Institute of Physiological Chemistry

Molecular Pathways Regulating Differentiation and Disease

Head: Thomas Wirth

We use conditional mouse genetics to investigate the functions of transcriptional regulators and key components of signaling pathways in normal differentiation processes as well as in animal disease models. In addition to Cre-loxP-based gene deletion, we use tetracycline-regulated gene expression systems to activate or block specific signaling pathways in transgenic mice. This type of approach has provided a deep insight into both developmental as well as pathophysiological processes.

A large part of our work deals with the IKK/NF-κβ signaling pathway. This pathway is activated in many cell types in response to stress and inflammatory signals and is itself not only a prime regulator of inflammation but also of cell proliferation and apoptosis.

Recent work focuses on the role of NF-κβ for efficient neuronal differentiation, its contribution to various types of heart and liver disease, and the analysis of the NF-κβ system for in vivo progression of pancreatic carcinoma. Lap Kwan Chan in his PhD project is trying to uncover the role of oxidative stress and inflammation in pancreatic diseases, such as pancreatic carcinoma, pancreatitis and diabetes.

We identified IKK/NF-κβ signaling in astrocytes as a major regulator of neuroinflammation. Notably, we demonstrated that NF-κβ activation in astrocytes impairs ciliogenesis and links neuroinflammation to hydrocephalus formation. Currently, we are analyzing the function of neuroinflammation in the development of neurodegenerative diseases, e.g. the PhD project of Alexander Magnutzki addresses Alzheimer's disease. He is also establishing a novel Alzheimer model allowing temporal and spatial regulation of neurotoxic Aβ forms. Christine Schurr studies the consequences of neuroinflammatory

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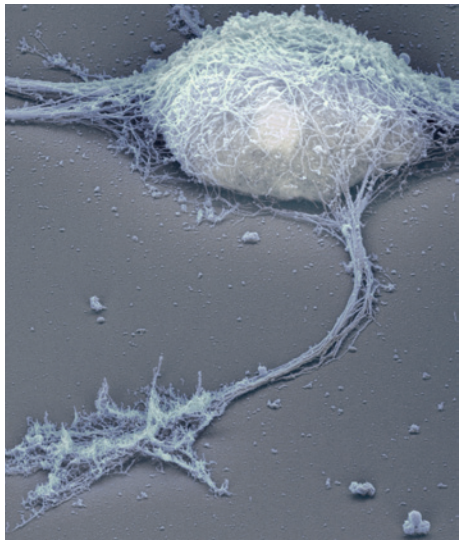
processes for the onset and progression of Amyothropic Lateral Sclerosis. She also addresses the question whether in Multiple Sclerosis neuroinflammation is initiated by an autoimmune process or represents secondary consequences to axonal degeneration and myelin degradation.
Cellular and tissue homeostasis are regulated by the FoxO transcription factors downstream of the insulin receptor signaling. We generated transgenic mice to allow cell type-specific modulation of FoxO3 activity. The role of FoxO3 in the liver is investigated in the PhD project of Sarah Gul. She found that FoxO expression blunts the insulin feedback to the liver and results in induction of hyperglycemia.

In our work on lymphomagenesis, we identified FOXO1 as a tumor suppressor in classical Hodgkin lymphoma (cHL). Marion Vogel tries to identify the role of FOXO1 repression in cHL pathogenesis and to identify tumor suppressor mechanisms deregulated by FOXO1 repression. Given that deregulation of miRNA expression plays a critical role in FOXO1 repression, as we have found recently, the MD project of Franziska Herrmann is dedicated to the investigation of the role of miRNA in block of terminal differentiation in CHL.

The PhD project of Manuel Gey investigates the role of the gene regulator ATF3 in facial nerve regeneration. In addition, the MD student Stephanie Haverkamp is analyzing transcriptional regulation of peripheral nerve regeneration. Further projects focus on gene regulatory programs provided by the serum response factor (SRF). Here, work by the PhD student Sofia Anastasiadou and MD student Sophie Liebenehm addresses potential roles of SRF in myelination and demyelination processes. Pascal Lösing, a PhD student in the laboratory, is analyzing SRF's contribution in neurodegenerative conditions elicited by epileptic seizures. Finally, the PhD student Christopher Meyer zu Reckendorf is trying to uncover and characterize novel cofactors interacting with SRF.



Electron microscopical image of a mouse hippocampal neuron grown in cell culture. The nucleus, center of gene activity, is highlighted in yellow. Cytoskeletal filaments are labelled in blue.

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Selected Publications:

- *Maier HJ, Schips TG, Wietelmann A, Krüger M, Brunner C, Sauter M, Klingel K, Böttger T, Braun T, Wirth T (2012): Cardiomyocyte-specific Iκβ kinase (IKK)/NF-κβ activation induces reversible inflammatory cardiomyopathy and heart failure. PNAS 109, 11794-9.*
- *Sunami Y, Leithäuser F, Gul S, Fiedler K, Güldiken N, Espenlaub S, Holzmann KH, Hipp N, Sindrilaru A, Luedde T, Baumann B, Wissel S, Kreppel F, Schneider M, Scharffetter-Kochanek K, Kochanek S, Strnad P, Wirth T (2012): Hepatic activation of IKK/NFκβ signaling induces liver fibrosis via macrophage-mediated chronic inflammation. Hepatology 56, 1117-28.*
- *Xie L, Ushmorov A, Leithäuser F, Guan H, Steidl C, Färbinger J, Pelzer C, Vogel MJ, Maier HJ, Gascoyne RD, Möller P, Wirth T (2012): FOXO1 is a tumor suppressor in classical Hodgkin lymphoma. Blood 119, 3503-3511.*
- *Beck H, Flynn K, Lindenberg KS, Schwarz H, Bradke F, Di Giovanni S, Knöll B (2012): Serum Response Factor (SRF)-cofilin-actin signaling axis modulates mitochondrial dynamics. Proc Natl Acad Sci USA 109, 2523-32.*
- *Lattke M, Magnutzki A, Walther P, Wirth T, Baumann B (2012): Nuclear factor κβ activation impairs ependymal ciliogenesis and links neuroinflammation to hydrocephalus formation. J Neurosci 32, 11511-23.*
- *Guan H, Xie L, Leithäuser F, Flossbach L, Möller P, Wirth T and Ushmorov A (2010): KLF4 is a tumor suppressor in B-cell non-Hodgkin lymphoma and in classical Hodgkin lymphoma. Blood 116, 1469-1478.*