INVITED ABSTRACT

Searching for cellular factors associated with HCV infection

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Abstract  Hepatitis C virus (HCV) infection is the leading cause of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma in many parts of the world. It is also often associated with steatosis and other alterations of lipid metabolism, such as hypocholesterolemia. To identify the potential biomarkers for HCV-associated diseases, we have used various approaches to identify the cellular factors involved in HCV replication and pathogenesis. These factors may serve as the biomarkers for various stages of the disease. We have approached this question by identifying cellular proteins coimmunoprecipitated with the viral proteins. We also screened for cellular factors by performing genome-wide or functional subset inhibitory RNA (RNAi) library screening. Many cellular proteins have been identified, among which are proteins belonging to the vesicular transport pathway. For example, vesicle-associated membrane protein (VAMP)-associated vesicular proteins A and B (VAP-A and -B) were found to be required for HCV replication. We also found that HCV RNA replication takes place on the lipid rafts in an induced double-membraned vesicle (termed the "membranous web"). Correspondingly, several cellular proteins involved in the vesicle formation and lipid raft rearrangement were found to be relocated or induced in HCV-infected cells. Among these are proline-serine-threonine phosphatase-interacting protein-2, a membrane-deforming protein, annexin A2 (a lipid raft organizer), and phosphatidyl inositol phosphate-4, a membrane component. The identification of the essential roles of these proteins in HCV replication indicates that the intracellular membrane and lipid metabolism undergo drastic reorganization during HCV infection. These and the related proteins may serve as biomarkers for HCV infection and disease progression.

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