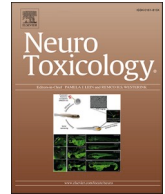




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Review

The role of the tyrosine kinase Lyn in allergy and cancer

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ABSTRACT

With worsening air pollution brought by global social development, the prevalence of allergic diseases has increased dramatically in the past few decades. The novel Lck/yes-related protein tyrosine kinase (Lyn) belongs to the Src kinase family (SFK) and plays a pivotal role in the pathogenesis of inflammation, tumor, and allergy. This signaling molecule is vital in the IgE/FcεRI signaling pathway that regulates allergy. The Lyn–FcεRIβ interaction is essential for mast cell activation. The signaling pathway of Lyn has become the focus of immune, inflammatory, tumor, and allergy research. This molecule has positive and negative regulatory effects, which have attracted researchers' attention. This paper reviews the basic characteristics of Lyn and its regulatory mechanism and role in tumor and other diseases, specifically in allergies.

1. Introduction

Lck/yes-related (Lyn) protein tyrosine kinase (PTK) is a member of the Src family, one the largest groups of nonreceptor tyrosine kinases (Ge et al., 2020). This molecule is mainly expressed in myeloid cells, B cells, and hematopoietic cells, including hematopoietic progenitor cells, platelets, and red blood cells (Castro-Ochoa et al., 2019; Siveen et al., 2018; Uhlén et al., 2015). Lyn participates in cell proliferation, differentiation, apoptosis, migration, and metabolism and plays an important role in inflammation and tumorigenesis (Ingley, 2012). With the increasing incidences of allergy, tumors, and other diseases, the function and mechanism of Lyn have attracted attention.

Immunoglobulin E (IGE) and its high affinity receptor (FcεRI) signaling pathway is vital for the regulation of allergic reactions. Lyn is an important signaling molecule with positive and negative regulatory effects on the IgE/FcεRI signaling pathway. This molecule also controls allergy. The Lyn–FcεRIβ interaction is essential for mast cell (MC) activation, and the underlying coordination mechanism must be further studied (Qian et al., 2019).

This article introduces the basic characteristics of Lyn and its regulatory mechanism and role of Lyn in related diseases, particularly in allergic reactions. This paper lays a foundation for future research and application of Lyn and provides a reference for the treatment of Lyn-

related diseases.

2. Basic characteristics of Lyn

Lyn belongs to the Src family, which shares a modular structure composed of an N-terminal with attachment sites for fatty acid modification, a unique domain, a Src-homology 3 (SH3) domain, a Src-homology 2 (SH2) domain, a tyrosine kinase domain, and a C-terminal kinase inhibitory domain (Kraskouskaya et al., 2013; Machiyama et al., 2015; Roskoski, 2015) (Fig. 1). Src kinases bind to the cytoplasmic portion of the surface receptor and participate in diverse signaling pathways. These molecules regulate the chromatin recombination and transcriptional activity of transcription factors and are involved in the carcinogenic transformation of tumor cells by inhibiting some tumor suppressor factors (Bagnato et al., 2020).

The structure of Lyn gene from N-terminal to C-terminal successively comprises SH4, SH3, and SH2 domains, and the tail contains a conserved tyrosine residues. SH4 is critical to the membrane target of the kinases (Ikeda et al., 2009), and the highly conserved SH2 and SH3 are necessary to regulate kinase activity and mediate the protein–protein phase in cell signaling cascade interaction. SH3 is composed of 60 amino acid residues that can recognize and bind to proline-rich sequences and then mediate SFK-substrate or intramolecular interaction. The SH2 domain is

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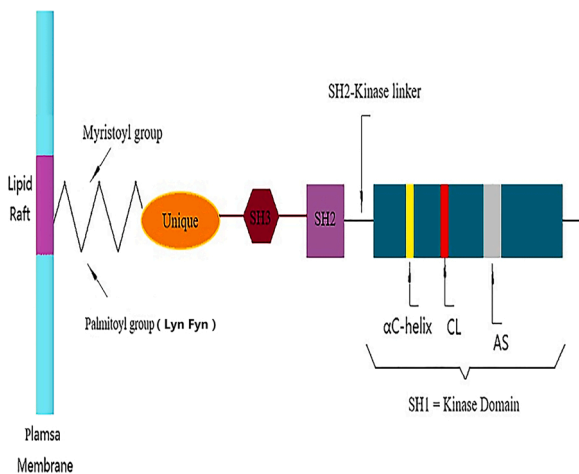


Fig. 1. Domain structure of Src family kinases. Src family kinases are myristylated and palmitoylated localizing it to lipid rafts within the plasma membrane. From N-terminal to C-terminal, Src contains an N-terminal myristoyl group, a unique domain, an SH3 domain, an SH2 domain, an SH2 kinase linker, a protein tyrosine kinase domain (SH1) and a C-terminal adjustment section. In addition, Lyn and Fyn may contain one or two palmitoyl groups at the N-terminus, respectively. SH3 controls the dynamics of Src at the cell membrane, SH2 SH2 recognizes and binds the peptide sequence of tyrosine phosphorylation on its target protein, which mediates the interaction between proteins in the cell. CL, catalytic loop; AS, activation segment.

composed of 100 amino acid residues that can bind to phosphorylated tyrosine residues on either its C-terminal regulatory domain or other proteins (Gangopadhyay et al., 2020; Roskoski, 2015).

The activity of Lyn is regulated by Csk and CD45. In resting-state cells, activated Lyn phosphorylates the Y314 site of lipid raft binding protein Cbp, which induces the binding and membrane localization of Csk that is normally localized in the cytoplasm. Csk can target the negative regulatory tyrosine residue at the C-terminal of Src kinases and phosphorylates the Y508 site of Lyn. This site then binds to its own SH2 domain to close the structure of Lyn. Upon FcεRI stimulation, CD45 dephosphorylates Y508 site, thus allowing the SH2 domain to bind to the receptor (Kovarova et al., 2006). The phosphorylation level of Y397 increases when the structure of Lyn is opened, thus enhancing the activity of Lyn and maintaining its open structure (Gilfillan and Rivera, 2009). The activated Lyn binds and phosphorylates the substrate protein with tyrosine residues, thereby further regulating the affinity of specific substrate through SH2 domain phosphorylation (Jin et al., 2015). The key substrates of Lyn include the near-end membrane-bound cell surface receptors that contain either the immunoreceptor tyrosine-based activation motif (ITAM) or immunoreceptor tyrosine-based inhibition motif (ITIM) in their cytoplasmic tails (Liu et al., 2017; Waterman and Cambier, 2010). Phosphorylation of ITAM and ITIM leads to the recruitment and activation of other kinases, phosphatases, and connective proteins and consequently enhance or inhibit downstream signal transduction. Acylation, anchoring to the plasma membrane, and Lyn activation are also related to the cyclodextrin consumption of cholesterol (Oneyama et al., 2009).

3. Lyn regulatory mechanism

3.1. Positive regulatory mechanism of Lyn

Researchers aim to determine the function of PTKs from the Src family and reveal their increasingly complex role in controlling MC activation. Given its lack of intrinsic kinase activity, FcεRI connects with kinase as a prerequisite for signal transduction to induce MC response (Beavitt et al., 2005; Draber et al., 2016). After FcεRI cross-linking, Lyn initiates the signal pathway of FcεRI (Wilson et al., 2002) and thus is the

most critical signal molecule for signal initiation.

The IgE/FcεRI signal transduction is initiated by co-localization with Lyn in ordered lipid regions (Shelby et al., 2016), and actin cytoskeletons can regulate this functional interaction (Wakefield et al., 2017). In the resting state, a small fraction of Lyn weakly interacts with FcεRIβ subunits, and the exclusion of Lyn from lipid rafts modestly affects FcεRI phosphorylation. After antigen stimulation, Lyn SH2 domain binds to the phosphorylated Y219 in FcεRIβ-ITAM (Furumoto et al., 2004; Kovarova et al., 2006). Hence, the interaction between Lyn and FcεRI is greatly enhanced. This kinase also positively regulates the biological outcomes of FcεRI aggregation in low intensity stimulations (Xiao et al., 2005). The interaction between Lyn and Y219 is the key to maintain the phosphorylation of the receptor, that is, Lyn phosphorylates FcεRI β and γ subunit ITAMs. The ITAMs on the phosphorylated γ chain provide the binding site for PTK72SYK kinase and activate the kinase (Wilson et al., 2002). Therefore, the activity of Lyn is important for the phosphorylation of tyrosine residues in ITAMs. Phosphorylated FcεRI γ recruits and activates Syk and further binds to downstream signal molecules. This phenomenon leads to the release of bioactive substances (vasoactive substances and inflammatory factors) and physiological disorders in the body, such as Ca²⁺ release, degranulation, transcription factor production, actin rearrangement, and chemotaxis, but not to tissue cell damage and chemotaxis. In a model of zebrafish larvae, Lyn acted as a redox sensor in neutrophils (Yoo et al., 2011).

Non-oxidized DJ-1 directly binds to Lyn in lipid rafts after MC activation. The activity of Lyn is subsequently increased, signal transduction is initiated. Oxidized DJ-1 can reduce the activity of SHP-2 and promote that of Syk (Kim et al., 2018). In addition, the p85 regulatory subunit of PI3K can interact with Lyn through the adaptor protein. The activated Lyn phosphorylates Cbl and provides the p85 binding site, therefore stabilizing the complex and activating PI3K (Congleton et al., 2014). Hence, the Lyn-PI3K-BTK signal is indispensable for CD180 inhibition on IFN-α signal transduction (You et al., 2017). Studies on the activation pathway of Lyn in cells are conducive to the discovery of new targets and have importance for the targeted treatment of allergic diseases.

3.2. Negative regulatory mechanism of Lyn

Although Lyn is the activator of the signal pathway, it also has the ability to phosphorylate inhibitory molecules and negatively regulate the signal pathway (Nishizumi et al., 1998) and the activity of PI3K (Xu et al., 2012). Some studies have described the opposite roles of Lyn after MC activation with high or low intensity: low-intensity stimulation inhibits the activity of Lyn kinase and its association with FcεRI receptor, whereas high-intensity stimulation has the opposite effect (Hong et al., 2007). B cells exhibit hyperresponsiveness in Lyn-deficient mice (Lyn-/-) (Tsantikos et al., 2010). Lyn has two main negative regulation mechanisms. When this molecule is strongly stimulated, the microdomains in lipid rafts are over aggregated, which induce the negative regulatory ability of Lyn for inflammatory reactions. The Lyn in the lipid rafts phosphorylates Csk, which in turn specifically phosphorylates Fyn Y525; this phenomenon leads to Fyn inactivation by inducing a closed conformation (Liu et al., 2017). In this process, Lyn plays an indirect negative role in regulating Fyn. Csk controls the activity of Fyn, and the absence of the latter leads to control loss on Fyn and hyper-responsiveness for MCs. PAG, a receptor related to CSK, can also be phosphorylated by Lyn and Fyn and plays a dual regulatory role in the IgE/FcεRI signaling pathway (Ohtake et al., 2002; Polakovicova et al., 2014). Lyn interacts with Fyn in the Src family and has a certain relationship with Hck. The lack of Hck increases the activity of Lyn and the phosphorylation level of FcεRI, but a reduction in the degranulation and phosphorylation of Syk does not affect the calcium response (Gilfillan and Rivera, 2009). SFKs show a hierarchical relationship, that is, HCK inhibits Lyn, which in turn inhibits Fyn.

In addition to ITAM motifs, Lyn can phosphorylate receptors with ITIM motif, such as CD22, FcγRIIB, PIR-B, PD-1, CD66a (CEACAM1),

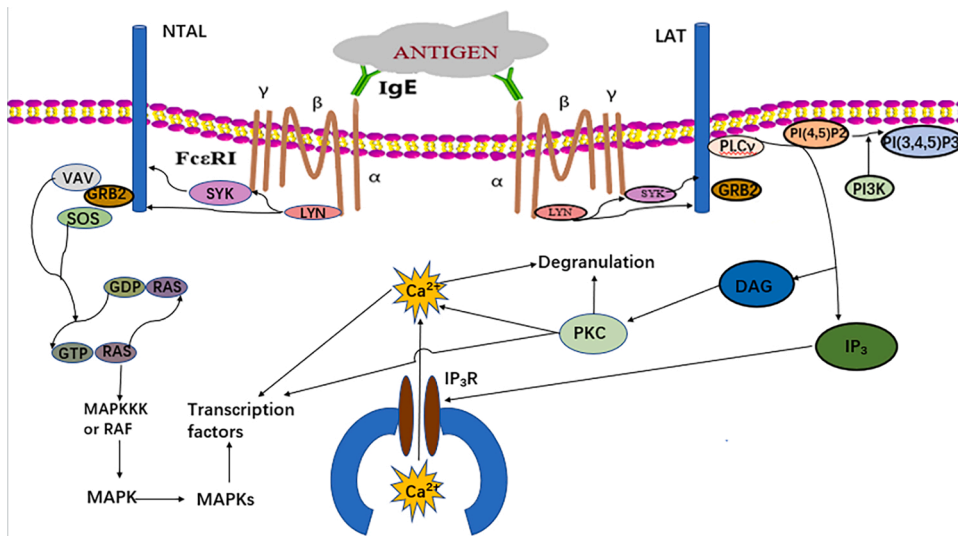


Fig. 2. The role of Lyn in IgE/FcεRI signal pathway in mast cells. Mast cells are activated when two or more FcεRI are cross-linked to IgE. After the aggregation of FcεRI, Lyn is activated and phosphorylates β chain and γ chain of FcεRI. In turn, the phosphorylation of the β chain and γ chain activates Lyn and Syk. Syk phosphorylates the transmembrane adapter proteins NTAL and LAT to create binding sites for some proteins, such as PI3K. PI3K phosphorylates PI(4, 5)P₂, and generates PI(3,4,5)P₃. PLC γ hydrolyzes PI(4,5)P₂ to produce diacylglycerol (DAG) and IP₃. IP₃ binds to the IP₃ receptor (IP₃R) on the endoplasmic reticulum, and the release of Ca²⁺ from the endoplasmic reticulum causes degranulation. Phosphorylation of NTAL and LAT directly or indirectly binds Grb2, exchange factor and junction molecules VAV and SOS (SON of Sevenless homologues), thereby activating the ras-raf-mitogen-activated protein kinase (MAPK) pathway and producing cytokines.

CD5, and CD72. These receptors can bind and activate non-receptor SH2 tyrosine phosphatase 1 and 2 (SHP-1 and SHP-2) (Adachi et al., 1998; Nishizumi et al., 1998; Ochi and Watanabe, 2000; Okazaki et al., 2001; Pereira and Lowell, 2003). SHP-1 belongs to inhibitory phosphatase, and its tyrosine 536 phosphorylated by Lyn activates the phosphatase-promoting inhibitory signaling through the immunoreceptor (Mkaddem et al., 2017). In the absence of Lyn, the activity of SHP-1 decreases and the concentration of intracellular PIP3 increases. As a result, the degranulation level of cells and the risk of diseases such as nephritis and arthritis increase, and other cell reactions occur. Furthermore, downregulating PTEN can increase the PIP3 level and enhance the degranulation and cytokines (Furumoto et al., 2006). Therefore, Lyn controls the PIP3 level, suppresses the extent of a MC response, and prevents the occurrence of signal transduction in autoimmune cases.

The role of Lyn in B cells involves the fine-tuning of BCR signaling, that is, balancing positive and negative signals to maintain tolerance to self-antigens while permitting responsiveness to foreign antigens (Brodie et al., 2018). Although the positive regulatory effect of Lyn is important, it can be compensated by other SFK members. However, Lyn is unique due to its negative feedback effect. Lyn regulates the downstream signaling molecules and limits SFK activity (Nishizumi et al., 1998; Smith et al., 1998).

4. Research progress on Lyn-related diseases

4.1. Lyn participates in allergic signaling network

Cell signaling regulates the immune system. Adaptive immune responses are controlled by immunoreceptors, which include the T cell receptor, B cell antigen receptor (BCR), and high-affinity receptor for IgE (FcεRI) (Chylek et al., 2014). MCs play a critical role in allergic disorders. IgE and FcεRI signaling pathways regulate allergic reactions and are important components of acquired immune system. During allergy, MCs exposed to antigens induce the IgE cross-linking of adjacent FcεRI binding and the aggregation of FcεRI on the surface. When FcεRI aggregation reaches specific time and intensity, it triggers MCs and basophils to initiate complex signal transduction and then secrete various bioactive products (Galli and Tsai, 2012). MCs can be used as a target for proinflammatory and anti-inflammatory cytokines. Interleukin-1 (IL-1) is a classic cytokine that mediates inflammatory responses. IL-1 activates MCs to release inflammatory chemical mediators and cytokines/chemokines, induce IL-33 in MCs, and amplify allergic reactions. As an anti-inflammatory cytokine, IL-37 can inhibit

IL-1 and IL-33. IL-36 is also a powerful cytokine with pro-inflammatory activity, and its combination with IL-38 can inhibit its pro-inflammatory activity (Caraffa et al., 2019b; Conti et al., 2020; Gallenga et al., 2019). Kritas et al. (2019) first proposed that coronavirus inflammation might be inhibited by anti-inflammatory cytokines belonging to the IL-1 family. Studying the mechanism of IgE-dependent MC activation is the key to understanding abnormal regulation and the small molecular inhibitors that inhibit MC activation. Lyn, Fyn, HCK, and FGR mainly exist in inflammatory cells and are involved in the early stages of FcεRI signaling (Draber et al., 2016) (Fig. 2). The receptor-proximal signaling events of signaling pathway are preferable as drug targets. Lyn exhibits this characteristic and also has positive and negative regulatory effects on the signal pathway. In animal models of conjunctivitis, quercetin as a Lyn kinase inhibitor prevents Lyn/PLCγ/IP3R-Ca, Lyn/ERK1/2, and Lyn/NF-κB signaling pathways to weaken the inflammatory response (Ding et al., 2020).

4.2. Research progress on allergic-related diseases that involve Lyn

Lyn-deficient mice are prone to specific allergic diseases, such as nephritis and arthritis; however, passive cutaneous anaphylaxis does not easily occur, and passive systemic anaphylaxis has a certain correlation with the age of mice (Odom et al., 2004).

Studies on asthma-related diseases revealed that Lyn is associated with high asthma severity in mouse models. This enzyme ameliorates airway mucus hypersecretion by down-regulating STAT6 and binding to the MUC5AC promoter and then regulates mucus thrombus and airflow obstruction related to severe asthma phenotype (Wang et al., 2017). In addition, Lyn is a key molecule of highly expressed blood eosinophils and airway in humans, which may aggravate airway inflammatory (Zhu and Bertics, 2011). This molecule is also associated with TGF-β in chronic myeloid leukemia, but the specific regulatory mechanism is still unclear (Li et al., 2013; Smith et al., 2012). A study on the effects of cigarette on asthma found that Lyn kinase is a SRC kinase that controls GATA-3 and induces TH2 cell differentiation and increases the susceptibility of epithelial cells and their response to cigarette smoke extracts (Lefaudeaux et al., 2017).

4.3. Research progress on Lyn and tumor pathogenesis

In gastric cancer progression, mRNA and protein expression levels are mainly elevated by Src and Lyn kinases, which play a key role in tumor progression and metastasis (Da Costa et al., 2018). Lyn is mainly involved in the study of allergy and has been recently found to regulate

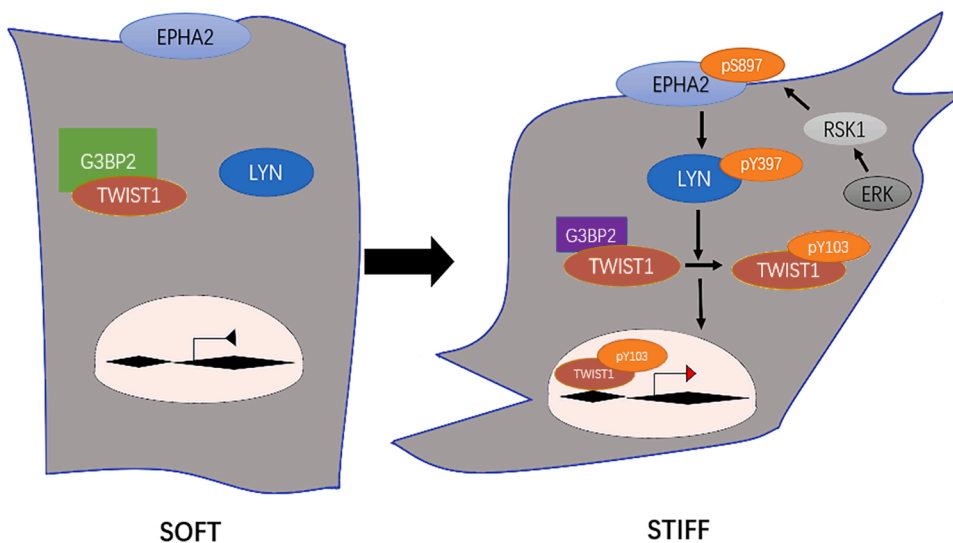


Fig. 3. Schematic model of the EPHA2/LYN/TWIST1 mechanotransduction pathway. High matrix stiffness activates ERK/RSK1 mediated EPHA2 non-canonical signaling. S897 phosphorylation of EphA2 activates Lyn and phosphorylates Y397. Y397 tightly controls Lyn conformation and accessibility to substrates. LYN phosphorylates the EMT(epithelial-to-mesenchymal transition) transcription factor TWIST1 on Y103 to release TWIST1 from its cytoplasmic anchor G3BP2 to enter the nucleus, thus triggering EMT and invasion.

the occurrence and migration of various tumors. The non-receptor Lyn controls cell proliferation and inhibits apoptosis (Kumar et al., 2015). This enzyme is also abnormally expressed in various tumors, such as breast cancer, prostate cancer, and lung cancer (Huang et al., 2013; Tabariès et al., 2015; Wang et al., 2015). In lung cancer, Lyn can activate the PI3K/AKT signaling pathway and enhance the activation of epidermal growth factor receptor and cell viability (Sutton et al., 2013). Hence, its controlled expression can be used as a new target for the treatment of lung cancer.

Lyn up-regulation in paracancerous tissues can promote the expression of oncogenes and the proliferation, migration, and invasion of cancer cells. In human breast cancer samples, Yang first discovered a mechanosensitive EPHA2/LYN protein complex that regulates epithelial-to-mesenchymal transition and metastasis in response to the increased extracellular matrix stiffness during tumor progression (Fattet et al., 2020) (Fig. 3). Lyn can cause B-lymphoblastic and myeloid leukemias by phosphorylating the proto-oncoprotein Cbl (Shen et al., 2018). Its constitutive activation can also increase the phosphorylation of transcription factor STAT5 and contribute to malignancy development (Wang et al., 2014). Therefore, the use of Lyn inhibitors can induce a corresponding inhibitory effect. In cervical cancer cells, Lyn is over-expressed, interacts with receptor tyrosine kinase erythropoietin-producing human hepatocellular receptor A4 (EphA4) protein. This enzyme also induces the chemotherapy resistance of Caski cells through a pathway involving reactive oxygen species. Thus, the underlying mechanism can be used as basis in developing new potential drug targets for chemotherapy resistance (Kina et al., 2018). Immunotherapy to induce tumor-antigen-specific immune responses is a current hotspot in tumor research. For example, Chang et al. studied the specific immunotherapy of melanoma and develop a treatment based on antigen-specific immune response (Chang and Xia, 2015). Lyn is highly correlated with the occurrence and development of tumor and could be key therapeutic target for this disease.

4.4. Role of Lyn in other diseases

Lyn has a strong effect on the immune cell signaling pathways and regulates the development and function of cells. This enzyme is an important sensor of autoimmune diseases such as psoriasis and systemic lupus erythematosus (SLE) (Ingley, 2012). SLE is a heterogeneous disease caused by genetic and environmental factors and mainly develops due to the spontaneous response of B cells to continuously produce various antibodies; hence, B cell disorder is crucial in SLE (Caraffa et al., 2019a; De Groof et al., 2020; You et al., 2017).

Lyn also has effects on diabetes and nervous system diseases. When the cholesterol content decreases, this enzyme can be activated as a membrane cholesterol sensor to regulate the expression of eNOS protein, which enhances the tube formation and migration of endothelial progenitor cells and participates in diabetes-associated vascular diseases (Shi et al., 2018). A study revealed that under chorea-acanthocytosis, Lyn phosphorylation substantially increases, and VPS13A is involved in the Lyn-mediated phosphorylation of the membrane proteins of red blood cells (Peikert et al., 2018).

Although several Src family inhibitors are discovered, the lack of structural data on this enzyme hinders the research and development of Lyn-specific inhibitors. Lyn is an important signal molecule in IgE/FcεRI signaling pathway and plays a pivotal role in the pathogenesis of inflammation, tumor, and allergy (Williams et al., 2009). Future studies should focus on the crystal structure of the non-ligand form of Lyn domain to quickly and effectively develop Lyn-specific inhibitors.

5. Conclusion and future perspectives

As an important signal molecule in immune response, PTK Lyn has multiple domain with different functions (Gangopadhyay et al., 2020). This enzyme has an important influence on the initiation of IgE/FcεRI signaling pathway and participates in cell proliferation, differentiation, apoptosis, migration, and metabolism. Lyn is also crucial in negative feedback. This molecule regulates downstream signaling molecules and limits the activity of SFKs (Odom et al., 2004). Lyn is directly or indirectly involved in various diseases and is related to autoimmune diseases such as psoriasis and systemic lupus erythematosus (Ingley, 2012). The effective application of Lyn inhibitor Bafetinib provides a direction for the treatment of Lyn-related tumor diseases (Yokota et al., 2007). Further research and applications must consider its role in the treatment of tumor diseases and focus on the crystal structure of the non-ligand form of Lyn domain to effectively develop specific inhibitors.

The specific mechanisms of Lyn in tumors and its interactions are still not fully understood. Hence, effective treatments cannot be developed. This situation requires a strengthened research with powerful new approaches, such as transcriptomics, bioinformatics analysis of proteomics, and protein-protein interaction networks in molecular biology.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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