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Review

Role of prostaglandin E_2 and its receptors in chronic liver disease

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Abstract: Chronic liver disease (CLD) is a major global health burden in terms of growing morbidity and mortality. Although many conditions can cause CLD, leading to cirrhosis and hepatocellular carcinoma (HCC), viral hepatitis, drug-induced liver injury (DILI), alcoholic liver disease (ALD) and non-alcoholic fatty liver disease (NAFLD) are the most common culprits. Prostaglandin E_2 (PGE_2), produced in the liver, is an important lipid mediator derived from the ω-6 polyunsaturated fatty acid, arachidonic acid, and plays a critical role in hepatic homeostasis. The physiological effects of PGE_2 are mediated through four classes of E-type prostaglandin (EP) receptors, namely EP1, EP2, EP3 and EP4. In recent years, an increasing number of studies has been done to clarify the effects of PGE_2 and EP receptors in regulating liver function and the pathogenesis of CLD to create a new potential clinical impact. In this review, we overview the biosynthesis and regulation of PGE_2 and discuss the role of its synthesizing enzymes and receptors in the maintenance of normal liver function and the development and progress of CLD. We also discuss the potential of the PGE_2-EP receptors system in treating CLD with various etiologies.

Key words: chronic liver disease; prostaglandin E_2; EP1; EP2; EP3; EP4

前列腺素E_2及其受体在慢性肝脏疾病中的作用研究进展

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摘 要：慢性肝脏疾病(chronic liver disease, CLD)是一个全球性的健康负担，其发病率和死亡率都在逐年增加。虽然多种情况可引起CLD，进而导致肝硬化和肝细胞癌，但是病毒性肝炎、药物性肝损伤、酒精性肝病和非酒精性脂肪性肝病是最常见的原因。前列腺素E_2 (prostaglandin E_2, PGE_2)是ω-6多不饱和脂肪酸花生四烯酸代谢产生的一种重要脂质介质，在维持肝脏稳态平衡中起着关键作用。PGE_2通过四种不同的E型前列腺素(EP)受体，即EP1、EP2、EP3和EP4，参与机体众多生理与病理生理过程。近年来，越来越多的研究表明PGE_2和EP受体在调节肝功能和CLD的发病机制中发挥重要作用。本文将结合最新研究进展对PGE_2和EP受体在CLD中的作用进行简要综述，并讨论PGE_2-EP受体系统在治疗各种病因导致的CLD中的潜力。

关键词：慢性肝脏疾病；前列腺素E_2；EP1；EP2；EP3；EP4

Chronic liver disease (CLD) leads to significant morbidity and mortality worldwide, resulting in 2 million deaths annually [1, 2]. CLD has become the 10th leading cause of death [1–3]. The most common etiologies of CLD include viral hepatitis, non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD) and

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drug-induced liver injury (DILI). Regardless of the etiology, a common end-stage of liver disease progression is cirrhosis, which can develop further into hepatocellular carcinoma (HCC). CLD is hallmarked by persistent liver inflammation, hepatocellular injury, progressive fibrosis, and ultimately vascular and architectural remodeling [4]. Prostaglandin E_2 (PGE_2) is a bioactive lipid with a variety of biological effects, including carcinogenesis, effects on inflammation and alteration of hepatic hemodynamics. The liver is not only the main metabolizing organ of PGE_2, but also an important target tissue of PGE_2. PGE_2 plays a critical role in maintaining hepatic homeostasis [5–7]. Accumulating data defines that PGE_2 has far-reaching effects on the occurrence, progression, prognosis, and treatment of CLD.

This review will summarize the detailed effects of PGE_2 and its receptors in the pathogenesis and progression of CLD and discuss the strategies for developing novel therapies by targeting the PGE_2-E-type prostaglandin (EP) receptors axis.

1 Biosynthesis of PGE_2

PGE_2 belongs to the eicosanoid family with a variety of biological activities and can be synthesized by nearly

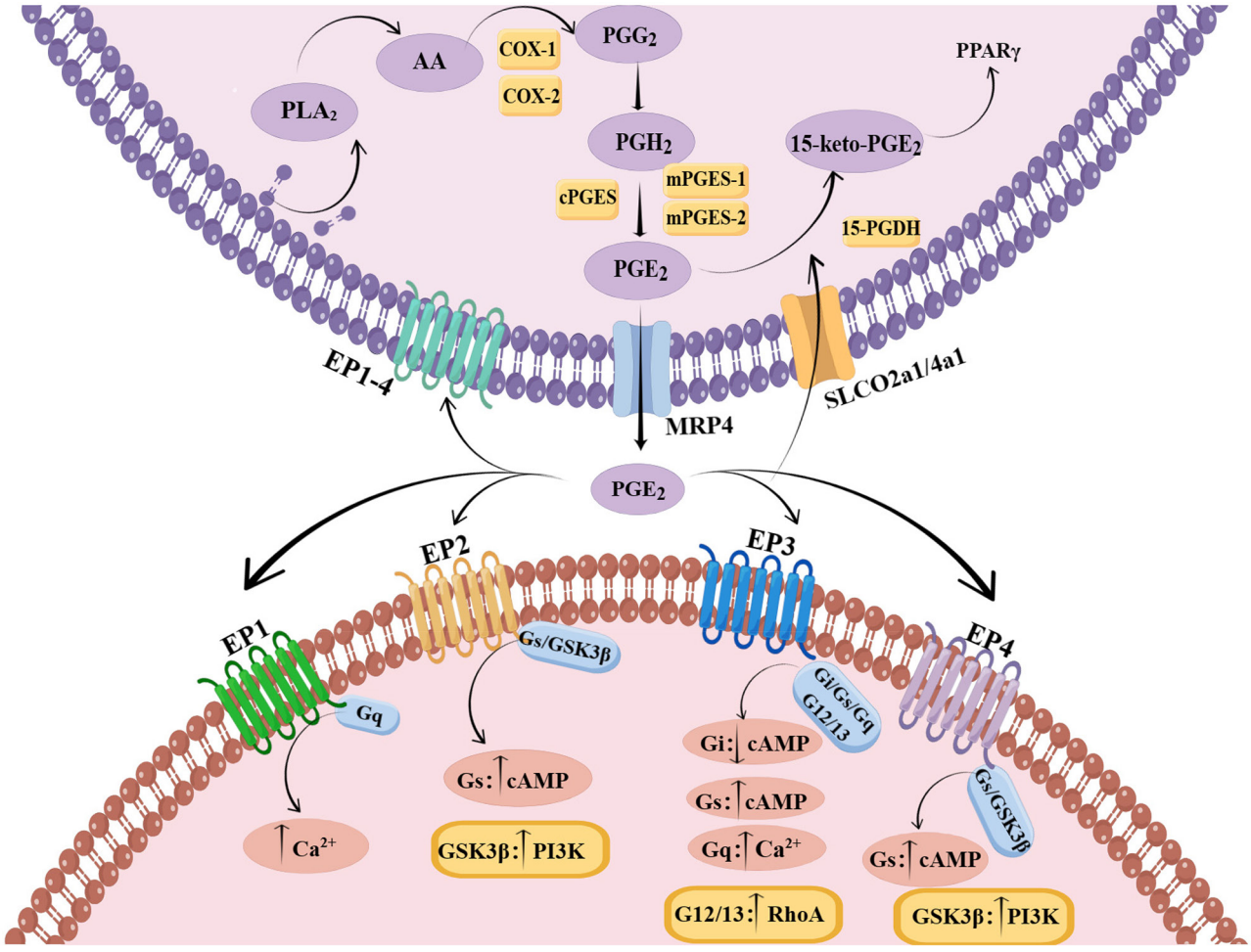

Fig. 1. Prostaglandin E_2 (PGE_2) synthesis and signaling pathways. Membrane phospholipids are catalyzed by phospholipase A_2 (PLA_2) to produce arachidonic acid (AA), which is subsequently converted to prostaglandin H_2 (PGH_2) via cyclooxygenase isoforms (COX-1 and COX-2). PGH_2 is then further metabolized into PGE_2 by three PGE synthases, including microsomal PGE synthase-1 (mPGES-1), microsomal PGE synthase-2 (mPGES-2), and cytosolic PGE synthase (cPGES). PGE_2 plays its role by combining with four G protein-coupled receptors, designated EP1–EP4. PGE_2 is released into extracellular environment by the membrane transporter multidrug resistance protein 4 (MRP4) and uptaked by the transporter SLCO2A1 and SLCO4A1. PGE_2 activates multiple EP receptors in an autocrine or paracrine manner. PGG_2, prostaglandin G_2; 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; PPARγ, peroxisome proliferator-activated receptor γ; GSK3β, glycogen synthase kinase-3β. Figure created using FigDraw.

all types of cells in human body [8, 9]. It is produced through three sequential enzymatic processes (Fig. 1). Firstly, under diverse stimulation, PGE_2 is produced by arachidonic acid (AA), which is liberated by membrane phospholipids catalyzed by phospholipase A_2 (PLA_2) [8, 10, 11]. Secondly, with the action of cyclooxygenases (COXs), AA is oxidized to the prostaglandin G_2 (PGG_2) and is then metabolized to unstable intermediate prostaglandin H_2 (PGH_2) [12]. COX is the crucial enzyme in prostanoid synthesis from AA. There are at least two different isoforms of COX enzymes, including COX-1 and COX-2. COX-1 is constitutively expressed throughout the body and produces stable levels of prostaglandins to maintain essential physiological functions, while COX-2 is an inducible enzyme that plays an important role in pathophysiological states, particularly inflammation and tumorigenesis [13, 14]. Finally, PGH_2 is catalyzed by PGE synthases (PGES) to produce PGE_2. Three PGES isozymes have been identified, including microsomal PGE synthase-1 (mPGES-1), microsomal PGE synthase-2 (mPGES-2), and cytosolic PGE synthase (cPGES) [15]. Generally, mPGES-1 is thought to be a heterodimer of inflammatory activation, whereas mPGES-2 and cPGES are constitutively expressed in almost all tissues [16]. With evidences suggesting a preferential functional coupling in the interaction of COX and PGES, mPGES-1 tends to couple with inducible COX-2 to stimulate PGE_2 synthesis, while cPGES is preferentially linked with constitutive COX-1 to maintain basal PGE_2 synthesis [17–19]. In addition, 15-hydroxyprostaglandin dehydrogenase (15-PGDH) is responsible for catalyzing PGE_2 to its inactive form 15-keto-PGE_2. PGE_2 can be released into the extracellular space or uptaked by cells via the multidrug resistance protein 4 (MRP4), SLCO2A1/PGT/OATP2A1 and SLCO4A1/OATP4A1 [20–22]. It has been well documented that PGE_2 can signal through four different G protein-coupled receptors (GPCRs) to exert its multiple biological functions [23].

2 The EP receptors

The physiological activity of PGE_2 is achieved by binding to its specific GPCRs, referred to as the EP1, EP2, EP3, and EP4 (Fig. 1). EP1 is coupled to Gq to mediate the activation of phospholipase C (PLC), resulting in the accumulation of inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) in order to mobilize intracellular Ca^{2+} from the endoplasmic reticulum, as well as to activate protein kinase C (PKC) [24]. Signal transduction mediated by PKC leads to activation of mitogen-activated protein kinase (MAPK), nuclear factor of activated T cells (NFAT) and nuclear factor-kappa B (NF-κB) [24]. Both EP2 and EP4 are linked to Gs and activate adenylate cyclase, which increases cAMP levels in cells, leading to activation of protein kinase A (PKA) [25]. PKA directly phosphorylates and activates the transcription factor cAMP-response element binding protein (CREB) [26]. According to the study, EP2 and EP4 signaling activates not only CREB, but also the glycogen synthase kinase-3β (GSK3β)/β-catenin pathway [26]. In mice, EP3 has three isoforms named EP3α, EP3β, and EP3γ, deriving from alternative splicing of the carboxyl terminal tail [24]. All three isoforms of EP3 can couple to Gi to inhibit the activation of cAMP [27], which can also increase intracellular Ca^{2+} levels and thus activate PLC. EP3γ can also bind to Gs proteins to activate adenylate cyclase and increase cAMP levels [28]. EP3β was found to increase cAMP via the Gq-PLC-Ca^{2+} pathway [29]. Furthermore, EP3 has been demonstrated to activate RhoA via the G12/13 proteins. The PGE_2-EP3 signaling triggers Ras/Raf and MAPK signaling pathways [28]. Overall, EP receptor signaling accounts for the multiple biological effects of PGE_2. Therefore, the function that PGE_2 exerts depends largely on the predominant type of receptor activated in the tissue.

3 Role of PGE_2 and its receptors in viral hepatitis

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are the major causes of chronic hepatitis, which can progress to liver fibrosis, cirrhosis and HCC [30]. Chronic HBV is a non-cytopathic virus, meaning that liver dysfunction is considered to be immune-mediated rather than a direct cytopathic effect of the virus [31]. PGE_2 exhibits potent immune-modulating activity on different immune cells [32]. Li *et al.* [33] showed that serum PGE_2 concentration was positively correlated with the severity of liver damage and the viral load in patients with HBV hepatitis, and blocking PGE_2 signaling restored $CD8^+$ T cell functionality and viral clearance. This study also identified that PGE_2 analogs promoted HBV replication, while antagonists of EP2 and EP4 inhibited viral replication in an AAV-HBV1.2 mouse model [33]. Hepatitis B virus X protein (HBx) plays a key role in promoting chronic hepatitis B to liver cancer [34]. HBx can activate the CREB/COX2/PGE_2/signal transducer and activator of transcription 3

(STAT3) signaling pathway [35]. Therefore, it was revealed that inhibition of PGE_2 synthesis in HBx-induced inflammation might help to eliminate inflammation and thus prevent HBV excess to cancer [36, 37]. Similarly, HCV infection can also cause an inflammatory response, and therefore the level of PGE_2 is significantly increased in HCV-expressing cells. PGE_2 binds to EP4 to activate the PI3K/Akt pathway, and its direct downstream substrates GSK-3 and Bad, thereby inhibiting apoptosis in the virus-infected cells [38]. When Trujillo-Murillo *et al*. inhibited COX-1/2 activity by acetylsalicylic acid (ASA, a COX-1/2 inhibitor) treatment in Huh7 HCV replicon cells exposed to ethanol, ASA significantly decreased COX-2 activity and blocked ethanol-induced HCV-RNA expression [39]. Contrary to that, a recent study has shown that inhibition of PGE_2 biosynthesis in cultured HCV-expressing cells resulted in increased levels of HCV-RNA. Consistently, exogenous addition of PGE_2 was found to downregulate HCV-RNA [38]. There are some explanations for the divergent results. Firstly, a different stable replisome cell line was used in this study compared to the Trujillo-Murillo's study, and secondly, the cell treatment times were different in the two studies. It is unclear what role the PGE_2 pathway may play in response to HCV infection. Taken together, PGE_2 affects numerous cellular processes that influence viral infectivity and replication efficiency in host cells or by modulating the host immune response to viral infection. PGE_2 could be a promising therapeutic target for hepatitis virus infection.

4 Role of PGE_2 in DILI

DILI is a relatively rare but potentially life-threatening pathological condition of the liver that usually occurs with the use of medications, herbal products, or illicit drugs [40]. These drugs can produce a wide range of hepatotoxicity, often in a dose-dependent manner. Growing evidence points to an important hepatoprotective role of PGE_2 after DILI [41–44]. Acetaminophen (APAP) hepatotoxicity remains a clinically important problem with multiple unmet medical needs. N-acetyl-*L*-cysteine (NAC), the sole available therapy, is effective for preventing APAP toxicity; however, it has a narrow time window for therapeutic intervention [45]. North *et al.* [42] established a physiologically relevant model of APAP hepatotoxicity in zebrafish. Notably, they observed that the co-administration of PGE_2 and NAC not only prolonged the treatment time window, but also significantly improved liver function and reduced mortality. However, there was no such effect with either of the above-mentioned agents alone. This was possibly due to the regulation of two different mechanisms of liver injury: NAC-mediated reduced glutathione (GSH) replenishment combined with PGE_2-mediated proliferative and anti-apoptotic effects via the Wnt signaling pathway. Recently, it has been reported that mPGES-2 gene deficient mice are resistant to APAP-induced liver injury due to depletion of hepatic antioxidant GSH content [46]. However, the deletion of the mPGES-2 gene may increase glucose transporter 2 (GLUT2)-mediated streptozotocin (STZ) uptake to promote STZ-induced hepatotoxicity [47]. These findings demonstrate that mPGES-2 plays an important role in the regulation of liver function. Reilly *et al*. found APAP-induced hepatotoxicity and lethality were markedly greater in *COX-2*$^{-/-}$ and *COX-2*$^{-/+}$ mice in which normal prostaglandin responsiveness was altered. Finally, they also proposed that COX-2 played an important role in protecting against the hepatotoxic effects of drugs, possibly through both nonimmune and immune-mediated mechanisms [44]. Carbamazepine (CBZ), a widely used antiepileptic drug, is one of the most common causes of atopic liver injury and immune response [48]. In CBZ-induced liver injury, elevated levels of hepatic PGE_2 expression demonstrated hepatoprotective effects to some extent [49]. Further investigation will be necessary to clarify the mechanism of DILI development. It was found that PGE_2 could attenuate APAP-induced acute liver failure in mice, and the mechanism was that PGE_2 could activate EP4 of macrophages, inhibit the secretion of TNF-α, and activate EP4 of hepatocytes to promote the autophagy of hepatocytes, and enhance the tolerance of hepatocytes to APAP [50]. Based on the key role of PGE_2 in protecting the liver from drug toxicity, the PGE_2-EP receptors axis has the potential to present a promising therapeutic measure on the preventive and therapeutic treatment of DILI.

5 Role of PGE_2 and its receptors in ALD

The liver is the principal site of ethanol metabolism, and chronic, heavy alcohol consumption can result in liver damage and a wide range of liver manifestations [51]. ALD involves alcoholic steatosis, alcoholic hepatitis, alcoholic steatohepatitis and alcoholic cirrhosis [52]. The pathogenesis of ALD is multifactorial and complex, including the direct toxic effects of alcohol and its metabolites, as well as inflammatory mediators and

cytokines. There are considerable evidences that steatosis is a critical factor in the progressive development of inflammation and fibrosis after long-term heavy alcohol intake [53, 54]. However, alcoholic steatosis is influenced by the prostaglandin system [55]. It is well-known that the roles played by PGE_2 are very complex during the progression of fatty liver. In a study using alcohol-fed rat models, Enomoto *et al.* [55] found that ethanol increased liver triglyceride (TG) and PGE_2 production by Kupffer cells over a short period of time, and the increased PGE_2 levels were blunted by the non-specific COX inhibitor indomethacin. *In vivo* treatment with PGE_2 and EP2/EP4 agonists resulted in a significant increase in hepatic TG content, whereas EP1/EP3 agonists had no effect on it. It is believed that PGE_2 secreted from Kupffer cells interacts with the receptors EP2 and EP4 on hepatocytes to increase intracellular cAMP levels, leading to the accumulation of TG in the liver. However, other studies have reported PGE_2 was proved to significantly diminish the production of enzymes engaged in *de novo* lipogenesis in the liver [56]. Lukivskaya *et al.* [57] reported that in a rat model of chronic alcoholic hepatic steatosis, hepatic PGE_2 levels were reduced, and ursodeoxycholic acid (UDCA) prevented the development of alcoholic steatosis by increasing hepatic PGE_2 levels. Thus far, it remains unclear why ethanol causes these differences among those studies. The different dose and duration of ethanol used in the experiments might be part of the reason. Future in-depth studies on the mechanisms by which ethanol regulates PGE_2 production will advance our understanding of the ethanol-induced hepatic inflammatory response and contribute to the development of new therapeutic candidates for the therapy of ALD.

6 Role of PGE_2 and its receptors in NAFLD

NAFLD comprises simple steatosis and nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis and HCC, ultimately causing liver-related death [58]. Previous studies have proposed that the primary biological mechanism of NAFLD involves insulin resistance, inflammation, hepatic lipid accumulation and hyperglycemia [59–61]. The precise relationship between PGE_2 and NAFLD remains unclear, and studies have shown variable results. Insulin resistance is considered to be a central causative factor of NAFLD [62, 63]. Growing evidence has indicated that PGE_2 plays an important role in the development of insulin resistance. Previous experimental studies have illustrated that the treatment of COX-2 inhibitors in a rat model of obesity can improve insulin resistance, specifically by the mechanism that COX-2 inhibitors reduce hepatic PGE_2 levels, thereby inhibiting hepatic glucose production and reducing TG levels [64, 65]. Another study showed that increased production of PGE_2 in Kupffer cells activated extracellular signal-regulated kinase 1/2 (ERK1/2) via EP3, which subsequently promoted serine phosphorylation of insulin receptor substrate (IRS) 1 and ultimately inhibited glycogen synthesis in hepatocytes [66]. Furthermore, PGE_2 in turn stimulates Kupffer cells to produce oncostatin M (OSM) which impairs insulin-dependent IRS/PI3K/Akt signaling, leading to inhibition of expression of key enzymes involved in hepatic lipid metabolism and increased TG accumulation [66]. However, PGE_2 can also exert a protective effect against hepatic insulin signaling. In high-fat diet (HFD)-fed mice, overexpression of hepatic COX-2 resulted in a significant increase in PGE_2 levels and caused protection against hepatic insulin resistance [67]. Fernández-Iglesias *et al.* found that $EP3^{-/-}$ mice fed with an HFD developed a more severe obesity phenotype and insulin resistance [68]. Taken together, the effect of PGE_2 on hepatic insulin resistance is ambiguous, and further study will be required to elucidate the exact mechanism.

The build-up of hepatic neutral lipid contents, especially TG, is the onset of hepatic steatosis. Roles of PGE_2 in the aetiopathogenesis of hepatic steatosis remains controversial. On one hand, PGE_2 inhibits *de novo* synthesis of hepatic fatty acids to resist hepatocyte steatosis. On the other hand, PGE_2 promotes hepatocyte lipid accumulation by inhibiting lipolysis, mitochondrial β-oxidation and VLDL synthesis [69]. Increased COX-2 activity and PGE_2 concentrations in HFD-fed mice lead to the development of nonalcoholic steatosis through NF-κB activation and enhanced lipid peroxidation [70]. PGE_2 is also involved in the evolution from steatosis to NASH. Henkel *et al.* [71] reported that hepatic expression of COX-2 and mPGES-1 was significantly higher in patients with NASH than that in the control group or patients with simple steatosis. A lipidomic analysis was performed in a clinical cohort in an attempt to characterize liver inflammation in NASH. It was found that only NASH patients had elevated plasma PGE_2 levels [72]. On the basis of such findings, it has been proposed that PGE_2 may exacerbate the development of NASH. However, an *in vivo* study using hepatocyte-specific COX-2 transgenic mice (hCOX-2-Tg) found an increased

levels of PGE_2 in the livers and improved hepatic steatosis and inflammatory response, likely by lowering levels of IL-6, TNF-α and monocyte chemoattractant protein-1 (MCP-1) [73]. Similarly, under a NASH-inducing diet, hepatic PGE_2 expression was reduced in the livers of mPGES-1 knockout mice, resulting in more severe NASH phenotypes than that in wild-type mice [71]. Thus, PGE_2 appears to play a protective role in metabolic disorders caused by NAFLD. Consistent findings are shown in studies examining PGE_2-EP3 signaling, which has a benefit for preventing insulin resistance and reducing fat deposit in adipose tissue. EP3 gene knockout in mice has been revealed to result in diabetes and obesity. It has also been shown that the $EP3^{-/-}$ mice gained more weight than the $EP3^{+/+}$ mice when fed with an HFD, and were endowed with more severe insulin resistance and adipose accumulation in the liver [74]. Collectively, PGE_2 participates in the development and progression of NAFLD with the underlying mechanisms incompletely understood. Targeting the PGE_2-EP receptors pathway may represent a promising strategy for the treatment of NAFLD, which is well worth further exploration.

7 Role of PGE_2 and its receptors in liver fibrosis

Liver fibrosis is a tissue repair response secondary to chronic liver injury of different etiologies [75]. The characteristics of liver fibrosis are the migration and activation of hepatic stellate cells (HSCs) and deposits of excessive extracellular matrix (ECM) [76]. In liver fibrosis, hepatic PGE_2 expression is increased, but its role in this pathological process is a controversial issue [77–79]. The effect of PGE_2 on fibrosis is complex and may depend on binding with different types of EP receptors. It has been previously reported that COX-derived PGE_2 can inhibit the advancement of fibrosis and NASH [80, 81]. It was found that under TGF-β1-induced conditions, COX-2-derived PGE_2 inhibited collagen synthesis by downregulating collagen type I α1 and α smooth muscle actin (α-SMA) in HSCs [82]. Consistent with the above findings, PGE_2 was reported to reduce apoptosis in hepatocytes, but lead to apoptosis and inactivation of HSCs by downregulating miR-23a-5p and miR-28a-5p expression in HSCs. Reduced miR-23a-5p and miR-28a-5p promoted fibrosis prevention by decreasing the expression of fibrotic markers α-SMA and collagen type I α1 [83], suggesting a protective effect of PGE_2 on liver fibrosis. However, the opposite role of PGE_2 in hepatic fibrogenesis has also been reported. Many studies indicate that the COX-2/PGE_2 axis is associated positively with hepatic fibrogenesis [78, 84–87]. Chen *et al.* showed that the level of PGE_2 was significantly increased in mouse liver infected with *Schistosoma japonicum* and in LPS-triggered HSCs, where PGE_2 activated HSCs via EP2 and EP4 [87]. In addition, several researches demonstrated that the selective COX-2 inhibitor JTE-522 decreased the PGE_2 levels and reduced fibrogenesis in CCL_4-induced cirrhotic livers [88–90]. Similar results were obtained in another experimental model with thioacetamide (TAA)-induced liver fibrosis in rats [85]. Recently, A few surveys noted that the COX-2 selective inhibitor celecoxib can effectively ameliorate liver cirrhosis through inhibiting epithelial-to-mesenchymal transition of hepatocytes [77], reducing the release of inflammatory cytokines, and inhibiting excessive oxidative stress [91]. The current debate on the role of PGE_2 in liver fibrosis is influenced by various aspects. Firstly, most investigations have obviously utilized primary HSCs, which may lead to differences in isolation techniques between experimenters, thus limiting direct comparison of results. Secondly, the stimuli that initiate hematopoietic stem cell activation may also be derived from their surrounding cells, including various immune cells. Thirdly, the current experiments are only *in vitro* analyses that may not reflect the dynamic signaling interactions during the formation of liver fibrosis *in vivo*. In fact, a most recent report by Tao *et al*. found that EP3 was significantly downregulated in NK cells from both hepatic fibrosis mice and cirrhotic patients. This research also identified that NK cell-specific knockdown of EP3 markedly exacerbated the development of liver fibrosis, however, activation of EP3 by sulphostrome attenuated CCL_4-induced liver fibrosis in mice. These findings demonstrate that EP3 in NK cells may serve as a therapeutic target for the management of liver fibrosis [92].

8 Role of PGE_2 and its receptors in HCC

HCC accounts for 90% of primary liver cancers [93]. Surgical resection is considered as the best clinical choice, but is not suitable for advanced-stage HCC, which remains a challenge. Given the importance of inflammation in tumorigenesis and progression, there is little doubt that the anti-inflammation is an important therapy strategy for tumors. It is generally known that

PGE_2 is an important lipid mediator in the inflammatory environment that influences malignant tumor initiation and progression. Clinical studies have revealed a significant increase of PGE_2 in the peripheral blood of HCC patients, mainly due to the increased synthesis of PGE_2 by HCC tissues [94, 95]. Overexpression of PGE_2-synthesizing COX-2 in HCC is also strongly associated with poor prognosis. A correlation analysis further indicated that higher circulating levels of PGE_2 in HCC patients were linked to worse tumor grade and shorter survival [96, 97]. Increasing evidence shows that PGE_2 can contribute to the progression of HCC in multiple ways through both autocrine and paracrine mechanisms. *In vitro* investigations have shown that knockdown of COX-2 expression in HCC reduces the expression of cyclin D1, a cell cycle-associated protein, and leads to cell cycle arrest, thereby significantly inhibiting the proliferation of HCC cells [98]. In a mouse xenograft model, Lu *et al*. found that mPGES-1 overexpressing HCC cells developed larger tumors with a faster tumor growth velocity in nude mice, whereas knocking out mPGES-1 resulted in the opposite [99]. It has been proposed that in HCC cells, PGE_2 may affect the development and progression of HCC by activating multiple pathways through its EP receptors. In a HCC cell line, Han *et al.* have found that the EP1/PKC/c-Src signaling pathway leads to epidermal growth factor receptor (EGFR) transactivation [100], which then induces the phosphorylation of p44/42 MAPK to promote invasion of HCC cells [101]. Activation of PKC by EP1 was also reported to induce β1-integrin overexpression through the NF-κB/FoxC2 signaling pathway and promote HCC cell migration [102]. Similarly, it has been reported that activation of EP2 enhanced the proliferation of Hep3B cells, while EP2 antagonism blocked PGE_2-induced cell growth and invasion [103, 104]. EP2 activation can also enhance tumor cell migration by upregulating snail proteins through the Src-EGFR-Akt-mTOR pathway [105]. In terms of EP3, its activation promotes cell growth by increasing the expression of FUSE-binding protein 1 (FBP1) through the Gs protein and PKA pathways [106]. Activation of EP4 also shows an accelerating effect on HCC cell migration through EGFR-associated upregulation of snail proteins [107]. Consistently, EP4 agonist ONO-AE1-437 treatment protects HepG2 cells with induction of the apoptosis-resistant protein Bcl-xL expression [108]. As the COX-2/PGE_2/EP receptors axis appears to have a significant effect on the occurence and development of HCC, numerous trials have been conducted to examine the potential of targeting this axis as a novel treatment for HCC. A recent study reported that the combination of the selective COX-2 inhibitor meloxicam and the anti-angiogenic T7 peptide showed greater antitumor effects in murine HCC tumors [109]. The combined use of epigallocatechin-3-gallate (EGCG), the most potent active ingredient in tea polyphenols, and ONO-8711, an EP1 inhibitor, significantly inhibited PGE_2-induced HCC proliferation and migration compared with the use of these two drugs alone [110]. In conclusion, PGE_2 exerts pleiotropic effects on the HCC tumorigenesis and progression, which positions PGE_2 as a potential therapy target for HCC. The combination of COX-2/PGE_2/EP receptors axis-based drugs and traditional antineoplastic agents might be a promising therapeutic strategy for patients with advanced HCC.

9 Summary and perspectives

A plenty of *in vitro* and *in vivo* studies have demonstrated that PGE_2 is involved in CLDs with various etiologies and plays complex roles in their pathogenesis. Most of studies reveal that PGE_2 can promote hepatitis virus infection and accelerate the development of HCC, while attenuates DILI. The role of PGE_2 in ALD, NAFLD and liver fibrosis is even more controversial. Hence, well-designed studies focusing on the underlying molecular mechanisms of each PGE_2 receptor in the development of CLD are urgent needed. Despite the multitude of preclinical studies exploiting PGE_2 as a therapeutic target in cancer have yielded early promising results, a number of key hurdles still need to be overcome for successful translation into clinical treatment. Currently, a great deal of works have focused on determining the signaling pathways activated by each EP receptor in the hope that targeting the EP receptors will avoid adverse effects mediated by COX-2 inhibition and achieve better therapeutic outcomes. The following basic questions will be the focus of further research. Can PGE_2 be used as a diagnostic or therapeutic marker for CLD? If so, how can PGE_2 be monitored in tissue in real time and how can endogenous PGE_2 levels be increased or exogenous PGE_2 be delivered to the site of action? Does PGE_2 interact with other molecules during the progression of liver injury? Addressing these questions will help to develop new and more precise therapeutic strategies based on the PGE_2-EP receptors pathway for the treatment of CLD.

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