Medical care, Drug development

Hepatitis C virus modulates signal peptide peptidase to alter host protein processing

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Abstract

Hepatitis C virus (HCV) evades immune surveillance to induce chronic infection; however, how HCV-infected hepatocytes affect immune cells and evade immune recognition remains unclear. We demonstrate that HCV core protein interfered with the maturation of MHC class I molecules catalyzed by the signal peptide peptidase (SPP) and induced their degradation via HMG-CoA reductase degradation 1 homolog, thereby impairing antigen presentation to CD8+ T cells. The expression of MHC class I in the livers of chronic hepatitis C patients was impaired but was restored in patients achieving sustained virological response. Finally, we show that the human cytomegalovirus US2 protein, possessing a transmembrane region structurally similar to the HCV core protein, targets SPP to impair MHC class I molecule expression. Thus, SPP represents a potential target for the impairment of MHC class I molecules by DNA and RNA viruses.

Background & Results

HCV infection becomes chronic in approximately 80% of patients. Antiviral therapies exist and can improve the patients' conditions, but liver disease, and consequentially the formation of liver cancer, is not sufficiently mitigated by this therapeutic approach. It is thus important to understand how HCV manages to evade the host's immune system in the first place to become chronically established, to help researchers develop novel and better therapies against the disease.

At the molecular level, HCV produces a single protein in infected cells that is then split into ten individual proteins. One of these proteins is the HCV core protein, which for stable function requires the action of one of the host cell's proteins, the signal peptide peptidase (SPP). Researchers know that blocking SPP results in the HCV core protein being broken down, and thus suppresses the production of infectious HCV particles. However, the ways in which the core protein affects the host's immune system have remained unclear – until now.

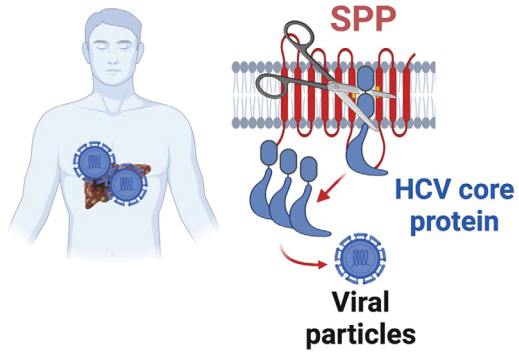
We employed a human liver cell line to understand how the HCV core protein, SPP and MHC class I proteins interact. We found that SPP is required for the production of MHC class I molecules to enable a proper immune response in liver cells. However, in the presence of the HCV core protein, SPP cannot properly interact with MHC class I proteins, which are then degraded via the actions of another protein, HMG-CoA reductase degradation 1 homolog (HRD1). As a result, cellular presentation of viral particles to immune cells is impaired and the infection continues to become chronic.

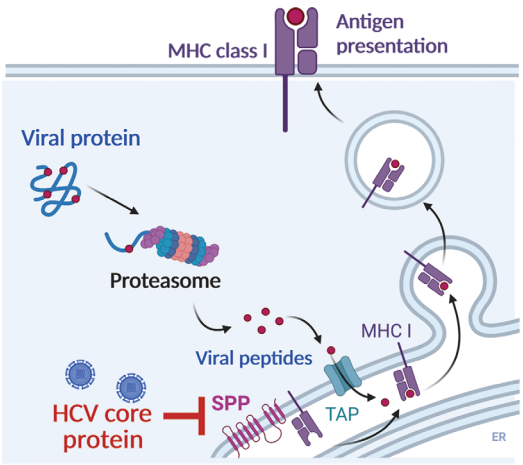
We then asked if this might be a common mechanism to evade the host's immune system in other virus infections. They found that a protein produced by Human cytomegalovirus (HCMV), US2 protein, is structurally similar to the HCV core protein and similarly induces degradation of MHC class I proteins by targeting SPP.

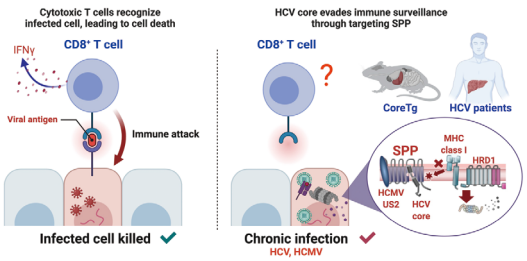
Thus, SPP represents a potential target for the impairment of MHC class I molecules by DNA and RNA viruses.

Significance of the research and Future perspective

Our study revealed a novel molecular mechanism by which these viruses target an important component of the human immune system, MHC class I molecules, to interfere with the proper immune response. These findings could help with development of novel therapies against persistent infection caused by these viruses.







Patent

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