·REVIEW·

Functions of Spleen Tyrosine Kinase (Syk) Gene and Its Correlation to Neoplasms

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[ABSTRACT] Spleen tyrosine kinase (Syk) was thought to be a hematopoietic cell-specific signaling molecule and plays an essential role in maturation of lymphocytes and activation of immune cells. Recent evidences show that it is also expressed by many non-hematopoietic cell types. Down-regulation of Syk expression was first observed during breast cancer progression, now its abnormal expression has also been detected in many other types of tumors. Syk could suppress tumorigenesis and metastasis, but the molecular mechanism remains unknown. Promoter hypermethylation is one of the mechanisms that lead to silencing of Syk gene. Increasing clinical evidences reveal a positive correlation of reduced Syk expression to increased risk for metastasis, and indicate that Syk may be a potential new tumor suppressor.

KEYWORDS: Tyrosine kinase; Syk; Neoplasms; Tumor suppressor

The spleen tyrosine kinase (Syk) gene was originally cloned from porcine spleen cDNA by Japanese scholars Taniguchi *et al.* in 1991 [1]. Its coding protein is a kind of non-receptor tyrosine kinase. Syk was first studied in hematopoietic cells exclusively, especially in immunologic cells. In these cells, Syk is involved in the immunoreceptor tyrosine-based activation motifs (ITAMs) mediated signaling transduction and is closely related to the cellular functions, such as cell proliferation, differentiation, and phagocytosis [2]. Recently, Syk has been found in nonhematopoietic cells. Since Coopman *et al.* [3]evidenced its expression in breast cancer cells in 2000, Syk has been detected in many other kinds of tumor cells. Increasing experimental results have indicated that Syk may be a candidate tumor suppressor. This review focused on the research advancement of the relationship between Syk and neoplasms.

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1. Molecular cloning and expressing, structure and distribution of Syk

In 1986 Zioncheck *et al.*[4] isolated a 40 ku enzyme (p40) from the bovine thymus. Their further studies revealed that p40 is most likely an activated proteolyticall fragment of p72 (an unknown enzyme protein) and p72 appears to be a protein-tyrosine kinase which can be autophosphorylated. In 1991, Taniguchi *et al.*[1] isolated a clone containing the coding sequence of p72 from a porcine spleen cDNA library. The clone has a 1884-base-pair-long open reading frame encoding a 628-amino-acid polypeptide with a calculated molecular weight of 71618. The amino acid sequence does not contain a ligand binding or membrane spanning region, but includes a well-conserved protein-tyrosine kinase domain and two src homology region 2 (SH2) domains. The sequences of these

domains show 30-40% identity to the other protein-tyrosine kinases, but those of the remaining sequences are quite unique. They proposed that p72 is a new member of non-receptor protein-tyrosine kinases and they named this gene Syk. Later on, human Syk was successfully cloned [5].

The human Syk locus is mapped to chromosome 9, q22 and shows the highest homology to porcine Syk, an overall 93% identity in the amino acid sequences. Syk contains 629 amino acids and its molecular weight is 72 ku. The protein contains two SH2 domains in tandem, which are SH2 (N) and SH2 (C), and a kinase domain which reflects the inherent character of PTK [2]. The SH2 domain contains about 100 amino acids, with which its tertiary structure has been definite, such as the center of SH2 are antiparallel β -sheet structures and the two sides are α helical structures. The former structure is the activate region between SH2 and phosphorylated tyrosine residues. The main function of SH2 is mediating the interconnection among the intracytoplasm signal proteins, to form protein compounds, and regulate signal transmit in the signal transduction pathway. In the activation processes of the immune cells, SH2 domains bind with the phosphorylated ITAMs to activate the downstream signaling pathways. A linker region, named interdomain B, contains multiple tyrosine sequences that separate SH2 domains from the kinase domain. These tyrosines, when phosphorylated, act as docking sites for proteins, such as phospholipase Cg1 (PLCg1), VAV and CBL, which might be the substrates of Syk. Beyond the catalytic domain lie the tyrosine residues, which give rise to gain-of-function mutants when they are mutated into phenylalanine. The mechanism of the inhibitory effect mediated by these C-terminal tyrosines is not clear. But this might involve the binding of a phosphatase which dephosphorylates Syk. SykB is a naturally occurring isoform of the full-length Syk, which lacks a 23-amino-acid insert in the linker region. The sequence of the 23 amino acids is highly conserved in mouse, rat, human and pig. Syk has unique functions in the immunoreceptor signaling. For example, in comparison with SykB, Syk is much more effective to activate inner-cell signal transduction. This may be related to the higher affinity of Syk than that of SykB to bind phosphorylated ITAMs, and the presence of the linker insert may enhance the ability of Syk to couple the engagement of ITAM or stabilize the binding-capacity between SH2 and ITAM, and so on [6]. ZAP-70 is another member of the Syk family and is only expressed in T cells and natural killer cells. ZAP-70 does not contain the 23- amino-acid insert in the linker region, which behaves much more like SykB.

Syk is expressed in all kinds of hematopoietic cells and its expression has also been observed in other non hematopoietic cells, such as breast epithelial cells [3], airway epithelial cells [7], human nasal fibroblasts [8], vascular endothelial cells [9], neuron-like cells [10], hepatocytes cells [11], melanocytes [12]and pancreas epithelial cells [13]. The subcellular localization of Syk is usually intracytoplasm, and its appearance in the nuclei has recently been reported. The histological distribution and subcellular localization of Syk and SykB may be different, and their functions may be different as well [14].

2. The cytobiological functions of Syk

2.1 Suppression of cell division and proliferation

Syk suppresses cell division and proliferation. Coopman *et al.* [3] injected Syk-transfected MDAMB-435 breast cancer cells in athymic mice. No obvious discrepancy of apoptosis was observed between the Syk and the control group by the immunohistochemical examination. However, unlike the control group, tumors in Syk group were enlarged with multilobes or multiple nuclei. In addition, spindles surrounding the metaphase chromosomes were abnormal, displaying multiple spindle poles and conflicting attachments to the condensed chromosomes. Fluorescent *in situ* hybridization (FISH) showed that the enlarged cells were hyperdiploid, having more chromosome X and 17 than the normal ones. Furthermore, the tumor growth was blocked after abnormal mitosis and failure of subsequent cytokinesis in cells transfected with Syk. Syk might therefore alter the microtubule/tubulin monomer equilibrium and ultimately affect mitosis. Recently, Zyss *et al.*[15] found that Syk is also localized on the centrosomes, exhibiting a catalytic activity. Its expression is strictly controlled in a spatio-temporal manner. Centrosomal Syk expression is persistent in

interphase, but promptly drops during mitosis. Abnormal cell division and cell death could be observed through an exogenous Syk chimera Discosoma sp. red fluorescent protein (DsRed) expressed in the breast epithelial cells: transient DsRed-Syk overexpression triggers an abrupt cell death lacking the hallmarks of classic apoptosis; but survived stable DsRed-Syk-transfected cells exhibit multipolar mitotic spindles and contain multiple abnormal-sized nuclei and supernumerary centrosomes. These observations demonstrate that Syk is a novel centrosomal kinase that negatively affects cell division.

2.2 Influence on cell migration

Currently, the effects of Syk on cell migration are conflicting between different studies. Syk is expressed in MCF-7 cells, but not in MDA-MB-231 cells. Mahabeleshwar *et al.*[16] made contradistinction studies on the effects of Syk on MCF-7 and MDA-MB-231 cell migration. They reported that the over-expression of wild-type Syk suppressed chemotactic cell migration in MDAMB-231 cells. Correspondingly, the transfection of a Syk-specific antisense oligonucleotide in MCF-7 cells dramatically increased cell migration. Extended studies indicated that the effect of Syk on breast cancer cell migration is in coordination with PI 3-kinase, NF κ appa B and urokinase-type plasminogen activator (uPA). A functional molecular link between Syk-regulated PI 3-kinase activity and NF kappa B-mediated uPA secretion exist, which ultimately control the motility of breast cancer cells. In another study, Li *et al.* [17] also investigated MCF-7 and MDA-MB-231 cells and they found that MDA-MB-231 cells transfected with Syk were regulated by growth related oncogene (GRO) and their chemoinvasion through Matrigel was inhibited. Inatome *et al.*[9] examined the effect of Syk expression on the cell proliferation and migration of cultured human umbilical vein endothelial cells (HUVECs) using an adenovirus-mediated expression system. They reported that adenovirus-mediated over-expression of Syk dominant negative mutants markedly suppressed the migration and proliferation of the HUVECs, suggesting that Syk plays a critical role in endothelial cell migration. It seems that Syk plays different roles on different cells.

2.3 Influence on cytokine secretion

Syk also appears to affect the secretion of different factors that may mediate the anti-invasive activity. uPA is a serine protease family member that induces the conversion of plasminogen to plasmin, and then regulates the cell invasion by degrading matrix proteins, therefore plays a significant role in tumor growth and metastasis. Mahabeleshwar *et al.*[16] showed that the secretion of uPA was dependent on NF-κ B activation and transfection of wild-type Syk in MDA-MB-231 breast cancer cells significantly inhibited uPA secretion by blocking NFkB activity through tyrosine phosphorylation of IkBa. GRO is a cytokine related to inflammation and growth regulation, including GROα , GROβ and GROγ subtypes. Using protein array technology, Li *et al.*[17] found that GRO is also expressed by human breast carcinoma cells and they evidenced a negative correlation between GRO secretion and Syk expression. Over-expression of Syk in MDA-MB-231 cells caused a marked reduction in GRO secretion. Conversely, down-regulation of the relatively high levels of Syk produced up-regulated GRO secretion in MCF-7 cells. At the mRNA level, over-expression of Syk in MDA-MB-231 down-regulated GROα and GROγ , while GROβ was not affected. Matrigel invasion assays demonstrated a link between Syk expression and GRO activity in mediating the invasive potential of MDAMB-231 cells and suggested that this cytokine acts as an essential mediator of the anti-invasive properties of Syk. The chemokine RANTES (regulated on activation, normal T cell expressed and secreted) induced by lipopolysaccharide (LPS), is produced by fibroblasts to attract and activate eosinophils. Yamada *et al.*[8] observed a positive correlation between Syk expression and LPS-induced RANTES production in human nasal fibroblasts. More directly, over-expression of wild-type Syk by gene transfer enhanced RANTES production, whereas decreased Syk expression by Syk antisense oligonucleotides inhibited the production. Azenshtein *et al.*[18] detected the expression of RANTES in MCF-7 and T47D breast cancer cells, and found that the expression was directly correlated with a more advanced stage of the disease. RANTES may promote breast cancer progression by its contribution to the monocyte migration into breast tumor and by promoting MMP-9 matrix metalloproteinase expression. However, whether the expression of RANTES in

epithelial cells is regulated by Syk is not clear.

2.4 Suppression of tumorigenic capacity

Experimental studies have demonstrated that Syk transfection not only affects the invasive and metastatic, but also the tumorigenic capacities. Syk re-expression in MDA-MB-435 cells suppressed the subcutaneous tumor growth in athymic mice, decreased their lung colonization capacity *in vivo* and decreased the invasive outgrowth *in vitro*[3]. Syk-transfected Mel-Juso melanoma cells also exhibited a delayed tumor take and reduced tumor size and metastasis *in vivo* in severe combined immunodeficient (SCID) mice[12]. More reports showed that there exist differences of tumorigenic capacities between tumor cells expressed Syk and SykB. Wang *et al.* [14] evidenced phenotypical and functional differences between cells expressed Syk or SykB by their different subcellular localizations, such as nucleus *versus* cytoplasm. While only Syk was detectable in normal mammary tissues, aberrant expression of SykB occurred frequently in primary breast tumors, indicating that Syk suppresses breast cancer cell invasiveness and SykB promotes cancer progression.

2.5 Other functions of Syk

Syk has effects on cell differentiation. It is reported that Syk was expressed in neuron-like cells and was involved in neuron-like differentiation of embryonal carcinoma P19 cells. Syk was found to be tyrosine phosphorylated during neuron-like differentiation. Furthermore, adenovirus-mediated over-expression of Syk induced supernumerary neurite formation and extracellular signal-regulated kinase (ERK) activation in P19 cells. These results suggest that Syk plays an important role in signaling leading to ERK activation in P19 cells[10]. The influence of Syk on cell growth in different types of matrices is also different. For example, Syk transfected MDA-MB-435 breast cancer cells displayed a significantly decreased ability to grow in soft agar as compared to the untransfected cells; however, this phenotype was fully reversed when seeding the tranfected cells in Matrigel[3].

3. Downstream signaling pathways of Syk and their functions

Depending on the cell type, receptors, and the context, Syk can affect a variety of signaling pathways that are mainly related to pro-proliferation and pro-survival. The downstream signaling pathways activated by Syk have been extensively studied in hematopoietic cells. Selected downstream signaling pathways that might have involved in neoplasms and their function were reviewed here.

3.1 Syk and NF-κ B signaling pathways

The NF-κ B system is mainly involved in organism defensive reaction, tissue damage, stress, cell differentiation and tumor growth inhibition. NF-κ B binds with repressible proteins, such as Iκ B to form an inactive compound in the cytoplasm of many kinds of cells. NF-κ B can be activated if it is separated from the protein that it binds to when the conformation of the compound changes under some conditions. The activated NF-κ B then enters the cellular nucleus to initiate or inhibit relevant gene transcription. Syk inhibits uPA secretion in MDA-MB-231 breast cancer cells by blocking NF-κ B activity through tyrosine phosphorylation of Iκ Bα [16]. Recently, Takada *et al.* [19,20] successively reported that Syk plays a critical role in the process of H_2O_2 and TNF induced NF-κ B signal pathway activation. Their results demonstrated that H_2O_2 induces NF-κ B activation, not through serine phosphorylation or degradation of Iκ Bα , but through Syk-mediated tyrosine phosphorylation of Iκ Bα , which is, firstly, H_2O_2 activates Syk; secondly, the activated Syk induces the tyrosine phosphorylation of Iκ Bα ; thirdly, the phosphorylated Iκ Bα induces the serine phosphorylation of the p65 subunit of NF-kappaB, and finally leads to NF-κ B activation. TNF induced Syk activation also happens before NF-κ B activation induced by TNF. Whether TNF-induced Syk can also directly induce the phosphorylation of Iκ Bα or through the activation of c-Src is not clear at present.

3.2 Syk and Src/EGFR signal pathways

Src and EGFR are two kinds of tyrosine kinases which have been investigated relatively explicit at present. Both of them are closely related to tumorigenesis and their increased expressions are seen in many types of tumors. Studies have demonstrated that Src and EGFR play synergistic action in growth signal process, especially in breast cancer. BT549 breast cancer cells own high endogenous levels

of EGFR and Src. Introduction of Syk results in the suppression of BT549 proliferation and aberrant mitosis and significant decrease of Src activity, indicating that Syk may suppress tumor growth by suppressing Src activity [21]. Ruschel *et al.* [22] investigated the Syk and EGFR expression in the human breast-derived cell line MCF-7. Their results showed that Syk expression interfered with EGFR and the phosphorylation of its downstream signaling molecular tyrosine residues, but not HER2 and HER3. On the other hand, EGFR is also negatively regulated with Syk. However, the mechanisms are not known.

3.3 Syk and Ras-Raf-MAPK cascades

As a kind of GTP enzyme, Ras is the main regulatory molecule in MAPK phosphorylation cascade reaction. MAPK acts as a common signal transduction molecule in multiple signal pathways and plays an important role in cell cycle regulation process. Ras-Raf-MAPK signal cascade is one of the main signal transduction systems in human and mammalian cells. Syk is closely related to some processes of Ras-Raf-MAPK cascade. Jabril-Cuenod *et al.* [23] reported that when Fcε RI receptor of mastocyte RBL-2H3 was combined with antigens, Syk dependent phosphorylation of the Shc adaptor increased the association of Shc with Grb2 and activated the ras/MAPK cascade. Activation of this receptor also induced Syk-dependent phosphorylation of protein kinase C (PKC) β I (T y r-6 6 2) and PKCα (T y r - 6 5 8) in the membrane compartment, resulting in the recruitment of the Grb2/Sos complex and full ras/MAPK activation[24].

3.4 Syk and PI3K signaling pathways

PI3K has become one of the research hot spots in the field of signal transduction for its extensive disposition, participation and production of esters second messengers and activation of enzyme cascades to regulate diverse cellular responses, including survival, activation, proliferation and differentiation. Multiple studies have found that Syk is related to PI3K signal transduction. In B cells, Syk plays a critical role in the Akt downstream activation after BCR combines with antigens, whereas Akt activation depends on PI3 kinase phosphorylation by Syk [25]. Moon *et al.* [26] made extensive studies on the molecular mechanism of the direct interaction of Syk with PI3K using yeast two-hybrid system technology. They found that p85, the regulatory subunit of PI3K, was the major Syk-binding protein and the binding of the C-terminal SH2 domain of p85 to pTyr-317 was a major contributor to this interaction. The affinity of the p85 C-terminal SH2 domain for pTyr-317 was even greater than that of the c-Cbl tyrosine kinase binding (TKB) domain. Recently, Li *et al.*[27] investigated the lethal effect of the monoclonal antibody (mAb) potentiator beta-glucan to the tumor cells. They reported that tumor-bearing mice treated with a combination of beta-glucan and an anti-tumor mAb showed almost complete cessation of the tumor growth. The mechanism may be that a 25-kDa fragment released by macrophages after the treatment with beta-glucan bound to neutrophil CR3, induced neoepitope expression, and elicited CR3-dependent cytotoxicity. These events require phosphorylation of the tyrosine kinase, Syk, and consequent PI3K activation. Beta-glucan enhances tumor killing involving CR3-Syk-PI3K signaling.

3.5 Syk and cytoskeletal organization

Cytoskeleton (including microbule, microfilament and intermediate) is the highest form of protein assembly in eucaryotic cells, which makes the cytoplasm to form organized and dynamic spatial structures. The cytoskeleton network not only mediates intra- and ecto-cellular transmembrane signal transduction, but also assigns cells tension, contraction force and motivation. Recent studies have shown that Syk not only phosphorylates signaling pathways, but also phosphorylates the substrates involved in the cytoskeletal organization and functions, which make it crucial for cell adhesion and motility. Peters *et al.*[28] explored the subcellular location of activated Syk. In their experiment, B-cells were divided into soluble and particulate fractions by ultracentrifugation. Activated Syk was found predominantly in the soluble fraction. A 54-ku protein that co-immunoprecipitated with Syk from the soluble fraction of activated B-cells was identified by the peptide mapping as alpha-tubulin, which was an excellent substrate for Syk *in vitro*. Once activated, Syk released from B-cells is free to associate with and phosphorylate alpha-tubulin. Cortactin was originally identified as a substrate of v-Src and it has emerged as an important molecular scaffold for actin assembly and organization.

Further studies showed that Cortactin interacts with other proteins, such as filamentous-actin and actin-related protein (Arp) 2/3 complex. Cortactin-based actin cytoskeletal network plays important roles in endocytosis, cell migration and invasion, adhesion, synaptic organization and cell morphogenesis. The role of cortactin in actin remodeling is subjected to the regulation of tyrosine and serine/threonine kinases[29].

Maruyama *et al.*[30] demonstrated that cortactin was phosphorylated and Syk was activated by 12-O-tetradecanoylphorbol-13-acetate (TPA) stimulation when inducing human leukemic cell line K562 to differentiate into the megakaryocytic lineage. TPA-induced tyrosine phosphorylation of cortactin was decreased profoundly by the over-expression of dominant-negative Syk. The experiment suggests that Syk phosphorylates cortactin in K562 cells upon TPA treatment.

4. Expressions and significant of Syk in neoplasms

Recently, accumulating data have indicated that Syk is closely related to tumorigenesis, tumor development and tumor prognosis, since it is expressed in malignant tumors such as human breast cancer, gastric cancer and lymph, hematopoietic carcinoma. Coopman *et al.*[3] showed that Syk mRNA and protein were low or undetectable in invasive breast carcinoma tissues. Transfection of Syk into a highly tumorigenic and metastatic breast cancer cell line was sufficient to suppress the tumor growth and metastasis. Conversely, over-expression of kinase-deficient Syk in a Syk-positive breast cancer cell line significantly increased the tumor incidence and growth. This study has subsequently been confirmed and complemented by multiple clinical investigations. In another study using immunohistochemistry, Nakashima *et al.*[31] observed nuclear Syk expression in gastric cancer patients. They observed that only 42% (106/250) of the primary lesions were Syk-positive. Syk expression was significantly associated with T1 tumors and the absence of lymphatic invasion, venous invasion and lymph node metastasis ($P<0.0001$). The 5-year survival rate was significantly higher among patients with nuclear Syk expression (92%) than among those without (67%) ($P= 0.0003$). Loss of nuclear Syk expression in biopsy specimens might be used as a useful predictor for lymph node metastasis in the early stage of gastric cancer before surgical resection, although Syk expression is not an independent prognostic factor. Goodman *et al.*[32] reported that Syk-mRNA in leukemic cells from pediatric CD19 (+)CD10 (-) pro-B cell acute lymphoblastic leukemia (ALL) revealed aberrant coding sequences. The abnormal sequences led to reduced Syk activity and the degraded Syk level. Examination of the genomic structure of the Syk gene by inter-exonic PCR and genomic cloning demonstrated that the aberrant coding sequences were caused by mis-splicing, exon skipping or the inclusion of alternative exons.

Moreover, Syk expression was also reported in human melanocytes [12], colorectal cancer [33], pancreatic cancer[13] and hepatic cellular cancer [34]. All the data demonstrate a general decrease or loss of Syk expression in different cancer types. Taken together, the experimental and clinical studies indicate that Syk has the capacity to suppress tumor growth and expansion. In addition, some studies using Syk transfection have directly provided that Syk could suppress tumor growth and metastasis [3]. Therefore, we presume that Syk may be a new tumor suppressor gene.

Some scholars have studied the regulatory mechanism of Syk expression in neoplasms and the preliminary cognitions: ①At present no mutation or homologous deletions has been detected in the naturally occurring neoplasms. But the reason why Syk gene is silenced remains unclear. ②The absence of the Syk protein is mostly reflected by the loss of its mRNA expression, suggesting a regulation problem exists at the transcriptional level. ③Hypermethylation of CpG-rich 5 regulatory sequences in Syk gene promoter has been found in breast cancer [35,36], gastric cancer [31], colorectal cancer [33], pancreatic cancer [13], hepatic cellular cancer [34], lymphoma [37]and granulosa cell tumor [38], which indicate that hypermethylation of Syk gene promoter may lead to the silence of Syk.

5. Epilogue

Syk is an immune system-specific signaling molecule which has been extensively studied recently. Many studies have revealed that Syk is not only expressed by many non-hematopoietic cells, but also a new

candidate tumor suppressor. The hypermethylation of the regulatory sequences in Syk gene promoter may lead to gene silencing. At present, tumor therapy targeting Syk is not yet launched and there are several theoretically feasible therapy ideas. ① gene therapy: activating more immunological cells by transfecting Syk gene into the immune cells; transfecting Syk gene into the tumor cells to prevent tumor growth and diffusion; or transfecting Syk gene into both immune and cancer cells to exert the synergic anti-tumor effect. ② treatment of tumor cells with methyltransferase inhibitors.

Extended research is needed to confirm Syk as a candidate tumor suppressor. The main problems need to be solved are as follows: ① the relationship between the Syk signaling transduction network and neoplasms; ② regulatory mechanisms of Syk expression in tumors; ③ detailed location (kytoplasm or nucleus) of Syk in the tumor cells and the functional discrepancy; ④ detection of Syk isoforms and understanding their functions.

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