Universität Basel

Research Project

Immunity and pathogenesis in persistent viral infection

Third-party funded project

Project title Immunity and pathogenesis in persistent viral infection
Principal Investigator(s) Pinschewer, Daniel ;
Organisation / Research unit
Departement Biomedizin / Experimental Virology (Pinschewer)
Department
Project start 01.10.2013
Probable end 30.09.2016
Status Completed

Background: Estimated 350 and 170 million people worldwide are persistently infected with hepatitis B and C virus (HBV, HCV), respectively, and more than thirty million people live with HIV. Antiviral therapy is only accessible to a minority of those in need, and preventive vaccines for HCV and HIV remain unavailable. Antibodies are a key component of antiviral vaccine protection, but their mechanism of protective efficacy remains incompletely understood, thus limiting our capacity to fully harness their potential for vaccine development. Similarly, adoptive immunotherapy and therapeutic vaccination have considerable potential for curing HBV and HCV, but a refined mechanistic understanding of viral clearance from hepatocytes is needed. Working hypothesis: I) Neutralization of virus in cell culture is a surrogate for detection of protective antibody specificities, but in vivo antibody efficacy relies critically on inflammation-induced pathways for scavenging and intracellular degradation of antibody-coated virions. II) In adoptive immunotherapy, hepatic inflammation and T cell infiltration dampen viral replication in hepatocytes and limit viral dissemination. This involves type I and type II interferon signaling to infected cells, triggering distinct transcriptional programs. Elimination of infection relies, however, critically on T cell cytotoxicity, resulting in the eventual replacement of most infected hepatocytes. Experimental models and methods: We will use genetically engineered lymphocytic choriomeningitis virus (LCMV) and vesicular stomatitis virus (VSV) for infection and protection experiments in new and innovative gene-targeted mouse models. Recombinant antibody engineering, genome-wide transcriptome analyses, TaqMan RT-PCR, immunohistochemistry and flow cytometry will be combined with state-of-the-art immunological and virological techniques. Specific aims: We aim to investigate the following fundamental questions in immunity and pathogenesis of systemic persistent viral infection: 1. Mechanisms underlying in vivo efficacy of neutralizing and non-neutralizing antiviral antibodies. 2. The role of innate and adaptive immune responses in augmenting protective antibody efficacy. 3. Non-cytolytic “cure” of virus-infected hepatocytes: proof-of-principle and molecular signature. 2. IFNa/ß and IFN-? signaling in virus-infected hepatocytes: role in T cell-mediated clearance. Significance: We will combine an array of cutting-edge molecular tools and methodology and will apply them to relevant animal models of viral infection. The project therefore has potential for a quantum leap in understanding of antiviral antibody protection and T cell-mediated elimination of persisting viruses from the liver. Fundamental novel concepts in these areas are urgently needed to combat persisting viral infections of global health impact.

Keywords Persistent infection, Virus, Hepatitis, T cells, Antibody
Financed by
Swiss National Science Foundation (SNSF)

Add publication

Add documents

Specify cooperation partners