S2 Table. Representative function(s) and supporting published experimental data for HCV-human PPI network modules 1–7

Network module	Description (literature evidence)
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 relocalizes 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

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