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Hepatoprotective and anti-inflammatory cytokines in alcoholic liver disease

Bin Gao
Laboratory of Liver Diseases, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Bethesda, MD 20892, USA

Abstract

The activation of innate immunity by various factors (e.g., lipopolysaccharide and complements) plays an important role in initiating and promoting alcoholic liver injury via the stimulation of Kupffer cells to induce oxidative stress and to produce pro-inflammatory cytokines (e.g., tumor necrosis factor [TNF]-α) that cause hepatocellular damage. Accumulating evidence suggests that the activation of innate immunity also stimulates Kupffer cells to produce the hepatoprotective cytokine interleukin-6 (IL-6) and the anti-inflammatory cytokine IL-10 during alcoholic liver injury. IL-6 protects against alcoholic liver injury via the activation of signal transducer and activator of transcription 3 (STAT3) and the subsequent induction of a variety of hepatoprotective genes in hepatocytes. IL-10 inhibits alcoholic liver inflammation via the activation of STAT3 in Kupffer cells/macrophages and the subsequent inhibition of liver inflammation. Recent studies have suggested that IL-10 may play a dual role in controlling ethanol-induced steatosis and liver injury via the inhibition of the pro-inflammatory cytokine TNF-α, thereby ameliorating alcoholic liver injury, or via the inhibition of the hepatoprotective cytokine IL-6, thereby potentiating alcoholic liver injury. IL-22 is another important hepatoprotective cytokine that protects against acute and chronic alcoholic liver injury by binding to a complex composed of IL-10R2 and IL-22R receptor chains on the surfaces of hepatocytes. Finally, IL-22 treatment is a potential therapeutic option for treating severe forms of alcoholic liver disease because of its antioxidant, antiapoptotic, antisteatotic, proliferative, and antimicrobial effects, as well as the potential added benefit of few side effects.

Keywords

IL-6; IL-10; IL-22; alcoholic liver disease

Introduction

Chronic alcohol consumption is a leading cause of chronic liver disease in developed countries and is becoming the leading cause of this disease in developing countries. [1, 2] The National Institute on Alcohol Abuse and Alcoholism recently released its latest surveillance report showing that 48% of the cirrhosis cases in the USA in 2007 were alcohol-related.[1] Early studies indicated that ethanol metabolism-associated oxidative stress, glutathione depletion, abnormal methionine metabolism, and malnutrition contribute to the pathogenesis of alcoholic liver disease (ALD).[3–6] The research findings from the last two decades have

Corresponding author: Bin Gao, M.D., Ph.D., Laboratory of Liver Diseases, NIAAA/NIH, 5625 Fishers Lane, Bethesda, MD 20892. Tel: 301-443-3998; bgao@mail.nih.gov.

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No conflicts of interest has been declared by the author.

suggested that the activation of innate immunity by various factors (e.g., lipopolysaccharide [LPS], complement, and tumor necrosis factor [TNF]-α) also plays an important role in initiating and promoting ALD.[7–10] It is believed that chronic alcohol consumption results in the activation of innate immunity followed by the production of pro-inflammatory cytokines, such as TNF-α, and the subsequent induction of hepatocellular damage. [7–10] In addition to the production of pro-inflammatory cytokines, the activation of innate immunity upregulates hepatoprotective cytokines (e.g., interleukin-6 [IL-6]) and anti-inflammatory cytokines (e.g., IL-10 and adiponectin) in ALD. [11, 12] Recent studies from our laboratory have suggested that both IL-6 and IL-10 play compensatory roles in protecting against alcoholic liver injury and inflammation, respectively; the results of these studies are summarized in this review. In addition, our recent research suggests that another hepatoprotective cytokine, IL-22, may have a therapeutic potential in treating severe forms of ALD.

Hepatoprotective (IL-6 and IL-22) and anti-inflammatory cytokine (IL-10): the activation of signal transducer and activator of transcription 3 (STAT3) in the liver

Although IL-6, IL-10, and IL-22 activate (via STAT3) similar signaling pathways in the liver, they target different types of liver cells (Fig. 1).[13] For example, IL-6R and its signal-transducing chain, gp130, are ubiquitously expressed on all types of liver cells, including hepatocytes, Kupffer cells, hepatic stellate cells, and sinusoidal endothelial cells, all of which respond to IL-6 stimulation. Upon binding to IL-6R on hepatocytes, IL-6 induces gp130 dimerization and the subsequent dimerization of gp130-associated Janus kinases (JAKs), which leads to JAK phosphorylation, followed by STAT3 activation. The activated STAT3 forms a dimer, translocates into the nucleus, and upregulates the expression of a variety of genes that play important roles in protecting against liver injury and promoting liver regeneration.[13] The activation of STAT3 by IL-6 in sinusoidal endothelial cells may also contribute to the hepatoprotective function of IL-6.[14, 15] In addition, IL-6 may regulate liver fibrosis and inflammation via the activation of STAT3 in hepatic stellate cells and Kupffer cells, respectively. However, the evidence for this role of IL-6 remains inconclusive. In addition, many other IL-6 family cytokines activate STAT3 in hepatocytes and likely play roles similar to those of IL-6 in protecting against hepatocellular damage and promoting liver regeneration.[13]

IL-22 exerts its functions via interactions with IL-10R2 and IL-22R on cell surface, the former of which is ubiquitously expressed on all types of liver cells, whereas the latter is expressed primarily on epithelial cells, such as hepatocytes.[16] Thus, IL-22 only targets hepatocytes that express both IL-10R2 and IL-22R, and plays important roles in hepatoprotection and liver regeneration.[17–20] The IL-10 homodimer signals through a receptor complex composed of two chains of IL-10R2 and two of IL-10R1. Because IL-10R1 is only expressed in immune cells, thus IL-10 only targets immune cells, including Kupffer cells, in the liver and acts as a key anti-inflammatory cytokine in controlling liver inflammation.

The interplay of the hepatoprotective (IL-6) and anti-inflammatory cytokine (IL-10) in controlling alcoholic liver injury

Serum and hepatic IL-6 levels are elevated in patients with ALD [21] and in animal models of alcoholic liver injury.[22] Although the serum levels of IL-6 positively correlate with the disease severity in ALD patients,[21] studies using animal models have suggested that IL-6 plays an important role in protecting against alcoholic liver injury. In a mouse model of

alcoholic liver injury, IL-6-deficient mice are more susceptible to ethanol-induced hepatic steatosis, apoptosis, and mitochondrial DNA damage than are wild-type animals.[23–25] *In vivo* treatment with IL-6 ameliorates ethanol-induced liver injury in mice,[26] and *ex vivo* treatment with IL-6 prevents fatty liver transplant failure in rats.[15] Here, I propose a model depicting the hepatoprotective role of IL-6 in alcoholic liver injury (Fig. 2).

In this model, chronic alcohol consumption results in an elevation of LPS levels in the liver via either the promotion of bacterial overgrowth [27] or an augmentation of gut permeability and the translocation of bacterial-derived LPS from the gut to the liver.[9] Elevated LPS stimulates Kupffer cells/macrophages to induce oxidative stress and to produce pro-inflammatory cytokines that cause hepatocellular damage. Chronic alcohol consumption also causes complement activation, followed by the induction of TNF-α and liver damage.[28, 29] However, LPS and complement activation also stimulate Kupffer cells to produce IL-6. The elevated IL-6 then stimulates STAT3 activation in hepatocytes and subsequently upregulates the expression of anti-apoptotic genes (e.g., *Bcl-2* and *BcI-xL*), anti-oxidative genes (e.g., *metallothioneins 1 and 2*), and mitochondrial DNA repair genes (e.g., *OGG-1 and Neil 1*)[23, 24] and downregulates the expression of lipogenic genes (e.g., *SREBP-1c*).[22] Thus, elevated IL-6 plays a key role in repairing ethanol-induced hepatocellular damage by ameliorating steatosis, preventing hepatocellular damage, and promoting liver regeneration. Consistent with these findings, the hepatocyte-specific deletion of STAT3, a key IL-6 downstream signal, has been shown to exacerbate ethanol-induced steatosis and liver injury.[22] At present, whether the activation of STAT3 is responsible for the IL-6-induced upregulation of the hepatoprotective genes discussed above remains obscure.

IL-10 is a well-documented anti-inflammatory cytokine, and as expected, IL-10-deficient mice exhibit increased liver inflammation after being fed ethanol or a high-fat diet.[30] However, surprisingly, IL-10-deficient mice have less steatosis and lower levels of serum ALT after being fed these diets compared with wild-type mice.[30] Moreover, IL-10-deficient mice display elevated hepatic and serum IL-6 levels and hepatic STAT3 activation after being fed ethanol or a high-fat diet. An additional deletion of IL-6 or hepatocyte STAT3 restores hepatic steatosis and the elevation of serum ALT in IL-10-deficient mice, suggesting that the elevation of inflammation-associated hepatic IL-6 and STAT3 activation contributes to the reduced steatosis and serum ALT in IL-10-deficient mice.[30] In addition, IL-10-deficient mice display increased liver regeneration after partial hepatectomy.[31] This increased regeneration is due, at least in part, to elevated hepatic IL-6 and STAT3 activation because the additional deletion of IL-6 or hepatic STAT3 reduces liver regeneration in IL-10-deficient mice.[31]

In summary, as shown in Fig. 2, IL-10 inhibits innate immunity activation (e.g., LPS and TNF-α),[11] thereby ameliorating steatosis and liver injury, and it inhibits hepatoprotective cytokines, such as IL-6,[30] thereby promoting steatosis and inhibiting liver regeneration. Thus, the overall effect of IL-10 on hepatic steatosis and liver injury is likely determined by the balance between pro-inflammatory cytokines that promote steatosis and liver injury and hepatoprotective cytokines that prevent steatosis and promote liver regeneration.

The therapeutic potential of the hepatoprotective cytokine IL-22 in treating severe forms of ALD

Although the hepatoprotective effect of IL-6 on alcoholic liver injury is well documented, [23–25] and *in vivo* IL-6 treatment ameliorates fatty liver in rodent models,[26] the therapeutic application of IL-6 in the treatment of patients with ALD is limited by the many potential side effects of IL-6, which likely result from the ubiquitous expression of IL-6R

and its signal-transducing chain gp130, as well as the existence of soluble IL-6R in the serum. Although *in vivo* treatments with IL-6 are impractical, a simple *in vitro* treatment of donor fatty liver with IL-6 may render marginal fatty livers usable for clinical transplantation.[15] Recent studies from our group have suggested that IL-22, another hepatoprotective cytokine, may have a therapeutic potential to treat severe forms of ALD.

IL-22 was originally described as an IL-10-related T-cell-derived inducible factor (IL-TIF) belonging to the IL-10 family of cytokines.[32] In 2004, we demonstrated for the first time that IL-22 is a critical survival factor for hepatocytes and plays a key role in protecting against Con A-induced T cell hepatitis.[17] The protective role of IL-22 in T cell hepatitis was further confirmed using IL-22-deficient mice[19] and IL-22 transgenic mice.[18] In addition, IL-22 ameliorates steatosis and hepatocellular damage in many other models of liver injury, including high fat diet-induced fatty liver[33] and acute and chronic alcoholic liver injury.[34, 35] The hepatoprotective effect of IL-22 in alcoholic liver injury is likely mediated via the activation of STAT3, followed by the upregulation of anti-apoptotic genes (e.g., *Bcl-2* and *BcI-xL*), anti-oxidative genes (e.g., *metallothioneins 1* and *2*), and the downregulation of lipogenic genes (e.g., *SREBP-1c*) in hepatocytes.[35]

In contrast to IL-6R, which is ubiquitously expressed, IL-22R expression is restricted to epithelial cells, including hepatocytes.[16] Thus, treatment of alcoholic hepatitis with IL-22 in combination with corticosteroids or TNF-α inhibitors may have minimal side effects. Corticosteroids have been widely used, and TNF-α inhibitors have been tested in the treatment of severe forms of alcoholic hepatitis; however, the results of these studies are controversial.[36–40] Both steroids and TNF-α inhibitors can block inflammation, but they also reduce liver regeneration and increase the rate of bacterial infection;[37–39] the last two events may be responsible for the poor outcomes associated with these treatments. Co-treatment with IL-22 may diminish corticosteroid- or TNF-α inhibitor-induced bacterial infection and may prevent the inhibition of liver regeneration because IL-22 has an antimicrobial effect [41] and promotes liver regeneration.[18, 20] Conversely, co-treatment with corticosteroids may prevent the potential pro-inflammatory effect of IL-22 treatment in the liver.[42, 43] Liver-specific IL-22 transgenic mice do not display obvious liver inflammation or chemokine upregulation,[18] which suggests that IL-22 treatment may have little effect on liver inflammation. Furthermore, IL-22 is not elevated in the livers of alcoholic hepatitis patients, whereas the expression of IL-22R1 is upregulated,[35] which suggests that these patients may be sensitive to IL-22 treatment because of low levels of endogenous IL-22 and elevated levels of IL-22R1 in the liver.

Finally, IL-22 has been shown to promote liver tumor cell growth *in vitro* and *ex vivo*.[17] Elevated levels of IL-22 are found in patients with hepatocellular carcinoma, and IL-22 has been implicated in hepatocellular carcinoma growth.[44] Recently, we demonstrated that mice overexpressing IL-22 in the liver do not spontaneously develop liver tumors, but they are more susceptible to diethylnitrosamine-induced liver cancer.[18] These results suggest that high levels of IL-22 alone may not initiate liver tumor development, but IL-22 may accelerate hepatic carcinogenesis via the promotion of cell survival and proliferation in existing liver tumors. Thus, the application of IL-22 should be safe for the treatment of alcoholic hepatitis patients without cirrhosis and without liver cancer, but it should not be used in patients with pre-cancerous cirrhosis or liver cancer.

Conclusions

The activation of innate immunity by various factors (e.g., LPS, Kupffer cells, and complement) results in the production of pro-inflammatory cytokines, including TNF-α, and contributes to the development and progression of ALD; [7–10] recent findings from our

laboratory have suggested that the activation of these innate immunity components also plays a significant role in alleviating hepatocellular damage and promoting liver regeneration via the production of the hepatoprotective cytokine IL-6 and the anti-inflammatory cytokine IL-10. The elevation of IL-6 and IL-10 levels in ALD patients could be part of a host defense strategy to repair the damaged liver and control inflammation, respectively. Interestingly, IL-10 inhibits pro-inflammatory cytokines, such as TNF-α, thereby ameliorating ALD, and it inhibits hepatoprotective cytokines, such as IL-6, thereby potentiating ALD and reducing liver regeneration. Thus, IL-10 likely plays a dual role in controlling the progression of ALD.

Although the hepatoprotective role of IL-6 is well documented, the clinical application of IL-6 in treating ALD is limited because of its numerous potential side effects. In contrast, IL-22, another important hepatoprotective cytokine, may have greater therapeutic potential in treating severe forms of ALD because of its well-documented hepatoprotective and antimicrobial functions, as well as its potentially minimal adverse side effects due to its restricted IL-22R expression in epithelial cells. Clinical trials examining combination therapy with IL-22 plus corticosteroids or plus TNF-α inhibitors for the treatment of patients with severe alcoholic hepatitis are warranted.

Acknowledgments

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Abbreviations

ALD	alcoholic liver disease
IL	interleukin
LPS	lipopolysaccharide
JAK	Janus kinases
STAT3	signal transducer and activator of transcription 3

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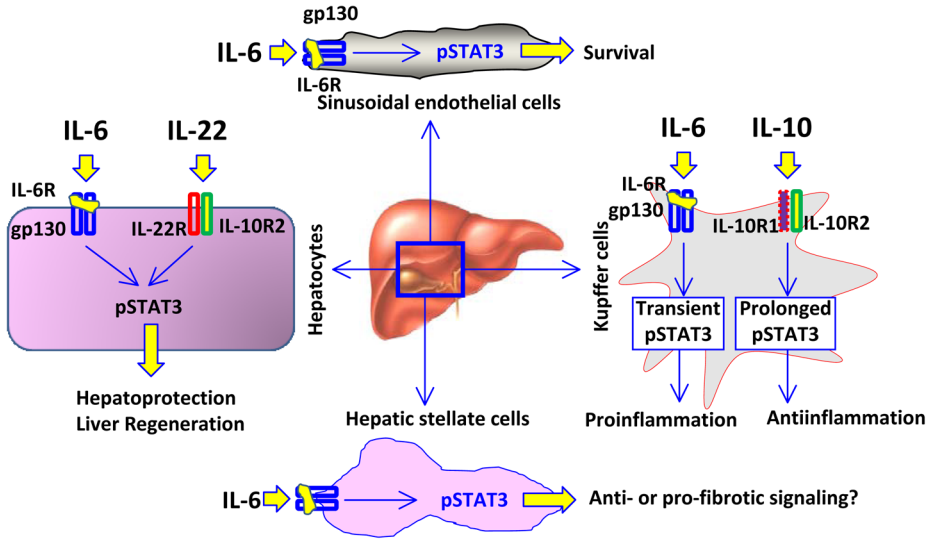

Fig. 1. IL-6-, IL-22-, and IL-10-induced activation of STAT3 in the liver

In hepatocytes, both IL-6 and IL-22 induce STAT3 activation and play important roles in hepatoprotection and liver regeneration. In Kupffer cells, IL-6 induces transient STAT3 activation and contributes to the pro-inflammatory response, whereas IL-10 induces prolonged STAT3 activation and contributes to the anti-inflammatory response. In sinusoidal endothelial cells, IL-6 induces STAT3 activation and subsequently promotes cell survival. In hepatic stellate cells, IL-6 induces STAT3 activation; however, the roles of STAT3 in stellate cell activation and fibrogenesis remain obscure.

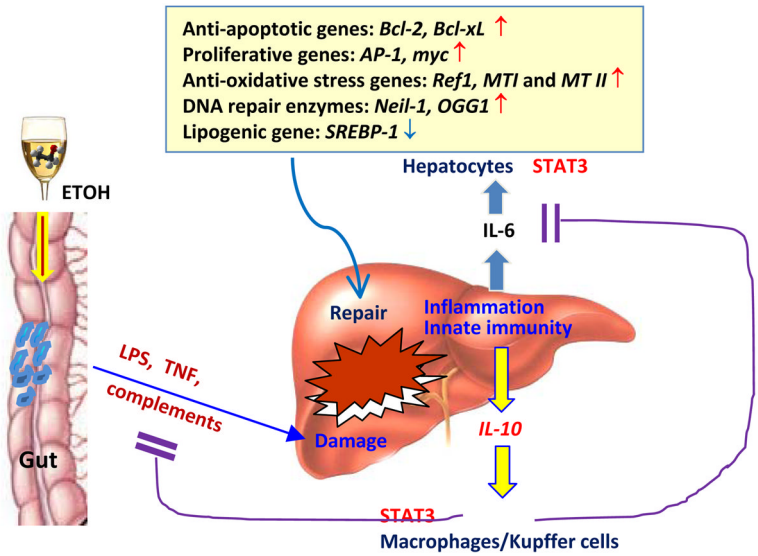

Fig. 2. Elevations of IL-6 and IL-10 are part of a host defense strategy to repair the injured liver and control inflammation in ALD

Chronic alcohol consumption leads to innate immunity activation via various factors (e.g., LPS, TNF-α, and complement), with subsequent hepatocellular damage. The activation of innate immunity also promotes the production of the hepatoprotective cytokine IL-6, which plays an important compensatory role in repairing liver damage via the activation of STAT3 and the upregulation of multiple hepatoprotective genes in hepatocytes. The activation of innate immunity also produces the anti-inflammatory cytokine IL-10, which activates STAT3 in Kupffer cells/macrophages and controls liver inflammation. However, IL-10 plays a dual role in controlling alcoholic fatty liver and liver injury: first, IL-10 inhibits LPS, TNF-α, and complement activation, thereby reducing steatosis and liver damage; second, IL-10 blocks IL-6 production, thereby reducing liver regeneration and enhancing steatosis and liver damage.