation, which was triggered by changes in neuronal activity. Substituting these cytokines in microglia-depleted cultures confirmed their essential contribution to the induction of synaptic plasticity.
We conclude that microglia adapt their functional activity in response to neuronal activation by rTMS, leading to the expression and release of plasticity-promoting cytokines. This finding reveals a novel mechanism underlying the induction of plasticity through rTMS and contributes to a deeper understanding of this clinically employed brain stimulation technique.

Vortrag 55:

Title:
Neuronal diversity – Why we should use non-human primates to understand the cellular basis of working memory

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Abstract:
In recent years more and more model organisms have been established which emphasizes the importance of selecting the right model for each research question, balancing the scientific costs and benefits. This is especially true for neuroscience and our understanding of higher brain functions like working memory. On the individual cell level, the morphological and functional differences beyond the general anatomical features are easily overlooked but nevertheless important.
Here, we compared major classes of excitatory and inhibitory neurons of layers 1-3 of prefrontal cortex or primary visual cortex in the common marmoset (Callithrix jacchus) and mouse (mus musculus). Whole cell patch clamp recordings were made in acute brain slices of either sex and cells were filled with biocytin for subsequent morphological reconstruction.
Excitatory cells in marmosets and mice have considerable overlap in anatomical and electrophysiological characteristics. In contrast, inhibitory neurons show a wider range of features than previously reported in the mouse, both for their electrophysiology behavior and their morphology. We found cells that fit multiple established interneuron subtypes and completely novel types.
These results suggest that the common marmoset might be an important and potentially better model organism than the mouse for understanding basic neuroscience principles that also apply to the human brain. Neurons that are not present in the mouse but in the marmoset (and human) could be crucial for decoding working memory and higher brain functions or help with addressing severe neurological diseases.