

Emerging Role of Interleukin 22 in Hepatitis B Virus Infection: a Double-edged Sword

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Abstract

Hepatitis B virus (HBV) infection remains a worldwide health problem, and is the major cause of hepatitis, liver cirrhosis, and hepatocellular carcinoma. The innate and adaptive immune responses of the HBV-infected host contribute greatly to the development and pathogenesis of chronic HBV infection, and often affect the efficacy of anti-HBV drugs. Interleukin (IL)-22 is a newly identified cytokine that is involved in the pathogenesis of liver disease, but its role in liver inflammation in patients with HBV infection remains controversial. In this report, we summarize the production and function of IL-22 in inflammatory environments, and review the current research into IL-22 biology in HBV infection. A better understanding of the intrahepatic micro-environments that directly influence the activity of IL-22 will be important for the development of new immunotherapeutic approaches that target IL-22-producing cells or IL-22 itself. © 2013 The Second Affiliated Hospital of Chongqing Medical University. Published by XIA & HE Publishing Ltd. All rights reserved.

Introduction

Hepatitis B virus (HBV) infection remains a worldwide health problem, and is the major cause of hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC).¹ Approximately 2 billion people are infected with HBV, and more than 360 million have chronic HBV infection.² It is commonly believed that the outcome of HBV infection depends on the balance between the host and virus.² The innate and adaptive immune responses of the HBV-infected host contribute to the

development and pathogenesis of chronic HBV infection, and often affect the efficacy of anti-HBV drugs.²⁻⁵ Innate immunity is responsible for recognition of viral nucleic acids, viral proteins, and host tissue damage.⁶ It induces an antiviral state against infected cells by producing type I interferons (IFNs), decreases the pool of infected cells by directing natural killer (NK) cell-mediated killing of virally infected cells, and supports the efficient maturation and site recruitment of adaptive immunity through production of proinflammatory cytokines and chemokines.⁶ These mechanisms decrease the spread of the virus until the adaptive immunity takes over. Adaptive immunity acts through functional maturation and expansion of distinct B and T cell clones that are able to specifically recognize the infectious agents, a process that requires time,⁷ but eventually leads to the control of HBV infection, and generates a memory response that increases the host's ability to block subsequent infections by the same pathogens.⁸

Many studies have shown that the numbers of regulatory T cells, Thelper (Th)17 cells, and Th22 cells are higher in patients with chronic hepatitis than in healthy subjects.⁹⁻¹² T-cell populations able to produce interleukin (IL)-17 and IL-22 are often enriched in the intrahepatic environment, and can carry CD161 and CXCR-6 receptors, a phenotypic profile that is enriched in tissue-homing T cells.^{13,14} These correlations do not, however, clarify the role of such cells in the pathogenesis of HBV infection. Th17 cells (a cell population that can play an important role in the pathogenesis of autoimmunity and other inflammatory diseases) are detectable at higher frequencies in patients with chronic HBV infection and severe liver damage.^{15,16} Th17-producing cells can secrete IL-22, a cytokine that has a prominent hepatoprotective role, although studies have shown that IL-22 also has a major proinflammatory role in HBV-transgenic mice.^{11,17,18}

Although the function of IL-22 in mouse hepatitis models has been extensively explored, there are only a few studies on IL-22 in human patients with viral hepatitis. It has been demonstrated that IL-22 can induce acute-phase reactants and chemokines, favor antimicrobial defense processes, promote hepatocyte survival and proliferation, and protect tissues from damage.¹¹ However, considering all of the findings in the current literature, the role of IL-22 in liver inflammation in patients with HBV remains controversial.^{9,10,19} It is possible that IL-22 could have a dual function, with protective or proinflammatory activity depending on the microenvironment. In this article, we summarize the state of

Keywords: Hepatitis B; Interleukin-22; Immune response; Interleukin-17.

Abbreviations: AHR, aryl hydrocarbon receptor; ALT, alanine aminotransferase; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IFN α interferons; IL, interleukin; ILC, innate lymphoid cell; LTI, lymphoid tissue inducer; NK, natural killer; ROR γ t, retinoic acid-related orphan receptor γ t; sIL-22R1, sequence similarity with an extracellular region of IL-22R1; TGF- β , transforming growth factor- β ; Th, Thelper; TNF- α , tumor necrosis factor α .

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knowledge on the production and function of IL-22 in inflammatory environments, and review the current advances in understanding the role of IL-22 biology in HBV infection.

IL-22 and IL-22 signaling pathway

IL-22 can contribute to immune disease through the stimulation of inflammatory responses, S100s, and defensins.^{20,21} IL-22 also promotes hepatocyte survival in the liver and epithelial cells in the lung and gut, similar to IL-10.^{22,23} In some contexts, the proinflammatory versus tissue-protective functions of IL-22 are regulated by the often co-expressed cytokine IL-17A.⁹ IL-22 belongs to the class II α -helical cytokines of the IL-10 family, which contains nine immunomodulatory proteins (IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28A, IL-28B and IL-29), and mediates cellular inflammatory responses.^{17,24} In cell signaling, IL-22 shares the receptor IL-10R2 with other members of this family, namely, IL-10, IL-26, IL-28A/B and IL-29.^{17,24} IL-22 initiates biological activity by binding to a cell-surface complex composed of IL-22R1 and IL-10R2 receptor chains, whose activity is regulated by interactions with a soluble binding protein, IL-22BP, and which share sequence similarity with an extracellular region of IL-22R1 (soluble (s)IL-22R1).^{20,21} IL-22 and IL-10 receptor chains play a role in cellular targeting and signal transduction to selectively initiate and regulate immune responses.

IL-22R is mainly expressed in epithelial cells, thus providing signaling specificity to tissues. The best-characterized IL-22 target cells include keratinocytes, hepatocytes, and colonic epithelial cells.⁹ Binding of the cytokine to this receptor leads to activation of Stat3 signaling cascades, as well as Akt and mitogen-activated protein kinase pathways.^{25,26} This, in turn, results in induction of various tissue-specific genes, including serum amyloid A, antimicrobial proteins (β -defensin, Reg3 γ , lipocalin-2), and mucins.^{25,26} IL-22 also induces proliferative and anti-apoptotic pathways in responsive cells, promoting tissue preservation.²⁰

Production of IL-22

Both innate and adaptive immune responses can contribute to the production of IL-22.²⁷ IL-22 is expressed by CD4⁺ T cells, of which several subsets are particularly important.²⁸ Th17 cells abundantly express IL-22, in addition to IL-17A, IL-17F, IL-26, and chemokine ligand, whereas Th22 cells express IL-22 but not IL-17(A/F).²⁸ Similarly, a subset of $\gamma\delta$ T cells expresses both IL-17A and IL-22 immediately upon IL-23 stimulation.^{29–31} In addition to T cells, several innate lymphoid cells (ILCs) are important sources of IL-17A and/or IL-22.³² These include a subset of NK cells that have high

expression of IL-22, and populations of lymphoid tissue-inducer cells that express the Th17 transcription factor retinoic acid-related orphan receptor (ROR) γ t.³² Although ILCs are best characterized for their roles in lymphoid organ formation and intestinal immunity, they have also been found in inflamed liver tissue.³³ Given the multiple cell types that express IL-22, it is likely that the specific *in vivo* cellular source of IL-22 in a specific inflammatory process varies depending on the specific tissue and disease state in which it is expressed (Table 1).

Th17 cells

Th17 has been found to have its highest expression in Th17 cells. IL-22 expression differs from that of IL-17A and other Th17-associated cytokines. The ideal *in vitro* culture conditions for generating IL-17A-expressing cells, mainly the presence of transforming growth factor- β (TGF)- β and IL-6, does not lead to optimal IL-22 expression because TGF- β is inhibitory to IL-22 expression.³⁴ It has been shown that IL-17A production is able to occur independently of TGF- β signaling by differentiating naive T cells in the presence of IL-6, IL-23 and IL-1 β , and this cytokine milieu also leads to IL-22 expression.^{35,36} Furthermore, *in vivo* IL-22 expression during infection has been found to be dependent on IL-23, but IL-17A expression is less so.³⁴

IL-17A is strongly dependent on the nuclear hormone receptor transcription factors ROR γ t and ROR α for its expression, whereas IL-22 was found to be less dependent on these.³⁶ By contrast, IL-22 expression requires the ligand-dependent transcription factor aryl hydrocarbon receptor (AHR).³⁷ Ligands include environmental toxins, such as halogenated aromatic hydrocarbons, and endogenous natural ligands, such as the breakdown products of aromatic amino acids.³⁸ In addition to these, AHR ligands in cell culture and animal model increase IL-22 expression during an immune response.³⁷ Furthermore, Notch signaling induces production of endogenous AHR ligands, leading to greater IL-22 expression.^{39,40}

Th22 cells

In humans, a subset of CD4 T cells that specifically expresses IL-22, and is mainly found in tissues, has been identified as 'Th22' cells.⁴¹ These cells express the chemokine receptor CCR6, and the skin-homing receptors CCR4 and CCR10, allowing for localization to the skin.^{42, 43} They do not express IFN- γ or IL-17A, or the Th1-associated and Th17-associated transcription factors T-bet and ROR γ t.⁴³ As has been described for murine Th17 cells, AHR is an important transcription factor for the expression of IL-22, but not IL-17A in humans.²⁶

Table 1. IL-22-producing cells and transcription factors

Cell subset	Stimulating cytokines	Transcription factor
Th17 cells	IL-6	AHR
Th22 cells	IL-6 and TNF α	AHR
$\gamma\delta$ T cells	IL-23	AHR
NK cells	IL-12 and IL-18 or IL-23	ROR γ t
ROR γ t-positive ILCs	IL-23	ROR γ t

Inflammatory cytokines, namely IL-6 and tumor necrosis factor (TNF)- α , promote priming of Th22 cells, and addition of active vitamin D (in sun-exposed skin) has been found to enhance IL-22 expression.⁴⁴ Langerhans cells, specialized professional antigen-presenting cells found in the epidermis, were found to be able to induce Th22 cells, as were plasmacytoid dendritic cells.⁴⁴ Th22 cells appear to be important for skin homeostasis and in inflammation, as the Th22 cell population was found to increase in patients with psoriasis.⁴⁵

$\gamma\delta$ T cells

The $\gamma\delta$ T cell subset comprises innate T cells that have rapid and immediate effector functions upon recognition of unknown ligands.⁴⁶ Unlike conventional CD4 T cells, these cells constitutively express IL-23R, and therefore immediately respond to IL-23 stimulation by expressing both IL-17A and IL-22.⁴⁶ As with Th17 and Th22 cells, AHR is an important transcription factor for the expression of IL-22, but not IL-17A in these cells. IL-22-expressing $\gamma\delta$ T cells are particularly important in pulmonary immune responses.⁴⁷

NK cells

NK cells are innate lymphocytes that lack somatically rearranged cell-surface antigen-specific molecules, and develop independently of the transcription factor ROR γ t.³³ Upon activation, conventional NK cells rapidly express IFN- γ , perforin, and granzymes, which play an important role in the control of viruses, intracellular bacteria, and tumors.³³ These cells can be activated by a synergy between two cytokines, IL-12 and IL-18, presumably secreted by macrophages activated by antigen/innate sensor encounter.⁴⁸ This activation by IL-12 and IL-18 can also induce NK cells to secrete IL-22. Additionally, stimulation with the cytokine IL-23 has been found to lead to induction of IL-22, but not IFN- γ , in NK cells. These NK1.1-positive IL-22-expressing cells contribute to IL-22 expression in inflammatory bowel disease, as well as in influenza.⁴⁹ Other studies have named IL-22-secreting NK cells as NK22 cells. However, as it currently stands, these cells are now better characterized as lymphoid tissue inducer (LTi)-like IL-22-expressing cells, which are discussed further in the following section.⁴⁹

ROR γ t-positive Innate lymphoid cells (ILCs)

LTi cells were originally discovered in the fetal tissue of mice.²⁴ These cells express lymphotoxin- α 1 β 2 and other factors that are important for the stromal reorganization and lymphocyte recruitment required for lymph node development.²⁴ More recent work has shown that LTi cell development is dependent on the transcription factor ROR γ t, and is also needed for the formation of Peyer's patches in the small intestine.⁵⁰ LTi-like cells also express IL-22 and share expression of NK-cell and LTi markers, and they express the NK cell-surface marker Nkp46 and the LTi cell transcription factor ROR γ t.⁵⁰ There are strong lineage relationships between NK cells and LTi-like cells.⁵¹ Both NK cells and LTi-like cells are dependent on the expression of the transcription factors ID2 (inhibitor of DNA binding) and TOX (Thymus High Mobility Group Box) for their development.⁵¹ However, these cells are dependent on different downstream transcription factors: NK cells are dependent on E4bp4/Nfil3, whereas

LTi-like cells are dependent on ROR γ t.⁵¹ Additionally, NK cells require IL-15 for their development, while IL-7 is important, but not essential, for LTi-like cells.⁵² An elegant study described a lineage relationship analysis of ROR γ t-expressing innate lymphocytes.⁵² These cells arise from distinct fetal liver ROR γ t precursors. The data suggested that LTi cells are required for lymph node development in the fetus, and that after birth, these cells undergo a programmed population change to what has been termed LTi-like cells, which migrate to the gastrointestinal tract to sustain intestinal homeostasis.^{53,54}

LTi-like cells are CD3-negative and express CD127 (a component of the IL-7 receptor) and IL-23R, and in mice the cells are also CD4-positive. Unlike other cell subsets that express IL-22 only upon activation, LTi-like cells express low constitutive levels of IL-22, which increase greatly upon activation by IL-23 stimulation.⁵⁴ LTi-like cells also express IL-17A, but not IFN- γ , perforin, or granzyme.⁵² In addition to being localized to the small intestine, LTi-like cells have also been found in lymphoid tissues such as the spleen.³³

Protective and pathological activity of IL-22 in liver diseases

In addition to its antimicrobial role, IL-22 is also involved in the regulation of genes responsible for cell proliferation, survival, and tissue repair, which is consistent with the protective activity of IL-22 reported in the gut.³⁴ It has also been shown that during activation of proinflammatory gene transcription, IL-22 signaling in intestinal epithelial cells is essential for wound healing and maintenance of the intestinal barrier through the induction of cell migration.³⁴ IL-22 was found to be protective in both innate and T-cell-driven colitis animal models, suggesting that IL-22 secretion by both CD4-positive T cells and NK cells in the colon can mediate protection.²⁷

However, in contrast to its antimicrobial and tissue-protective properties, IL-22 can play a proinflammatory role in some disease processes. In mice, intraperitoneal delivery of IL-22 protein, or infection with a recombinant adenovirus expressing IL-22, induced a wide range of proteins in the acute-phase response, including fibrinogen, CXCL1, and serum amyloid A, as well as changes in platelet, neutrophil, and red blood cell counts, in body weight, and in renal proximal tubule metabolism.⁵⁵ IL-22 may also exert a proinflammatory and pathological role in autoimmune disease. IL-22 was observed to be expressed by CD45RO-positive CD4 T cells in the brains of individuals with multiple sclerosis, and mediated disruption of tight junctions, leading to permeabilization of the blood-brain barrier.⁵⁶

Considering the obvious paradoxical dual nature of IL-22 in modulating tissue immune responses, the effects that it exerts are likely to be dependent on the specific microenvironment in which the cytokine is expressed. For instance, IL-17A has been shown to regulate the pathogenic and protective functions of IL-22 in airway inflammation.⁵⁷ Co-expressed with IL-17A, IL-22 acts synergistically to promote chemokine expression, neutrophil recruitment, and airway inflammation. However, in the absence of IL-17A coexpression, IL-22 strengthens the integrity of the lung epithelial barrier, thereby functioning in a tissue-protective manner.⁵⁸ Taken together, these studies suggest that the inflammatory microenvironment within tissues plays a critical role in the function of IL-22.

Protective activity of IL-22

Most of the existing studies have demonstrated the protective activity of IL-22 in the prevention of liver damage, although dual protective and pathogenic activities for this cytokine in this organ have been reported.⁵⁹ IL-22 has been shown to promote hepatocyte growth and cell migration, and intrahepatic expression of IL-22 provides protection against liver damage in various animal models. IL-22 expression was significantly elevated in the liver from T cell-dependent hepatitis models.⁵⁹ By contrast, IL-22 blockade has been reported to decrease STAT3 (Signal Transducer and Activator of Transcription 3) activation and lead to increased liver injury mediated by concanavalin A. Recombinant IL-22 protein injection resulted in a reduction of liver damage in this model.⁵⁹ Further studies demonstrated that IL-22-deficient mice are also highly sensitive to liver injury mediated by ConA.⁶⁰ Adoptive transfer of IL-22-expressing Th17 cells into IL-22^{-/-} mice decreased serum alanine aminotransferase (ALT) and aspartate aminotransferase levels after ConA injection, suggesting that IL-22 provides protection against liver damage.⁶⁰ Recent work demonstrated that liver-specific IL-22 transgenic mice were resistant to ConA-induced hepatitis.⁶¹ Overexpression of IL-22 in these mice also accelerated liver regeneration after partial hepatectomy, with minimal effects on liver inflammation.⁶¹ IL-22 transgenic mice were more susceptible to diethylnitrosamine-induced liver cancer. Microarray analyses revealed that a variety of antioxidant, mitogenic, acute-phase genes were upregulated in the livers of IL-22 transgenic mice compared with those from wild-type mice.⁶¹

IL-22 treatment ameliorated alcoholic fatty liver, liver damage, and hepatic oxidative stress in a mouse model of alcohol-induced liver injury, and deletion of STAT3 from hepatocytes eliminated the hepatoprotection stimulated by IL-22 in this model.⁶² These findings support the role of IL-22 as a hepatocellular survival factor against toxin-induced liver injury, because of its ability to induce anti-apoptotic and mitogenic protein expression through STAT3 activation. Recent studies in patients with chronic HBV infection demonstrated that IL-22-positive cells co-localize with liver progenitor cells.¹¹ In patients with chronic HBV infection, IL-22 expressed by CD3-positive T cells promoted liver progenitor cell proliferation, which was also dependent on STAT3 activation.¹¹

Pathogenic activity of IL-22

A transgenic mouse model of HBV replication demonstrated that IL-22 neutralization ameliorated liver damage after transfer of HBV-specific T cells.¹⁸ Furthermore, IL-22 neutralization significantly reduced chemokine expression and subsequent recruitment of inflammatory cells into the liver.⁶³ Taken together, these studies suggested that, in certain contexts, IL-22 may directly or indirectly contribute to the pathogenesis of liver disease by promoting the migration of inflammatory cells into the liver, which can increase T-cell-induced hepatocyte injury. Although the potential proinflammatory activity of IL-22 in the liver may seem contrary to its well-established protective activity, one function is not necessarily mutually exclusive of the other. In fact, differences between the model systems used to study the role of IL-22 in the liver may provide important clues to the physiological roles of this cytokine in different disease states.

For example, unlike chemical-induced liver injury, the liver inflammation and subsequent elevation of ALT levels seen in the HBV-transgenic mouse T-cell adoptive transfer model are potentiated by recruitment of inflammatory cells into the liver.⁶³

Another potentially adverse effect of IL-22 expression relates to its ability to promote growth of liver tumor cells, which has been observed both *in vitro* and *in vivo*.^{59,61} Tumor-infiltrating lymphocytes from patients with HCC displayed elevated IL-22 expression, and these IL-22-positive lymphocytes promoted HCC tumor growth and metastasis in a mouse model.⁶⁴ However, other studies demonstrated that IL-22 overexpression alone in transgenic mice is not sufficient for the development of HCC, although these same mice are more susceptible to diethylnitrosamine-induced liver cancer.⁶⁴ Consistent with these findings, diethylnitrosamine-treated IL-22-deficient mice had decreased tumorigenesis.⁶⁴ These results indicate that the proliferative and anti-apoptotic activities of IL-22 may accelerate the growth of existing HCCs.

Dual function of IL-22 in hepatitis B virus infection

Increased IL-22 expression has been reported in the livers of patients with chronic HBV and hepatitis C virus infections.^{61,65} Furthermore, patients with HBV infection also show increased percentages of Th17 cells in peripheral blood and liver, and increased concentrations of IL-22 in serum.¹⁵ However, consistent with the fact that IL-22 does not induce expression of traditional IFN-stimulated antiviral proteins, such as MxA and 2'5'-OAS in hepatocytes, IL-22 had only a minor direct antiviral effect on HBV replication in cell culture or in a transgenic mice model.⁶⁶

Considering the difficulties in ascribing mechanistic functions from correlative data in humans, it is unclear whether IL-22 upregulation is anti-inflammatory or proinflammatory in HBV infection. For example, although IL-22 expression in the liver is positively correlated with serum ALT levels, this may be indicative of a compensatory mechanism that, rather than causing damage, is preventing further injury.⁶¹ Based on findings supporting both protective and proinflammatory roles for IL-22 in other tissues, it is tempting to speculate that the function of IL-22 may be dependent on the liver-specific microenvironment. For instance, IL-22 may play a proinflammatory role during acute HBV infection, perhaps to amplify immune cell infiltration and virus clearance, whereas it may play a more protective role during chronic HBV infection, compensating for long-term inflammatory damage by promoting hepatocellular proliferation and survival.¹¹ IL-22-producing ROR γ t-dependent innate lymphoid cells have been reported to play a novel protective role in murine acute hepatitis.⁶⁷ In ConA-induced liver injury, AHR has a crucial protective role via promoting IL-22 production from ILCs and suppressing IFN- γ expression from NK T cells.⁶⁸

However, even during chronic HBV infection, IL-22 may be mainly protective in some situations, yet pathogenic in others. Chronic HBV is a complex heterogeneous disease that progresses through different phases of immune tolerance (high HBV and low ALT), immune activity (high HBV and high ALT), and immune inactivity (low HBV and low ALT).⁶¹ In fact, IL-22 expression levels may correlate with either high or low ALT levels, suggesting that perhaps the balance between its dual protective and proinflammatory effects can change throughout chronic HBV infection.

Conclusions

Despite significant progress in research into IL-22, the mechanisms underlying HBV persistence and pathogenesis remain relatively poorly defined. There is still much that we do not understand about the role of IL-22 in HBV-infected liver. To more thoroughly characterize the intrahepatic features that influence IL-22 function in chronic HBV infection, it is necessary to study large human patient populations with well-defined clinical cohorts, and to use more physiological animal models of virus infection. A thorough characterization of intrahepatic IL-22-producing cells, including Th17 cells, Th22 cells, or ILCs, and their function in chronic HBV infection, is another critical area for future research. A better understanding of the intrahepatic microenvironments that influence the pathological versus protective effects of IL-22 will be significant for the development of new immunotherapeutic approaches that target IL-22-producing cells or IL-22 itself.

Conflict of interest

None.

Author contributions

Literature search and acquisition of relevant literature (WG, YCF), drafting the article (WG), critical revision of important intellectual content (YCF, JYZ, MHZ), final approval of the version to be published (WG, YCF, JYZ, MHZ).

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