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Several Key Players Involved in Hepatitis-B Virus Innate Response

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Commentary

Both innate and adaptive immune responses play a central role in fighting off infection. The innate production of proinflammatory cytokines and interferon type (IFN) I and II secretion are central to activating adaptive immunity. The cell types associated to innate immune responses include macrophages, monocytes, natural killer (NK) cells and dendritic cells as well as non haemopoietic cells such as hepatocytes [1]. Innate immunity begins when pathogen recognition receptors (PRRs) detect viral infection. Ideally hepatocytes which host Hepatitis-B Virus (HBV) in the liver should initiate innate immune responses by sensing viral components through PRRs but this is not the case. In fact, many reports highlight HBV inhibition of type I IFN production via PRR stimulation through TLR3, or RIG I expressed in hepatocytes [2-5]. Many argue that this block explains the lack of innate responses towards HBV. However, the possibility that the virus activates innate immune pathways by non-parenchymal liver cells or blood circulating immune cells to limit viral replication cannot be ruled out. Hosel et al., showed that upon infection of primary human liver cells, HBV envelope proteins can activate liver cells (most likely Kupffer cells (KC). Within 3 hours, this recognition led to the activation of nuclear factor kappa B (NF-κB) and subsequent release of interleukin-6 (IL-6) and other proinflammatory cytokines (IL-8, TNF-α, IL-1β) [6]. Although no information is available on KC, studies using THP-1 monocytic cells, monocytes, and dendritic cells have shown binding of HBV or HBV proteins, leading to their activation. For instance, TLR2 and heparan sulfate proteoglycan (HSPG) were suggested to be responsible for HBcAg recognition on THP-1 cells, and HBcAg-induced activation of THP-1 cells resulted in production of IL-6, IL-12p40, and TNF-α [7]. Furthermore in patients' detection of the surface antigen (HBsAg) and HBV-DNA revealed an increase in the number of circulating NK cells [8]. However, NK activation and function was suppressed as viral load increased, and only peaked once viremia had resolved. This inhibition of NK cell activation was temporally associated with an induction of IL-10, raising the possibility that HBV can actively evade immune responses [9]. Recently shown was the ability of the HBeAg protein to inhibit IL-18 activity on the NF-κB pathway and thereby down regulating NK cell IFN-γ production [10]. Few data are available regarding the involvement of NK cells in the immediate response to infection, and only recent results obtained in woodchucks infected with high woodchuck hepatitis virus (WHV) dose (10) [11] show an activation of a gene related to NK cell activation immediately after infection (8 to 12 h) [11].

HBV has been shown to activate cells at the frontier of innate-adaptive responses such as NKT cells. Zeissig et al. [12] showed in a murine model supporting HBV-adenoviral infection, that hepatocytes upon HBV infection present endogenous antigenic lipophospholipids to intra-hepatic invariant and non invariant NKT cells via the CD1d MHC-like molecule and trigger their activation. Such activation was important for the induction of NK and HBV-specific T and B cell responses required for viral clearance However would the same occur in human liver? Already reports show that the percentage of iNKT in the mouse liver is much higher than that of the human liver i.e. 20–30% iNKT vs <1% [12]. Indeed, the role of NK cells and other innate T cell like cells in the human liver was highlighted in a recent publication [13]. Jo et al., observed the ability of NK^{bright} and Innate mucosal-associated invariant T (MAIT) cells in the human liver to produce high IFN-γ secretion in response to a TLR8 agonist [13]. Of note was a subtle drop in TLR8 mediated- IFN-γ responses in patients that were chronically infected with HBV [13]. What we can appreciate from the Zeissig group and other studies is that local liver immune cell responses are required as well as circulating cells to control HBV infection. In addition the responses generated by innate immune cells are critical in the acute phase of infection. During the acute phase in a chimp model of HBV infection, IFN α and γ genes were induced that helped to clear infection [14]. This study provided further evidence that immune cell activation in the liver such as NK cell death effectors granzyme A and granzyme K peaked during acute hepatitis, as did a large number of IFN-regulated genes. This was consistent with the detection of IFN-mRNA and the decreasing viral DNA content of the HBV infected chimpanzee livers. For example, STAT1, which mediates IFN receptor signaling, was induced, as were several MHC class II genes. In addition, the IFN-induced GTPases, GBP1 and -2, as well as IFI27 and IFI16, peaked at this time. Thus, further investigation into the role of these genes in the clearance of HBV infection appears to be warranted both in the murine models and in humans. These data indicate that in primates the secretion of IFN-α play an essential role in HBV clearance. Plasmacytoid dendritic cells (pDCs) produce large amounts of IFN-α in response to TLR9 and TLR7 stimulation. We and others have demonstrated that HBV is able to demodulate TLR9 signaling in circulating pDCs and B cells and to inhibit TLR9-mediated IFNα and IL-6 secretion [15,16]. Unlike many viruses which trigger type I IFNs and have evolved to counteract this activation, our data indicated that HBV does not trigger IFN-α secretion in pDCs although it can impair its function by selectively targeting TLR9 but not TLR7. Indeed the virus blocked the transcription of TLR9, indicating that HBV has evolved an immune escape strategy to avoid potential detection by this dsDNA PRR sensor. Furthermore we corroborated our findings in PBMC from HBV infected patients and observed the loss of TLR9 expression in chronically infected individuals as well as in those patients who had developed hepatocarcinomas [15]. In parallel the role of TLR9 signaling in B cells (which leads to cell proliferation and antibody production) during

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HBV acute infection could be relevant in light of the importance of the humoral response in the outcome of HBV infection and therefore deserves more attention. The mechanism of TLR9 transcriptional abrogation by HBV is currently being elucidated by our group. Taken together, these data highlight the efficiency of HBV in silencing the innate response but a role of pDC in the clearance of HBV infection cannot be ruled out. Indeed pDCs are reported to accumulate in the liver during HBV acute infection [17] and to express higher activation markers during chronic infection suggesting the detection by pDC of HBV [18]. Thus it's possible that circulating and intra-hepatic pDCs play a role in the delicate balance between protective and pathogenic antiviral responses following HBV infection. Interplay, activation and dysfunction between several innate immune cell populations in the blood and the liver is likely to be important during HBV infection.

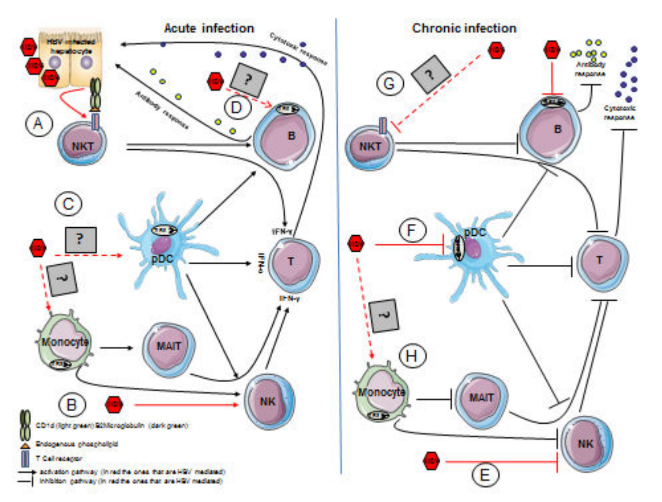

Figure 1: HBV infection-acute and chronic infections.

HBV infection clearance (occurring among 95% of infected adults) is due to a vigorous and efficient immune response which is characterized by multi-specific T cells, neutralizing antibodies produced by B cells and a strong NK and MAIT IFN-γ and cytotoxic response. In the early stage of HBV acute infection intra-hepatic NKT cells are activated by HBV infected hepatocytes and produce IFN-γ.

(A) Such response is important for the appropriate activation of the cytotoxic T and the humoral B cell responses [12]. NK cells also are activated by HBV infection at very early stage during HBV infection [8,19]

(B) During viral infections pDCs play a capital role in initiating the antiviral response and in shaping the NK response and B and T cell adaptive immunity: pDCs rapidly sense the presence of viruses via the detection of their nucleic acids through the TLR-7 and -9 and produce large amounts of IFN-α and pro-inflammatory cytokines which are required for the activation of the NK, T and B cells responses. Therefore pDC are important determinants of disease outcome. However the role of pDC and specifically the role of TLR9 signaling in pDC in the outcome of HBV still needs to be addressed

(C) In parallel the role of TLR9 signaling in B cells (which leads to cell proliferation and antibody production) during HBV acute infection could be relevant in light of the importance of the humoral response in the outcome of HBV infection and therefore deserves more attention

(D) HBV chronic infected patients (which represent 5% of total HBV infected individuals) are characterized by immune dysfunctions against HBV at different levels. NK cell and anti-viral properties are reduced [20]

(E) pDCs also are impaired in their functions in that they do not respond to TLR9 by secreting pro-inflammatory cytokines and IFN-α [15]

(F) In this scenario it's important to clarify whether NKT

(G) Monocytes

(H) Immune functions are also targeted by HBV in the context of chronic infection. Decrypting the immune responses against HBV and the mechanisms of immune evasion adopted by HBV is of capital importance for the development of new therapeutical strategies.

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