Editorial

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Interplay between hepatitis B virus and TLR2-mediated innate immune responses: Can restoration of TLR2 functions be a new therapeutic option?

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The persistence of HBV replication in patients with chronic hepatitis B (CHB) is, as for many other chronic viral infections, a consequence of viral escape from immune responses [1,2]. Indeed in the so-called immunotolerant phase, patients with HBeAg+ CHB have usually high viremia levels due to an active intra-hepatic replication of HBV genome. And yet, these patients do not present with significant liver injury because there is little attack of infected cells by cytotoxic immune cells [3]. The determinants of this blockade are far from being understood, and are likely to be numerous and complex, including modulation of innate as well as adaptive immune responses. As innate responses are crucial for an accurate orchestration of cellular adaptive responses [2], there is a growing body of evidence that HBV may blunt immune responses at the most upstream point, i.e. interactions between pathogen recognition receptors (PRR)-pathogen associated molecular pattern (PAMP). In the liver, innate responses are mediated by immune professional cells, such as dendritic cells, Kupffer cells, natural killer (NK), and NK-T cell, but also by non-professional cells [4], such as hepatocytes, which are the site of HBV replication and therefore the site of production of viral PAMPs. PRRs are the main cellular receptors involved in the detection of pathogens that circulate in an infected organism [5]. They include cell surface-associated (or endosomal) molecules, such as Toll-like receptors (TLR), as well as cytoplasmic ones, such as RIG-like or NOD-like receptors. To persistently evade innate immunity, viruses that establish chronic infection have to subvert the function of these PRRs by either down regulating their expression, blocking PRR-PAMP interactions, or interfering with downstream signalling pathways [6].

In the context of CHB, a strong interplay between HBV and TLR2 was convincingly observed *in vivo*. Indeed, a seminal paper has shown that TLR2 is less expressed at the surface of PBMC, Kupffer cells, and infected hepatocytes in HBeAg+ patients compared to control patients [7]. The presence of HBeAg in the blood of these patients with CHB was positively correlated to this phenotype, although a direct causal effect was not clearly demonstrated. Indeed, HBeAg positivity also correlates to a higher replication of the virus and therefore to a higher production of other potential viral inhibitory components [3]. However, it is worth noting that the inhibitory role of HBeAg in the control of immune response was convincingly demonstrated in the context of perinatal transmission of HBV. In this case, the diffusion of HBeAg through the placental barrier renders the foetus' immune system tolerant to HBV infection [8]. These immunotolerant properties of HBeAg were also analysed in transgenic mouse models [8]. Yet, there is no underlying molecular mechanistic framework to explain this phenotype. The potential blockade of TLR2 pathway by HBV was also suggested in an HBV transgenic mouse model, in which TLR2 ligands did not exhibit a potent inhibitory effect on the synthesis of HBV intermediate, in contrast to other ligands [9]. However, in this study, TLR2 protein expression was not observed in freshly prepared mouse hepatocytes and mRNA expression was not investigated to substantiate this hypothesis. It could also be that TLR2 ligand activation might not lead to interferon production in mice, therefore explaining the lack of antiviral effect (see Fig. 1).

With respect to the potential "direct" inhibition of TLR2 activation/signalling by secreted HBeAg (i.e. direct action of extracellular HBeAg on TLR2 activation or signalling after exposure to TLR2 ligands), data are so far not conclusive. Such a "direct" inhibition of PRR activation in various cell types (i.e. liver resident cells and circulating pDC) by secreted HBV proteins was recently reported, but concerned only TLR3, TLR4 or TLR9 sensors, not TLR2 [10–12]. In the study by Wu *et al.*, it was shown that HBV virions, HBeAg, and HBsAg could inhibit the activation of TLR3 and TLR4 by their cognate ligands, thus leading to an inhibition of the secretion of antiviral and pro-inflammatory cytokines in the supernatants of stimulated cells (i.e. hepatocytes, Kupffer, and endothelial cells) [11,12]. Regarding the inhibition of TLR9 signalling in pDC, two different mechanisms could be at work: interaction of HBs with inhibitory receptors present in pDC (i.e. DCIR-$_{ITIM}$ and/or BDCA2-$_{ITAM}$) [13] and/or inhibitory CpG sequences within HBV genome [11,12] could both/either block

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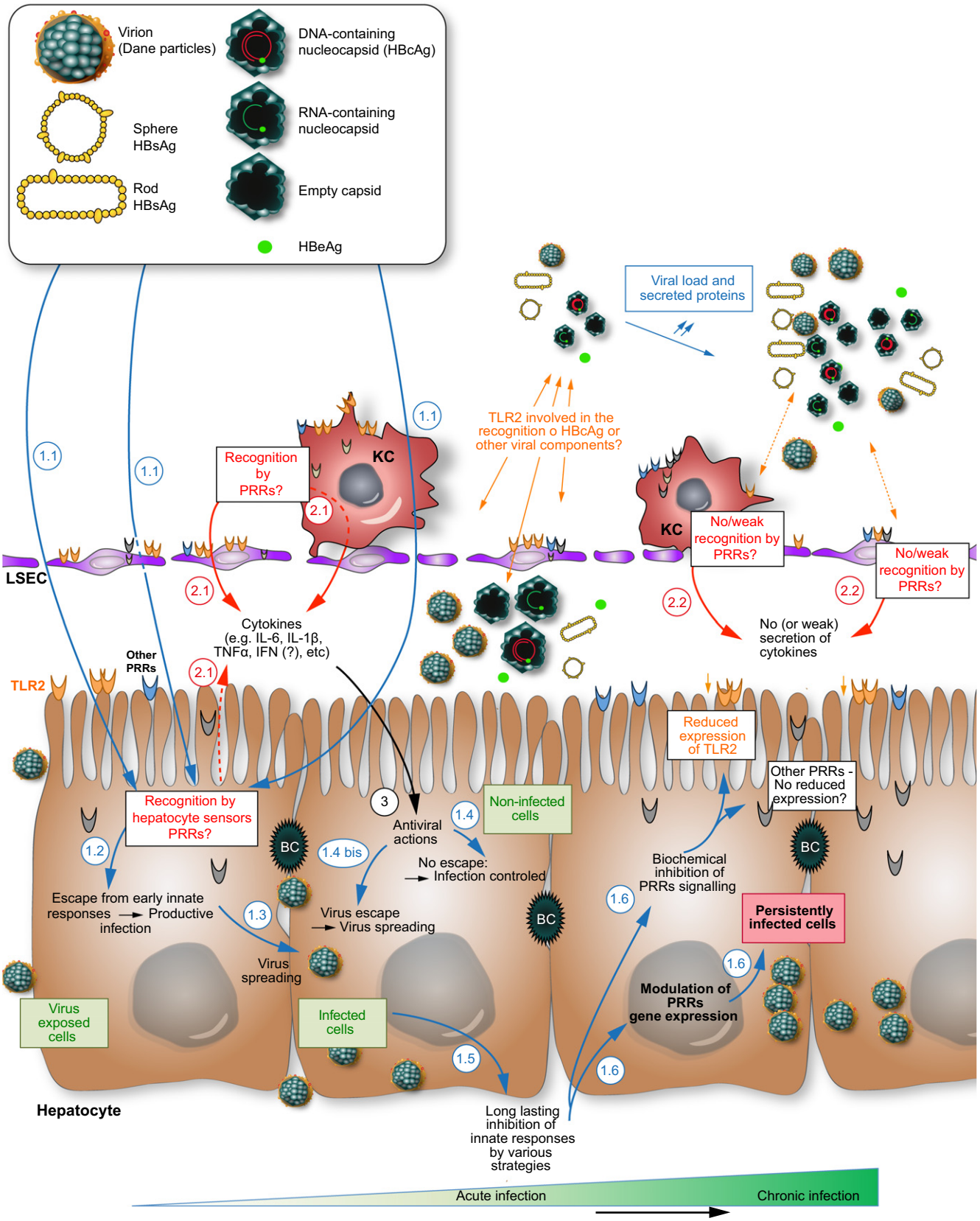
Virion
(Dane particles)
DNA-containing
nucleocapsid (HBcAg)
Sphere
HBsAg
RNA-containing
nucleocapsid
Rod
HBsAg
Empty capsid
HBeAg
Viral load and
secreted proteins
TLR2 involved in the
recognition o HBcAg or
other viral components?
1.1
Recognition
by
PRRs?
KC
2.1
LSEC
No/weak
recognition by
PRRs?
2.2
Cytokines
(e.g. IL-6, IL-1β,
TNFα, IFN (?), etc)
No (or weak)
secretion of
cytokines
Other
PRRs
TLR2
Recognition by
hepatocyte sensors
PRRs?
1.2
BC
3
Antiviral
actions
1.4
Non-infected
cells
1.4 bis
No escape:
Infection controled
Escape from early innate
responses → Productive
infection
1.3
Virus escape
→ Virus spreading
Virus
spreading
Virus
exposed
cells
Infected
cells
1.5
Hepatocyte
Reduced
expression
of TLR2
Other PRRs -
No reduced
expression?
Biochemical
inhibition of
PRRs signalling
1.6
Persistently
infected cells
Modulation of
PRRs
gene expression
Long lasting
inhibition of
innate responses
by various
strategies
Acute infection
Chronic infection