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REVIEW

Therapeutic potential of targeting protein tyrosine phosphatases in liver diseases

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Abstract Protein tyrosine phosphorylation is a post-translational modification that regulates protein structure to modulate demic organisms' homeostasis and function. This physiological process is regulated by two enzyme families, protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs). As an important regulator of protein function, PTPs are indispensable for maintaining cell intrinsic physiology in different systems, as well as liver physiological and pathological processes. Dysregulation of PTPs has been implicated in multiple liver-related diseases, including chronic liver diseases (CLDs), hepatocellular carcinoma (HCC), and liver injury, and several PTPs are being studied as drug therapeutic targets. Therefore, given the regulatory role of PTPs in diverse liver diseases, a collated review of their function and mechanism is necessary. Moreover, based on the current research status of targeted therapy, we emphasize the inclusion of several PTP members that are clinically significant in the development and progression of liver diseases. As an emerging breakthrough direction in the treatment of liver diseases, this review summarizes the research status of PTP-targeting compounds in liver diseases to illustrate their potential in clinical treatment. Overall, this review aims to support the development of novel PTP-based treatment pathways for liver diseases.

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1. Introduction

Proteins are the basic components that make up cells, and healthy cells and even the normal life activities of organisms are the result of their functional homeostasis. The function of proteins is affected by chemical modifications, and this class of modifications catalyzed by different enzymes is referred to as post-translational modification (PTM)[1]. Protein tyrosine phosphorylation is one of the key modifications in the physiological function of proteins, and most proteins in eukaryotic cells have one or more amino acid residues that can be phosphorylated[2]. As a dynamic reversible PTM, protein tyrosine phosphorylation is regulated by the balanced and cooperative coordination of two opposing enzymatic processes: PTKs which add phosphate groups to tyrosine residues and PTPs, which remove these phosphate groups[3,4]. Tyrosine phosphorylation is highly related to the physiological and pathological processes of the body, and regulates most, if not all, intracellular or intercellular basic functions which include cell proliferation, migration and differentiation[5]. Although it is generally accepted that the regulatory relationship between PTPs and PTKs in tyrosine phosphorylation is balanced and interdependent, the study on PTPs has lagged behind that of PTKs, in part because PTKs were discovered and purified before PTPs[6]. PTKs are known to disrupt key cellular pathways and are well-established regulators of many human diseases, such as cancer and immune system diseases[7,8]. Several small molecule PTK inhibitors have been approved for clinical cancer therapy[9]. Furthermore, despite the involvement of PTPs in cellular signaling pathways through both enzymatic and non-enzymatic activities, the functional roles and mechanisms of tyrosine phosphatases, as well as their inhibitors in human diseases, still require further elucidation.

In the late 1980s, a decade after the initial discovery of protein tyrosine kinases, protein tyrosine phosphatase 1B (PTP1B) was identified as the first tyrosine phosphatase. Subsequently, the identification and research of PTPs entered a period of rapid development. The latest research has expanded the PTPs to encompass a PTP superfamily consisting of 125 members[10]. These enzymes exhibit tyrosine dephosphorylation activity and the majority of them contain domains of catalytic activity, as well as domains that determine their mechanisms, subcellular localization, and substrate specificity[10]. The PTPs can be further divided into Cys-based, His-based, and Asp-based families, which are classified by the differences in their nucleophilic catalytic residues, and Cys-based accounts for the majority. Cys-based PTPs consist of three classes, each characterized by a conserved CX_5R motif. Class I represents the classical receptor PTPs (RPTPs), non-receptor PTPs (NRPTPs) and dual-specificity phosphatases (DUSPs). There are two members in class II: Low molecular weight PTP (LMW-PTP) and suppressor of Sua72 (SSu72). Class III consists of three cell division cycle 25 (CDC25) PTPs, named CDC25A, CDC25B, and CDC25C[11] (Fig. 1).

PTPs are widely expressed in almost all types of cells and thus act as a key regulator in cell-to-cell signaling communication, the initiation and progression of diseases, as well as their recovery. For example, glucose metabolic homeostasis is essential for the body's energy balance[12]. PTPs are involved in signal transduction at multiple nodes of glucose homeostasis, including early events of leptin signaling, which elicits leptin resistance by dephosphorylation of Janus kinase 2 (JAK2)[12]. Similarly, PTPs control hepatic glucose metabolism. Several PTPs have been shown to attenuate insulin signaling in peripheral tissues, reduce insulin receptor phosphorylation levels in the liver, cause insulin resistance, and they also induce inflammation and stress responses[13]. In addition, the presence of PTPs in the immune system enables their participation in the downstream signaling of T cell receptors, and allows them to control effector T cells, such as TH cells and Treg cells[14,15]. The broad expression profile and critical role of this superfamily of enzymes in cell signaling suggest that they have great potential as drug targets for metabolic-related diseases and cancer immunotherapy. Notably, recent studies have shown that targeting the activity of specific PTPs can control metabolic diseases and even tumor growth *in vivo*[16].

2. Liver and liver-related diseases

Liver, the largest organ of the body, is a primary part of digestive and detoxification system. It serves as the hub for a multitude of physiological activities, encompassing the storage of proteins and vitamins, regulating the synthesis and metabolism of lipids and hormones, and is also involved in maintaining immunological homeostasis[17]. The centrality of the liver in detoxification and metabolic regulation renders it particularly susceptible to a spectrum of detrimental stimuli, encompassing viral onslaughts (hepatitis B/C), chronic overindulgence in alcohol, metabolic imbalances, and additional injurious factors. These persistent provocations precipitate the onset of CLDs, characterized by chronic inflammation. Prolonged injury may manifest as structural changes and functional deterioration within the hepatic system, ultimately leading to liver fibrosis, cirrhosis, and potentially advancing to HCC.

Liver pathologies are characterized by a constellation of physiological and pathological features, often engendered by a series of maladaptive responses enacted by an intricate network of both resident and migratory cellular populations within the hepatic milieu[17]. The liver's cellular framework is predominated by parenchymal hepatocytes, supplemented by a heterogeneous assemblage of non-parenchymal cells, including liver sinusoidal endothelial cells (LSECs), hepatic stellate cells (HSCs), and specialized immune cells such as Kupffer cells[18]. In these conditions, hepatocellular damage precipitates cellular necrosis, which in turn catalyzes the recruitment and subsequent activation of immune effector cells, with monocytes and macrophages being particularly instrumental[19]. This cascade fosters an inflammatory milieu within the hepatic tissue. Simultaneously, there is a notable escalation in the proliferation and phenotypic metamorphosis of HSCs into profibrogenic myofibroblasts. The secretory profile of these activated HSCs, rich in extracellular matrix (ECM) constituents, is a critical factor in the pathogenesis of liver fibrosis[19]. The advancement of fibrosis often precedes the development of cirrhosis, which is marked by portal hypertension and dysregulated angiogenesis. These conditions collectively create a permissive environment for the emergence of HCC[17,19,20] (Fig. 2).

An alarming trend to note is that the morbidity and mortality associated with liver diseases have been on an upward trajectory over the past several decades. Beyond viral hepatitis, non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH), as well as alcohol-related liver disease have emerged as the predominant forms of CLDs. They have become major contributors to the incidence of HCC and are leading indications for liver transplantation[21]. However, liver transplantation, which represents the last line of defense in the management of liver diseases, meets less than 10% of the global demand due to socio-economic and cultural factors. Consequently, elucidating the

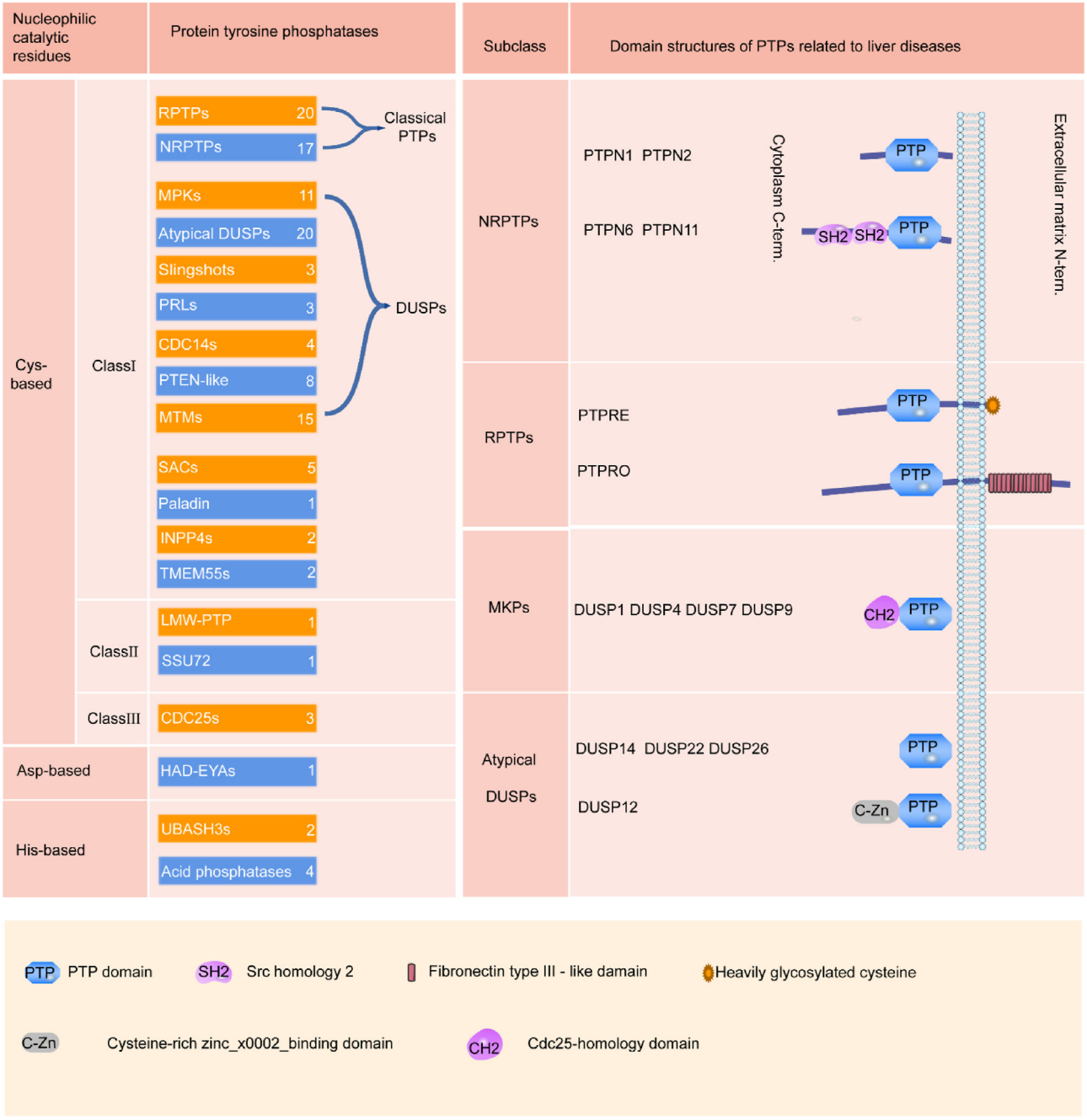

Figure 1 Classification of the PTP superfamily and domains of PTPs involved in liver disease. PTPs are classified based on their nucleophilic catalytic residues (Cys, Asp, or His). The number of members in each group and the domains of the associated PTPs in liver disease are shown. (MKP, MAP-kinase phosphatase; LMPTP, low-molecular-weight PTP; SSu72, suppressor of Sua7-2; CDC25, cell division cycle 25; HAD, haloacid dehalogenase; EYA, eyes absent; UBASH3, ubiquitin-associated and Src homology 3 domain-containing).

pathogenic mechanisms of these diseases and identifying valuable diagnostic or therapeutic targets are particularly critical for the assessment, diagnosis, and the halting or reversal of the progression of CLDs[22]. Interestingly, PTPs are implicated in metabolic and immunoinflammatory processes, and aberrant expression, activation, and mutations of certain members are considered risk factors for a variety of diseases. Consequently, the selective targeting of PTPs has emerged as a focal point in the development of targeted therapeutics, with their potential in the treatment of liver-associated diseases garnering increasing attention. In this review, we provide an updated understanding of the diverse functions and signaling pathways mediated by PTPs, underscoring their pivotal role in orchestrating the complex network governing hepatic pathologies. Additionally, we delineate the prospective utility of current PTP inhibitors in the therapeutic armamentarium against liver-related diseases.

3. PTPs in hepatocellular carcinoma

In 2007, sorafenib, a multi-kinase inhibitor, was approved for the treatment of advanced HCC. marking a significant shift from traditional chemotherapy and heralding a new era in HCC

management[23]. Sorafenib targets various enzymes pivotal for tumor growth and angiogenesis, disrupting the processes essential for cancer proliferation. However, over the past decade, resistance to sorafenib has become a significant hurdle, limiting its therapeutic effectiveness[24]. This resistance often arises from genetic mutations in tumor cells, which allow them to circumvent the drug's inhibitory effects[24]. As the medical community seeks alternatives, the regulatory role of phosphatases has come to the forefront. Phosphatases, therefore, represent a novel and promising therapeutic target[25]. In-depth structural and functional studies have revealed that differential expression of specific PTPs plays a critical role in key tumorigenic events[26]. PTPs, such as SHP2, are recruited by immune inhibitory receptors like programmed cell death protein 1 (PD1) in T lymphocytes, modulating immune responses within the tumor microenvironment[27]. PTP1B has recently been recognized as a novel immune checkpoint in T cells and chimeric antigen receptor T (CAR-T) cells, where it attenuates the JAK/signal transducer and activator of transcription (STAT) 5 signaling pathway, undermining the expansion and activation of T cells and consequently inhibiting anti-tumor immunity[28].

Moreover, PTPs are integral to the regulation of cancer-associated signaling pathways, including RAS and mitogen-activated protein kinase (MAPK), which are essential for tumor cell growth and migration[29-31]. The complexity of creating specific inhibitors for PTPs, due to their highly conserved active sites and the potential for off-target effects, presents a significant challenge. Nevertheless, targeting PTPs has been considered a potential strategy for developing anti-cancer treatments. This approach holds promise for overcoming the limitations of current therapies and addressing the urgent need for novel HCC treatments[32]. As we continue to explore the roles of PTPs in HCC progression, their influence on cell proliferation, survival, and migration is becoming increasingly apparent, solidifying their position as potential targets in the fight against liver cancer[26,33]. In the following, we summarize the roles of several PTPs involved in HCC progress (Figs. 1 and 2, Table 1).

3.1. *PTP1B*

PTP1B, ubiquitously expressed and encoded by the *PTPN1* gene, is a classical non-receptor PTP. Its structure features a highly

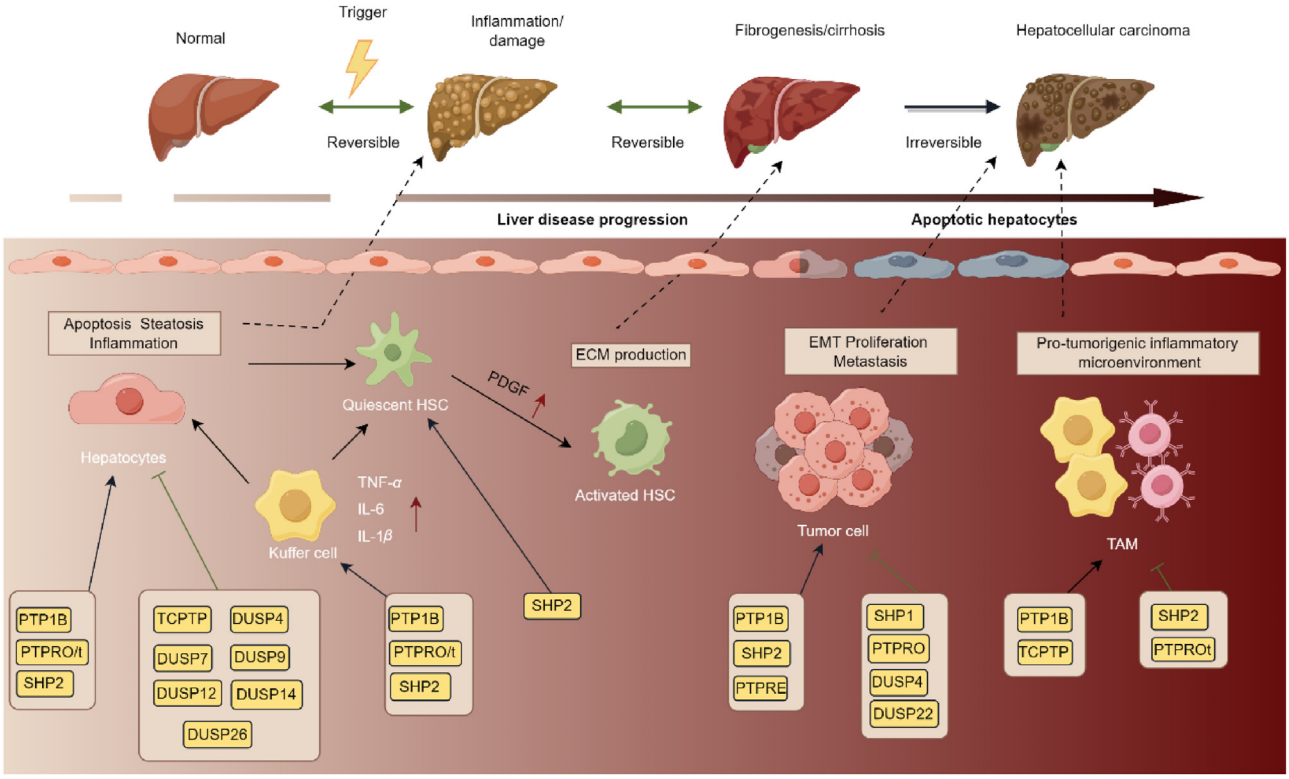

Figure 2 The regulatory role of PTPs in the progression of liver disease. Multiple triggers induce liver disease (*e.g.*, hepatitis virus, alcohol consumption, high-calorie diet, and unhealthy lifestyle), which then causes reversible damage and inflammation. They may progress to fibrosis, which can lead to irreversible cirrhosis and the most severe types of disease such as hepatocellular carcinoma (HCC) if these triggers persist. PTP is involved throughout the progression of liver disease. PTP1B, PTPRO/t, and SHP2 promote apoptosis, steatosis, and inflammation in hepatocytes. They also induce Kuffer cells to release inflammatory factors, which will further aggravate liver steatosis and inflammation. SHP2 can induce the release of profibrotic factors from HSCs, leading to the activation of HSCs and the accumulation of ECMs, leading to disease progression to liver fibrosis. The presence of TCPTP, DUSP4, DUSP7, DUSP9, DUSP12, DUSP14, DUSP26 in hepatocytes can alleviate abnormal apoptosis and inflammatory responses in hepatocytes. During the progression of liver fibrosis to HCC, PTP1B, SHP2, PTPRE induce EMT, proliferation, and migration of tumor cells, in addition, PTP1B is also involved in the regulation of the tumor microenvironment, leading to the generation of inflammatory and pro-tumor microenvironments. SHP1, PTPRO, DUSP1, DUSP22 can inhibit EMT and proliferative migration of tumor cells. SHP2 and PTPROt can inhibit the generation of a pro-tumor microenvironment.

Table 1 PTPs involved in HCC.

Liver disease	PTP	Substrate	Pathway and function involved	Ref.
HCC	SHP1	STAT3	Inhibits the formation and metastasis of primary liver cancer	34
HCC	SHP2	RAS	Activates downstream RAF/ERK signaling and promotes HCC growth	35
HCC	SHP2	PI3K	Activates PI3K/AKT/mTOR pathway and enhancing HCC metastasis	35
HCC	SHP2	STAT3	Inhibits the inflammatory response and necrosis of the liver, relieving the development of HCC	36
HCC	PTPRE	TGF-βR1	Maintains the continuous activation of SMAD3 and promotes HCC cells metastasis	37
HCC	PTPRO	JAK2	Inactivates STAT3 and inhibits the growth of HCC	38
HCC	DUSP4	MEK	Inhibits HCC resistance and growth	39
HCC	DUSP22	FAK	Inhibits NASH and NAFLD-related HCC progression	40

conserved N-terminal catalytic domain responsible for the dephosphorylation of phosphotyrosine residues on substrates, and a C-terminal hydrophobic region that anchors the enzyme to the endoplasmic reticulum[41,42]. PTP1B is integral to the regulation of metabolic pathways, highlighting its potential as a therapeutic target for metabolic disorders such as diabetes and obesity[12,43]. Aberrant PTP1B expression has been observed in various cancers, including lung, gastric, and pancreatic cancer, implicating its role in oncogenic processes[44]. Conflicting studies in HCC suggest that initially, PTP1B was thought to be downregulated, with lower levels correlating with tumor progression and poor prognosis[45]. However, emerging research portrays PTP1B as having an oncogenic role, where its inhibitory activity could represent a novel therapeutic avenue for HCC (Figs. 1 and 2).

PTP1B's interaction with paired-like homeodomain transcription factor 1 (PITX1), a suppressor of RAS-related proteins, is particularly noteworthy. PTP1B can bind to PITX1, leading to its dephosphorylation and subsequent degradation, which in turn activates the RAS pathway and potentially exacerbates HCC progression[46,47]. PTP1B can directly bind to PITX1, leading to its dephosphorylation, degradation, and inactivation, resulting in the activation of the RAS pathway and exacerbating the progression of HCC[48]. The complexity of PTP1B's role is further exemplified in the tumor microenvironment, where it acts as an intracellular immune checkpoint in T cells, including CAR-T cells. By dephosphorylating STAT5, PTP1B attenuates interleukin-2's effects on T cell proliferation and differentiation, thus modulating antitumor immunity. Inhibiting PTP1B with compounds such as MSI-1436 has been shown to enhance T cell-mediated suppression of solid tumors, signifying its therapeutic promise in cancer immunotherapy[28]. Despite these findings, the research on PTP1B inhibitors, particularly in the context of HCC treatment, is nascent, and more studies are required to validate the efficacy and safety of such therapeutic strategies. The therapeutic targeting of PTP1B in HCC remains an area ripe for exploration, with the potential to yield new treatments that can complement existing therapies, especially for patients who do not respond to current treatment modalities.

3.2. *SHP1*

SHP1, encoded by the *PTPN6* gene, is a non-receptor PTP that plays a vital role in the regulation of cellular signaling. Predominantly expressed in hematopoietic and epithelial cells, SHP1's structure includes a C-terminal tail, a catalytic PTP domain, and two Src homology 2 (SH2) domains[49-52]. This arrangement allows SHP1 to undergo conformational changes essential for its phosphatase activity, which, in turn, modulates various cellular processes either through direct dephosphorylation of substrates or through non-enzymatic interactions[53]. Abnormal expression of SHP1 is linked to the progression of several cancers, including HCC. SHP1 negatively regulates the JAK/STAT signaling pathway, a key intracellular route controlling cell proliferation, differentiation, and apoptosis[34,54,55].

In many cancers, including HCC, aberrant activation of the JAK/STAT pathway, particularly the phosphorylation of STAT3, contributes to enhanced tumor cell proliferation, abnormal epithelial-mesenchymal transition (EMT), and metastasis. SHP1 can counteract this by dephosphorylating STAT3, thus inhibiting the pathway and its downstream oncogenic effects[56-58]. Notably, SHP1 expression is often downregulated in HCC, particularly in cases associated with hepatitis B virus infection, and this downregulation correlates with poor patient prognosis[34]. Research has indicated that the overexpression of SHP1 in mouse models of HCC can inhibit both JAK/STAT and AKT signaling pathways, suggesting potential therapeutic benefits[34]. Interestingly, Sorafenib has been shown to activate SHP1, particularly in hepatitis B virus-induced HCC in mice, indicating that its therapeutic effectiveness may be partly due to SHP1's activity[59]. Moreover, compounds like phloretin and α-mangostin have been identified as potential agents that could upregulate or stabilize SHP1 expression, offering a way to counteract the proliferation of sorafenib-resistant HCC cell lines[58,60]. These findings highlight the potential of SHP1 as a therapeutic target in HCC, suggesting that dual targeting of PTKs and PTPs could address current challenges with kinase inhibitor resistance. By manipulating both kinase and phosphatase activities, there may be an opportunity to enhance the therapeutic effects against HCC, pointing to a multifaceted approach that could yield significant benefits in the treatment of this malignancy. Further research is warranted to explore these interactions and to develop targeted therapies that leverage the regulatory balance between PTKs and PTPs in cancer.

3.3. *SHP2*

SHP2, encoded by *PTPN11*, is a widely expressed non-receptor PTP. Similar to its counterpart SHP1, SHP2 consists of two SH2 domains (N-SH2 and C-SH2) and a PTP domain[61]. It was the first oncogenic tyrosine phosphatase to be discovered and functions as a direct downstream effector of receptor tyrosine kinases (RTKs)[26]. The RTK/RAS pathway is one of the most common targets for cancer-causing mutations, and SHP2 acts as a signaling nexus between them, mediating the activation of RAS[62,63]. Moreover, SHP2 is involved in the signal transduction of several cancer-related pathways, including PI3K−AKT, JAK−STAT, and PD1/PDL1. It also mediates the reconstitution and activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome in mitochondrial homeostasis[64-66]. The inhibition

of SHP2 activity has been recognized as an extremely attractive target for cancer therapy[67]. Despite traditional active site inhibitors of PTPs being characterized by low selectivity and poor bioavailability, which led to SHP2 being considered an 'undruggable' target for a time[68]. Advancements in structure-based allosteric modulators have propelled drug development to new heights. SHP099, as the first SHP2 allosteric inhibitor, has overcome the limitations of traditional active inhibitors and has demonstrated promising anti-tumor effects. Subsequently, various SHP2 allosteric inhibitors, developed based on SHP099, have entered different stages of clinical trials[16]. SHP2 plays an important role in the complex regulatory network of HCC, but studies have identified potentially contradictory roles for SHP2 in this cancer, presenting new challenges for the clinical application of SHP2 inhibitors.

During liver regeneration, SHP2 is highly active, recruiting growth factors to promote hepatocyte proliferation and division[69]. This function is critical in tumor tissue growth, leading to its classification as an oncogene in various cancers, including HCC. However, subsequent research has challenged this view. Increased levels of liver inflammation were observed in mice with a hepatocyte-specific SHP2 deficiency, and in a DEN-induced HCC model, SHP2-deficient mice exhibited aggravated liver fibrosis and enhanced tumor formation[36]. Furthermore, reduced SHP2 expression was detected in 11.5% of human HCC samples. Additional studies showed that SHP2 deficiency led to increased STAT3 activity in liver cells, accompanied by elevated levels of inflammatory factors such as IL-6, thus creating a pro-tumorigenic inflammatory microenvironment[36]. Conversely, mice with both SHP2 and STAT3 deficiencies showed attenuated HCC development compared to those with SHP2 deficiency alone, suggesting that SHP2 may have tumor-suppressive effects in HCC by inhibiting STAT3 phosphorylation[36]. Similarly, Du et al. demonstrated that deletion of SHP2 in Kupffer cells (liver macrophages) and hepatocytes leads to the recruitment of bone marrow-derived macrophages in the liver, worsening HCC progression[70].

SHP2 also acts as a critical mediator in the transduction of various oncogenic signals that promote HCC development. The aberrant activation of Myc, c-MET, and PIK3CA genes drives HCC progression, with co-activation of MET and β-catenin signaling observed in human HCC patients[16,35,71,72]. Interestingly, despite SHP2 deficiency in liver cells causing liver inflammation and fibrosis, there was a significant inhibition in the development of MET/CAT injection-driven mouse HCC[71]. This suggests SHP2's role in relaying specific carcinogenic signals in the liver. Additionally, studies have indicated that downregulating SHP2 can increase the sensitivity of liver cancer cells to sorafenib, implying that SHP2 inhibitors, when combined with sorafenib, may offer improved therapeutic benefits[35]. Recent studies using the specific allosteric inhibitor SHP099 in a mouse HCC model have shown that pharmacological inhibition of SHP2, unlike the liver inflammation and damage triggered by SHP2 gene deletion, can attenuate the pro-tumorigenic inflammatory microenvironment in the liver[16]. This pharmacological inhibition induces increased interferon β secretion from macrophages, leading to tumor suppression in the liver. SHP2's dual role in liver cancer, akin to other conflicting regulatory molecules in HCC such as I kappa B kinase 2/nuclear factor kappa-B (NF-κB) and c-jun N-terminal kinase (JNK) has been established[73,74]. However, further validation with human HCC samples is required. The bidirectional action poses challenges for the application of SHP2-specific inhibitors in HCC. Consequently, the concept of cocktail therapy targeting multiple pathways has gained traction. For example, combining SHP2 inhibitors with MEK inhibitors might benefit patients with KRAS-mutant pancreatic cancer[75], non-small cell lung cancer (NSCLC)[76], and triple-negative breast cancer[77]. Additionally, research has shown that combining SHP099 with the mTOR inhibitor AZD8055 synergistically induces apoptosis in HCC cells and demonstrates better tolerance and efficacy than monotherapy in various mouse HCC models[78].

Given the complex metabolic and immune responses in the liver, the mechanisms underlying HCC's onset and progression may differ across etiologies and developmental stages. Aspects of the regulatory pathways involving SHP2 in HCC are not yet fully understood, necessitating further research to define its regulatory network and improve targeted therapies. Tailoring combination therapies to specific cancer mutations and inducers may enhance the targeted therapeutic effects of SHP2 inhibitors in HCC, potentially providing a strategy to navigate the complexities of this disease.

3.4. *Other PTPs in HCC*

The previous sections have summarized the potential of PTP1B, SHP1, and SHP2 within the PTP family as targets for therapeutic intervention in HCC. However, other PTPs also play regulatory roles in the pathogenesis and progression of HCC[79]. Among these, receptor-like PTPs such as PTPRE and PTPRO, as well as certain members of the DUSPs, have been well-recognized in research.

RPTPs comprise a single transmembrane domain and exhibit diverse N-terminal extracellular domains that show homology with cell adhesion molecules[80]. Within their intracellular regions, most RPTPs possess two adjacent PTP domains. The PTP domain proximal to the membrane is typically responsible for the majority of the catalytic activity, whereas the distal PTP domain often exhibits minimal or no catalytic activity[81]. Collectively, the structural features of RPTPs integrate extracellular adhesion and migration functions with the regulation of intracellular signaling pathways in HCC cells.

PTPRε, encoded by *PTPRE*, is a member of the PTPε family, which includes PTPRε, p67 PTPε, p65 PTPε, and Cyt-PTPε, and is widely expressed in the liver[82]. Upregulated expression of PTPRε is positively associated with poor prognosis in HCC patients. In the later stages of tumor progression, transforming growth factor (TGF) β signaling contributes to cancer metastasis by enhancing the EMT of cancer cells[37]. Binding of TGFβ to its receptor (TGFβR1) leads to the phosphorylation and activation of SMAD family member 3 (SMAD3). Phosphorylated SMAD3, acting as a transcription factor, regulates the transcription of genes related to cell migration and invasion[83]. It has been identified that activated SMAD3 can upregulate the transcription of PTPRE, and the increased expression of PTPRε, through its phosphatase activity, results in the dephosphorylation of TGFβR1[37]. This dephosphorylation promotes the recruitment of SMAD3 to TGFβR1, leading to further phosphorylation and activation of SMAD3. Such a positive feedback loop enhances the migration and invasion of HCC cells, with PTPRε serving as a crucial mediator within this mechanism[37]. Consequently, these findings suggest that targeting PTPRε's phosphatase activity or concurrently inhibiting TGFβR1 represents a potential therapeutic strategy against HCC (Figs. 1 and 2).

PTPRO is a receptor-like protein tyrosine phosphatase that encodes various transcripts, with expression controlled by separate promoters. The most studied isoforms are the full-length PTPRO

and the truncated PTPRO (PTPROt)[84]. These two major isoforms have tissue- and cell-specific expression patterns: full-length PTPRO is primarily expressed in the epithelial cells of the kidney and brain, whereas PTPROt is mainly found in hematopoietic and immune cells[84]. Functionally, both isoforms are closely associated with immune cells and are known to promote the infiltration of such cells, including $CD8^+$ T cells and neutrophils, in pancreatic and breast cancer tissues, potentially exacerbating cancer development[85,86]. Conversely, PTPRO is implicated in the reprogramming of fatty acid metabolism and inhibits colorectal cancer tumorigenesis[85]. Notably, PTPRO's role in immunomodulation renders it a significant target for potential therapies aimed at enhancing liver anti-tumor immunity and mitigating inflammatory damage[38,87].

PTPRO dephosphorylates JAK2, and the absence of PTPRO has been associated with a significant increase in both the number and size of liver tumors in mice, underscoring its tumor-suppressive function[38]. Moreover, PTPROt is vital in sustaining an anti-tumor immune microenvironment. It modulates the balance between T effector (Teff) cells and regulatory T (Treg) cells, which are crucial for the immune response against tumors. The deletion of PTPROt impairs T-cell-mediated anti-tumor immunity, leading to weakened immune surveillance and enhanced proliferation of HCC cells in mice[87]. The lack of PTPROt not only disrupts the Teff/Treg balance but also undermines the overall immune response to tumor cells[87]. This dysregulation permits unchecked growth of HCC tumors and proliferation of HCC cells, further emphasizing the pivotal role of PTPROt in orchestrating the anti-tumor immune response (Table 1)[87]. These findings elucidate the multifaceted role of PTPRO in tumor suppression, involving both direct dephosphorylation of JAK2 and the preservation of an optimal immune microenvironment. A deeper understanding of PTPRO's complex functions could yield valuable insights for developing targeted therapies that enhance anti-tumor immune responses, ultimately improving outcomes for patients with liver cancer.

The MAPK pathways comprise a conserved family of kinase modules that are essential for the transmission of external signals to cellular effectors. These effectors regulate critical cellular processes, including proliferation, differentiation, migration, and apoptosis[88]. Due to the MAPK pathway's extensive involvement in many aspects of cancer initiation and progression, aberrations in MAPK signaling have been implicated in a wide variety of liver malignancies[89]. DUSPs are a diverse group of Cys-based enzymes that exhibit phosphatase activity[10,90]. They share a common C-terminal catalytic domain. Unlike typical DUSPs that have an N-terminal non-catalytic region containing a kinase interaction motif (KIM) for MAPK interaction, most atypical DUSPs lack this region[89]. These domain differences also lead to variations in their catalytic substrates, which is significant in the context of liver disease.

Dual-specificity phosphatase-1 (DUSP1), also known as MAPK phosphatase-1 (MKP1), plays a dual role in cancer through its ability to dephosphorylate components of the MAPK pathway[91]. Inhibition of JNK activation, which correlates with upregulated expression of DUSP1, has been observed in pancreatic, lung, and breast cancer[92]. Mechanistic studies have confirmed that DUSP1 inactivates JNK through dephosphorylation, which in turn promotes the proliferation of cancer cells. In contrast, gene expression analyses of HCC tissues have revealed a significant reduction in DUSP1 expression, with higher DUSP1 expression levels being associated with longer survival in patients[93,94]. When DUSP1 is overexpressed in HCC cells, it leads to cell cycle arrest and apoptosis. Further investigations indicated that DUSP1 dephosphorylates p38, a process that inhibits heat shock protein 27 activation, resulting in enhanced phosphorylation of p53. Intriguingly, p53 also upregulates the transcription of DUSP1, creating an inhibitory feedback loop that suppresses liver tumorigenesis[94]. Given its pivotal role in the p53 signaling pathway, reactivation of DUSP1 could be advantageous for HCC treatment.

Despite most atypical DUSPs lacking an N-terminal region and being of low molecular mass, some have emerged as potential targets for treating human diseases[95]. The putative regulatory roles of atypical DUSPs in cell proliferation and apoptosis suggest their value in cancer-related research. DUSP22, which is broadly expressed in various tissues and cell types, has been identified to regulate inflammatory responses, cell cycles, and other cellular biological events[96,97]. Similar to MKPs, DUSP22 can also modulate MAPK signal transduction. In mammalian cells, DUSP22 specifically promotes JNK activation, with JNK failing to respond to tumor necrosis factor-α treatment in DUSP22-deficient mouse embryonic fibroblasts[98]. However, recent studies have indicated that DUSP22's regulatory mechanism in obesity-related HCC operates independently of the MAPK pathway. Hepatocyte-specific deletion of DUSP22 significantly accelerates HCC progression in various mouse models by inducing liver inflammation and fibrosis. Notably, DUSP22 inactivates focal adhesion kinase (FAK) by inhibiting its phosphorylation at tyrosine residues Y397 and Y576/Y577, thereby mitigating the inflammatory response and collagen accumulation that occurs due to the activation of the downstream ERK1/2 and NF-κB signaling cascades[40]. These findings collectively highlight the DUSP22-FAK axis as a promising therapeutic target for NASH-HCC.

4. PTPs in CLDs

CLDs, which develop through the multi-stage processes of fibrosis, cirrhosis, and HCC, can be triggered by persistent viral infections, excessive alcohol consumption, accumulation of excess fat, biotransformed metabolites, and cholestasis[99]. NAFLD is a term that encompasses a spectrum of liver conditions characterized by varying degrees of damage, ranging from simple steatosis (non-alcoholic fatty liver, NAFL) to more severe inflammatory hepatocellular damage (non-alcoholic steatohepatitis, NASH)[100]. Over the past half-century, NAFLD has become the most prevalent form of CLDs, affecting over a quarter of the adult population worldwide[101]. Clinically, NAFLD is often associated with metabolic syndrome, which includes conditions such as obesity, insulin resistance (IR), and type 2 diabetes (T2D), indicating a bidirectional relationship[102-104]. NAFLD is a significant contributor to the development of cirrhosis and hepatocellular carcinoma[105,106]. The auto-phosphorylation of insulin receptors is critical for insulin signaling, and defects in these receptors contribute to IR, a precursor for T2D[107,108]. Numerous studies have established that PTPs are implicated in metabolic diseases, particularly IR, T2D, and NAFLD, positioning them as a novel paradigm for therapeutic targets[12,109]. In the following section, we will review the role of PTPs in metabolic syndrome associated with NAFLD (Figs. 1 and 2, Table 2).

4.1. PTP1B

PTP1B occupies a pivotal role in the nuanced orchestration of energy balance and glucose homeostasis[126]. It serves as a critical

Table 2 PTPs involved in CLDs.

Liver disease	PTP	Substrate	Pathway and function involved	Ref.
NAFLD	PTP1B	AMPK	Exacerbates liver damage, inflammation and steatosis	110,111
NAFLD	TCPTP	STAT1/5	Inhibits steatosis and inflammation of the liver	112,113
NAFLD	SHP2	AKT, GSK3β	Reduces IL-18 levels and promotes hepatic steatosis and insulin resistance	114
NAFLD	PTPRO/t	NF-κB	Promotes hepatic steatosis, and inflammatory	115,116
NAFLD	DUSP4	p38 MAPK	Promotes hepatic steatosis and insulin resistance	117
NAFLD	DUSP7	TAK1	Inhibits lipid deposition, inflammatory and ROS production	118
NAFLD	DUSP9	ASK1	Inhibits lipid accumulation, disorders of glucose metabolism, inflammation and fibrosis	119
NAFLD	DUSP12	ASK1	Inhibits ASK1-related JNK and p38 MAPK and inhibits lipogenesis under high-fat conditions	120
NAFLD	DUSP14	TAK1	Maintains metabolic homeostasis and suppresses inflammation in the liver	121
NAFLD	DUSP26	TAK1	Inhibits hepatic steatosis and inflammatory responses	122
Liver fibrosis	PTP1B	AMPK	Promotes the activation of hepatic stellate cells and the progression of liver fibrosis	123,124
Liver fibrosis	SHP2	PDGFRα	Enhances the release of PDGF-enriched EVs by HSC and promotes the liver fibrogenesis	125

modulator by dephosphorylating essential components within the leptin and insulin signaling pathways—pathways that are foundational to the body's metabolic regulation[12]. Dysfunctional PTP1B activity disrupts these signaling pathways, precipitating hepatic metabolic disorders that may manifest as steatosis and inflammation[12]. Recent scholarly endeavors have unearthed disruptions in PTP1B expression across a spectrum of CLDs, particularly those marked by metabolic dysregulation and immunological disturbances, such as liver fibrosis and NAFLD. These findings pivot the modulation of PTP1B expression and activity into a promising therapeutic avenue for CLDs intervention.

The pathogenesis of liver fibrosis is frequently precipitated by chronic hepatotoxic and cholestatic injuries, which instigate sustained inflammatory responses in hepatic tissues. The activation of hepatic stellate cells (HSCs) emerges as a cardinal event in this fibrotic process and therefore represents a focal point for therapeutic reversal[20]. PTP1B's regulatory influence on the communication between hepatocytes and HSCs has been substantiated in mouse models of bile duct ligation-induced cholestatic liver fibrosis[123]. Notably, the attenuation of PTP1B expression mitigates bile acid-induced hepatocyte apoptosis and curtails the release of cytokines that facilitate HSC activation, conferring protection against fibrogenesis[123]. Elevated PTP1B expression has also been documented in alcoholic hepatitis, contributing to the exacerbation of the inflammatory response by hepatic macrophages[111,127]. The targeted deletion or pharmacological inhibition of PTP1B has yielded promising results, attenuating hepatic inflammation and damage in models of alcohol-induced liver injury[111]. Complementing these findings, PTP1B deficiency enhances autophagy and lipid droplet formation in progenitor oval cells, bolstering the hepatic defense against NAFLD-associated lipotoxicity and thereby mitigating liver damage[110]. Collectively, these insights underscore the therapeutic potential of targeting PTP1B in combating CLDs.

The pharmaceutical landscape has expanded to include a variety of inhibitors aimed at PTP1B, with the intention of mitigating the hepatic manifestations of T2D and obesity[128]. The pursuit of PTP1B-specific drugs, however, confronts the challenge of the PTP family's conserved structural characteristics, which impede the development of highly selective and bioavailable agents, thereby limiting these compounds to the realm of preclinical research. Advances in the structural and functional characterization of PTP1B have pointed to allosteric inhibition as a strategy to enhance specificity. Compounds like DPM-1001 exemplify this approach, exhibiting the ability to diminish oxidative stress and inflammation in alcoholic liver disease[111,129,130]. Innovations in therapeutic strategies have also emerged, as evidenced by Krishnan et al.'s development of a recombinant antibody, scFv45, utilized to screen small-molecule inhibitors. This novel approach has led to the identification of chelerythrine, an inhibitor that modulates PTP1B activity by stabilizing its oxidized, inactive state, thereby demonstrating potential for the amelioration of diabetes and obesity[131].

4.2. *SHP2*

Prior investigations have elucidated that macrophage-specific ablation of SHP2 activates the NLRP3 inflammasome and elevates inflammatory cytokine production, thus exacerbating peritonitis in murine models[66]. Contrasting this pro-inflammatory role, SHP2 has been implicated in diet-induced obesity, with evidence suggesting that SHP2 deletion significantly diminishes hepatic steatosis[114]. In models of high-fat diet (HFD)-induced murine NAFLD, targeted deletion of SHP2 in macrophages has been associated with a reduction in body weight, hepatic steatosis, and improved insulin sensitivity. This attenuation of disease markers has been mirrored by the administration of SHP2-specific inhibitors, SHP099 and Phps1, which have demonstrated efficacy in alleviating hepatic steatosis and insulin resistance[114]. Building on these observations, further research probed the function of SHP2 in liver fibrosis by employing HSC-specific SHP2 knockout mice. The genetic modification curtailed the release of platelet-derived growth factor (PDGF)-rich extracellular vesicles (EVs) and mitigated liver fibrogenesis induced by CCl_4 and bile duct ligation[125]. Notably, the infusion of SHP2-deficient HSC-derived EVs into mice resulted in a substantial reduction of liver fibrosis, underscoring the therapeutic promise of SHP2 inhibition. Corroborating these findings, Kostallari et al.[132] observed a decrease in the circulating levels of PDGF-enriched EVs following SHP099 treatment, which coincided with a remission of liver fibrosis in CCl_4-treated mice. In addition, the natural compound linderalactone (LIN) has been identified as a direct inhibitor of SHP2 phosphatase activity. LIN administration in murine models of liver fibrosis impeded the progression of the disease[133].

The aforementioned findings underscore SHP2's potential as a therapeutic target for CLDs. While previous sections have indicated a dual role of SHP2 in HCC, suggesting varied outcomes influenced by different etiological factors, the genetic or

pharmacological suppression of SHP2 seems to confer therapeutic advantages in treating pre-HCC stages of liver diseases, such as liver fibrosis and NAFLD. These insights highlight the criticality of stage-specific targeted interventions in the management of liver disease progression.

4.3. Other PTPs in CLDs

TCPTP, encoded by *PTPN2*, a non-receptor PTP, is expressed in two isoforms: TC45 (45 kDa) and TC48 (48 kDa)[134]. TCPTP regulates inflammatory signaling by dephosphorylating JAKs and STATs, attenuating the action of pro-inflammatory cytokines such as IL-2, IL-6, and IFNγ. Its regulatory function extends to various pathological conditions, including autoimmune diseases, oncogenesis, and cancer immunosurveillance, positioning TCPTP as a candidate for therapeutic intervention in immune-related disorders[135-138]. Obesity, a critical factor for insulin resistance, exacerbates the risk of type 2 diabetes and liver inflammation[139,140]. Gurzov et al. observed that TCPTP activity was compromised in the context of obesity in mice, correlating with lipid dysregulation and hepatic steatosis. Hepatocyte-specific ablation of PTPN2 exacerbated STAT-5 signaling, hepatic steatosis, and the progression of obesity and type 2 diabetes[112]. Subsequent research indicated that TCPTP becomes increasingly inactivated through oxidative mechanisms during the transition from NAFLD to NASH. This inactivation at the molecular level potentiates tyrosine phosphorylation of STAT-1, which in turn drives T-cell infiltration and the development of NASH[113]. These findings suggest that the loss of TCPTP function constitutes a risk factor for liver metabolic disturbances.

Research conducted by Shintani et al. revealed that PTPRO is highly expressed in visceral white adipose tissue and macrophages[115]. Mice deficient in PTPRO exhibited reduced diet-induced hepatic steatosis and inflammation, and pharmacological inhibition of PTPRO mirrored these effects. This underscores the therapeutic potential of PTPRO inhibition in ameliorating hepatic steatosis and metabolic dysregulations linked to NAFLD[115]. Additionally, during NASH progression, macrophage PTPRO expression increased proportionally with disease severity[116]. Targeted deletion of PTPRO in macrophages dampened the activity of NF-κB and decreased inflammatory factor expression, which in turn mitigated NASH symptoms in mice fed a methionine-choline-deficient diet[116]. However, the development of specific PTPRO inhibitors remains an unmet challenge representing a frontier for therapeutic innovation in the treatment of liver diseases.

MAPK phosphatase-2 (MKP-2, encoded by *DUSP4*) is a member of the MKP family that regulates metabolic homeostasis through the inactivation of MAPKs[141,142]. Observations have indicated the activation of MKP-2 in liver tissues from patients with obesity and fatty liver disease. MKP-2 deficiency in mice confers resistance to HFD-induced obesity, hepatic steatosis, and insulin resistance, implicating MKP-2 as a significant contributor to the pathogenesis of NAFLD[117]. Conversely, levels of DUSP7 and DUSP9 are diminished in NAFLD, exhibiting an inverse relationship with metabolic pathologies within the liver[118,119]. DUSP7 interaction with TGF-β-activated kinase (TAK1) in hepatocytes inhibits TAK1 activation, ameliorating HFD-induced oxidative stress, lipid dysregulation, and inflammation-associated fibrosis. DUSP9 maintains insulin sensitivity and mitigates HFD-induced steatosis and inflammatory response by suppressing ASK1-p38/JNK signaling[118].

DUSP12 expression is notably decreased in HFD-fed obese mice, with DUSP12-deficient mice exhibiting aggravated hepatic steatosis compared to their wild-type counterparts[120]. Hepatocyte-specific overexpression of DUSP12 demonstrates an anti-inflammatory effect, chiefly through antagonizing the ASK1 signaling pathway[120]. DUSP14 and DUSP26 similarly counteract metabolic disorders and inflammation associated with NAFLD. TAK1 is a mutual substrate for both DUSPs, and their binding inhibits TAK1 activation, which is a key inflammatory and stress response mediator[121,122].

PTPs are integral to the progression of diseases linked with NAFLD and are actively studied in this context. Given that NAFLD can often progress asymptomatically or with minimal clinical signs, there is an elevated risk of advancement to HCC[99]. Research on PTPs has predominantly focused on liver cancer; however, their significance in NAFLD and other CLDs is becoming increasingly recognized. The insidious nature of CLDs highlights the urgent need for reliable biomarkers for early detection and therapeutic intervention to prevent progression to more severe liver conditions, including HCC. PTPs, through their involvement in pivotal signaling pathways related to inflammation, fibrosis, metabolism, and oncogenesis, stand out as potential biomarkers and therapeutic targets. Advancements in the understanding of PTP functions and the development of PTP-targeted pharmacological agents could pave the way for innovative treatments for CLDs. Such interventions may not only improve management outcomes for these conditions but also contribute to the prevention of their escalation into HCC.

5. Progress in drug development targeting PTPs

Since the discovery of PTP1B, research into PTP inhibitors began. PTP1B was established as a key negative regulator of the leptin and insulin signaling pathways, which sparked interest in developing drugs that target PTP1B to treat diabetes and obesity[143]. However, the initial compounds targeting PTP1B were mostly unsuccessful. Subsequently, PTP1B inhibitors such as MSI-1436 and ISIS-113715 advanced into clinical trials, but these were halted in 2008. A similar story unfolded with SHP2. Recognizing the crucial role of SHP2 in cancer, a multitude of modulators targeting the catalytic active site of SHP2 were developed, such as Phps1[144]. However, the high degree of homology in the active sites of PTPs and the electrophilic nature of the inhibitors meant that these traditional active site inhibitors struggled with selectivity and bioavailability. The development of allosteric inhibitors, which act as "molecular glue" to maintain PTPs in an inhibited conformation, has broken the shackles of "undruggable" targets of PTPs and opened new avenues for the development of compounds targeting PTPs[145]. SHP099 was the first breakthrough allosteric tyrosine phosphatase inhibitor, and its derivative compound, TNO155, has entered clinical trials[145-147]. Current research on PTP-targeting compounds is largely focused on PTP1B and SHP2, with few other PTP-targeting compounds advancing to clinical trial stages. However, an emerging trend that cannot be ignored is the increasing number of potential compounds and novel targeting strategies that have been demonstrated to target PTPs in preclinical studies, which we will discuss in the following section (Table 3 and Fig. 3).

5.1. Targeting SHP2

The activity of SHP2 is regulated by its molecular conformation. When the N-SH2 residue inserts into the PTP catalytic domain, it

Table 3 Small molecule compounds targeting PTPs with potential for liver diseases therapy.

Compound	PTP	IC_{50}	Stage of development	Comment	Ref.
Chelerythrine	PTP1B	5 μmol/L	Tool compound	Identify and stabilize PTP1B in oxidized and inactive states, improves glucose tolerance and insulin sensitivity	131
MSI-1436	PTP1B	600 nmol/L	Discontinued	Improve oxidative stress and inflammatory in ALD	111
DPM-1001	PTP1B	100 nmol/L	Preclinical	Enhances insulin leptin signaling to exert anti-diabetic properties and improve oxidative stress and inflammatory in ALD	111,129
ABBV-CLS-484 (AC484)	PTP1B/TCPTP	1.8 nmol/L and 2.5 nmol/L	Phase I clinical trials	The first active-site phosphatase inhibitor to enter clinical evaluation for cancer immunotherapy	148
ABBV-CLS-579	PTP1B/TCPTP	Not report	Phase I clinical trials	Like AC484, it is a dual inhibitor of PTP1B and TCPTP	
Compound 182	PTP1B/TCPTP	0.63 nmol/L and 0.58 nmol/L	Preclinical	Effectively inhibit the growth of immunogenic tumors and promote the recruitment and activation of effector T cells	149
DU-14	PTP1B/TCPTP	24 nmol/L and 30 nmol/L	Preclinical	Effectively enhance the intensity of IFN-γ signaling pathway and promote the activation and recruitment of cytotoxic T cells	150
SHP099 and TNO155	SHP2	71 and 11 nmol/L	Phase I and I/II clinical trials (Replaced by TNO155)	TNO155 improves the phototoxicity caused by SHP and is currently undergoing clinical trials for advanced cancer and non-small cell lung cancer, among others	145,147
RMC-4550 and RMC-4630	SHP2	583 pmol/L and not report	Phase I and I/II clinical trials (RMC-4630)	At present, it has shown potential therapeutic effects in clinical trials of KRAS non-small-cell lung cancer	29
IACS-13909 and BBP-398 (IACS-15509)	SHP2	15.7 nmol/L and not report	Phase I and I/II clinical trials	–	151
SHP-D26 and SP4	SHP2	Not report	Tool compound	SHP099-based PROTACs molecules that target and induce SHP2 degradation	152,153
Linderalactone (LIN)	SHP2	1.87 μmol/L	Tool compound	Inhibition of carbon tetrachloride-induced hepatic stellate cell activation and liver fibrosis process in mice after *in vivo* injection	133
JMS-053	PRL1/PRL2/PRL3	~30 nmol/L	Tool compound	Mice bearing HeyA8-MDR ovarian tumors lose tumor weight after administration	154
NRT-870-59	PRL3	133.2 nmol/L	Tool compound	–	155

–Not available.

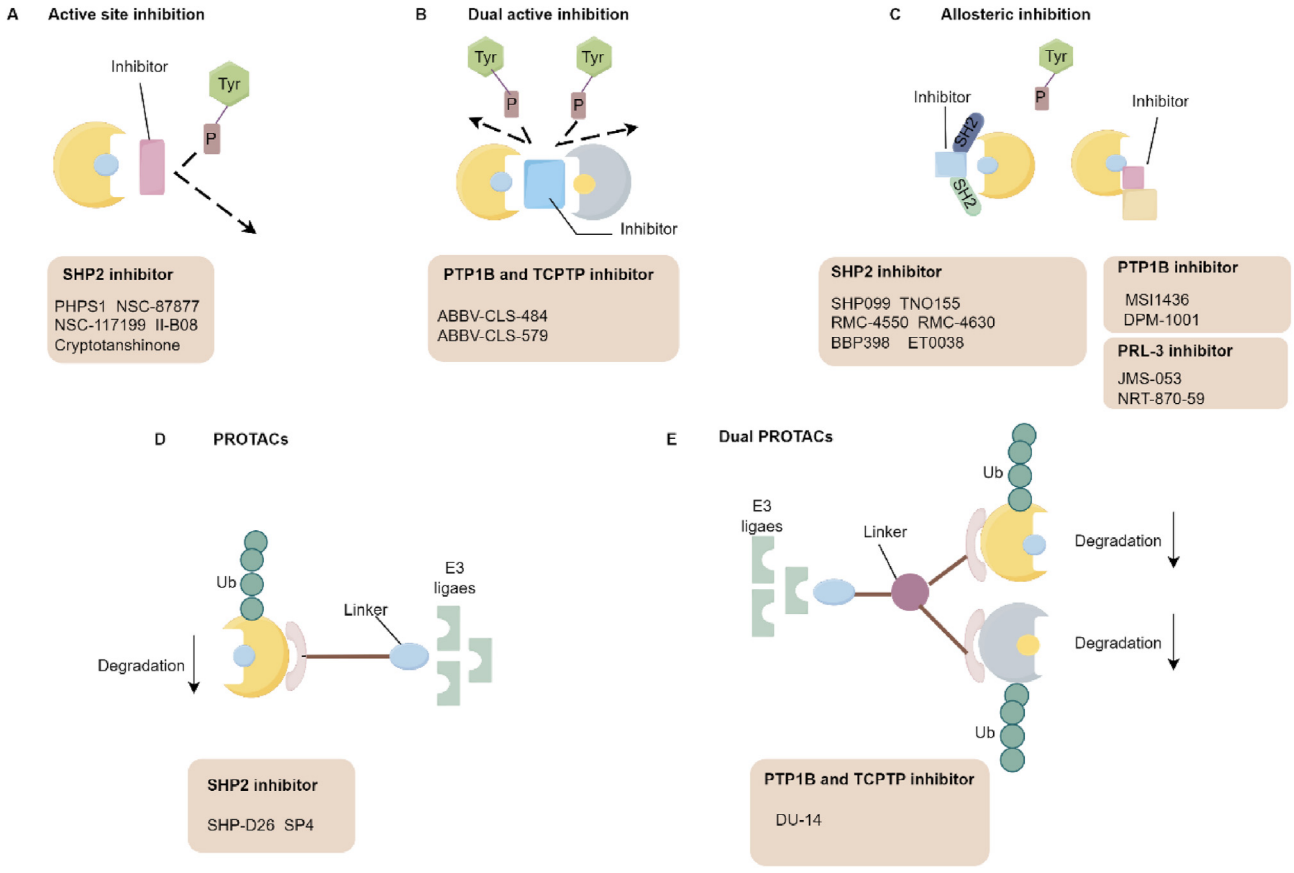

Figure 3 Schematic of action of PTP-targeted drugs. (A) Active site inhibitors bind to PTP catalytic active site. (B) Dual-activity inhibitors simultaneously targets the catalytic sites of two structurally similar enzymes. (C) Allosteric inhibitors bind to the PTP allosteric site, so that the phosphatase catalytic site structure changes, and cannot bind to the substrate. (D) PROTACs technology binds the E3 ubiquitin chain coupled with ubiquitin molecules to PTP protein through a special linker and induces protein degradation. (E) Dual PROTACs simultaneous ligation of two target proteins by linkers induces their simultaneous degradation.

adopts an autoinhibitory conformation. The interaction between the phospho-Tyr residues of interacting proteins and the SH2 domain induces a conformational change in SHP2 to an active, open conformation[156,157]. Additionally, the phosphorylation of the terminal tyrosine residue opens the binding site for interacting proteins or the C-SH2 domain, thereby enhancing SHP2 activity to a certain extent. Inhibitors that target the modulation of SHP2 activity have been extensively elaborated elsewhere[67,154,158,159]. Three widely studied SHP2 inhibition strategies include: active site inhibitors that target the PTP catalytic domain; allosteric inhibitors that bind to the channel-like regions between the N-terminal SH2 and the C-terminal SH2 domains or the PTP domain, thereby maintaining SHP2 in an autoinhibitory conformation; and the most recent strategy involves proteolysis targeting chimera (PROTAC) molecules, which promote the degradation of SHP2[152,160].

PTP catalytic domain inhibitors represent the earliest class of SHP2-targeted inhibitors, including compounds such as Phps1[144], NSC-87877[161], NSC-117199[162], II-B08[163], and the natural product cryptotanshinone[164]. These agents exhibit inhibitory activity against SHP2 and the cancer signaling pathways it mediates, suggesting their potential utility in the therapeutic intervention of malignancies such as leukemia and prostate cancer[158]. However, due to the high degree of homology among members of the PTP family, these inhibitors suffer from a lack of selectivity for SHP2 over SHP1 and PTP1B. Moreover, their cellular permeability and oral bioavailability are suboptimal[160]. These limitations have precluded the progression of PTP catalytic domain-targeted SHP2 inhibitors to the stage of clinical trials.

In 2016, Novartis achieved a significant milestone by reporting the first allosteric inhibitor of SHP2, named SHP099[145]. This compound stabilizes SHP2 in an inactive conformation by binding to a channel-like region that spans the N-terminal, C-terminal SH2 domains, and the PTP catalytic domain, rather than targeting the active site of the PTP[145]. The discovery of SHP099's mechanism of action has significantly influenced the development of SHP2-targeted pharmaceuticals. Currently, numerous SHP2 allosteric inhibitors are undergoing Phase I and Phase I/II clinical trials, demonstrating antitumor activity and potential synergistic effects when used in combination with other targeted therapies and immunotherapies[158]. For example, combining SHP099 with the KRAS-G12C inhibitor ARS1620 (ARS) enhanced GDP binding to KRAS, which led to increased survival in a mouse model of pancreatic ductal adenocarcinoma (PDAC)[165]. Preliminary data from a Phase 1b/2 clinical trial indicate that TNO155, a pyrazine derivative of SHP099, exhibits antitumor activity in patients with solid tumors harboring the KRAS G12C mutation, including NSCLC[147] (NCT04699188). RMC-4550, an oral SHP2 allosteric inhibitor developed by Revolution Medicines, and its derivative RMC-4630, are under evaluation in combination with Sotorasib in

clinical trials (NCT04185883), achieving disease control in a majority of patients with KRAS G12C mutant NSCLC. Additionally, BBP398 (IACS-15509), resulting from a collaboration between Novartis and The University of Texas MD Anderson Cancer Center, is in Phase I trials either as monotherapy or in combination with PD1 and KRAS G12C inhibitors (NCT05480865, NCT05621525, NCT06032936, NCT04528836, NCT05375084, NCT06024174). Etern BioPharma has also entered the field with their SHP2 allosteric inhibitor, ET0038, which is in a Phase I trial as a monotherapy for patients with advanced solid tumors (NCT05354843). The collective efforts in developing SHP2 allosteric inhibitors signify a leap forward in clinical applications, potentially broadening the therapeutic landscape for SHP2 inhibitors in various human diseases, including CLDs and HCC.

PROTACs represent a novel paradigm in drug development, offering an innovative approach to targeted therapy[166]. PROTAC molecules induce the ubiquitination and subsequent proteasomal degradation of target proteins, effectively reducing the levels of a protein of interest (POI)[167]. Several PROTACs, such as ARV-110 and ARV-471, have progressed to clinical trials[168,169]. Recently, this strategy has been applied to the development of molecules targeting the degradation of SHP2. SHP-D26, which is the first SHP2-directed PROTAC, comprises compound **8**—a known inhibitor of SHP2 enzymatic activity—the E3 ubiquitin ligase VHL ligand, and a linker that connects the two[153]. In KYSE520 esophageal carcinoma cells and MV4-11 acute myeloid leukemia cells, SHP-D26 successfully reduced SHP2 protein levels to less than 5% of their normal levels. Furthermore, SHP-D26 demonstrated an inhibitory effect on extracellular signal-regulated kinase (ERK) phosphorylation and cell proliferation that was more than 30 times greater than that of SHP099[153]. Building on this, a novel PROTAC molecule named SP4, which exhibits increased selectivity and potency for SHP2, has been synthesized. SP4 links pomalidomide with SHP099 and has shown significant inhibition of HeLa cell proliferation, with efficacy improved by 100-fold relative to SHP099[152]. Additionally, research has conjugated pomalidomide with RMC4550[170], and another study has connected CRBN (cereblon, a widely expressed E3 ubiquitin ligase) with TNO155 using a thalidomide-based linker[171]. Despite their preclinical status, the pronounced activity and selectivity offered by PROTACs targeting SHP2 provide a strong incentive for further development of this class of SHP2-directed therapeutics. This approach holds considerable promise as a strategic avenue in drug development.

5.2. *Targeting PTP1B and TCPTP*

The quest to modulate PTP1B activity has led to the synthesis of many inhibitors[172,173]. These efforts, akin to those with SHP2, have grappled with challenges related to cellular permeability and selectivity. DepYmed's MSI-1436 emerged as the first allosteric inhibitor of PTP1B to reach the clinical stage, targeting a novel allosteric site on the α-9 helix of the C-terminal regulatory region[130]. In the HER2-positive breast cancer xenograft mouse model, MSI-1436 showed significant anti-proliferative effects on cancer cells. Nonetheless, due to suboptimal *in vivo* bioavailability, its clinical trial was halted[172]. Its successor, DPM-1001, is currently undergoing preclinical evaluation and has demonstrated promising results in enhancing insulin and leptin signaling in animal models, which could benefit diabetes treatment[129,174].

Beyond metabolic diseases, PTP1B and TCPTP are gaining attention in immunotherapy. PTP1B has been recognized as a novel T-cell immune checkpoint, while TCPTP is being targeted in cancer immunotherapy[28,175]. Recently in 2023, a study introduced a first-in-class, orally bioavailable inhibitor, ABBV-CLS-484 (AC484), that targets the active sites of both TCPTP and PTP1B[148]. *In vitro*, AC484 augmented interferon responses, enhancing activation and function across various immune cell subsets. As a monotherapy, AC484 elicited strong antitumor immunity in a mouse model resistant to PD-1 blockade[148]. Currently, two PTP1B/TCPTP inhibitors, AC484 and ABBV-CLS-579, are in phase I clinical trials for treating advanced or metastatic tumors, either as monotherapies or in combination with α-PD1 (NCT04777994, NCT04417465). In parallel, Liang et al.[149] reported a competitive inhibitor, compound 182, with potent and selective activity against both PTP1B and TCPTP, which increased T-cell recruitment and activation in mice, while minimizing immune-related side effects. In 2021, the concept of dual PROTACs was introduced, involving the synthesis of bivalent degrader molecules that target two distinct proteins for degradation within the cell[176]. This concept has since been applied to simultaneously target PTP1B and TCPTP. Zhang et al.[150] initially developed a compound, DI-03, that inhibits both phosphatases and then created dual PROTACs using a variety of linkers and E3 ubiquitin ligase ligands, leading to a highly selective dual degrader, DU-14. Early studies suggest that DU-14 can enhance IFN-γ signaling and T-cell activation, both crucial for antiviral and antitumor responses[150]. Besides cancer therapy, PROTAC technology is being explored for liver diseases. For instance, targeting the degradation of PNPLA3 with PROTACs has shown promise in mitigating NAFLD progression[177]. In HCC, PROTACs that trigger the degradation of cyclin-dependent kinases 4/6 have displayed potential therapeutic benefits[178]. Given the significant function of PTP1B and TCPTP in liver metabolism, their integration with PROTAC technology could herald new advances in treating liver diseases.

5.3. *Targeting other tyrosine phosphatases*

The PTP superfamily harbors a plethora of potential drug targets. Despite this rich reservoir, beyond the aforementioned examples, the vast majority of inhibitors remain in preclinical research, with few advancing into clinical trial phases. For instance, JMS-053 binds to a site proximal to the catalytic domain of phosphatase of regenerating liver (PRL) 3, inhibiting the functional movement of its catalytic pocket[179]. JMS-053 also exhibits allosteric inhibitory effects on PRL1 and PRL2, and its derivative, NRT-870-59, has shown high selectivity in inhibiting PRL3[155]. Additionally, derivatives SC-40/43, which possess greater enhance the activity of SHP1, have been developed based on the structural modification of sorafenib, but these are only used as tool compounds in preclinical research[180,181].

The high degree of structural homology among PTPs presents significant challenges in developing specific inhibitors. Consequently, inhibitors targeting PTPN22, RPTPs, and DUSPs are exceedingly rare and are primarily utilized as tool compounds or in preclinical studies. It is encouraging that despite these challenges, research efforts to explore novel mechanisms and structures as well as targeting strategies for PTPs continue unabated.

6. Conclusion and future prospects

The pathogenesis of CLDs and HCC involves a complex interplay between metabolic dysregulation, immune responses, and cellular transformation. Within this intricate network, PTPs have emerged

as key regulatory elements, particularly SHP2, SHP1, and PTP1B, due to their roles in crucial cell signaling pathways relevant to liver pathophysiology. Despite their potential, the development of PTP inhibitors remains challenging, including issues of selectivity, due to the high structural homology among PTPs, and their bioavailability. The advent of allosteric modulators has been a watershed moment in the field of PTP drug development, with agents such as SHP099 and its clinical-stage derivative, TNO155, overcoming historic barriers of selectivity and bioavailability that have impeded the progress of active site-directed inhibitors. The discovery of novel modulators with unique mechanisms of action, such as PROTACs, further expands the therapeutic potential for PTP inhibition. Additionally, the reciprocal regulation between PTPs and PTKs is a critical aspect of cell signaling, and targeting both processes simultaneously may yield greater benefits. A clinical trial that combines the SHP2 inhibitor GH21 with the EGFR inhibitor osimertinib to treat NSCLC is currently in progress (NCT06306456), representing a new strategy for targeting PTPs in the treatment of liver diseases.

Looking forward, the development of PTP-targeted therapies may benefit from a deeper molecular understanding of these enzymes and the refinement of cell-based assays to confirm the involvement of cellular targets. High-throughput screening and alternative structural approaches will be instrumental in identifying and characterizing novel therapeutic drug candidates. Additionally, the expression profile of PTPs could be seen as a double-edged sword. While their ubiquitous expression may pose challenges for specificity, it also offers the potential for broad-spectrum therapeutic effects, particularly in immunotherapy contexts. Over the next decade, several PTP-targeted drugs are anticipated to receive FDA approval, especially as cancer immunotherapy agents. The success of PTP inhibitors in immuno-oncology, along with preclinical validation in liver disease models, may pave the way for clinical trials of PTP-targeted drugs for liver diseases. Furthermore, enhanced characterization of PTP structures, catalytic kinetics, and biological interactions will undoubtedly deepen our understanding of this promising yet-untapped target family, paving the way for innovative treatments for liver diseases and other disorders.

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Author contributions

Ao Wang: Writing − review & editing, Writing − original draft, Methodology, Investigation. Yi Zhang: Writing − review & editing, Resources, Methodology. Xinting Lv: Writing − review & editing, Resources, Investigation. Guang Liang: Writing − review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used GPT4 in order to improve readability and language. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Conflicts of interest

The authors declare no conflicts of interest.

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