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EDITORIAL

Roles of transforming growth factor-β signaling in liver disease

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Abstract

In this editorial we expand the discussion on the article by Zhang *et al* published in the recent issue of the *World Journal of Hepatology*. We focus on the diagnostic and therapeutic targets identified on the basis of the current understanding of the molecular mechanisms of liver disease. Transforming growth factor-β (TGF-β) belongs to a structurally related cytokine super family. The family members display different time- and tissue-specific expression patterns associated with autoimmunity, inflammation, fibrosis, and tumorigenesis; and, they participate in the pathogenesis of many diseases. TGF-β and its related signaling pathways have been shown to participate in the progression of liver diseases, such as injury, inflammation, fibrosis, cirrhosis, and cancer. The often studied TGF-β/Smad signaling pathway has been shown to promote or inhibit liver fibrosis under different circumstances. Similarly, the early immature TGF-β molecule functions as a tumor suppressor, inducing apoptosis; but, its interaction with the mitogenic molecule epidermal growth factor alters this effect, activating anti-apoptotic signals that promote liver cancer development. Overall, TGF-β signaling displays contradictory effects in different liver disease stages. Therefore, the use of TGF-β and related signaling pathway molecules for diagnosis and treatment of liver diseases remains a challenge and needs further study. In this editorial, we aim to review the evidence for the use of TGF-β signaling pathway molecules as diagnostic or therapeutic targets for different liver disease stages.

Key Words: Transforming growth factor-β signaling; Liver disease; Molecular mechanism; Targets; Diagnosis

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Core Tip: Transforming growth factor-β (TGF-β) participates in diverse signaling pathways and exhibits contradictory roles in liver immunity, inflammation, repair, fibrosis, and other biological processes. In this editorial, we review the evidence for potential TGF-β signaling pathway molecules as diag-nostic or therapeutic targets for different liver disease stages.

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INTRODUCTION

Transforming growth factor-β (TGF-β) is a superfamily of cytokines with 33 member proteins, including TGF-β isoforms (TGF-β1/2/3), bone morphogenetic protein (BMP), growth and differentiation factor (GDF), activin, nodal, inhibin, and AMH (anti-Mullerian hormone). These proteins exhibit time- and tissue-specific expression patterns (Figure 1), and they participate in the development of pathological processes such as autoimmunity, inflammation, fibrosis, and tumorigenesis. In different liver diseases, TGF-β and its related signaling pathways regulate the progression from inflammation to fibrosis, to cirrhosis, and to liver cancer[1]. TGF-β1, TGF-β2, and TGF-β3-mediated signals are essential for liver homeostasis and repair, and they are key immune system regulators[2]. TGF-β/SMAD is a classical signaling pathway with effects that can both promote and inhibit liver fibrosis[3]. Immature TGF-β inhibits tumor factors during early liver cancer stages, but it has the opposite effect during late stages. Thus, TGF-β signaling affects different stages of liver disease progression, and the study of TGF-β and its signaling pathways to improve liver disease diagnoses and treatments remains an active field of study. In this paper, we review the evidence for diagnostic or therapeutic targets of TGF-β signaling pathways at different stages of liver disease.

TGF-β AND HEPATITIS

When the liver is affected by factors such as viruses, alcohol, drugs and autoimmune, liver cells are damaged, triggering an immune response that leads to liver inflammation. When liver disease is in a state of injury, white blood cells rapidly infiltrate liver parenchyma and promote liver inflammation by producing soluble mediators that activate other immune cells and non-parenchymal cell populations[4].

GDF-15 is a GDF subfamily member of the TGF-β superfamily, and although the exact mechanism of GDF-15 in liver disease has not been elucidated, elevated expression of GDF-15 has been detected in the liver of animal models of diet-induced non-alcoholic steatohepatitis (NASH). The study found that mice with GDF-15 knocked out exhibited a more severe phenotype, with more steatosis, fibrosis, inflammation, metabolic disorders, or liver damage, but the mechanism of action is unclear[5]. Endogenous GDF-15 expression directly inhibits fibrosis-related genes and osteopontin in hepatic stellate cells to prevent further progression of NASH and related metabolic disorders. Given the findings of this animal study, it is feasible to consider GDF-15 as a potential innovative therapeutic target for patients with NASH.

BMP contains more than 15 ligands in the TGF-β superfamily. BMP8B is not clearly characterized in the members of this superfamily. Although the liver pathophysiology of BMP8B is still in its infancy, BMP8B has been found to signal the SMAD2/3 and SMAD1/5/9 branches of the TGF-β-BMP pathway in hepatic astrocytes (HSC) to promote the expression of inflammatory phenotypes[6]. At the same time, in vivo, the deficiency of BMP8B prevents HSC activation, reduces inflammation and affects the wound healing response, thus limiting the progression of NASH[6]. Since BMP8B is virtually absent in healthy livers, it may provide a promising new therapeutic target for the treatment of NASH.

TGF-β1 is one of the three subtypes of the TGF-β family, and numerous studies have demonstrated that TGF-β1 inhibits hepatitis C virus (HCV) reproduction throughout the viral hepatitis life cycle through the TGF-β/SMAD signaling pathway. Although the antiviral mechanism of TGF-β1 remains to be elucidated, a new discovery has been made that when α-helix3 of TGF-β1 is deleted, it remains active against HCV transmission[7]. Therefore, TGF-β1 may inhibit HCV transmission in a manner independent of the TGF-β/SMAD signaling pathway. Based on the findings of this study, exploring the mechanism of action of TGF-β1 outside the TGF-β/SMAD signaling pathway provides another possibility for the TGF-β subtype to treat viral hepatitis.

TGF-B AND HEPATIC FIBROSIS

Liver fibrosis is the result of excessive extracellular matrix (ECM) deposition after liver injury, and it can lead to cirrhosis and hepatocellular carcinoma[8]. In essence, liver fibrosis is a response to repeated wound repair after continuous liver tissue damage. Continuous liver inflammation can lead to activation of stationary hepatic stellate cells and differentiation into myofibroblasts, which are the main source of ECM when hepatic astrocyte cells are injured[9].

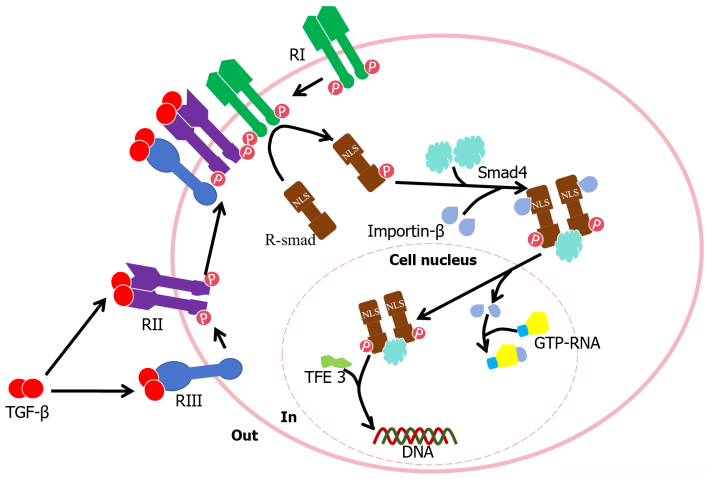

Figure 1 Transforming growth factor-β signaling pathway on hepatocytes. During transforming growth factor-β (TGF-β) signaling, TGF-β ligands first bind to the RIII receptor. RIII receptors recruit ligands near the plasma membrane, increase the local concentration of TGF-β ligands on the cell surface, and then transmit TGF-β to RII, activating the RII kinase domain. After RII kinase activation, the intracellular kinase domain is also phosphorylated, leading to RI kinase activation and signal transduction to the cytoplasm. Phosphorylated Smads proteins change their structure, exposing nuclear localization signals to be sent to the nucleus and activate DNA transcription. TF: Transcription factor; P: Phosphorylation; NLS: Nuclear localization signals; TGF-β: Transforming growth factor-β.

Activin A stimulates fibroblasts and hepatic stellate cells to produce TGF-β1, a central regulator of the fibrotic response [10]. Activin A can also induce the expression of TGF-β1 and other fibrotic regulators and intermediates, such as tissue inhibitor of metalloproteinase-1, plasminogen activator inhibitor 1, endothelin and collagen type 1, and a range of cell types[11]. In addition, TGF-β itself stimulates the production of activin A by fibroblasts. Other fibrotic regulators such as TNF-α, IL13, endothelin, angiotensin, and thrombin also drive activin A production in various cell types and tissues[12]. These data suggest that activin A is an important fibrosis mediator and it may be useful as a diagnostic tool and therapeutic target against fibrotic diseases.

BMP-2 is a negative regulator of hepatocyte proliferation that is down-regulated in regenerated livers. BMP-2 significantly inhibits the expression of TGF-β and its homologous type I and type II receptor peptides, and it induces Smad3 phosphorylation in hepatic astrocytes. Moreover, the expression levels of α-SMA and fibronectin (stimulated by TGF-β1) are significantly reduced, and so are the expression levels of TGF-β1-regulated epithelial–mesenchymal transformation (EMT) markers in hepatic astrocytes[13]. The interaction between BMP-2 and the TGF-β1 signaling axis may underlie the anti-fibrosis mechanism of BMP-2 during liver fibrosis, and BMP-2 may be a new therapeutic target for the treatment of that disease.

The TGF-β subtype may also participate in liver fibrosis according to the evidence: Increased levels of TGF-β1 have been found in animal models of liver fibrosis caused by carbon tetrachloride or by poisoning from schistosomiasis[14]; and, increased mRNA levels of TGF-β1 have also been observed in patients with liver fibrosis[14]. Therefore, these studies suggest that TGFβ1 may provide effective drug targets for liver fibrosis treatment[15].

SMAD proteins mediate intracellular TGF-β signaling. Growing evidence suggests that miRNAs are involved in liver fibrosis processes and hepatic astrocyte activation by targeting SMAD proteins[16]. MiR-199a is important for EMT and promotes liver fibrosis by enhancing the expression of fibrosis genes encoding α1 procollagen, collagenase 3, and metallo-proteinase inhibitor 1[17]. In addition, overexpression of miR-200 inhibits SMAD3 activity and attenuates TGF-β1-induced fibrosis. This suggests that miR-200a is regulated by TGF-β1/SMAD3 and that it interacts with SMAD3 to demonstrate its functional activity[18]. Thus, inhibition of SMAD3 signaling may be a potential fibrotic disease intervention strategy.

GDF-15 has been associated with hepatitis and liver fibrosis. Blocking GDF-15 with neutralizing antibodies results in delayed activation of primary hepatic stellate cells and remission of carbon tetrachloride-induced hepatic fibrosis. In primary hepatic astrocytes, TGF-β pathway activation is partially inhibited by GDF-15 neutralizing antibodies[19]; and, GDF-15 can activate AMPK in mouse hepatocytes and inhibit gluconeogenesis by preventing TGF-β1/SMAD3 signaling pathway activation. Liver fibrosis is suppressed by SMAD3 phosphorylation inhibition in this pathway[20]. The positive effects of GDF-15 on hepatic astrocyte activation and liver fibrosis make it a potentially therapeutic target to alleviate liver fibrosis.

TGF-B AND LIVER CIRRHOSIS

Chronic hepatitis and persistent liver fibrosis lead to cirrhosis with pseudo-lobular formation, an end-stage disease that kills more than one million people globally each year. Cirrhosis blocks essential liver functions such as albumin production, bilirubin metabolism, and clotting factor synthesis, resulting in edema, ascites, and spontaneous bleeding episodes[21]. The cirrhosis diagnosis is based on physical findings, histological examination, or imaging evidence.

However, cirrhosis is often asymptomatic during its initial stages and is difficult to detect.

TGF-β1 seems to increase in proportion to the severity of fibrosis rather than the presence of myofibroblasts (MFBs) during early and middle fibrosis development stages. With cirrhosis progression, the number of macrophages expressing TGF-β1 decreases, but the levels of TGF-β1 keep increasing. And, in advanced fibrotic and cirrhotic liver disease, the hepatocytes in several pseudo-lobules continue to express TGF-β1[22]. Therefore, in hepatic tissues presenting advanced fibrosis and cirrhosis, TGF-β1 production is associated with hepatocytes and offers a therapeutic strategy targeting TGF-β signaling. In the presence of cirrhosis, many hepatocytes in peri-lobular regions express higher levels of TGF-β than the hepatocytes in central regions[23]. TGF-β expression gets increased in both early and advanced primary biliary cirrhosis [24]. Given the importance of TGF-β in the pathogenesis of cirrhosis, TGF-β signaling pathways may prove effective targets for cirrhosis treatment.

Activins are composed of homologous or heterodimer subunits (βA, βB, βC, βE), each encoded by a single gene. During liver regeneration, the activin βA gene expression is decreased during hepatocyte replication and increased after the completion of liver regeneration[25]. Activin βA is thought to act as an autocrine inhibitor of hepatocyte growth that can induce hepatocyte apoptosis and inhibit liver regeneration in vivo, leading to increased liver damage during advanced cirrhosis stages[26].

BMP-7, a member of the BMP ligand family, can inhibit the downstream signals to TGF-β. BMP-7 actively induces type I collagen deposition by increasing matrix metalloproteinases-13 and decreasing tissue inhibitor of matrix metalloproteinases-2 expression, thereby suppressing fibrosis in a mouse cirrhosis model[27]. Thus, BMP-7 may be a useful therapeutic target in the TGF-β signaling pathway.

TGF-B AND LIVER CANCER

The liver is a regenerative tissue prone to cancer[28]. Hepatocellular carcinoma (HCC) is a major cause of cancer deaths worldwide[29]. The disease usually occurs in the context of inflammation caused by a chronic viral infection or metabolic liver disease[30]; therefore, clarifying the pathogenesis of liver cancer can help identify high-risk patients and guide the development of new tumor intervention and treatment strategies. TGF-β signaling is a key pathway involved in the pathogenesis of HCC and its role needs further elucidation.

TGF-β1 has been shown to play a dual role in carcinogenesis: On the one hand, it acts as a tumor suppressor during the early liver cancer stages by inducing apoptosis and eliminating precursor lesions. On the other hand, liver tumor cells produce large amounts of TGF-β, but become resistant to its pro-apoptotic effects during advanced stages[31].

Activins (members of the TGF-β superfamily subgroup) may also have an important role in the development of liver cancer[31]. Activin E, may have growth-limiting functions similar to those of activin A[32]. Studies have shown that activin E has a negative regulatory effect on the growth of liver cancer cells and inhibits regenerative DNA synthesis[33]. The mRNA levels of activin E have been shown to increase rapidly and then get decreased to near the basal levels 48 h after a partial hepatectomy[34]. Therefore, activin E has been associated with growth inhibition and apoptosis induction, suggesting that its cell growth regulatory function may serve as a new therapeutic target against liver cancer.

The signal transduction signals between TGF-β1 and BMP-7 are key for differentiation and development of many cell types, including mucosal Langerhans cells[35], myoblasts[35], and embryonic stem cells[36]. Therefore, we hypothesized that the dynamic transformation from TGF-β1 signals to BMP-7 signals is necessary for the development of HCC. The results of a study seem to corroborate this idea: when TGFBR2 and overexpressed ACVR1 are knocked down simultaneously to interfere with the TGF-β1/BMP-7 pathway balance, the TGF-β1 is inhibited while the BMP-7 pathway is promoted and strongly activated in HCC cells, significantly exacerbating the aggressiveness and stemness of the cells [37]. Thus, TGF-β1/BMP-7 pathway biomarkers may be useful to predict the clinical outcomes of patients with HCC.

BMP-9 is present in large quantities in healthy livers and helps to stabilize existing blood vessels and the epithelial phenotype of liver cells. However, under chronic injury, hepatocytes undergo malignant transformation and produce large amounts of BMP-9, which down-regulate the production of molecules necessary for maintaining the interstitial contact of cells around the tumor, inducing EMT of tumor cells and promoting the development of metastasis[38]. Thus, BMP-9 enhances tumor cell growth and metastases in HCC. But, the effects of BMP-9 on the surrounding stromal cells (fibroblasts) or other cell types around the tumor remain to be studied.

CONCLUSION

Liver diseases remain a major health threat, and exploring TGF-β and its signaling pathways is important to improve diagnosis and therapeutic strategies. Herein, we summarized the research progress on TGF-β and its signaling pathways in the context of liver diseases (Table 1). On the basis of the evidence, we believe that the TGF-β/Smad signaling pathway, the TGF-β/BMP pathway, and TGF-β/GDF proteins may be useful targets for diagnosis and treatment of these diseases. Although some signals involved in different liver disease stages have shown contradictory effects, the discovery and study of these potential targets is important. For example, metformin, a commonly used drug in the clinical practice, has been shown to inhibit the expression of TGF-β1 and liver fibrosis *via* its effects on the TGF-β/Smad signaling pathway [39]. The available diagnostic tools and treatment options against liver diseases remain inadequate. Exploring possible diagnostic and treatment strategies based on TGF-β and its signaling pathways is a promising source of improved tools against different liver diseases.

Table 1 Potential targets of transforming growth factor-β signaling in liver disease

Potential targets	Members of the family	Disease	Research progress	Ref.
GDF	GDF-15	Hepatitis	GDF-15 directly inhibits fibrosis-related genes and osteopontin in hepatic stellate cells	[5]
		Hepatic fibrosis	GDF 15 attenuates chemically induced hepatic fibrosis and delays hepatic stellate cell activation	[5, 19]
		Hepatic fibrosis	Through TGF-β1/SMAD3 signaling pathway, SMAD3 phosphorylation is blocked and liver fibrosis is inhibited	[20]
BMP	BMP8B	Hepatitis	BMP 8B signals through the SMAD 2/3 and SMAD1/5/9 branches of the TGFβ-BMP pathway in hepatic stellate cells to promote their pro-inflammatory phenotype	[6]
	BMP-2	Hepatic fibrosis	BMP-2 significantly inhibits the expression of TGF-β and its homologous type I and Type II receptor peptides, and induces Smad3 phosphorylation	[13]
	BMP-7	Liver cirrhosis	Adenovirus BMP-7 transduction induces a decrease in type I collagen deposition by increasing MMP-13 and decreasing TIMP-2 expression	[27]
	BMP-9	Liver cancer	Down-regulating the interstitial contact of cells surrounding the tumor induces epithelial–mesenchymal transformation of tumor cells, thereby promoting tumor metastasis and growth	[38]
TGF-β	TGF-β1	Hepatitis	TGF-β1 with its α-helix3 deleted is still effective against HCV, and TGF-β1 may inhibit HCV transmission in a manner independent of the TGF-β/SMAD signaling pathway	[7]
	TGF-β1	Liver cirrhosis	Few macrophages express TGF-β1 when cirrhosis is present; however, the protein is expressed in hepatocytes within several pseudolobules of the liver with advanced fibrosis and cirrhosis	[22-24]
	TGF-β	Liver cancer	TGF-β is a tumor suppressor in the early stages of liver cancer by inducing apoptosis and eliminating precursor lesions. During later stages, liver tumor cells often become resistant to apoptosis and produce large amounts of TGF-β	[31]
	TGF-β1/BMP-7	Liver cancer	Simultaneous knockdown of TGFBR2 and overexpressed ACVR1 induces complete activation of the BMP-7 pathway in HCC cells, significantly aggravating the invasiveness and stemness of HCC cells	[35-37]
Activin	Activin A	Hepatic fibrosis	Activin A can induce the expression of TGFβ1 and other fibrotic regulators and intermediates	[11-13]
	Activin βA	Liver cirrhosis	Activin βA induces hepatocyte apoptosis and inhibits liver regeneration *in vivo*, resulting in increased damage to liver regeneration during the later cirrhosis stages	[25, 26]
	Activin βE	Liver cancer	Activin can negatively regulate the growth of hepatocellular carcinoma cells and inhibit the synthesis of raw DNA	[31-34]
miRNA	miR-199a	Hepatic fibrosis	miR-199a enhances the expression of fibrotic genes to promote liver fibrosis, such as genes encoding α1 procollagen, collagenase 3, and metalloproteinase inhibitor 1	[16, 17]
	miR-200		miR-200 inhibits SMAD3 activity and attenuates TGF-β1-induced fibrosis	[18]

GDF: Growth and differentiation factor; TGF-β: Transforming growth factor-β; BMP: Bone morphogenetic protein; MMP: Matrix metalloproteinases; TIMP: Tissue inhibitor of matrix metalloproteinases; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus.

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