Review

Cytokines, STATs and Liver Disease

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The Janus kinase-signal transducers and activators of transcription (JAK-STAT) signaling pathway, activated by more than 50 cytokines or growth factors, plays critical roles in a wide variety of cellular functions in the hematopoietic, immune, neuronal and hepatic systems. In the liver, this signaling pathway, activated by more than 20 cytokines, growth factors, hormones, and hepatitis viral proteins, plays critical roles in antiviral defense, acute phase response, hepatic injury, repair, inflammation, transformation, and hepatitis. This article reviews the biological significance of STAT1, 2, 3, 4, 5, 6 in hepatic functions and diseases. *Cellular & Molecular Immunology*. 2005;2(2):92-100.

Key Words: cytokine, STAT, liver

The Janus kinase-signal transducers and activators of transcription (JAK-STAT) signaling pathway, activated by more than 50 cytokines or growth factors, has been implicated in a variety of cellular functions in the hematopoietic, immune, neuronal and hepatic systems. In general, as shown in Figure 1, the ligation of these cytokines to their receptors induces receptor dimerization, which is followed by activation of the receptor-associated tyrosine kinases, known as JAK1, JAK2, JAK3 and Tyk2. This receptor-kinase complex interacts with and activates members of the SH2-containing cytoplasmic transcription factor STAT family, including STAT1, 2, 3, 4, 5, 6. The phosphorylated STATs form a dimer and translocate to the nucleus to activate the transcription of many target genes (1, 2). These STATs are activated by many cytokines and growth factors, and play a variety of functions in the liver, which are summarized in Table 1 and discussed at length in the following sections.

STAT1: antiviral defense, inflammation, injury in the liver

In the liver, STAT1 is mainly activated by IFN-α/β and IFN-γ. Data from STAT1 knockout mice suggest that STAT1 plays a key role in antiviral defense, inflammation, and injury in the liver (3-7).

Interferon-α/β

IFN-α has been used as primary choice for the treatment of viral hepatitis for more than a decade (8, 9). Therefore, IFN-α induces activation of signal transduction and downstream antiviral genes in the liver has been extensively investigated (10-13). Action of IFN-α/β is mediated *via* targeting IFNAR1 and IFNAR2 complex. The human IFNAR1 chain presents only a single form and is primarily involved in signal transduction, whereas human IFNAR2 presents three forms, including full-length hIFNAR2c, short form hIFNAR2b, and soluble form hIFNAR2a (14). The full-length hIFNAR2c is involved in both ligand binding and signal transduction, whereas both the short form hIFNAR2b and the soluble form hIFNAR2a have been implicated in suppression of IFN-α signaling (14, 15). Upon IFN-α/β binding, IFN-α/β-receptor-associated tyrosine kinases (JAK1 and Tyk2) are activated, followed by phosphorylation of Y466 of the IFNAR1. This in turn phosphorylates STAT2 on Y690 and STAT1 on Y701. Phosphorylated STAT1 and STAT2 form heterodimers or homodimers, which then translocate into the nucleus to activate the transcription of many target genes, including several antiviral proteins, tumor suppressors, and proapoptotic proteins (14, 16, 17).

The antiviral action of IFN-α/β in treatment of viral hepatitis is believed to be mediated through targeting human hepatocytes and modulating the immune system *via* activation of the JAK-STAT signaling pathway (18). Primary human hepatocytes express high levels of IFN-α/β receptor (IFNAR)

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Received Apr 2, 2005. Accepted Apr 14, 2005.

Abbreviations: JAK-STATs, Janus kinase-signal transducers and activators of transcription; IL, interleukin; IFN, interferon; LIF, leukemia inhibitory factor; CNTF, ciliary neurotrophic factor; OSM, oncostatin M; CT-1, cardiotrophin-1.

Table 1. Functions of STATs in the liver

STATs	Major cytokines responsible for activation in the liver	Major functions in the liver
STAT1	IFN-α/β IFN-γ	Antiviral defense Antitumor Inflammation Proapoptotic function
STAT2	IFN-α/β IFN-λ (IL-28/IL-29)	Antiviral defense
STAT3	IL-6 and its related cytokines IL-22	Acute phase response hepatoprotective function liver regeneration
STAT4	IL-12	Promotion of hepatic ischemia/reperfusion
STAT5	Growth hormones	Regulation of a wide range of hepatic genes, including metabolism enzymes, growth factors, etc.
STAT6	IL-4 IL-13	Promotes T cell hepatitis Inhibits ischemia/reperfusion injury

1 and full-length functional IFNAR2c, and respond very well to IFN-α stimulation (10). IFN-α/β activates STAT1, STAT2, STAT3, and STAT5 in primary human hepatocytes and human hepatoma cells. Microarray analyses have revealed that IFN-α upregulates expression of about 50 genes by 2 fold and downregulates expression of about 10 genes by 50%. These include induction of four antiviral genes (such as MxA, OAS, protein kinase R, and 9-27) and a wide variety of proapoptotic/tumor suppressor genes (10), which may contribute to the antiviral and antitumor activity of IFN-α/β in the liver, respectively. The essential role of STAT1 in the antiviral and antitumor activity of IFN-α/β has been clearly demonstrated in STAT1-deficient mice (3). Activation of STAT3 has also been implicated in IFN-α-mediated antiviral activity in hepatitis C virus replicon cell line (19).

Although IFN-α/β is primary choice for the treatment of viral hepatitis, more than 60-80% patients respond poorly to IFN-α/β therapy (8, 9). Inhibition of IFN-α/β-activated signals in the liver by several viral proteins and host factors may contribute to IFN-α treatment failure in patients with hepatitis virus infection (18). These hepatitis viral proteins include hepatitis C virus (HCV) E2 protein (20), HCV core protein (21, 22), HCV nonstructural 5A (NS5A) (23). Several host factors such as alcohol drinking (24), elevation of TNF-α (25), IL-1β (26), and IL-10 (27) have been found to inhibit IFN-α/β-activated STAT1 in the liver or in hepatocytes, which may contribute to IFN-α treatment failure in viral hepatitis patients with alcohol drinking or high serum levels of TNF-α, IL-1β, and IL-10, respectively. These host factors could be potential targets for improving IFN-α therapy.

Interferon-γ

Interferon-γ (IFN-γ) is a pleiotropic cytokine that plays a crucial role in host defense due to its antiviral, anti-proliferative, proapoptotic, pro-inflammatory, and immunoregulatory activities. The action of IFN-γ is mediated through activation of the JAK-STAT signaling pathway (14, 17). Binding of IFN-γ to IFNGR1 induces IFNGR1 and IFNGR2 dimerization, followed by activation of the receptor-associated kinases, such as JAK1 and JAK2. The receptor-kinase complex then activates STAT1, which induces expression of a wide variety of genes including antiviral, proapoptotic, and antiproliferative genes. STAT1 knockout mice have defective IFN-γ signaling and absent innate response to viral or bacterial infection (3).

In the liver, activation of STAT1 by IFN-γ has been implicated in hepatic inflammation and injury, and suppression of liver regeneration. STAT1 is activated in several models of liver injury, including Concanavalin A-induced T cell hepatitis and LPS/D-galactosamine-induced liver damage, and IFN-γ is mainly responsible for such activation (4, 5). Disruption of the STAT1 gene abolishes Concanavalin A-induced hepatitis and LPS/D-galactosamine-induced liver damage (4, 5, 7), suggesting that IFN-γ/STAT1 plays an essential role in hepatic inflammation and injury. Recently, we have demonstrated that IFN-γ, secreted by natural killer (NK) cells, is also involved in negative regulation of liver regeneration by double-stranded RNA (dsRNA) or virus infection, likely *via* activation of STAT1 (28). Interestingly, high levels of IFN-γ mRNA (29-31) and STAT1 protein (32, 33) were detected in the livers of patients with chronic hepatitis C infection, implicating that the possible involvement of IFN-γ/STAT1 in pathogenesis of chronic viral hepatitis.

STAT2: antiviral defense in the liver

STAT2 is only activated by type I IFN (IFN-α and IFN-β)

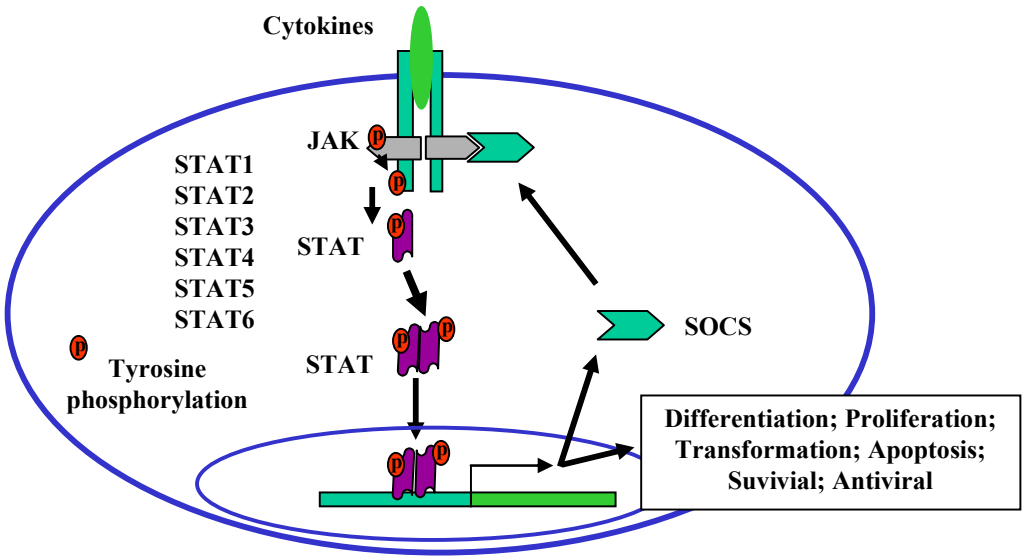

Figure 1. Model for the JAK-STAT signal pathway. Binding of cytokines to their receptors induces receptor dimerization, which is followed by activation of the receptor-associated tyrosine kinases, known as JAKs. This receptor-kinase complex interacts with and activates members of the SH2-containing cytoplasmic transcription factor STAT family, including STAT1, 2, 3, 4, 5, 6. The phosphorylated STATs form a dimer and translocate to the nucleus to activate the transcription of many target genes, including a family of suppressors of cytokine signaling (SOCS), which acts in a negative feedback loop to turn off the JAK-STAT signaling pathway by binding to JAKs. SOCS proteins include SOCS1, 2, 3 and CIS.

(14) and IFN-λ (IL-28/29) (34, 35). STAT2-deficient mice have an increased susceptibility to viral infection and the loss of a type I IFN autocrine/paracrine loop (36). Treatment with IFN-α induces significant STAT2 activation in primary human hepatocytes (10), suggesting that STAT2 activation is a key signal involved in the antiviral therapy of IFN-α in viral hepatitis patients. It has been reported that expression of STAT2 protein is decreased in the liver of alcoholic patients, which could be an important mechanism contributing to the IFN-α treatment failure in these patients (37).

STAT3: Acute phase response, hepatoprotective signal, and liver regeneration

In the liver, STAT3, mainly activated by IL-6 and its related cytokine, and IL-22, has been shown to play key roles in acute phase response, protection against liver injury, promotion of liver regeneration, glucose homeostasis, and hepatic lipid metabolism. In addition, several other factors were also reported to activate STAT3 in the liver. These include IL-10, EGF, hepatitis viral proteins.

Interleukin-6 and its related cytokines

There are six IL-6 family members identified to date, including IL-6, leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF), oncostatin M (OSM), cardiotrophin-1, and IL-11. They share significant similarity in four helical bundle structure and utilize the gp130 protein as common subunits for signal transduction (38). Cytokine binding to its receptor induces either homodimerization of gp130, or heterodimerization of gp130 with cytokine-specific receptors. Primary human hepatocytes express high levels of gp130, IL-6R, LIFR, CNTFR, OSMR, IL-11R, and cardiotrophin-1R. The biological functions of IL-6 in the liver have been extensively investigated, whereas the roles of other IL-6-related cytokines in the liver have been paid less attention.

Interleukin-6 (IL-6)

Interleukin-6 (IL-6) is a multifunctional cytokine that has been implicated in a variety of cellular functions in the hematopoietic, immune, neuronal and hepatic systems (38, 39). In the liver, IL-6 stimulates hepatocytes to produce a variety of acute-phase proteins, including serum amyloid A, C-reactive protein, complement C3, fibrinogen, and macro-globulin (40). Recent evidence from knockout mice suggests that IL-6 also plays an important role in liver regeneration and protection against liver injury. Mice with targeted disruption of the IL-6 gene have impaired liver regeneration (41, 42), whereas increasing evidence suggests that IL-6 may play more important roles in protection against liver injury during liver regeneration (43-45). IL-6-deficient mice are more susceptible to liver injury induced by carbon tetrachloride (46), Fas (47), ethanol (48), Concanavalin A (4), acetaminophen (49). Administration of IL-6 has been shown to protect against liver injury induced by Concanavalin A (4), ischemia/reperfusion (50, 51), partial liver transplantation (52). Delivery of a single low dose of a hyper-IL-6-encoding adenoviral vector, a superagonistic designer cytokine

consisting of human IL-6 linked by a flexible peptide chain to the secreted form of the IL-6 receptor, maintained liver function, prevented the progression of liver necrosis, and induced liver regeneration, leading to dramatically enhanced survival in a mouse model of acute liver failure induced by D-galactosamine administration (53). On contrast, liver regeneration is attenuated in transgenic mice overexpressing the human soluble IL-6 receptor/gp80 (hsgp80) in hepatocytes (54). In addition, *in vitro* treatment with IL-6 prevents mortality associated with fatty liver transplants in rats *via* improving hepatic microcirculation and protecting against cell death of endothelial cells and hepatocytes (55), and *in vivo* treatment with IL-6 ameliorates alcohol- and obesity-associated fatty liver diseases in mice *via* downregulation of TNF-α and induction of peroxisome proliferators-activated receptor expression (51). Taken together, IL-6 is a hepatoprotective factor and may have therapeutic potentials in preventing fatty liver transplant failure (51, 56) and treating fatty liver disease (51).

The role of IL-6 in the liver is believed to be linked through the IL-6R1 and gp130 protein, which are expressed on hepatocytes at high levels. The interaction of IL-6 with the IL-6Rα induces homodimerization of gp130, which is followed by activation of the receptor-associated Janus kinases, known as JAK1, JAK2 and Tyk2. This receptor-kinase complex interacts with and activates the SH2-containing cytoplasmic STAT3 transcription factor, which then translocates to the nucleus to activate the transcription of many target genes, such as: c-jun, c-myc, Jun B, cycline D1, C/EBP, $p21^{WAF1/Cip1}$, and acute-phase genes (38, 39). Treatment with IL-6 induces activation of STAT3 in primary human hepatocytes (unpublished observation), human hepatoma cells (57), and primary rat hepatocytes (58). Conditional deletion of the gp130 gene in hepatocytes promotes liver injury (59, 60). Disruption of the STAT3 gene impairs liver regeneration (61) and causes insulin resistance associated with increased hepatic expression of gluconeogenic genes (62), whereas overexpression of constitutively activated STAT3 reduces blood glucose, plasma insulin concentrations and hepatic gluconeogenic gene expression in diabetic mice (62) and protects against Fas-induced fulminant hepatitis *via* a redox-dependent and -independent mechanisms (63). Several STAT3 downstream genes have been identified as important factors contributing to the hepatoprotective and hepatomitogenic effect of IL-6/STAT3. These genes include Bcl-2, Bcl-xL, Mcl-1, FLIP, Ref-1, cyclin D1, c-myc, etc. (64). Inhibition of natural killer T cells may be another mechanism contributing to the hepatoprotective effect of IL-6 (65). Interestingly, recent studies have demonstrated that *in vivo* treatment with IL-6 or overexpression of constitutively activated STAT3 ameliorates fatty liver disease (51, 62), indicating that IL-6/STAT3 may also contribute to the regulation of hepatic fat metabolism. Taken together, these findings suggest that STAT3, activated by IL-6, plays an important role in hepatoprotection, liver regeneration, and glucose homeostasis *via* induction of a variety of anti-apoptotic and mitogenic proteins, glucose homeostasis, and fat metabolism.

IL-6-related cytokines

In addition to IL-6, several other IL-6-related cytokines also target hepatocytes; however, their functions have not been extensively investigated. Oncostatin M (OSM) is mainly produced by activated monocytes and T lymphocytes and plays important roles in anti-inflammatory response, cell proliferation and differentiation of several cell types (66). The action of human OSM is mediated by binding to hOSMR or hLIFR, followed by inducing heterdimerization of gp130 with hOSMR or gp130 with hLIFR, resulting in activation of several signaling pathways and a wide variety of biological functions, whereas mOSM only binds to mOSMR and induces heterdimerization of gp130 with mOSMR (66). OSM has been shown to 1) stimulate production of acute phase proteins in hepatocytes (67); 2) induce development, maturation, and differentiation of hepatocytes (68-70); 3) inhibit cell cycle of progression of hepatocytes (71), and regulate expression of cytochromes p450 and low density lipoprotein receptor in hepatocytes (72). Mice deficient in the OSM receptor showed impaired liver regeneration with persistent parenchymal necrosis after carbon tetrachloride exposure or partial hepatectomy, suggesting that OSM also plays an important role in liver regeneration and protection against liver injury (73).

Leukemia inhibitory factor (LIF) is a polyfunctional cytokine that has been shown to play important roles in hematopoietic, neuropoietic, endocrine system (74). The action of LIF is mediated through binding to LIF receptor, followed by inducing heterdimerization of LIFR and gp130, resulting in activation of STAT1, STAT3, STAT5, p42/44 MAP kinase (74). The role and signaling of LIF in the liver have not been extensively studied. *In situ* hybridization shows a strong expression of LIF, LIFR, and gp130 in the oval cells but only a weak expression in the parenchyma, suggesting that the LIF/LIFR gp130 system may be involved in the expansion and differentiation of the liver stem cell compartment (75). LIF also stimulates hepatic lipid metabolism (76) and expression of acute phase proteins in hepatocytes (77, 78).

Ciliary neurotrophic factor (CNTF) was initially identified by its ability to support the survival of para-sympathetic neurons of the chick ciliary ganglion *in vitro*, and now has found to play essential roles in neuronal system (79). Receptors for CNTF are also detected on peripheral tissues including liver (80), however the role of CNTF in the liver is less clear. Signal transduction by CNTF is mediated by binding first to CNTFRα, followed by recruiting gp130 and LIFRβ, forming a tripartite receptor complex. CNTF-induced heterodimerization of the LIFRβ subunits leads to tyrosine phosphorylation (through constitutively associated JAKs) and activation of multiple STATs (79). Injection of CNTF rapidly induces STAT3 tyrosine phosphorylation in the liver (79), which may contribute to the CNTF-induction of acute phase response in the liver (81, 82) and amelioration of diabetic parameters and hepatic steatosis in db/db mice (83).

Cardiotrophin-1 (CT-1) was originally identified to induce hypertrophy of cardiac myocytes and is now found to

play a wide variety of cellular functions in multiple organs (84). In the liver, CT-1 was found to induce acute-phase protein gene expression in hepatocytes (85, 86) and act as a survival factor for hepatocytes (87). Activation of STAT3, ERK1/2, and PI3 kinase/Akt has been implicated in the hepatoprotective function of CT-1 in the liver (87).

Interleukin-11 (IL-11) was first isolated from transformed stromal cells in 1990 and has now been shown to have a wide variety of biological functions in hematopoietic, lymphopoietic, and neuronal systems (88). The action of IL-11 is mediated through binding to IL-11Rα, followed by inducing heterodimerization, tyrosine phosphorylation, and activation of gp130. The activated gp130/IL-11α complex activates tyrosine kinases of the JAK family, which in turn causes activation of STAT3 and ERK (88). Although IL-11Rα is detected in the liver and hepatocytes, few studies were conducted to investigate the significance of IL-11 in the liver. It has been reported that IL-11 protects against liver injury induced by acetaminophen (89) and Concanavalin A (90).

Interleukin-22

Interleukin-22 (IL-22) is a recently identified cytokine, which belongs to IL-10 family of cytokines, including IL-10, IL-19, IL-20, and IL-24 (91, 92). The action of IL-22 is mediated *via* binding to a receptor complex composed of two chains: IL-10Rβ and IL-22R (93, 94), and subsequent activation of the JAK-STAT and ERK pathways (95). Although IL-22 and its receptor have been well characterized, the biological function of IL-22 remains obscure. Recent data from our laboratory indicate that IL-22 plays a protective role in T cell-mediated hepatitis and is a survival factor for hepatocytes (96). Activation of STAT3 and subsequent induction of a variety of anti-apoptotic and proliferation-associated genes seem to contribute to the hepatoprotective and mitogenic effect of IL-22 in the liver (96).

Other factors that activate STAT3 in the liver

Treatment of mice with IL-10 and EGF significantly induces STAT3 activation in the liver (27, 97); however, both IL-10 and EGF do not induce significantly STAT3 activation in isolated hepatocytes. These suggest that IL-10 and EGF may activate STAT3 in non-parenchymal cells. IL-10 has been shown to prevent hepatocellular damage in a variety models of liver injury (98), and it is believed that the hepatoprotective effect of IL-10 is mediated *via* its anti-inflammation action (98). Recently, several hepatitis viral proteins have also been shown to activate STAT3 in hepatic cells. For example, overexpression of HCV NS5A and HBX constitutively activates STAT3 tyrosine phosphorylation in Huh-7 cells and HepG2 cells, respectively (99, 100). Activation of reactive oxygen species is believed to play an important role in HCV NS5A- and HBX-mediated activation of STAT3 (99, 100). Since STAT3 is the major inducer of acute phase liver disease and has been implicated in tumor transformation, HCV NS5A- and HBX-induced STAT3 activation may be relevant to the acute hepatitis and high incidence of HCC associated with HCV and HBV infection, respectively.

STAT4

STAT4, mainly activated by IL-12, has been shown to play a key role in Th1 differentiation (101). STAT4 expression is restricted in myeloid cells, thymus and testis (102). Activation of STAT4 was also detected in several models of liver injury including Con A-induced T cell hepatitis (4) and hepatic ischemia/reperfusion injury (103). Whether IL-12 is responsible for STAT4 activation in these liver injury models remains unclear. Disruption of the STAT4 gene has been reported to reduce liver injury after ischemia/reperfusion insult (104), which was not confirmed by other investigators (103). The discrepancy between these two studies remains unclear. IL-12 has been implicated in the development and progression of liver injury in several models including hepatic ischemia/reperfusion (103) and Th1-dependent mouse liver injury (105); however, it is not clear whether IL-12 promotion of liver injury is mediated *via* activation of STAT4.

STAT5

STAT5 can be activated by a wide variety of cytokines in the immune and hematopoietic systems. In the liver, STAT5 is mainly activated by growth hormone, which regulates the expression of a wide range of hepatic genes, including cytochrome P450, glutathione S-transferase, sulfotransferase enzyme, growth homone receptor, serine protease inhibitor Sp12.1, insulin-growth factor I, and hepatocyte growth factor (106, 107). These genes are essential for metabolism, growth, and differentiation in the liver. Injection of mice with growth hormone was found to activate ERK, STAT1, STAT3 and STAT5 in the liver (108, 109). It is believed that ligation of growth hormone with its receptor induces receptor dimerization, which is followed by activation of the receptor-associated JAK2 kinase. This receptor-kinase complex then stimulates tyrosine phosphorylation of a number of intracellular signaling molecules, notably STAT5, STAT1, STAT3, insulin receptor substrate-1, SHC and mitogen activated protein kinase (110). Studies from STAT5-deficient mice suggest that STAT5b mediates the sexually dimorphic effects of growth hormone pulses in the liver, on body growth rate, and perhaps on other target tissues as well (111, 112).

STAT6

STAT6, mainly activated by IL-12, IL-4, and IL-13, plays an important role in Th2 differentiation (101). Activation of STAT6 has been reported in Con A-induced T cell hepatitis, and IL-4 is mainly responsible for such activation because STAT6 activation is markedly suppressed in IL-4-deficient mice after injection of Con A (113). The essential role of IL-4/STAT6 was demonstrated in Con A-induced T cell

hepatitis (113, 114) and SOCS-1 deficiency-induced hepatitis (115). Evidence suggests that IL-4/STAT6 plays a key role in T cell hepatitis *via* enhancing expression of eotaxins in hepatocytes and sinusoidal endothelial cells, and induces IL-5 expression, followed by inducing infiltration of eosinophils and neutrophils into the liver and leading to hepatitis (113). In contrast to the detrimental effect of IL-4/STAT6 in hepatitis model, IL-4/STAT6 was also shown to protect against ischemia/reperfusion liver injury. Injection of IL-4 and IL-13 activates STAT6 in the liver (116, 117) and reduces hepatic ischemia/reperfusion injury and STAT6 knockout mice are more susceptible to endotoxin-induced liver injury (118). These findings suggest that activation of STAT6 may play either a protective role or a harmful role in liver disease dependent on the liver injury models applied.

In conclusion

In summary, STAT1, mainly activated by IFN-α/β and IFN-γ not only plays a key role in the antiviral defense in hepatitis virus infection but also contributes to liver inflammation and injury, and suppression of liver regeneration. STAT2 activated by IFN-α/β and IFN-λ mainly contributes to the antiviral defense. STAT3 are activated by a wide variety of cytokines and viral proteins including IL-6 and its related cytokines, IL-22, hepatitis viral proteins. Activation of STAT3 plays a key role in acute phase response, protection against liver injury, promotion of liver regeneration, glucose homeostasis, and hepatic lipid metabolism. The function of STAT4 in the liver is less clear and is likely involved in promotion of hepatic ischemia/reperfusion injury. STAT5, mainly activated by growth hormone, plays an important role in controlling the expression of a wide range of hepatic genes, which are essential for metabolism, growth, and differentiation in the liver. Activation of STAT6 by IL-12, IL-4, and IL-13 has been shown to promote T cell hepatitis and inhibit ischemia/reperfusion liver injury. In addition, activation of these STATs may mutually regulate each other through induction of suppressors of cytokine signaling (SOCS) and tightly control the development and progression of liver diseases. Modulation of these STATs could offer a novel approach in the treatment of human liver diseases.

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