S99
Symposium
Hepatitis C virus entry - molecular mechanism and clinical implications
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Hepatitis C virus (HCV) is a major cause of liver cirrhosis and hepatocellular carcinoma world-wide. The development of efficient strategies for prevention and treatment of HCV infection has been hampered by rapid development of viral resistance and escape. Viral entry into target cells is a promising target for antiviral preventive and therapeutic strategies since it is essential for initiation, spread and maintenance of infection. Indeed, cross-neutralizing antibodies inhibiting HCV entry have been shown to be associated with control of HCV infection and prevention of HCV re-infection in cohorts with self-limited acute infection. HCV entry is a multistep process involving several host factors including heparan sulfate, CD81, scavenger receptor B1, claudin-1 and occludin. Using a functional genome-wide RNAi kinase screen we have recently identified a network of receptor tyrosine kinases (RTKs) as HCV entry factors. Functional studies indicate that kinases act on postbinding steps by interfering with CD81-claudin-1 co-receptor associations and membrane fusion. Using an infectious cell culture model, we demonstrate that targeting of host entry factors by receptor-specific monoclonal antibodies or inhibition of RTKs by approved protein kinase inhibitors block entry and infection of all HCV genotypes including viral escape variants that are resistant to autologous host immune responses. These results suggest that targeting host entry factors using receptor-specific monoclonal antibodies or small molecules constitutes a novel antiviral approach to prevent primary HCV infection, such as after liver transplantation and may also restrain virus spread in chronically infected patients.