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Cytokines and STATs in liver fibrosis

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Liver fibrosis, or cirrhosis, is a common end-stage condition of many chronic liver diseases after incomplete recovery from hepatocyte damage. During fibrosis progression, hepatocellular damage and inflammation trigger complex cellular events that result in collagen deposition and the disruption of the normal liver architecture. Hepatic stellate cell activation and transdifferentiation into myofibroblasts are key events in liver fibrogenesis. Research findings from cell culture and animal models have revealed that the Janus kinase-signal transducer and activator of transcription (Jak-STAT) signaling pathway, which can be activated by many cytokines, growth factors, and hormones, plays a critical role in hepatic fibrogenesis. This review summarizes the biological significance of diverse cytokines and their downstream signaling protein STATs in hepatic fibrogenesis.

Keywords: stellate cells, interferon, interleukin, STATs

INTRODUCTION

Liver fibrosis, or scarring of the liver, is induced by various types of chronic liver diseases and is a major cause of morbidity and mortality worldwide. During fibrosis progression, inflammation and liver injury trigger complex cellular events that result in collagen deposition and the disruption of the normal liver architecture. Generally, following liver injury from any causes, hepatic stellate cells (HSCs) undergo activation and transformation. HSCs are considered the most important cell type for the production of collagens (Friedman, 2008). Many other types of cells, such as bone marrow-derived progenitor cells, portal fibroblasts, cholangiocytes, and hepatocytes may also contribute to the production of collagens to a lesser extent (Kaimori et al., 2007; Higashiyama et al., 2009; Novo et al., 2009). In addition, immune cells may regulate fibrogenesis via the secretion of a wide variety of growth factors and cytokines.

Many inflammatory cytokines have been shown to play key roles in regulating liver fibrogenesis (Bataller and Brenner, 2005; Friedman, 2008). Following liver injury, many types of cells in the liver, including Kupffer cells, hepatocytes, HSCs, natural killer cells, lymphocytes, and dendritic cells, have been shown to produce pro-inflammatory cytokines and hepatoprotective cytokines. Many of these cytokines can activate the Janus kinase–signal transducer and activator of transcription (JAK–STAT) signaling pathway in the liver, including interleukin-6 (IL-6), interferon-γ (IFN-γ), IFN-α/β, and IL-22 (Gao, 2005). Signaling through the JAK–STAT pathway is initiated when an extracellular cytokine protein binds to its corresponding transmembrane receptor complex. This leads to activation of the JAKs, including Jak1, 2, 3, and TYK2. The JAKs mediate phosphorylation at specific receptor tyrosine residues, which then serve as docking sites for the STATs (STAT1, 2, 3, 4, 5a, 5b, and 6). Studies from animal models have revealed that activation of the JAK–STAT pathway by an array of cytokines plays a variety of important functions in liver pathophysiology (Gao, 2005; Mair et al., 2011; Wang et al., 2011a; Gao et al., 2012). In this review, we update the biological significance of cytokines and their downstream STAT signaling pathways in liver fibrogenesis (**Table 1**).

Abbreviations: CDE diet, choline-deficient, ethionine-supplemented diet; DDC diet, 3,5-diethoxycarbonyl-1,4-dihydrocollidine diet; HSC, hepatic stellate cell; IL, interleukin; JAK–STATs, Janus kinase–signal transducers and activators of transcription; TGF-β, transforming growth factor-beta; TIMP-1, tissue inhibitor of metalloproteinase 1.

STAT1: A NEGATIVE REGULATOR OF LIVER FIBROSIS

It is well established that STAT1-deficient mice display increased sensitivity to infection by microbial pathogens. Using STAT1-deficient mice, we have previously demonstrated that STAT1 negatively regulates liver fibrosis through the inhibition of HSC proliferation and the stimulation of NK cell killing of activated HSCs (Jeong et al., 2006). Consistent with these findings, several cytokines that activate the STAT1 signaling pathway have been shown to inhibit liver fibrosis.

IFNs/STAT1 IN LIVER FIBROSIS

STAT1 is mainly activated by IFN-α/β and IFN-γ in the liver. Treatment with IFN-α has been shown to significantly improve the serum levels of fibrotic markers and the degree of hepatic fibrosis in mice. IFN-α directly suppresses collagen gene transcription through the interaction of phosphorylated Stat1 and p300 (Inagaki et al., 2003). IFN-β treatment reduces concanavalin A-induced hepatic fibrosis via the inhibition of transforming growth factor-beta (TGF-β), basic fibroblast growth factor, collagen type I A2, and tissue inhibitor of metalloproteinase 1 (TIMP-1) mRNA expression (Tanabe et al., 2007). IFN-γ displays anti-fibrotic effects in the liver via the induction of STAT1 phosphorylation, the upregulation of Smad7 expression, and the impairment of TGF-β signaling (Weng et al., 2007).

Table 1 | Functions of STATs in liver fibrogenesis.

STATs	Cell types	Target genes	Major cellular effects on liver fibrogenesis
STAT1	HSCs	Collagen↓ TGF-β↓ TIMP-1↓ Smad7↑ Fibroblast growth factor ↓	Anti-fibrotic effects
	NK cells	TRAIL↑ NKG2D↑	Anti-fibrotic effects
	Hepatocytes	IRF-1↑ p21↑ caspase-3↑	Liver injury, pro-fibrotic effects
STAT2	Hepatocytes	Unknown	Unknown
STAT3	Hepatocytes	Bcl-2↑ Bcl-xL↑ cyclin D↑	Hepatoprotection, anti-fibrotic
	Hepatocytes, HSCs	TIMP-1↑	Pro-fibrotic effects
STAT4	NK and NKT cells	IFN-γ↑	Anti-fibrotic effects
STAT5	Hepatocytes	Insulin-like growth factor 1↑ Hepatoprotective genes↑	Hepatoprotection, anti-fibrotic
STAT6	HSCs	Fibrotic genes↑ Collagens↑	Pro-fibrotic effects?

IL-27/STAT1 IN LIVER FIBROSIS

In addition to IFNs, IL-27 also induces STAT1 activation in the liver. IL-27 belongs to the IL-6/IL-12 cytokine family and is secreted by activated macrophages and dendritic cells. Treatment with IL-27 activates STAT1 and, to a lesser extent, STAT3 in the human HSC cell line LX2 and in primary rat HSCs (Schoenherr et al., 2010), suggesting that IL-27 may inhibit liver fibrosis. However, further studies are required to confirm the anti-fibrotic effects of the IL-27/STAT1 pathway *in vivo*.

STAT2

STAT2 is exclusively activated by IFN-α, IFN-β, and IFN-λ (Radaeva et al., 2002; Balagopal et al., 2010; Afdhal et al., 2011). Treatment with IFN-α induces significant STAT2 activation in primary human hepatocytes (Radaeva et al., 2002). The activation of STAT2 likely plays a key role in the antiviral effects of IFN-α in patients with viral hepatitis. Although the antiviral function of STAT2 is well documented, the role of STAT2 in liver injury and fibrosis has not yet been explored.

STAT3

A variety of cytokines have been shown to induce STAT3 activation in the liver, playing key roles in inducing the acute-phase response, protecting against hepatocellular damage, and promoting liver regeneration (Wang et al., 2011a). However, the roles of STAT3 in liver fibrogenesis remain largely unknown. Hepatocyte-specific STAT3 knockout mice displays a higher degree of liver fibrosis compared with wild-type mice in various models of liver fibrosis induced by CCl_4 administration (Wang et al., 2011b), feeding with a 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC) diet (Plum et al., 2010), feeding with a choline-deficient, ethionine-supplemented (CDE) diet (Kroy et al., 2010), or upon deletion of the multidrug resistance gene 2 (Mair et al., 2010). The obvious mechanism by which hepatocyte STAT3 protects against liver fibrosis is that hepatocyte STAT3 activation prevents hepatocellular damage and subsequently reduces injury-driven liver fibrogenesis. A recent study suggests that activation of STAT3 in hepatocytes inhibits liver fibrosis by stimulating hepatocytes to produce unknown soluble factors that inhibit HSC activation (Shigekawa et al., 2011). Further studies are needed to identify these soluble factors.

Because HSC-specific STAT3 knockout mice are not available, the role of HSC STAT3 in liver fibrogenesis *in vivo* has not been determined. Mice or rats deficient in leptin or leptin signaling are resistant to the development of liver fibrosis (Honda et al., 2002; Ikejima et al., 2002; Saxena et al., 2002), suggesting that leptin may promote liver fibrosis via the activation of STAT3 in HSCs *in vivo*. *In vitro* experiments demonstrate that the inhibition of JAK/STAT3 activation by the specific JAK2 inhibitor AG490 prevents HSC early activation, which suggests that leptin activation of STAT3 promotes HSC survival and activation (Lakner et al., 2010). In addition, STAT3 is also involved in the leptin- and IL-6-mediated production of TIMP-1 in HSCs and hepatocytes, respectively (Cao et al., 2004; Wang et al., 2011c). TIMP-1 is a survival factor for HSCs; thus, activation of STAT3 in HSCs and hepatocytes may increase liver fibrogenesis via the upregulation of TIMP-1.

Until recently, the roles of STAT3 in other non-parenchymal cells and inflammatory cells in liver fibrogenesis remain largely unclear. Recently, Wang et al. (2009) provided evidence suggesting that leptin can promote TGF-β1 production in Kupffer cells via the activation of STAT3 and consequently augment liver fibrogenesis. This suggests that STAT3 activation in Kupffer cells by leptin exacerbates liver fibrosis. However, it is known that the activation of STAT3 by IL-10 in macrophages and Kupffer cells is a key anti-inflammatory signal for the attenuation of liver inflammation (Horiguchi et al., 2008, 2010; Lafdil et al., 2009). Thus, the activation of STAT3 by IL-10 in Kupffer cells and macrophages may prevent liver inflammation and fibrogenesis. Further studies are needed to clarify the functions of STAT3 in Kupffer cells as well as in other types of sinusoidal cells and inflammatory cells in the pathogenesis of liver fibrogenesis.

Clinical data have shown that STAT3–DNA binding is markedly suppressed in alcoholic and HCV fibrotic patients when compared with normal healthy livers, and fibrosis progression in HCV-infected patients is positively correlated with a continuous decline in STAT3–DNA binding activity (Starkel et al., 2005, 2007), indicating that STAT3 may also protect against liver fibrosis in patients.

In the liver, STAT3 is mainly activated by IL-6 and its related cytokines leptin, and IL-22. The roles of these cytokines in liver fibrogenesis are discussed below.

IL-6/STAT3 IN LIVER FIBROSIS

IL-6 is a critical proregenerative factor and an acute-phase inducer in the liver. IL-6 stimulates hepatocytes to produce a variety of

acute-phase proteins, including C-reactive protein, complement C3, and serum amyloid A (Ramadori and Christ, 1999). However, numerous studies demonstrated the hepatoprotective role of IL-6 against liver injury in spite of its pro-inflammatory effect (Blindenbacher et al., 2003; Wuestefeld et al., 2003). With respect to liver fibrosis, there are some conflicting reports. First, IL-6 knockout mice are reported to be more susceptible to CCl_4-induced liver injury and fibrosis (Kovalovich et al., 2000). Another study showed that the lack of gp130/STAT3-mediated signaling in hepatocytes resulted in enhanced chronic cholestatic liver injury and fibrosis progression induced by DDC diet feeding (Plum et al., 2010). Other studies have demonstrated that liver fibrosis is reduced in IL-6-deficient mice after CCl_4 treatment (Sun et al., 2004; Rio et al., 2008). The reasons for the differences observed in these experiments remain unclear. *In vitro* cell culture experiments showed that Kupffer cell-derived IL-6 promotes HSC survival and proliferation (Nieto, 2006). Clinical studies showed that hepatic IL-6 expression is upregulated and correlates positively with the degree of liver fibrosis in *opisthorchiasis periductal* fibrosis and in non-alcoholic steatohepatitis (Dogru et al., 2008; Wieckowska et al., 2008; Sripa et al., 2009). Furthermore, genetic polymorphisms of IL-6 are linked with fibrosis progression in patients with chronic HCV infection (Cussigh et al., 2011). Because IL-6 receptors are expressed ubiquitously on all types of liver cells, it is plausible to speculate that IL-6 may positively and negatively regulate liver fibrosis by targeting different types of liver cells. For example, IL-6 protects against hepatocellular damage, thereby reducing injury-driven liver fibrosis, while it may also directly promote HSC survival and proliferation, followed by enhanced liver fibrosis. The final effect of IL-6 on liver fibrosis is likely determined by the balance between these inhibitory and stimulatory effects and is dependent on the stage and etiology of liver fibrosis.

LEPTIN/STAT3 IN LIVER FIBROSIS

The critical role of leptin in inducing liver fibrogenesis was first noticed from the findings that leptin-deficient ob/ob mice and leptin-receptor-deficient Zucker rats are resistant to the development of liver fibrosis (Honda et al., 2002; Ikejima et al., 2002; Saxena et al., 2002). A recent study showed that the administration of leptin increases thioacetamide-induced liver fibrosis, while the injection of mouse leptin antagonist attenuates it (Elinav et al., 2009). *In vitro* treatment of primary rat HSCs with a leptin antagonist, either alone or with leptin, has been shown to suppress the pro-fibrotic effects of leptin (Elinav et al., 2009). Furthermore, *in vitro* experiments with leptin have shown to induce STAT3 activation in HSCs, and the blockade of STAT3 activation diminishes leptin-mediated promotion of HSC survival and activation (Lakner et al., 2010). Finally, STAT3 is also involved in the leptin-mediated production of TIMP-1, an important survival factor for HSCs (Cao et al., 2004). Collectively, the pro-fibrotic effect of leptin is likely mediated via the direct promotion of HSC survival and proliferation or the indirect upregulation of TIMP-1, which subsequently promotes HSC survival.

IL-22/STAT3 IN LIVER FIBROSIS

IL-22 has been shown to play an important role in protecting against liver injury (Radaeva et al., 2004; Zenewicz et al., 2007; Park et al., 2011), ameliorating fatty liver disease (Ki et al., 2010; Yang et al., 2010), and promoting liver cancer development (Jiang et al., 2011; Park et al., 2011). An *in vitro* study showed that IL-22 promotes liver cell regeneration by increasing hepatic cell proliferation and hepatocyte migration through the activation of Akt and STAT signaling, which is abrogated by SOCS-1/3 overexpression (Brand et al., 2007). Although the hepatoprotective effects of IL-22 have been extensively studied, the effects of IL-22 on liver fibrogenesis have not been investigated.

STAT4

It is well documented that IL-12 and IFN-α/β can induce STAT4 activation in several types of immune cells and subsequently generate inflammation during protective immune responses and immune-mediated diseases (Kaplan, 2005). The activation of STAT4 has not been reported in hepatocytes, and the functions of STAT4 in liver injury and fibrosis remain obscure. IL-12-deficient mice are resistant to autoimmune cholangitis in dominant negative TGF-β receptor type II mice (Yoshida et al., 2009) and to Con A-induced T cell hepatitis (Zhu et al., 2007), while the overexpression of IL-12 in the liver induces liver injury (Rodriguez-Galan et al., 2009). In addition, IL-12 treatment has been shown to induce liver inflammation and inhibit liver tumor growth in several animal models (Harada et al., 2004; Chang et al., 2007), which is likely mediated via IL-12 activation of NK and NKT cells and the subsequent production of IFN-γ (Subleski et al., 2006). This suggests that IL-12 acts as a pro-inflammatory cytokine to promote liver injury and fibrosis likely via the activation of STAT4 in immune cells. In contrast, a recent study has demonstrated that IL-$10^{-/-}$ IL-12/23(p40)$^{-/-}$ IL-13Rα$2^{-/-}$ triple knockout mice are more susceptible to *S. mansoni*-induced liver fibrosis, portal hypertension, hepatosplenomegaly, gastrointestinal bleeding, ascites, thrombocytopenia, esophageal and gastric varices, anemia, and increased levels of liver enzymes (Mentink-Kane et al., 2011), suggesting that IL-10, IL-12p40, and IL-13Rα2 act cooperatively to suppress liver fibrosis in mice following infection with *S. mansoni*. Collectively, IL-12 activation of STAT4 in immune cells induces inflammation in the liver, which promotes liver injury and fibrosis, but may also protect against infection, thereby ameliorating liver injury and fibrosis.

STAT5

The activation of STAT5 in hepatocytes is mainly induced by growth hormone (GH) and other cytokines to a lesser extent. Hepatocyte-specific STAT5 knockout mice were initially generated in Dr. Lothar Hennighausen's laboratory (Cui et al., 2007). Using this strain of knockout mice, they have demonstrated that loss of STAT5 in hepatocytes results in elevated TGF-β levels and enhanced GH-induced STAT3 activity in the liver after chronic carbon tetrachloride treatment, suggesting that STAT5 inhibits liver fibrogenesis via the downregulation of TGF-β and STAT3 (Hosui et al., 2009; Baik et al., 2011). The anti-fibrotic effect of STAT5 is also demonstrated in another murine model of liver fibrosis induced by deleting the multidrug resistance gene 2 (Blaas et al., 2010). Deletion of both multidrug resistance gene 2 (global deletion) and STAT5 (hepatocyte and cholangiocyte-specific deletion) results in an early and severe liver fibrosis phenotype, accompanied

by reduced expression of important hepatoprotective genes, such as epidermal growth factor receptor, hepatocyte nuclear factor 6, prolactin receptor, and leukemia inhibitory factor receptor as well as increased numbers of apoptotic hepatocytes. Furthermore, deletion of STAT5 in the liver promoted carbon tetrachloride-induced hepatic tumorigenesis in wild-type mice (Hosui et al., 2009) and induced spontaneous liver cancer development in liver-specific glucocorticoid receptor knockout mice (Mueller et al., 2011) or in GH transgenic mice (Friedbichler et al., 2012). The protective effect of STAT5 on hepatic carcinogenesis is likely mediated via the induction of a key cell cycle inhibitor–p15INK4B expression in hepatocytes (Yu et al., 2010) and protection against fatty liver disease and liver injury (Mueller et al., 2011; Friedbichler et al., 2012).

Although the functions of hepatocyte STAT5 have been extensively investigated, little is known about STAT5 activation in HSCs and other non-parenchymal cells, and how STAT5 activation in these cells affects the pathogenesis of liver fibrogenesis remains obscure.

STAT6

STAT6 is mainly activated by Th2 cytokines, including IL-4 and IL-13. The roles of both IL-4 and IL-13 in liver fibrosis have been extensively investigated, especially in a model of *S. mansoni* infection (Barron and Wynn, 2011), while the functions of STAT6 in liver fibrogenesis remain obscure. Disruption of the IL-13 gene or blockage of IL-13 with inhibitors leads to markedly reduced liver fibrosis after infection with *S. mansoni* (Chiaramonte et al., 1999a, 2001; Fallon et al., 2000), indicating that IL-13 is a pro-fibrogenic cytokine during *S. mansoni* infection. Expression of IL-13 is elevated and correlates with liver fibrosis in some patients with HBV or HCV infection. This suggests that IL-13 may also contribute to the pathogenesis of liver fibrosis in viral hepatitis (Weng et al., 2009). The pro-fibrogenic effect of IL-13 is likely mediated via the upregulation of a wide variety of fibrotic proteins in HSCs and the induction of HSC activation (Chiaramonte et al., 1999a; Weng et al., 2009). IL-13 may also regulate liver fibrosis via the activation of macrophages, which plays an important role in the induction and resolution of liver fibrosis (Barron and Wynn, 2011).

IL-4 is also considered a pro-fibrotic cytokine because IL-4 can directly stimulate HSC activation and the production of collagens (Aoudjehane et al., 2008; Jin et al., 2011). The potency of IL-4 stimulation of HSC activation *in vitro* appears to be similar to that of TGF-β (Aoudjehane et al., 2008). In addition, the expression of IL-4 is upregulated in the fibrotic liver of *S. mansoni*-infected baboons (Farah et al., 2000), and blockage of IL-4 significantly reduces liver fibrosis in *S. mansoni*-infected mice (Cheever et al., 1994). However, several other studies suggest that although both IL-4 and IL-13 are critical in the progression of the *S. mansoni*-induced disease, IL-13, but not IL-4, plays a key role in *S. mansoni* mediated granuloma formation and liver fibrosis as the reduction in fibrosis observed in IL-4-deficient mice was much less pronounced than that in sIL-13Ralpha2-Fc-treated animals (Chiaramonte et al., 1999a,b; Fallon et al., 2000)

Both IL-4 and IL-13 predominately induce STAT6 activation in HSCs. Blockage of STAT6 with siRNA attenuates HSC activation *in vitro* (Aoudjehane et al., 2008). After infection with *S. mansoni*, STAT6-deficient mice have smaller granulomas and decreased amounts of collagen deposition in the liver compared with wild-type mice (Kaplan et al., 1998). However, a recent study (Liu et al., 2011) has demonstrated that ERK1/2 pathway rather than STAT6 in HSCs contributes to IL-13 induction of connective tissue growth factor, a key mediator in stimulating extracellular matrix deposition in the liver. In addition, although IL-13 immunostaining correlates with fibrotic stage in patients with HCV infection and steatohepatitis, pSTAT6 was only detected in 5 out of 120 fibrotic tissues from these patients, suggesting that the pro-fibrotic effect of IL-13 in human liver diseases is mediated via an STAT6-independent pathway (Weng et al., 2009). Finally, in lung fibrosis, two studies showed that STAT6-deficient mice still develop into fibrosis in two murine models induced by transient ectopic overexpression of oncostatin M (Fritz et al., 2011) or by an intratracheal challenge with live *A. fumigatus conidia* (Blease et al., 2002). Collectively, although IL-13 plays an important role in promoting liver fibrogenesis in *S. mansoni* infection, the role of STAT6 in HSCs and

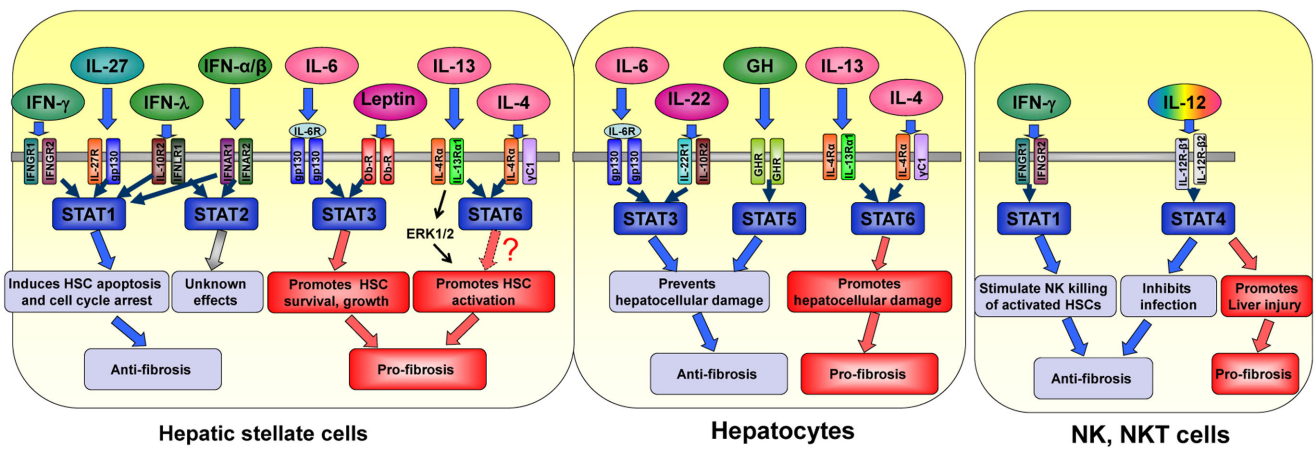

FIGURE 1 | The effects of cytokines and their downstream STATs in different cell types in liver fibrogenesis.

liver fibrogenesis seems controversial, which needs to be clarified by further studies.

CONCLUSIONS AND CLINICAL PERSPECTIVES

In summary, the activation of the JAK–STAT signaling pathways plays a complex role in controlling liver fibrogenesis. In general, as shown in **Figure 1**, STAT1 acts as an anti-fibrotic signaling molecule via the induction of HSC apoptosis and cell cycle arrest. STAT3 and STAT5 may also act as anti-fibrotic signaling molecules via their hepatoprotective functions, thereby preventing injury-driven liver fibrosis. However, the functions of STAT3 and STAT5 activation in HSCs remain obscure and require further studies. Although the antiviral effect of STAT2 is well documented, it is not clear whether or not STAT2 also plays a role in contributing to the IFN-α/β-mediated anti-fibrotic effects in the liver. Finally, the biological functions of STAT4 and STAT6 in the pathogenesis of liver diseases, including liver fibrogenesis, remain largely unknown.

Despite extensive research on the functions of STATs in liver fibrogenesis, the translation of these basic research findings into new therapies has been modest. Based on research findings that IFN-γ activation of STAT1 is effective in ameliorating liver fibrosis in animal models, IFN-γ has been tested in clinical trials for treating liver fibrosis in patients. It has been reported that IFN-γ treatment for 9 months does not reduce viral load but improves fibrosis scores in patients with chronic HBV infection (Weng et al., 2005; Wu et al., 2011); however, another large double-blind, placebo-controlled trial showed that IFN-γ therapy was not able to reverse fibrosis in patients with advanced liver disease (Pockros et al., 2007). The disappointing results from the anti-fibrotic therapy of IFN-γ in the latter study may be due to the selection of patients with end-stage of liver disease, poor efficacy, or to unwanted off-target effects. To overcome this problem, Bansal et al. (2011) recently developed an engineered, targeted IFN-γ, in which IFN-γ is conjugated to a cyclic recognizing PDGF-β, a receptor that is highly upregulated on activated HSCs. Administration of this conjugated IFN-γ markedly inhibits liver fibrosis but does not induce IFN-γ-related side effects in animal models (Bansal et al., 2011), suggesting that this conjugated IFN-γ is a promising anti-fibrotic drug for the treatment of liver fibrosis in patients. Further studies on the anti-fibrotic effect of this targeted IFN-γ in patients are warranted.

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