S3 Table. Published experimental evidence for relations between SLiMs and R6 proteins and between R6 proteins and module functions in Fig 3

R6 protein	Interacting HCV SLiM	Description
ABL1	LIG_SH2_STAT5, LIG_SH3_3	Proteins of the ABL tyrosine kinase family, to which ABL1 belongs, regulate *cell-cell adhesion* (module 1)[1]. ABL1 also modulates the organization of *F-actin cytoskeleton* (module 1 and module 7)[1, 2].
AKT1	MOD family*	(a) Active AKTs regulate many cellular processes, including *apoptosis* (module 5)[3]. (b) HCV E2 induces the phosphorylation of AKT, which enhances HCV entry. This phosphorylation is mediated by the interactions between HCV E2 and two HCV entry host factors, CD81 and CLDN1[4].
CHUK	MOD family*	(a) CHUK is a subunit of the IKK complex, which when active can induce the NF-κB pathway to inhibit *apoptosis* (module 5)[5]. (b) HCV infection induces CHUK activity[6].
CSNK2A1, CSNK2A2	MOD family*	CSNK2A1 and CSNK2A2 are subunits of CK2 protein kinase[7]. CK2 regulates *cell proliferation* (module 4)[8] and *ion channel* activity[9], which is a function associated with module 8 although its enrichment in module 8 was not considered significant (P = 0.055).
CTTN	LIG_SH3_3	CTTN regulates *actin cytoskeleton organization* (module 1) by binding and regulating the Arp2/3 complex[10].
DLG1, DLG4	LIG_SH3_3	DLG1 and DLG4 are PDZ domain-containing proteins that can regulate *cell-cell junctional signaling* and *organization* (module 6)[11].
GABARAP	LIG_LIR_Gen_1, LIG_LIR_Nem_3	GABARAP, a functional homologue of LC3, is a key protein involved in the initial steps of autophagosome formation, which is a critical step of autophagy, a process that regulates *cellular homeostasis* (module 3)[12].
GRB2	LIG_SH2_STAT5, LIG_SH3_3	(a) GRB2 plays a role in modulating *actin-based cytoskeleton functions* (module 1 and module 7)[13]. GRB2 is also an adaptor protein that mediates EGFR downstream *signaling* (module 7) and promotes *cell proliferation* (module 4)[14]. (b) Silencing of GRB2 expression inhibits HCV entry[15].
GRK5	MOD family*	GRK5 is a G–protein-coupled receptor kinase that can enhance the *growth* (module 4) of cancer[16, 17].
MLLT4	LIG_FHA_1, LIG_FHA_2	MLLT4 is a cell-cell junction-associated protein, which bridges *Ras signaling toward regulation of cell-cell contact* (module 6)[18].
NCK1	LIG_SH2_STAT5, LIG_SH3_3	NCK1 regulates *actin remodeling* (module 1 and module 7) by activating the WASp/Arp2/3 pathway, linking this pathway to *receptor signaling* (module 7)[19] .

S3 Table. Published experimental evidence for relations between SLiMs and R6 proteins and between R6 proteins and module functions in Fig 3 (continued)

R6 protein	Interacting HCV SLiM	Description
NEDD4	DOC_WW_Pin1_4	NEDD4 is a ubiquitin ligase that can mediate ubiquitination of the *ion transporter* NHE1[20], a module 8 function although not found to be enriched to a statistical significant level (P = 0.055).
NEDD4L	DOC_WW_Pin1_4	NEDD4L is a ubiquitin ligase that can regulate *epithelial sodium transport* (module 8)[21].
PIK3R1	LIG_SH2_STAT5	(a) PIK3R1, a regulatory subunit of PI3K, is a pivotal member of the PI3K-AKT *signaling pathway* (module 7)[22] and induces *actin skeleton reorganization* (module 7) in a Cdc42-mediated manner[23]. (b) The PI3K-AKT pathway transiently activated by HCV enhances viral entry[4].
PRKCA	MOD family*	(a) Activation of PRKCA promotes tumor cell *proliferation* (module 4) and inhibits *apoptosis* (module 5)[24]. Furthermore, PRKCA can promote internalization of integrin β1, which is involved in *integrin signaling* (module 6)[25], via *caveolae-mediated endocytosis* (module 6)[25]. (b) PRKCA is a conventional protein kinase C, which plays a role in alpha interferon-mediated HCV clearance[26].
PRKCD	MOD family*	PRKCD, a member of the kinase C (PKC) family, can mediate cell *apoptosis* (module 5)[27].
SRC	LIG_SH2_STAT5, LIG_SH3_3	(a) SRC modulates *actin cytoskeleton organization* (modules 1 and 7)[28] and the activity of *EGFR* (module 7)[29]. Activation of SRC is regulated by Na/K-ATPase, an *ion transporter* (module 8)[30]. (b) The HCV replicon activates SRC by inducing generations of reactive oxygen species[31].
SHC1	LIG_SH2_STAT5	(a) SHC1 is an adaptor protein that links EGFR to its downstream *signaling* (module 7)[32]. (b) Silencing of SHC1 expression inhibits HCV entry[15].
TGFBR1	MOD family*	(a) Formation of the ligand-receptor complex of TGFBR1 and TGF-β activates TGF-β signaling, which is involved in *apoptosis* (module 5)[33]. (b) Hepatocytic TGF-β signaling, a tumor-suppression signaling, can be shifted to fibrogenesis by HCV infection and increase risk for HCC[34].

*MOD family: MOD_CK1_1, MOD_CK2_1, MOD_GSK3_1, MOD_NEK2_1, MOD_NEK2_2, and MOD_ProDKin_1.

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