Editorial Commentary

Innate immune control of HCV infection through the JAK/STAT signaling

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Hepatitis C virus (HCV) is a positive-strand RNA virus that frequently overcomes host innate and adaptive immune response leading to a stage of chronic HCV infection. The mechanisms through which HCV develops such a high rate of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC) remain elusive. During HCV infection, the innate and adaptive immune responses are generated through a cascade of virus-host signaling (1,2). Hepatocytes quickly sense the conserved pathogen-associated molecular pattern (PAMP) receptors present in HCV (HCV genomic RNA, structural and non-structural proteins) by different pattern recognition receptors (PRRs) such as RIG-I, MDA5, and toll like receptors (TLRs) (3). The damage-associated molecular pattern (DAMP) released in response to cell death (called sterile agents) during integrated cellular stress and cell damage leads to an inflammatory response. The innate immune signaling pathways are amplified through the production of type 1 and type III interferon (IFN), interferon-stimulated genes (ISGs), and proinflammatory cytokines to eliminate the virus. The multifaceted host antiviral response suppresses viral replication but cannot eradicate it completely in most cases. Only 25% of HCV-infected individuals resolve infection naturally, whereas the majority of the cases develop chronic stage of infection (3,4). Although HCV is a curable disease, the mechanism of innate immune activation that controls virus replication and viral clearance is unknown. This knowledge is essential to develop novel therapeutic strategies to control emerging new RNA virus infections such as SARS-COV-2.

Many earlier studies have demonstrated HCV infection using primary human hepatocytes (PHH), human pluripotent stem cells, and induced pluripotent stem cells (5-8). All these primary non-transformed cells are permissive for HCV infection. However, these model systems support a low-level of HCV replication. Therefore, the Huh-7.5 cell line was used extensively in the past to study virus-host interaction. Carpentier *et al.* reported a new HCV infection model using human stem cell-derived hepatocyte-like cells (HLCs) (9). This model was used to understand the mechanism by which innate immune response controls HCV clearance. We feel that this study brings some new information worth discussing that will have important implications for natural immune mechanisms.

First, the authors determined that HLCs cells express the critical component of host innate immune signaling such as RIG-I-like receptors (RLRs) and TLRs. They also demonstrated that HLCs maintains a high-level replication of a unique HCV strain called JC1 and the replication declines with innate immune activation. This model system seems appropriate to address the molecular mechanisms of innate immune activation. The authors found that host cell sensing of HCV through RIG-I and MDA5 results in the production of type I and type III IFN. The endogenously produced type I and type III IFN in the infected culture requires the JAK-STAT feedback loop for antiviral suppression. They found that inhibition JAK-STAT signaling could prolong HCV infection from acute to chronic stage. Published data indicate that the treatment of ruxolitinib, a JAK inhibitor, led to a higher level of viral

replication, suggesting that JAK-STAT-dependent feedback is necessary for the innate immune clearance of HCV in this model. Furthermore, the withdrawal of ruxolitinib, restores innate immunity and clears the infection. Moreover, the induction of RLRs such as RIG-I and MDA5 was dependent on JAK-STAT signaling, which explains why ruxolitinib treatment affected HCV-dependent induction of type I and type III IFN mRNAs. These pieces of information indicate that this authentic HCV infection model is appropriate to study the mechanisms of intrinsic immune regulation through the JAK-STAT signaling.

Second, the authors claimed that protein kinase R (PKR) has a proviral role in HCV infection because inhibition of PKR using small molecule inhibitor (C16) in the HCV infection model decreased viral replication. This finding, however, is the opposite of many earlier studies demonstrating that IFN-induced PKR serves as an antiviral by inducing phosphorylation of eIF2alpha and inhibits translation (10,11). These results suggest that PKR activation occurs as an integrated stress response to virus infection that favors virus-cell survival (12). These results also support the previous finding that the activation of PKR may help adaptive cellular response to HCV infection through degradation of p53 tumor suppressor (13).

Third, the study found that HCV-induced interferon-regulated genes (IRGs) expression in Huh-7.5 cells is quite different from HLCs. Using comprehensive RNA-Seq data, they showed that the majority of IRGs induced in HLCs and PHH were similar. The IRF7 and IRF9 and other IRGs (MXA, ISG15, OAS, and Viperin) are important for restricting HCV infection. These data suggest that Huh-7.5 cells represent a poor model to study innate immune response to HCV infection. Data presented in this report suggest that the selection primary human hepatocyte model is an appropriate system for understanding host sensing of virus infection and natural immune mechanisms. The mechanisms why some individuals infected with HCV are able to clear infection better than the other is unclear. The HCV infection of HLCs provides an authentic model to study the differences in host innate sensing to virus infection, mainly how IL-28B genotype contributes to HCV clearance (14).

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Footnote

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