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Review Article

Cytokines Involved in the Progression of Liver Fibrosis by Influencing DNA Synthesis

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Abstract

Liver fibrosis is a pathological change in which the connective tissue in the liver proliferates abnormally, resulting in abnormal liver function or structure. Long-term liver fibrosis can develop cirrhosis or liver cancer, which poses a great threat to human health. This article reviews the cytokines closely related to liver fibrosis in recent years These cytokines affect the development of liver fibrosis mainly through processes that affect DNA synthesis. Platelet-derived growth factor promotes the division and proliferation of hepatic stellate cells by stimulating cellular DNA synthesis. Insulin-like growth factor, on the other hand, shows the proliferation of myofibroblastic cells in a manner that promotes the cell cycle to enter the DNA synthesis phase. Interleukin-6 promotes the progression of DNA synthesis in a manner that activates cyclins. We aim to find new approaches for the treatment of liver fibrosis by means of regulating DNA synthesis as the main approach by summarizing existing studies.

Keywords: Liver fibrosis; Cytokines; DNA synthesis

Introduction

Liver fibrosis is a pathological change in which the connective tissue in the liver is abnormally proliferated by chemical or viral infection, causes the abnormality of liver structure or function. It is characterized by massive deposition of fibrous connective tissue (such as collagen), ECM compounds and secretion of chemokines and fibrotic factors caused by acute or chronic injury. Liver fibrosis is a typical scar response to almost all forms of chronic liver injury [1]. Liver fibrosis has historically been considered a passive and irreversible process due to rupture of the liver parenchyma and replacement by collagen-rich tissue [2,3]. Current studies have shown that liver fibrosis could be reversible in the early stages. However, persistent liver damage and scar formation can still lead to advanced liver cirrhosis and even hepatocellular carcinoma (HCC) [4,5]. The characteristic of liver disease is the gradual progression from chronic hepatitis to liver fibrosis. Persistent liver fibrosis can lead to impaired liver function and destruction of liver tissue structure, which can lead to liver cirrhosis or hepatocellular carcinoma. Liver disease is a disease with a high mortality rate as the disease advances [6]. Chronic liver disease and cirrhosis are the 11th leading cause of death in the United States [7], with more than one million death each year worldwide [8].

The process of DNA synthesis is embodied in the process of cell proliferation. The cell cycle is the basic process of cell proliferation. It refers to the whole process that a cell goes through from the completion of one division to the end of the next division. It has been divided into two stages: interphase and division. Furthermore, the interval is divided into three phases which are early DNA synthesis period (G1 period), the DNA synthesis period (S period) and the late DNA synthesis period (G2 period). The division period is the DNA division period (M period) [9,10]. The G1 phase of the cell cycle prepares for DNA replication, the S phase replicates chromosomes, the G2 phase prepares for mitosis before chromosome separation,

and the final M phase undergoes mitosis. G0/G1 is an important checkpoint, which is the restriction point occurs in the middle of G1, after this R point, the cell is committed to cell division. All those processes could be related to liver fibrosis. Here we summarized Cytokines involved in the progression of liver fibrosis which might help us to understand the mechanisms and look for the potential therapeutic targets or approaches for liver fibrosis.

Pathogenesis of Liver Fibrosis

Liver fibrosis is the result of the liver's wound healing response after repeated damage to liver cells [11]. After acute liver injury, parenchymal cells regenerate and replace necrotic or apoptotic cells. If liver injury keeps existing, liver regeneration might eventually fail, liver cells were then replaced by abundant ECM and fibrous collagen, and normal cells such as metabolic activity could be disappeared, resulting in liver fibrosis [1].

The damaged liver cells release ROS and fibrosis mediators and induce inflammatory cells to recruit white blood cells and activate Kupffer cells. Studies have also suggested that the activation of hepatic stellate cells (HSC) plays an important role in the formation of liver fibrosis [12]; in addition to HSC, portal myofibroblasts and bone marrow-derived cells also have the potential for fibrogenesis [13].A variety of cells such as lymphocytes, polymorphonuclear cells and other inflammatory cells, damaged hepatocytes, bile duct cells and Kupffer cells [14] can secrete inflammatory cytokines to activate HSC; activated HSC could also secrete inflammation which maintains its activated state Sex cytokines. Therefore, vicious cycle of mutual stimulation of inflammatory cells and HSC could keep existing, which can also aggravate the occurrence of liver fibrosis, if the factors that cause liver cell damage remain existed [15]. This inflammatory environment will stimulate the transdifferentiation of native HSC into activated myofibroblasts (MFB), and the apoptosis of damaged liver cells can stimulate MFB to undergo fibrosis [16]. Then promoting HSC apoptosis can reduce the production of MFB cells, thereby interfering with the process of liver fibrosis [17]. Hepatocyte apoptosis directly triggers HSC activation through the phagocytosis of apoptotic bodies, or indirectly triggers HSC activation through injury-related molecular patterns that induce HSC migration and activation [18]. If liver damage persists, the accumulation of activated HSC and portal fibroblast MFB could be activated, a large amount of extracellular matrix protein (ECM) could also be synthesized [19]. Moreover, ECM protein has been proven to directly stimulate liver fibrosis. Studies have shown that, for delaying or reversing the progression of liver fibrosis, the cause of liver damage should be eliminated, or ECM degradation should be achieved through intervention (ECM degradation is inhibited by cytokines such as TIMPs, TGF-β).

Cytokines that Influence the Inflammatory Caused by Liver Injury

Damaged hepatocytes and bile duct cells can release inflammatory cytokines and soluble factors, which activate kupffer cells and stimulate the recruitment of activated T cells. This inflammatory environment stimulates the activation of resident HSCs into fibroblasts. HSC is the main fibroblast cell that is considered to play a role in liver fibrosis [20]. The HSC activation process is driven by cytokines released by damaged liver cells, bile duct cells, and T cellssuch as transforming growth factor (TGF-β) [21], platelet-derived growth factor (PDGF) [22], Interleukin-6 (IL-6) [23]. In the process of liver fibrosis, the transformation of static HSCs into activated fibroblasts is the central step of development. Therefore, inhibition of activated HSC is considered an important strategy for anti-fibrosis therapy [24].

TGF-β

TGF-β is a typical inflammatory cytokine secreted by a variety of hepatocytes including human hepatic stellate cells HSC, MFB [25], kupffer cells [26] and hepatocytes [27] with a typical pro-fibrotic effect. It has obvious effects in HSCs activation The pro-fibrotic effect [28] is the main fibrotic cytokine that activates HSCs [29,30]. This effect may be related to the stimulation of TGF-β that also activates other growth factors involved in HSC activation, including PDGF, CTGF, VEGFA and Fibroblast growth factor-2; and the release of TGF-β from necrotic hepatocytes is likely to be one of the primary signals for the activation of adjacent HSCs and subsequent transdifferentiation into MFB [31]. Therefore, TGF-β plays a key role in the HSC activation process, and epigenetic modification may be involved in this process [32]. Some studies have explored the epigenetic regulation of TGF-β signaling in other biological environments, and have shown that DNA methylation [33,34], MicroRNA (miRNA) and histone modifications regulate the gene expression of key effector factors of this pathway [35].

TGF-β activates HSC through the classical Smad signaling pathway and JNK signaling pathway. In the TGF-β/SMAD signaling pathway, TGF-β binds to the type I TGF-β receptor to initiate the pathway, activates and phosphorylates the downstream mediators SMAD2 and SMAD3, then forms a complex with SMAD4 and translocates to the nucleus, through binding to DNA or combined with DNA binding protein to regulate gene transcription [30,36], this process is negatively regulated by inhibitory SMAD7 [37]. SMAD7 is an effective inhibitor of TGF-β signaling. The overexpression of SMAD7 not only inhibits the activation of SMAD2/3, but also blocks NF-κB signaling during fibrosis and inflammation. In terms of liver fibrosis, SMAD3 is a cause sick, and SMAD7 is protective [38]. It

has been proposed that SMAD7 is a potential therapeutic target for liver fibrosis.

PDGF

PDGF is produced by many types of cells. When hepatocytes are damaged, it is mainly secreted by non-parenchymal Kupffer cells and sinusoidal endothelial cells [39]. It is one of the most effective mitogens for activating HSC. PDGF has significant mitogenic and motor-promoting effects [40], which can promote cell division and control maturity. PDGF can activate HSC through autocrine and paracrine signals [41] and plays an important role in stimulating the proliferation of HSC and changing its cytoskeleton distribution. PDGF can also promote the differentiation of HSC into myofibroblasts (MFBs) and regulate the process of liver fibrosis [42]. Studies [43] have proved that PDGF promotes the secretion and release of IGF and its binding protein in rat HSC and promotes the division and proliferation of HSC by stimulating cell DNA synthesis.

IGF

Insulin-like growth factor (IGF) is a polypeptide mitogen similar to proinsulin. Therefore, it plays an important role in regulating cell proliferation, differentiation and apoptosis, and mediates cell growth, immune regulation and anabolism [44]. After acute liver injury, hepatocytes secrete IGF-I in the pre-inflammatory stage. During the inflammation process of liver fibrosis, kupffer cells and activated HSC secrete IGFI [45]. There are two main pathways for IGF-I intracellular signal transduction, the PI3-K pathway and the extracellular signal-regulated kinase (ERK) pathway [46]. These pathways can mediate the interaction between IGF-I mitogenic response and anti-apoptotic response. In many cell types, IGF-I regulates proliferation by affecting the cell cycle [47]. In skeletal muscle, IGF-I enhances the G1/S phase process in a PI3 kinase-dependent manner [48] and can play a mitogenic effect. Studies [44] indicate that for HSCs in either the stationary or active phases, the effect of IGF-I on DNA synthesis is through the ERK1/2 pathway.

Cytokines Involved in the Hepatic Fibrogenesis

Chronic liver injury of various etiologies can lead to liver cell apoptosis, the repair mechanism is triggered, and an inflammatory response occurs [49]. Inflammatory cells such as lymphocytes or polymorphonuclear cells [50] can activate HSCs by releasing inflammatory cytokines. Therefore, makes those static, non-proliferative cells enriched with vitamin A transform into an activated contractile myofibroblast phenotype which is characterized by increased activation of DNA synthesis, proliferation, α-smooth muscle Actin (α-SMA) expression and synthesis of various ECM components [51]. Then, the production of ECM protein could be triggered. Accumulation of ECM protein could thereby replace the liver parenchymal area and lead to fibers into a state of liver cirrhosis [52]. MFB is the main source of ECM protein accumulation and the main mediator of fibrosis. Increased expression of fibrotic ECM plays an important role in liver fibrosis [53-55].

TGF-β

TGF-β is a powerful fibrotic factor responsible for the synthesis of extracellular matrix [56], which forms liver fibrosis by inducing MFB to express α-SMA. TGF-β1 activates intracellular mediators through TGF-β type I and type II receptors, such as Smad protein, p38 mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase pathway [57]. Phosphatidylinositol 3-kinase (PI3K) and MAPK signaling pathways must both be activated to induce mitogen-mediated DNA synthesis, while Janus kinase (JAK) triggers DNA synthesis by activating PI3K and MAPK [58].

TGF-β1 stimulates the secretion of activated HSC to induce the up-regulation of the two indicators of fibrosis, COL1A2 and α-SMA, and leads to excessive deposition of ECM protein. Studies have shown that the binding sites of transcription factors Sp1, AP-1 and Smad in the promoter region of Col1A2 are related to the transcription of fibroblasts induced by TGF-β1 [59]. The site is related to the transcription of fibroblasts induced by TGF-β1. Subsequent studies have shown that both Physalin D and Maleic acid derivative anti-oxidant can inhibit liver fibrosis by reducing the activity of the Col1A2 promoter [60]. Studies have shown that calcineurin is necessary for TGF-β-mediated ECM protein deposition. The regulator of calcineurin 1 (RCAN1) is an endogenous inhibitor of CaN [61]. Studies have shown that RCAN1.4 can reduce TGF-β-mediated liver fibrosis by inhibiting CaN / NFAT3 signaling [62]. On the other hand, overexpression of RCAN1.4 may induce cell cycle arrest in G0/G1 phase of activated HSCs and reduce the expression of cell cycle-related proteins. Therefore, RCAN1.4 can be used as a therapeutic target for the treatment of liver fibrosis.

IGF

In MFB, the ERK1/2 signaling pathway is necessary to promote proliferation [63]. In the process of MFB proliferation, IGF-I also promotes DNA synthesis. Research [44] displayed that IGF-I can initiate the process of DNA synthesis phase in the cell cycle, increases the number of cells in S phase, and also exerts an anti-apoptotic effect on the bcl system which locates in the upstream of ERK1/2. Therefore, increased proliferation of MFB cells promoted by IGF-I could be observed that instead of cell apoptosis.

Cytokines Involved in Fibrosis Resolution

Once the liver had been injured, a regeneration process could be initiated. During this process, the quiescent liver cells exit the quiescent phase (G0) and re-enter the cell cycle to proliferate and compensate for the lost liver tissue [57]. A variety of cytokines including hepatocyte growth factor (EGF), epidermal growth factor

(EGF), tumor necrosis factor-α (TNF-α), IL-6, insulin and TGF-β Coordinating cell cycle progression. They integrate with each other in the mitogen-sensitive G1 phase of the cell cycle until the restriction point (R), turning the cell into the S phase dedicated to proliferation, and starting the process of DNA synthesis [64]. HGF and EGF are powerful hepatocyte mitogens [65]. Although IL-6 is much smaller than the former, it can induce DNA synthesis. All three are important cytokines that promote hepatocyte proliferation [66]. Compared with IL-6, HGF and EGF, TGF-β1 is one of the most well-known hepatocyte anti-proliferation factors which can regulate the termination of liver regeneration and keep liver cells remaining under normal conditions [67].

A large amount of ECM proteins are deposited during liver fibrosis, resulting in changes in liver tissue and distortion of vascular structure. Therefore, digestion of ECM proteins is also one of the pathways to eliminate hepatic fibrosis [68]. Protein degradation mainly regulated by two pathways, one is mediated by autophagy-lysosomal pathway (ALP), which mainly degrades long-lived proteins and insoluble protein aggregates. The other one is dependent on ATP, non-lysosomal pathways mediated by the ubiquitin-protease pathway. It participates in the regulation of biological processes such as cell cycle, cell apoptosis, DNA repair, and intracellular signal transduction.

IL-6

IL-6 is a key factor in the mitotic response in the liver. IL-6 plays a protective role by arresting the cell cycle, allowing excision of bases, and repairing oxidized DNA. Studies [69] have demonstrated that IL-6 is important for latent Signal transducers and activators of transcription 3 (STAT3) activation, expression of cell cycle-related immediate early genes (IEGs), and initiation of cell cycle progression after partial hepatectomy. STAT3 protein plays a role in the progression from G1 phase to S phase of the cell cycle, and its activation depends on the release of IL-6 [70]. Studies [71] have shown that after the IL-6/STAT3 signaling pathway is initiated, the cell cycle enters the DNA synthesis phase. It leads to extensive cell regeneration.

TGF-β

TGF-β inhibits the proliferation of hepatocytes and keeps hepatocytes quiescent in the normal liver [7]. In addition, at the stage of liver regeneration, TGF-plays an important role in the process of reorganization of liver regenerative tissue and establishment of extracellular matrix [72]. Cyclin D1, CDK4 and P21 are factors that regulate proliferation and cell cycle [73]. Studies have shown that [10] TGF-β1 is involved in the expression of p21 in LX-2 cells, which affects the synthesis of DNA.

IGF

Although IGF-I can induce DNA synthesis in HSC, it still has pro-apoptotic and anti-proliferative effects. IGF can induce HSC proliferation and also can promote HSC apoptosis in a dose-dependent manner [46]. One study [44] showed that low doses of IGF-I had an anti-fibrotic effect in a model of CCl4-induced liver fibrosis. And IGF-I can promote the healing response of liver wounds by regulating the migration of HSCs through the PI3K signaling pathway [74]. The experiments of HSCs in rats showed that NFkB and ERK1/2 were involved in the regulation of IGF apoptosis [44]. IGF-I regulates apoptosis by regulating Bcl-2 upstream of ERK. The Bcl-2 gene family is a major modulator of the mitochondrial apoptotic pathway. These results indicate that IGF-I is inducing HSC apoptosis through the mitochondrial pathway [75]. From the perspective of DNA synthesis, while IGF-I promotes the initiation of cell cycle progression in HSCs, it is possible that IGF-I induces apoptotic processes earlier than affecting the cell cycle. Therefore, IGF-I showed the performance to promote HSC DNA synthesis, but hsc reduce the number of cells, increased apoptosis.

HGF

HGF is one of the first cytokines to be found to promote liver regeneration [76,77]. HGF binds and activates the tyrosine receptor kinase MET, a multifunctional receptor involved in many cellular processes such as proliferation, growth, survival, and metabolism [78]. The mitogenic activity of HGF-initiated signal requires the function of transcription factor C/EBPβ [79]. Hepatocyte growth factor/scatter factor (HGF/SF) stimulates hepatocytes to initiate DNA synthesis during the cell cycle. It protects hepatocytes from apoptosis, promotes liver regeneration in vivo, and reduces fibrosis [80]. However inhibition of PI3K or MAPK pathways can prevent HGF-induced DNA synthesis during hepatocyte proliferation [62].

Discussion

Cirrhosis caused by liver fibrosis is the leading cause of death from chronic liver disease, and chronic liver disease and cirrhosis are the 12th leading causes of death in the United States in 2016, rising to the 11th place in 2017 [7]. Liver cancer is the sixth most common cancer worldwide and the fourth leading cause of cancer death worldwide. In 2018, there were 841,080 new cases of liver cancer and 781,631 deaths worldwide, including 392,868 new cases of liver cancer and 368,960 deaths in China [81]. More importantly, more than 80% of HCCs develop from liver fibrosis [82].

HSCs and kupffer cells can activate each other to form a persistent inflammatory environment with massive monocyte infiltration, which includes lymphocytes, macrophages, plasma cells and eosinophils [83]. Lymphocytes are activated upon contact with antigens, which produce lymphokines that activate macrophages. Activated macrophages produce cytokines and chemokines that can activate lymphocytes [84]. This inflammatory environment stimulates the activation of resident HSCs into myofibroblasts. TGF-β and PDGF are the main cytokines involved

in the process. The TGF-β/Smad signaling pathway binds to DNA or DNA-binding proteins mainly by producing protein complexes. This pathway is involved in the regulation and expression of genes to activate HSCs [36]. Elevated expression of Smad7 protein was found in this pathway as a form of therapeutic fibrosis. In addition, PDGF released from platelets is a serum mitogen that plays a role in various processes of cell biology, enhancing cell division and controlling maturation [38]. PDGF activates HSCs through autocrine and paracrine signaling and stimulates cellular DNA synthesis in a dose-dependent manner to promote HSC division and proliferation, which can alter their cytoskeleton and thus promote HSC transdifferentiation into MFBs [41]. Moreover, studies have shown that amygdalin can reduce the transcription of PDGF and IGF mRNA and the expression of PDGF protein. Amygdalin reduces the development of liver fibrosis by reducing the synthesis and release of PDGF and IGF, thus attenuating their effects on HSCs [38]. The anti-apoptotic effect of IGF-I was postulated in vitro by Issa [85]. However, IGF-I was found to induce apoptosis in quiescent and activated HSCs in another experiment of HSC in rats, proposing that although IGF initiates the progression of HSC cell cycle, it may simultaneously arrest HSCs in G2 phase, therefore induce HSC apoptosis [44].

Cytokines secreted by damaged hepatocytes, inflammatory cells, and kupffer cells transdifferentiates hscs into MFB-expressing α-SMA, thereby acquiring fibrogenic properties that produce ECM proteins. Suffering a continuous inflammatory environment of liver injury, HSCs will continuously express MFB. MFB will then continuously proliferate to produce ECM, which ultimately leads to massive deposition of ECM and thus irreversible fibrosis. Therefore, in this stage, inhibiting MFB proliferation is an idea to eliminate fibrosis. Experimental studies showed IGF-I has a great effect on the cell cycle and proliferation as well as apoptotic signaling of MFB in rats. IGF signals intracellularly regulated by two pathways, PI3-K and ERK, and during MFB proliferation, IGF-I initiates the progression of DNA synthesis cell cycle and increases S-phase cells, but also exerts anti-apoptotic effects by acting on the bcl system upstream of ERK1/2 [44]. Therefore, inhibiting IGF synthesis or EPK signaling may be the approaches for the treatment of fibrosis.

Fibrosis can be digested by three aspects before ECM proteins deposited to form irreversible fibrosis, mainly including HSC apoptosis, ECM protein degradation, and regeneration of hepatocytes. In this paper, we mainly introduce three cytokines, IL-6, HGF, and EGF, which induce DNA synthesis and make hepatocytes proliferate by promoting the rapid entry of the cell cycle into the S phase. IGF induces HSC apoptosis by regulating the Bcl system upstream of the ERK signaling pathway [41]. As the important cytokine in the process of liver fibrosis [30], TGF-β is not only involved in the process of activating HSCs to promote the synthesis of matrix proteins by cells, but also involved in preventing ECM degradation. During liver fibrosis, TGF-β may affect cell proliferation, exhibiting its cell cycle arrest in G1 phase or frequently responding by apoptotic responses [72].

In the process of hepatocarcinogenesis, TGF-β plays a dual role. In early cancer, TGF-β plays a role in inhibiting tumor activity and inducing cell cycle arrest and apoptosis. However, in advanced cancers, once cells acquire resistance to their inhibitory effects, TGF-β action is switched to pro-carcinogenesis, conferring cell survival, inducing cell migration and invasion, and microenvironmental alterations [51,86].

Therefore, preventing, delaying or revising liver fibrosis have absolute positive effect on liver cancer or liver cirrhosis prevetion and also treatment. That makes explaining the basic mechanisms involved in liver fibrosis extremely important. By illuminating the effects of liver fibrosis related cytokines, the potential therapeutic targets could be located, then those bioactive protein could be intervened specifically for treatment goal. Beside treatment, effective prevention approach for liver cirrhosis and primary liver cancer are also deeply needed. As the basic pathological process in early stage before liver cancer or liver cirrhosis, fibrosis is the main disease that needs to be intervened for preventing liver cell from denaturation or cancerization. Effective prevetion methods could save patients from subsequent and harmful treatment, such as liver transplantation, radiotherapy, chemotherapy and target therapy, etc. that is also the reason we summarized those liver cytokines here. Certainly, further related in vivo, in vitro and clinical studies are indispensable.

Conclusion

The process of liver fibrosis involves a variety of cells and cytokines and affects its development through multiple signaling pathways. We summarized the cytokines that affect liver fibrosis by regulating DNA synthesis. Among them, the literature on the regulation of liver fibrosis by TGF-β through various signaling pathways is well-established, but there are few studies on affecting the process of DNA synthesis. In the future, more extensive and comprehensive experiments can be done on the effect of TGF-β on the process of DNA synthesis, its new target for the treatment of liver fibrosis was discovered.

Authors' Contributions

Shixin Li and Jiayin Li contributed equally to this work as co-first authors.

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