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Research interests

Our laboratory is investigating signaling pathways implicated in cancer formation. We focus on Ras and Jak/Stat signaling and study the importance of these pathways in tumor cells and cells of the tumor microenvironment. For that purpose we have established novel mouse tumor models and employ conditional gene inactivation approaches to identify Ras and Jak/Stat functions during tumor initiation and tumor progression. In particular, we are interested in Stat1 and Stat3 functions in liver and colorectal cancer. Activation of Stats is mediated by cytokines. Therefore, these transcription factors are considered as promising candidates that could provide a molecular link between inflammation and cancer development.

Thesis projects

1. Functions of Stat3 in the tumor microenvironment of colorectal cancer

Stat3 has been described as a key modulator of tumor surveillance that regulates cytokine expression in immune cells and tumor cells. However, the impact of Stat3 signaling in inflammatory cells on the outcome of tumorigenesis has not been investigated *in vivo*. We will conditionally inactivate Stat3 in T-cells (Lck-cre), macrophages (LysM-cre) and natural killer cells (NCR1-cre) and use the conditional knockout mice for tumor induction in the small intestine (using APC^{Min} mice) and the colon (using AOM/DSS treatment). This approach will allow us to investigate Stat3 functions in the inflammatory compartment of intestinal tumors.

2. Functions of Stat1 in the tumor microenvironment of colorectal cancer

We have demonstrated that loss of Stat3 promotes development of invasive carcinomas in APC^{Min} mice (Musteanu et al., *Gastroenterology* 2010) that display increased activation of Stat1 and induction of type-I-interferon responsive genes. A substantial amount of pY-Stat1 is present in inflammatory cells of the tumor stroma. We intend to identify the mechanism leading to Stat1 activation in inflammatory cells and will address the question if Stat1 activity in tumor cells or inflammatory cells influences the outcome of intestinal tumorigenesis.

These projects employ genetically modified mice (conventional and conditional knock-out mice, knock-in mice and transgenic mice) to address the function of Jak/Stat signaling in colorectal cancer *in vivo*. Additional methods include generation of genetically modified mice, ES cell technology, genetic and chemical tumor induction, tumor analysis using HC, IHC, IF and other staining techniques, PCR, quantitative histomorphometry, FACS, shRNA, ChIP, Affymetrix Microarray, primary intestinal epithelial cell (IEC) isolation, immortalization of IECs, culture of colorectal cancer cell lines.

Selected publications

Mair, M., G. Zollner, D. Schneller, M. Musteanu, P. Fickert, J. Gumhold, C. Schuster, A. Fuchsichler, M. Bilban, S. Tauber, H. Esterbauer, L. Kenner, V. Poli, L. Blaas, J. W. Kornfeld, E. Casanova, W. Mikulits, M. Trauner, and **R. Eferl**. 2010. Stat3 Protects from Liver Injury and Fibrosis in a Mouse Model of Sclerosing Cholangitis. *Gastroenterology*. 138:2499-508.

Musteanu, M., L. Blaas, M. Mair, M. Schlederer, M. Bilban, S. Tauber, H. Esterbauer, M. Mueller, E. Casanova, L. Kenner, V. Poli, and **R. Eferl**. 2010. Stat3 is a negative regulator of intestinal tumor progression in Apc(Min) mice. **Gastroenterology** 138:1003-1011.

Eferl, R., P. Hasselblatt, M. Rath, H. Popper, R. Zenz, V. Komnenovic, M. H. Idarraga, L. Kenner, and E. F. Wagner. 2008. Development of pulmonary fibrosis through a pathway involving the transcription factor Fra-2/AP-1. **PNAS** 105:10525-10530.

Eferl, R., R. Ricci, L. Kenner, R. Zenz, J. P. David, M. Rath, and E. F. Wagner. 2003. Liver tumor development. c-Jun antagonizes the proapoptotic activity of p53. **Cell** 112:181-192.