HBV-induced microenvironment reduces pDC response to TLR7/9 stimulation

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Hepatitis B virus (HBV) is an infectious agent that causes acute hepatitis, but can also lead to chronic inflammation, and, consequently, to hepatocellular carcinoma. HBV is described as “stealth virus”, since it avoids recognition by the innate immune system in HBV-infected hepatocytes.

Nonparenchymal plasmacytoid dendritic cells (pDCs) present in the liver massively produce proinflammatory cytokines such as IFNα, Il-6 and TNFα, upon the TLR7/9 activation. These cytokines inhibit HBV replication in hepatocytes. Conversely pDC function is regulated by miRNA146, which is one of the most highly expressed miRNA in hepatocytes, with immunosuppressive and proliferative properties. Specifically, miRNA146 negatively regulates TLR7/9 pathway in pDCs pathway by silencing proteins TRAF6 and IRAK1/4.

Mature miRNA together with Ago (1-4) proteins and GW182 forms the RISC complex that binds target mRNA and leads to its silencing. The RISC complex can be sorted through multivesicular bodies (MVB) into extracellular vesicles (EV), and transported to the different cells, where the RISC complex can regulate protein expression.

We hypothesize that HBV-infected hepatocytes produce miRNA146 packaged in EVs, which can be actively up-taken by pDC, leading to the inhibition of the immune response.

Our results show that the conditioned medium from HBV producing cells inhibits IFNα secretion from pDCs induced by TLR7/9 activation. In addition, the HBV-producing hepatocytes have higher miRNA146 levels than their HBV-free counterparts.

Future investigation will focus on the characterisation of EVs content, such as miRNA, viral and cellular proteins, or other RNA molecules, which could have the immunoregulatory effect on pDCs. This work aims to investigate the immune inhibitory mechanism involved in HBV infection, and possibly identify novel therapeutic targets.

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