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Review article

Periostin in chronic liver diseases: Current research and future perspectives

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ABSTRACT

The liver is importantly metabolic and detoxifying organ in the body. When various pathogenic factors affect the liver, the normal physiological and biochemical functions are weakened, resulting in liver diseases. Liver fibrosis is a common pathological process of chronic liver disease. During hepatic fibrosis the changes in the components of the extracellular matrix (ECM) provide an environment that facilitates tissue remodeling. Among these ECM components, periostin, a glycoprotein that is predominantly secreted by osteoblasts and their precursors, playing an important role in bone formation, has attracted great attention. Periostin not only involves in bone metabolism, but also functions in modulating the cell fate determination, proliferation, inflammatory responses, even tumorigenesis of many other tissues and organs including liver. In different categories of liver disease patients, the serum and liver tissue levels of periostin were closely related to the decline of liver function, and the pathological stage. Numerous animal studies and experiments in vitro subsequently demonstrated that the abnormal expression of periostin resulted in metabolic disorders, liver inflammation, fibrosis and even tumorigenesis. Here we review the current progress on the role of periostin in pathologic pathways of liver system to explore whether periostin is a potential therapeutic target for the treatment of different liver diseases.

1. Introduction

The liver is not only an importantly metabolic and detoxifying organ in the body , but also a vital site of protein synthesis and immune privilege [1,2]. At the same time, it has regenerative capacity, high vascular capacitance [3,4]. When various pathogenic factors damage the liver, the physiological and biochemical function is weakened, resulting in liver diseases. Liver injury is divided into acute and chronic injuries according to duration. Acute liver injury results from acute liver failure, defined as a sharp decline in the number of hepatocytes [5]. Chronic liver injury is a long-term liver damage caused by inflammation or intracellular stress responses. Common examples of chronic liver injury include steatohepatitis (alcoholic and non-alcoholic), chronic viral hepatitis, and autoimmune-hepatitis. The continuous hepatic injury leads to the activation of hepatic stellate cells (HSCs). Activated HSCs could transdifferentiate into myofibroblasts, and then induce excessive tissue repair responses, resulting in liver fibrosis, cirrhosis and ultimately liver cancer [6]. In recent years, the incidence and mortality of chronic liver diseases have continued to rise, seriously threatening human health. Chronic liver diseases have become a major societal and economic burden for national health systems [7].

During the last years, a major focus in the deeper understanding of pathogenesis of liver disease, allows the development of prognostic markers, including histopathology, liver elastography and model for end-stage liver disease (MELD) score and therapeutic treatments (e.g.: antiviral agents). Attractively, these collective efforts also contribute to the discovery of several novel mediators and promising targets of liver diseases. Emerging evidence indicate that the dysfunction of periostin expression plays a prominent role in liver disease. Periostin, a cell-

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associated protein, involves in cell fate determination, proliferation, tumorigenesis, and inflammatory response. Signaling pathways regulating periostin expression are also pleiotropic and complicated. In the present review, we summarized the role and regulation of the periostin in non-alcoholic fatty liver disease (NAFLD), liver fibrosis, and liver cancer. The goal of this work is to provide implications and mechanisms of periostin in the pathogenesis of liver diseases and support evidence for drug development of targeting periostin as a mean of treating these diseases.

2. Biological characteristics and functions of periostin

Periostin, also known as osteoblast-specific factor 2 (OSF-2), is a 90 kDa multifunctional extracellular matrix (ECM) protein mainly secreted by osteoblasts. Periostin consists of 811 amino acid residues, belonging to the fascicle family member. Although it has the same homologous protein structure with the insect cell adhesion molecule fasciclin I, periostin has no glycosylphosphatidyl alcohol ester plasma membrane anchor point [8,9]. Periostin contains NH2-terminal signal peptide sequence, cysteine domain, four characteristic homologous weights complex structure domain and hydrophilic COOH-domain, where amino-terminus is highly conserved and binds to integrin in cytoplasm membrane through a homologous repeat structure (factor associated suicide domain), regulating cell function. Homo isomers at the carboxyl end of periostin, could regulate the composition and mutuality of ECM by adhering to ECM proteins [10].

Periostin has physiological protective effects on the organism, including remodeling ECM and wound repair in muscle and vascular injury, the formation and maintenance of bone and teeth, heart development, and the healing of tissues after acute myocardial infarction [11–14]. A growing number of researches show that the expression of periostin is at a low level in most normal adult tissues, but is significantly up-regulated in patients with tumor. For example, Zinn et al. determined causality between MRI-extracted radiomic-features in glioblastoma and POSTN expression, showing periostin levels are positively correlated with tumor phenotype in glioblastoma patients and orthotopic xenografts [15]. Besides, bone marrow mesenchymal stem cells (BMMSC) could enhance the expression of periostin in tumor tissues, and BMMSC–induced periostin promoted proliferation, invasion, survival, tumorigenicity and migration of head and neck cancer through PI3K/Akt/mTOR activation [16]. Furthermore, higher periostin expression in pancreatic neuroendocrine tumors (PNETs) promotes PNET revascularization by up-regulating fibroblast growth factor (FGF2), resulting in resistance to anti-angiogenic drugs [17]. Periostin is also upregulated in non-small cell lung cancer (NSCLC), and the overexpression of periostin could enhance stat3 and Akt phosphorylation and survivin expression, contributing to A549 cells more resistant to cisplatin-induced apoptosis [18]. On the other hand, it can interact with a variety of cytokines and inflammatory mediators, mediating inflammation and fibrosis, during tissue and organ lesions, including skin, kidney, heart, lung diseases [19–22], as well as liver diseases (Fig. 1).

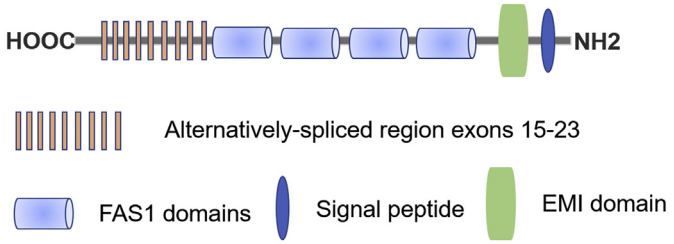

Fig. 1. A comparison of periostin.
The primary structure of periostin mainly comprises an alternatively spliced region consisting of nine exons at the C-terminus, four consecutive FAS1 domains in the central portion of the protein, and the EMILIN (EMI) domain and signal peptide sequence at the N-terminus.

3. The role of periostin in chronic liver diseases

3.1. Periostin and NAFLD

NAFLD, the major cause of chronic liver disease worldwide, includes a spectrum of diseases ranging from simple steatosis to non-alcoholic steatohepatitis (NASH). Some patients with NASH are likely to develop into cirrhosis and even hepatocellular carcinoma (HCC) [23]. NAFLD is characterized by excess accumulation of triglyceride (TG) in the hepatocyte due to both increased inflow of free fatty acids and de novo hepatic lipogenesis [24]. Obesity has been regarded as a threatening risk for the pathogenesis of hepatic steatosis and NASH [24]. Periostin was first implicated in the progression of NAFLD by a study that identified high expression of periostin in high-fat diet (HFD)-fed mice, as well as in ob/ob mice and db/db mice [25]. Lu et al. found that blocking periostin by shRNA and neutralizing antibody could dramatically improve hepatosteatosis and hypertriglyceridemia in obese mice. Mechanistically, overexpression of periostin in hepatocytes resulted in down-regulation of peroxisome proliferator–activated receptor α (PPARα) expression, a powerful regulator to reduce fatty acid oxidation, by activating the JNK signaling pathway [25]. Furthermore, a recent study indicated that the eicosapentaenoic acid ingestion suppressed hepatic lipogenesis by restraining the translation of hepatic peroxisome sterol regulatory element-binding protein (SREBP1c), carbohydrate response element-binding protein (ChREBP), and periostin in KKAy mice, which was independent on Notch and ubiquitin E3 ligase (gp78)-mediated hepatic lipogenesis pathways [26]. Chronic inflammation is a key contributor to the progression of NAFLD to NASH [27]. Methionine-choline-deficient (MCD) diet is widely accepted to induce mice NASH. Li et al. showed that periostin was markedly increased in mice liver and mainly distributed around steatotic hepatocytes after giving MCD diet, which was determined by immunohistochemical staining. Importantly, periostin knockout mice exhibited a markedly lower degree of steatosis, inflammation and fibrosis in their livers, compared to the wild type group [28]. This study revealed preliminarily the potential roles of periostin in NASH.

In clinical research, investigators found that serum and hepatic periostin expression levels were higher in NAFLD patients than controls, where NAFLD was diagnosed by liver ultrasonic examination [25,29]. Moreover, periostin levels were correlated with alanine aminotransferase (ALT), aspartate aminotransferase (AST), waist circumference, fasting plasma insulin, and TG [29]. The work also verified that overweight and obese individuals were susceptible to NAFLD and insulin resistance, result from elevated circulating periostin level [29]. Mimic results were later obtained by a clinical sex-/age-matched case–control study. Enzyme-linked immunosorbent assay showed that periostin expression is significantly up-regulated due to the release of proinflammatory cytokines in NAFLD patient liver, whereas negatively related to adiponectin, an anti-inflammatory and insulin-sensitizing adipokine [30]. Besides, R. Ali Khan et al. showed that compared with group hypocaloric diet alone, orlistat treatment evidently reversed the fatty liver ultrasound (US) grades in NAFLD patients, along with decreased serum levels of periostin and increased serum adiponectin levels, [31]. However, whether orlistat ameliorated the fatty infiltration in obese NAFLD patient liver effectively by reducing periostin needs to be further proved. In addition, detailed studies are necessary to promise periostin in liver or serum as an early and sensitive marker of NAFLD in clinic. Interestingly, the latest research showed that aging-induced loss of periostin in adipose tissue contributed to the development of metabolic disease by negatively affecting nutrient homeostasis. Further study found that periostin level in healthy subjects was significantly higher in subcutaneous white adipose tissue (WAT) than visceral WAT and this difference was blunted in patients with impaired glucose

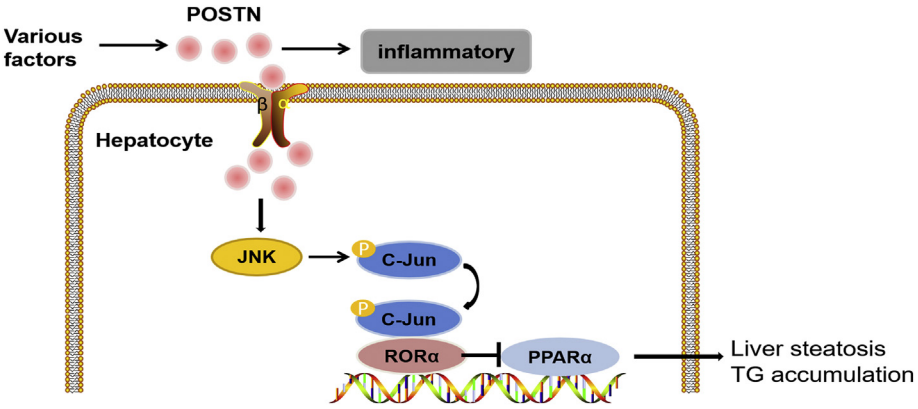

Fig. 2. The diagram of periostin regulation in NAFLD.
After an initial aggression, different growth factors, cytokines and signaling pathways upregulate periostin expression, amplifying the inflammatory. Moreover, periostin from autocrine or paracrine interacts with its integrin receptors on the hepatocyte surface, and induces hepatic steatosis. ShRNA targeting periostin inactivated the JNK signaling pathway, and subsequently down-regulating the expression of PPARα in both cell and mouse models of NAFLD.

tolerance or overt type 2 diabetes [32]. There is also evidence suggesting that abnormal levels of bone turnover biomarkers, including lower periostin expression in bone may promote hepatic lipogenesis of post-menopausal women or in patients with type 2 diabetes mellitus (T2DM) [33]. Consequently, the respective contribution of different tissues to circulating periostin and their involvement in the clinical manifestation of metabolic diseases remains to be clarified in further detail. In light of the proposed targeting of periostin for NAFLD treatment, subsequent studies will require tissue-specific ablation strategies before target therapy can be considered clinically (Fig. 2).

3.2. Periostin and liver fibrosis

Nearly, different chronic liver diseases are associated with liver fibrosis, a wound healing response, characterized by the excessive deposition of ECM proteins. As the pathological process without effective treatment in time, it will result in liver microcirculation disorders, the damage of blood vessel anatomy and structure, and formation of fibrous connective tissue, finally culminating in cirrhosis and HCC [34,35]. Liver transplantation is the only treatment available for patients with advanced stages of liver fibrosis [36]. Therefore, new therapeutic agents and strategies are needed for the management of this disease. Recent studies have analyzed the close relationship between periostin and liver fibrosis. Huang et al. firstly reported the expression of periostin increased dramatically in carbon tetrachloride (CCl_4) and bile duct ligation (BDL)-treated mice [37]. Hepatic inflammation and fibrosis in periostin-knockout mice were significantly inhibited. Besides, they found that the expression of periostin in acute or chronic hepatitis patients was up-regulated, correlated with high serum levels of transforming growth factor-β1 (TGF-β1) and TGF-β2. Interestingly, primary mouse HSCs did not express periostin, whereas the expression of periostin was dramatically increased in primary HSCs after 10 ng/mL TGF-β1 stimulation [37]. Hong et al. also showed that periostin was up-regulated in activated HSC, siRNA-periostin suppressed TGF-β1-induced HSC proliferation by attenuating Smad2/3 activation in HSCs [38]. Therefore, the mechanism that periostin mediates profibrogenic effect is probably related to periostin-induced transcription and translation of TGF-β1/SMAD signaling pathway. [38]

Recently, researchers have further conducted discussions on the intrinsic mechanisms of periostin-induced hepatic fibrosis. Akiko Sugiyama et al. suggested that periostin exerted potential profibrotic effect, which was mediated by alphav integrin, revealing the periostin–alphav integrin axis as a powerful intervention target for hepatic fibrosis [39]. Besides, Suneetha Amara et al. identified the binding sites between periostin and transcription factors by computational promoter sequence analysis, they found that TNF-α induced periostin via c-Jun signaling, while IL-17 induced periostin through STAT3-dependent mechanisms, both contributing to hepatic fibrogenesis [40]. This study was consistent with recent research that IL-17 might be a key factor involved in the pathogenesis of liver inflammation and progression to fibrosis, which promoted HSC activation and synthesis of periostin [41]. Interestingly, Takeda et al. built fibrotic-rat model, which were received choline deficient L amino acid (CDAA)-diet for 12 weeks to develop into steatohepatitis with liver fibrosis. Rats were administrated by losartan, an angiotensin II type I receptor blocker, and its hepatic fibrosis was ameliorated significantly. Experiments in vitro found that angiotensin II in human LX2 cells could increase the transcription of TGF-β1 and type I collagen α1 by promoting the expression of periostin, indicating that blocking angiotensin II mediated up-regulation of periostin might improve liver fibrosis effectively [42]. Collectively, periostin plays an important role in activated HSCs, and then aggravates the accumulation of fiber and matrix, ultimately induced liver fibrosis. Selectively blocking periostin in activated HSCs might emerge as a novel anti-fibrotic strategy in liver diseases (Fig. 3).

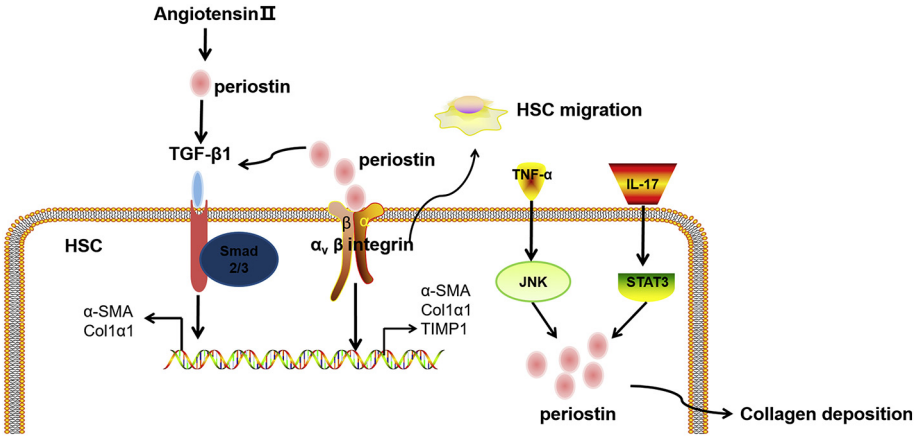

Fig. 3. The possible network of periostin machinery in liver fibrosis.
Mechanical stress, chemokines and changes in matrix composition trigger signaling pathways which induce periostin expression and subsequent secretion. Periostin interacts with αvβ1, β3, and β5 integrin signaling. In turn, a pro-fibrotic phenotype is further established in a feed-forward signaling cascade. Besides, periostin could promote HSC activation through TGF-β1/Smad signaling pathway. In addition, periostin leads to hepatic fibrogenesis through c-Jun and STAT-3 signaling mechanism.

It is well known that therapy with nevirapine (NVP), HIV inhibitor, triggers hepatotoxicity in 1–5% of patients [43]. Recently, H. Roger et al. investigated the effect of NVP on immunoallergic hepatitis. Female rats were dosed with either vehicle or NVP alone or galactosamine alone or a combination of NVP and galactosamine. No fibrosis occurred with NVP alone or galactosamine alone. Interestingly, hepatic fibrosis was noted in rats treated with the combination of NVP and galactosamine. Gene expression of the liver showed a viral-like response initiated by galactosamine via RNA sensors, resulting in toll-like receptor (TLR), and dendritic cell responses. NVP-induced periostin effects and growth factors exacerbated these responses and induced hepatic fibrosis [44]. Besides, other groups have found that chemotherapeutic agents, cisplatin, increased the number of nodules in the B16F10 liver metastasis model. At the same time, pretreatment with cisplatin increased the mRNA expression of periostin, which could cause serious neutrophil recruitment and inflammation to promote liver fibrosis [45]. These findings warn that it should be cautious against exacerbation of fibrosis by clinical drug application, such as NVP, cisplatin in patients with hepatitis or tumor, respectively.

3.3. Periostin and liver cancer

Liver cancer, as the terminal stage of all chronic liver diseases, has become the second commonest cause of cancer death worldwide. Liver cancer includes three different pathological types: HCC, Intrahepatic cholangiocarcinoma (ICC) and HCC-ICC hybrid [46]. Currently, surgery resection and liver transplantation are effective treatments for early liver cancer [47]. However, advanced liver cancer lacks effective treatment interventions, hematogenous metastasis occurring easily. There is an urgent need for valid molecular biology markers for preconditioning, diagnosis, and treatment of liver cancer in clinic, especially finding diagnostic markers with high specificity and sensitivity in early stage of liver cancer. It is essential for cancer progression that tumor cells interact with the ECM. ECM proteins (including periostin) are secreted by cancer cells and their surrounding stromal cells, which could create a microenvironment to promote the initiation, growth and metastasis dissemination of primary tumor [48]. The expression of periostin is significantly up-regulated in a large quantity of solid tumors and its expression is intimately related to tumor invasiveness and progression [49]. Serum periostin has functioned as an adverse marker in clinical prognosis of non-small cell lung cancer [50]. In recent years, many scholars have revealed that periostin played a vital role in liver tumorigenesis. Lv et al. firstly reported that the serum level of periostin was higher in HCC tissues than their adjacent tissues, and high POSTN levels were closely relevant with tumor metastasis and angiogenesis [51]. Importantly, they suggested that in comparison to normal controls and patients with hepatolithiasis and hepatic cirrhosis, serum periostin levels were most significantly high in HCC patients. Besides, they found that the increased level of serum periostin in patients with liver cirrhosis was second only to HCC. The elevated levels of serum periostin marked the decrease of overall and relapse-free survival in patients with HCC. What's more, it could be more applicable to combine serum periostin with α-fetoprotein (AFP) for discriminating HCC from non-HCC cirrhosis than each of the markers alone [52]. The results from the study by Jang et al. were in accordance with the works by previous study. They evaluated 149 patients who underwent surgical resection between 2006 and 2010, the result of immunohistochemical staining indicated that periostin overexpression and microvascular invasion in HCC were correlated with a poor prognosis [53]. These studies reveal that periostin might be a good prognostic marker for HCC.

A few recent studies have focused on the pathological mechanism of periostin-induced HCC. Molecules involved in the communication between HCC cells and stromal cells are potential drug targets. Engelmann et al. found that paracrine factors transmitted messages from activated HSCs to HCC cells through observational transcriptome profiles. This study showed that periostin secreted from activated HSCs might induced growth, invasion and migration of HCC cells [54]. Apart from inter-cellular communication with stromal cells being important for cancer cells, hypoxia has been suggested to induce chemoresistance in tumor cells [55,56]. Xenograft mouse studies in vivo showed that inhibiting periostin by shRNA significantly enhanced arsenic trioxide cytotoxicity to SMMC7721 tumors. Experimental evidence in vitro implicated that blocking hypoxia inducible factor-1α (HIF-1α) by shRNA reduced the expression of periostin in HCC cells upon hypoxia. Moreover, the upregulation of periostin enhanced HIF-1α-dependent gene transcriptional activity, including vascular endothelial growth factor (VEGF), myeloid cell leukemia-1 (MCL-1) [57]. Another study examined the influence of periostin and sulfatase 2 (SULF2) on angiogenesis in diethylnitrosamine (DEN) induced-primary liver tumors. SULF2-knockout (KO) mice displayed down-regulated periostin expression in HCC cells coupled with decreased angiogenesis and tumor growth. In vitro co-culture model of endothelial cells with HCC cells was performed to investigate the role of periostin in SULF2-induced angiogenesis. Silence of periostin in HCC cells suppressed SULF2-induced angiogenesis and tumor growth, and further studies confirmed that SULF2 regulated periostin transcription through TGFβ1-Smad signaling pathways, thereby mediating tumor angiogenesis of HCC cells [58]. Together, these findings defined the effects of periostin on drug resistance, angiogenesis, as well as tumor growth in HCC, and provided a theoretical foundation for the development of rational drug (Fig. 4).

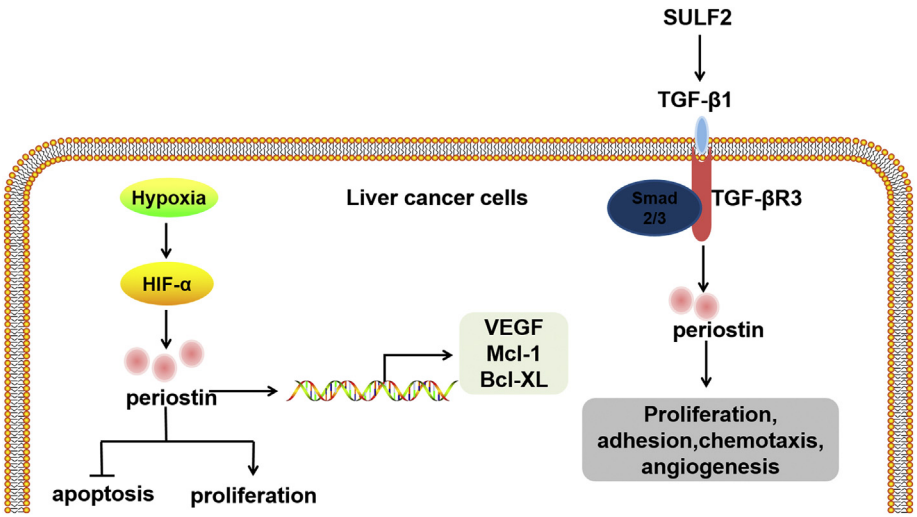

Fig. 4. The possible regulated pathway of periostin in liver cancer.
Hypoxia resulted in HIF-1α-dependent upregulation of periostin, enhancing a HIF-1α-dependent gene transcriptional activity, including VEGF, MCL-1. Besides, Heparan sulfate proteoglycans, SULF2 promoted the periostin transcription through TGFβ1-smad signaling pathways, thereby mediating tumor angiogenesis and tumor growth.

Table 1
Physiopathological functions of periostin in animal models of chronic liver diseases.

Animal models	Main findings	Comments	References
HFD-fed mice db/db mice ob/ob mice	Periostin contributed to the accumulation of hepatic TG and hepatic steatosis through activating the JNK signaling pathway, and subsequently down-regulating the expression PPARα.	Further studies are necessary to investigate whether abnormal periostin levels in liver can be applied in the clinic as an early and sensitive marker of NASH.	[25]
MCD diet-fed mice	Periostin was mainly distributed around steatotic hepatocytes and aggravated hepatic TGs, inflammatory, and collagen deposition significantly.		[28]
CCl_4 and BDL-treated mice	Periostin promoted hepatic fibrosis in mice by modulating HSC activation via alphav integrin interaction. TNF-α induced periostin through c-Jun and IL-17 induced periostin via STAT-3 signaling mechanisms led to hepatic fibrogenesis.	Selectively blocking periostin in activated HSCs emerges as an attractive candidate antifibrotic strategy.	[39,40]
CDAA diet-fed rat	Blocking the up-regulation of periostin could inhibit the progression of steatohepatitis with liver fibrosis in rats.		[42]
NVP-treated rat	NVP-induced periostin exacerbated apoptosis, toll-like receptor, and dendritic cell responses in rats.	Used female mice (most studies have used male mice); profibrotic effect of drug treatment for patients with hepatitis C should be considered clinically.	[44]
Cisplatin-treated mice	Cisplatin increased the mRNA expression of periostin, resulting in fibrosis and neutrophil recruitment.	Supporting clinical reports warning against exacerbation of fibrosis by cisplatin in patients with tumor.	[45]
Xenograft mice	Inhibiting periostin by shRNA significantly enhanced arsenic trioxide cytotoxicity to SMMC7721 tumors.	Provided a mechanistic foundation for liver cancer treatment drug development.	[57]
Diethylnitrosamine-treated mice	Periostin expression was down-regulated in HCC cells of SULF2-KO mice, accompanied by decreased angiogenesis and tumor growth.		[58]

Table 2
The functions of periostin in clinic patients with liver diseases.

Clinical liver sample	Main findings	Comments	References
NAFLD patients	NAFLD subjects had higher serum periostin levels than normal group, up-regulated periostin was positively correlated with ALT, AST, proinflammatory factor, fasting plasma insulin, and TG, negatively with adiponectin, an insulin-sensitizing and anti-inflammatory adipokine.	Periostin antagonists may render a rational therapeutic alternative for NFLAD treatment.	[25,29,30]
Chronic HBV infection-patients	Periostin was up-regulated and induced by TGF-β1 and TGF-β2	A large number of clinical researches and further study on the molecular mechanisms underlying the relationship between periostin and hepatitis is necessary.	[37]
HCC patients	The elevated serum periostin levels marked the decrease of overall survival (OS) and relapse-free survival (RFS) in HCC patients.	Serum periostin is a potential prognostic marker for liver cancer, and the development of periostin serum Kit has significant clinical applications.	[51–53]
ICC patients	The expression of serum periostin increased dramatically.		[59]

In addition, in vitro study verified that periostin promoted malignant potential by induction of epithelial-mesenchymal transition (EMT) in ICC, accompanied by significantly increased cell migration and invasion. Interestingly, periostin depletion by siRNA obviously improved the chemosensitivity to gemcitabine [59]. Subsequent studies in patient biopsies confirmed the elevated expression of serum periostin in ICC patients and highlighted the potential utility of periostin as a diagnostic biomarker of ICC progression [59]. Summarizing the above studies, it is suggested that serum periostin is a potential diagnostic and prognostic marker for liver cancer, and the development of periostin serum Kit has significantly clinical applications (Tables 1 and 2).

4. Conclusions

Current evidences indicate that periostin is a novel mediator of liver pathological processes, including hepatic steatosis, inflammation, fibrosis and tumorigenesis. To date, periostin antagonists have been investigated in breast and gastric cancer [60,61]. Therefore, a wider and deeper understanding of the mechanisms of periostin in the development of liver diseases may render periostin antagonists a reasonable therapeutic alternative for liver disease treatment. At the same time, when drugs function as regulating pathological periostin, we should pay attention to controlling the degree to maintain the dynamic balance and consider tissue-specific ablation strategies before target therapy can be applied clinically. The above studies also show that serum periostin could act as a prognostic marker for liver cancer. Thus, role of serum periostin level, which is definitely more accessible means of testing, may need to be investigated and validated in other studies. On the other hand, periostin deletion decreased macrophages infiltration and TNF-α and IL-6 levels in the liver, which inactivated the STAT3 signaling in hepatocytes and subsequently inhibited hepatocyte proliferation in the mice after partial hepatectomy (PHx). Furthermore, periostin deficiency impaired angiogenesis in the late phase of liver regeneration [62]. Periostin overexpression efficiently promotes mice liver regeneration after PHx, which reminds us that periostin has a protective effect under the specific liver pathology.

Abbreviations

AFLD	alcoholic fatty liver disease
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BDL	bile duct ligation
CCl_4	carbon tetrachloride
CDAA	choline deficient L amino acid
ChREBP	carbohydrate response element-binding protein
ECM	extracellular matrix
EMT	epithelial-mesenchymal transition
FFA	free fatty acids
HCC	hepatocellular carcinoma
HFD	high-fat diet
HSCs	hepatic stellate cells
ICC	intrahepatic cholangiocarcinoma
IR	insulin resistance
MCD	methionine-choline-deficient diet
MELD	model for end-stage liver disease

NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NVP	nevirapine
OSF-2	osteoblast-specific factor 2
PHx	partial hepatectomy
PPARα	peroxisome proliferator–activated receptor α
SREBP1c	sterol regulatory element-binding protein
SULF2	sulfatase 2
TG	triglyceride
TGF-β1	transforming growth factor-β1
US	ultrasound
VEGF	vascular endothelial growth factor

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Disclosure statement

The authors declare that they have no conflicts of interest.

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