Institute of Biochemistry – Emil-Fischer-Center

Professorship of Molecular Medicine with focus on Molecular Imaging

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Research focus
- Transcriptional programs in the regulation of adult neurogenesis
- Metabolic control of stem cell development and adult neurogenesis
- Role of autophagy in stem cell function and adult neurogenesis
- Functional characterization of intellectual disability factors

Structure of the Professorship

Professorship: 1
Personnel: 7
- Scientists: 3 (there of funded externally: 1)
- Graduate students: 4

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

Neurons and glia cells form functional networks that are the structural basis for learning, cognition, and behavior. Perturbation of the formation, maturation, and plasticity of neural circuits contributes to the pathogenesis of neurodevelopmental disorders, such as intellectual disability and neuropsychiatric diseases, like schizophrenia. Our research aims to better understand the genetic and cell biological mechanisms that regulate development and homeostasis of neuronal networks.

Transcriptional programs in the regulation of adult neurogenesis

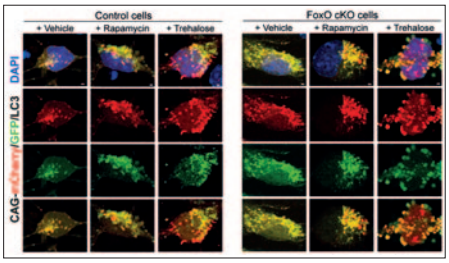
The discovery of adult neurogenesis, i.e. the lifelong generation of new hippocampal and olfactory bulb neurons from stem cells, has added a new layer of complexity to our understanding of the mechanisms underlying plasticity and regeneration in the mammalian central nervous system. There is now strong evidence that adult neurogenesis significantly contributes to hippocampus-dependent learning and memory processes as well as to the pathophysiology of cognitive and affective symptoms during aging and in neurodegenerative and neuropsychiatric diseases. Thus, understanding of the mechanisms regulating adult neurogenesis is of major basic neuroscientific and clinical interest. The generation of new functional neurons from stem cells is a complex multistep process. Current data indicate that each developmental step is controlled by stage-specific transcription factors. In collaboration with the research group of Prof. Dr. M. Wegner, we discovered the SoxC group transcription factors SOX4 and SOX11 as key regulators of neuronal fate determination of adult neural stem cells. Intriguingly, our new data indicate that SoxC proteins fulfill additional critical functions in the synaptic integration of adult-born neurons. Moreover, we recently demonstrated that posttranslational modification by phosphorylation controls the neurodevelopmental function of SOX11. Collectively our data uncover SOXC factors as pleiotropic regulators of adult hippocampal neurogenesis.
Funding: DFG

Metabolic control of stem cell development and adult neurogenesis

In contrast to adult neural stem cells, neurons are postmitotic, have a highly complex morphology, and communicate with each other via high-energy consuming mechanisms. It is assumed that the generation of a functional neuron from a stem cell is accompanied by profound changes in cellular metabolism. We now found that specific mitochondrial metabolic pathways control distinct steps in neuronal development. Thus, we demonstrated that the generation of highly proliferative precursor cells from stem cells is critically dependent on electron transport chain function and oxidative phosphorylation. Interestingly, we found that inhibition of these metabolic pathways reproduced multiple hallmarks of aging in hippocampal neurogenesis, whereas pharmacological enhancement of mitochondrial function ameliorates age-associated neurogenesis defects. Together with the finding of age-associated alterations in mitochondrial function and morphology in neural stem cells, our data suggest mitochondrial function as a potential target to ameliorate neurogenesis-defects in the ageing hippocampus.

Role of autophagy in stem cell function and adult neurogenesis

Degradation and recycling of dysfunctional cellular components are critical pathways for cellular homeostasis. In particular, somatic stem cells are highly dependent on degradation and recycling pathways to maintain their lifelong capacity for regeneration. We now demonstrated that the longevity associated transcription factors of the FoxO family are critical to regulate autophagy, i.e., a central pathway for proteins and organelles, in adult neural stem cells. Loss of FoxOs does not only impair activity of the autophagic pathway, but is associated with stem cell dysfunction and impaired integration of adult-born neurons. In ongoing projects we are now investigating if and how FoxO dysfunction may contribute to neural stem cell and neurogenesis dysfunction during aging. This project is conducted in close collaboration with Prof. J. Klucken (Division of Molecular Neurology).
Funding: IZKF Erlangen



Analysis of autophagolysosomal flux using a genetic reporter system indicates impaired autophagolysomal flux in adult neural stem cells upon deletion of FoxO transcription factors.
Control cells contain both autophagosomes (red and green, yellow in the merge) and autophagolysosomes (red only). Note the almost complete absence of autophagolysosomes in FoxO-deficient cells. Treatment with Rapamycin or Trehalose enhances autophagolysomal flux in FoxO-deficient cells.

Functional characterization of intellectual disability factors

Sox11 mutations were recently identified in a subset of patients suffering from Coffin-Siris Syndrome, a developmental disorder associated with intellectual disability. Proteomic analysis of the SOX11 interactome and of SOX11 target genes revealed that SOX11 interacts with a number of intellectual disability-related transcription factors and regulates the expression of intellectual disability (ID) genes. These data suggest that a subset of ID causing genes is connected via a SOX11-dependent transcriptional network and that perturbation of this network contributes to the pathophysiology of intellectual disability. Using human pluripotent stem cells to model human neurodevelopment, we

are now investigating how SOX11 drives CNS development in conjunction with intellectual disability-related transcription to understand the function of the SOX11-transcriptional network in the pathogenesis of intellectual disability. This project is conducted in close collaboration with Prof. Dr. B. Winner (Division of Stem Cell Biology) and Prof. Dr. A. Reis (Institute of Human Genetics).
Funding: DFG

Teaching

The Professorship of Molecular Medicine with focus on Molecular Imaging contributes to the teaching curriculum of Medicine and Dentistry by offering obligatory and elective courses. It provides interdisciplinary training for students of the master degree program Molecular Medicine that is performed together with the departments of Psychiatry and Psychotherapy and of Nuclear Medicine, the Institute of Radiology, and the Division of Molecular Neurology. Aim is to theoretically and practically teach the students state-of-the-art technologies of molecular imaging.
Bachelor and master students as well as medical and scientific graduate students are supervised in our group to successfully finish their thesis projects.

Selected publications

Beckervordersandforth R et al. Role of Mitochondrial Metabolism in the Control of Early Lineage Progression and Aging Phenotypes in Adult Hippocampal Neurogenesis. Neuron, 2017, 93: 560-576

Schaffner I, Minakaki G, Khan MA, Balta EA, Schlotzer-Schrehardt U, Schwarz TJ, Beckervordersandforth R, Winner B, Webb AE, DePinho RA, Paik J, Wurst W, Klucken J, Lie DC. FoxO Function Is Essential for Maintenance of Autophagic Flux and Neuronal Morphogenesis in Adult Neurogenesis. Neuron, 2018, 99: 1188-1203

Minakaki G et al. Autophagy inhibition promotes SNCA/alpha-synuclein release and transfer via extracellular vesicles with a hybrid autophagosome-exosome-like phenotype. Autophagy, 2018, 14: 98-119

Jung M, Haberle BM, Tschaikowsky T, Wittmann MT, Balta EA, Stadler VC, Zweier C, Dorfler A, Gloeckner CJ, Lie DC. Analysis of the expression pattern of the schizophrenia-risk and intellectual disability gene TCF4 in the developing and adult brain suggests a role in development and plasticity of cortical and hippocampal neurons. Molecular Autism, 2018, 9:20

Balta EA, Schaffner I, Wittmann MT, Sock E, von Zweydorf F, von Wittgenstein J, Steib K, Heim B, Kremmer E, Haberle BM, Ueffing M, Lie DC, Gloeckner CJ. Phosphorylation of the neurogenic transcription factor SOX11 on serine 133 modulates neuronal morphogenesis. Scientific Reports, 2018, 8 (1):16196

Balta EA, Wittmann MT, Jung M, Sock E, Haeberle BM, Heim B, von Zweydorf F, Heppt J, von Wittgenstein J, Gloeckner CJ, Lie DC. Phosphorylation Modulates the Subcellular Localization of SOX11. Frontiers in Molecular Neuroscience, 2018, 11:211

International cooperations

Prof. S. Jessberger, University of Zurich, Zurich: Switzerland

Prof. H. Song, Perelman School of Medicine, University of Pennsylvania, Pittsburgh: USA

Dr. A. Schinder, Instituto Leloir, Buenos Aires: Argentina

Prof. N. Toni, University of Lausanne, Lausanne: Switzerland

Prof R. DePinho, The University of Texas MD Anderson Cancer Center, Houston, Texas: USA