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REVIEW ON SRC KINASES AS A PROMISING PHARMACOLOGICAL TARGET FOR VARIOUS DISEASES

Ajeet Pal Singh [*1, 2], Ashish Kumar Sharma [1] and Thakur Gurjeet Singh [3]

NIMS Institute of Pharmacy [1], NIMS University, Jaipur - 303121, Rajasthan, India.
St. Soldier Institute of Pharmacy [2], Lidhran Campus, Behind NIT (R.E.C.), Jalandhar - 144011, Punjab, India.
Chitkara College of Pharmacy [3], Chitkara University, Rajpura - 140401, Punjab, India.

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Correspondence to Author:
Ajeet Pal Singh

NIMS Institute of Pharmacy,
NIMS University, Jaipur - 303121,
Rajasthan, India.

E-mail: ajeetakarpuria@gmail.com

ABSTRACT: This review explores the multifaceted roles of Src kinases, a subfamily of non-receptor tyrosine kinases, shedding light on their involvement in diverse diseases. Src-family protein tyrosine kinases (SFKs) exhibit widespread expression across various cell types, influencing their behavior and functionality. Src's presence in distinct subcellular locations, such as plasma membranes, perinuclear membranes, and endosomal membranes, underscores its versatility and potential impact on cellular processes. Research indicates a significant association between SFKs and various disorders, emphasizing their relevance as potential therapeutic targets. The intricate interplay of SFKs in cellular membranes suggests a nuanced role in disease pathogenesis. The comprehensive examination of Src kinase's involvement in different cellular contexts contributes to a better understanding of its potential implications in disease development. In conclusion, this study underscores the pivotal role of Src kinase and positions it as a promising therapeutic target for addressing a spectrum of illnesses. By elucidating the intricate mechanisms through which SFKs operate in cellular membranes, this review advocates for further exploration of Src kinases as crucial players in disease pathology. Recognizing the diverse roles of SFKs provides a foundation for the development of effective and secure treatments, opening avenues for targeted interventions in diseases where Src kinases play a pivotal role.

INTRODUCTION: A family of non-receptor tyrosine kinases includes the Src family kinases (SFKs), a collection of different proteins. Of all non-receptor tyrosine kinases, SFKs are the most numerous. During research to understand the mechanism by which retroviruses cause tumours, Src kinase was found.

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The first tyrosine kinase to be discovered was the viral oncogene of the virus (Rous Sarcoma Virus), v-Src kinase. The intrinsic protein tyrosine kinase functionality of a gene product was first identified in Src.

There are now 10 members of the SFK that have been discovered; nine of these members (Src, Yes, Fgr, Fyn, Lyn, Hck, Lck, Blk and Frk) are expressed in mammals, while the tenth member (Yrk) is only present in chickens [1, 2]. Depending on their bodily expression pattern, these members can be further categorized. Most tissues express Src, Yes, Fgr and Fyn from the first group, whereas

Lyn, Hck, Lck and Blk from the second group are mostly expressed in hematopoietic cells [2–4]. Src and Src family protein kinases take role in a variety of cellular activities such as transcription, apoptosis, differentiation, development, immunological response and nervous system function [56]. Cancer has been linked to dysregulation of the Src protein kinase, which has drawn a lot of interest in this family of protein kinase enzymes [7]. The structure, regulation, and most recent research about the function of SFKs in various disorders will all be examined in the article.

Structure of Src Family Kinases:

General Structure: SFKs are a family of cytoplasmic tyrosine kinases that belong to the Src family. It has a short C-terminal tail, two SH2 and SH3 Src homology domains, a catalytic tyrosine-protein kinase domain (SH1) and an N-terminal region containing a 14-carbon myristoyl group [5]. All three domains are crucial for signal transduction with the SH1 domain having a catalytic role and the SH2 & SH3 domains possessing non-catalytic regulatory properties [8, 9]. **Fig. 1** depicts the distinctive structure of SFKs.

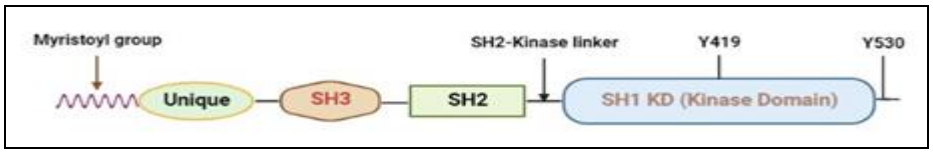

FIG. 1: STRUCTURE OF SRC KINASE

Active Sites: There is an ATP-binding lobe and a peptide-binding lobe in the c-Src kinase catalytic domain. The 180 residues and peptide-binding lobe that make up the substrate-docking site are not all participate in docking.

According to the Ala scanning experiments, six of them (Ser-273, Arg-279, Ser-280, Arg-281, Arg-283 and Phe-382) are important substrate-docking site determinants. Using two mutants, one with quadruple mutations (QM) of Ser280Ala, Arg281Ala, Arg283Ala and Phe382Ala, Lee *et al.* [10] confirmed the significance of these six residues. The Tyr527-containing region of the viral Src (v-Src) is missing in the cellular protein (c-Src), which differs from it. The kinase activity is inhibited by Tyr527 phosphorylation; therefore the enzyme is still active even without it [9].

Biological Function of Enzyme: Src tyrosine kinase enzymes are involved in the signalling pathways that regulate a wide range of biological activities including gene transcription, immune response, cell adhesion, cell cycle progression, cell differentiation, apoptosis, movement, transformation, proliferation and other crucial cellular functions [9].

Activation of Enzyme: The process by which SFKs are activated involves several steps, and the specific molecular mechanism depends on the type of cell and extracellular cues.

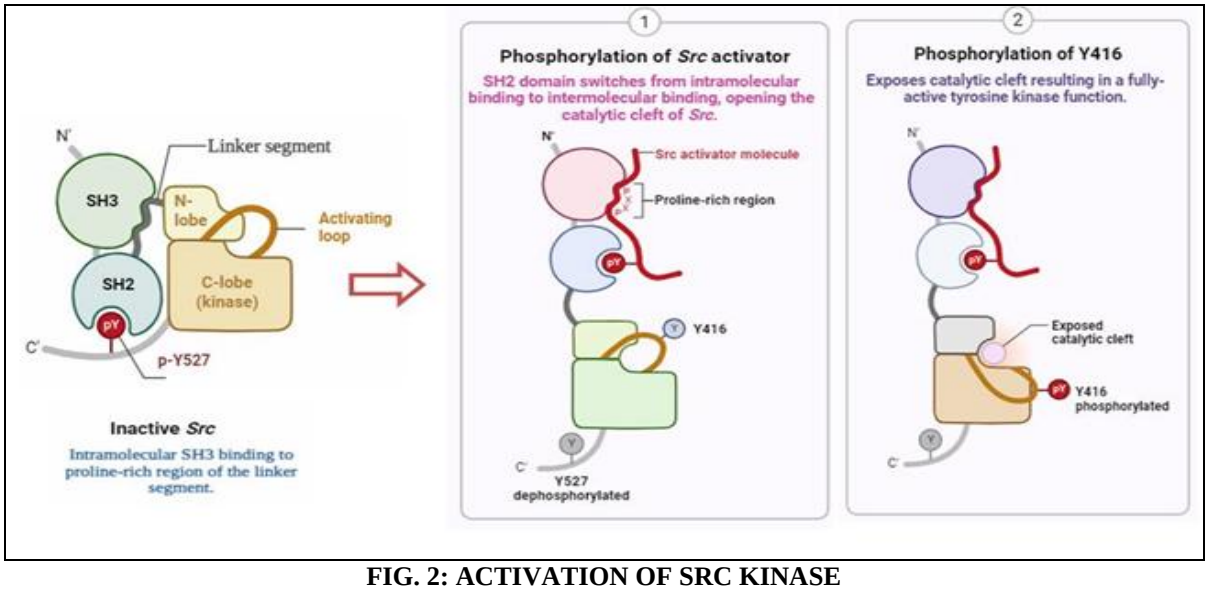

FIG. 2: ACTIVATION OF SRC KINASE

The first step in the activation process is the stimulation of receptors, adaptors, or effectors, which then interact with the inactive SFKs' SH2/3 domains to open the closed conformation. In order to stabilise the active conformation, exposed pTyr-527 dephosphorylates and the activated SFKs relocate to the proper intracellular locations [11]. The activation loop Tyr419 of the Src protein is where intermolecular auto-phosphorylation takes place [5]. To remove restrictions and create a functional kinase, the helix C needs to be reoriented [12]. In response to activation, Src tyrosine kinase enzymes can phosphorylate a number of different proteins, including p38, mitogen-activated protein kinase (MAPK), and extracellular signal-regulated kinase (ERK). Cell development, differentiation, senescence, and inflammation are all regulated by MAPKs. Endothelial cell migration, survival, and permeability are all related to p38, whereas inflammation and cell proliferation are related to ERK. One of the main by-products of lipid peroxidation is 4-hydroxynonenal (4-HNE). Src modulates the HNE-induced activation of the MAPKs/AP-1 signalling pathway and increased COX-2 expression [13, 14].

Members of Src Kinases

Src kinase: Src has been discovered to be involved in a number of cellular activities including migration, differentiation and proliferation. Src has been discovered to have a function in oligodendrocyte maturation and neuronal development [15]. Osteopetrosis, a deficiency in bone resorption that causes an overgrowth of bone develops in Src knockout mice. Despite having a large number of osteoclasts, these animals suffer from severe osteopetrosis. Therefore, the problem does not represent poor osteoclast activity especially disruption of the cell's actin cytoskeleton but rather poor osteoclast recruitment [16]. Recently, it was shown that Src knockout mice had problems lactating, supporting the theory that Src is also involved in the formation of the mammary gland [17].

Fyn kinase: Fyn (59 kDa) is widely expressed SFK. Fyn comes in isoforms a, b and c. Isoform a also known as Fyn (B) was originally discovered and determined to be strongly expressed in the brain; Isoform b also known as Fyn (T) is unique to hematopoietic cells (T cells); and Isoform C has been discovered in blood cells.

These isoforms result from alternate splicing of the Fyn gene's seventh exon which codes for the kinase domain [18]. Fyn has the capacity to bind and phosphorylate several intracellular signalling molecules which allows it to participate in a wide range of cellular processes. Cellular adhesion, T-cell signaling and brain functioning have all been linked to Fyn [18].According to research using Fyn knockout mice, Fyn is involved in some brain processes [19]. The formation of the hippocampus region is aberrant in Fyn knockout mice, and they also exhibit problems in learning and memory, myelination lossandthymocyte signaling [15, 20].

Lyn kinase: Within the distinct domain, alternative splicing produced two Lyn isoforms: isoform at (53 kDa) and isoform b (56 kDa). In B-cells, Lyn is the SFK that is most abundantly expressed. Lyn has an interesting dual function in B cell receptor signalling; it is crucial for signal initiation but also participates in the signal's subsequent negative regulation dependent on the stimulus and the cell's stage of development [21, 22].

It has been discovered to play a role in regulating cellular growth and inhibiting apoptosis. It has also been demonstrated to express itself in healthy prostate epithelium [23]. Lyn knockout mice exhibit aberrant prostate gland morphogenesis decreased B-cell activity and autoimmune illness.Although the number of B-cells in the bone marrow of lyn knockout mice is similar to that seen in normal mice, the number of peripheral B-cells is reduced by more than 50% [23–25].

Yes kinase: Another widely expressed SFK is yes kinase (62 kDa) which is notably abundant in fibroblasts, endothelial cells and the brain [26]. The tyrosine phosphorylation levels of FAK, p130Cas and paxillin are significantly reduced in mutant animals and immunoglobulin A (IgA) transport through epithelial cells is also significantly reduced [27]. Only Yes was discovered to be functionally implicated in the increased signalling that contributes to the malignant phenotypes of melanoma cells, despite the fact that numerous members of the Src family kinases were expressed in the melanoma cells. Yes kinase has also been found in malignant melanomas, gastric cancers and breast cancers but less often [28].

Fgrkinase: In addition to being highly expressed in mouse osteoclasts, Fgr (58 kDa) is mostly detected in hematopoietic cells [29]. Fgr expression is shown in mature B-cells, neutrophils, monocytes and macrophages. A number of intracellular signalling pathways in myeloid cells including cytokine receptor signalling and fc fragment of IgG receptor signalling have been revealed to be regulated by Fgr, just as Hck and Lyn [29].

According to Fgr knockout mice, Fgr is involved in signalling in a variety of immune cells and favourably modulates mast cell degranulation and phospholipase D activation.

Lckkinase: Due to the fact that T-cells (natural killer cells) are the major source of Lck (56 kDa) expression, hematopoietic cells are the main subset to express Lck [30]. The maturation of oligodendrocytes, mitochondrial apoptosis and neuronal development have all been linked to Lck [15, 31]. T-cell development is said to be halted in Lck knockout mice and T-cell receptor signalling is also said to be affected [21, 32].

Additionally, it was discovered that Lck knockout mice lack the ability to produce Lck and this prevented them from expressing Lck when anticancer medicines were administered [31].

Hckkinase: Embryonic stem cells and hematopoietic cells of the myeloid and monocytic lineage are the major locations where Hck (59 kDaand 61 kDa) is expressed. When cytokines are present, Hck is discovered to be activated and is a crucial part of the signalling pathways in activated macrophages. Hck levels rise when monocytes differentiate and it is involved in apoptosis, granule secretion, adhesion, phagocytosis and other processes [29, 33].

Blkkinase: Blk (56 kDa) is mostly expressed in hematopoietic cells primarily in B-cells, although it is also present in early thymic precursors, interleukin-17-producing T cells and pancreatic -cells [34].

It is essential for the growth of T cells that produce IL-17, according to Blk knockout mice. Blk also plays a role in controlling the cellularity of the thymus during ontogeny and is expressed in lymphoid precursors [35].

Intracellular Compartmentalization of Src Kinase:

Intracellular Migration of Src Kinase to the Nucleus: Remarkably, the acetylated iteration of Src, marked by modifications on Lys5, Lys7, and Lys9, undergoes translocation towards the nucleus. Within this nuclear domain, it establishes a dynamic partnership with STAT3, instigating precise gene regulatory mechanisms and fostering cancer cell proliferation. Furthermore, the acetylated Src variant, characterized by changes at Lys401, Lys423, and Lys427, heightens its intrinsic kinase activity, thereby intensifying its proficiency in enlisting and activating STAT3 [36].

In the context of osteosarcoma, the SaOS-2 cell line, characterized by diminished aggressiveness, manifests a conspicuous nuclear abundance of Src. This phenomenon occurs concomitantly with subdued myristoylation of Src and attenuated expression of N-myristoyltransferase (NMT) enzyme within the cells. Conversely, the 143B osteosarcoma cells, exemplifying heightened metastatic potential, display diminished nuclear accumulation of Src, accompanied by pronounced myristoylation and elevated NMT expression [37].

Src Translocation to the Mitochondrial Domain: The initiation of Src activation by EGF triggers a subsequent phosphorylation event on Tyr845 of EGFR. This molecular cascade culminates in the targeted migration of both Src and EGFR to the mitochondrial precinct. Remarkably, the suppression of Src activity leads to a complete abrogation of EGFR and Src translocation to the mitochondria, underscoring the intricate interplay between these molecules in orchestrating this intracellular event [38]. Within the intricate milieu of mitochondria, the EGFR establishes a binding affinity with the cytochrome C oxidase subunit II (CoxII). This molecular engagement initiates a cascade that involves the phosphorylation of CoxII, eliciting a discernible dampening effect on the activity of complex IV. This, in turn, gives rise to a notable decrease in the levels of ATP production, subsequently impacting cellular energy dynamics.AKAP121 functions as a central scaffold, binding PKA, PTPD1, and Src, where PTPD1 activates Src on AKAP121, driving mitochondrial localization of both PTPD1 and Src [39]."

Role of SFKs in Various diseases:

Role of SFKs in Chronic Pain:

Inflammatory Pain: The activation of immune cells in the peripheral or central nociceptive networks and maladaptive plastic alterations are linked to inflammatory pain [40]. Inducible nitric oxide synthase (iNOS), TNF-α and cyclo-oxygenase (COX)-2 are only a few of the inflammation-related genes that are induced by transcription factors like NF-κB and other factors [41]. NF-κB upstream regulatory molecule, Src, was shown to be phosphorylated in a recent research. Furthermore, *Momordica cochinchinensis* Spreng, popularly known as gac or red melon, can lessen the production of NF-κB, iNOS, and COX-2 in LPS-activated RAW264.7 cells by directly blocking Src/Syk activation [42]. The c-Src/NF-B relationship may therefore constitute a different therapeutic target for the treatment of inflammatory pain. Previous research has demonstrated that improving NMDAR 2B subunit activity in the spinal cord following intradermal injection of CFA required phosphorylation of the NMDAR 2B subunit by Src or Fyn [43, 44]. This mechanism involves a number of transmembrane receptors, including EphBRs, GPCR/protein kinase A (PKA) and GPCR/protein kinase C (PKC) [44, 45]. Furthermore, CFA-induced mechanical allodynia is delayed by intrathecal infusion of the Src inhibitor PP2 [45]. Supraspinal processes appear to be implicated in the involvement of Src in pain transmission in addition to spinal mechanisms. According to this research, ARC Src/GluN2BR activation may be a factor in inflammatory pain [44].

Neuropathic Pain: In the CNS, a pathologically changed state is referred to as neuropathic pain [46]. The symptoms of neuropathic pain include tactile allodynia which is an aberrant pain response to harmless stimuli and hyperalgesia which is an increase in sensitivity to painful stimuli [47, 48]. Treatment of neuropathic pain is still a significant issue in clinical practise despite growing understanding of the processes behind chronic pain [49]. The causes of neuropathic pain of various etiologies have been studied using a variety of animal models, including those for PNI, diabetes, spinal cord injury (SCI) and chemotherapy-induced pain [48, 49]. The importance of SFKs in neuropathic pain brought on by PNI and diabetes has recently come to light, according to a growing body of research [50, 51].

Diabetic Neuropathy: One of the most frequent consequences of diabetes is neuropath which is still an unresolved clinical issue [52]. Due to the fact that the cellular and molecular causes of diabetic neuropathy are largely unclear, it frequently resists the effects of modern analgesics. Increased NMDAR activity has been shown in prior research to significantly contribute to central sensitization in diabetic neuropathy [52, 53]. It has been demonstrated that the widely distributed enzyme protein tyrosine phosphatase 1B (PTP1B) stimulates Src and increases the tyrosine phosphorylation of NMDAR in the spinal cord which aids in the onset of diabetic neuropathy [51].

In addition, siRNA-mediated PTP1B or PTP inhibitor knockdown suppresses Src activity and restores mechanical allodynia in rats that have received STZ injections. These results show that PTP1B exaggerates pain responses via a critical route involving Src/GluN2B signalling. The current data further support the activation of spinal microglia in rats given STZ injections, not only through changes in morphology but also through activation of intracellular signalling involved in microglia activities. When STZ is injected, microglia becomes activated, as demonstrated by Tsuda *et al.* [54] and this process involves the SFK/ERK signalling pathway. Furthermore, intrathecal injection of the ERK activation inhibitor U0126 significantly reduces tactile allodynia in diabetic rats.

Cancer Pain: Both neuropathic and inflammatory pain may include elements in the mechanism of cancer pain, but it also has unique features [55]. Src, a protein tyrosine kinase that is not a receptor is involved in the development of the disease, angiogenesis and metastasis, all of which can cause pain in patients with bone cancer [56]. Osteoclasts, platelets and neurons all have high levels of Src expression [57]. In terms of pain pathology, several studies have shown that Src activation causes the NMDARs to get phosphorylated which in turn phosphorylates the Src causing bone cancer pain. Recombinant IL-18 can cause pain hypersensitivity and the activation of GluN2B as demonstrated by Liu *et al.* in spinal injection to naive rats [56].

Role of SFKs in Cardiovascular diseases:

Hypertension: Ineffective peptide hormones that cause vasoconstriction such as angiotensin II (Ang II), catecholamines and calcium channels are the focus of the principal hypertension treatments now on the market [58]. In the homeostasis and pathophysiology of the cardiovascular system, the bioactive peptide Ang II is essential [59]. A number of cellular signalling pathways according to earlier investigations have been shown to promote vasoconstriction. In order to bind Gq/11 and Gi/o proteins, it activates the AT1 receptor. Ca2+ concentrations in the cytosol rise as a result of activating phospholipase C (PLC). Protein kinase C, ERK1/2, JNK and p38 kinases as well as tyrosine kinases like SFK are all activated as a result [60–63].

Activation of SKF is the first step in Ang II-induced signal transduction, and SKF is crucial for Ang II-induced vascular responses such ERK1/2 activation, cell migration, and proliferation [64–66]. However, it is still unknown how SFK affects arterial contractions and how it contributes to the hypertension brought on by Ang II. Bo Qin et al. discovered that SKF inhibitors SU6656 significantly reduced the level of systemic blood pressure in Ang II-treated animals, which is associated with phosphorylation of the smooth muscle myosin light chain (MLC) in the mesenteric-resistant blood arteries [67]. By activating Yap through Src kinase, Gp130 is a possible therapeutic target to enhance heart regeneration following myocardial damage [68].

Arrhythmia: In addition to various systemic disorders, medicines, food, exercise and a number of structural cardiac abnormalities, arrhythmias frequently occur [69]. Dasatinib and all-trans retinoic acid were combined in a first-phase clinical research with patients who had acute myeloid neoplasms. One negative effect of dasatinib was discovered by Redner *et al.* to be the development of grade 3 QTcprolongations in patients having a history of coronary artery disease and coronary artery bypass grafting [70]. Therefore, it becomes sense to surmise that SFKs and arrhythmia are related. In a study by Lin *et al.,* they investigated the effects of Src, Fyn and Yes on the hyperpolarizing-activated cyclic nucleotide-gated 4 pacemaker channels with its mutant D553N which was discovered in a patient with cardiac arrhythmias. The gating characteristics of D553N were enhanced by the active SFKs Src, Fyn and Yes, as was demonstrated in this work [71]. Through increasing tyrosine phosphorylation in the heart, these three SFKs were able to restore the surface expression of D553N for normal current expression. The validity of SFKs activity in relation to cardiac pacemaker activity has been confirmed by a number of later investigations [72]. Another study found that Src inhibition decreased the internalisation and degradation of connexin 43, a crucial component of gap connections throughout the heart to increase conduction speed and diminish arrhythmia inducibility after MI [73, 74]. As a preview of our future research efforts, it does not here comprehensively explore the precise impact of SFKs on the pathophysiology of arrhythmia. Finding the efficient endogenous regulating mechanism of SFKs to treat cardiac arrhythmias is crucial.

Other Heart diseases: Lck and other SFKs could primarily control CVB3 replication in T cells, dendritic cells, B cells and macrophages, alleviating the viral myocarditis brought on by group B coxsackieviral (CVB) infection in mice [75]. By following the path of its downstream signalling molecules, Opavsky *et al.* discovered that BERK-1/2, a signal protein downstream of Lck may be activated by Lck and other SFKs to complete the effective CVB3 replication in both infected T cells and cardiac myocytes. The creation of medications that specifically interfere with the replication and persistence of this virus in vivo may be made possible by the discovery of SFKs, particularly Lck as an important regulator of CVB3 replication [76].

This would prevent the onset of viral myocarditis. Additionally, it has been shown in studies on hypertrophic cardiomyopathy that Fyn and NADPH oxidase 4 (NOX4) are both present in the perinuclear region of cardiomyocytes. Through their interaction, the N-terminal unique domain of Fyn phosphorylated tyrosine 566 in the C-terminus of NOX4 which in turn negatively regulated NOX4-induced exacerbation of pathological myocardial hypertrophy, Further; several investigations discovered a strong connection between SFKs and the emergence of heart valvular disease [77].

In order to slow down TGF-1-induced myofibroblast activation of dormant aortic valve interstitial cells, a differentiation process linked to calcific aortic valve disease, Hutcheson *et al.* discovered that 5-HT2B antagonism altered the function and spatial location of Src and physically restricted it [78]. In other words, it is not difficult to conclude that SFKs also play a significant role in other cardiovascular disorders in light of the facts mentioned above.

Role of SFKs in nNeurological disorders:

Learning and Memory: It appears that SFKs are crucial for memory and learning. Through modulation of the NMDA receptors, it is hypothesised that a few members of the Src family may be crucial in the control of neuronal plasticity and memory formation [79]. The NMDA receptor's NR2A and NR2B subunits are phosphorylated by Src which strengthens the currents that are generated by the receptor [79, 80]. A cellular model for memory and learning is thought to be the process of inducing long-term potentiation (LTP) in the hippocampus. The application of anti-src1 and the distinct domain peptide fragment Src (40-58) directly into the neurons by diffusional exchange from the patch electrode has been demonstrated to suppress LTP. Along with this, the NMDA receptor conductance was upregulated via Src and NR2B's tyrosine residues were more often phosphorylated [81].

A phosphopeptide (pYEEI peptide) SFK activator which is a ligand for SFK SH2 domains and an antibody, anti-cst1 which inhibit SFKs but not other protein tyrosine kinases have been used to link SFKs to endogenous upregulators of NMDAR activity [79,82]. According to research, Src expression and activity are both elevated in the hippocampal following spatial learning and Src activity is necessary for the correct establishment of one-trial avoidance memory in rats [83]. Furthermore, Fyn knockout mice have problems with hippocampus long-term potentiation and have trouble learning specific kinds of spatial memory. It was discovered that Src family kinase activity is required for memory extinction and reacquisition in the CA1 area of the dorsal hippocampus by utilizing the particular inhibitor of the Src family, PP2 [84]. Further research revealed that blocking the establishment of memory when Src kinase inhibitor (PP2) is injected into the CA1 area of the dorsal hippocampus immediately or 30 minutes after training [83].

Parkinsonism: Parkinsonism has been discovered to be significantly impacted by SFKs. According to research, nicotinic acetylcholine receptor activation protective treatment can slow the progression of neurodegenerative illnesses including parkinson's and alzheimer's through the Src pathway [85]. It was discovered that the src kinase inhibitor PP2 therapy decreased the protective effect of nicotine indicating that Src is involved in the protective effect's mechanism. Src-family protein tyrosine kinase (PTKs) activity in the striatum of parkinsonian rats has been significantly altered as evidenced by the downregulation of the genes encoding Src and Lyn by dopamine deafferentation [86]. Compared to normal mice, Lyn knockout mice showed less spontaneous motor activity [87]. In Lyn knockout mice, the increased NMDA signalling appears to be related to this impairment. The striatum's NMDA receptors are regarded to be a potential target for cutting-edge parkinson's disease treatment strategies since they play a significant role in the motor function [88].

Epilepsy: In epilepsy, aberrant brain activity leads to recurring seizures, strange behaviour, feelings and even unconsciousness. Epilepsy is a chronic central nervous system (neurological) illness [89]. The development of axons and dendrites, variations in receptor compositions, synaptic growth and preservations can all be used to identify an epileptic brain. Cell signalling pathways are in charge of controlling the inflammatory processes [90–94].

The prevention of the establishment of epileptic circuitry and/or the delay of the onset of epilepsy following brain damage is both possible with the inhibition of these pathways. In animal and *in-vitro* models of chronic epilepsy, kinase signalling with activated JAK-STAT, BDNF-TrkB and PI3K-Akt-mTOR pathways has been shown [95–102]. Few kinases have been discovered to yet to have a significant impact on epilepsy [103]. There are a number of kinases that function in glia, neurons and microglia [104], and it's possible that they have a significant impact on epileptogenesis and/or the onset of epilepsy. It is necessary to conduct experiments in order to identify the specificity of

certain kinase inhibitors [105–107]. Only a few kinases such as FGFRs, VEGFRs, Flt, EGFR, Erbb receptors, IGF-1R, c-Met, cFMS, GM-CSFR and PDGFRs as well as several neurotrophin receptors have been investigated for preventing or changing epilepsy due to the availability of inhibitors. The phosphorylation alterations in the epileptic brain and all of the receptor tyrosine kinase described above have been studied in the literature [108–111]. While Src-pY416 expression was considerably reduced in human symptomatic epileptic tissues, total Src protein expression increased as compared to the control group. According to study findings, the NRG1-ErbB4-Src signalling pathway may control the reduced phosphorylation of GluN2B in human symptomatic epileptic tissues [112].

Tuberculosis: In the top 10 global mortality, tuberculosis continues to be a pandemic. Infection with Mycobacterium tuberculosis is estimated to affect 1.7 billion people worldwide or 23% of the world's population, resulting in an annual increase of more than 10 million new cases of TB. Approximately 1.5 million individuals died of TB according to a report by the WHO. However, the lengthy length of therapy and the advent of multidrug-resistant tuberculosis (MDR-TB) significantly heightened the need for the development of more selective new anti-TB medications for successful treatment. According to Chandra *et al.*, Src is essential for defining cellular reactions to Mycobacterium tuberculosis infection. As a result, they draw the conclusion that signalling processes downstream of activated Src (pY416) and upstream of transcriptionally regulated Src would be crucial in determining the process's mechanistic viability [113]. A considerable impact on the survival of the H37Rv, MDR and exceptionally drug-resistant (XDR) strains of Mycobacterium TB has also been demonstrated by investigations on Src inhibition. Src inhibition, which can control TB infection in guinea pigs is similarly important in THP-1 macrophages for lowering survival [114]. In order to develop host-directed anti-TB medications, Src kinase inhibitors were therefore included.

Mammary Gland Development: In order to produce milk, the mammary gland must develop. Numerous stimuli and signalling channels control it. A critical part in cell signalling is played by the Src family of non-receptor tyrosine kinases. In the growth of the mammary gland, Src has been shown to be a crucial signalling modulator. A block in secretory activation that leads in lactation failure was seen in a research by Watkin *et al.*[17] on Src knockout mice. Src appears to be necessary, they conclude, for effective downstream signalling, enhanced prolactin receptor expression, and alveolar cell structure [17, 115]. Additionally, Src is reported to be active in breast tumours, where it is believed to play a crucial role in fostering the malignant phenotype. In breast cancer transgenic mice models, Src activity is also observed to be increased [116]. Therefore, based on the aforementioned investigations, it is determined that the growth of the mammary gland requires a balance in the activation of Src kinase activity.

Hematopoietic disorders: In general, a number of factors control hematopoiesis (growth hormones). In hematopoiesis, SFKs may play a significant role. SFKs are discovered to be involved in a number of cellular processes that lead to the formation of hematopoietic cells. Lyn, Hck, Lck and Blk are among the SFKs that are said to be particularly expressed in hematopoietic cells whereas Src, Yes, Fgr and Fyn are SFKs that are widely expressed. Study of knock-out animals that have displayed distinct deficits in either the growth or function of hematopoietic cells has provided direct proof that SFKs are involved in hematopoiesis [117].

B-cells are where Blk and Lyn are largely expressed. While Lyn is necessary for typical B-cell growth and communication, any interruption of the gene producing Blk does not result in any B cell abnormality. Peripheral B-cell numbers in Lyn knockout mice were reported to have dropped (by more than 50%) [24]. Lyn deletion mice have B-cells that are hyper-responsive to B-cell signalling. According to theory, this causes aberrant B-cell growth which in turn triggers the creation of self-antibodies and the emergence of an autoimmune illness [118]. Specifically in T cells, Lck and Fyn are expressed. The proper growth and operation of thymocytes are hampered by any alteration to the genes that encode this SFKs. Thymocyte formation is slowed down when the Lck gene is disrupted. Along with T-cell receptor (TCR) signalling, Lck activity is also necessary for T-cell development [119]. When functional Lck is reintroduced into T cells that are nonresponsive to TCR stimulation

because of a deficiency in functional Lck expression, the T cells' functions may return. Furthermore, the Fyn (T) T-cell-specific isoform exhibits normal thymocyte development despite deficient TCR signalling. None of the hematopoiesis-related defects in Hck and Fgr knockout mice were particularly pronounced. The production of reactive oxygen species and degranulation in neutrophils derived from Hck and Fgr knockout mice are both shown to be defective [120].

Chronic kidney diseases: A growing global public health concern is CKD [121]. The therapies that are currently used to treat CKD are unsuccessful. Therefore, identifying and evaluating novel treatment targets is essential to researching effective and secure solutions. In-depth investigations of the pathophysiology of CKD's several important signal routes and mediators have been published in recent decades [122, 123].

Transforming growth factor-b1 (TGF-b1) and Ang II are among the several factors that have so far been identified as powerful fibrogenic mediators. The therapeutic efficiency of these elements however, is insufficient as evidenced by their pharmacological limitations. Src kinase is activated in kidney fibroblasts in response to TGF-b1 or serum, and the fibrotic kidney following unilateral ureteral obstructions, according to Yan *et al.* [124]. After unilateral ureteral obstructions, renal fibrosis is alleviated (in vivo) by blocking Src with PP1 or silencing it with small interfering RNA (siRNA). TGFb1/Smad3 and epidermal growth factor receptor (EGFR) signalling appear to be interrupted by Src inhibition caused by PP1. This work demonstrates that Src kinase functions as an integrator of various fibrogenic signals brought on by the activation of many membrane receptors. Activation of the Ang II receptor can trigger Src activation, according to Chen *et al.* [125]. It controls the TGF-induced production of EGFR and its ongoing phosphorylation. As a result, Src could be a new target for therapeutic intervention in fibrotic CKD.

Src Kinase Inhibitors: The Src proto-oncogene, sometimes known as the "sarcoma gene," is a transcription factor that might possibly cause certain cells to undergo malignant changes. Src inhibitors are a class of inhibitors that target the Src kinase family of tyrosine kinase.

Dasatinib: Chronic myeloid leukemia and Philadelphia chromosome acute lymphoblastic leukemia are both diseases that can be treated with dasatinib, a once-daily oral tyrosine kinase inhibitor. Dasatinib is rapidly absorbed and takes 0.25 to 1.5 hours for its concentration in the blood to reach its maximum level. Food has little effect on oral absorption. The absolute bioavailability of dasatinib in humans remains unknown due to the absence of an intravenous formulation that would allow the calculation of a reference exposure [126, 127]. With a terminal half-life of 3–4 hours, dasatinib is eliminated by cytochrome P450 (CYP) 3A4-mediated metabolism [127]. Only 20% of an oral dose (100 mg), based on total radioactivity is recovered after 168 hours in unchanged faeces (19%, including probable non-absorption), urine (1%) or both. Age (including toddlers and people up to 86 years of age), race, and renal insufficiency had no effect on the pharmacokinetics of dasatinib. Antacids, H2-receptor blockers and proton pump inhibitors are pH-adjusting agents that reduce the absorption of dasatinib. Dasatinib may also interact with inducers or inhibitors of CYP3A4 [128].

Saracatinib: Another ATP-competitive SRC and SFK inhibitor, saracatinib (formerly AZD0530; AstraZeneca) is active against ABL and activated mutant versions of EGFR (L858R and L861Q) [129, 130]. Four cell lines (derived from colon, prostate and lung cancer) in a panel of 13 human cancer cell lines treated with saracatinib showed submicromolar growth suppression and inhibitory effects on migration and invasion [131, 132]. Saracatinib reduced FAK, paxillin and STAT3 activity along with the development of 3 of 16 human-derived pancreatic cancer xenografts in-vivo. In addition, to predict growth inhibition in an independent sample of eight xenografts, researchers generated and validated a gene expression profile based on LRRC19 and IGFBP2 expression, which demonstrated 100% sensitivity and 83% specificity [133]. In addition, saracatinibhas demonstrated activity in *in-vitro* and *in-vivo* models of castration-resistant prostate cancer (CRPC) [134].

Ponatinib: A third-generation kinase inhibitor called ponatinib is designed to correct the

intermediate T315I mutation. ABL1 mutations and the native BCR-ABL1 kinase were inhibited by this drug in several experiments. Since imatinib is no longer recommended for the treatment of chronic myeloid leukemia (CML) or for patients with the T315I mutation, ponatinib is now approved for the treatment of CML in all stages of the disease that are resistant to dasatinib and nilotinib. Ph+ acute lymphoblastic leukemia (ALL) is another indication for treatment. Thrombotic cardiovascular events occurred in 2013 leading to temporary discontinuation of ponatinib. Since then, other researchers have examined the baseline characteristics of patients before ponatinib administration, particularly the cardiovascular profile [135].

Imatinib: The tyrosine kinase inhibitor imatinib is also known by its experimental designation STI-571 and is marketed by Novartis under the trade names Gleevec (in Canada, South Africa and the United States) and Glivec (in Australia, Europe and Latin America). Imatinib is absorbed after oral administration and after a brief interaction with P-glycoprotein (P-gp) on the membrane of intestinal epithelial cells, it moves into the intestinal lumen. Organic cation transporter 1 (OCT1) transports imatinib to hepatocytes in the liver where the hepatic enzyme cytochrome P450 (CYP) 3A4 can continue to convert imatinib to N-desmethyl. Then, a portion of imatinib and N-desmethylimatinib is glucuronidated to O- or N-glucuronides by UDP-glucuronosyltransferases [136]. Breast cancer resistance protein (BCRP) located in the hepatocyte apical membrane and facilitates transport from hepatocytes to bile. Colonic bacterial glucuronidases can convert imatinib and N-desmethyl imatinib glucuronides back to their original formsimatinib and N-desmethylimatinib during enterohepatic recirculation. Imatinib has an oral bioavailability of 98.3% [137].

Nilotinib: Second-generation TKIs with increased activity against imatinib-resistant mutant BCR-ABL1 cells include nilotinib and dasatinib. The target range of nilotinib and imatinib is comparable although nilotinib is 30-fold more potent against BCR-ABL1 (type 2 inhibition) *in-vitro* [138]. It can kill certain CML cells with ABL1 domain mutations that are resistant to imatinib[139]. It has a major molecular response (MMR) and a deep molecular response (DMR defined as a 4.0 log decrease in BCR-ABL1 transcript (MR4.0) or greater) of 77 and 66% at 5 years and 82.6% and 73% at 10 years, respectively in TKI-naive patients with CML CP [140, 141]. Nilotinib is known to increase the risk of cardiovascular events (CVEs) such as heart failure, arrhythmias, QT prolongation and coronary heart disease. In light of this, nilotinib is contraindicated in individuals with a history of cerebrovascular events, ischemic heart disease or peripheral arterio-occlusive disease [142] and should be administered with caution to patients with metabolic or cardiovascular comorbidities such as diabetes mellitus.

The ability of nilotinib to accelerate atherosclerotic processes and increase the risk of cardiovascular damage is not fully known. In contrast to cardiomyopathy, frequent hyperglycemia and dyslipidemia with nilotinib may promote the development of atherosclerosis and coronary artery disease. In addition, there is evidence that it increases the risk of pancreatitis. In patients receiving nilotinib 400 mg twice daily for 5 years [141], coronary heart disease was 3–4 degrees recorded in 6.1% and cerebrovascular disease in 2.2%.

Bosutinib: BCR-ABL1 (type 1 inhibition) and SRC family kinases are the main targets of the 2nd generation TKI bosutinib. Compared to imatinib, it is 200 times more effective in inhibiting ABL1 kinase [143, 144]. According to the current BFORE investigation, bosutinib had a higher MMR rate at 1 year compared to imatinib in the context of first-line CML CP [145]. Except for more frequent diarrhea and liver damage with bosutinib, the toxicity profiles of the two TKIs were not statistically different. Bosutinib, which increases the amount of circulating serotonin, inhibits the serotonin reuptake transporter (SERT), which is associated with diarrhea[146].Elevated liver enzymes are also often seen, especially early in bosutinib treatment, but they can last longer than 12 months [147] and force some patients to stop taking the medication.

Notably, bosutinib inhibits other molecules linked to cell cycle control and calcium/calmodulin-dependent protein kinases (CAMK) but lacks clinically meaningful efficacy against KIT or PDGFRA [148, 149]. Investigations into long-term

effectiveness and adverse event characteristics are still ongoing.

Trametinib: A second-generation small molecule inhibitor of MEK kinase is trametinib (GSK1120212, JTP-74057). It works as an allosteric, ATP-uncompetitive inhibitor with nano-molar action against both MEK 1 and MEK 2 kinases with a half-maximal inhibitory dose of 0.7-14.9 nmol/L for MEK1/MEK2 [150, 151]. Prior to trametinib, MEK inhibitors had limited clinical activity because non-malignant cells were dependent on the MAPK pathway, making it difficult to administer an adequate dose of the inhibitor. Inhibitors of MEK1/2 had been previously investigated as targeted therapies for tumours dependent on activating mutations in the MAPK pathway [152, 153].

Trametinib has a different pharmacokinetic profile compared to other MEK inhibitors that have been reported with a prolonged half-life and low peak-to-trough ratios which allowed it to overcome the limited therapeutic index of the MEK inhibitor. A panel of more than 180 kinases including B-Raf, C-Raf and MEK5, the closest kinase homolog to the active site and defined on one side by an activation loop was used to demonstrate drug specificity for MEK1/2. Trametinib has been shown to suppress p-ERK 1/2 which in turn inhibits cell proliferation. Consequently, tumor cell lines containing mutant B-RAF or Ras had the greatest inhibition [150]. According to *in-vitro* research, trametinib inhibits cell growth, arrests the G1 cell cycle and triggers apoptosis.

Tirbanibulin: Athenex, Inc. (previously Kinex Pharmaceuticals) and international partners are developing tirbanibulin, a first-in-class Src kinase signalling inhibitor and tubulin polymerization inhibitor for the topical treatment of actinic keratosis and psoriasis. Src activity has been related to actinic keratosis and squamous cell carcinoma and elevated levels of Src have been demonstrated to play a role in both primary tumour growth and metastasis [154]. As a result, tubulin polymerization inhibitors may be able to treat actinic keratosis. There are no active studies examining oral tirbanibulin at the moment, however it has been studied in early phase clinical trials in patients with a variety of malignancies including acute myeloid leukaemia [155], prostate cancer [156] and other solid tumours [157].

CONCLUSION: In addition to their physiological roles in hematopoiesis, mammary gland development, learning, and memory, SFKs have pathophysiological roles in a number of illnesses, including cancer and several neurological conditions. Thus, SFKs are becoming novel pharmaceutical targets, and in the near future, SFK inhibitors may offer new therapeutic options for a variety of diseases like cancer, epilepsy, and Parkinsonism. Therefore, more focused and therapeutically applicable medicines targeting SFKs should be used in future broad exploratory research and clinical trials.

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