POSTER 2:

Hepatitis B virus hijacks host E2/E3 ubiquitin ligase, UBE2O, for viral nucleocapsid assembly and virion egress

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Chronic hepatitis B (CHB) represents a serious liver disease that is caused by infection of Hepatitis B virus (HBV). CHB is associated with severe liver conditions ranging from fibrosis and cirrhosis to hepatocellular carcinoma or acute liver failure. Current antiviral drugs can suppress HBV replication and reduce the progression of liver disease, but do not eradicate the virus. Since HBV replication is completely dependent upon host cell pathways, the study of virus-host interactions promises to reveal novel cellular targets for development of new therapies Here, we identified and characterized the association of host hybrid E2/E3 ubiquitin ligase, UBE2O, with viral core protein (HBc). Co-immunoprecipitation analysis with wt and various HBc deletion mutants demonstrated that HBc interacted with UBE2O via its C-terminal domain. Co-expression of HBc and UBE2O resulted in HBc protein mono-ubiquitination at lysin K96 and serine S157 of a 185-aa HBc variant. Interestingly, single Ser-to-Ala mutations of two major phosphorylation sites involving serines at positions 164 and 172 resulted in increased UBE2O-mediated mono-ubiquitination, suggesting that HBc hypo-phosphorylation is vital for efficient ubiquitination. The role of UBE2O in viral lifecycle was investigated in HBV-infected HepG2-NTCP cells as well as primary human hepatocytes (PHH) upon downregulation of endogenous UBE2O. The knock-down of UBE2O expression led to suppression of HBV replication as estimated by the levels of intracellular HBV DNA, pgRNA and extracellular HBeAg. Notably, the assembly of intracellular nucleocapsids and secretion of enveloped virions was also significantly impaired in cells with UBE2O knockdown. In conclusion, our results implicated UBE2O in HBV replication and suggested that UBE2O is an important cellular regulator required for efficient assembly and maturation of nucleocapsids and release of enveloped virions.