Research projects on hepatitis viruses

The characterisation of the life cycle of hepatitis viruses and virus-associated pathogenesis is another focus of our work. Worldwide, more than 1.2 million people die each year as a result of infection with hepatitis viruses. Our work focuses on four different types of viruses: the hepatitis B virus (HBV), the hepatitis C virus (HCV), the hepatitis E virus (HEV) and, more recently, the hepatitis delta virus (HDV), which is known as a satellite virus, as it can only replicate in HBV-positive cells. HBV is an enveloped DNA virus with a life cycle that shares some steps in common with a retrovirus. HCV is an enveloped virus with an RNA genome of positive polarity. HEV is an unenveloped, positive-sense strand of RNA virus. HDV has a negative-sense RNA genome and HBV envelope proteins. Despite their differences, all three viruses can trigger an inflammatory disease of the liver (hepatitis), which can become chronic, especially in HCV and HBV, and can lead to fibrosis or cirrhosis. Cirrhosis causes functional liver tissue to be replaced by connective tissue, so that the liver can no longer perform its central functions, such as acting as a detoxification organ. Hepatocellular carcinoma (HCC) can also develop. One focus of our research in this regard is on the characterisation of intracellular signalling pathways and their deregulation by these viruses with regard to their importance for virus replication and virus-associated pathogenesis. Our research in this area is particularly focussed on the influence of these viruses on the process of liver regeneration and on the effect of these pathogens on signalling pathways that control the cell cycle in order to better understand the process of virus-associated tumour formation and thus ultimately modulate it therapeutically. Radicals also play an essential role in virus-associated pathogenesis. An especially important role is played by reactive oxygen intermediates. These are highly reactive molecules that modulate a large number of intracellular processes but exert a strongly inhibiting effect on liver regeneration via processes such as inhibiting insulin receptor-dependent signalling pathways. Due to their high reactivity, reactive oxygen intermediates can react with the DNA of the host genome and thus trigger mutations.

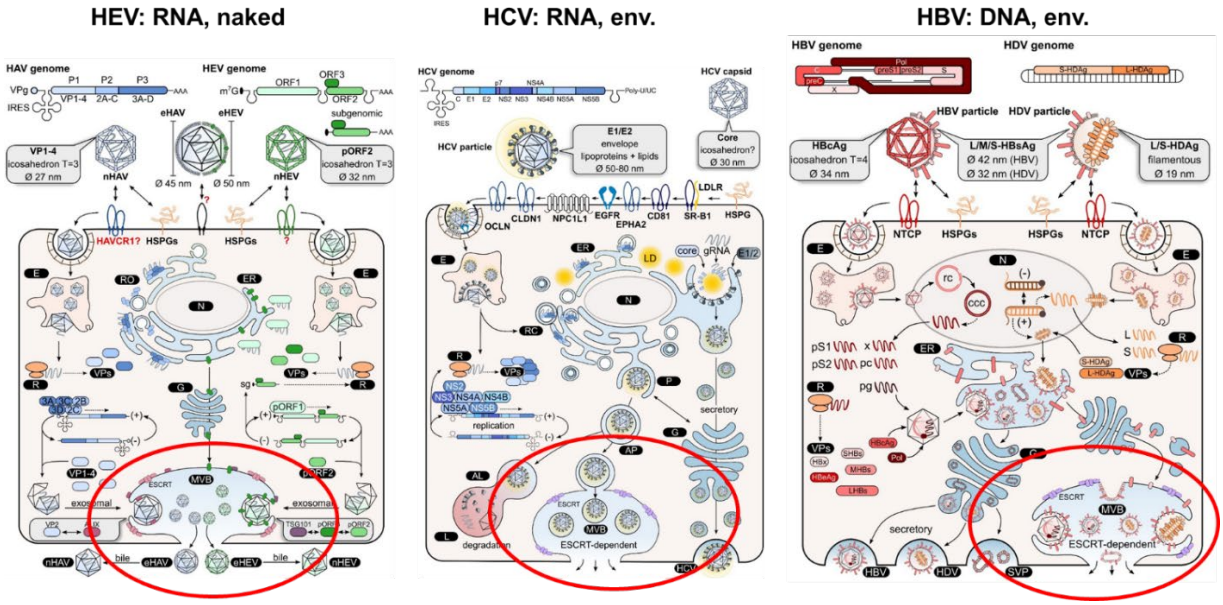

Fig.1: Despite the differences in the structure and life cycle of the three hepatitis viruses shown, HBV, HCV and HEV, all three viruses can escape from the cell via exosomes (circled in red).
Source: Paul-Ehrlich-Institut

As already described above, hepatitis viruses have fundamental differences in their molecular blueprint. However, HBV, HCV and HEV can all leave the cell in the form of exosomes, i.e. in the form of vesicles encasing the virus. We are still researching the question of whether HDV can undergo this process. Autophagy plays a central role in exosomal release. It is both a defence strategy of the infected cell to break down pathogens intracellularly (autophagein (Greek) = self-digestion) as well as an intracellular, vesicular system that can be used to transport viruses out of the cell in order to release them in the form of exosomes. These two processes (release and degradation) are in balance with one another. We are researching the regulation of the two in order to find points of attack for the development of antiviral strategies that inhibit the release of viruses and promote their intracellular degradation. Using the example of these different viruses, we investigate basic mechanisms that can be used for this purpose.

Build broad antiviral response by modulating innate immune response

The modulation of innate immunity plays a special role in this work. We identify kinases that increase innate immunity activity in order to induct interferon-stimulated genes (ISGs) to activate both antiviral mechanisms and autophagosomal processes that promote the intracellular degradation of pathogens, with particular emphasis on the latter. This strategy is interesting and relevant for inhibiting the replication of novel pathogens, especially for the phase between when they first appear and the onset of rapid spread, during which no specific antiviral agents and no effective vaccines are yet available. Naturally, it takes several months before an effective and safe vaccine can be authorised and thus made available. The strategy of taking broad action against a wide range of pathogen classes can reduce the viral load. A reduced viral load results in a milder course of the disease for the infected person and significantly slows down the spread of the pathogen, which prevents the healthcare system from being overloaded and ensures that public life will continue to function. Through kinome analyses, we were able to identify kinases whose specific inhibition is associated with the activation of different areas of innate immunity and thus has a clear antiviral effect against a large number of different viruses. We are currently investigating the detailed molecular mechanisms and identifying inhibitors with highly specific efficacy. A particular focus here is on active ingredients that have already been authorised for other applications or are well advanced in clinical trials. These could be applied more quickly thanks to drug repurposing, i.e. developing authorised drugs for the treatment of completely different diseases.