# Hepatitis B Virus-induced modulation of liver macrophage function promotes hepatocyte infection

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Introduction. Liver macrophages are the largest macrophages population, acting as the main liver sentinel. They are involved in pathogen clearance and/or pathogenesis. Hepatitis B Virus (HBV) chronically infects more than 250 million people worldwide and is responsible for liver diseases. The severity of the disease may differ according to the HBV genotype. Our aim was to characterize the interplay between HBV (genotypes B, C and D) and liver as well as infiltrating macrophages in order to understand how HBV may escape the immune system to establish and maintain its infection.
Methods. Liver biopsies from HBV patients were stained for total macrophage, anti-inflammatory macrophage, and HBV capsid protein (HBc). Primary Liver Macrophages (PLMs) were isolated from several non-infected human liver resections and monocytes from non-infected human blood pocket to generate ex vivo Monocytes Derived Macrophages (MDMs) differentiated in pro- or anti-inflammatory macrophages (M1- and M2-MDMs respectively).
Results. We observed HBc within macrophages in liver biopsies from HBV-infected patients. This correlated with higher levels of anti-inflammatory macrophage markers, compared to non-infected ones. Ex-vivo very short-term exposure of naive PLM to HBV-C and HBV-D led to a reduced secretion of IL-1β with no influence on IL-10. Interestingly, HBV-B led to a strong increase of IL-10 secretion without any effect on IL-1β. In the MDM model, HBV-D impaired the differentiation of M1-MDM, decreasing the secretion of IL-6 and IL-1β, and increasing the activation of M2-MDM, which secreted more IL-10. Interestingly, HBV-C had a stronger inhibitory effect on pro-inflammatory secretion than HBV-D in M1-MDM. Finally, conditioned media (containing IL-6 and IL-1β) from M1-MDM cells strongly decreased the establishment of HBV in hepatocytes. This anti-viral phenotype was abrogated when supernatant from M1-MDMs, exposed to HBV during their differentiation, was used.
Conclusion. Altogether, our data suggest that HBV strongly modulates liver and infiltrating macrophages in favor of a tolerogenic environment that promote its establishment and that this phenotype can be recapitulated in short term experiment ex vivo. Worth noting, these modulations vary from one HBV strain to another and further analyses should be done to understand if they may be related to the severity of the disease.

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Keywords : Macrophages, Hepatitis B Virus,phenotypic immune modulation, anti-inflammatory, anti-viral effect
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