



## Role of spleen tyrosine kinase in liver diseases

Dhadhang Wahyu Kurniawan, Gert Storm, Jai Prakash, Ruchi Bansal

**ORCID number:** Dhadhang Wahyu Kurniawan (0000-0003-4843-3756); Gert Storm (0000-0003-4296-2761); Jai Prakash (0000-0003-1050-650X); Ruchi Bansal (0000-0003-2470-5876).

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**Dhadhang Wahyu Kurniawan, Gert Storm, Jai Prakash, Ruchi Bansal**, Department of Biomaterials Science and Technology, Faculty of Science and Technology, Technical Medical Centre, University of Twente, Enschede 7500, the Netherlands

**Dhadhang Wahyu Kurniawan**, Department of Pharmacy, Universitas Jenderal Soedirman, Purwokerto 53132, Indonesia

**Gert Storm**, Department of Pharmaceutics, University of Utrecht, Utrecht 3454, the Netherlands

**Ruchi Bansal**, Department of Pharmacokinetics, Toxicology and Targeting, Groningen Research Institute of Pharmacy, University of Groningen, Enschede 7500, the Netherlands

**Corresponding author:** Ruchi Bansal, PhD, Assistant Professor, Department of Biomaterials Science and Technology, Technical Medical Centre, Faculty of Science and Technology, Zuidhorst 245, University of Twente, Enschede 7500, the Netherlands. [r.bansal@utwente.nl](mailto:r.bansal@utwente.nl)

### Abstract

Spleen tyrosine kinase (SYK) is a non-receptor tyrosine kinase expressed in most hematopoietic cells and non-hematopoietic cells and play a crucial role in both immune and non-immune biological responses. SYK mediate diverse cellular responses *via* an immune-receptor tyrosine-based activation motifs (ITAMs)-dependent signalling pathways, ITAMs-independent and ITAMs-semi-dependent signalling pathways. In liver, SYK expression has been observed in parenchymal (hepatocytes) and non-parenchymal cells (hepatic stellate cells and Kupffer cells), and found to be positively correlated with the disease severity. The implication of SYK pathway has been reported in different liver diseases including liver fibrosis, viral hepatitis, alcoholic liver disease, non-alcoholic steatohepatitis and hepatocellular carcinoma. Antagonism of SYK pathway using kinase inhibitors have shown to attenuate the progression of liver diseases thereby suggesting SYK as a highly promising therapeutic target. This review summarizes the current understanding of SYK and its therapeutic implication in liver diseases.

**Key words:** Spleen tyrosine kinase; Liver diseases; Inflammation; Targeted therapeutics; Spleen tyrosine kinase inhibitors

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**Core tip:** Spleen tyrosine kinase has reported to be positively correlated with disease severity and has shown to play a crucial role in the pathogenesis of liver diseases. Therefore, specific targeting of spleen tyrosine kinase pathway using kinase inhibitors is

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a highly promising therapeutic approach for the treatment of liver diseases.

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## INTRODUCTION

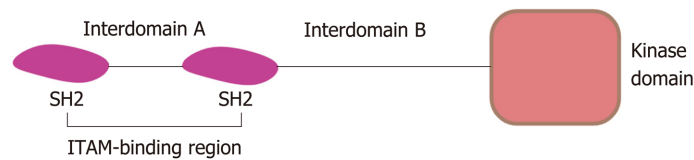
Spleen tyrosine kinase (SYK) is a cytoplasmic non-receptor protein tyrosine kinase (PTK) that consists of two SYK homology 2 domains (SH2) and a C-terminal tyrosine kinase domain. These domains are interconnected by two linker regions: Interdomain A between the two SH2 domains and Interdomain B between the C-terminal SH2 domain and the kinase domain (Figure 1). SYK is a member of the Zeta-chain-associated protein kinase 70/SYK family of the PTKs, with the estimated molecular weight of 70 kDa<sup>[1,2]</sup>. SYK is highly expressed in hematopoietic cells including mast cells, neutrophils, macrophages, platelets, B cells and immature T cells, and is important in signal transduction in these cells<sup>[2,3]</sup>. In Immune cells, SYK mainly functions *via* interaction of its tandem SH2 domains with immunoreceptor tyrosine-based activation motifs (ITAMs). In mast cells, SYK mediates downstream signaling *via* high-affinity IgE receptors, FcεRI and in neutrophils, macrophages, monocytes and platelets downstream signalling is mediated *via* Igγ receptors, FcγR<sup>[4-6]</sup>. SYK plays a key role in signaling downstream of the B and T cell receptors, hence also exhibit an important role in early lymphocyte development<sup>[4,7-10]</sup>. Upon activation, SYK modulates downstream signaling events that drive inflammatory pathways of both the innate and adaptive immune systems<sup>[11]</sup>. Besides ITAM-dependent signalling pathway, SYK also mediates ITAM-independent signaling *via* integrins and C-type lectins. For instance, SYK induces β2 integrin-mediated respiratory burst, spreading, and site-directed migration of neutrophils towards inflammatory lesions<sup>[12]</sup>.

The multifactorial role of SYK in the immune system has attracted attention in the past years. SYK is recognized as a potential target for the treatment of inflammatory diseases such as rheumatoid arthritis, asthma, allergic rhinitis, renal disorders, liver fibrosis and autoimmune diseases<sup>[3,7,13-23]</sup>. In particular, the prevention of activation of cells *via* immune complexes or antigen-triggered Fc receptor signaling and prevention of B cell receptor-mediated events are believed to have increasing therapeutic potential of SYK<sup>[24,25]</sup>.

Besides hematopoietic cells, SYK has also been shown to be expressed in non-hematopoietic cells including fibroblasts, epithelial cells, hepatocytes, neuronal cells, and vascular endothelial cells<sup>[7,26]</sup>. Here, SYK has shown to be involved in signalling events leading to activation of mitogen activated protein kinase (MAPK) by G-protein-coupled receptors in hepatocytes<sup>[26,27]</sup>. Besides being implicated in hepatocytes, SYK is also expressed in hepatic macrophages, hepatic stellate cells (HSCs) and hepatic sinusoidal endothelial cells in liver<sup>[28]</sup>. However, studies investigating SYK signalling pathway in liver diseases are still limited. This review highlights and discusses the opportunities and challenges of SYK as a potential target for the treatment of liver diseases.

## SPLEEN TYROSINE KINASE SIGNALLING MECHANISMS

Immunoreceptor signalling through SYK requires the SYK kinase activity as well as both SH2 domains<sup>[29]</sup>. The SYK kinase domain remain inactive during resting state but can be activated by interaction of both SH2 domains to dual phosphorylated ITAMs<sup>[30]</sup>. Phosphorylation of tyrosine residues within the linker regions (interdomain A or B) also results in kinase activation even in the absence of phosphorylated ITAM binding<sup>[29,30]</sup>. Binding of the SH2 domains of SYK to phosphorylated ITAMs is a critical step in SYK activation and downstream signalling<sup>[31]</sup>. SYK itself can catalyse the autophosphorylation of its linker tyrosine's, leading to sustained SYK activation after a transient ITAM phosphorylation. In addition, SYK itself can phosphorylate ITAMs, suggesting the existence of a positive-feedback loop during initial ITAM-mediated SYK activation<sup>[32]</sup>. Tsang *et al*<sup>[33]</sup> showed that SYK can be fully triggered by phosphorylation or binding of its SH2 domains to the dual-phosphorylated immune-



**Figure 1 Structure of spleen tyrosine kinase.** Spleen tyrosine kinase contains tandem pair of spleen tyrosine kinase homology 2 which connected by interdomain A and separated by interdomain B from the catalytic (kinase) domain. SYK: Spleen tyrosine kinase; SH2: Spleen tyrosine kinase homology 2; ITAM: Immune-receptor tyrosine-based activation motifs.

receptor tyrosine based activity motif (ppITAM) (Figure 2)<sup>[33,34]</sup>. Recently, Slomiany and Slomiany demonstrated lipopolysaccharides (LPS)-induced SYK activation and phosphorylation on serine residues mediated by protein kinase C $\delta$  that is required for its recruitment to the membrane-anchored TLR4, followed by subsequent SYK activation through tyrosine phosphorylation. Hence, the intermediate phase of protein kinase C $\delta$ -mediated SYK phosphorylation on serine residues affects the inflammatory response<sup>[35]</sup>. The activated SYK binds to a number of downstream signalling effectors and amplifies the inflammatory signal propagation by affecting transcription factors activation and their assembly to transcriptional complexes involved in expression of the proinflammatory genes<sup>[36]</sup>.

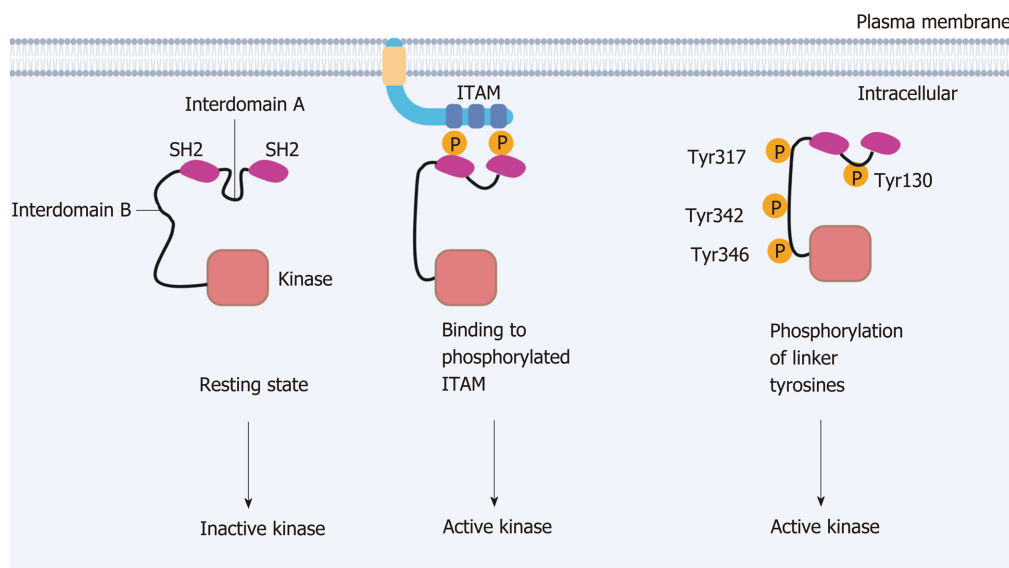
## SPLEEN TYROSINE KINASE IN LIVER FIBROSIS

Liver fibrosis, triggered by hepatitis B/C viral infection (viral hepatitis), alcohol abuse (alcoholic liver disease) or non-alcoholic steatohepatitis (NASH) *etc.*, is characterized by an excessive deposition of extracellular matrix (ECM) proteins<sup>[37]</sup>, leading to tissue scarring that further progresses to end-stage liver cirrhosis and hepatocellular carcinoma<sup>[38]</sup>.

Liver fibrosis poses a major health problem accounting for more than 1 million people deaths per year worldwide<sup>[39]</sup>. Moreover, there is no therapeutic treatment available to date<sup>[40]</sup>. The central player that produces ECM resulting in liver fibrosis is HSCs<sup>[41]</sup>. HSCs are normally localized in the peri-sinusoidal area, termed as space of Disse, as quiescent cells in a healthy liver and functions as retinoid storage cells<sup>[42]</sup>. Owing to hepatic injury, quiescent HSCs phenotypically transdifferentiate into activated, contractile, highly proliferative and ECM-producing myofibroblasts<sup>[43]</sup>.

SYK has been documented to play a critical role in the activation of HSCs and its upregulation is evidenced in hepatic fibrosis/cirrhosis in hepatitis B and C patients, alcoholic hepatitis as well as in NASH patients<sup>[28,44]</sup>. Upregulated SYK further aggravate fibrosis by augmenting trans-communication between hepatocytes and HSCs<sup>[28]</sup>. Blockage of SYK pathway using SYK inhibitors abrogated HSCs activation, thereby ameliorated liver fibrosis and hepatocellular carcinoma (HCC) development *in vivo* in animal models<sup>[28]</sup>. SYK has also shown to mediate its function *via* expression of transcription factors associated with HSCs activation (cAMP response element-binding protein, CBP; myeloblastosis proto-oncogene, MYB and myelocytomatosis proto-oncogene, MYC) and proliferation (MYC and cyclin D1, CCND1)<sup>[28]</sup>. Furthermore, two isoforms of SYK *i.e.*, the full-length SYK (L) and an alternatively spliced SYK (S) have been suggested whereby SYK (L) but not SYK (S) found to play a major role in liver fibrosis while SYK (S) has been associated with increased tumorigenicity, HCC invasiveness and metastases<sup>[28]</sup>.

Interestingly, the crosstalk between SYK and Wnt (portamanteau of int and wg, wingless-related integration site) signalling pathways also mediates activation of HSCs and accumulation of immune cells at the site of fibrosis<sup>[28]</sup>. Wnt signalling has been shown to be upregulated in activated HSCs and blockade of canonical Wnt pathway by adenoviral mediated transduction of Wnt antagonist (Dickkopf-1) or *via* selective inhibitors reinstates quiescent phase of HSCs in cultured cells<sup>[45,46]</sup>. In-depth investigation at a genetic level revealed overexpression of certain transcriptional factors (MYB, CBP and MYC) which plays a vital role in the activation of HSCs<sup>[47,48]</sup>. Notably, both the canonical Wnt pathway and SYK has shown to regulate the expression of MYC and CBP<sup>[23,49]</sup> highlighting SYK-Wnt crosstalk during liver fibrogenesis. SYK has also shown to promote expression of several other target genes including Wnt in activated macrophages in a similar manner as in HSCs and this potential crosstalk between SYK and other signalling pathways warrants further investigation. Dissection of the trans-communication between signalling pathways is



**Figure 2 Basis of spleen tyrosine kinase activation.** In the resting state, spleen tyrosine kinase is auto-inhibited, because of the binding of interdomain A and interdomain B to the kinase domain. This auto-inhibited conformation can be activated by binding of the two spleen tyrosine kinase homology 2 domains to dually phosphorylated immune-receptor tyrosine-based activation motifs or by phosphorylation of linker tyrosine's in interdomain A or B. SH2: Spleen tyrosine kinase homology 2; ITAM: Immune-receptor tyrosine-based activation motifs.

of great importance in order to highlight prominent therapeutic targets to hinder liver inflammation and fibrogenesis. SYK is the major signalling pathway and is also shown to be expressed in recruited macrophages, besides HSCs, in the hepatic fibrosis<sup>[20,28]</sup>. Selective blocking of SYK or its deletion in macrophages has been correlated with the diminished activation of macrophages, which is indicated by a reduction in the expression of Fc gamma receptors, monocyte chemoattractant protein 1 (MCP-1), tumour necrosis factor  $\alpha$  (TNF- $\alpha$ ) and interleukin 6 (IL-6)<sup>[9]</sup>. In summary, activation of HSCs under the influence of SYK signalling leads to the secretion of soluble factors in the form of cytokines and chemokines. These factors not only facilitate the recruitment of macrophages (and other immune cells) but also arbitrates their activation to further worsen the site of fibrosis.

## SPLEEN TYROSINE KINASE IN VIRAL HEPATITIS

In the recent study, SYK expression was found to be highly induced in the liver tissues of HBV- and HCV-infected patients. Furthermore, markedly increased expression of SYK was observed in HCV-infected hepatocytes which in turn promoted reciprocal higher SYK expression in HSCs thereby inducing HSCs activation and disease development<sup>[28,50]</sup>. Furthermore, the preliminary study analysing gene expression profiles in Egyptian HCC patients associated with HCV, showed that SYK is one of the most up-regulated gene out of 180 genes that were up-regulated<sup>[51]</sup>.

HCV is also associated with B lymphocyte proliferative disorders, as evidenced by the binding of HCV to B-cell surface receptor CD81<sup>[52]</sup>. CD81 (cluster of differentiation 81, also known as TAPA1), is identified as a target of an antibody that controlled B-cell proliferation. Engagement of CD81 with HCV<sup>[53,54]</sup>, leads to ezrin and radixin phosphorylation through SYK activation<sup>[55,56]</sup>. Ezrin and radixin are members of the ERM (ezrin, radixin, moesin) family of actin-binding proteins<sup>[56]</sup>. Hence, ezrin-moesin-radixin proteins and SYK are important therapeutic host targets for the development of HCV treatment<sup>[57]</sup>.

SYK is also an important regulator and therapeutic target against HCV infection in hepatocytes<sup>[55]</sup>. SYK expression has been observed near the plasma membrane of hepatocytes in HCV-infected patients<sup>[57,58]</sup>. HCV non-structural protein 5A has been shown to physically and directly interact with SYK hence promoting the malignant transformation of HCV-infected hepatocytes<sup>[58]</sup>. These studies suggests that the strategies blocking SYK activation before HCV-CD81 interaction, and/or modulating HCV post-entry and trafficking within target cells involving SYK, F-actin, stable microtubules and EMR proteins provide novel opportunities for the development of anti-HCV therapies<sup>[55]</sup>.



## SPLEEN TYROSINE KINASE IN ALCOHOLIC LIVER DISEASE

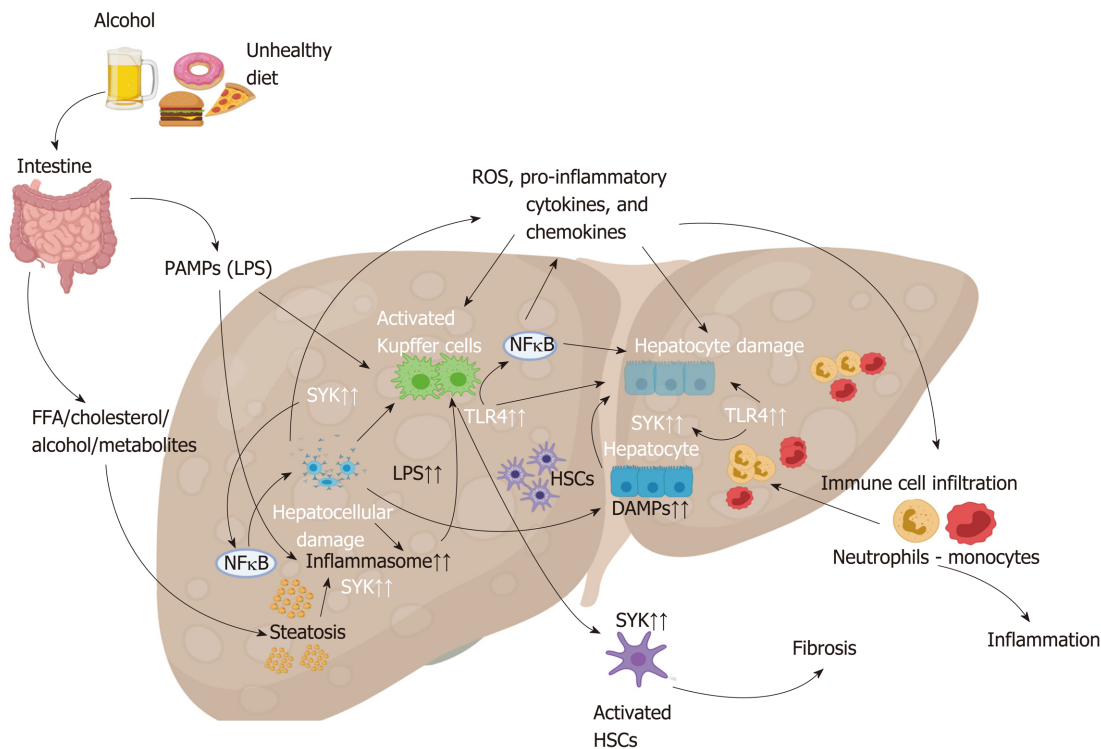
The pathogenesis of alcoholic liver disease (ALD) is multifactorial involving many complex processes including ethanol-mediated liver injury, inflammation in response to the injury, and intestinal permeability and microbiome changes<sup>[59-61]</sup> as depicted in **Figure 3**. Alcohol and its metabolites generate reactive oxygen species (ROS) and induce hepatocyte injury through mitochondrial damage and endoplasmic reticulum (ER) stress<sup>[62-64]</sup>. Damaged hepatocytes release pro-inflammatory cytokines and chemokines resulting in the recruitment and activation of immune cells. Central cell types involved in ALD progression are macrophages that have an important role in inducing liver inflammation<sup>[65]</sup> by stimulating infiltration of immune cells (including monocytes) and activation of Kupffer cells (KCs, resident hepatic macrophages)<sup>[59]</sup>. The early communication of hepatocyte damage is mediated by KCs through damage-associated molecular patterns (DAMPs) released by dying hepatocytes or pathogen-associated molecular patterns (PAMPs) including lipopolysaccharides (LPS) *via* pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) signalling and inflammasome activation *etc.* In ALD, resident and recruited macrophages in the liver are activated by TLR4 (Toll-like receptor 4) signalling pathway regulated by bacterial endotoxin (LPS) that is elevated in the portal and systemic circulation due to increased intestinal permeability after excessive alcohol intake<sup>[66,67]</sup>. However, there are also other mechanisms that regulate macrophage activation, such as hepatocyte injury and lipid accumulation, histone acetylation in ethanol-exposed macrophages and complement system<sup>[68]</sup>. SYK also plays an important role in TLR4 signalling, and SYK phosphorylation in neutrophils and monocytes has been correlated with pro-inflammatory cytokine secretion including TNF- $\alpha$  and MCP-1<sup>[69]</sup>. Interestingly, SYK phosphorylation has also been shown to be regulated by LPS/TLR adaptor molecules MyD88/IRAKM (IL-1R-associated kinase M)/mincle axis linking LPS-induced hepatocyte cell death with inflammation during ALD disease pathogenesis. Zhou *et al.*<sup>[70]</sup> has shown that damaged hepatocytes releases endogenous mincle ligand spliceosome-associated protein 130 as a danger signal that together with LPS synergistically drives liver inflammation including inflammasome activation during ALD<sup>[70]</sup>.

Several studies have documented the increased SYK expression and phosphorylation in the livers of alcoholic hepatitis (AH) patients<sup>[44]</sup>. Interestingly, increased SYK phosphorylation was observed in ballooned hepatocytes with Mallory-Denk Bodies, co-localized with ubiquitinated proteins in the cytoplasm suggesting the critical role of SYK in hepatocytes during ER stress<sup>[71,72]</sup>. SYK regulates hepatic cell death *via* TRAF family member associated NF- $\beta$  activator (TANK)-binding kinase 1/interferon (IFN) regulatory factor 3 (TBK1/IRF3) signaling<sup>[20]</sup>. SYK has also been reported to play an important role in lipid accumulation, and treatment with SYK inhibitor prevented progressive steatosis by suppressing lipid biogenesis and increasing lipid metabolism in both *in vitro* cell culture and *in vivo* in ALD mouse models exhibiting moderate ASH and chronic alcohol drinking<sup>[20]</sup>. SYK<sup>Y525/526</sup> phosphorylation indicates SYK activation and is a prerequisite for its downstream modulatory function<sup>[73]</sup>. In addition, total SYK and activated pSYK<sup>Y525/526</sup> expression was found to be significantly increased in the circulating blood monocytes, and PBMCs in AH/cirrhosis patients<sup>[20]</sup>. Since SYK is closely involved in the pathogenesis of ALD, SYK inhibition could prevent and/or attenuate alcohol-induced liver inflammation, cell death, steatosis and subsequently fibrosis in various phases of ALD<sup>[20,73]</sup>.

## SPLEEN TYROSINE KINASE IN NON-ALCOHOLIC STEATOHEPATITIS

NASH is characterized by increasing accumulation of so-called toxic lipids in hepatocytes, that can develop into cirrhosis and primary liver cancer<sup>[74]</sup>. NASH is the more severe and clinically significant form of NAFLD (non-alcoholic fatty liver disease)<sup>[75]</sup>, characterized by hepatic cell injury, steatosis together with inflammation, resulting into fibrosis signified by deposition of extracellular matrix mainly composed of collagen/fibrin fibrils<sup>[76]</sup>. The progression of NASH is associated with a progressive build-up of danger signals particularly PRRs including TLRs, and nucleotide oligomerization domain-like receptors (NLRs)<sup>[77]</sup> that engage multiple receptors during immune response<sup>[78]</sup>.

As also mentioned earlier, the interaction of LPS with TLR4 plays a major role in linking innate immunity with inflammatory response and the activation of KCs<sup>[77,79,80]</sup>.



**Figure 3 Role of spleen tyrosine kinase in alcoholic liver disease and non-alcoholic steatohepatitis pathogenesis.** Excessive alcohol consumption and increased fat accumulation due to an increased fat biogenesis and reduced metabolism, causes hepatocellular injury that generates reactive oxygen species, release of pro-inflammatory cytokines and chemokines leading to activation of resident macrophages (Kupffer cells), and recruitment of circulating immune cells including neutrophils and monocytes. Overconsumption of alcohol also trigger the production of lipopolysaccharides due to increased intestinal permeability. Increased levels of pathogen-associated molecular patterns (Lipopolysaccharides) and damage-associated molecular patterns (released from dying hepatocytes) that in turn interacts with toll-like receptors e.g., toll-like receptor 4 resulting in the activation of spleen tyrosine kinase signaling pathway, NF- $\kappa$ B signaling pathway, and inflammasome activation. These processes develop into liver inflammation and fibrosis via increased infiltration and activation of immune cells and hepatic stellate cells, respectively. SYK: Spleen tyrosine kinase; LPS: Lipopolysaccharides; PAMPs: Pathogen-associated molecular patterns; DAMPs: Damage-associated molecular patterns; TLRs: Toll-like receptors; HSCs: Hepatic stellate cells; ROS: Reactive oxygen species.

Activated KCs produce inflammatory cytokines and chemokines such as IL-1 $\beta$ , IL-6, iNOS, Fc $\gamma$ R1, and CCL2 that contribute to the recruitment of circulating monocytes and macrophages into the inflamed liver during NASH development mostly similar to ASH<sup>[81]</sup>. Activated KCs also secrete TNF superfamily ligands such as TNF- $\alpha$  and TNF-related apoptosis-inducing ligand, inducing apoptosis of adjacent hepatocytes and inflammation, and is crucial for triggering NASH development<sup>[81-83]</sup> as shown in Figure 3.

Activated KCs instigates TLR4 and recruit an activated SYK, which is also expressed in HSCs, hepatocytes, and cholangiocytes<sup>[77,84-86]</sup>. SYK plays a role in IL1-induced chemokine release via association with TRAF-6 (TNF receptor activating factor 6), which is a shared molecule in multiple signalling pathways and is recruited through interactions of adaptor MyD88 and IRAK-1 (IL1 receptor-associated kinase 1) with TLR4<sup>[87-89]</sup>. Likewise, TLR4 transduces signals via the B-cell receptor (BCR) leading to activation of SYK, which is important for B-cell survival, proliferation<sup>[90]</sup>, and BCR-mediated immune response<sup>[5]</sup>. Lipid peroxidation products, derived from phospholipid oxidation are one of the sources of neo-antigens that are able to promote an adaptive immune response in NASH<sup>[91]</sup>. The involvement of T and B cells in the progression of NASH automatically implicate role of SYK in this process.

Recently, we have shown the positive correlation of SYK expression with the increasing NAS score (NAFLD activity score) in livers from NASH patients as compared to normal livers<sup>[44]</sup>. As aforementioned, the role of SYK in NASH is not only via PRR pathways, but also through NLR pathways. The role of several NLRs have been crucial in the formation of inflammasomes and the nomenclature of inflammasomes is hence based on the NLR<sup>[92]</sup>. SYK is required for NLRP3 (NLR protein 3) inflammasome activation<sup>[93]</sup>, that forms an IL-1 $\beta$ -processing inflammasome complex. Inflammasome activation has been shown to be associated with the late stages of NASH, and not in early steatosis in mice<sup>[94]</sup>. Inflammasome activation can be induced by free fatty acids and these free fatty acids can also induce apoptosis and the release of danger signals in hepatocytes<sup>[94,95]</sup>. Consequently, pharmacological

inhibition of NLRP3 inflammasome *in vivo* has been demonstrated to reduce liver inflammation, hepatocyte injury, and liver fibrosis in NASH<sup>[44,96]</sup>.

## SPLEEN TYROSINE KINASE IN HEPATOCELLULAR CARCINOMA

Hepatocyte apoptosis and compensatory proliferation are the key drivers for HCC development, and SYK has been suggested to play a key role in HCC progression. In HCC, intestinal microbiota and TLR4 link inflammation and carcinogenesis in the chronically injured liver, and SYK regulate this link mediated *via* LPS-TLR4 interaction<sup>[97]</sup>. The intimate correlation between SYK methylation and loss-of-expression, together with the role of SYK methylation in gene silencing, indicates that epigenetic inactivation of SYK contributes to the progression of HCC<sup>[98]</sup> signifying SYK methylation and loss of SYK expression as predictors of poor overall survival in patients with HCC. Furthermore, methylation of SYK promoter was found to be inversely regulated in HCC cells. Restoring SYK expression in SYK-silenced HCC cell lines decreased hepatocellular growth, cell migration and invasion but increased cell adhesion<sup>[99,100]</sup>.

On the other hand, checkpoint kinase 1 (CHK1) was found to be overexpressed and correlated with poor survival of HCC patients. CHK1 phosphorylate tumor suppressor SYK isoform, SYK (L) at Ser295 and induce its proteasomal degradation. However, non-phosphorylated mutant form of SYK (L) has been shown to suppress proliferation, colony formation, migration and tumor growth in HCC lines. Therefore, a strong inverse correlation between the expression levels of CHK1 and SYK (L) was observed in patients with HCC<sup>[101]</sup>. Interestingly, Hong *et al.*<sup>[102]</sup> showed that another SYK isoform, SYK (S) promotes tumour growth, downregulates apoptosis, enhances metastasis and counteracts the opposing effects of SYK (L). These studies suggest that SYK (L) downregulation or SYK (S) upregulation are the strong predictors of poor clinical outcome in patients with HCC.

## SMALL MOLECULES SPLEEN TYROSINE KINASE INHIBITORS

Over the past decade, SYK signalling pathway has been recognized as a promising target for the therapeutic intervention in different diseases including autoimmune and inflammatory disorders, fibrotic diseases and tumour. However, specificity and selectivity remain the major concern for the development of drugs targeting ubiquitously expressed kinases. Hence, debate about the specificity of SYK inhibitors has been a major point of discussion and has still not reached an appropriate conclusion since the first SYK inhibitors entered into medicinal chemistry optimization<sup>[25,103,104]</sup>. Over the past few years, several SYK inhibitors have been designed while many are still in development, and the molecular structures of some of these SYK inhibitors are depicted in **Figure 4**. Several SYK inhibitors have been evaluated in preclinical and clinical studies in different diseases<sup>[103,105]</sup>, as highlighted in **Table 1**<sup>[106-127]</sup>.

Some of the above mentioned SYK inhibitors have been explored in liver diseases and are presented in **Table 2**. R406 has been shown to reduce SYK expression and phosphorylation in macrophages, and other hepatic cells and has been shown to ameliorate non-alcoholic and alcoholic steatohepatitis by inhibiting steatosis, inflammation and fibrosis suggesting multi-faceted effects of this highly selective SYK inhibitor<sup>[20,44]</sup>. GS-9973 is a new emerging, selective and potent inhibitor of SYK that was evaluated in activated HSCs and showed anti-fibrotic effects in rodent liver fibrosis models<sup>[28]</sup>. Very recently, two new inhibitors PRT062607 and Piceatannol have been investigated in myeloid cells to reveal their protective effect against liver fibrosis and hepatocarcinogenesis *in vivo*. Both inhibitors selectively blocked SYK phosphorylation, significantly reduced the infiltration of inflammatory cells and HSCs trans-differentiation, and inhibited malignant transformation in fibrotic livers<sup>[128]</sup>.

Despite the encouraging results with SYK inhibitors, some issues remain unresolved *e.g.*, their long-term safety has not yet been demonstrated. Moreover, due to the ubiquitous expression of SYK in different cells, concerns have been raised about the possibility of side-effects owing to the overall inhibition of the multiple cellular functions<sup>[2,127]</sup>. A major challenge therefore is how to inhibit pathological processes without disrupting physiological cell functions<sup>[129]</sup>. Nanotechnology is an interesting and promising alternative to improve the efficacy and therapeutic effect of the SYK

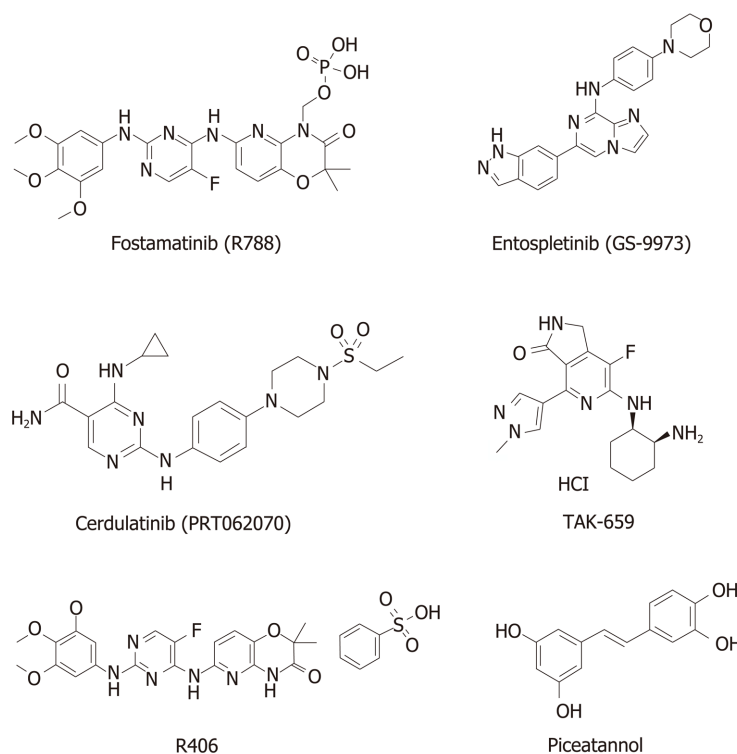
**Table 1 Summary of pre-clinical and clinical studies using spleen tyrosine kinase inhibitors**

Compound	Medical condition	Description/effect	Ref.
Fostamatinib (R788)	Ulcerative colitis	Suppression of TNF $\alpha$ , T cells and neutrophils	[106]
	Rheumatoid arthritis	Reduced inflammation and tissue damage, suppressed clinical arthritis, pannus formation and synovitis	[107,108]
	Chronic lymphocytic leukemia and Non-Hodgkin lymphoma	Disruption of BCR signaling inhibiting the proliferation and survival of malignant B cells	[109,110]
	Ischemia-reperfusion induced intestinal and lung damage	Impaired release of pro-inflammatory and coagulation mediators, reduced neutrophils, macrophages and platelet accumulations	[111]
	Glomerulonephritis	Reduced proteinuria, glomerular macrophage and CD8 cells, MCP-1 and IL-1 $\beta$ , and renal injury	[112]
Entospletinib (GS-9973)	Chronic lymphocytic leukemia	Decreased inflammation and disruption of chemokine/cytokine circuits (BCR signaling)	[113-115]
	Diffuse large B-cell lymphoma	Disruption of BCR signaling inhibiting the proliferation and survival of malignant B cells	[116]
	Cherubism (craniofacial disorder)	Ameliorates inflammation and bone destruction in the mouse model of cherubism	[117]
Cerdulatinib (PRT062070)	Diffuse large B-cell lymphoma	Disruption of BCR signalling inhibiting the proliferation and survival of malignant B cells	[118,119]
TAK-659	Epstein-Barr virus-associated lymphoma	Inhibited tumour development and metastases	[120]
	Chronic lymphocytic leukemia	Decreased tumour survival, myeloid cell proliferation and metastasis	[121]
R406 (tamatatinib)	Immunocomplexes mediated inflammation	Inhibits several critical modes of the inflammatory cascade	[122]
	Human platelets	Inhibition of activation of CLEC-2 (C-type lectin 2, platelet receptor), and platelet activation	[123]
	Chronic lymphocytic leukemia	Inhibition of constitutive and BCR-induced SYK activation, abrogation of CLL cell survival, migration, and paracrine signalling	[124]
	Leukemia	Reduced tyrosine phosphorylation and c-Myc expression, blockade of tumorigenic cells proliferation transformed by oncogenes	[125]
	Megakaryocytic leukemia	Induced apoptosis, reduced cell proliferation and blockade of STAT5 signalling	[126]
	Glomerulonephritis	Downregulated MCP-1 production from mesangial cells and macrophages	[112]
	Oral squamous cell carcinoma	Inhibited tumour cell proliferation, induced of apoptosis, attenuated VEGF and MMP9 expression, and decreased metastases	[127]

TNF- $\alpha$ : Tumour necrosis factor  $\alpha$ ; BCR: B-cell receptor; MCP-1: Monocyte chemoattractant protein 1; SYK: Spleen tyrosine kinase; VEGF: Vascular endothelial growth factor.

inhibitor. Using polymeric poly lactic-co-glycolic acid (PLGA) nanoparticles, we have demonstrated improved therapeutic effectivity of R406 in MCD-diet induced NASH<sup>[44]</sup>. In this study, we have shown that R406, when encapsulated in PLGA polymeric nanoparticles, reduced expression of total SYK and activation of pSYK in macrophages *in vitro*, and attenuated steatosis, inflammation and fibrosis *in vivo* in MCD-diet induced NASH mouse model<sup>[44]</sup>.





**Figure 4** Molecular structure of several spleen tyrosine kinase inhibitors. R406, GS-9973, PRT062070, and Piceatannol have been studied in liver diseases, while R788 and TAK-659 are being investigated in other diseases.

## CONCLUSION

In this review, we have highlighted the implication of SYK signalling pathways in different diseases, more importantly in liver diseases. SYK plays a multifaceted role in liver diseases such as liver fibrosis, alcoholic liver disease, non-alcoholic steatohepatitis, viral hepatitis, and hepatocellular carcinoma. Furthermore, several SYK-related mechanisms have been understood in the past decade which led to the development of numerous small-molecule inhibitors that have been and are currently evaluated *in vitro*, *in vivo* in different animal models and in clinical trials in patients for different indications. These inhibitors have shown highly potent effects in the tested models and therefore is a promising therapeutic target that should be explored further in pre-clinical and clinical studies. To improve the therapeutic efficacy and clinical use of SYK inhibitors with improved safety profile and reduce the side effects, nanotechnology approaches, such as polymeric nanoparticles, liposomal-mediated delivery, or micelles, and finally organ (tumour)-targeted drug delivery could be explored.

**Table 2 Spleen tyrosine kinase inhibitors implicated in liver diseases**

Inhibitor	Mechanism of action	Therapeutic effect	Ref.
R406	Blocking of Fc receptor signalling pathway, NF- $\kappa$ B signalling pathway and inflammasome activation	Reduced SYK expression and phosphorylation resulting in attenuated liver steatosis, inflammation and fibrosis in ASH and NASH murine models	[20,44]
GS-9973	Decreased expression of HSCs activation (CBP, MYB, MYC) and HSCs proliferation factors (MYC and CCND1)	Inhibition of HSCs proliferation and HSC activation resulting in amelioration of fibrosis and hepatocarcinogenesis	[28]
PRT062607 and piceatannol	Increased intra-tumoral p16, p53 and decreased expression of Bcl-xL and SMAD4. Decreased expression of genes regulating angiogenesis, apoptosis, cell cycle regulation and cellular senescence. Down-regulation of mTOR, IL-8 signalling and oxidative phosphorylation	Reduced HSCs differentiation and infiltration of inflammatory cells including T cells, B cells and myeloid cells, reduced oncogenic progression. Marked attenuation of toxin-induced liver fibrosis, associated hepatocellular injury, intra-hepatic inflammation and hepatocarcinogenesis	[128]

SYK: Spleen tyrosine kinase; NASH: Non-alcoholic steatohepatitis; ASH: Alcoholic steatohepatitis; HSCs: Hepatic stellate cells; IL-8: Interleukin-8.

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