<table>
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<th>Network module</th>
<th>Description (literature evidence)</th>
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| Module 1: Actin cytoskeleton organization and cell adhesion | (a) HCV E1/E2 can promote actin reorganization to induce internalization of the virion\(^1\).  
(b) Adhesion between host cells can prevent invasion of pathogens\(^2\). However, during HCV entry, OCLN, a cell adhesion protein, interacts with HCV E2\(^3\) and relocates HCV to tight junctions where HCV internalization occurs\(^1,4,5\). |
| Module 2: Peptide hormone processing | HCV infection has been associated with insulin resistance, a risk factor for hepatocellular carcinoma (HCC)\(^6\). |
| Module 3: Cellular homeostasis | HCV E1/E2 can trigger the unfolded protein response (UPR)\(^7\), a cellular homeostatic process triggered in response to stress induced by unfolded/misfolded proteins at the endoplasmic reticulum\(^8\). HCV-triggered UPR can lead to autophagy, which is also a cellular homeostatic response\(^9\). |
| Module 4: Growth | HCV infection enhances the growth of HCC\(^10\). For instance, in HCV-associated cirrhosis tissues, upregulation of IGFBP3, an IGF-binding protein, can potentiate IGF signaling and contribute to tumor growth\(^11,12\). |
| Module 5: Apoptosis and cell junction organization | (a) During HCV infection, apoptosis in infected cells is triggered to decrease the spread of the virus\(^13,14\). However, HCV has evolved several anti-apoptotic strategies to increase its survival: 1) HCV E1 induces the production of reactive oxygen species (ROS) and the phosphorylation of STAT3\(^15\), leading to cell survival; 2) HCV infection activates CHUK\(^16\), which can upregulate the activity of NF-κB and lead to enhancement of the expression of anti-apoptotic genes\(^17\); 3) HCV E1/E2 can induce the phosphorylation of AKT proteins and activate PIK3-AKT signaling to enhance cell survival\(^18\).  
(b) Based on an in vitro study, HCV infection can regulate tight junction organization by downregulating the expression of CLDN1 and OCLN, which may lead to the observed morphological and functional alterations of HCV-infected hepatocytes\(^19\). |
| Module 6: Endocytosis and cell-cell signaling | (a) Several studies have demonstrated that clathrin-dependent endocytosis is the main route for HCV to enter human hepatocytes, mediated by HCV E1/E2\(^20,22\).  
(b) Upon HCV infection, cell-cell signaling in the host cell can be triggered to induce a systematic immune response against viral infection\(^23\). |
| Module 7: Receptor signaling and cytoskeleton organization | (a) Receptor signaling, e.g., EGFR signaling and its downstream signaling by HRAS\(^24\) and PI3K-AKT\(^18\) are pivotal to HCV entry\(^24\). These signaling events stimulate hepatocyte proliferation, which may contribute to hepatocellular carcinogenesis\(^25,26\).  
(c) During HCV entry, the virus induces cytoskeleton reorganization so that it is relocalized to the tight junction, where internalization and endocytosis occur\(^1,4,5\). PTPN11 upregulated by HCV infection\(^27\) may reorganize the cytoskeleton\(^28\). |
S2 Table references


