Electronic Supplementary Material (ESI) for Molecular BioSystems

Identification and Comparative Analysis of Hepatitis C Virus-Host Cell Protein Interactions

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Supplemental Information

Supplemental Methods

Yeast two-hybrid (Y2H) Screens - HCV genes and gene fragments were cloned into the yeast two-hybrid DNA-binding domain (DBD) plasmid pOBD2 by homologous recombination in the yeast strain R2HMet (*MATa ura3-52 ade2-101 trp1-901 leu2-3,112 his3-200 met2Δ::hisG gal4Δ gal80Δ*) and verified by PCR and sequencing [1-4]. The DBD-HCV fusion proteins were tested for their ability to activate expression of the yeast two-hybrid reporter gene *HIS3* (self-activation) by growth on medium lacking histidine and containing a range of concentrations of 3-amino-1,2,4-triazole (3-AT); the lowest 3-AT concentration that inhibited yeast growth was used for the yeast two-hybrid assays. Yeast two-hybrid screens were performed by mating with yeast strain BK100 (*MATa ura3-52 ade2-101 trp1-901 leu2-3,112 his3-200 gal4Δ gal80Δ GAL2-ADE2 LYS2::GAL1-HIS3 met2::GAL7-lacZ*, a derivative of PJ69-4A) [3, 5, 6] that contained a human liver yeast two-hybrid library cloned into the activation domain (AD) plasmid pOAD.103 [7, 8]. Positive colonies were selected on synthetic dropout (SD) medium lacking tryptophan, leucine, uracil, and histidine, and containing 3-AT at the concentration determined above (SD–TLUH + 3-AT). All screens were performed at least in duplicate. Human gene fragments from colonies that grew on SD–TLUH + 3-AT were PCR-amplified, sequenced from the 5' end, and identified using Cross_Match to query the human RefSeq database (downloaded 3/4/08) [9]. To confirm the interactions in the yeast two-hybrid assay, PCR products encoding the human AD inserts were cloned into pOAD.103 by homologous recombination in BK100. Each clone was arrayed in 384-spot format in quadruplicate, mated with yeast expressing the DBD-HCV fusions, and selected for growth on (i) SD–TLUH + 3-AT and (ii) SD medium lacking tryptophan, leucine, uracil and adenine (SD–TLUA) as described [7]. In parallel, all HCV-DBD fusion proteins were screened against a set of human genes identified in a similar screen with dengue virus (DENV) proteins [7].

Split-luciferase assays - The full-length NS5B gene was cloned in frame with the N-terminal fragment of firefly luciferase in p424-BYDV-NFLUC. Human gene fragments from activation domain plasmids isolated from positive yeast two-hybrid colonies were inserted into plasmid p424-BYDV-CFLUC between sequences encoding three FLAG epitope tags and the C-terminal fragment of luciferase. Fusion proteins were expressed *in vitro* in wheat germ extract (Promega) and the relative expression level analyzed by densitometric analysis of western blots using ImageJ software (http://rsbweb.nih.gov/ij/) [10]. Binding assays were performed by combining equivalent amounts of NFLUC and CFLUC fusion proteins in PBS supplemented with 1% BSA and protease inhibitor cocktail (Roche), incubated for 16 hours at 4°C and assayed for luciferase activity.

Co-purification assays. The full-length NS5B gene was cloned as a 3' fusion to the maltose binding protein (MBP) gene in a modified pMALc-4e plasmid engineered to encode a C-terminal hexahistidine (6X-His) tag. MBP-6X-His and MBP-6X-His-NS5B were expressed in Rosetta *E. coli* (Novagen) and purified with His-Pur Cobalt resin (Pierce) according to the manufacturer's protocol. Fusion proteins were eluted in PBS supplemented with phenylmethylsulfonyl fluoride and 150 mM imidazole. For pull-downs, equimolar amounts of MBP-6X-His and MBP-6X-His-NS5B were incubated with amylose resin overnight at 4°C with rotation, washed with PBS + 100uM phenylmethylsulfonyl fluoride + 0.5% Triton X-100, and distributed to individual tubes. Equivalent amounts of *in vitro* expressed 3XFLAG/C-FLUC-human prey protein were added to each binding reaction, incubated for 4 hours at 4°C with rotation, washed vigorously three times and eluted in Laemmli sodium dodecyl sulfate-polyacrylamide gel electrophoresis loading buffer for analysis by western blot.

siRNA knockdown experiments. RNAi assays to assess the contribution of cellular proteins to HCV replication were performed as previously described [11, 12]. To assess the role of cellular proteins in DENV replication, Huh7 cells (10,000 cells/well of a 96 well plate) were transfected in triplicate with siRNA pools (Dharmacon) using RNAiMax transfection reagent (Invitrogen). At 48 h post-siRNA transfection, cells were infected with DENV2 16681 at a multiplicity of infection of 0.5. Virus production at 24 h post infection was assessed by plaque assays on BHK cells. Percentage change in DENV release from siRNA-treated cells was normalized to nonspecific siRNA-treated cells. Cell viability of siRNA-treated cells was measured using the CellTiter-Glo Luminescent Cell Viability Assay (Promega). Significance determined by one-tailed, unpaired t-test using the GraphPad Prism 5 software.

SUPPLEMENTAL DISCUSSION

Targets in replication and assembly. Formation of membrane-associated replication compartments is a universal feature of positive-sense RNA virus replication [13]. The emerging picture of RC formation is revealing critical roles for host factors such as the endosomal sorting complex required for transport (ESCRT) machinery [14]. ESCRT and mutlivesicular body formation have been implicated in diverse viruses, including HSV1 [15]; HIV [16, 17]; the arenaviruses, Lassa virus and lymphocytic choriomeningitis virus [18]; filoviruses [19, 20]; and hepatitis E virus [21], suggesting it is a common pathway for coordinating viral replication, assembly and egress. One ESCRT protein, TSG101, in particular appears to be a common target upon which numerous viruses have converged [21-23]. We identified interactions between TSG101 and three non-structural proteins, NS5A, NS5B and NS3, that are required for replication and initiation of viral assembly.

HCV NS3 also binds to a number of partners that may be directly relevant to viral replication and egress: SESTD1, a key regulator of the membrane turnover and assembly of membrane channels [24]; MYH14, a non-muscle myosin required for cytokinesis, which may have a role in the tropomyosin-regulated reorganization of actin filaments [25]; and a tropomyosin, TPM4 [26]. These genes have been implicated in previous studies in HCV and other viruses. SESTD1 was shown to bind NS3 of HCV 1a in a previous Y2H screen [27] and its transcription in cultured cells is significantly up-regulated in response to HCV 2a infection [28]. TPM4 transcription and translation are also up-regulated during HCV 2a infection in cell culture [28]. Furthermore, SESTD1 and TPM4 have been implicated in the replication of HIV by genome-wide siRNA screens [29].

MYH14, on the other hand, has not been implicated in HCV infection previously, but has been reported to interact with the vaccinia virus (VACV) C6 protein [30]. The repeated identification of these proteins in independent data sets and their role in the replication of other viruses strongly suggest a role for them in HCV replication. Furthermore, the interaction of these proteins with NS3 suggests a role for NS3 in regulating the membrane and cytoskeletal rearrangements required for HCV replication and trafficking of viral and cellular factors to and/or from the site of viral replication.

Extracellular targets: clotting and complement. The complement system acts as a link between the adaptive and innate immune system and there is increasing interest in complement as a common viral antagonist and a major target in viral immune evasion (reviewed in [31]). In the context of HCV infection, liver injury resulting from the immune modulatory activities of complement and the subsequent action of clotting and coagulation factors have been implicated in the development of pathologies associated with chronic HCV infection [32]. Decreased serum levels of complement proteins are associated with the development of more severe disease, including cirrhosis and fibrosis [33, 34]. Furthermore, hepatic inflammation resulting from HCV core expression is blocked in mice when complement activation is inhibited [35]. Consistent with these observations, complement and coagulation proteins were over-represented in the set of human proteins that bound to HCV GT 2a. The complement proteins C3, C4, Complement factor H (CFH) and the C3-like protein, LOC100133511, were all identified in this screen (Figs. 4B and 5C). Other viruses, including herpes simplex virus (HSV) [36], variola, and vaccinia [37] also target the complement pathway through direct physical interaction. Circulating NS1 from the flaviviruses inhibits complement activation by targeting CFH and C3 and this activity has been associated with increased severity and shock in patients infected with DENV [38, 39]. C3 deficiency exacerbates West Nile virus (WNV) pathogenesis by delaying antibody responses [40].

The role of the complement proteins in HCV infection is not well understood, however a number of observations support a role for complement and coagulation in HCV-related disease progression and severity [35, 41]. There is also evidence that complement transcription is targeted by HCV. Reduced levels of complement genes has been demonstrated during HCV infection and appears to be the direct result of transcriptional repression by NS5A [42, 43]. Until now, no direct links have been observed between complement and HCV proteins. These interactions may represent an antagonistic relationship similar to that observed in other viral systems.

HCV targets proteins that regulate metabolism. Our study revealed targeting of pathways governing cell survival and anti-apoptotic activities by HCV (Figs. 4B and 5B). Among these targets were canonical and non-canonical activators of the mechanistic/mammalian Target of Rapamycin (mTOR), and two downstream, anti-apoptotic transcription factors, b-catenin and TCF7L2. The PI3K-Akt-mTOR pathway integrates diverse metabolic signals resulting in the regulation of cell proliferation, autophagy and immune activation [44]. The activation of mTOR also drives cell growth, proliferation and metastasis in many types of cancer including HCC [45-47]. Numerous observations have identified roles for Akt-mTOR activation during infection of HCV (122)[48-51] as well as other tumorigenic viruses that establish chronic infection [52-57]. Activation of the canonical PI3K-Akt-mTOR pathway has been suggested as a means to limit replication of HCV RNA to low levels, facilitating the establishment of chronic infection [48].

In this study, we observed a previously characterized interaction between HCV NS5A and PIK3R1 [58, 59]. Binding of PI3KR1 by NS5A causes activation of Akt and mTOR through the canonical pathway [47]. This activation subsequently inhibits the expression of pro-apoptotic genes, such as the BCL2 homologue, Bad, and caspase 9 [60]. In addition to the interaction with PI3KR1, we also identified interactions between HCV NS5B and NS3 with MYCBP2, an E3 ubiquitin ligase that activates mTOR through two, non-canonical, Akt-independent mechanisms. MYCBP2 can activate mTOR though ubiquitination and degradation of its repressor, the small GTPase, Rheb [45] and tuberin [61]. The identification of these interactions further emphasizes the important role that this pathway likely plays in HCV.

Activation of Akt also positively regulates the activity of two anti-apoptotic genes identified in our screen, b-catenin (CTNNB1) and T-cell factor 7-like 2 (TCF7L2). Once translocated to the nucleus, b-catenin, in combination with other factors in the TCF/Lef family, including TCF7L2, drives transcription of genes involved in cell proliferation and survival including c-myc, survivin and cyclin D1 [62, 63]. Additionally, TCF7L2 and CTNNB1 play specific regulatory roles in the inhibition of adipogenesis by TNFα [64] and TCF7L2 has been implicated in the development of type 2 diabetes [65]. The interactions of HCV proteins with these transcription factors may contribute to the development of HCV-related steatosis and diabetes.

Finally, we observed interactions between NS5A and NS5B with EIF4G2, or death-associated protein 5, which appears to play a key role in regulating cellular translation in response to diverse stress signals and controlling the balance between apoptosis and survival. EIF4G2 promotes IRES-mediated translation following caspase activation [66, 67] and in cases of ER stress [68]. It also promotes the translation of prosurvival genes, Bcl-2 and CDK1 during mitosis [69].

SUPPLEMENTAL FIGURE LEGENDS

SI Fig. 1. Entire list of annotation terms significantly enriched among the cellular targets of HCV. Enriched features in the set of human proteins that interacted with HCV 2a were identified using the DAVID Bioinformatics Database. Graph shows the $-log_{10}$-transformed Benjamini-corrected p-values for each term. Terms were considered significantly enriched if the Benjamini-adjusted P-value was less than 0.05.

SI Fig 2. Heatmap summarizing the annotation terms enriched in the set of human proteins that interacted with HCV GT 2a. Terms were identified using the DAVID Bioinformatics database and GSEA enrichment analyses. Blue squares represent the association of a protein with an annotation term. Dendrograms indicate the hierarchical clustering of annotation terms by their associated proteins (top), and proteins according to their associated annotation terms (left). These clusters were used to generate Fig. 4B.

SI Fig. 3. The complete set of HCV 2a-human interaction identified in this study and DENV-human interactions identified in parallel Y2H screens. Human proteins are shown as white rectangles. Viral proteins are shown as black rectangles with DENV on the left and HCV proteins on the right. Human proteins that interacted with both HCV and DENV are shown in the center column while interactions unique to either virus are shown in the outer columns. The total number of cellular proteins in the unique and shared groups are shown below each column. Cellular proteins that interacted with the same viral protein(s) were grouped together.

SI Fig. 4. Workflow employed for analysis of HCV and DENV comparative analysis. Either the unique and shared targets (left) or the entire interactome for each virus (right) were used to identify cellular functions targeted by the two viruses. The results of these analyses are shown in Fig. 7.

SI Fig. 5. Cellular toxicity assay data for HCV (A) and DENV (B) siRNA experiments. Cell viability of siRNA-treated cells was measured using the CellTiter-Glo Luminescent Cell Viability Assay (Promega) or the MTT assay, for the HCV and DENV experiments, respectively.

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Supplemental References for HCV Interactions from HCVpro database (Refers to Figure 6)

HCV Genotype 1a Interactions:

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