MOI Project 3

How do hepatitis viruses reprogramme the host cell response to inflammatory cytokines?

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The interference of pathogens with host signalling mechanisms and the intracellular processing of signals in the context of inflammatory processes are central themes of our current work. In previous work, we demonstrated that chronic hepatitis C virus (HCV) infection is associated with increased plasma concentrations of IL-1b and EGF in patients with chronic hepatitis C, and that HCV comprehensively rewires the host cell response to IL-1β and epidermal growth factor (EGF), thereby affecting their intercellular communication. Observations from the current funding period suggest that an important mechanism by which HCV rewires the host cell response to inflammatory factors is through increased activability of NF-kB and AP1, mediated by mechanisms that are not yet understood.

This project aims to further investigate the molecular mechanisms involved in the dysregulation of NFκB and AP1-mediated signalling, the significance of these observations for host cell response to cytokines such as IL-1β and the resulting functional changes.

In particular, the project aims to elucidate the level at which HCV, but also HBV, interferes with the NF-κB signalling pathway and the activation of AP1. A particular focus will be on the role of endogenous repressors in this context. It will also be investigated whether epigenetic changes at the level of activating or inactivating histone modifications are also important.

In addition to virological techniques, these aspects will be investigated using technologies such as chromatin immunoprecipitation (ChIP) with antibodies recognizing activating or inactivating histone modifications, deep sequencing, siRNA-mediated gene silencing or CRISPR-Cas-mediated knockout.