Institute of Biochemistry – Emil-Fischer-Center

Chair of Biochemistry and Pathobiochemistry

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Research focus
- SoxC proteins
- SoxE proteins
- Chromatin-modifying complexes in glial development
- MicroRNAs in glial development
- Physiological and pathophysiological signal transduction pathways in myogenesis and at the neuromuscular synapse

Structure of the Chair

Professorships: 2
Personnel: 26
- Scientists: 6 (thereof funded externally: 1)
- Graduate students: 12

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 processes with methods of biochemistry, molecular genetics, and cell biology. Several groups are interested in the characterization of transcriptional regulators and chromatin-modifying complexes that participate during development of the mammalian nervous system in determination and differentiation of neural stem cells to glia and neurons. Work on transcription factors is mainly focused on members of the Sox protein family and their interacting partners. Analysis of these transcription factors will lead to a better understanding of developmental defects, tumor formation, and regenerative processes in the nervous system. Among chromatin-modifying complexes, Brg1-dependent BAF complexes have been analyzed for their role in the specification and terminal differentiation of myelin-forming glia. An additional group studies neuromuscular signal transduction pathways in skeletal muscle.

SoxC proteins

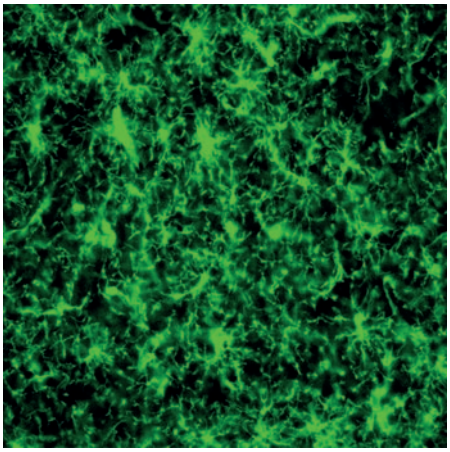
PI: PD Dr. E. Sock

All SoxC proteins occur in many tissues and organs during embryogenesis. Whereas loss of Sox4 or Sox11 leads to severe developmental defects (such as heart and outflow tract malformations, B-cell maturation defects, asplenia, skeletal malformations, and hypoplasias of several organs), Sox12 deletion remains without obvious phenotypic consequences in the mouse. Despite strong expression of all three SoxC proteins in the developing nervous system, neural defects become visible only upon combined deletion of more than one SoxC protein. Nervous system defects are predominantly caused by changes in proliferation and apoptosis of neuronal precurosor cells. Overexpression studies in the mouse have also pointed to an influence of SoxC proteins on neural maturation. An important target gene of SoxC proteins in neuronal precursor cells is the homeodomain transcription factor Prox1.

SoxE proteins

PI: Prof. Dr. M. Wegner

Transgenic mouse models have shown that the three closely related group E Sox proteins, Sox8, Sox9, and Sox10, have numerous functions during nervous system development. Sox9 and Sox10 are essential for survival and pluripotency of neural crest stem cells, the source for most cells of the peripheral nervous system. Sox9 and Sox10 furthermore determine which derivatives develop from neural crest stem cells. In Sox10-deficient mice, glial cells are missing from the peripheral nervous system. The enteric nervous system is completely absent. Schwann cells as the myelinating cells of the peripheral nervous system depend on Sox10 at all times during their development and differentiation. In the central nervous system, Sox9 and Sox10 together regulate gliogenesis. Sox9 is responsible for the specification of neural stem cells into oligodendrocytes, whereas Sox10 guides terminal differentiation and myelination in oligodendrocytes. In the absence of Sox10 und Sox10-induced Nfat proteins, oligodendrocytes would neither express Nkx2.2 nor Myrf. The myelination program could not be induced by the interplay of these transcription factors with Sox10. During the period between specification and terminal differentiation, oligodendrocyte development is jointly regulated by Sox9 and Sox10. Functional support comes from the related Sox8 which gains importance in mature oligodendrocytes during 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 group E Sox proteins were not only obvious in transgenic mouse models, but are equally reflected in human disease. Heterozygous haploin-sufficient 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.



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

Chromatin-modifying complexes in glial development

PI: Prof. Dr. M. Wegner

Development and differentiation of myelin-forming glial cells goes along with substantial alterations in chromatin structure that are brought about by chromatin-modifying complexes. Function and importance of single complexes varies considerably between Schwann cells and oligodendrocytes. In oligodendrocytes, the Brg1-containing BAF complex participates already in the process of specification, whereas it becomes essential in Schwann cells only during maturation by inducing transcriptional regulators of differentiation in cooperation with Sox10. In contrast, the Ep400-containing Tip60 complex supports

the timely downregulation of early regulators during Schwann cell development, whereas it secures differentiation and survival in maturing oligodendrocytes.

MicroRNAs in glial development

PI: Dr. S. Reiprich

Control of proliferation and differentiation of oligodendrocytes depends on a complex regulatory network. Several studies have shown over the last years that microRNAs are important components of this network in addition to transcription factors. A number of functional interactions between Sox transcription factors and microRNAs were detected. Sox10, for instance, activates expression of miR-335, miR-338, and miR-155. In turn, miR-335 und miR-338 inhibit Sox9 as a regulator expressed in immature oligodendrocytes. MiR-338 and miR-155 inhibit the transcription factor Tcf7l2. By doing so, these microRNAs play a decisive role during oligodendrocyte differentiation.

Physiological and pathophysiological 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. Own work 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. Own work 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 electrophysiological 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

Reiprich S, Cantone M, Weider M, Baroti T, Wittstatt J, Schmitt C, Küspert M, Vera J, Wegner M. Transcription factor Sox10 regulates oligodendroglial Sox9 levels via microRNAs. Glia 2017, 65: 1089-1102

Parfejevs V, Debbache J, Shakhova O, Schaefer S, Glausch M, Wegner M, Suter U, Riekstina U, Werner S, Sommer L. Injury-activated glial cells promote wound healing of the adult skin in mice. Nat. Commun. 2018, 9: 236

Truch K, Arter J, Turnescu T, Weider M, Hartwig AC, Tamm ER, Sock E, Wegner M. Analysis of the human SOX10 mutation Q377X in mice and its implications for genotype-phenotype correlation in SOX10-related human disease. Hum. Mol. Genet. 2018, 27: 1078–1092

Weider M et al. Nfat/calcineurin signaling promotes oligodendrocyte differentiation and myelination by transcription factor network tuning. Nat. Commun. 2018, 9: 899

Jacob A, Wüst HM, Thalhammer JM, Fröb F, Küspert M, Reiprich S, Balta EA, Lie DC, Wegner M, Sock E. The transcription factor prospero homeobox protein 1 is a direct target of SoxC proteins during developmental vertebrate neurogenesis. J Neurochem. 2018 Aug;146(3):251-268

Kravic B et al. In mammalian skeletal muscle, phosphorylation of TOMM22 by protein kinase CSNK2/CK2 controls mitophagy. Autophagy 2018, 14: 311-335

International cooperations

Prof. M. Sandri, University of Padova, Padova: Italy

Prof. L. Sommer, Universität Zürich, Zurich: Switzerland

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

Prof. W. Tetzlaff, University of British Columbia, Vancouver, BC: Canada

Prof. A. Schedl, Université Nice Sophia Antipolis, Nice: France