Heliyon 9 (2023) e15625

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Spleen tyrosine kinase (SYK) signals are implicated in cardio-cerebrovascular diseases

Mohan Li [a], Pengbo Wang [a], Yuanming Zou [a], Wenbin Wang [a], Yuanhui Zhao [a], Mengke Liu [a], Jianlong Wu [a], Ying Zhang [a,b,***], Naijin Zhang [a,b,c,**], Yingxian Sun [a,b,*]

[a] *Department of Cardiology, First Hospital of China Medical University, 155 Nanjing North Street, Heping District, Shenyang, 110001, Liaoning Province, People's Republic of China*

[b] *Institute of Health Sciences, China Medical University, 77 Puhe Road, Shenbei New District, Shenyang, 110001, Liaoning Province, People's Republic of China*

[c] *Key Laboratory of Reproductive and Genetic Medicine (China Medical University), National Health Commission, 77 Puhe Road, Shenbei New District, Shenyang, 110001, Liaoning Province, People's Republic of China*

ARTICLE INFO

Keywords:
Spleen tyrosine kinase
Atherosclerosis
Cardio-cerebrovascular diseases
Phosphorylation

ABSTRACT

Post-translational modifications regulate numerous biochemical reactions and functions through covalent attachment to proteins. Phosphorylation, acetylation and ubiquitination account for over 90% of all reported post-translational modifications. As one of the tyrosine protein kinases, spleen tyrosine kinase (SYK) plays crucial roles in many pathophysiological processes and affects the pathogenesis and progression of various diseases. SYK is expressed in tissues outside the hematopoietic system, especially the heart, and is involved in the progression of various cardio-cerebrovascular diseases, such as atherosclerosis, heart failure, diabetic cardiomyopathy, stroke and others. Knowledge on the role of SYK in the progress of cardio-cerebrovascular diseases is accumulating, and many related mechanisms have been discovered and validated. This review summarizes the role of SYK in the progression of various cardio-cerebrovascular diseases, and aims to provide a theoretical basis for future experimental and clinical research targeting SYK as a therapeutic option for these diseases.

Abbreviations: PTMs, Post-translational modification; SYK, Spleen tyrosine kinase; SH2, SRC homology 2; HCM, Hypertrophic cardiomyopathy; DCM, Diabetic cardiomyopathy; CHD, Coronary heart disease; BTK, Bruton's tyrosine kinase; SAH, Subarachnoid hemorrhage; NLRP3, Nucleotide-binding oligomerization domain-like receptor pyrin domain containing 3; HF, Heart failure; Dot1l, Disruptor of Telomeric silencing 1-like; TGF, Transforming growth factor; ANCA, Anti-neutrophil cytoplasmic antibody; AS, Atherosclerosis; AF, Atrial fibrillation.

* Corresponding author. Department of Cardiology, First Hospital of China Medical University, 155 Nanjing North Street, Heping District, Shenyang, 110001, Liaoning Province, People's Republic of China.

** Corresponding author. Department of Cardiology, First Hospital of China Medical University, 155 Nanjing North Street, Heping District, Shenyang, 110001, Liaoning Province, People's Republic of China.

*** Corresponding author. Department of Cardiology, First Hospital of China Medical University, 155 Nanjing North Street, Heping District, Shenyang, 110001, Liaoning Province, People's Republic of China.

E-mail addresses: yzhang02@cmu.edu.cn (Y. Zhang), njzhang@cmu.edu.cn (N. Zhang), yxsun@cmu.edu.cn (Y. Sun).

https://doi.org/10.1016/j.heliyon.2023.e15625
Received 22 October 2022; Received in revised form 14 April 2023; Accepted 17 April 2023
Available online 22 April 2023

1. Introduction

Protein post-translational modification (PTMs) [1] is an important area of protein chemistry research. PTMs, including phosphorylation [2], ubiquitination [3–7], acetylation [8–10] and etc., regulates numerous biochemical reactions and functions by covalently attaching to the protein. Phosphorylation [11–13] is one of the most common and important modifications, mainly occurs on three amino acids in the peptide chain [14], namely tyrosine [15] and serine and threonine residues. Generally, protein kinases could be divided into: serine/threonine (Ser/Thr) protein kinase, tyrosine (Tyr) protein kinase, histidine (His)/lysine (Lys)/arginine (Arg) protein kinase, cysteine (Cys) protein kinase and aspartate (Asp)/glutamate (Glu) protein kinase according to the difference of amino acid residues [16]. Among them, tyrosine protein kinases (TPK) [17,18] can be divided into three categories: ①receptor tyrosine kinases [19]; ②cytoplasmic tyrosine kinases, such as SYK family [20,21], Src family [22–25], JAK family [26,27] and etc.; ③nuclear tyrosine kinases [28]. As a member of the non-receptor cytoplasmic tyrosine kinase family, the SYK family is mainly involved in the phosphorylation of protein amino acids. The SYK family includes two members [29]: spleen tyrosine kinase (SYK) and zeta-chain-associated protein of 70 kDa (ZAP70) [30,31].

SYK is a 72 kDa non-receptor tyrosine kinase containing two SRC homology 2 (SH2) structural domains and a C-terminal tyrosine kinase structural domain [32], which is highly expressed in hematopoietic cells and is a key molecule in signal transduction and differentiation, especially in B-cell signaling. SYK is known to play a crucial role in the hematological system, and is involved in the proto-oncogene of lymphocyte transformation and actively participates the pathogenesis of non-Hodgkin's lymphoma and chronic lymphocytic leukemia [33]. Meanwhile, SYK has been identified as a new therapeutic target of acute myeloid leukemia (AML). In addition, upregulated expression of SYK has been reported in sarcoid lymphoma, and both SYK and ZAP70 are upregulated in ALL [34,35].

SYK expression was also evidenced in other tissues, especially in myocardium, cardiac/cerebral vessels. SYK participates the pathology of atherosclerosis, stroke, heart failure, diabetic cardiomyopathy and other diseases. Several SYK inhibitors have been developed and shown initial effects on retarding the progression of pathologic diseases [36,37], Inhibition of SYK may slow down the progression of activated macrophage-mediated atherosclerosis [38]. Now, basic research on the role of SYK in cardiovascular and cerebrovascular-related diseases is still in its prototype, through understanding of the working mechanism of SYK might promote the development of clinical efficient SYK inhibitors or drugs in the treatment of cardiovascular and cerebrovascular diseases. This review comprehensively summarizes the role of the SYK signaling pathway in cardiovascular and cerebrovascular -related diseases, aiming to provide a theoretical basis for future experimental and clinical studies targeting SYK as a therapeutic option for patients with cardiovascular and cerebrovascular diseases.

2. Structure and function of SYK

In 1991, Taniguchi and colleagues detected the 40-kDa cytoplasmic protein tyrosine kinase [39,40] that had been discovered by Kobayashi and colleagues in 1990, but also a 72-kDa protein. The 40-kDa kinase was hydrolyzed by this newly discovered 72-kDa protein, which was found to be one of the members of the cytoplasmic tyrosine protein kinase [22] p72syk and named spleen tyrosine kinase (SYK). SYK belongs to the non-receptor type of cytoplasmic tyrosine kinases [41], is encoded by a gene located on human chromosome 9q22 [42] and comprises 629 amino acids [41]. Although SYK and ZAP70 belong to the same family [21], they differ in various respects [43]. ZAP70 is involved in the T-cell activation process [44], while SYK is considered the more important kinase, mainly regulating the signaling pathways of B cells, neutrophils and macrophages [45–47]. Generally, SYK binds to B-cell antigen receptors to activate itself, thereby exerting its molecular function [48].

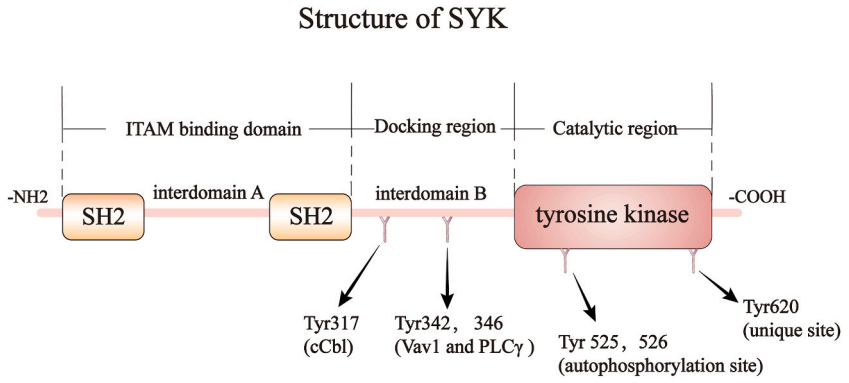

Fig. 1. The molecular structure of Spleen tyrosine kinase (SYK). This protein contains two adjacent Src homology 2 (SH2) domains at the N-terminus and a tyrosine kinase domain at the C-terminus. The helical coil-like region between two SH2s is called the A domain, and the segment between the kinase and SH2 is called the B domain. Two SH2 domain and the A domain are considered to be ITAM-binding regions. The B domain, as a docking region, includes most of its phosphorylation sites, including Tyr290, Tyr317 (a binding site for c-Cbl), Tyr342 (a binding site for Vav1 and PLC-γ), Tyr346 (a binding site for PLC-γ) and etc. Of note, the catalytic region contains Tyr620 which is a unique site in SYK.

At the molecular level, SYK has two adjacent SH2 domains and a tyrosine kinase domain at the C-terminus [41,49,50]. Generally, the helical coil-like region between two SH2s is called the A domain, and the segment between the kinase and SH2 is called the B domain. Reportedly, the kinase close to the C-terminal SH2 domain has a significant affinity for immunoreceptor tyrosine-based activation motifs (ITAMs), which are found in B-cell receptors (BCRs), T-cell receptors, natural killer-cell receptors and other cell-surface receptors; thus, the two SH2 domains and the A domain between them are considered to be ITAM-binding regions. The B domain, as a docking region [47], includes most of its phosphorylation sites, including Tyr290, Tyr317 (a binding site for c-Cbl), Tyr342 (a binding site for Vav1 and phospholipase C [PLC]-γ) and Tyr346 (a binding site for PLC-γ) Notably, the catalytic region contains Tyr620, which is a unique site in SYK (Fig. 1). Generally, phosphorylation can be classified into four categories, depending on the phosphorylated amino acid residues: O-linked, N-linked, phosphoanhydride and phosphorothioate phosphorylation. SYK phosphorylation belongs to the O-linked category. The phosphorylation process is essential for the activation and propagation of downstream signals [51].

SYK is expressed in multiple organs in mice, with the highest expression in spleen, heart, mammary gland, thymus and some lymphocyte lines [52]. SYK is also expressed in non-hematopoietic cells, including epithelial cells and vascular endothelial cells [53]. Information on the role of SYK in the field of cardiovascular diseases is accumulating. Studies show that SYK is involved in the pathogenesis and progress of hypertrophic cardiomyopathy (HCM), diabetic cardiomyopathy (DCM), coronary heart disease (CHD) and arterial thrombosis [54].

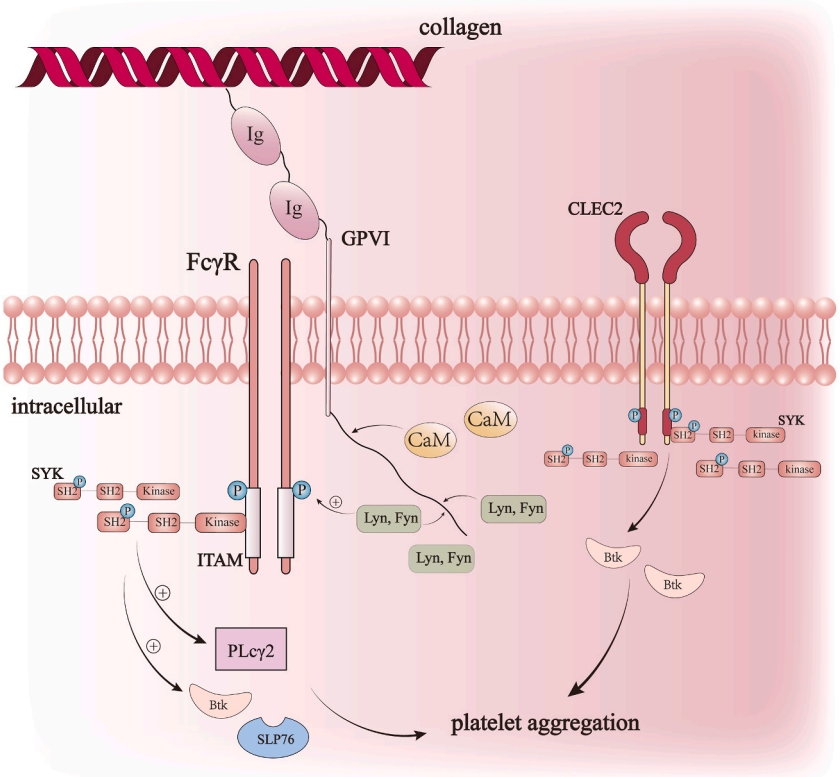

Fig. 2. Diagram of the collagen-FCγR-GPVI-SYK pathway under high-shear stress. In the pathological conditions (atherosclerosis and vascular endothelial damage), collagen-FCγR-GPVI compound could be formed. ITAM will be phosphorylated by Src family tyrosine kinase (SFKs , a non-receptor tyrosine kinase which can transmit activation signals from platelet surfaces. The signal transmission of GPVI receptors mainly depends on SFKs) .The phosphorylated ITAM can then bind to the non-receptor tyrosine kinase SYK, forming the collagen-FCγR-GPVI-SYK compound and activate several downstream key proteins (BTK proteins, joint protein SLP76, and so on) and effecting enzymes (Phospholipase Cγ2 (PLCγ2), and so on), thus promotes a series of couplet reactions including calcium mobilization and the activation of PKC. These activated signals further promote platelets adherence to the endothelial injury site, eventually resulting in platelet aggregation and thrombosis. SYK is also involved in the C-type lectin-like receptor 2 (CLEC2)-related signaling pathway on the platelet membrane. Similar to the above process, after phosphorylation on the ITAM motif of the CLEC2 receptor, SYK could bind to it and be phosphorylated, then activate downstream key proteins, actively participate in the process of platelet activation and aggregation.

3. SYK in atherosclerosis

3.1. Platelet activation

AS is a chronic inflammatory process that mainly affects the walls of large- and medium-sized arteries, such as the aorta, carotid and coronary arteries [55]. When the endothelium is damaged, platelets can be activated by inflammatory triggers; the activated platelets then aggregate, adhere to each other and interact with the endothelium, contributing to endothelial activation, a critical initiation component of the atherosclerotic process and pathologic thrombosis [56,57]. SYK is involved in the platelet activation process via modulating the platelet glycoprotein VI (GPVI) signal [58]. GPVI has been regarded as a key signal [59] of platelet activation for decades. In pathological conditions (e.g. AS and vascular endothelial damage), a collagen-FCγ receptor (FCγR)-GPVI compound can be formed [60–62]. ITAMs are phosphorylated by Src family tyrosine kinase (SFKs), which are non-receptor tyrosine kinases that can transmit activation signals from platelet surfaces. The signal transmission of GPVI receptors mainly depends on SFKs [63,64]. The phosphorylated ITAM can then bind to the non-receptor tyrosine kinase SYK, form a collagen-FCγR-GPVI-SYK compound, activate several downstream key proteins (e.g. Bruton's tyrosine kinase [BTK] proteins and joint protein SLP76) and affect the activities of various enzymes (e.g. PLCγ2), thus promoting a series of couplet reactions, including calcium mobilization and the activation of protein kinase C [65]. These activated signals further promote platelet adherence to the endothelial injury site, eventually resulting in platelet aggregation and thrombosis [66,67]. SYK is also involved in the C-type lectin-like receptor 2 (CLEC2)-related signaling pathway on the platelet membrane. Similar to the above process (Fig. 2), after the ITAM motif of the CLEC2 receptor has been phosphorylated, SYK can bind to it, become phosphorylated and activate downstream key proteins, actively participating in the process of platelet activation and aggregation [68].

SYK hyperphosphorylation, which is caused by different factors, is believed to be associated with the pathogenesis of various cardio-cerebrovascular diseases. For example, hyperglycemia has been shown to increase the phosphorylation level of SYK four-fold. Phosphorylated SYK can mediate the activation of Plcγ2, which plays an important role in early collagen-induced platelet aggregation [69]. Chen et al. found that galectin-3, a β-galactoside-binding lectin, binds to and activates Dectin-1, then phosphorylates SYK, thus increasing Ca2+ influx, activating protein kinase C and promoting reactive oxygen species (ROS) production to enhance platelet hyperreactivity [70]. The aforementioned studies indicate that high phosphorylation levels of SYK are often associated with abnormal platelet activation and contribute to the hypercoagulable state of blood and thrombosis. Accordingly, reducing the phosphorylation level of SYK might have potential as a therapeutic tool for targeting the blood hypercoagulation process in various cardio-cerebrovascular diseases.

3.2. Lipid metabolism and calcification

Phosphorylation of SYK has been shown to be involved in the formation of foam cells, a characteristic pathological cell type of AS [71]. Guo et al. initially discovered that overexpression of SYK further increased the blood levels of total cholesterol, low-density and high-density lipoprotein cholesterol, and reduced superoxide dismutase levels, aggravating AS in $ApoE^{-/-}$ mice fed a high-fat diet [72]. The evidence suggests that inhibiting SYK might also promote metabolic redistribution, upregulate cellular hydrogen sulfide production, and reduce oxidative phosphorylation and ROS levels [73]. Therefore, SYK may promote AS by increasing oxidative stress and cellular lipid accumulation. Additionally, studies show that very-low-density lipoprotein cholesterol is enriched in apolipoprotein C3, which can bind to Toll-like receptors 2/4 and upregulate Lyn (one of several Src-family tyrosine kinases in immune cells), thereby accelerating phosphorylation of SYK by Lyn, mediating calcium inward flow and activating nucleotide-binding oligomerization domain-like receptor pyrin domain containing 3 (NLRP3) inflammatory vesicles, and ultimately promoting AS [74].

3.3. Myocardial infarction

The collagen-FCγR-GPVI-SYK axis is the critical pathway involved in the formation of atherosclerotic plaque and arterial thrombosis [75–77]. Knockdown of the platelet collagen receptor FCγR/GPVI chain was shown to virtually entirely eradicate platelet thrombi formed after endothelial damage [78]. Furthermore, Takaya et al. showed that SYK activity was significantly downregulated and infarct size was significantly reduced after 30 min of occlusion and 24 h of reperfusion of the left anterior descending artery in $FC\gamma R^{-/-}$ mice. These findings suggest that downregulating the FCγR-GPVI-SYK pathway might be a promising option to attenuate myocardial insult post myocardial infarction [78].

Mechanistically, high-shear stress in the atherosclerotic vascular region can enhance the phosphorylation level of SYK. High phosphorylation levels of SYK may activate blood platelets and enhance thrombosis formation, which would in turn increase the risk of myocardial infarction. Speich and colleagues showed that pretreatment with SYK inhibitors not only reduced shear stress-induced platelet aggregation and SYK phosphorylation in isolated platelets, but also diminished, by up to 50%, the platelet-mediated thrombosis formation that occurred when whole blood was perfused over type-III collagen [58]. In a clinical study, Liang and colleagues found that SYK expression on peripheral blood monocytes was significantly higher in patients with non-ST segment elevation acute coronary syndrome, ST segment elevation, acute myocardial infarction or stable angina pectoris compared with that in control patients with non-congenital heart disease. Furthermore, the SYK expression level was positively related to the disease severity of CHD [54]. Such experimental and clinical studies highlight the role of upregulated SYK and its phosphorylation level in the pathogenesis of myocardial infarction.

4. SYK in stroke

Strokes can be divided into two main categories: ischemic [79] and hemorrhagic [80]. Platelet overactivation can enhance thrombus formation and block the cerebral blood vessels, causing ischemic stroke (IS) [81]. Considered a global public health problem, more than 25% of IS can be attributed to AS [72,82]. Ye and colleagues constructed an IS model in C57 mice [83]. They found that Dectin-1 receptors bound to necrotic substances after a stroke and promoted the activation of SYK, enhancing the expression of inflammatory genes and resulting in further brain tissue damage. The expression levels of SYK and phosphorylated (p)-SYK were significantly upregulated in this model. Piceatannol, an SYK inhibitor, reversed the upregulated expression of SYK and p-SYK and reduced the size of cerebral infarction [83,84]. Previous studies have confirmed that microRNAs (miRNAs) modulate SYK and are associated with stroke and AS [85,86]. Overexpressed miR-135b and miR-377 (which had the best combining capacity) bound to the 3′-untranslated region (UTR) of SYK mRNA, thereby downregulating the expression of SYK and attenuating its AS-promoting effect by decreasing CD68 numbers [72]. Additionally, Huang et al. found that the expression of miR-129-2-3p was negatively correlated with the occurrence of IS through negatively regulating the SYK 3′-UTR site [87].

Subarachnoid hemorrhage (SAH) is a severe subtype of hemorrhagic stroke, accounting for 5% of strokes [88,89]. SYK is involved in this injury via the macrophage-inducible C-type lectin (Mincle), which is expressed in both glial cells and neurons of SAH rats [90]. Mincle binds to SAP130 ligand (a subunit of histone deacetylase) released by necrotic cells, promotes SYK phosphorylation and activates inflammatory pathways, resulting in increased accumulation of inflammatory factors. He et al. found that the expression of Mincle, SYK and p-SYK was increased at 12 h and peaked at 24 h in the SAH rat model. Intervention with SYK inhibitor piceatannol reduced brain edema at 24 h after the SAH. Thus, targeting Mincle and SYK might also serve as a potential therapeutic option in the setting of hemorrhagic brain insult [91]. Thus, SYK is actively involved in the pathogenesis of IS.

5. SYK in cardiomyopathy

5.1. Diabetic cardiomyopathy

Persistent diabetes may induce cardiac insufficiency, and the pathological mechanisms of diabetic cardiomyopathy (DCM) include alterations in intracellular ion homeostasis (K^+, Na^+, Ca^{2+}), disturbances in intracellular energy metabolism (mitochondrial damage), increased ROS production, upregulated accumulation of advanced glycation end products, and activation of signaling targets such as the nuclear factor (NF)-κB pathway and the renin–angiotensin system [92]. Diabetes mellitus damages cardiomyocytes through the above pathological processes, and can result in pathological myocardial remodeling and dysfunction, as well as heart failure (HF) [93–96]. Through construction of a protein–protein interaction (PPI) network, SYK was found to be one of the pivotal genes in the pathogenesis of type 2 diabetes in patients with HF [97]. Konigsberger et al. reported that disruption of SYK expression altered BCR signaling quality [98]. A previous study found that hyperglycemia increased the phosphorylation of SYK and promoted platelet aggregation [69]. It is thus reasonable to assume that both platelet-related signaling pathways and BCR pathways are involved in the pathogenesis of DCM, and that SYK might play pivotal roles in these disease processes. The specific interactions between these signaling pathways through the hub of SYK remain to be further investigated.

Previous studies revealed that the NLRP3 inflammasome is involved in regulating the progression of DCM and changes in myocardial structure and function [99–101]. Li et al. recently found that SYK indirectly caused diabetic myocardial injury through activation of the NLRP3 inflammasome and that, compared with the findings in the control group, SYK phosphorylation was significantly increased in DCM rats. They summarized the role of SYK on DCM as follows: high glucose stimulation activated SYK, which further activated the NLRP3 inflammasome through the phosphorylation of c-Jun N-terminal kinase (JNK, a key transcriptional regulator of inflammation), thus indirectly lead to diabetic myocardial injury. As expected, SYK inhibitors attenuate diabetic myocardial injury by inhibiting NLRP3 activation. Thus, it is postulated that the SYK/JNK/NLRP3 signaling pathway plays a key role in the pathogenesis of DCM, making SYK inhibition a feasible option to attenuate cardiomyocyte injury caused by DCM [102]. In patients with DCM, inhibiting the expression of the SYK gene (e.g. via supplementation with melatonin) may block the SYK/COX-1/sarcoendoplasmic reticulum calcium ATPase (SERCA) signaling pathway to attenuate DCM. Specifically, once SYK is activated, it can indirectly lead to an increase of ROS in mitochondria; these superoxides then lead to intracellular calcium overloading, which in turn induces mitochondrial (caspase-9 related) and endoplasmic reticulum (caspase-12-related) apoptosis, thus jointly promoting high glucose-induced cardiomyocyte death. Blocking the SYK pathway might not only protect the myocardial function of patients with DCM, but also reduce myocardial fibrosis and maintain the activity of cardiomyocytes (Table 1) [103].

Table 1
Summary of new findings of SYK in DCM-related events.

Glucose-state	Events	New findings of SYK	references
Hyperglycemia (DCM)	Heart failure and diabetes	being one of the pivot genes in the pathogenesis of HF and type 2 diabetes.	[97]
		disruption of SYK expression could alter BCR signaling quality.	[98]
	Cardiomyocyte injury	activates the SYK/JNK/NLRP3 signaling pathway and ultimately indirectly leads to diabetic heart dysfunction.	[102]
	Myocardial fibrosis	inhibits SYK gene in DCM patients blocks the SYK/COX-1/SERCA signaling pathway thus reduces myocardial fibrosis and maintains cardiomyocytes activity.	[103]
	Thrombus	phosphorylated level increased.	[69]

5.2. Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM), a common inherited heart disease, is the most common cause of nontraumatic cardiac death in adolescents [104]. Numerous studies have found that ubiquitination in protein PTM is closely related to HCM [105]. The ubiquitination process is generally carried out by a cascade reaction involving three enzymes: activating enzyme E1, conjugating enzyme E2 and ligase E3 [3]. Various E3 enzymes play important roles in HCM. The E3 MDM2 was found to be capable of inhibiting cardiac hypertrophy [106], while downregulation of *Murf-1* promoted pressure overload-induced cardiac hypertrophy [107]. Tumor necrosis factor receptor-associated factor 2 promotes cardiac hypertrophy by modulating the NF-κB and JNK pathways [108]. It is worth mentioning that ubiquitination modification and other modification processes (e.g. phosphorylation) are actively involved in the pathogenesis of HCM. Using coexpression analysis of genes, Chen et al. found that the expression level of SYK was significantly increased in HCM rats and demonstrated that SYK played a central role in the disease process of HCM. Notably, the mechanism by which SYK affects cardiac hypertrophy is not fully understood [109], necessitating future studies.

6. SYK in heart failure

HF is one of the most common insidious diseases requiring hospital admission, burdening public health worldwide [110]. Cardiac fibrosis is a crucial mechanism of HF [111,112]. SYK might aggravate HF by promoting inflammatory responses and cardiac interstitial fibrosis.

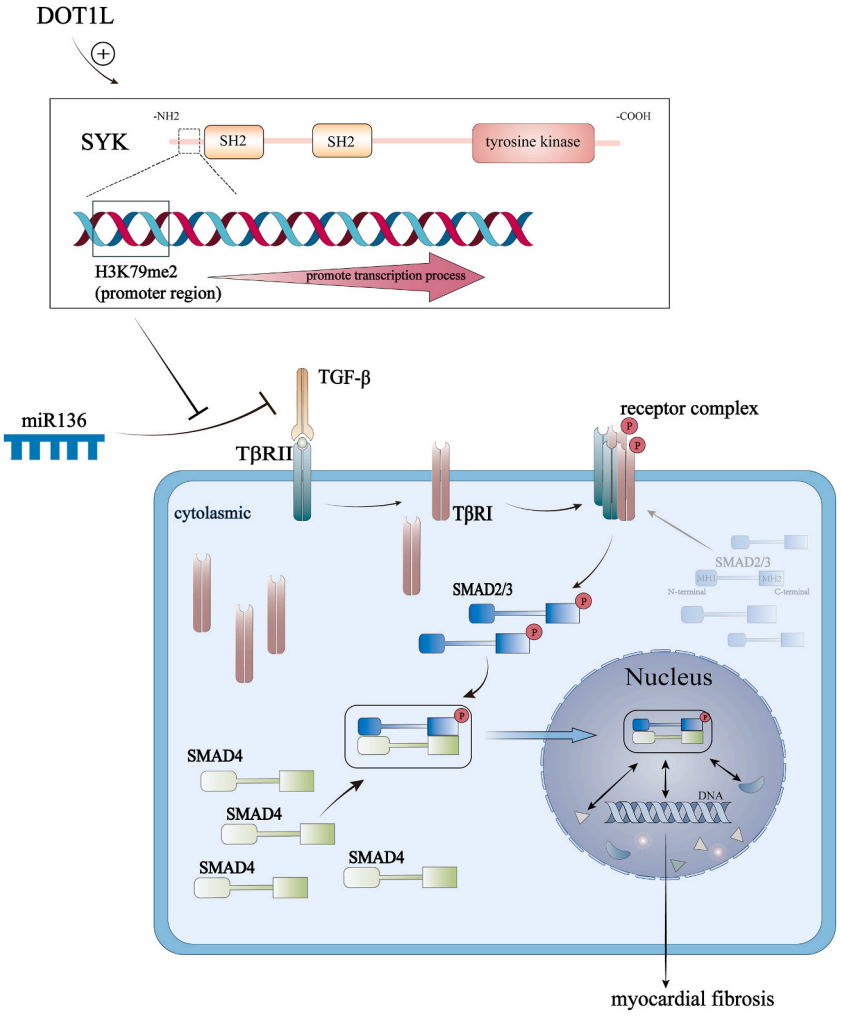

Fig. 3. SYK plays a role in mediating TGF-β1/Smad3 signaling pathway in myocardial fibrosis. Dot1l may activate the gene transcription of SYK. Dot1l-knockout could downregulate the modification level of H3K79me2 on the promoter of SYK, thereby reduce the expression of SYK. SYK was discovered to bind to and inhibit miR136, which can reduce epithelial–mesenchymal transition by targeting TGF-β1/Smad3 signaling pathway, thus ultimately promotes fibrosis. Abbreviations: Dot1l, Disruptor of Telomeric silencing 1-like; SYK, spleen tyrosine kinase; TGFβ, transforming growth factor-beta; SMAD2/3, Mothers against decapentaplegic homolog 2/3; SMAD4, Mothers against decapentaplegic homolog 4.

Recently, the relationship between SYK and myocardial fibrosis has been explored. SYK can bind to and inhibit miR136, which can reduce epithelial–mesenchymal transition by targeting transforming growth factor (TGF)-β1/Smad3 signaling pathway, thus ultimately promoting fibrosis [113]. Li et al. investigated the association between disruptor of telomeric silencing 1-like (Dot1l), SYK and fibrosis in vivo and in vitro, showing that the knockout of Dot1l downregulated the modification level of histone 3 K79 dimethylation (H3K79me2) on the promoter of SYK, thereby reducing the interaction between SYK and miR136 and ultimately attenuating cardiac fibroblast proliferation and fibrosis. These effects were reversed by upregulating SYK via activation of the TGF-β1/Smad3 signaling pathway (Fig. 3) [114]. A very recent publication (2023) suggested that the SYK/NF-κB signaling pathway could be activated by angiotensin II (AngII)-induced Dectin-1 homodimerization, which in turn upregulated the expression of inflammation-related molecules including tumor necrosis factor-α, interleukin-1β and others. These altered pathways were found to be important players in AngII-induced cardiac remodeling and dysfunction [115].

Additionally, SYK is a major immunological player in HF. In the pathogenesis of HF, the BCR-SYK pathway is known to play a major role. SYK is inactive and nonphosphorylated in resting B cells. In response to antigen stimulation [116], the BCR is activated, leading to phosphorylation of SYK at site Y348. The downstream substrate proteins, which include PLCγ2, B-cell linker protein and others, are subsequently activated [116], thereby promoting B-cell survival and proliferation [117]. It is believed that this immune response activation process could induce left ventricular dysfunction and related adverse cardiac remodeling in the setting of HF [118], indicating a strong connection between SYK-related innate and adaptive immunity and the development of HF [119]. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a small-vessel disease that causes direct endothelial injuries and promotes diffuse AS, vascular stiffening and cardiac dysfunction [120,121]. Epidemiological studies have found that AAV patients have a high risk of developing chronic HF [122,123]. Recently, Prendecki et al. found that there p-SYK is increased in circulating neutrophils and monocytes from patients with active AAV. Mechanistically, ANCA immunoglobulin G could phosphorylate SYK at Y348. Accordingly, SYK inhibition could inhibit ANCA-mediated PLCγ/Vav/Ras/mitogen-activated protein kinases/NF-κB signaling [124,125]. Collectively, SYK is involved in the HF process by inducing myocardial fibrosis via activation of the TGF-β1/Smad3 pathway in cardiac tissues and modulating immune responses.

7. Research on inhibitors of the SYK signaling pathway

The above experimental and clinical studies illustrated a fundamental role of activation of platelets in promoting the occurrence of AS [126]. Accordingly, antiplatelet drugs, including SYK inhibitors, have been tested and widely applied for the prevention and treatment of AS and related diseases [127–130]. Many pharmaceutical companies, including Rigel, Pfizer, Bayer and ZaBeCor, are actively involved in the development of small molecule inhibitors. Four structurally related analogs of competitive SYK inhibitors, namely SYK R406, R788, R112 and R343, are currently being developed and evaluated for the treatment of cardiovascular-related inflammatory diseases [47,131].

Previous studies have demonstrated that the highly selective SYK inhibitors fostamatinib (R406) [132–134] and entospletinib (GS-9973) inhibit platelet aggregation without increasing bleeding events [116,135]. Lindau and colleagues showed that fostamatinib significantly reduced the occurrence of early neo-atherosclerotic plaques in *Apoe*$^{-/-}$ mice fed a high-fat diet (inhibition rate >70%). However, for mice with established AS, fostamatinib was only able to reduce the infiltration and differentiation of monocytes, and did not affect cell proliferation or cell death of macrophages in the plaque [136]. Because the selective SYK inhibitor fostamatinib completely prevented FcγR chain and CLCE-2 receptor activation-induced human platelet aggregation and reduced platelet spreading on fibrinogen, its mitigating effects on cardiovascular diseases such as thrombotic wandering-induced myocardial infarction are being investigated intensively [137].

Andre and colleagues found that PRT060318, a highly specific SYK inhibitor, inhibited the formation of arterial thrombus in vivo in mouse, rabbit and pig models [138]. Irfan et al. explored the role of gintonin, a glycolipoprotein extracted from ginseng. This team established a mouse model of pulmonary thromboembolism and found that gintonin significantly inhibited collagen-induced platelet aggregation and inhibited related signaling molecules in the GPVI signaling pathway, including SYK and PLCγ2, in this model [139]. Gintonin also downregulated the early signals of platelet activation, thereby reducing the formation of arterial thrombi [139,140]. Wang and coworkers analyzed the antithrombotic effect of Xinmailong (XML), and revealed that treatment with XML (10 mg/mL) inhibited collagen-induced phosphorylation of signaling molecules such as SYK and PLCγ2 [141]. Additionally, infarct size was reduced by the SYK inhibitor BI1002494 in mice [76,142]. The SYK inhibitor OXSI-2 dose dependently inhibited thrombosis formation on type-III collagen under high shear stress [58]. All of these results imply that inhibiting SYK could be a potentially effective antithrombotic option in various clinical settings, including cardiovascular disorders. Natural SYK inhibitors, such as curcumin and piceatannol, have also been reported to inhibit the SYK signaling pathway. Several oral SYK inhibitors, including fostamatinib (R788), entospletinib (GS-9973), cerdulatinib (PRT062070) and TAK-659, are being evaluated in clinical trials [143]. Among them, fostamatinib is also used in the treatment of ischemia-reperfusion injury, particularly for improving coronary flow after myocardial infarction [144,145].

Inhibition of SYK might be able to attenuate brain tissue damage following an IS [146–148]. Piceatannol, an SYK inhibitor derived from passion fruit seeds, rescued cerebral ischemic injury by reducing infarct volume and brain edema [90]. Piceatannol also reduced the ischemia-induced release of inflammatory cytokines, thereby partially reversing the inflammatory response after IS, in mice [83]. In fact, BI1002494, another SYK inhibitor, was also found to slow down the progression of stroke and improve prognosis in a mouse IS model [76,82]. Many studies have found that the overexpression of miR-148a-3p downregulates T-cell ubiquitin ligand-2 (a tyrosine kinase detectable in platelets), resulting in increased SYK phosphorylation, while targeted inhibition of miR-148a-3p reduces thrombus formation after platelet activation [149]. Clinically, targeting miRNA-SYK-related pathways may be a promising option in the field of

stroke prevention and treatment.

Moreover, activated SYK is capable of promoting phosphorylation of BTK, which is an essential downstream signal of SYK, thereby enhancing platelet-related pathological processes. Studies have shown that low-dose irreversible BTK inhibitor ibrutinib (PCI-32765), which is generally used to treat patients with chronic lymphocytic leukemia, can inhibit CLEC2 activation of the tyrosine pathway, resulting in reduced platelet aggregation and activation, thus protecting against atherosclerotic plaque formation. Similar results were seen with another irreversible BTK inhibitor, acalabrutinib [150]. Recent studies have also demonstrated that reversible inhibitors of BTK (e.g. fenebrutinib) are more effective at inhibiting platelet activation than ibrutinib [151]. Payrastre and colleagues found that the use of low-dose (140 mg/day) ibrutinib effectively prevented thombus formation in mice [150]. These data imply that targeting BTK might be a promising and potentially meaningful therapeutic strategy for treating or preventing the formation of platelet-related thrombi (Table 2).

Notably, in addition to its potential beneficial effects, ibrutinib also has unexpected off-target side effects [152] that can lead to increases in the incidence of hypertension and atrial fibrillation (AF), and other adverse reactions including diarrhea and fatigue [153]. Additionally, the prevalence of hypertension increases in proportion to the duration of prolonged application of ibrutinib [154,155]. A recent study found that the incidence of new-onset hypertension was as high as 70% in 562 patients receiving ibrutinib treatment [156]. In another retrospective study of 144 patients with B-cell malignancies, the authors reported significantly higher systolic and diastolic blood pressure in patients treated with ibrutinib chemotherapy than in the control group [155]. New-onset AF is another common side effect of ibrutinib treatment, with clinical studies confirming an increased incidence of new-onset AF in patients with chronic myeloid leukemia post ibrutinib treatment [154,157–161]. Therefore, to achieve the best clinical benefit, the decision-making process in the use of ibrutinib should include an assessment of the clinical benefit–risk balance; namely, the consideration of dose-dependent effects.

8. Conclusion

As one of the non-receptor tyrosine kinases, in addition to the key role in hematologic oncologic diseases, SYK also plays important roles in the pathogenesis of various cardiovascular-related diseases. Activation of SYK-related pathways largely contribute to the pathogenesis of various cardio-cerebrovascular diseases, evidence is accumulating on the application of SYK inhibitors, including BTK inhibitors, for the prevention and treatment of related cardio-cerebrovascular diseases. Ongoing researches on SYK in the cardiovascular and cerebrovascular field will deepen our understanding at the molecular basis on the pathological mechanism of various cardio-cerebrovascular diseases, which might pave the way of developing more effective target medication for the prevention and treatment of cardio-cerebrovascular diseases. At present, the role of various SYK inhibitors on the clinical treatment of cardiovascular diseases are in the stage of in-depth researching and special attention is needed to keep an eye on the related progresses.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Table 2
Researches on inhibitors of SYK signaling pathway.

Inhibitors	Medicine name	Biological mechanism	references
SYK-related inhibitors	Fostamatinib (R406)	● inhibits platelet aggregation and has no adverse bleeding events. ● reduces the incidence of early atherosclerosis, but could not effectively affect established atherosclerosis. ● improving coronary flow after myocardial infarction	[132–134,136,144,145]
	Entospletinib (GS-9973)	● inhibits platelet aggregation and has no adverse bleeding events.	[116,135]
	PRT060318	● inhibits arterial thrombus formation.	[138]
	Gintonin	● significantly inhibits collagen-induced platelet aggregation and inhibits related signaling molecules in GPVI signaling pathway including SYK, PLCγ2. ● reduces the formation of arterial thrombi.	[139,140]
	Xinmailong (XML)	● inhibits collagen-induced phosphorylation of signaling molecules such as SYK and PLCγ2.	[141]
	BI1002494	● alleviates the infarct size. ● slows down the progression of stroke and improve prognosis	[76,142]
	OXSI-2	● inhibits thrombosis formation (dosage dependence) of type-III collagen under high shear stress.	[58]
	Piceatanol	● rescues cerebral ischemic injury by reducing infarct volume and brain edema. ● reduces ischemia-induced releasing of inflammatory cytokines, thereby partially reversed the inflammatory response after ischemic stroke. ● inhibits the SYK signaling pathway.	[83,90]
BTK-related inhibitors	Ibrutinib (PCI-32765); Acalabrutinib	● reduces platelet aggregation and activation, thus protect against atherosclerotic plaque formation.	[150]
	Fenebrutinib	● inhibits platelet activation more effectively than Ibrutinib.	[151]

Funding statement

The present study was funded by the National Natural Science Foundation of China (82171572, 82171571 and 81970211). Naijin Zhang was supported by National Natural Science Foundation of China {82171572}.

Ying Zhang was supported by National Natural Science Foundation of China {82171571}.

Yingxian Sun was supported by National Natural Science Foundation of China { 81970211}.

Data availability statement

Data used to support the findings of this study are available from the corresponding author upon request.

Declaration of interest's statement

The authors declare no conflict of interest.

Acknowledgments

We thank Michelle Kahmeyer-Gabbe, PhD, from Liwen Bianji for editing the English text of a draft of this manuscript.

References

[1] L.C. Czuba, K.M. Hillgren, P.W. Swaan, Post-translational modifications of transporters, Pharmacol. Therapeut. 192 (2018) 88–99.
[2] L.S. Treviño, N.L. Weigel, Phosphorylation: a fundamental regulator of steroid receptor action, Trends Endocrinol. Metabol.: TEM (Trends Endocrinol. Metab.) 24 (10) (2013) 515–524.
[3] M. Li, et al., Research progress of Nedd4L in cardiovascular diseases, Cell Death Dis. 8 (1) (2022) 206.
[4] D. Popovic, D. Vucic, I. Dikic, Ubiquitination in disease pathogenesis and treatment, Nat. Med. 20 (11) (2014) 1242–1253.
[5] N. Zhang, et al., Selective targeting of ubiquitination and degradation of PARP1 by E3 ubiquitin ligase WWP2 regulates isoproterenol-induced cardiac remodeling, Cell Death Differ. 27 (9) (2020) 2605–2619.
[6] N. Zhang, et al., Role of WW domain E3 ubiquitin protein ligase 2 in modulating ubiquitination and Degradation of Septin4 in oxidative stress endothelial injury, Redox Biol. 30 (2020), 101419.
[7] N. Zhang, et al., An unexpected role for BAG3 in regulating PARP1 ubiquitination in oxidative stress-related endothelial damage, Redox Biol. 50 (2022), 102238.
[8] Y. Zhang, et al., WWP2 regulates SIRT1-STAT3 acetylation and phosphorylation involved in hypertensive angiopathy, J. Cell Mol. Med. 24 (16) (2020) 9041–9054.
[9] N. Zhang, et al., Septin4 prevents PDGF-BB-induced HAVSMC phenotypic transformation, proliferation and migration by promoting SIRT1-STAT3 deacetylation and dephosphorylation, Int. J. Biol. Sci. 16 (4) (2020) 708–718.
[10] N. Zhang, et al., Deacetylation-dependent regulation of PARP1 by SIRT2 dictates ubiquitination of PARP1 in oxidative stress-induced vascular injury, Redox Biol. 47 (2021), 102141.
[11] E.K. Day, N.G. Sosale, M.J. Lazzara, Cell signaling regulation by protein phosphorylation: a multivariate, heterogeneous, and context-dependent process, Curr. Opin. Biotechnol. 40 (2016) 185–192.
[12] E.L. Martin, V.M. Ranieri, Phosphorylation mechanisms in intensive care medicine, Intensive Care Med. 37 (1) (2011).
[13] S.M. Iqbal, R. Lemmens-Gruber, Phosphorylation of cardiac voltage-gated sodium channel: potential players with multiple dimensions, Acta Physiol. 225 (3) (2019), e13210.
[14] E.D. Martin, R. Bassi, M.S. Marber, p38 MAPK in cardioprotection - are we there yet? Br. J. Pharmacol. 172 (8) (2015) 2101–2113.
[15] M.L. Taddei, et al., Role of tyrosine phosphorylation in modulating cancer cell metabolism, Biochim. Biophys. Acta, Rev. Cancer 1874 (2) (2020), 188442.
[16] B. Huang, et al., NMR-based investigation into protein phosphorylation, Int. J. Biol. Macromol. 145 (2020) 53–63.
[17] A.H. Andreotti, et al., Regulatory intramolecular association in a tyrosine kinase of the Tec family, Nature 385 (6611) (1997) 93–97.
[18] D.R. Robinson, Y.M. Wu, S.F. Lin, The protein tyrosine kinase family of the human genome, Oncogene 19 (49) (2000) 5548–5557.
[19] R. Trenker, N. Jura, Receptor tyrosine kinase activation: from the ligand perspective, Curr. Opin. Cell Biol. 63 (2020) 174–185.
[20] L. Wang, et al., Gain-of-function variants in SYK cause immune dysregulation and systemic inflammation in humans and mice, Nat. Genet. 53 (4) (2021) 500–510.
[21] D.H. Chu, C.T. Morita, A. Weiss, The Syk family of protein tyrosine kinases in T-cell activation and development, Immunol. Rev. 165 (1998) 167–180.
[22] J.M. Bradshaw, The Src, Syk, and Tec family kinases: distinct types of molecular switches, Cell. Signal. 22 (8) (2010) 1175–1184.
[23] N.H. Shah, et al., The Src module: an ancient scaffold in the evolution of cytoplasmic tyrosine kinases, Crit. Rev. Biochem. Mol. Biol. 53 (5) (2018) 535–563.
[24] E. Tibaldi, et al., Src-Tyrosine kinases are major agents in mitochondrial tyrosine phosphorylation, J. Cell. Biochem. 104 (3) (2008) 840–849.
[25] G. Bagnato, et al., Nuclear functions of the tyrosine kinase Src, Int. J. Mol. Sci. 21 (8) (2020).
[26] A.V. Villarino, Y. Kanno, J.J. O'Shea, Mechanisms and consequences of Jak-STAT signaling in the immune system, Nat. Immunol. 18 (4) (2017) 374–384.
[27] J.J. O'Shea, et al., The JAK-STAT pathway: impact on human disease and therapeutic intervention, Annu. Rev. Med. 66 (2015) 311–328.
[28] C. Cans, et al., Nuclear tyrosine phosphorylation: the beginning of a map, Biochem. Pharmacol. 60 (8) (2000) 1203–1215.
[29] T. Sadras, et al., Developmental partitioning of SYK and ZAP70 prevents autoimmunity and cancer, Mol. Cell 81 (10) (2021).
[30] B.B. Au-Yeung, et al., The structure, regulation, and function of ZAP-70, Immunol. Rev. 228 (1) (2009) 41–57.
[31] A.C. Chan, et al., ZAP-70: a 70 kd protein-tyrosine kinase that associates with the TCR zeta chain, Cell 71 (4) (1992) 649–662.
[32] M.S. Mansueto, et al., A reevaluation of the spleen tyrosine kinase (SYK) activation mechanism, J. Biol. Chem. 294 (19) (2019) 7658–7668.
[33] T. Wossning, et al., Deregulated Syk inhibits differentiation and induces growth factor-independent proliferation of pre-B cells, J. Exp. Med. 203 (13) (2006) 2829–2840.
[34] N. Guillaume, et al., ZAP-70 tyrosine kinase is constitutively expressed and phosphorylated in B-lineage acute lymphoblastic leukemia cells, Haematologica 90 (7) (2005) 899–905.
[35] A. Rinaldi, et al., Genomic and expression profiling identifies the B-cell associated tyrosine kinase Syk as a possible therapeutic target in mantle cell lymphoma, Br. J. Haematol. 132 (3) (2006) 303–316.
[36] C. Liao, et al., Selective inhibition of spleen tyrosine kinase (SYK) with a novel orally bioavailable small molecule inhibitor, RO9021, impinges on various innate and adaptive immune responses: implications for SYK inhibitors in autoimmune disease therapy, Arthritis Res. Ther. 15 (5) (2013) R146.
[37] T. Kobayashi, et al., Purification and characterization of a cytosolic protein-tyrosine kinase from porcine spleen, Eur. J. Biochem. 188 (3) (1990) 535–540.
[38] Y.-S. Yi, et al., Functional Roles of Syk in Macrophage-Mediated Inflammatory Responses, vol. 2014, Mediators of Inflammation, 2014, 270302.

[39] R.B. Rowley, J.B. Bolen, J. Fargnoli, Molecular cloning of rodent p72Syk. Evidence of alternative mRNA splicing, J. Biol. Chem. 270 (21) (1995) 12659–12664.
[40] T. Taniguchi, et al., Molecular cloning of a porcine gene syk that encodes a 72-kDa protein-tyrosine kinase showing high susceptibility to proteolysis, J. Biol. Chem. 266 (24) (1991) 15790–15796.
[41] K. Sada, et al., Structure and function of Syk protein-tyrosine kinase, J. Biochem. 130 (2) (2001) 177–186.
[42] C.L. Law, et al., Molecular cloning of human Syk. A B cell protein-tyrosine kinase associated with the surface immunoglobulin M-B cell receptor complex, J. Biol. Chem. 269 (16) (1994) 12310–12319.
[43] H.T. Hobbs, et al., Differences in the dynamics of the tandem-SH2 modules of the Syk and ZAP-70 tyrosine kinases, Protein Sci. : Pub. Prot. Soci. 30 (12) (2021) 2373–2384.
[44] E. Leveille, et al., SYK and ZAP70 kinases in autoimmunity and lymphoid malignancies, Cell. Signal. 94 (2022), 110331.
[45] J.E. Hutchcroft, M.L. Harrison, R.L. Geahlen, B lymphocyte activation is accompanied by phosphorylation of a 72-kDa protein-tyrosine kinase, J. Biol. Chem. 266 (23) (1991) 14846–14849.
[46] F. Fallah-Arani, et al., Redundant role for Zap70 in B cell development and activation, Eur. J. Immunol. 38 (6) (2008) 1721–1733.
[47] P. Ruzza, B. Biondi, A. Calderan, Therapeutic prospect of Syk inhibitors, Expert Opin. Ther. Pat. 19 (10) (2009) 1361–1376.
[48] M. Turner, et al., Perinatal lethality and blocked B-cell development in mice lacking the tyrosine kinase Syk, Nature 378 (6554) (1995) 298–302.
[49] K. Fütterer, et al., Structural basis for Syk tyrosine kinase ubiquity in signal transduction pathways revealed by the crystal structure of its regulatory SH2 domains bound to a dually phosphorylated ITAM peptide, J. Mol. Biol. 281 (3) (1998) 523–537.
[50] L. Shiue, et al., Interaction of p72syk with the gamma and beta subunits of the high-affinity receptor for immunoglobulin E, Fc epsilon RI, Mol. Cell Biol. 15 (1) (1995) 272–281.
[51] S. Latour, et al., A unique insert in the linker domain of Syk is necessary for its function in immunoreceptor signalling, EMBO J. 17 (9) (1998) 2584–2595.
[52] M. Flück, et al., Molecular characterization of the murine syk protein tyrosine kinase cDNA, transcripts and protein, Biochem. Biophys. Res. Commun. 213 (1) (1995) 273–281.
[53] S. Yanagi, et al., Syk expression and novel function in a wide variety of tissues, Biochem. Biophys. Res. Commun. 288 (3) (2001) 495–498.
[54] K. Liang, et al., The expression and clinical significance of spleen tyrosine kinase in patients with coronary heart disease, Med. Sci. Mon. Int. Med. J. Exp. Clin. Res. : Int. Med. J. Exp. Clin. Res. 25 (2019) 2112–2121.
[55] G.K. Hansson, Inflammation, atherosclerosis, and coronary artery disease, N. Engl. J. Med. 352 (16) (2005) 1685–1695.
[56] P. Libby, G.K. Hansson, Inflammation and immunity in diseases of the arterial tree: players and layers, Circ. Res. 116 (2) (2015) 307–311.
[57] G. Davì, C. Patrono, Platelet activation and atherothrombosis, N. Engl. J. Med. 357 (24) (2007) 2482–2494.
[58] H.E. Speich, et al., Platelets undergo phosphorylation of Syk at Y525/526 and Y352 in response to pathophysiological shear stress, Am. J. Physiol. Cell Physiol. 295 (4) (2008) C1045–C1054.
[59] B. Kehrel, et al., Glycoprotein VI is a major collagen receptor for platelet activation: it recognizes the platelet-activating quaternary structure of collagen, whereas CD36, glycoprotein IIb/IIIa, and von Willebrand factor do not, Blood 91 (2) (1998) 491–499.
[60] R.K. Andrews, et al., Interaction of calmodulin with the cytoplasmic domain of platelet glycoprotein VI, Blood 99 (11) (2002) 4219–4221.
[61] Y. Miura, et al., Analysis of the interaction of platelet collagen receptor glycoprotein VI (GPVI) with collagen. A dimeric form of GPVI, but not the monomeric form, shows affinity to fibrous collagen, J. Biol. Chem. 277 (48) (2002) 46197–46204.
[62] T. Bori-Sanz, et al., Delineation of the region in the glycoprotein VI tail required for association with the Fc receptor gamma-chain, J. Biol. Chem. 278 (38) (2003) 35914–35922.
[63] D. Locke, et al., Fc Rgamma -independent signaling by the platelet collagen receptor glycoprotein VI, J. Biol. Chem. 278 (17) (2003) 15441–15448.
[64] Y.A. Senis, A. Mazharian, J. Mori, Src family kinases: at the forefront of platelet activation, Blood 124 (13) (2014) 2013–2024.
[65] B. Payrastre, A. Ribes, Low-dose Btk inhibitors: an 'aspirin' of tomorrow? Haematologica 106 (1) (2021) 2–4.
[66] S. Feng, et al., Pathological shear stress directly regulates platelet alphaIIbbeta3 signaling, Am. J. Physiol. Cell Physiol. 291 (6) (2006) C1346–C1354.
[67] C. Fujii, et al., Involvement of protein-tyrosine kinase p72syk in collagen-induced signal transduction in platelets, Eur. J. Biochem. 226 (1) (1994) 243–248.
[68] K. Suzuki-Inoue, Platelets and cancer-associated thrombosis: focusing on the platelet activation receptor CLEC-2 and podoplanin, Blood 134 (22) (2019) 1912–1918.
[69] S.I. Yamagishi, et al., Hyperglycemia potentiates collagen-induced platelet activation through mitochondrial superoxide overproduction, Diabetes 50 (6) (2001) 1491–1494.
[70] Y. Chen, et al., Galectin 3 enhances platelet aggregation and thrombosis via Dectin-1 activation: a translational study, Eur. Heart J. 43 (37) (2022) 3556–3574.
[71] S. Kotla, et al., ROS-dependent Syk and Pyk2-mediated STAT1 activation is required for 15(S)-hydroxyeicosatetraenoic acid-induced CD36 expression and foam cell formation, Free Radical Biol. Med. 76 (2014) 147–162.
[72] Y. Guo, et al., MiR-377 mediates the expression of Syk to attenuate atherosclerosis lesion development in ApoE mice, Biomed. Pharm. Biomedecine Pharmacotherapie 118 (2019), 109332.
[73] W. Wang, et al., Inhibition of Syk promotes chemical reprogramming of fibroblasts via metabolic rewiring and H S production, EMBO J. 40 (11) (2021) e106771.
[74] S. Zewinger, et al., Apolipoprotein C3 induces inflammation and organ damage by alternative inflammasome activation, Nat. Immunol. 21 (1) (2020) 30–41.
[75] M.H. Harbi, et al., Novel antiplatelet strategies targeting GPVI, CLEC-2 and tyrosine kinases, Platelets 32 (1) (2021) 29–41.
[76] J.M.M. van Eeuwijk, et al., The novel oral syk inhibitor, Bl1002494, protects mice from arterial thrombosis and thromboinflammatory brain infarction, Arterioscler. Thromb. Vasc. Biol. 36 (6) (2016) 1247–1253.
[77] D. Zhang, et al., Glycoprotein VI is not a functional platelet receptor for fibrin formed in plasma or blood, Thromb. Haemostasis 120 (6) (2020) 977–993.
[78] N. Takaya, et al., Platelets activated by collagen through the immunoreceptor tyrosine-based activation motif in the Fc receptor gamma-chain play a pivotal role in the development of myocardial ischemia-reperfusion injury, J. Mol. Cell. Cardiol. 39 (6) (2005) 856–864.
[79] S.K. Feske, Ischemic stroke, Am. J. Med. 134 (12) (2021) 1457–1464.
[80] X. Wu, et al., The roles of thrombospondins in hemorrhagic stroke, BioMed Res. Int. 2017 (2017), 8403184.
[81] M.L. Weisfeldt, S.J. Zieman, Advances in the prevention and treatment of cardiovascular disease, Health Aff. 26 (1) (2007) 25–37.
[82] S.E. McKenzie, Syk inhibition in ischemic stroke, Arterioscler. Thromb. Vasc. Biol. 36 (6) (2016) 1054–1055.
[83] X.-C. Ye, et al., Dectin-1/Syk signaling triggers neuroinflammation after ischemic stroke in mice, J. Neuroinflammation 17 (1) (2020) 17.
[84] N.C. Rogers, et al., Syk-dependent cytokine induction by Dectin-1 reveals a novel pattern recognition pathway for C type lectins, Immunity 22 (4) (2005) 507–517.
[85] K. Di Gregoli, et al., MicroRNA-181b controls atherosclerosis and aneurysms through regulation of TIMP-3 and elastin, Circ. Res. 120 (1) (2017) 49–65.
[86] M.W. Feinberg, K.J. Moore, MicroRNA regulation of atherosclerosis, Circ. Res. 118 (4) (2016) 703–720.
[87] S. Huang, et al., miR-129-2-3p directly targets SYK gene and associates with the risk of ischaemic stroke in a Chinese population, J. Cell Mol. Med. 23 (1) (2019) 167–176.
[88] K.J. Becker, Epidemiology and clinical presentation of aneurysmal subarachnoid hemorrhage, Neurosurg. Clin. 9 (3) (1998) 435–444.
[89] J. van Gijn, R.S. Kerr, G.J.E. Rinkel, Subarachnoid haemorrhage, Lancet (London, England) 369 (9558) (2007) 306–318.
[90] Y. Suzuki, et al., Involvement of Mincle and Syk in the changes to innate immunity after ischemic stroke, Sci. Rep. 3 (2013) 3177.
[91] Y. He, et al., Macrophage-inducible C-type lectin/spleen tyrosine kinase signaling pathway contributes to neuroinflammation after subarachnoid hemorrhage in rats, Stroke 46 (8) (2015) 2277–2286.
[92] L.E. Wold, A.F. Ceylan-Isik, J. Ren, Oxidative stress and stress signaling: menace of diabetic cardiomyopathy, Acta Pharmacol. Sin. 26 (8) (2005) 908–917.
[93] G. Jia, A. Whaley-Connell, J.R. Sowers, Diabetic cardiomyopathy: a hyperglycaemia- and insulin-resistance-induced heart disease, Diabetologia 61 (1) (2018) 21–28.
[94] W.H. Dillmann, Diabetic cardiomyopathy, Circ. Res. 124 (8) (2019) 1160–1162.

[95] Y. Tan, et al., Mechanisms of diabetic cardiomyopathy and potential therapeutic strategies: preclinical and clinical evidence, Nat. Rev. Cardiol. 17 (9) (2020) 585–607.
[96] I. Falcão-Pires, A.F. Leite-Moreira, Diabetic cardiomyopathy: understanding the molecular and cellular basis to progress in diagnosis and treatment, Heart Fail. Rev. 17 (3) (2012) 325–344.
[97] Z. Wang, et al., Analysis of communal molecular mechanism and potential therapeutic targets in heart failure and type 2 diabetes mellitus, Int. J. Gen. Med. 14 (2021) 6549–6561.
[98] S. Königsberger, et al., Altered BCR signalling quality predisposes to autoimmune disease and a pre-diabetic state, EMBO J. 31 (15) (2012) 3363–3374.
[99] B. Vandanmagsar, et al., The NLRP3 inflammasome instigates obesity-induced inflammation and insulin resistance, Nat. Med. 17 (2) (2011) 179–188.
[100] B. Luo, et al., NLRP3 inflammasome as a molecular marker in diabetic cardiomyopathy, Front. Physiol. 8 (2017) 519.
[101] B. Luo, et al., NLRP3 gene silencing ameliorates diabetic cardiomyopathy in a type 2 diabetes rat model, PLoS One 9 (8) (2014) e104771.
[102] S. Li, et al., Spleen tyrosine kinase-induced JNK-dependent NLRP3 activation is involved in diabetic cardiomyopathy, Int. J. Mol. Med. 43 (6) (2019) 2481–2490.
[103] H. Zhou, et al., Melatonin therapy for diabetic cardiomyopathy: a mechanism involving Syk-mitochondrial complex I-SERCA pathway, Cell. Signal. 47 (2018).
[104] B.J. Maron, et al., Sudden deaths in young competitive athletes: analysis of 1866 deaths in the United States, 1980-2006, Circulation 119 (8) (2009) 1085–1092.
[105] I. Gupta, N.K. Varshney, S. Khan, Emergence of members of TRAF and DUB of ubiquitin proteasome system in the regulation of hypertrophic cardiomyopathy, Front. Genet. 9 (2018) 336.
[106] L. Hauck, et al., Cardiac-specific ablation of the E3 ubiquitin ligase Mdm2 leads to oxidative stress, broad mitochondrial deficiency and early death, PLoS One 12 (12) (2017) e0189861.
[107] Y. Maejima, et al., Muscle-specific RING finger 1 negatively regulates pathological cardiac hypertrophy through downregulation of calcineurin A, Circul. Heart Failure 7 (3) (2014) 479–490.
[108] Y. Huang, et al., Cardiac-specific Traf2 overexpression enhances cardiac hypertrophy through activating AKT/GSK3β signaling, Gene 536 (2) (2014) 225–231.
[109] R. Chen, et al., Identification of biomarkers correlated with hypertrophic cardiomyopathy with co-expression analysis, J. Cell. Physiol. 234 (12) (2019) 21999–22008.
[110] L. Nedkoff, C. Weber, Heart failure: not just a disease of the elderly, Heart 108 (4) (2022) 249–250.
[111] B. López, et al., Diffuse myocardial fibrosis: mechanisms, diagnosis and therapeutic approaches, Nat. Rev. Cardiol. 18 (7) (2021) 479–498.
[112] J.G. Travers, et al., Cardiac fibrosis: the fibroblast awakens, Circ. Res. 118 (6) (2016) 1021–1040.
[113] L. Liu, et al., miR-136 improves renal fibrosis in diabetic rats by targeting down-regulation of tyrosine kinase SYK and inhibition of TGF-β1/Smad3 signaling pathway, Ren. Fail. 42 (1) (2020) 513–522.
[114] F. Li, et al., Histone methyltransferase DOT1L mediates the TGF-β1/Smad3 signaling pathway through epigenetic modification of SYK in myocardial infarction, Hum. Cell 35 (1) (2022).
[115] S. Ye, et al., Dectin-1 Acts as a Non-classical Receptor of Ang II to Induce Cardiac Remodeling, Circulation Research, 2023.
[116] J. Sharman, et al., An open-label phase 2 trial of entospletinib (GS-9973), a selective spleen tyrosine kinase inhibitor, in chronic lymphocytic leukemia, Blood 125 (15) (2015) 2336–2343.
[117] R. Flynn, et al., Targeting Syk-activated B cells in murine and human chronic graft-versus-host disease, Blood 125 (26) (2015) 4085–4094.
[118] R.M. Mortensen, Immune cell modulation of cardiac remodeling, Circulation 125 (13) (2012) 1597–1600.
[119] Y. Zhang, J. Bauersachs, H.F. Langer, Immune mechanisms in heart failure, Eur. J. Heart Fail. 19 (11) (2017) 1379–1389.
[120] K. Raza, et al., Suppression of inflammation in primary systemic vasculitis restores vascular endothelial function: lessons for atherosclerotic disease? Circulation 102 (13) (2000) 1470–1472.
[121] K. de Leeuw, et al., Patients with Wegener's granulomatosis: a long-term follow-up study, Clin. Exp. Rheumatol. 28 (1 Suppl 57) (2010) 18–23.
[122] D. Massicotte-Azarniouch, et al., Association of anti-neutrophil cytoplasmic antibody-associated vasculitis and cardiovascular events: a population-based cohort study, Clin. Kid. J. 15 (4) (2022) 681–692.
[123] R.K. Pilania, et al., ANCA-Associated vasculitis presenting as severe pulmonary hypertension and right heart failure, Indian J. Pediatr. 84 (10) (2017) 799–801.
[124] M. Prendecki, et al., Syk activation in circulating and tissue innate immune cells in antineutrophil cytoplasmic antibody-associated vasculitis, Arthritis Rheumatol. 75 (1) (2023) 84–97.
[125] S.P. McAdoo, et al., Spleen tyrosine kinase inhibition is an effective treatment for established vasculitis in a pre-clinical model, Kidney Int. 97 (6) (2020) 1196–1207.
[126] C. Patrono, et al., Antiplatelet agents for the treatment and prevention of atherothrombosis, Eur. Heart J. 32 (23) (2011) 2922–2932.
[127] J.L. Mega, T. Simon, Pharmacology of antithrombotic drugs: an assessment of oral antiplatelet and anticoagulant treatments, Lancet (London, England) 386 (9990) (2015) 281–291.
[128] J.D. McFadyen, M. Schaff, K. Peter, Current and future antiplatelet therapies: emphasis on preserving haemostasis, Nat. Rev. Cardiol. 15 (3) (2018) 181–191.
[129] V. Aboyans, et al., Antithrombotic therapies in aortic and peripheral arterial diseases in 2021: a consensus document from the ESC working group on aorta and peripheral vascular diseases, the ESC working group on thrombosis, and the ESC working group on cardiovascular pharmacotherapy, Eur. Heart J. 42 (39) (2021) 4013–4024.
[130] A. McNicol, S.J. Israels, Platelets and anti-platelet therapy, J. Pharmacol. Sci. 93 (4) (2003) 381–396.
[131] M. Kaur, M. Singh, O. Silakari, Inhibitors of switch kinase 'spleen tyrosine kinase' in inflammation and immune-mediated disorders: a review, Eur. J. Med. Chem. 67 (2013) 434–446.
[132] J.B. Bussel, et al., Long-term fostamatinib treatment of adults with immune thrombocytopenia during the phase 3 clinical trial program, Am. J. Hematol. 94 (5) (2019) 546–553.
[133] S. Braselmann, et al., R406, an orally available spleen tyrosine kinase inhibitor blocks fc receptor signaling and reduces immune complex-mediated inflammation, J. Pharmacol. Exp. Therapeut. 319 (3) (2006).
[134] J. Bussel, et al., Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: results of two phase 3, randomized, placebo-controlled trials, Am. J. Hematol. 93 (7) (2018) 921–930.
[135] P. Blomgren, et al., Discovery of lanraplenib (GS-9876): a once-daily spleen tyrosine kinase inhibitor for autoimmune diseases, ACS Med. Chem. Lett. 11 (4) (2020) 506–513.
[136] A. Lindau, et al., Atheroprotection through SYK inhibition fails in established disease when local macrophage proliferation dominates lesion progression, Basic Res. Cardiol. 111 (2) (2016) 20.
[137] J.C. Spalton, et al., The novel Syk inhibitor R406 reveals mechanistic differences in the initiation of GPVI and CLEC-2 signaling in platelets, J. Thromb. Haemostasis : JTH 7 (7) (2009) 1192–1199.
[138] P. Andre, et al., Critical role for Syk in responses to vascular injury, Blood 118 (18) (2011) 5000–5010.
[139] M. Irfan, et al., Gintonin modulates platelet function and inhibits thrombus formation via impaired glycoprotein VI signaling, Platelets 30 (5) (2019) 589–598.
[140] M. Irfan, M. Kim, M.H. Rhee, Anti-platelet role of Korean ginseng and ginsenosides in cardiovascular diseases, J. Gins. Res. 44 (1) (2020) 24–32.
[141] H. Wang, et al., Xinmailong modulates platelet function and inhibits thrombus formation the platelet αIIbβ3-mediated signaling pathway, Front. Pharmacol. 10 (2019) 923.
[142] K. Chihara, et al., *Syk inhibitors.* nihon rinsho men'eki gakkai kaishi = Japanese, J. Clin. Immunol. 36 (4) (2013) 197–202.
[143] D. Liu, A. Mamorska-Dyga, Syk inhibitors in clinical development for hematological malignancies, J. Hematol. Oncol. 10 (1) (2017) 145.
[144] O.N. Pamuk, et al., Spleen tyrosine kinase inhibition prevents tissue damage after ischemia-reperfusion, Am. J. Physiol. Gastrointest. Liver Physiol. 299 (2) (2010) G391–G399.

[145] P.H. Lapchak, et al., Inhibition of Syk activity by R788 in platelets prevents remote lung tissue damage after mesenteric ischemia-reperfusion injury, Am. J. Physiol. Gastrointest. Liver Physiol. 302 (12) (2012) G1416–G1422.
[146] V. Friedrich, et al., Reduction of neutrophil activity decreases early microvascular injury after subarachnoid haemorrhage, J. Neuroinflammation 8 (2011) 103.
[147] M.B. Ystgaard, et al., Early upregulation of NLRP3 in the brain of neonatal mice exposed to hypoxia-ischemia: No early neuroprotective effects of NLRP3 deficiency, Neonatology 108 (3) (2015) 211–219.
[148] T. Kawai, S. Akira, The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors, Nat. Immunol. 11 (5) (2010) 373–384.
[149] Y. Zhou, et al., Anti-miR-148a regulates platelet FcγRIIA signaling and decreases thrombosis in vivo in mice, Blood 126 (26) (2015) 2871–2881.
[150] P.L.R. Nicolson, et al., Low-dose Btk inhibitors selectively block platelet activation by CLEC-2, Haematologica 106 (1) (2021) 208–219.
[151] L. Goldmann, et al., Oral Bruton tyrosine kinase inhibitors block activation of the platelet Fc receptor CD32a (FcγRIIA): a new option in HIT? Blood Adv. 3 (23) (2019) 4021–4033.
[152] T.J. Zheng, et al., Assessment of the effects of Syk and BTK inhibitors on GPVI-mediated platelet signaling and function, Am. J. Physiol. Cell Physiol. 320 (5) (2021) C902–C915.
[153] S. Ganatra, et al., Ibrutinib-associated atrial fibrillation, JACC. Clin. Electrophys. 4 (12) (2018) 1491–1500.
[154] T.E. Wiczer, et al., Cumulative incidence, risk factors, and management of atrial fibrillation in patients receiving ibrutinib, Blood Adv. 1 (20) (2017) 1739–1748.
[155] D.H. Lee, et al., Association between ibrutinib treatment and hypertension, Heart 108 (6) (2022) 445–450.
[156] T. Dickerson, et al., Hypertension and incident cardiovascular events following ibrutinib initiation, Blood 134 (22) (2019) 1919–1928.
[157] J.A. Burger, et al., Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia, N. Engl. J. Med. 373 (25) (2015) 2425–2437.
[158] J.C. Byrd, et al., Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia, N. Engl. J. Med. 371 (3) (2014) 213–223.
[159] T.D. Shanafelt, et al., Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL), Leuk. Lymphoma 58 (7) (2017) 1630–1639.
[160] J.R. Brown, et al., Incidence of and risk factors for major haemorrhage in patients treated with ibrutinib: an integrated analysis, Br. J. Haematol. 184 (4) (2019) 558–569.
[161] S. Yun, et al., *Risk of atrial Fibrillation and bleeding diathesis associated with ibrutinib treatment: a systematic Review and pooled Analysis of four randomized controlled trials.* Clinical lymphoma, Myel. Leukemia 17 (1) (2017).