Journal of Inflammation Research

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REVIEW

Antigen Recognition and Immune Response to Acute and Chronic Hepatitis B Virus Infection

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Abstract: The antigen recognition and immune response to acute and chronic hepatitis B virus (HBV) infections are the result of both the innate and adaptive immune response. The innate immune response comprises Dendritic Cells (DCs), which served as professional antigen-presenting cells and a bridge between innate and adaptive immunity, Kupffer cells and inflammatory monocytes for the continuous inflammation of hepatocyte, neutrophils for hepatic tissue damage due to acute inflammation, type I interferons (IFN), which induce an antiviral state on infected cells, directs natural killer (NK) cells to kill virally infected cells, reduces the population of infected cells, and promotes the effective maturation and site recruitment of adaptive immunity through the production of pro-inflammatory cytokines and chemokines. Through stimulating B cells, T-helper, and cytotoxic T cells, the adaptive immune system also protects against hepatitis B infection. During HBV infection, a network of cell types that can either play protective or harmful functions creates the anti-viral adaptive immune response. These many elements, such as Cluster of differentiation four (CD4) T cells (traditionally known as helper T cells), are potent cytokine producers and necessary for the effective maturation of effector cytotoxic cluster of differentiation eight (CD8) T cells and B cell antibody production. By cytolytic and non-cytolytic processes, CD8 T cells are able to eliminate HBV-infected hepatocytes and directly detect virus-infected cells, and circulating CD4+ CD25+ regulatory T cells for the modulation of immune system. In order to avoid reinfection, B cells can produce antibodies that destroy free viral particles. Moreover, by presenting HBV antigens to helper T cells, B cells may also influence how well these cells operate.

Keywords: antigen recognition, immune response, HBV, innate immunity, adaptive immunity

Introduction

In spite of the existence of an efficient vaccination, the hepatitis B virus (HBV) affects more than 350 million people globally and puts them at a high risk of developing liver cirrhosis and hepatocellular cancer, continues to pose a serious threat to public health.[1] Due to the chronic interactions between the virus and the host immune response, more than a million deaths occur in every year.[2,3] The combined operation of both innate and adaptive immune responses is necessary for the effective management of Hepatitis B virus (HBV) infections. The innate immune system is elicited by pattern-recognition receptors (PRRs) that recognize specific structures on HBV.[4]

Innate immunity has developed to quickly detect viral proteins, nucleic acids, and tissue damage and produces type I interferons (IFN), which induce an antiviral state on infected cells, directs natural killer (NK) cells to kill virally infected cells to reduce the number of infected cells, and supports the effective maturation and site recruitment of adaptive immunity by producing pro-inflammatory cytokines and chemokines.[5]

B cells, T-helper, and cytotoxic T cells must all be effectively expanded for the adaptive immune system to be able to control HBV infection.[6] A poor induction of intracellular innate responses during the initial stages of infection proceeds functionally effective, multi-specific antiviral T-cell responses that are associated with the resolution of acute hepatitis B virus infection. Long-lasting protective memory and continuing immune system activation allow ongoing infection control. Instead, the absence of protective T-cell memory formation and the exhaustion of HBV-specific T-cell responses are signs of chronic viral persistence.[7]

Received: 7 March 2023
Accepted: 2 May 2023
Published: 18 May 2023

Despite those immune responses, about 5% of infected adults and over 90% of infected newborns fail to clear the infection, and as a result, the infection progresses to chronicity. Once chronicity has set in, these individuals will eventually develop serious liver diseases like cirrhosis and hepatocellular carcinoma.[8] This review will focus on how HBV interacts with host immunity and how the host immunity recognizes the HBV antigen.

Antigen Recognition and Innate Immune Response to Hepatitis B Virus Infection

Interferon Response to Hepatitis B Virus (HBV) Infection

The ability of HBV to activate the interferon pathway of the innate immune response in the early stages of infection has been assessed in earlier research. There is a lag between HBV injection and effective replication, according to patient and animal model data. Around 5 weeks after infection, HBV-DNA and HBV antigens are both detectable. At this point, viral titers enter a logarithmic expansion phase, and the majority of hepatocytes are infected. Animal investigations have shown that this is not the case; rather, the virus manages to elude being detected, despite the fact that it is tempting to hypothesize that this initial lag of replication is the result of the virus being effectively controlled by the innate immune response.[9,10]

The Role of Cytokine Against HBV Infection

By binding to specific receptors expressed on the target cells, cytokines limit viral replication directly or indirectly.[11] Interleukin (IL)-6 and IL-1β regulate sodium-taurocholate cotransporting polypeptide (NTCP) expression and prevent HBV from entering cells. According to a recent study, cells pretreated with IL-6 reduced HBV entrance by up to 90%, significantly reducing the release of cccDNA and HBsAg. Research showed that IL-6 blocks HBV entrance by down-regulating the viral entry receptor NTCP.[12] According to reports, interleukin-1β inhibits cccDNA transcription by causing hepatocyte dedifferentiation.[13,14] Injection of a single dosage of IL-22 boosted the expression of proinflammatory genes in the liver of HBV transgenic mice, and it appears to be a key mediator of the inflammatory response that occurs when T cells in the liver recognize HBV.[15] Interleukin-12 concentrations in the patient serum may be a measure for cellular immunity to HBV infection. Increased IL-12 improves the antiviral characteristics of HBV-specific T cells including cytotoxicity, polyfunctionality, and multispecificity.[16,17] The pro-apoptotic molecule, which can cause premature attrition of HBV-specific CD8 T cells, was greatly reduced by IL-12. Most patients' CD8 functioning was further boosted when IL-12 and PD-1 pathway inhibition were combined.[18]

The Role of Chemokine in HBV Infection

There is growing evidence that particular chemokines in the liver are essential for creating the ideal conditions for naive cell activation and proliferation in response to hepatitis virus infection. According to earlier research, immune and non-immune cells both create CCR5 ligands (CCL3, 4, and 5) in response to HBV antigens.[19,20] Using a mouse model of HBV infection, it was discovered that the chemokine C-X-C-chemokine ligand 13 (CXCL13), which is involved in lymphoid architecture and development and hepatic B-lymphocyte trafficking, is expressed differently in different age-groups of mouse hepatic macrophages and is crucial for promoting an efficient immune response against HBV. CXCL13 is chemotactic for mature B cells and T follicular helper (Tfh) cells and facilitates the co-migration of B cells and Tfh cells into B cell follicles and germinal centers (GCs).[21] Many effector immune cells, including NK cells, T lymphocytes, and macrophages, express the CC chemokines receptor 5 (CCR5), which is essential for controlling immune cell activation and migration during immunological responses to HBV.[22]

The Role of Dendritic Cells (DCs) in HBV Infection

Initiating primary immune responses that combine innate and adaptive immunity are known as dendritic cells (DC), which are regarded as professional antigen-presenting cells. The activation of CD8+ CTL and CD4+ T cells depends heavily on DC.[23] Impairment of DC function is critical for dampening host immune responses and promoting viral persistence in chronic HBV infection.[24] Hepatitis B virus is phagocytosed by DCs, which then converts them into antigenic peptides and presents them to CD4+ and CD8+ T lymphocytes.[25]

Through pattern recognition receptors on DC, such as C-type lectins and Toll-like receptors (TLR), HBV can directly activate DC and cause internalization of the virus within early endosomes. By capturing viral byproducts and reacting to

cytokines made by other cells in response to viral infection, DC can also be indirectly triggered by viruses.[26,27] In the context of HBV, a failure in the maturation process of DC may result in tolerogenic T-cell responses and HBV persistence since immature and semi-mature DC are linked to tolerogenic responses.[28,29] HBV infection can result in levels of 10^9–10^{10} infectious particles per milliliter in the liver and peripheral circulation, which permits numerous contacts between the virus and DC.[30]

Kupffer Cells and Monocytes

The majority of immunological liver cells, known as Kupffer cells, are found in the liver sinusoids.[31] Studies conducted in living organisms have shown that chronic liver inflammation and liver regeneration can occur from the prolonged activation of Kupffer cells and inflammatory monocytes. Increased liver damage was seen in HBs-transgenic animals with CD205-expressing Kupffer cells as a result of natural killer T (NKT) cell activation through the Fas signaling pathway.[32] Patients with persistent HBV infection may be able to activate CD8+ T cells by upregulating CD137 ligand through circulating CD14+ monocytes.[33] Kupffer cells interacted with the hepatitis B core antigen-TLR2 to support the exhaustion of CD8+ T lymphocytes in mice after HBV infection.[34]

The Role of Neutrophil in HBV Infection

HBV may prevent the release of neutrophil (NET) by regulating the formation of reactive oxygen species (ROS) and autophagy in order to bypass the immune system and encourage the development of persistent infection.[35] Acute inflammation and neutrophil buildup in the liver frequently result in collateral hepatic tissue damage. Several mediators that have the power to affect inflammatory and immunological responses can be made to express themselves in neutrophils.[36] Neutrophils' improper activation and homing to the microvasculature is a factor in the pathogenic effects of HBV infection.[37]

The Role of Natural Killer Cell (NK) Cell in HBV Infection

Natural killer (NK) cells are the primary effector population of the innate immune system and the most prevalent in the human liver, which accounts 31% of the hepatic lymphocytic population.[38] Natural killer (NK) cells function as an innate immune modulator to cause microbially infected cells to die by exerting substantial cytotoxic activity and increasing the production of certain cytokines and chemokines.[39] Due to the low levels of MHC class I expression that hepatocytes typically exhibit, NK cells may be more crucial to the early defense against HBV infection than major histocompatibility complex (MHC) class I expression.[40] Recent research has shown that NK cells can control adaptive immune responses by deleting HBV-specific CD8+ T cells in addition to their antiviral activities.[41] In mice and humans, NK cells make up roughly 30–40% and 5–10% of the intrahepatic lymphocytes, respectively.[42] When HBV infection is active, NK cells become activated and skewed toward cytotoxicity, increasing levels of IL-12, IL-15, and IL-18 that damage the liver. A cytokine binds to a particular receptor and enables the accompanying Janus Kinases to be transactivated (JAKs) (Figure 1).[43,44]

Antigen Recognition and Adaptive Immune Response to HBV Infection

The Role of B -Cell in HBV Infection

Aspects other than the generation of antibodies may potentially play a role in the possible significance of B cells in HBV infection. Neutralizing antibodies stop viral spread from infected hepatocytes that are still producing. The severity of chronic hepatitis B (CHB) may be significantly influenced by antibodies produced by antibody-secreting B cells, notably those against anti-HBcAg. Individuals with HBV-associated acute liver failure displayed a huge B-cell response that seemed to be concentrated in the liver, with a buildup of plasma cells secreting IgG and IgM, complement deposition, and involvement of anti-HBcAg.[45–47]

Similar to the findings for HBV-specific T cells, patients with acute hepatitis B were more likely to have anti-HB generating B cells than patients with chronic hepatitis B, who often have neither HBsAg-specific B cells nor HBsAb. Because the restoration of these cells was linked to HBsAg seroconversion in chronic HBV infection, it was thought that the lack of BsAg-specific B cells was to blame for the persistence of the infection.[45]

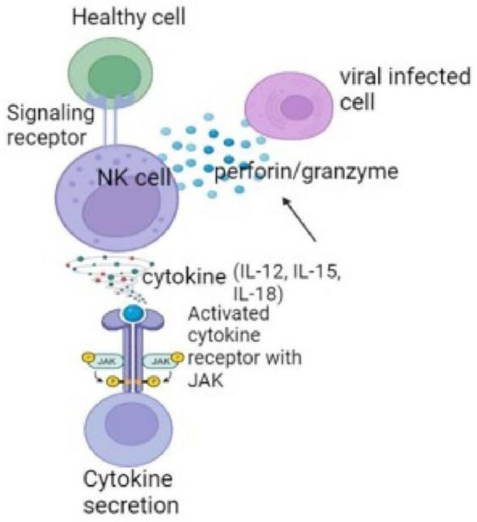

Figure 1 The role of natural (NK) cells in hepatitis B virus infection.

The Role of Cytotoxic T-Cell in HBV Infection

Liver damage is brought on by the human leukocyte antigen (HLA) class I-restricted cytotoxic T lymphocytes' identification of HBV-infected hepatocytes since the virus is predominantly hepatotropic rather than cytopathic. A transgenic mouse model of HBV infection that shows liver damage after the introduction of virus-specific CD8 cells supports this theory.[48] Interferon [IFN] the major antiviral cytokine secreted by CD8+ T cells, prevents HBV multiplication non- cytopathologically by killing infected cells.[49]

When T-Cell Receptors (TCRs) are ligated with peptide-MHC I complexes during HBV infection, Programmed cell death 1(PD-1), which is inducibly produced on CD8+ T cells and exists as a monomeric surface glycoprotein, can be recruited to the TCR signalosome.[50] PD-1 expression on HBV-specific T lymphocytes is elevated in chronic HBV infection. Blocking the PD-1 pathway may be able to effectively reverse T cell depletion and enhance control over viral infection by boosting T cell multiplication, the ability of CD8+ T cells to destroy viruses and the production of cytokines.[51–53] Cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) is an immune suppressor factor that send signals that are counterproductive and reduces the activation of T cells during HBV infection.[54] By altering immunological checkpoint molecules, blocking CTLA-4 pathways is an intriguing potential tactic to revive virus-specific T cell responses. These policies treat chronic viral hepatitis and hepatocellular carcinoma (HCC)-related T cell fatigue.[55]

During acute HBV infection, CD8+viral clearance and disease pathogenesis are mediated by both non-cytolytic and cytolytic effector activities of the CD8+ cells.[56] The widespread consensus is that cytotoxic T lymphocyte (CTL) mediate viral clearance by destroying infected cells. By secreting antiviral cytokines that disrupt the HBV life cycle, CTL can non-cytopathologically suppress HBV gene expression and replication in the liver of transgenic mice. The primary method of viral clearance during HBV infection may be CTL-induced intracellular inactivation of HBV because it is far more effective than killing.[57] IFN- and TNF, two cytokines produced by CD8+ T cells, are in charge of inactivating HBV in the target cells. IFN- and TNF-blockade reversed the non-cytolytic repression of HBV, demonstrating that these two cytokines are involved in the non-cytolytic regulation of HBV infection (Figure 2).[58]

The Role of T-Helper Cell in HBV Infection

Both acute and chronic hepatitis B has been used to study the T cell reactions to various HBV antigens. In individuals with acute self-limited hepatitis B, all studies have consistently observed increased T helper (Th) cell responses directed against HBcAg, which occurred concurrently with viral clearance. The HBcAg-specific Th cell responses were much reduced, and in many individuals undetectable, in chronic HBV carriers. The idea that the Th cell response to nucleocapsid antigens may affect how HBV infection develops is supported by the difference in HBcAg-specific Th

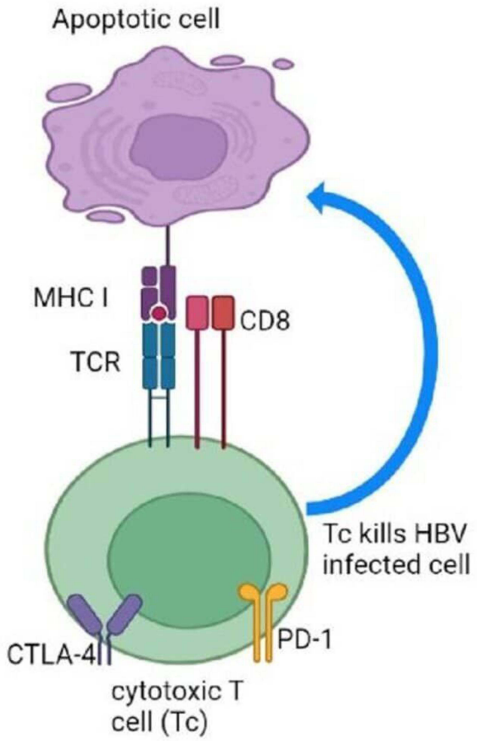

Figure 2 The role of cytotoxic T-cell in hepatitis B virus infection.

cell activity between acute and chronic HBV infection.[59] Both acute and chronic HBV infections may be impacted by the balance of TH1 and TH2 cells that are specific for the HBc/HBeAgs.[60] One of the most significant subsets of effector T cells in lymphoid tissues is the group of T cells known as T follicular helper cells (TFH cells), which support B cells. Interleukin (IL)-21, a "helper" cytokine produced by TFH cells, encourages B cells to develop into antibody-forming cells through the IL-21 receptor. A distinct subpopulation of T helper cells called TFH cells controls humoural immune reactions.[61]

The Role of Circulating CD4+CD25+ Regulatory T Cells in HBV Infection

Patients with persistent hepatitis B infection have higher rates of circulating CD4+ CD25+ Tregs, which may have a significant impact on viral persistence by modifying virus-specific immune responses.[62] Study shows that circulating CD4+CD25+ Treg frequency in acute hepatitis B patients was initially low and increased over time. CD4+CD25+ Treg actively contribute to the modulation of immune effectors in response to HBV infection as well as the prognosis of the disease in hepatitis B patients.[63] The frequency of peripheral regulatory T cells is linked with the chronic condition of hepatitis B. These CD4+CD25+ regulatory T cells concentrate in the liver. After recognizing viral antigens during HBV, CD4+CD25+ regulatory T cells may undergo modulation in the periphery. The activation of CD8+ T lymphocytes specific for HBV can be effectively suppressed by circulating CD4+ CD25+ Treg cells. When the CD4+ CD25+ cell population is depleted, patients with persistent HBV infection experience modest increases in HBV-specific CD8 responses.[64,65]

Conclusion

In conclusion, studies on the antigen recognition and immune response to hepatitis B virus infection have very much examined the innate and adaptive immune responses in individuals with both acute and chronic HBV infections. We now have a better understanding of the immunological variances between transitory and ongoing HBV infection because to these studies. The immunological interaction between the virus and host that affects the course of HBV infection has

been described in this review. The host immune response is in charge of both the establishment of HBV infection (due to continuous hepatocyte inflammation) and the removal of the virus in HBV-infected individuals.

Disclosure

The author declares no conflicts of interest in this work.

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