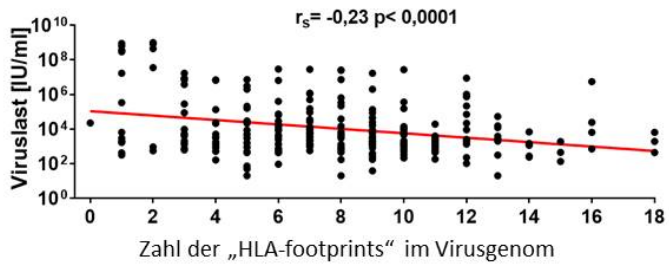
Project 4: Influence of selection pressure by CD8+ T cells on the replication of the hepatitis B virus (Supervising Investigator: Prof. Dr. Jörg Timm)

Worldwide, about 2 billion people have serological markers for HBV infection. Despite the availability of prophylactic vaccination, the prevalence of persistent HBV infection remains high, estimated at about 250 million people. A functional cure with sustained control of viral replication in the absence of antiviral treatment is extremely rare. An important reason for the low cure rate in chronic hepatitis B is the stability of the viral genome as so-called cccDNA in the nucleus of hepatocytes, which is used by cellular polymerases as a template for the transcription of different viral RNA species even in the case of efficient treatment. By expression of various viral proteins, infected hepatocytes remain "visible" to cytotoxic CD8+ T cells. Therefore, the activation of HBV-specific CD8 T cells is of great importance in the development of new therapeutic strategies against HBV with the aim of virus elimination.

The antiviral CD8 T-cell response is essential for spontaneous resolution of acute HBV infection, in turn, development of a chronic infection is characterized by different mechanisms of T-cell failure. In our group there is long term experience in studying the interaction between the CD8 T cell response and viral sequence variability (1, 2). In the context of hepatitis B, analyses of the CD8 T cell response together with the sequence variability of HBV have provided evidence for the selection of mutations that lead to immune evasion (3). At the population level, these "escape" mutations are found as associations between viral sequence polymorphisms and certain HLA haplotypes (so-called "HLA footprints"). For this purpose, the complete HBV genome of more than 500 patients was analyzed together with the HLA class I haplotype using bioinformatic methods. From these investigations it is increasingly clear that the HBV genome is under extensive selection pressure by CD8 T cells. Interestingly, with an increasing number of "HLA footprints" in the genome, the virus concentration in the blood decreases. Our working hypothesis is that mutations in the virus genome selected by the CD8 T cell immune response impair viral fitness.



With an increasing number of HLA-dependent substitutions in the viral genome, the virus concentration in serum decreases. This may indicate reduced fitness of virus variants.

In this project, the mechanisms and kinetics of the development of "HLA footprints" in the HBV genome will be investigated in more detail. In the data set of more than 500 HBV genomes, it will be examined whether individual substitutions are associated with a reduced virus concentration. These will be functionally investigated in replication models with regard to their impact on viral fitness. Furthermore, the kinetics of the development of the substitutions will be investigated in more detail using patients with acute HBV infection. For this purpose, there is access to corresponding cohorts through a long-term cooperation with the MGH in Boston (USA). Finally, HBV-specific CD8 T cells from different phases of HBV infection and with different patterns of "HLA footprints" will be investigated.

1. Timm J, Walker CM (2015), Med Microbiol Immunol 204 29-38.
2. Ruhl M, Knuschke T, (...) Hoffmann D, Timm J (2011) Gastroenterology 140, 2064-73.
3. Kefalakes H, Budeus B, Walker A, Jochum C, Hilgard G, Heinold A, Heinemann FM, Gerken G, Hoffmann D, Timm J (2015) Hepatology 62, 47-56.