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MINI-REVIEW

Protective and Pathological Properties of IL-22 in Liver Disease

Implications for Viral Hepatitis

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Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infection affect >500 million people worldwide and are significant causes of liver cirrhosis and hepatocellular carcinoma. The pathogenesis of HBV and HCV infection can vary widely with respect to the outcome of initial infection to self-resolving acute or chronic disease, the extent of viremia and liver inflammation during chronic infection, and the eventual development of liver cirrhosis and hepatocellular carcinoma. The host immune response is an important factor in the variable consequences of these infections, because the innate and adaptive intrahepatic antiviral responses are an intricate balance of immune effector cells and cytokines that control virus replication but can also cause liver damage. IL-22 is an important cytokine that plays a pleiotropic protective, but sometimes also pathological, role in several tissues/organs, including the liver. Therefore, IL-22 is likely to be an important factor in the pathogenesis and clinical outcome of HBV and HCV infection. However, the precise beneficial, and possible detrimental, effects of this cytokine may vary among different disease states that are associated with distinct inflammatory microenvironments. This review summarizes our understanding of the protective and pathological activities of IL-22, with an emphasis on the liver, and discusses the implications of these effects as they relate to viral hepatitis. *(Am J Pathol 2013, 182: 21–28; http://dx.doi.org/10.1016/j.ajpath.2012.08.043)*

IL-22 and IL-22 Receptor Expression

IL-22 is a class II α-helical cytokine of the IL-10 cytokine family, which is composed of nine immunomodulatory proteins (IL-10, IL-19, IL-20, IL-22, IL-24, IL-26, IL-28A, IL-28B, and IL-29). These nine family members are grouped together on the basis of similarities among their encoding genes, primary and secondary protein structures, and receptor complexes. Despite these similarities, the IL-10 family members have distinct functions, which are dictated, in part, by differences in expression of their respective receptors. The expression of the IL-22 receptor complex (IL-22 receptor α subunit paired with IL-10 receptor β subunit) is restricted to specific tissues, including hepatocytes and epithelial cells of the gastrointestinal tract, skin, and lungs.[1–3] Because the IL-22 receptor is not expressed on immune cells, IL-22 has no direct effects on immune cell function, but appears to instead play an important role in regulating the consequences of inflammation in IL-22–sensitive tissues. The effects of IL-22 have been best characterized in keratinocytes, hepatocytes, and colonic epithelial cells, where the cytokine primarily signals through the STAT3 pathway.[4]

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Downstream IL-22 signaling in these tissues leads to the expression of acute inflammatory proteins,[5,6] activation of proliferative and anti-apoptotic programs,[7,8] and induction of antimicrobial genes and cytokines/chemokines.[9,10]

Among the IL-10 family cytokines, IL-22, in particular, shares several structural and other similarities with the type III interferons [IL-29, IL-28A, and IL-28B, alias interferon (IFN)-λ1, IFN-λ2, and IFN-λ3, respectively]. The crystal structure of IFN-λ3 revealed that it has a higher level of structural similarity to IL-22 than to the type I interferons.[11] Furthermore, similar to IL-22, IFN-λ signals through a heterodimeric receptor complex consisting of both a unique subunit (IL-28 receptor α) and the IL-10 receptor β subunit, which it shares with IL-10, IL-22, and IL-26. Similar to the IL-22 receptor α subunit, IL-28 receptor α has a restricted expression profile, and is strongly expressed on intestinal epithelial cells and hepatocytes.[12,13] These unique receptor subunits are encoded in adjacent loci on chromosome 1p36.11. Both cytokines play a role in defense against infection at epithelial barriers, suggesting that the two may have evolved as part of an innate system to provide protection in tissues that are highly susceptible to infection.[11] Nevertheless, these functions appear to be distinct, because IFN-λ and IL-22 induce different patterns of gene expression. For example, in hepatocytes, IFN-λ activates STAT1 and induces a transcriptional response more similar to IFN-α/β and IFN-γ, whereas IL-22 activates STAT3 and induces a gene expression program more similar to the acute-phase response elicited by IL-6.[14]

Both innate and adaptive immune responses can contribute to the production of IL-22. IL-22 is expressed by $CD4^+$ T cells, of which several subsets are particularly important. T helper (Th)17 cells abundantly express IL-22, in addition to IL-17A, IL-17F, IL-26, and chemokine ligand 20, whereas Th22 cells express IL-22 but not IL-17 (A/F).[15–19] Similarly, a subset of γδ T cells expresses both IL-17A and IL-22 immediately on IL-23 stimulation.[20] In addition to T cells, several innate lymphoid cells (ILCs) are important sources of IL-17A and/or IL-22.[21] These include a subset of natural killer cells that highly express IL-22 and populations of lymphoid tissue–inducer cells that express the Th17 transcription factor RORγt.[21–23] Although ILCs are best characterized for their roles in lymphoid organ formation and intestinal immunity, they have also been found in inflamed liver tissue.[24] 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.

IL-22 in Extrahepatic Immune Responses

A number of studies have described various situations in which IL-22 production is elevated, primarily during inflammation or infection. Interestingly, these studies indicate that IL-22 may play dual roles, protective or pathogenic, depending on the context in which it is expressed (Table 1). More important, at many epithelial barrier surfaces, IL-22 expression is protective against infection and inflammation. This is likely due, in part, to IL-22–dependent induction of antimicrobial proteins, including β-defensin, psoriasin, mucin, regenerating islet-derived protein III, and calgranulins A and B at these barrier surfaces.[1,10,26–28] For example, IL-22 restricts replication and dissemination of the bacteria *Klebsiella pneumoniae* and *Citrobacter rodentium* in the lung and intestine, respectively. Infection with either pathogen in IL-22–deficient mice leads to rapid mortality, demonstrating that an innate IL-22–induced response is essential for protective immunity during these infections.[25,26] Furthermore, the importance of IL-22–induced protective immunity is supported by evidence demonstrating higher mucosal infection rates in patient populations with deregulated IL-22 function. Job's syndrome is characterized by a hypomorphic mutation in the *STAT3* gene and lower IL-22 production, and these patients experience severe and recurrent secondary infections in the lung, skin, and intestine.[31] Similarly, patients with autoimmune polyendocrine syndrome 1 have high levels of autoantibodies against IL-17A, IL-17F, and IL-22, which correlates with chronic mucocutaneous candidiasis.[31,32] In fact, additional studies demonstrated that protective immunity to candidiasis involves an early, IL-22–dominated response, which controls initial fungal growth and tissue homeostasis during infection.[33]

Table 1 Examples of IL-22 Protective and Pathogenic Actions

Activity by disease or model	Tissue or cell	Reference
Protective Actions		
Extrahepatic		
K. pneumoniae	Lung	25
C. rodentium	Intestine	26
Colitis	Intestine	27–29
Airway inflammation	Lung	30
Candidiasis	GI tract	31–33
SIV	GI tract	34
Intrahepatic		
ConA hepatitis	Hepatocytes	7, 8, 35, 36
CCL_4 or FasL	Hepatocytes	7
Alcohol	Hepatocytes	37
HBV	LPCs	38
Fibrosis	HSC	39–41
Pathogenic Actions		
Extrahepatic		
T. gondii	Intestine	42
Psoriasis	Skin	43
Autoimmune	CNS and synovium	44–46
Airway inflammation	Lung	30
Intrahepatic		
HBV	Hepatocytes	47
HCC	Tumor	8, 36, 48

CCL, chemokine ligand; CNS, central nervous system; GI, gastrointestinal; HSC, hepatic stellate cell; LPC, liver progenitor cell; SIV, simian immunodeficiency virus.

In addition to its antimicrobial properties, IL-22 can also regulate genes responsible for cell proliferation, survival, and tissue repair, consistent with its protective roles in certain contexts, especially the gut. Along with activating proinflammatory gene transcription, IL-22 signaling in intestinal epithelial cells also induces the migration of these cells, which is important for wound healing and maintenance of the intestinal barrier.[49] Further supporting the role of IL-22 in cell proliferation and tissue repair, delays in mucosal wound healing were observed in colonic biopsy specimens obtained from IL-22−deficient mice compared with their wild-type counterparts, thus demonstrating that IL-22 promotes wound healing *in vivo*.[27] Also consistent with its tissue-protective properties, IL-22 is protective in both innate and T-cell−driven colitis animal models, suggesting that IL-22 secretion by both $CD4^+$ T cells and natural killer cells in the colon can mediate protection.[29] Loss of IL-22−producing mucosal lymphocyte populations from simian immunodeficiency virus−infected rhesus macaques is also associated with damage to the tight epithelial barrier of the gastrointestinal tract.[34] Furthermore, IL-22 gene delivery rapidly reduces local intestinal inflammation in a mouse model of ulcerative colitis, and IL-22−mediated tissue repair was achieved by enhancing mucus production through STAT3-dependent expression of the mucus-associated molecules, mucins 1, 3, 10, and 13.[28] Finally, genetic evidence supports a role for IL-22 in inflammatory bowel disease, as a risk loci for ulcerative colitis has been identified in the 12q14 chromosome region encoding IFN-γ, IL-26, and IL-22,[50] and increased serum IL-22 levels in patients with Crohn's disease are associated with *IL23R* gene variants that are linked to an increased risk of developing this disease.[51]

However, in contrast to its antimicrobial and tissue-protective properties, IL-22 can play a proinflammatory role in some disease processes. Systemic administration of exogenous IL-22 alone is sufficient to promote inflammation. In mice, i.p. delivery of IL-22 protein or infection with a recombinant adenovirus that expresses IL-22 induces changes indicative of an acute-phase response, including the induction of fibrinogen, CXCL1, and serum amyloid A, along with changes in platelet, neutrophil, and red blood cell counts, body weight, and renal proximal tubule metabolism.[52] Highlighting the potential context-dependent nature of IL-22 function, some of these IL-22−mediated systemic inflammatory effects may be dependent on the amount of IL-22, because they were not observed in another study that administered a lower dose of adenovirus IL-22 expression vector to mice.[37] Unlike its protective role against infection with *K. pneumoniae* and *C. rodentium*, IL-22 plays a pathogenic role during oral infection with *Toxoplasma gondii*.[42] During *T. gondii* infection, mice treated with an anti-IL-22 antibody had significantly less intestinal pathological characteristics than their control antibody-treated counterparts, even though parasite burdens were similar between the two groups. Furthermore, local induction of IL-22 expression results in keratinocyte migration, epidermal hyperplasia, and dermal inflammation[43] and may, therefore, be a key mediator in the pathogenesis of psoriasis.

IL-22 may also play a proinflammatory, pathogenic role in some autoimmune diseases. IL-22 is expressed by $CD45RO^+$ CD4 T cells in the brain of individuals with multiple sclerosis, and can mediate disruption of tight junctions, leading to permeabilization of the blood-brain barrier.[44] This indicates that IL-22 may play a pathogenic role in this disorder, because it may potentiate the trafficking of peripheral autoreactive T cells into the central nervous system.[44] Furthermore, increases in IL-22 expression have also been correlated with the chronic inflammatory disease rheumatoid arthritis.[45] Synovial fibroblasts derived from patients with rheumatoid arthritis undergo increases in proliferation and production of the chemokine ligand 2 after treatment with IL-22, suggesting a proinflammatory role for the cytokine in this disease process. The pathogenic role of IL-22 during rheumatoid arthritis is further supported in a mouse model of arthritis in which IL-22 deficiency results in a less severe disease course and decreased mRNA expression of the inflammatory markers IL-1β, IL-6, tumor necrosis factor-α, matrix metalloproteinase-9, and IL-17A in the synovium.[46]

Given the seemingly paradoxical dual nature of IL-22 in modulating tissue immune responses, the effects that it exerts are likely dependent on the specific context in which the cytokine is expressed. For instance, it was recently shown that IL-17A regulates the pathogenic and protective functions of IL-22 in airway inflammation.[30] Coexpressed 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 strengthened the integrity of the lung epithelial barrier, thereby functioning in a tissue-protective manner. Furthermore, despite the induction of antimicrobial protein expression and protective effects of IL-22 during *K. pneumoniae* and *C. rodentium* infection, IL-22 is proinflammatory in the intestine after oral infection with *T. gondii*.[53] Taken together, these studies suggest that the inflammatory microenvironment within tissues plays a critical role in the function of IL-22.

Protective Actions of IL-22 in the Liver

At present, most studies support a clear protective role for IL-22 in the prevention of hepatocellular damage, although there is evidence indicating dual protective and pathogenic roles for the cytokine in this organ as well. IL-22 promotes hepatocyte growth and migration in cell culture,[8,54] and expression of IL-22 in the liver protects hepatocytes in a variety of tissue damage models. In mouse models of T-cell−dependent hepatitis [concanavalin A (ConA) injection, murine cytomegalovirus infection], IL-22 expression is significantly

induced in the liver.[8,54] On IL-22 blockade with neutralizing antibody, ConA-mediated liver injury increases while STAT3 activation decreases, and injection of recombinant IL-22 protein in this model reduces hepatocellular damage.[8] Additional studies demonstrated that IL-22−deficient mice are also highly sensitive to liver injury caused by ConA-mediated hepatitis.[35] Adoptive transfer of IL-22−expressing Th17 cells into IL-22$^{-/-}$ mice resulted in a reduction of serum alanine aminotransferase (ALT) and aspartate aminotransferase levels after ConA injection, indicating that IL-22 provides protection against liver damage in this model. Further supporting the protective role of IL-22, recent work demonstrated that liver-specific IL-22−transgenic mice are resistant to ConA-induced hepatitis.[36] The overexpression of IL-22 in these mice also accelerated liver regeneration after partial hepatectomy, while having minimal effects on liver inflammation.[36] In addition to providing protection against ConA-mediated hepatitis, hydrodynamic gene delivery of IL-22 to the liver protects against hepatocellular injury, necrosis, and apoptosis after carbon tetrachloride and Fas ligand−induced damage.[7] Finally, bile acid−induced apoptosis of steatotic hepatocytes is also accompanied by an increase in IL-22 mRNA expression, further implicating IL-22 in a liver-specific response to cellular damage.[55]

IL-22 treatment also ameliorates alcoholic fatty liver, liver damage, and hepatic oxidative stress in a mouse model of alcohol-induced liver injury, and deletion of STAT3 from hepatocytes eliminates the hepatoprotection provided by IL-22 in this model.[37] Because of its ability to induce anti-apoptotic and mitogenic protein expression through STAT3 activation, these findings support the role of IL-22 as a hepatocellular survival factor against toxin-induced liver injury. Further confirming the hepatoprotective role of IL-22, recent findings in patients with chronic hepatitis B virus (HBV) infection demonstrate that IL-22−expressing cells colocalize with liver progenitor cells. In patients with chronic HBV, IL-22 expressed from CD3$^+$ T cells promoted liver progenitor cell proliferation, which was again dependent on STAT3 activation.[38]

After liver injury, the activation of hepatic stellate cells and the accumulation of extracellular matrix proteins result in liver fibrosis. Several studies have examined the association between IL-22 and liver fibrosis in humans and mice.[39−41] Intrahepatic IL-22 expression negatively correlates with fibrosis stage in the liver of patients with chronic hepatitis B,[53] and administration of IL-22 decreases hepatic fibrosis in mice.[39,40] Hepatic stellate cells express high levels of the IL-22 receptor complex, and IL-22 induces senescence of these cells via activation of STAT3, SOCS3, and p53, thus reducing liver fibrosis.[39]

Pathogenic Activities of IL-22 in the Liver

By using a transgenic mouse model of HBV replication in the liver, we recently demonstrated that IL-22 neutralization ameliorates liver damage after transfer of HBV-specific T cells.[47] Furthermore, IL-22 neutralization significantly reduced chemokine expression and the subsequent recruitment of inflammatory cells into the liver. Taken together, these studies suggest that, in certain contexts, IL-22 may directly or indirectly contribute to liver disease pathogenesis by promoting the migration of inflammatory cells into the liver, which can increase T-cell−induced hepatocyte injury.[56]

Although this potential proinflammatory role of IL-22 in the liver may seem paradoxical to its well-established protective role, one function is not necessarily mutually exclusive of the other. In fact, distinctions between the model systems used to study the role of IL-22 in the liver may provide important clues to its physiological roles in different disease states. For example, unlike chemically induced liver injury, the liver inflammation and subsequent elevation of ALT levels in the HBV-transgenic mouse T-cell adoptive transfer model are potentiated by recruitment of inflammatory cells into the liver. This recruitment requires specific cellular and protein mediators, including neutrophils, chemokines, and matrix metalloproteinases,[56,57] all of which can be induced by IL-22.[9,52] IL-22 also increases the proinflammatory activity of tumor necrosis factor-α,[15] which is expressed in the liver after transfer of HBV-specific T cells. In total, these factors may all contribute to the proinflammatory effect of IL-22 in this particular model.

Another potentially deleterious effect of IL-22 expression relates to its ability to promote liver tumor cell growth, which has been observed both *in vitro*[8] and *in vivo*.[36,48] Tumor-infiltrating lymphocytes from patients with hepatocellular carcinoma (HCC) display elevated IL-22 expression, and these IL-22$^+$ lymphocytes promote HCC tumor growth and metastasis in mice.[48] Additional studies have demonstrated, however, 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.[36] Consistent with these findings, diethylnitrosamine-treated IL-22−deficient mice display reduced tumorigenesis.[48] These results indicate that the proliferative and anti-apoptotic activities of IL-22 may accelerate the growth of existing HCCs.[36]

Consequences for Viral Hepatitis

IL-22 expression is up-regulated in the liver of patients with chronic HBV and hepatitis C virus (HCV) infection.[36,41,54,58,59] Furthermore, patients with HBV infection display increased percentages of Th17 cells, a major producer of IL-22, in peripheral blood and liver, and increased concentrations of IL-22 in serum.[41,47,60] Similarly, Th17 cells are also found in the liver of patients with chronic HCV.[59,61] 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,[14,58] IL-22 has only minor direct antiviral effects on HBV[14] or HCV[58] replication in cell culture, or on HBV replication in transgenic mice.[47] Furthermore, IL-22 does not affect the antiviral activity of IFN-λ in hepatocytes, a cytokine with which it shares the IL-10 receptor β subunit.[14] Thus, the influences of IL-22 on HBV and HCV infection do not appear to include direct antiviral effects. Nevertheless, similar to other inflammatory conditions, such as Crohn's disease and ulcerative colitis, genetic evidence supports a role for IL-22 in HCV infection, because single-nucleotide polymorphisms in the IL-22 gene influence treatment response and viral clearance.[62]

Because of the difficulties in ascribing mechanistic functions from correlative data in humans, it is unclear whether IL-22 up-regulation is protective or proinflammatory in HBV and HCV infection. For example, although IL-22 expression in the liver is positively correlated with serum ALT levels,[36] this may be indicative of a compensatory mechanism that, rather than causing damage, is preventing further injury. Based on the number of 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 dictated by the specific microenvironment within the liver as well, with the net result being a reflection of the balance between these functions (Figure 1). For instance, IL-22 may play a proinflammatory role during acute HBV infection, perhaps to amplify immune cell infiltration and clearance of virus, whereas it may play a more protective role during chronic HBV infection, compensating for long-term inflammatory damage by promoting hepatocellular proliferation and survival.

However, even during chronic HBV infection, IL-22 may be mainly protective in some situations, yet pathogenic in others. Chronic hepatitis B 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). In fact, IL-22 expression levels may correlate with either high or low ALT levels,[36,41] suggesting that perhaps the balance between its dual protective and proinflammatory effects can be tipped throughout chronic HBV infection.

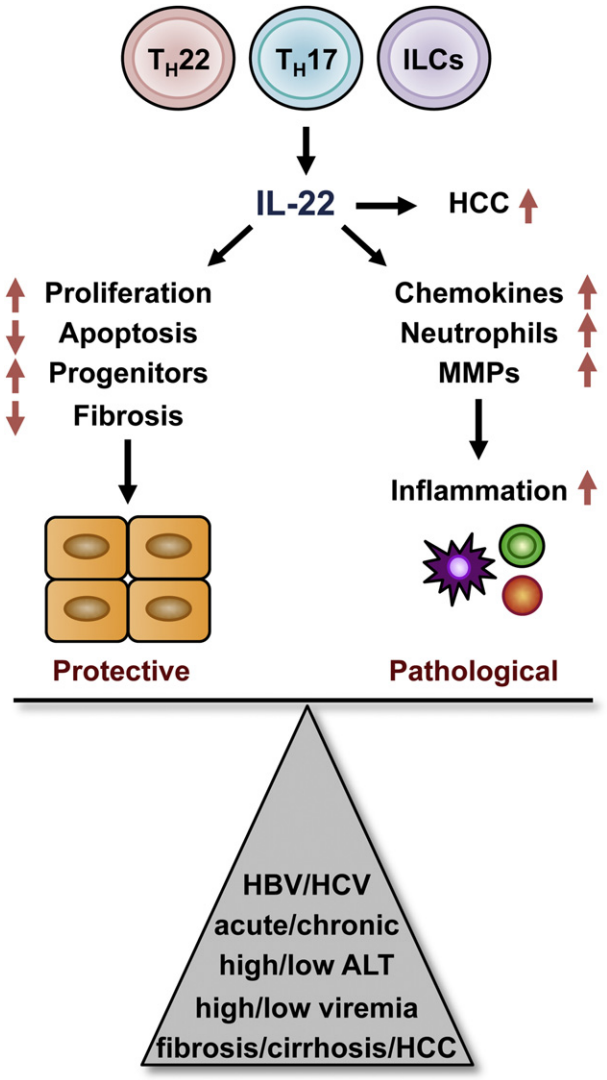

Figure 1 Protective versus pathological effects of IL-22 in viral hepatitis. IL-22, expressed by Th17 cells, Th22 cells, or liver-resident ILCs, can have dual protective and pathogenic hepatocellular effects. Although Th17 cells are found in the liver of patients with chronic HBV and HCV infection, the presence of intrahepatic Th22 cells and ILCs is not defined. IL-22 can increase hepatocyte proliferation, inhibit apoptosis, stimulate liver progenitor cells, and down-regulate fibrosis. Conversely, IL-22 may also up-regulate chemokine and matrix metalloproteinase expression, and promote neutrophil migration in the liver. IL-22 may also promote the development of HCC. The balance between these two seemingly paradoxical functions may be dependent on the tissue microenvironment present during different disease and inflammation states.

Summary and Perspectives

Despite significant progress, the mechanisms underlying HBV and HCV persistence and pathogenesis remain relatively poorly defined. A tremendous amount has been learned about IL-22 in the 12 years since its discovery, but the diverse and pleiotropic nature of its activity has made a precise determination of its function challenging, and there is still much that we do not understand about the role of this fascinating cytokine in viral hepatitis and other diseases. To more thoroughly characterize the intrahepatic determinants that influence IL-22 function in chronic HBV and HCV infection, it will be necessary to use large human patient populations with well-defined clinical disease characteristics and to employ more physiological animal models of virus infection, such as humanized mice. A thorough characterization of intrahepatic IL-22–producing cells, including Th17 cells, Th22 cells, or ILCs, and their role in chronic

HBV- and HCV-associated liver disease, 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 or IL-22−producing cells.

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