Translational researches on HBV

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Chronic hepatitis B virus (HBV) infection, affecting approximately 240 million people worldwide, is a major public health problem that elevates the risk of developing liver cirrhosis and hepatocellular carcinoma. Although nucleos(t)ide analogs inhibiting viral reverse transcriptase are clinically available as anti-HBV agents, emergence of drug resistant virus highlights the need for new anti-HBV agents. It is thus important to discover novel targets molecules for the anti-HBV drug development. In this regard, we need to understand precise mechanisms of HBV life cycles. Viral entry is the the initial step of viral life cycle. Recently, sodium taurocholate cotransporting polypeptide (NTCP) was identified as an HBV entry receptor and enabled the establishment of a susceptible cell line that can efficiently support HBV infection. This finding allowed us a deeper understanding of the requirements for efficient HBV infection, including the elucidation of the molecular entry mechanism. In addition, pharmacological studies suggest that NTCP is able to serve as a therapeutic target. We have already identified several compounds can efficiently blocks HBV entry process. We also focused on the possible mechanism of interferon independent pathway leading to viral clearance. RIG-I like helicases were previously reported to recognize viral nucleic acids and induce anti-viral state. Using arrayed shRNA targeting 133 human helicases and Hep38.7-Tet cells, we performed a functional screening assay to identify helicases supressing HBV. We identified SKIV2L RNA helicase dependent mechanism that degradeds HBV-RNAs. This mechanism is interferon independent and dependent on the phospholyration of SKIV2L. Phospholyrated SKIV2L binds HBV-RNAs and transport to the RNA-exosome. This result suggests a possible novel host anti-HBV pathway using RNA-exosome.