**Name of Journal:** *World Journal of Gastroenterology*

**Manuscript NO:** 52854

**Manuscript Type:** Review

**Role of spleen tyrosine kinase in liver diseases**

Kurniawan DW *et al*. SYK in liver diseases

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

**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

**Author contributions:** Kurniawan DW drafted and wrote the review; Bansal R critically reviewed and revised the review; Storm G and Prakash J read the review and provided their feedback; All the authors have read the review, contributed in language editing, and approved the final version.

**Supported by** the Endowment Fund for the Education Republic of Indonesia (Lembaga Pengelola Dana Pendidikan/LPDP RI), No. 44/LPDP/2015.

**Corresponding authors: 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

**Received:** November 29, 2019

**Revised:** January 14, 2020

**Accepted:** February 28, 2020

**Published online:**

**Abstract**

Spleen tyrosine kinase (SYK), a non-receptor tyrosine kinase, is 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

Kurniawan DW, Storm G, Prakash J, Bansal R. Role of spleen tyrosine kinase in liver diseases. *World J Gastroenterol* 2020; In press

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

**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 linked by two linker regions: interdomain A between the two SH2 domains and interdomain B between the C-terminal SH2 domain and the kinase domain. 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[1,2] (Figure 1). 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[2,3]. 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* high affinity Igγ receptors, FcγR[4-6]. SYK plays a key role in signaling downstream of the B and T cell receptors, hence also play a crucial role in early lymphocyte development[4,7-10]. Upon activation, SYK modulates downstream signaling events that drive inflammatory pathways of both the innate and adaptive immune systems[11]. 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[12].

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[3,7,13-23]. 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[24,25].

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[7,26]. Here, SYK has shown to be involved in signalling steps leading to mitogen activated protein kinase activation by G-protein-coupled receptors in hepatocytes[26,27]. Besides being implicated in hepatocytes, SYK is also expressed in hepatic macrophages, hepatic stellate cells (HSCs) and hepatic sinusoidal endothelial cells in liver[28]. However, studies investigating SYK signalling pathway in liver diseases are still limited, hence 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[29]. The SYK kinase domain is inactive in the resting state of the protein but can be activated by interaction of both SH2 domains to dual phosphorylated ITAMs[30]. 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[29,30]. Binding of the SH2 domains of SYK to phosphorylated ITAMs is a critical step in SYK activation and downstream signalling[31]. 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[32]. Tsang *et al*[33] showed that SYK can be fully triggered by phosphorylation or binding of its SH2 domains to the dual-phosphorylated immune-receptor tyrosine based activity motif (ppITAM) (Figure 2)[33,34]. Recently, Slomiany and Slomiany demonstrated lipopolysaccharides (LPS)-induced SYK activation through protein kinase Cδ-mediates SYK phosphorylation on serine residues that is required for its recruitment to the membrane-anchored TLR4, followed by SYK subsequent activation through tyrosine phosphorylation. Hence, the intermediate phase of protein kinase Cδ-mediated SYK phosphorylation on serine residues affects the inflammatory response[35]. 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 proinflammatory genes expression[36].

**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[37], leading to tissue scarring that further progresses to end-stage liver cirrhosis and hepatocellular carcinoma[38].

Lately, liver fibrosis poses a major health problem accounting for more than 1 million people deaths every year worldwide because of this disease[39]. Moreover, there is no therapeutic treatment available to date[40]. The central player that produces ECM resulting in liver fibrosis is HSCs[41]. HSCs are no9rmally localized in the peri-sinusoidal area, termed as space of Disse, as quiescent cells in healthy liver and functions as retinoid storage cells[42]. Owing to hepatic injury, quiescent HSCs phenotypically transdifferentiate into activated, contractile, highly proliferative and ECM-producing myofibroblasts[43].

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[28,44]. Upregulated SYK further aggravate fibrosis by augmenting trans-communication between hepatocytes and HSCs[28]. Blockage of SYK pathway using SYK inhibitors abrogated HSCs activation, thereby ameliorated liver fibrosis and hepatocellular carcinoma (HCC) development *in vivo* in animal models[28]. SYK has 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)[28]. 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[28].

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[28]. 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[45,46]. 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[47,48]. Notably, both the canonical Wnt pathway and SYK has shown to regulate the expression of MYC and CBP[23,49] highlighting SYK-Wnt crosstalk during liver fibrogenesis. SYK has also shown to promote expression of several 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 of great importance in order to highlight prominent therapeutic targets to hinder 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[20,28]. 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 α (TNF-α) and interleukin 6 (IL-6)[5]. 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 elements not only facilitate the recruitment of resident and migrated macrophages 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[28,50]. 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 genes out of 180 of genes were up regulated[51].

HCV is also associated with B lymphocyte proliferative disorders, as evidenced by the binding of HCV to B-cell surface receptor CD81[52]. 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[53,54], leads to ezrin and radixin phosphorylation through SYK activation[55,56]. Ezrin and radixin are members of the ERM (ezrin, radixin, moesin) family of actin-binding proteins[56]. Hence, ezrin-moesin-radixin proteins and SYK are important therapeutic host targets for the development HCV treatment[57].

SYK is also an important regulator and therapeutic target against HCV infection in hepatocytes[55]. SYK expression has been observed near the plasma membrane of hepatocytes in HCV-infected patients[57,58]. HCV non-structural protein 5A has been shown to physically and directly interact with SYK thereby promoting the malignant transformation of HCV-infected hepatocytes[58]. 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[55].

**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[59-61] as shown in Figure 3. Alcohol and its metabolites generate reactive oxygen species (ROS) and induce hepatocyte injury through mitochondrial damage and endoplasmic reticulum (ER) stress[62-64]. Damaged hepatocytes release pro-inflammatory cytokines and chemokines resulting in recruitment and activation of immune cells. Central cell types involved in ALD progression are macrophages that have an important role in inducing liver inflammation[65] by stimulating infiltration of immune cells (mainly monocytes) and activation of Kupffer cells (KCs, resident macrophages)[59]. The early communication of hepatocyte damage is mediated by KCs through damage-associated molecular patterns released by dying hepatocytes or pathogen-associated molecular patterns including lipopolysaccharides (LPS) *via* pattern recognition receptors (PRRs) such as TLRs (Toll-like receptors), and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) 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 owing to increased intestinal permeability after excessive alcohol intake[66,67]. 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[68]. SYK plays an important role in TLR4 signalling, and SYK phosphorylation in neutrophils and monocytes has been correlated with pro-inflammatory cytokine secretion including TNF-α and MCP-1[69]. Interestingly, SYK phosphorylation has 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*[70] has shown that damaged hepatocytes releases endogenous Mincle ligand spliceosome-associated protein 130 as a danger signal that synergistically with LPS drives inflammation including inflammasome activation during ALD[70].

Several studies have documented the increased SYK expression and phosphorylation in the livers of alcoholic hepatitis (AH) patients[44]. 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[71,72]. SYK regulates hepatic cell death *via* TANK (TRAF family member-associated NF-Ƙβ activator)-binding kinase 1/interferon (IFN) regulatory factor 3 (TBK1/IRF3) signaling[20]. 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[20]. SYKY525/526 phosphorylation indicates SYK activation and is a prerequisite for its downstream modulatory function[73]. In addition, total SYK and activated pSYKY525/526 expression was found to be significantly increased in the circulating blood monocytes, and PBMCs in AH/cirrhosis patients[20]. 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[20,73].

**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[74]. NASH is the more severe and clinically significant form of NAFLD (non-alcoholic fatty liver disease)[75], characterized by hepatic cell injury, steatosis together with inflammation, resulting into fibrosis signified by deposition of extracellular matrix mainly composed of collagen/fibrin fibrils[76]. The progression of NASH is associated with a progressive build-up of danger signals particularly PRRs including TLRs, and nucleotide oligomerization domain-like receptors (NLR)[77] that engage multiple receptors during immune response[78].

As mentioned earlier, the interaction of LPS with TLR4 plays a major role in linking innate immunity with inflammatory response and the activation of KCs[77,79,80]. Activated KCs produce inflammatory cytokines and chemokines such as IL-1β, IL-6, iNOS, FcγR1, and CCL2 that contribute to the recruitment of circulating monocytes and macrophages into the inflammed liver during NASH development mostly similar to ASH[81]. Activated KCs also secrete TNF superfamily ligands such as TNF-α and TNF-related apoptosis-inducing ligand, inducing apoptosis of adjacent hepatocytes and inflammation, and is crucial for triggering NASH development[81-83] as depicted in Figure 3.

Activated KCs instigates TLR4 and recruit an activated SYK, which is also expressed in HSCs, hepatocytes, and cholangiocytes[77,84-86]. 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[87-89]. Likewise, TLR4 transduces signals *via* the B-cell receptor (BCR) leading to activation of SYK, which is important for B-cell survival, proliferation[90], and BCR-mediated immune response[5]. 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[91]. 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[44]. 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[92]. SYK is required for NLRP3 (NLR protein 3) inflammasome activation[93], that forms an IL-1β-processing inflammasome complex. Inflammasome activation has been shown to be associated with the late stages of NASH, and not in early steatosis in mice[94]. 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[94,95]. Consequently, pharmacological inhibition of NLRP3 inflammasome *in vivo* has been demonstrated to reduce liver inflammation, hepatocyte injury, and liver fibrosis in NASH[44,96].

**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[97]. The tight 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[98] 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[99,100].

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 inducing 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[101]. Interestingly, Hong *et al*[102] showed that another SYK isoform, SYK (S) promotes tumor growth, downregulate apoptosis, enhances metastasis and counteract 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 disease 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[25,103,104]. 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 are been evaluated in preclinical and clinical studies in different diseases[103,105], as highlighted in Table 1[106-127].

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[20,44]. 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[28]. 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[128].

Despite the encouraging results with SYK inhibitors, some issues remain unsolved (*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[2,127]. A major challenge therefore is how to inhibit pathological processes without disrupting physiological cell functions[129]. Nanotechnology is an interesting and promising alternative to improve the efficacy and therapeutic effect of the SYK inhibitor *e.g.,* using poly lactic-co-glycolic acid nanoparticles, we have demonstrated improved therapeutic effectivity of R406 in MCD-diet induced NASH[44]. In this study, we have shown that R406, encapsulated in poly lactic-co-glycolic acid nanoparticles, reduced expression of SYK in macrophages *in vitro*, and attenuated steatosis, inflammation and fibrosis *in vivo* in NASH mouse model[44].

**CONCLUSION**

In this review, we have highlighted the implication of SYK signaling 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. 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 (tumor)-targeted drug delivery could be explored.

**REFERENCES**

1 **Lowell CA**. Src-family and Syk kinases in activating and inhibitory pathways in innate immune cells: signaling cross talk. *Cold Spring Harb Perspect Biol* 2011; **3** [PMID: 21068150 DOI: 10.1101/cshperspect.a002352]

2 **Riccaboni M**, Bianchi I, Petrillo P. Spleen tyrosine kinases: biology, therapeutic targets and drugs. *Drug Discov Today* 2010; **15**: 517-530 [PMID: 20553955 DOI: 10.1016/j.drudis.2010.05.001]

3 **Pamuk ON**, Tsokos GC. Spleen tyrosine kinase inhibition in the treatment of autoimmune, allergic and autoinflammatory diseases. *Arthritis Res Ther* 2010; **12**: 222 [PMID: 21211067 DOI: 10.1186/ar3198]

4 **Mócsai A**, Ruland J, Tybulewicz VL. The SYK tyrosine kinase: a crucial player in diverse biological functions. *Nat Rev Immunol* 2010; **10**: 387-402 [PMID: 20467426 DOI: 10.1038/nri2765]

5 **Schweighoffer E**, Nys J, Vanes L, Smithers N, Tybulewicz VLJ. TLR4 signals in B lymphocytes are transduced via the B cell antigen receptor and SYK. *J Exp Med* 2017; **214**: 1269-1280 [PMID: 28356391 DOI: 10.1084/jem.20161117]

6 **Turner M**, Schweighoffer E, Colucci F, Di Santo JP, Tybulewicz VL. Tyrosine kinase SYK: essential functions for immunoreceptor signalling. *Immunol Today* 2000; **21**: 148-154 [PMID: 10689303 DOI: 10.1016/S0167-5699(99)01574-1]

7 **Bradshaw JM**. The Src, Syk, and Tec family kinases: distinct types of molecular switches. *Cell Signal* 2010; **22**: 1175-1184 [PMID: 20206686 DOI: 10.1016/j.cellsig.2010.03.001]

8 **Cornall RJ**, Cheng AM, Pawson T, Goodnow CC. Role of Syk in B-cell development and antigen-receptor signaling. *Proc Natl Acad Sci U S A* 2000; **97**: 1713-1718 [PMID: 10677523 DOI: 10.1073/pnas.97.4.1713]

9 **Keller B**, Stumpf I, Strohmeier V, Usadel S, Verhoeyen E, Eibel H, Warnatz K. High SYK Expression Drives Constitutive Activation of CD21low B Cells. *J Immunol* 2017; **198**: 4285-4292 [PMID: 28468967 DOI: 10.4049/jimmunol.1700079]

10 **Burton AR**, Pallett LJ, McCoy LE, Suveizdyte K, Amin OE, Swadling L, Alberts E, Davidson BR, Kennedy PT, Gill US, Mauri C, Blair PA, Pelletier N, Maini MK. Circulating and intrahepatic antiviral B cells are defective in hepatitis B. *J Clin Invest* 2018; **128**: 4588-4603 [PMID: 30091725 DOI: 10.1172/JCI121960]

11 **Frommhold D**, Mannigel I, Schymeinsky J, Mocsai A, Poeschl J, Walzog B, Sperandio M. Spleen tyrosine kinase Syk is critical for sustained leukocyte adhesion during inflammation in vivo. *BMC Immunol* 2007; **8**: 31 [PMID: 18045459 DOI: 10.1186/1471-2172-8-31]

12 **Mócsai A**, Zhou M, Meng F, Tybulewicz VL, Lowell CA. Syk is required for integrin signaling in neutrophils. *Immunity* 2002; **16**: 547-558 [PMID: 11970878 DOI: 10.1016/s1074-7613(02)00303-5]

13 **Pamuk ON**, Lapchak PH, Rani P, Pine P, Dalle Lucca JJ, Tsokos GC. Spleen tyrosine kinase inhibition prevents tissue damage after ischemia-reperfusion. *Am J Physiol Gastrointest Liver Physiol* 2010; **299**: G391-G399 [PMID: 20522642 DOI: 10.1152/ajpgi.00198.2010]

14 **Geahlen RL**. Getting Syk: spleen tyrosine kinase as a therapeutic target. *Trends Pharmacol Sci* 2014; **35**: 414-422 [PMID: 24975478 DOI: 10.1016/j.tips.2014.05.007]

15 **McAdoo SP**, Reynolds J, Bhangal G, Smith J, McDaid JP, Tanna A, Jackson WD, Masuda ES, Cook HT, Pusey CD, Tam FW. Spleen tyrosine kinase inhibition attenuates autoantibody production and reverses experimental autoimmune GN. *J Am Soc Nephrol* 2014; **25**: 2291-2302 [PMID: 24700868 DOI: 10.1681/ASN.2013090978]

16 **Patterson H**, Nibbs R, McInnes I, Siebert S. Protein kinase inhibitors in the treatment of inflammatory and autoimmune diseases. *Clin Exp Immunol* 2014; **176**: 1-10 [PMID: 24313320 DOI: 10.1111/cei.12248]

17 **Kaur M**, Singh M, Silakari O. Inhibitors of switch kinase 'spleen tyrosine kinase' in inflammation and immune-mediated disorders: a review. *Eur J Med Chem* 2013; **67**: 434-446 [PMID: 23917087 DOI: 10.1016/j.ejmech.2013.04.070]

18 **Ma TK**, McAdoo SP, Tam FW. Spleen Tyrosine Kinase: A Crucial Player and Potential Therapeutic Target in Renal Disease. *Nephron* 2016; **133**: 261-269 [PMID: 27476075 DOI: 10.1159/000446879]

19 **Chen KH**, Hsu HH, Yang HY, Tian YC, Ko YC, Yang CW, Hung CC. Inhibition of spleen tyrosine kinase (syk) suppresses renal fibrosis through anti-inflammatory effects and down regulation of the MAPK-p38 pathway. *Int J Biochem Cell Biol* 2016; **74**: 135-144 [PMID: 26948651 DOI: 10.1016/j.biocel.2016.03.001]

20 **Bukong TN**, Iracheta-Vellve A, Saha B, Ambade A, Satishchandran A, Gyongyosi B, Lowe P, Catalano D, Kodys K, Szabo G. Inhibition of spleen tyrosine kinase activation ameliorates inflammation, cell death, and steatosis in alcoholic liver disease. *Hepatology* 2016; **64**: 1057-1071 [PMID: 27302565 DOI: 10.1002/hep.28680]

21 **McAdoo S**, Tam FWK. Role of the Spleen Tyrosine Kinase Pathway in Driving Inflammation in IgA Nephropathy. *Semin Nephrol* 2018; **38**: 496-503 [PMID: 30177021 DOI: 10.1016/j.semnephrol.2018.05.019]

22 **Sanderson MP**, Lau CW, Schnapp A, Chow CW. Syk: a novel target for treatment of inflammation in lung disease. *Inflamm Allergy Drug Targets* 2009; **8**: 87-95 [PMID: 19530990 DOI: http://dx.doi.org/10.2174/187152809788462626]

23 **Coffey G**, DeGuzman F, Inagaki M, Pak Y, Delaney SM, Ives D, Betz A, Jia ZJ, Pandey A, Baker D, Hollenbach SJ, Phillips DR, Sinha U. Specific inhibition of spleen tyrosine kinase suppresses leukocyte immune function and inflammation in animal models of rheumatoid arthritis. *J Pharmacol Exp Ther* 2012; **340**: 350-359 [PMID: 22040680 DOI: 10.1124/jpet.111.188441]

24 **Koyama** **Y**, Brenner DA. Liver inflammation and fibrosis. *J Clin Invest* 2017; **127**: 55-64 [PMID: 28045404 DOI: 10.1172/JCI88881]

25 **Singh R**, Masuda ES, Payan DG. Discovery and development of spleen tyrosine kinase (SYK) inhibitors. *J Med Chem* 2012; **55**: 3614-3643 [PMID: 22257213 DOI: 10.1021/jm201271b]

26 **Yanagi S**, Inatome R, Takano T, Yamamura H. Syk expression and novel function in a wide variety of tissues. *Biochem Biophys Res Commun* 2001; **288**: 495-498 [PMID: 11676469 DOI: 10.1006/bbrc.2001.5788]

27 **Tsuchida S**, Yanagi S, Inatome R, Ding J, Hermann P, Tsujimura T, Matsui N, Yamamura H. Purification of a 72-kDa protein-tyrosine kinase from rat liver and its identification as Syk: involvement of Syk in signaling events of hepatocytes. *J Biochem* 2000; **127**: 321-327 [PMID: 10731700 DOI: 10.1093/oxfordjournals.jbchem.a022610]

28 **Qu C**, Zheng D, Li S, Liu Y, Lidofsky A, Holmes JA, Chen J, He L, Wei L, Liao Y, Yuan H, Jin Q, Lin Z, Hu Q, Jiang Y, Tu M, Chen X, Li W, Lin W, Fuchs BC, Chung RT, Hong J. Tyrosine kinase SYK is a potential therapeutic target for liver fibrosis. *Hepatology* 2018; **68**: 1125-1139 [PMID: 29537660 DOI: 10.1002/hep.29881]

29 **Keshvara LM**, Isaacson C, Harrison ML, Geahlen RL. Syk activation and dissociation from the B-cell antigen receptor is mediated by phosphorylation of tyrosine 130. *J Biol Chem* 1997; **272**: 10377-10381 [PMID: 9099676 DOI: 10.1074/jbc.272.16.10377]

30 **Zhang Y**, Oh H, Burton RA, Burgner JW, Geahlen RL, Post CB. Tyr130 phosphorylation triggers Syk release from antigen receptor by long-distance conformational uncoupling. *Proc Natl Acad Sci U S A* 2008; **105**: 11760-11765 [PMID: 18689684 DOI: 10.1073/pnas.0708583105]

31 **Grucza RA**, Fütterer K, Chan AC, Waksman G. Thermodynamic study of the binding of the tandem-SH2 domain of the Syk kinase to a dually phosphorylated ITAM peptide: evidence for two conformers. *Biochemistry* 1999; **38**: 5024-5033 [PMID: 10213605 DOI: 10.1021/bi9829938]

32 **Rolli V**, Gallwitz M, Wossning T, Flemming A, Schamel WW, Zürn C, Reth M. Amplification of B cell antigen receptor signaling by a Syk/ITAM positive feedback loop. *Mol Cell* 2002; **10**: 1057-1069 [PMID: 12453414 DOI: 10.1016/s1097-2765(02)00739-6]

33 **Tsang E**, Giannetti AM, Shaw D, Dinh M, Tse JK, Gandhi S, Ho H, Wang S, Papp E, Bradshaw JM. Molecular mechanism of the Syk activation switch. *J Biol Chem* 2008; **283**: 32650-32659 [PMID: 18818202 DOI: 10.1074/jbc.M806340200]

34 **Kulathu Y**, Hobeika E, Turchinovich G, Reth M. The kinase Syk as an adaptor controlling sustained calcium signalling and B-cell development. *EMBO J* 2008; **27**: 1333-1344 [PMID: 18369315 DOI: 10.1038/emboj.2008.62]

35 **Slomiany BL**, Slomiany A. Helicobacter pylori LPS-induced gastric mucosal spleen tyrosine kinase (Syk) recruitment to TLR4 and activation occurs with the involvement of protein kinase Cδ. *Inflammopharmacology* 2018; **26**: 805-815 [PMID: 29353412 DOI: 10.1007/s10787-017-0430-4]

36 **Slomiany BL**, Slomiany A. Syk: a new target for attenuation of Helicobacter pylori-induced gastric mucosal inflammatory responses. *Inflammopharmacology* 2019; **27**: 203-211 [PMID: 30820719 DOI: 10.1007/s10787-019-00577-6]

37 **Bataller R**, Brenner DA. Liver fibrosis. *J Clin Invest* 2005; **115**: 209-218 [PMID: 15690074 DOI: 10.1172/jci24282]

38 **Parola M**, Pinzani M. Liver fibrosis: Pathophysiology, pathogenetic targets and clinical issues. *Mol Aspects Med* 2019; **65**: 37-55 [PMID: 30213667 DOI: 10.1016/j.mam.2018.09.002]

39 **Asrani SK**, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. *J Hepatol* 2019; **70**: 151-171 [PMID: 30266282 DOI: 10.1016/j.jhep.2018.09.014]

40 **Schuppan D**, Ashfaq-Khan M, Yang AT, Kim YO. Liver fibrosis: Direct antifibrotic agents and targeted therapies. *Matrix Biol* 2018; **68-69**: 435-451 [PMID: 29656147 DOI: 10.1016/j.matbio.2018.04.006]

41 **Gieseck RL 3rd**, Wilson MS, Wynn TA. Type 2 immunity in tissue repair and fibrosis. *Nat Rev Immunol* 2018; **18**: 62-76 [PMID: 28853443 DOI: 10.1038/nri.2017.90]

42 **Tsuchida T**, Friedman SL. Mechanisms of hepatic stellate cell activation. *Nat Rev Gastroenterol Hepatol* 2017; **14**: 397-411 [PMID: 28487545 DOI: 10.1038/nrgastro.2017.38]

43 **Nishikawa K**, Osawa Y, Kimura K. Wnt/β-Catenin Signaling as a Potential Target for the Treatment of Liver Cirrhosis Using Antifibrotic Drugs. *Int J Mol Sci* 2018; **19** [PMID: 30308992 DOI: 10.3390/ijms19103103]

44 **Kurniawan DW**, Jajoriya AK, Dhawan G, Mishra D, Argemi J, Bataller R, Storm G, Mishra DP, Prakash J, Bansal R. Therapeutic inhibition of spleen tyrosine kinase in inflammatory macrophages using PLGA nanoparticles for the treatment of non-alcoholic steatohepatitis. *J Control Release* 2018; **288**: 227-238 [PMID: 30219279 DOI: 10.1016/j.jconrel.2018.09.004]

45 **Cheng JH**, She H, Han YP, Wang J, Xiong S, Asahina K, Tsukamoto H. Wnt antagonism inhibits hepatic stellate cell activation and liver fibrosis. *Am J Physiol Gastrointest Liver Physiol* 2008; **294**: G39-G49 [PMID: 18006602 DOI: 10.1152/ajpgi.00263.2007]

46 **Akcora BÖ**, Storm G, Bansal R. Inhibition of canonical WNT signaling pathway by β-catenin/CBP inhibitor ICG-001 ameliorates liver fibrosis in vivo through suppression of stromal CXCL12. *Biochim Biophys Acta Mol Basis Dis* 2018; **1864**: 804-818 [PMID: 29217140 DOI: 10.1016/j.bbadis.2017.12.001]

47 **Wang X**, Tang X, Gong X, Albanis E, Friedman SL, Mao Z. Regulation of hepatic stellate cell activation and growth by transcription factor myocyte enhancer factor 2. *Gastroenterology* 2004; **127**: 1174-1188 [PMID: 15480995 DOI: 10.1053/j.gastro.2004.07.007]

48 **Mann J**, Mann DA. Transcriptional regulation of hepatic stellate cells. *Adv Drug Deliv Rev* 2009; **61**: 497-512 [PMID: 19393271 DOI: 10.1016/j.addr.2009.03.011]

49 **Tokunaga Y**, Osawa Y, Ohtsuki T, Hayashi Y, Yamaji K, Yamane D, Hara M, Munekata K, Tsukiyama-Kohara K, Hishima T, Kojima S, Kimura K, Kohara M. Selective inhibitor of Wnt/β-catenin/CBP signaling ameliorates hepatitis C virus-induced liver fibrosis in mouse model. *Sci Rep* 2017; **7**: 325 [PMID: 28336942 DOI: 10.1038/s41598-017-00282-w]

50 **Aouar B**, Kovarova D, Letard S, Font-Haro A, Florentin J, Weber J, Durantel D, Chaperot L, Plumas J, Trejbalova K, Hejnar J, Nunès JA, Olive D, Dubreuil P, Hirsch I, Stranska R. Dual Role of the Tyrosine Kinase Syk in Regulation of Toll-Like Receptor Signaling in Plasmacytoid Dendritic Cells. *PLoS One* 2016; **11**: e0156063 [PMID: 27258042 DOI: 10.1371/journal.pone.0156063]

51 **Zekri AR**, Hafez MM, Bahnassy AA, Hassan ZK, Mansour T, Kamal MM, Khaled HM. Genetic profile of Egyptian hepatocellular-carcinoma associated with hepatitis C virus Genotype 4 by 15 K cDNA microarray: preliminary study. *BMC Res Notes* 2008; **1**: 106 [PMID: 18959789 DOI: 10.1186/1756-0500-1-106]

52 **Pileri P**, Uematsu Y, Campagnoli S, Galli G, Falugi F, Petracca R, Weiner AJ, Houghton M, Rosa D, Grandi G, Abrignani S. Binding of hepatitis C virus to CD81. *Science* 1998; **282**: 938-941 [PMID: 9794763 DOI: 10.1126/science.282.5390.938]

53 **Brazzoli M**, Bianchi A, Filippini S, Weiner A, Zhu Q, Pizza M, Crotta S. CD81 is a central regulator of cellular events required for hepatitis C virus infection of human hepatocytes. *J Virol* 2008; **82**: 8316-8329 [PMID: 18579606 DOI: 10.1128/JVI.00665-08]

54 **Zhang J**, Randall G, Higginbottom A, Monk P, Rice CM, McKeating JA. CD81 is required for hepatitis C virus glycoprotein-mediated viral infection. *J Virol* 2004; **78**: 1448-1455 [PMID: 14722300 DOI: 10.1128/jvi.78.3.1448-1455.2004]

55 **Bukong TN**, Kodys K, Szabo G. Human ezrin-moesin-radixin proteins modulate hepatitis C virus infection. *Hepatology* 2013; **58**: 1569-1579 [PMID: 23703860 DOI: 10.1002/hep.26500]

56 **Coffey GP**, Rajapaksa R, Liu R, Sharpe O, Kuo CC, Krauss SW, Sagi Y, Davis RE, Staudt LM, Sharman JP, Robinson WH, Levy S. Engagement of CD81 induces ezrin tyrosine phosphorylation and its cellular redistribution with filamentous actin. *J Cell Sci* 2009; **122**: 3137-3144 [PMID: 19654214 DOI: 10.1242/jcs.045658]

57 **Bukong TN**, Kodys K, Szabo G. A Novel Human Radixin Peptide Inhibits Hepatitis C Virus Infection at the Level of Cell Entry. *Int J Pept Res Ther* 2014; **20**: 269-276 [PMID: 25379035 DOI: 10.1007/s10989-013-9390-8]

58 **Inubushi S**, Nagano-Fujii M, Kitayama K, Tanaka M, An C, Yokozaki H, Yamamura H, Nuriya H, Kohara M, Sada K, Hotta H. Hepatitis C virus NS5A protein interacts with and negatively regulates the non-receptor protein tyrosine kinase Syk. *J Gen Virol* 2008; **89**: 1231-1242 [PMID: 18420802 DOI: 10.1099/vir.0.83510-0]

59 **Dunn W**, Shah VH. Pathogenesis of Alcoholic Liver Disease. *Clin Liver Dis* 2016; **20**: 445-456 [PMID: 27373608 DOI: 10.1016/j.cld.2016.02.004]

60 **Gao B**, Bataller R. Alcoholic liver disease: pathogenesis and new therapeutic targets. *Gastroenterology* 2011; **141**: 1572-1585 [PMID: 21920463 DOI: 10.1053/j.gastro.2011.09.002]

61 **Szabo G**, Mandrekar P. A recent perspective on alcohol, immunity, and host defense. *Alcohol Clin Exp Res* 2009; **33**: 220-232 [PMID: 19053973 DOI: 10.1111/j.1530-0277.2008.00842.x]

62 **Stickel F**, Datz C, Hampe J, Bataller R. Pathophysiology and Management of Alcoholic Liver Disease: Update 2016. *Gut Liver* 2017; **11**: 173-188 [PMID: 28274107 DOI: 10.5009/gnl16477]

63 **Petrasek J**, Iracheta-Vellve A, Csak T, Satishchandran A, Kodys K, Kurt-Jones EA, Fitzgerald KA, Szabo G. STING-IRF3 pathway links endoplasmic reticulum stress with hepatocyte apoptosis in early alcoholic liver disease. *Proc Natl Acad Sci USA* 2013; **110**: 16544-16549 [PMID: 24052526 DOI: 10.1073/pnas.1308331110]

64 **Lieber CS**. Alcoholic fatty liver: its pathogenesis and mechanism of progression to inflammation and fibrosis. *Alcohol* 2004; **34**: 9-19 [PMID: 15670660 DOI: 10.1016/j.alcohol.2004.07.008]

65 **Guo J**, Friedman SL. Toll-like receptor 4 signaling in liver injury and hepatic fibrogenesis. *Fibrogenesis Tissue Repair* 2010; **3**: 21 [PMID: 20964825 DOI: 10.1186/1755-1536-3-21]

66 **Szabo G**. Gut-liver axis in alcoholic liver disease. *Gastroenterology* 2015; **148**: 30-36 [PMID: 25447847 DOI: 10.1053/j.gastro.2014.10.042]

67 **Roh YS**, Seki E. Toll-like receptors in alcoholic liver disease, non-alcoholic steatohepatitis and carcinogenesis. *J Gastroenterol Hepatol* 2013; **28 Suppl 1**: 38-42 [PMID: 23855294 DOI: 10.1111/jgh.12019]

68 **Petrasek J**, Mandrekar P, Szabo G. Toll-like receptors in the pathogenesis of alcoholic liver disease. *Gastroenterol Res Pract* 2010; **2010** [PMID: 20827314 DOI: 10.1155/2010/710381]

69 **Miller YI**, Choi SH, Wiesner P, Bae YS. The SYK side of TLR4: signalling mechanisms in response to LPS and minimally oxidized LDL. *Br J Pharmacol* 2012; **167**: 990-999 [PMID: 22776094 DOI: 10.1111/j.1476-5381.2012.02097.x]

70 **Zhou H**, Yu M, Zhao J, Martin BN, Roychowdhury S, McMullen MR, Wang E, Fox PL, Yamasaki S, Nagy LE, Li X. IRAKM-Mincle axis links cell death to inflammation: Pathophysiological implications for chronic alcoholic liver disease. *Hepatology* 2016; **64**: 1978-1993 [PMID: 27628766 DOI: 10.1002/hep.28811]

71 **Afifiyan N**, Tillman B, French BA, Masouminia M, Samadzadeh S, French SW. Over expression of proteins that alter the intracellular signaling pathways in the cytoplasm of the liver cells forming Mallory-Denk bodies. *Exp Mol Pathol* 2017; **102**: 106-114 [PMID: 28089901 DOI: 10.1016/j.yexmp.2017.01.011]

72 **Afifiyan N**, Tillman B, French BA, Sweeny O, Masouminia M, Samadzadeh S, French SW. The role of Tec kinase signaling pathways in the development of Mallory Denk Bodies in balloon cells in alcoholic hepatitis. *Exp Mol Pathol* 2017; **103**: 191-199 [PMID: 28935395 DOI: 10.1016/j.yexmp.2017.09.001]

73 **Bukong TN**, Iracheta-Vellve A, Gyongyosi B, Ambade A, Catalano D, Kodys K, Szabo G. Therapeutic Benefits of Spleen Tyrosine Kinase Inhibitor Administration on Binge Drinking-Induced Alcoholic Liver Injury, Steatosis, and Inflammation in Mice. *Alcohol Clin Exp Res* 2016; **40**: 1524-1530 [PMID: 27177528 DOI: 10.1111/acer.13096]

74 **Machado MV**, Diehl AM. Pathogenesis of Nonalcoholic Steatohepatitis. *Gastroenterology* 2016; **150**: 1769-1777 [PMID: 26928243 DOI: 10.1053/j.gastro.2016.02.066]

75 **Dowman JK**, Tomlinson JW, Newsome PN. Pathogenesis of non-alcoholic fatty liver disease. *QJM* 2010; **103**: 71-83 [PMID: 19914930 DOI: 10.1093/qjmed/hcp158]

76 **Fang YL**, Chen H, Wang CL, Liang L. Pathogenesis of non-alcoholic fatty liver disease in children and adolescence: From "two hit theory" to "multiple hit model". *World J Gastroenterol* 2018; **24**: 2974-2983 [PMID: 30038464 DOI: 10.3748/wjg.v24.i27.2974]

77 **Bieghs V**, Trautwein C. Innate immune signaling and gut-liver interactions in non-alcoholic fatty liver disease. *Hepatobiliary Surg Nutr* 2014; **3**: 377-385 [PMID: 25568861 DOI: 10.3978/j.issn.2304-3881.2014.12.04]

78 **Ganz M**, Bukong TN, Csak T, Saha B, Park JK, Ambade A, Kodys K, Szabo G. Progression of non-alcoholic steatosis to steatohepatitis and fibrosis parallels cumulative accumulation of danger signals that promote inflammation and liver tumors in a high fat-cholesterol-sugar diet model in mice. *J Transl Med* 2015; **13**: 193 [PMID: 26077675 DOI: 10.1186/s12967-015-0552-7]

79 **Kiziltas S**. Toll-like receptors in pathophysiology of liver diseases. *World J Hepatol* 2016; **8**: 1354-1369 [PMID: 27917262 DOI: 10.4254/wjh.v8.i32.1354]

80 **Nath B**, Levin I, Csak T, Petrasek J, Mueller C, Kodys K, Catalano D, Mandrekar P, Szabo G. Hepatocyte-specific hypoxia-inducible factor-1α is a determinant of lipid accumulation and liver injury in alcohol-induced steatosis in mice. *Hepatology* 2011; **53**: 1526-1537 [PMID: 21520168 DOI: 10.1002/hep.24256]

81 **Alisi A**, Carpino G, Oliveira FL, Panera N, Nobili V, Gaudio E. The Role of Tissue Macrophage-Mediated Inflammation on NAFLD Pathogenesis and Its Clinical Implications. *Mediators Inflamm* 2017; **2017**: 8162421 [PMID: 28115795 DOI: 10.1155/2017/8162421]

82 **Day CP**. From fat to inflammation. *Gastroenterology* 2006; **130**: 207-210 [PMID: 16401483 DOI: 10.1053/j.gastro.2005.11.017]

83 **Carpino G**, Nobili V, Renzi A, De Stefanis C, Stronati L, Franchitto A, Alisi A, Onori P, De Vito R, Alpini G, Gaudio E. Macrophage Activation in Pediatric Nonalcoholic Fatty Liver Disease (NAFLD) Correlates with Hepatic Progenitor Cell Response via Wnt3a Pathway. *PLoS One* 2016; **11**: e0157246 [PMID: 27310371 DOI: 10.1371/journal.pone.0157246]

84 **Caligiuri A**, Gentilini A, Marra F. Molecular Pathogenesis of NASH. *Int J Mol Sci* 2016; **17** [PMID: 27657051 DOI: 10.3390/ijms17091575]

85 **Yu J**, Marsh S, Hu J, Feng W, Wu C. The Pathogenesis of Nonalcoholic Fatty Liver Disease: Interplay between Diet, Gut Microbiota, and Genetic Background. *Gastroenterol Res Pract* 2016; **2016**: 2862173 [PMID: 27247565 DOI: 10.1155/2016/2862173]

86 **Mao Y**, Yu F, Wang J, Guo C, Fan X. Autophagy: a new target for nonalcoholic fatty liver disease therapy. *Hepat Med* 2016; **8**: 27-37 [PMID: 27099536 DOI: 10.2147/HMER.S98120]

87 **Chattopadhyay S**, Sen GC. Tyrosine phosphorylation in Toll-like receptor signaling. *Cytokine Growth Factor Rev* 2014; **25**: 533-541 [PMID: 25022196 DOI: 10.1016/j.cytogfr.2014.06.002]

88 **Seki E**, Brenner DA. Toll-like receptors and adaptor molecules in liver disease: update. *Hepatology* 2008; **48**: 322-335 [PMID: 18506843 DOI: 10.1002/hep.22306]

89 **Chaudhary A**, Fresquez TM, Naranjo MJ. Tyrosine kinase Syk associates with toll-like receptor 4 and regulates signaling in human monocytic cells. *Immunol Cell Biol* 2007; **85**: 249-256 [PMID: 17228323 DOI: 10.1038/sj.icb7100030]

90 **Flynn R**, Allen JL, Luznik L, MacDonald KP, Paz K, Alexander KA, Vulic A, Du J, Panoskaltsis-Mortari A, Taylor PA, Poe JC, Serody JS, Murphy WJ, Hill GR, Maillard I, Koreth J, Cutler CS, Soiffer RJ, Antin JH, Ritz J, Chao NJ, Clynes RA, Sarantopoulos S, Blazar BR. Targeting Syk-activated B cells in murine and human chronic graft-versus-host disease. *Blood* 2015; **125**: 4085-4094 [PMID: 25852057 DOI: 10.1182/blood-2014-08-595470]

91 **Magee N**, Zou A, Zhang Y. Pathogenesis of Nonalcoholic Steatohepatitis: Interactions between Liver Parenchymal and Nonparenchymal Cells. *Biomed Res Int* 2016; **2016**: 5170402 [PMID: 27822476 DOI: 10.1155/2016/5170402]

92 **Szabo G**, Csak T. Inflammasomes in liver diseases. *J Hepatol* 2012; **57**: 642-654 [PMID: 22634126 DOI: 10.1016/j.jhep.2012.03.035]

93 **Malik AF**, Hoque R, Ouyang X, Ghani A, Hong E, Khan K, Moore LB, Ng G, Munro F, Flavell RA, Shi Y, Kyriakides TR, Mehal WZ. Inflammasome components Asc and caspase-1 mediate biomaterial-induced inflammation and foreign body response. *Proc Natl Acad Sci USA* 2011; **108**: 20095-20100 [PMID: 22109549 DOI: 10.1073/pnas.1105152108]

94 **Csak T**, Ganz M, Pespisa J, Kodys K, Dolganiuc A, Szabo G. Fatty acid and endotoxin activate inflammasomes in mouse hepatocytes that release danger signals to stimulate immune cells. *Hepatology* 2011; **54**: 133-144 [PMID: 21488066 DOI: 10.1002/hep.24341]

95 **Mehal WZ**. The inflammasome in liver injury and non-alcoholic fatty liver disease. *Dig Dis* 2014; **32**: 507-515 [PMID: 25034283 DOI: 10.1159/000360495]

96 **Mridha AR**, Wree A, Robertson AAB, Yeh MM, Johnson CD, Van Rooyen DM, Haczeyni F, Teoh NC, Savard C, Ioannou GN, Masters SL, Schroder K, Cooper MA, Feldstein AE, Farrell GC. NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice. *J Hepatol* 2017; **66**: 1037-1046 [PMID: 28167322 DOI: 10.1016/j.jhep.2017.01.022]

97 **Song IJ**, Yang YM, Inokuchi-Shimizu S, Roh YS, Yang L, Seki E. The contribution of toll-like receptor signaling to the development of liver fibrosis and cancer in hepatocyte-specific TAK1-deleted mice. *Int J Cancer* 2018; **142**: 81-91 [PMID: 28875549 DOI: 10.1002/ijc.31029]

98 **Yuan Y**, Wang J, Li J, Wang L, Li M, Yang Z, Zhang C, Dai JL. Frequent epigenetic inactivation of spleen tyrosine kinase gene in human hepatocellular carcinoma. *Clin Cancer Res* 2006; **12**: 6687-6695 [PMID: 17121887 DOI: 10.1158/1078-0432.CCR-06-0921]

99 **Shin SH**, Lee KH, Kim BH, Lee S, Lee HS, Jang JJ, Kang GH. Downregulation of spleen tyrosine kinase in hepatocellular carcinoma by promoter CpG island hypermethylation and its potential role in carcinogenesis. *Lab Invest* 2014; **94**: 1396-1405 [PMID: 25310533 DOI: 10.1038/labinvest.2014.118]

100 **Carone C**, Olivani A, Dalla Valle R, Manuguerra R, Silini EM, Trenti T, Missale G, Cariani E. Immune Gene Expression Profile in Hepatocellular Carcinoma and Surrounding Tissue Predicts Time to Tumor Recurrence. *Liver Cancer* 2018; **7**: 277-294 [PMID: 30319985 DOI: 10.1159/000486764]

101 **Hong J**, Hu K, Yuan Y, Sang Y, Bu Q, Chen G, Yang L, Li B, Huang P, Chen D, Liang Y, Zhang R, Pan J, Zeng YX, Kang T. CHK1 targets spleen tyrosine kinase (L) for proteolysis in hepatocellular carcinoma. *J Clin Invest* 2012; **122**: 2165-2175 [PMID: 22585575 DOI: 10.1172/JCI61380]

102 **Hong J**, Yuan YF, Wang JP, Liao Y, Zou RH, Zhu CL, Li BK, Liang Y, Huang PZ, Wang ZW, Lin WY, Zeng YX, Dai JL, Chung RT. Expression of variant isoforms of the tyrosine kinase SYK determines the prognosis of hepatocellular carcinoma. *Cancer Res* 2014; **74**: 1845-56 [DOI: 10.1158/0008-5472.CAN-13-2104]

103 **Liu D**, Mamorska-Dyga A. Syk inhibitors in clinical development for hematological malignancies. *J Hematol Oncol* 2017; **10**: 145 [PMID: 28754125 DOI: 10.1186/s13045-017-0512-1]

104 **Thoma G**, Veenstra S, Strang R, Blanz J, Vangrevelinghe E, Berghausen J, Lee CC, Zerwes HG. Orally bioavailable Syk inhibitors with activity in a rat PK/PD model. *Bioorg Med Chem Lett* 2015; **25**: 4642-4647 [PMID: 26320624 DOI: 10.1016/j.bmcl.2015.08.037]

105 **Lucas MC**, Bhagirath N, Chiao E, Goldstein DM, Hermann JC, Hsu PY, Kirchner S, Kennedy-Smith JJ, Kuglstatter A, Lukacs C, Menke J, Niu L, Padilla F, Peng Y, Polonchuk L, Railkar A, Slade M, Soth M, Xu D, Yadava P, Yee C, Zhou M, Liao C. Using ovality to predict nonmutagenic, orally efficacious pyridazine amides as cell specific spleen tyrosine kinase inhibitors. *J Med Chem* 2014; **57**: 2683-2691 [PMID: 24520947 DOI: 10.1021/jm401982j]

106 **Can G**, Ayvaz S, Can H, Demirtas S, Aksit H, Yilmaz B, Korkmaz U, Kurt M, Karaca T. The Syk Inhibitor Fostamatinib Decreases the Severity of Colonic Mucosal Damage in a Rodent Model of Colitis. *J Crohns Colitis* 2015; **9**: 907-917 [PMID: 26116555 DOI: 10.1093/ecco-jcc/jjv114]

107 **Weinblatt ME**, Genovese MC, Ho M, Hollis S, Rosiak-Jedrychowicz K, Kavanaugh A, Millson DS, Leon G, Wang M, van der Heijde D. Effects of fostamatinib, an oral spleen tyrosine kinase inhibitor, in rheumatoid arthritis patients with an inadequate response to methotrexate: results from a phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheumatol* 2014; **66**: 3255-3264 [PMID: 25223724 DOI: 10.1002/art.38851/abstract]

108 **Gomez-Puerta JA**, Mócsai A. Tyrosine kinase inhibitors for the treatment of rheumatoid arthritis. *Curr Top Med Chem* 2013; **13**: 760-773 [PMID: 23574525 DOI: 10.2174/15680266113139990094]

109 **Suljagic M**, Longo PG, Bennardo S, Perlas E, Leone G, Laurenti L, Efremov DG. The Syk inhibitor fostamatinib disodium (R788) inhibits tumor growth in the Eμ- TCL1 transgenic mouse model of CLL by blocking antigen-dependent B-cell receptor signaling. *Blood* 2010; **116**: 4894-4905 [PMID: 20716772 DOI: 10.1182/blood-2010-03-275180]

110 **Friedberg JW**, Sharman J, Sweetenham J, Johnston PB, Vose JM, Lacasce A, Schaefer-Cutillo J, De Vos S, Sinha R, Leonard JP, Cripe LD, Gregory SA, Sterba MP, Lowe AM, Levy R, Shipp MA. Inhibition of Syk with fostamatinib disodium has significant clinical activity in non-Hodgkin lymphoma and chronic lymphocytic leukemia. *Blood* 2010; **115**: 2578-2585 [PMID: 19965662 DOI: 10.1182/blood-2009-08-236471]

111 **Lapchak PH**, Kannan L, Rani P, Pamuk ON, Ioannou A, Dalle Lucca JJ, Pine P, Tsokos GC. Inhibition of Syk activity by R788 in platelets prevents remote lung tissue damage after mesenteric ischemia-reperfusion injury. *Am J Physiol Gastrointest Liver Physiol* 2012; **302**: G1416-G1422 [PMID: 22492694 DOI: 10.1152/ajpgi.00026.2012]

112 **Smith J**, McDaid JP, Bhangal G, Chawanasuntorapoj R, Masuda ES, Cook HT, Pusey CD, Tam FW. A spleen tyrosine kinase inhibitor reduces the severity of established glomerulonephritis. *J Am Soc Nephrol* 2010; **21**: 231-236 [PMID: 19959716 DOI: 10.1681/ASN.2009030263]

113 **Burke RT**, Meadows S, Loriaux MM, Currie KS, Mitchell SA, Maciejewski P, Clarke AS, Dipaolo JA, Druker BJ, Lannutti BJ, Spurgeon SE. A potential therapeutic strategy for chronic lymphocytic leukemia by combining Idelalisib and GS-9973, a novel spleen tyrosine kinase (Syk) inhibitor. *Oncotarget* 2014; **5**: 908-915 [PMID: 24659719 DOI: 10.18632/oncotarget.1484]

114 **Sharman J**, Hawkins M, Kolibaba K, Boxer M, Klein L, Wu M, Hu J, Abella S, Yasenchak C. An open-label phase 2 trial of entospletinib (GS-9973), a selective spleen tyrosine kinase inhibitor, in chronic lymphocytic leukemia. *Blood* 2015; **125**: 2336-2343 [PMID: 25696919 DOI: 10.1182/blood-2014-08-595934]

115 **Sharman J**, Di Paolo J. Targeting B-cell receptor signaling kinases in chronic lymphocytic leukemia: the promise of entospletinib. *Ther Adv Hematol* 2016; **7**: 157-170 [PMID: 27247756 DOI: 10.1177/2040620716636542]

116 **Burke JM**, Shustov A, Essell J, Patel-Donnelly D, Yang J, Chen R, Ye W, Shi W, Assouline S, Sharman J. An Open-label, Phase II Trial of Entospletinib (GS-9973), a Selective Spleen Tyrosine Kinase Inhibitor, in Diffuse Large B-cell Lymphoma. *Clin Lymphoma Myeloma Leuk* 2018; **18**: e327-e331 [PMID: 29934062 DOI: 10.1016/j.clml.2018.05.022]

117 **Yoshimoto T**, Hayashi T, Kondo T, Kittaka M, Reichenberger EJ, Ueki Y. Second-Generation SYK Inhibitor Entospletinib Ameliorates Fully Established Inflammation and Bone Destruction in the Cherubism Mouse Model. *J Bone Miner Res* 2018; **33**: 1513-1519 [PMID: 29669173 DOI: 10.1002/jbmr.3449]

118 **Coffey G**, Betz A, DeGuzman F, Pak Y, Inagaki M, Baker DC, Hollenbach SJ, Pandey A, Sinha U. The novel kinase inhibitor PRT062070 (Cerdulatinib) demonstrates efficacy in models of autoimmunity and B-cell cancer. *J Pharmacol Exp Ther* 2014; **351**: 538-548 [PMID: 25253883 DOI: 10.1124/jpet.114.218164]

119 **Ma J**, Xing W, Coffey G, Dresser K, Lu K, Guo A, Raca G, Pandey A, Conley P, Yu H, Wang YL. Cerdulatinib, a novel dual SYK/JAK kinase inhibitor, has broad anti-tumor activity in both ABC and GCB types of diffuse large B cell lymphoma. *Oncotarget* 2015; **6**: 43881-43896 [PMID: 26575169 DOI: 10.18632/oncotarget.6316]

120 **Cen O**, Kannan K, Huck Sappal J, Yu J, Zhang M, Arikan M, Ucur A, Ustek D, Cen Y, Gordon L, Longnecker R. Spleen Tyrosine Kinase Inhibitor TAK-659 Prevents Splenomegaly and Tumor Development in a Murine Model of Epstein-Barr Virus-Associated Lymphoma. *mSphere* 2018; **3** [PMID: 30135222 DOI: 10.1128/mSphereDirect.00378-18]

121 **Purroy N**, Carabia J, Abrisqueta P, Egia L, Aguiló M, Carpio C, Palacio C, Crespo M, Bosch F. Inhibition of BCR signaling using the Syk inhibitor TAK-659 prevents stroma-mediated signaling in chronic lymphocytic leukemia cells. *Oncotarget* 2017; **8**: 742-756 [PMID: 27888629 DOI: 10.18632/oncotarget.13557]

122 **Braselmann S**, Taylor V, Zhao H, Wang S, Sylvain C, Baluom M, Qu K, Herlaar E, Lau A, Young C, Wong BR, Lovell S, Sun T, Park G, Argade A, Jurcevic S, Pine P, Singh R, Grossbard EB, Payan DG, Masuda ES. R406, an orally available spleen tyrosine kinase inhibitor blocks fc receptor signaling and reduces immune complex-mediated inflammation. *J Pharmacol Exp Ther* 2006; **319**: 998-1008 [PMID: 16946104 DOI: 10.1124/jpet.106.109058]

123 **Spalton JC**, Mori J, Pollitt AY, Hughes CE, Eble JA, Watson SP. The novel Syk inhibitor R406 reveals mechanistic differences in the initiation of GPVI and CLEC-2 signaling in platelets. *J Thromb Haemost* 2009; **7**: 1192-1199 [PMID: 19422460 DOI: 10.1111/j.1538-7836.2009.03451.x]

124 **Quiroga MP**, Balakrishnan K, Kurtova AV, Sivina M, Keating MJ, Wierda WG, Gandhi V, Burger JA. B-cell antigen receptor signaling enhances chronic lymphocytic leukemia cell migration and survival: specific targeting with a novel spleen tyrosine kinase inhibitor, R406. *Blood* 2009; **114**: 1029-1037 [PMID: 19491390 DOI: 10.1182/blood-2009-03-212837]

125 **Wossning T**, Herzog S, Köhler F, Meixlsperger S, Kulathu Y, Mittler G, Abe A, Fuchs U, Borkhardt A, Jumaa H. Deregulated Syk inhibits differentiation and induces growth factor-independent proliferation of pre-B cells. *J Exp Med* 2006; **203**: 2829-2840 [PMID: 17130299 DOI: 10.1084/jem.20060967]

126 **Sprissler C**, Belenki D, Maurer H, Aumann K, Pfeifer D, Klein C, Müller TA, Kissel S, Hülsdünker J, Alexandrovski J, Brummer T, Jumaa H, Duyster J, Dierks C. Depletion of STAT5 blocks TEL-SYK-induced APMF-type leukemia with myelofibrosis and myelodysplasia in mice. *Blood Cancer J* 2014; **4**: e240 [PMID: 25148222 DOI: 10.1038/bcj.2014.53]

127 **Baluom M**, Grossbard EB, Mant T, Lau DT. Pharmacokinetics of fostamatinib, a spleen tyrosine kinase (SYK) inhibitor, in healthy human subjects following single and multiple oral dosing in three phase I studies. *Br J Clin Pharmacol* 2013; **76**: 78-88 [PMID: 23190017 DOI: 10.1111/bcp.12048]

128 **Torres-Hernandez A**, Wang W, Nikiforov Y, Tejada K, Torres L, Kalabin A, Wu Y, Haq MIU, Khan MY, Zhao Z, Su W, Camargo J, Hundeyin M, Diskin B, Adam S, Rossi JAK, Kurz E, Aykut B, Shadaloey SAA, Leinwand J, Miller G. Targeting SYK signaling in myeloid cells protects against liver fibrosis and hepatocarcinogenesis. *Oncogene* 2019; **38**: 4512-4526 [PMID: 30742098 DOI: 10.1038/s41388-019-0734-5]

129 **Kyttaris VC**, Tsokos GC. Syk kinase as a treatment target for therapy in autoimmune diseases. *Clin Immunol* 2007; **124**: 235-237 [PMID: 17662659 DOI: 10.1016/j.clim.2007.06.005]

**Footnotes**

**Conflict-of-interest statement:** Authors declare no conflict of interests for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Corresponding Author's Membership in Professional Societies:** Netherlands Society of Gastroenterology; American Association for the Study of Liver Diseases; European Association for the Study of Liver.

**Peer-review started:** November 29, 2019

**First decision:** January 7, 2020

**Article in press:**

**Specialty type:** Gastroenterology and hepatology

**Country of origin:** Netherlands

**Peer-review report classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P- Reviewer:** El-Razek AA,Slomiany BL **S- Editor:** Zhang L **L- Editor:** **E- Editor:**

**Figure Legends**

 **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 TNFα, 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-1β, 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] |
| Cherubisme (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 (tamatinib) | 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] |
| Piceatannol  | Oral squamous cell carcinoma | Inhibited tumour cell proliferation, induced of apoptosis, attenuated VEGF and MMP9 expression, and decreased metastases | [127] |

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

**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-κB 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.

**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.



**Figure 2 Basis of spleen tyrosine kinase activation.** In the resting state, spleen tyrosine kinase is autoinhibited, 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. This is a logic “OR” relationship between those two activation mechanisms. SH2: Spleen tyrosine kinase homology 2; ITAM: Immune-receptor tyrosine-based activation motifs.



**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-κB 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.

Fostamatinib (R788)

Cerdulatinib (PRT062070)

TAK-659

Tamatinib (R406)

Entospletinib (GS-9973)

Piceatannol

**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.