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Review

Innate immunity related pathogen recognition receptors and chronic hepatitis B infection

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ABSTRACT

Innate immunity consists of several kinds of pathogen recognition receptors (PRRs), which participate in the recognition of pathogens and consequently activation of innate immune system against pathogens. Recently, several investigations reported that PRRs may also play key roles in the induction/stimulation of immune system related complications in microbial infections. Hepatitis B virus (HBV), as the main cause of viral hepatitis in human, can induce several clinical forms of hepatitis B and also might be associated with hepatic complications such as cirrhosis and hepatocellular carcinoma (HCC). Based on the important roles of PRRs in the eradication of microbial infections including viral infections and their related complications, it appears that the molecules may be a main part of immune responses against viral infections including HBV and participate in the HBV related complications. Thus, this review article has brought together information regarding the roles of PRRs in immunity against HBV and its complications.

1. Introduction

Hepatitis B is a worldwide life threatening disease which is caused by hepatitis B virus (HBV) (Assar et al., 2012; Ayoobi et al., 2013; Khorramdelazad et al., 2012). Hepatitis B has several clinical presentations which are described in the next sections. Active and inactive chronic HBV infected patients are suffering from attenuated immune responses and, hence, are unable to detect and eradicate HBV completely (Arababadi et al., 2009; Chan and Jia, 2011). Nowadays, our knowledge regarding the mechanisms which result in attenuation of immune responses in the patients is growing. Accordingly, it appears that both innate and adaptive immunities play critical roles in recognition and suppression of HBV. In the meantime, it seems that innate immunity significantly participates in the HBV antigens detection and suppression of the virus as well as activation of effector adaptive immune cells. The important roles played by innate immunity against HBV were highlighted considering the point that, recent data demonstrated several mechanisms in which HBV escapes from innate

Abbreviation: acLDL, acylated LDL; AIM2, absent in melanoma 2; AP-1, activator protein 1; BDCA-2, blood DC antigen; BEC, biliary epithelial cells; CARD, caspase recruitment and activation domains; cDC, common dendritic cells; CL-L1, collectin liver 1; CL-K1, collectin kidney 1; CL-P1, collectin placenta 1; CpG-ODN, CpG-oligodeoxy nucleotides; CR, consensus repeats; CRD, carbohydrate recognition domain; CTD, C-terminal regulatory domain; CTLD, C-type lectin domains; DAI, DNA-dependent activator of IFN regulatory factors; DAMP, damage associated molecular patterns; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; DGCR2, diGeorge syndrome critical region 2; DMBT1, deleted in malignant brain tumors 1; DMXAA, 5,6-dimethylxanthenone-4-acetic acid; DNMT-1, DNA methyltransferase 1; EGF, epidermal growth factor; EMBP, eosinophil major basic protein; FMLP, *N*-formylmethionyl-leucyl-phenylalanine; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HIN, hematopoietic interferon-inducible nuclear proteins; HSC, hepatic stellate cells; IFI16, interferon-inducible protein 16; IFIX, interferon-inducible protein X; IPS-1, IFN-β promoter stimulator 1; IRAK1, interleukin-1 receptor associated kinase-1; KCs, Kupffer cells; LGP2, laboratory of genetics and physiology-2; LOX-1, lectin-like oxidized LDL receptor-1; LPS, lipopolysacharide; LRR, leucine-rich repeats; LTA, lipoteichoic acid; MAPK, mitogen-activated protein kinase; MBL, mannose-binding lectin; MDA5, melanoma differentiation-associated gene 5; MNDA, myeloid cell nuclear differentiation antigen; MYD88, myeloid differentiation primary response; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NLR, nod-like receptors; OBI, occult HBV infection; oxLDL, oxidized low density lipoproteins; PAMPs, pathogen associated molecular patterns; PBIC, peripheral blood immune cells; PBMC, peripheral blood mononuclear cell; pDC, plasmacytoid DC; PRR, pattern recognition receptors; PYHIN, pyrin and HIN domain; RIG-I, retinoic acid-inducible gene 1; RLRs, RIG like receptors; SCARA5, SR class A, member 5; sE-selectin, soluble E-selectin; sL-selectin, soluble L-selectin; SP-A, SP-D, surfactant protein A, D; SR, scavenger receptor; SR-BI, scavenger receptor class BI; STING, stimulator of interferon genes; TAK1, transforming growth factor b-activated kinase 1; TBK1, tank binding kinase 1; TIR, toll/interleukin-1 receptor; TLR, toll-like receptor; TRAF6, TNF receptor associated factor; ZBP1, Z-form DNA binding protein 1

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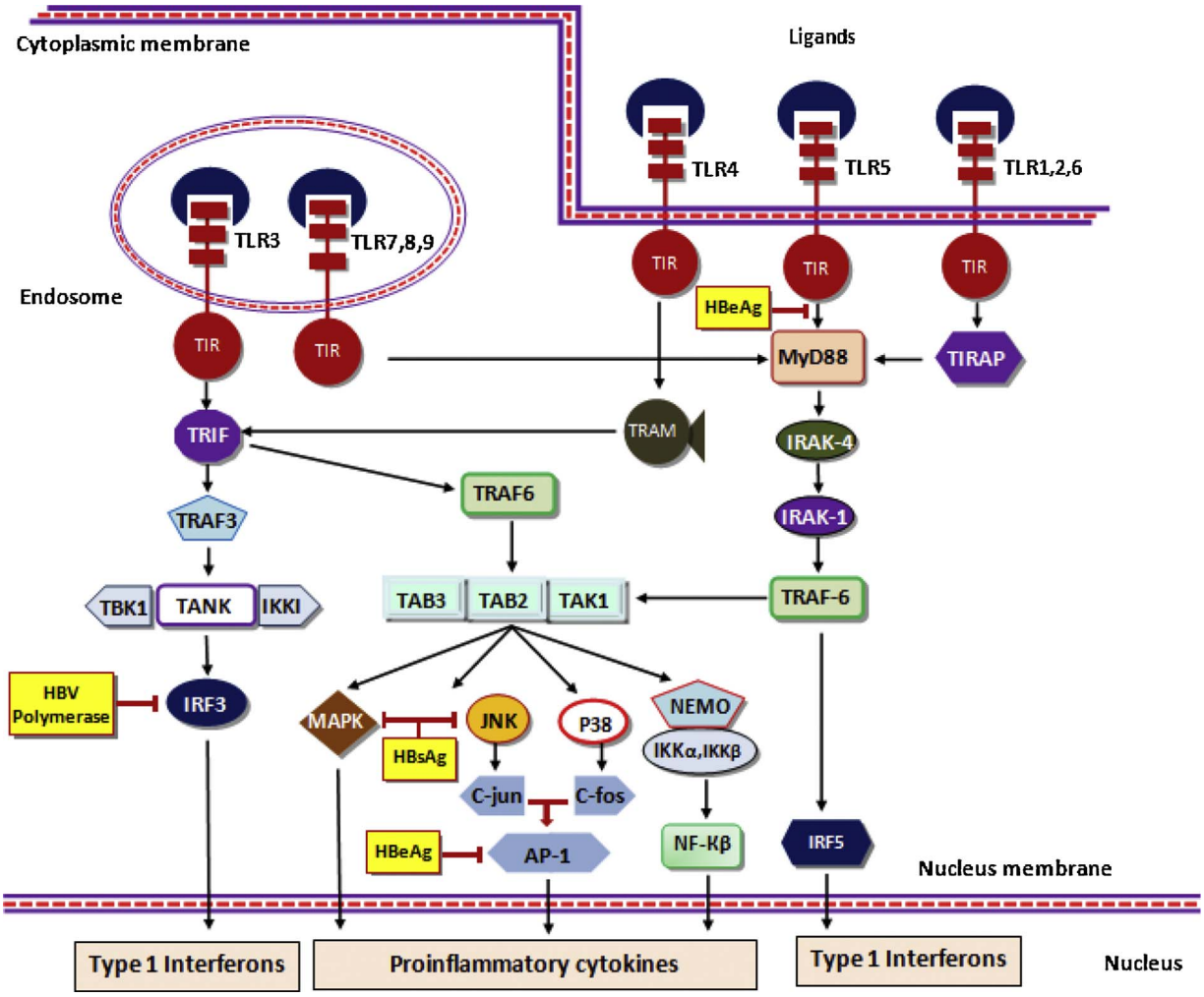

Fig. 1. TLRs signaling and effects of HBV to inhibit the pathways. The figure illustrates that all TLRs use MYD88 dependent pathway, TLR4 uses both MYD88 and TRIF dependent pathways and TLR3 uses TRIF dependent pathway only. HBV related molecules including HBeAg, HBsAg and HBV polymerase inhibit the pathways in several stages.

immunity recognition (Ait-Goughoulte et al., 2010). Therefore, it conveys the idea that the innate immunity parameters are the crucial factors to determine the successful clearance of HBV infection. Innate immunity receptors play significant roles in recognition of HBV and consequently activation of intracellular signaling which leads to activation of innate immunity cells (Liu and Zhang, 2015). Thus, it can be hypothesized that HBV targets expression and functions of the receptors to overcome immune responses, based on the fact that innate immunity plays important roles in the fight against microbes either in the early or late phases of immune response. Immunity can complete immune responses via cross-talk with adaptive immunity. Additionally, innate immunity plays key roles in induction of fibrosis in the inflamed tissues and induction of damages to the tissues. Thus, innate immunity not only inhibits infections in the early phases of infection, but also participates in the clearance of microbe infection and their complications including tissue fibrosis. This review aimed to gather recent information regarding the status of innate immune receptors expression and their roles in the pathogenesity of chronic HBV infected patients in the current review article. This review also addresses the main mechanisms used by HBV to overcome the pathways.

2. Innate immune receptors categories

It has been demonstrated that innate immune cells apply several receptors which are known as pathogen recognition receptors (PRRs), to recognize viral PAMPs (Pathogen Associated Molecular Patterns), including HBV (Leong et al., 2015). Accordingly, they have been categorized into two classes as cell-associated PRRs and soluble recognition molecules. The main cell-associated pattern recognition receptors are toll-like receptors (TLRs), C-type lectins, scavenger receptors, *N*-Formylmethionyl-leucyl-phenylalanine (FMLP), retinoic acid-inducible gene 1 (RIG-I)-like receptors (RLRs), DNA-dependent activator of IFN regulatory factors (DAI) which are also known as Z-form DNA binding protein 1 (ZBP1), pyrin and HIN domain (PYHIN) protein family, and Nod-like receptors (NLRs) (Bagheri et al., 2014; Chen et al., 2012c; Matsumiya et al., 2014; Zoulim et al., 2013). Moreover, the main soluble recognition molecules are classified as pentraxins, collectins and ficolins (Gedik et al., 2007; Miwata et al., 1993; Unterholzner et al., 2010; Wu et al., 2013). Chronic hepatitis B infected patients are not only unable to recognize and eradicate HBV completely, but also are suffering from the related complications such as liver cirrhosis and hepatocellular carcinoma (HCC) (Arababadi et al., 2012; Arababadi et al., 2010; Khorramdelazad et al., 2012). PRRs have become the target of recent investigations. Accordingly, the patterns of the PRRs in the chronic hepatitis B and also their relations with chronic hepatitis B complications will be discussed in the following sections.

3. Innate immunity sensors and chronic hepatitis B

3.1. Toll like receptors and chronic hepatitis B

There are several publications regarding the roles played by TLRs in