Institute of Biochemistry – Emil-Fischer-Center

Chair of Biochemistry and Pathobiochemistry

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Research focus
- Sox proteins in glia
- Chromatin-remodeling & histone modifying complexes in glia
- Direct lineage reprogramming
- Cellular decision taking in neural stem cells
- Signal transduction pathways in myogenesis and at the neuromuscular synapse

Structure of the Chair

Professorships: 2
Personnel: 38
- Scientists: 10 (thereof funded externally: 4)
- Graduate students: 18

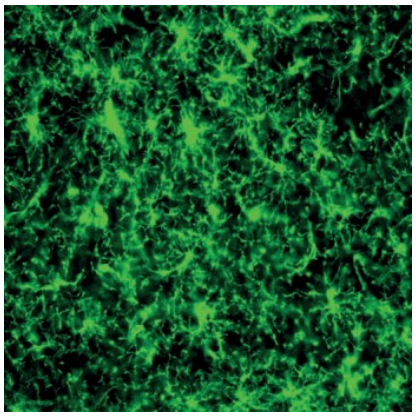
Special structural feature
The Institute of Biochemistry comprises the Chair of Biochemistry and Molecular Medicine and the Chair of Biochemistry and Pathobiochemistry, as well as the professorships of Bioinformatics and of Molecular Medicine with focus on Molecular Imaging.

Research

The groups belonging to the Chair of Biochemistry and Pathobiochemistry work in the field of neuroscience and attempt to unravel regulatory mechanisms of physiological and pathophysiological relevance with a broad spectrum of biochemical, cellular, genetic, bioinformatics and imaging methods. Among others we focus on the impact of transcription factors, chromatin remodelers and histon modifiying enzymes on glial cells and their development, as well as on mechanisms of direct reprogramming and cellular decision taking in neural contexts. An additional group studies neuromuscular signal transduction pathways.

Studying Sox proteins in glia
PI: Prof. Dr. M. Wegner
The three closely related Sox proteins, Sox8, Sox9, and Sox10 (jointly referred to as SoxE proteins), have numerous roles during neural crest development, and ensure survival and pluripotency of neural crest stem cells, generation of melanocytes, enteric nervous system, Schwann cells and satellite glia as well as myelination throughout the peripheral nervous system. In the central nervous system, Sox9 regulates the specification of neural stem cells into oligodendrocytes and astrocytes, whereas Sox10 guides the terminal differentiation of oligodendrocytes and central myelination. Sox10 acts via induction of other transcription factors that are essentially required for oligodendroglial differentiation and cooperate with Sox10 during the process such as Nfat and Myrf proteins. Sox8 gains importance in mature oligodendrocytes for myelin maintenance. SoxE proteins act through recruitment of the basal transcription machinery in a mediator dependent manner as well as through interactions with chromatin-remodeling complexes. Functions of SoxE proteins are also reflected in human disease. Heterozygous haploinsufficient Sox10 mutations lead to Waardenburg-Hirschsprung disease, whereas dominant-negative heterozygous mutations present as a combination of Waardenburg-Hirschsprung disease, peripheral neuropathy, and central leukodystrophy.

Analyzing chromatin-remodeling complexes in glia
PI: Prof. Dr. M. Wegner



Detection of oligodendrocyte precursor cells in the adult brain by staining for NG2

Development and differentiation of myelin-forming glial cells goes along with substantial alterations in chromatin structure that are brought about by chromatin-remodeling complexes. Function and importance of single complexes vary considerably between myelinating glia in central and peripheral nervous systems. In oligodendrocytes, the Brg1-containing BAF complex participates predominantly in the process of specification, whereas in Schwann cells it is essential during maturation by inducing transcriptional regulators of differentiation in cooperation with Sox10. The histone exchanging Ep400/Tip60 complex is required for the timely down-regulation of early regulators during Schwann cell development. In maturing oligodendrocytes, it ensures survival and supports differentiation.

Clarifying the role of histone-modifying complexes in glia
PI: Prof. Dr. E. Sock
Changes in chromatin structure are often accompanied by altered patterns of posttranslational histone modifications. The Rnf20/Rnf40 E3 ligase monoubiquitinates histone 2B. In the absence of Rnf40, Schwann cells in the peripheral nervous system fail to efficiently induce the myelination program despite the fact that all required transcription factors are present including Egr2, the master regulator of myelination. Genome- and transcriptome-wide studies showed that several essential building blocks of the myelin sheath cannot be produced in sufficient amounts and that immaturity factors are not properly turned off. This is caused by failure of Egr2 to recruit the E3 ligase to the corresponding gene promoters, leading to the local absence of histone 2B monoubiquitination and altered gene expression.

Using direct lineage reprogramming to study neural fate acquisition and identity
PI: Prof. Dr. M. Karow
Direct lineage reprogramming entails changing the identity of one cell into the new identity of a target cell. Following this strategy human brain pericytes can be reprogrammed into induced neurons by forced expression of the neurogenic transcription factors Ascl1 and Sox2. By studying the intermediate phases that bridge start and end cell populations, we identified the molecular framework underlying the changes in cell identity. Single cell RNA-sequencing and live imaging technologies are employed to further dissect the sequence of molecular and cellular changes underlying direct lineage conversion. In addition, human induced pluripotent stem cell-derived brain organoids are used as a model system to study the role of specific genes during early human brain development.

Dissecting decision-taking in neural stem cells
PI: Dr. S. Falk
During development a small starting population of neural stem cells (NSCs) gives rise to all neurons and macroglial cells in the mature central nervous system. Hence, controlling NSC decisions is crucial for the accurate production of the precise amount of the desired cell types at the correct time and place. Dynamically orchestrating these stem cell decisions is therefore essential for organogenesis during development, but also represent the key evolutionary mechanism underlying neocortical expansion, in particular in humans. At the very core of the challenge to build a functional nervous system is the cellular choice of NSCs to either divide symmetrically or asymmetrically. Combining time-lapse live imaging and single cell RNA-sequencing of human brain organoid NSCs we aim at uncovering the molecular logic of decision-taking processes governing human brain development.

Studying signal transduction pathways in myogenesis and at the neuromuscular synapse

PI: Prof. Dr. S. Hashemolhosseini

Various molecular signaling pathways participate in myogenesis and guarantee homeostasis and physiology of the neuromuscular synapse. We characterized the activity of Wnt and Hippo pathways including downstream transcriptional effectors in muscle fibers. The signaling pathway activated by the muscle-specific receptor tyrosine kinase (Musk) plays an essential role for the accumulation of postsynaptic proteins at the neuromuscular synapse. We identified the protein kinase CK2 as a MuSK interaction partner. It turned out that CK2 regulates the stability of clusters of acetylcholine receptors by binding and phosphorylation of postsynaptic proteins. CK2 also influences mitochondrial import. In CK2-deficient mice the Pink1- and Parkin-mediated mitophagy is disturbed. Behavioral tests and electro-physiological recordings established a muscle weakness in these mice. The LAP protein Erbin was identified as a second interactor of MuSK and turned out to link MuSK- and ErbB-dependent signaling pathways. Lano und Scribble as further LAP proteins function during maintenance of the neuromuscular synapse, endocytic transport and as scaffold proteins in muscle stem cells. By identifying the molecular causes of neuromuscular pathologies, a foundation is laid for therapeutic interventions in patients.

Teaching

The Chair of Biochemistry and Pathobiochemistry participates in the curricula in Medicine, Molecular Medicine, and Dentistry. Special mention deserves the interdisciplinary teaching in developmental biology and neurosciences in the master degree program Molecular Medicine. Additionally, the chair organizes teaching for the bachelor degree program medical engineering of the Faculty of Engineering. The Chair supervises Bachelor's and Master's theses as well as MD and PhD theses.

Selected publications

Elsesser, O., Fröb, F., Küspert, M., Tamm, E.R., Fujii, T., Fukunaga, R., Wegner, M. Chromatin remodeler Ep400 ensures oligodendrocyte survival and is required for myelination in the vertebrate central nervous system. Nucleic Acids Res. 2019, 47: 6208-6224.

Fröb, F., Sock, E., Tamm, E.R., Saur, A.-L., Hillgärtner, S., Williams, T.J., Fujii, T., Fukunaga, R., Wegner, M. Ep400 deficiency in Schwann cells causes persistent expression of early developmental regulators and peripheral neuropathy. Nat. Commun. 2019, 10: 2361

Aprato, J., Sock, E., Weider, M., Elsesser, O., Fröb, E., Wegner, M. Myrf guides target gene selection of transcription factor Sox10 during oligodendroglial development. Nucleic Acids Res. 2020, 48:1254-1270

Wedel, M., Fröb, F., Elsesser, O., Wittmann, M.-T., Lie, D.C., Reis, A., Wegner, M. Transcription factor Tcf4 is the preferred heterodimerization partner for Olig2 in oligodendrocytes and required for differentiation. Nucleic Acids Res. 2020, 48: 4839–4857

Wüst, H.M., Wegener, A., Fröb, F., Hartwig, A.C., Wegwitz, F., Kari, V., Schimmel, M., Tamm, E.R., Johnsen, S.A., Wegner, M., Sock, E. Egr2-guided histone H2B monoubiquitination is required for peripheral nervous system myelination. Nucleic Acids Res. 2020, 48: 8959-8976

Camargo Ortega G*, Falk S*, Johansson PA, Peyre E, Broix L, Sahu SK, Hirst W, Schlichthaerle T, De Juan Romero C, Draganova K, Vinopal S, Chinnappa K, Gavranovic A, Karakaya T, Steininger T, Merl-Pham J, Feederle R, Shao W, Shi SH, Hauck SM, Jungmann R, Bradke F, Borrell V, Geerlof A, Reber S, Tiwari VK, Huttner WB, Wilsch-Bräuninger M, Nguyen L, Götz M. The centrosome protein AKNA regulates neurogenesis via microtubule organization Nature. 2019 567: 113-117

International cooperations

Prof. R. Fukunaga, Osaka University, Osaka: Japan

Prof. S. Dracheva, Icahn School of Medicine at Mount Sinai, New York: USA

Prof. S.A. Johnsen, Mayo Clinic, Rochester: USA

Prof. Q.R. Lu, Cincinnati Children's Hospital Medical Center, Cincinnati: USA

Prof. P Roussos, Icahn School of Medicine at Mount Sinai, New York: USA