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Editorial

Immune Response against HCV Infection

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Introduction of HCV

HCV is a small single-stranded RNA which could establish acute and chronic hepatitis in infected people. As a RNA virus which lacks proofreading activity during replication, HCV is highly mutable, which could contribute to its existence as quasi species (a group of closely related but genetically distinct HCV variants) in infected individuals and its elaborate set of mechanisms of immune escape. Compared to other hepatitis viruses (HAV, HBV, HDV and HEV), HCV is the most successful one in establishing chronic infections. Currently, HCV is the only hepatitis virus without an approved vaccine against it [1,2].

Primarily transmitted via blood, HCV is very successful in establishing chronic infections. After the first 6 months of acute infection, over 80% of HCV-infected individuals develop chronic hepatitis C in the natural course of HCV infection. About 175 million people have chronic HCV infections worldwide, and are at risk of developing liver cirrhosis and hepatocellular carcinoma. HCV infection is the leading cause of liver transplantation in North America [1,2].

HCV-Specific Immune Response

Adaptive cellular immune response determines the outcome of acute HCV infection. Although there are neutralizing antibodies against HCV envelope proteins in infected individuals, cell-to-cell transmission of HCV could be observed in the presence of these antibodies. This indicates that humoral immunity may not be the determining factor in HCV clearance [3]. In contrast, HCV-specific T-cell response correlates with the outcome of HCV infection. The small percentage of patients who could clear HCV usually have more broad and potent CD4 T-cell responses, which include T-cell proliferation and IL-2, IFN-γ, and TNF-α production, compared to patients who develop chronic infections. HCV-specific CD8 T cells directly clear the HCV-infected cells, and their activation status always correlates with that of HCV-specific CD4 T-cell response in infected individuals. Besides the down-regulation of CD4 and CD8 T-cell responses, programmed death 1 (PD-1), an inhibitory receptor on immune cells, is over-expressed on HCV-specific T cells in chronic hepatitis C patients. When PD-1 pathway is blocked, a significant but transient reduction in HCV viremia could be observed [1,4,5]. This indicates that PD-1 pathway may contribute to HCV persistence.

Adaptive Immune Response against HCV

Innate cellular immune response plays a crucial role in regulating adaptive cellular immune response against HCV infection. Dendritic Cells (DCs) and Natural Killer (NK) cells are important components of innate response. Myeloid DCs of chronic HCV-infected patients express decreased level of HLA-DR and CD86, which are necessary molecules for T-cell activation [6]. Furthermore, patient myeloid DCs express up-regulated level of Fas Ligand (FasL) and PD-1 Ligand 2 (PD-L2), which are inhibitory molecules and could lead to T-cell apoptosis [7]. The increased expression of PD-L2 on myeloid DCs [7] correlates with the increase expression of PD-1 on T cells in chronic HCV-infected patients [4,5].

Besides, there are NK-DC interactions during HCV infection. The interaction between NK cells with plasmacytoid DCs and monocytes efficiently produces Interferon-γ (IFN-γ) in response to HCV-infected cells, which is critical for IFN-γ production and regulation of innate and adaptive immunity during HCV infection [8].

HCV Animal Models

The lack of small animal model for HCV has been a major problem limiting the research progress of HCV-host interactions, as *in vitro* studies of HCV could not replace the *in vivo* studies.

Chimpanzees are the only host of HCV infection except human beings, and are the most complete model that could support the complete HCV life cycle with host responses similar to that observed in human patients. However, chimpanzees are endangered species, expensive and difficult to obtain, and are illegal to be used for research in some countries [9].

Although mice are not the natural host of HCV infection, a mouse model for HCV was established in 2001 by transplanting human hepatocytes into immune-deficient mice with special deficiency in liver function. The Severe Combined Immune Deficient (SCID) mice carry a plasminogen activator transgene under the control of an albumin promoter (Alb-uPA).The mouse model has greatly facilitated HCV research; however, it does not support studies on immune responses as it lacks T-cells [10].

The HCV mouse model has been improved continuously by multiple studies. For example, a humanized mouse model of HCV infection could establish human liver cells and immune systems in NOD-*scid IL2 rg*$^{-/-}$ mouse. It supports HCV infection and associated disease development. In this model, human fetal liver progenitor stem cells, CD34+ cells, were transplanted into the mouse liver. The new mouse model could support HCV infection, liver inflammation, HCV-specific human immune responses, and liver fibrosis. In this mouse model, HCV infection leads to liver leukocyte infiltration and progressive lesions. Hepatic stellate cells are activated, and fibrotic genes are up-regulated with consequential liver fibrosis and cirrhosis. In addition, HCV infection could induce intrahepatic human immune cell infiltration, most of which are hepatic human T cells (CD45+CD3+) and macrophages (CD45+ CD14+). The human inflammatory cytokine profiles in these HCV-infected mice, which include elevated levels of IL-8 and TNF-RII, are similar to those in

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human patients. In the spleens of these mice, HCV infection elicits robust HCV-specific immune cell responses, which include significant expansion of human CD4 and CD8 T-cell, and increase of B cells, NK cells and macrophages. Furthermore, antiviral treatment of IFN could block the progression of HCV-associated liver pathogenesis, which is similar to that in human patients. The most interesting results of this study are that depletion of human T cells results in a drastic reduction of inflammation and immune response, and IFN treatment blocks the progression of liver disease in these infected mice. These results demonstrate that this mouse model could be a good candidate for the *in vivo* study of HCV-host immune interaction and of vaccine research [11].

HCV Vaccine Research

There is an urgent need for a prophylactic HCV vaccine against various HCV genotypes, and a therapeutic vaccine which could aid in the therapy of HCV-infected patients. Given the high level of HCV mutation, multiple genotypes, and its capacity in immune escape, the researchers have not developed a clinical approved vaccine for HCV yet.

To develop a prophylactic vaccine for HCV, most of current research either targets the HCV envelope glycoproteins E1/E2 to induce neutralizing antibodies, or target relatively conserved viral proteins within the Non-Structural (NS) region of the genome to induce a broad T-cell response [12]. Several studies demonstrate that immunization with recombinant glycoprotein (rE1E2) of HCV genotype 1a strain could elicit monoclonal antibodies targeting multiple cross-neutralizing epitopes, and support the use of such a vaccine antigen to induce cross-genotype neutralization [12-14].

Since the region encoding the NS proteins of HCV is less diverse than its structural protein-encoding region, targeting the conserved NS region for HCV vaccines has an attractive advantage over targeting the glycoprotein approach. A phase II clinical trial showed that pre-treatment of HCV-infected patients with the HCV-NS vaccine prior to antiviral treatment could increase the early virological response [15]. The delivery of the HCV NS3, NS4a, NS4b, NS5a and NS5b genes of genotype 1b using a combination of replication-defective modified vector could effectively suppress acute HCV viremia and acute hepatitis after heterologous genotype 1a virus challenge in chimpanzees. Currently, this vaccine is being tested for efficacy in intravenous drug users in the United States [16,17].

Besides vaccine research, the clinical use of HCV-specific Direct Acting Antivirals (DAAs) is being developed against various virus-specific genes and proteins, and could represent a possible treatment to overcome HCV infection in the future. The DAAs are very costly and may lead to drug resistance. Therefore a therapeutic vaccine is also in need, and it could be used together with DAAs [18,19].

In general, the research on HCV vaccine and drugs need more and better *in vivo* studies, and the improved HCV mouse model could help in testing them.

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