論文の内容の要旨

論文題目

Modulation of Hepatitis B Virus Infection by Epidermal Growth Factor

(B 型肝炎ウイルス感染に対する Epidermal growth factor の作用)

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Hepatitis B virus (HBV) is a member of the *Hepadnaviridae* family of viruses and enters hepatocytes via sodium-taurocholate co-transporting polypeptide (NTCP). After virus entry, it establishes a nuclear pool of episomal covalently closed circular DNA (cccDNA), which is then copied into RNA. The viral RNA is transported to the cytoplasm where it is reverse transcribed into DNA and packed in a virus particle. This complicated life cycle is a major problem to develop effective antivirus therapeutics. For the development of antiviral therapeutics, it is necessary to develop an in vitro infection system that faithfully recapitulates the complicated viral life cycle. Primary human hepatocytes have been used for studies on HBV infection, however, these cells are phenotypically unstable and the availability is limited. Because there are many genotypes of HBV and genetic backgrounds of individuals affect infection of each HBV genotypes. Therefore, it would be beneficial to establish hepatocytes derived from human induced pluripotent stem cells (hiPSCs) with different genetic backgrounds. However, hiPSC-derived hepatocytes showed immature phenotypes and also

exhibited limited capacity for the infection and replication of HBV.

Previously it was shown that hiPSC-derived non-parenchymal cells, liver sinusoidal endothelial cells (LSECs) and hepatic stellate cells (HSCs), promoted hepatic-maturation of hiPSC-derived hepatocytes. I therefore developed a co-culture system of hiPSC-derived hepatocytes with LSEC and HSC and found LSEC enhanced HBV infection to hepatocytes by secreting epidermal growth factor (EGF). While EGF receptor (EGFR) is known as a co-receptor for HBV, I found that EGF enhanced HBV infection at a low dose of EGF, whereas EGF at a high dose suppressed HBV infection. EGFR is internalized by clathrin-mediated endocytosis (CME) and clathrin-independent endocytosis (CIE) pathways depending on the dose of EGF. At a high dose of EGF, the endocytosed EGFR via CIE is degraded in the lysosome. I found that HBV is endocytosed *via* CME and CIE pathways at a low and high dose of EGF, respectively. In conclusion, I have developed an *in vitro* system of HBV infection using iPSC-derived liver cells, and revealed that EGF secreted from LSEC modulates HBV infection dose dependently *via* different endocytosis pathways.