O-GlcNAcylation

O-GlcNAcylation is a form of posttranslational modification, and serves various functions, including modulation of location, stability, and activity for the modified proteins. O-linked-N-acetylglucosamine (O-GlcNAc) transferase (OGT) is an essential cellular enzyme that posttranslationally modifies the cellular proteins with O-GlcNAc moiety. Early studies reported that the decreased O-GlcNAcylation regulates cellular autophagy, a process relevant for hepatitis B virus replication (HBV) and assembly. Therefore, we addressed the question how O-GlcNAcylation regulates cellular autophagy and HBV replication. Inhibition of OGT activity with a small molecule inhibitor OSMI-1 or silencing OGT significantly enhanced HBV replication and HBsAg production in hepatoma cells and primary human hepatocytes (PHHs). Western blotting analysis showed that inhibition of O-GlcNAcylation-induced endoplasmic reticulum (ER) stress and cellular autophagy, two processes subsequently leading to enhanced HBV replication. Importantly, the numbers of autophagosomes and the levels of autophagic markers LC3-II and SQSTM1/p62 in hepatoma cells were elevated after inhibition of O-GlcNAcylation. Further analysis revealed that inhibition of O-GlcNAcylation blocked autophagosome-lysosome fusion and thereby prevented autophagic degradation of HBV virions and proteins. Moreover, OSMI-1 further promoted HBV replication by inducing autophagosome formation via inhibiting the O-GlcNAcylation of Akt and mTOR. In conclusion, decreased O-GlcNAcylation enhanced HBV replication through increasing autophagosome formation at multiple levels, including triggering ER-stress, Akt/mTOR inhibition, and blockade of autophagosome-lysosome fusion [1].

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