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Research interests

The focus of our laboratory is on the Jak-Stat signaling pathway and its direct or indirect interconnection with the host response to infection, inflammation and carcinogenesis. A total of four Janus kinases (Jak1-3, Tyk2) and seven Stats (Stat1-4, Stat5a, Stat5b, Stat6) act in various combinations to stimulate appropriate nuclear responses to cytokines and growth factors. Upon ligand binding, receptor-associated Jaks phosphorylate recruited Stats thereby initiating nuclear translocation and DNA binding. This linear pathway constitutes the canonical Jak-Stat signaling. Jaks also initiate non-Stat signaling pathways and show kinase-independent functions. In addition to phosphorylation, Stats exert biological activity through additional or alternative modifications. Jaks and Stats also show non-receptor associated functions. These activities are summarized as non-canonical. We employ mouse reverse genetics to study signaling involved in infection and immunity and consequences of non-canonical Jak-Stat activities. The molecular focus on Tyk2 and Stat1/3. For these molecules the lab has generated a comprehensive collection of mutant mice enabling to study loss of function, tissue-specificity and non-canonical functions.

Thesis projects

Stat1 and Stat3 are key transcription factors involved in innate and adaptive immunity, tumor suppression and tumor promotion. Mice exposed to viruses produce local and systemic interferons (IFNs), which in turn signal through tissue-specific combinations of Stats, especially Stat1 and 3. Both Stats are reported to have anti- as well as pro-inflammatory and synergistic as well as specific functions. Systemic loss of Stat1 leads to severe impairment of the defense mechanisms against viruses in general. Stat3 deficiency can be studied only in a tissue specific manner, since the complete knockout is embryonic lethal. Yet, very little has been reported with respect to Stat3 biological functions in the context of viral infections. Aim of the project is to further elucidate the Stat1/3 and cell type specific contribution to the host response to viral infection.

1. How do Stat1 and 3 contribute to the IFN response and antiviral defense of macrophages?

Macrophages are key players in innate immunity against viruses and in the initiation of the adaptive immune response. Upon challenge with viruses in vitro Stat1 deficient macrophages

fail to restrict viral replication due to impaired production of and responses to cytokines, most importantly interferons. As mentioned above, Stat3 has not been studied with respect to antiviral properties in macrophages. We aim to extend the studies to in vivo models and take advantage of Stat1fl/fl (generated in our lab) and Stat3fl/fl mice that have been crossed to LysCre mice and will be in vivo challenged with VSV and MCMV. Depending on the outcome, virus induced macrophage function is further analysed by expression profiling and functional in vitro assays.

2. How do Stat1 and 3 contribute to the IFN response and antiviral defense of NK cells?
NK cells are termed after their cytotoxic capabilities but are also potent cytokine producers and important mediators of the immune defence against viruses. Interferons and Stat1 are required for NK cells functions, i.e. normal cytolytic activity and homeostasis as well as activation and proliferation. Again, Stat3 has not been studied in the context of interferon or viral dependent NK cell activity. Hence, the experimental setup is similar to project 1 except for intercossing a NKCre mouse line.

Selected publications

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