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Gene Section
Review

SYK (spleen tyrosine kinase)

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Abstract

Review on SYK, with data on DNA, on the protein encoded, and where the gene is implicated.

Identity

Other names: P72-Syk

HGNC (Hugo): SYK

Location: 9q22.2

DNA/RNA

Description

The spleen tyrosine kinase (SYK) gene encodes a member of the family of non-receptor type Tyr protein kinases (http://www.genecards.org/cgi-bin/carddisp.pl?gene=SYK). The cDNA clone encoding porcine SYK was identified by Taniguchi et al (Taniguchi 1991; Yamada 1993), and thereafter the SYK cDNA for mouse and human, respectively, was cloned (Hutchcroft 1991; Hutchcroft 1992; Müller 1994; Ku 1994). Initially, a smaller porcine SYK protein product was purified and was found to be proteolytically cleaved from the mature SYK protein (Kobayashi 1990). The PTK72 was at the same time found to be identical with the cloned SYK (LePrince 1993; Law 1994).

Transcription

The transcript encodes 635 amino acids with a mass of 72,066 Da. Two isoforms have been described, isoform long (L) and isoform short (S) (http://www.uniprot.org/uniprot/P43405): Isoform 1 (full-length); Isoform 2 (283-305 missing)

Protein

Description

SYK is a 72 kDa non-receptor type protein tyrosine kinase (PTK) that contains two SRC homology 2 (SH2) domains, interdomains A and B, and a C-terminal kinase domain (Fig. 2). SYK was initially shown to be expressed in lymphocytes and associated with the IgM and IgD receptor complexes in B cells (Taniguchi 1991; Hutchcroft 1992). The requirement for Src-PTKs associated with the B cell receptor (BCR) for phosphorylation of SYK was investigated early, and was shown to enhance the activity of SYK (Kurosaki 1994).

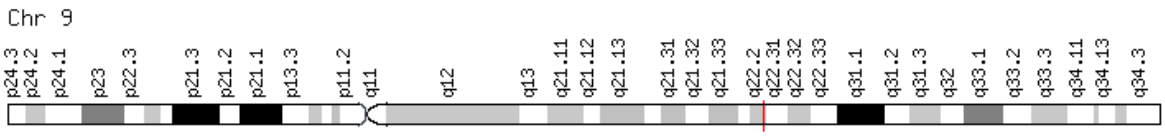

Figure 1. Mapping of SYK gene on chromosome 9q22.2 (from GeneCards Syk gene).

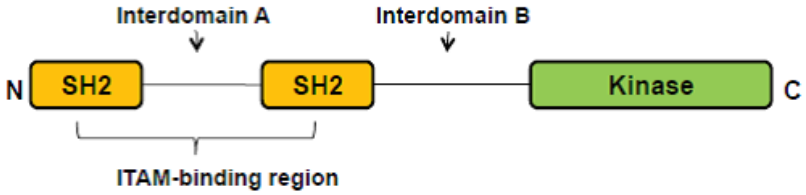

Figure 2. Schematic structure of spleen tyrosine kinase (SYK) protein (adopted from Pamuk et al 2010). The protein includes two tandem SH2 domains and a tyrosine kinase domain. Between the two SH2 domains is interdomain A while interdomain B is located between the tyrosine kinase domain and C-terminal domain. ITAM, immunoreceptor tyrosine-based activation motif; SH2, Src homology 2.

The PTK ZAP70 was cloned in T lymphocytes and shown to be homologous to SYK (Chan 1992). An alternatively spliced form of SYK also exists, missing 23 amino acids from interdomain A (Sada 2001). The topology of the N-terminal part of SYK is similar to its counterpart ZAP70 as revealed by the crystal structure (Narula 1995; Hatada 1995). In 1998, Fütterer et al presented the crystal structure of the tandem SH2 domain of SYK complexed with a dually phosphorylated ITAM peptide (Fütterer 1998). The tandem SH2 domains selectively bind to diphosphorylated immunoreceptor tyrosine based activating motifs (ITAM) of the cytoplasmic region of the BCR (Sada 2001). The crystal structure of a full-length version of ZAP70 has given a greater understanding of the activation process for both SYK and Zap-70 (Deindl 2007).

Atwell et al determined the structure of the unphosphorylated form of the SYK kinase catalytic domain (SYK-KD) in order to understand the molecular mechanism responsible for its enzymatic activity (Atwell 2004). The SYK kinase domain has a subdomain structure composed of a largely β-sheet N-terminal lobe, a largely α–helical C-terminal lobe, with the active site being sandwiched between the two lobes. The N-terminal lobe consists of a five-stranded β -sheet plus a single α –helix. The larger C-terminal lobe is predominantly α –helical with three short β -strands: one at the hinge region and two between the activation loop and the main body of the C-lobe. From the structure of the SYK kinase domain it was deduced that the SYK catalytic activity does not require activation loop phosphorylation.

SYK have multiple sites of phosphorylation which both regulate activity and serve as docking motifs for other proteins (Sada 2001). Phosphorylation sites include Tyr-348 and Tyr-352 within the SH2-linker region (Brdicka 2005), Tyr-525 and Tyr-526 within the activation loop of the kinase domain (Zhang 2000), Tyr-630 in the C terminus of SYK, and others (Kulathu 2008; Tsang 2008; and reviewed by Sada 2001). In B cells, the phosphorylation of two tyrosines within the ITAM leads to the physical recruitment of SYK to the site of the clustered receptor in an interaction mediated by its tandem pair of SH2 domains (reviewed in Geahlen 2009). Shortly following BCR engagement, SYK that has been recruited to the receptor becomes phosphorylated on multiple tyrosines through both autophosphorylation and phosphorylation by Lyn.

Expression

SYK expression in hematopoietic cells has been extensively determined by studying SYK as an effector of BCR signalling. Turner and co-workers found that after BCR activation, SYK-dependent signaling pathways regulate the clonal expansion, differentiation, or apoptosis of B cells (Turner 2000). Most of the cells of the hematopoietic system express SYK, but the PTK is also expressed at lower levels in some epithelial cells, fibroblasts, hepatocytes, vascular smooth muscle cells, endothelial cells and neuronal cells where it mediates various responses including adipogenesis, cell division, tumor suppression, ERK activation and neuronal differentiation (Turner 2000; Yanagi 2001; Zhou 2006; Tohyama 2009; Geahlen 2009; Mócsai 2010; Krisenko 2015).

In hepatocytes, after the use of the SYK-selective inhibitor piceatannol, it was indicated that SYK is necessary for mitogen activated protein kinase (MAPK) activation by G-protein coupled receptors in this cell type (Tsuchida 2000). Additionally, SYK expression has also been observed in normal human breast tissue, benign lesions and low-tumourigenic breast cancer cell lines (Coopman 2000).

Localisation

SYK is an intracellular PTK, known to function at the plasma membrane, where the receptors to which it is recruited are located (Zhou 2006). In lymphoid and epithelial cells, SYK has been found to reside in both the nucleus and cytoplasm (Ma 2001; Wang 2003; Wang 2004). The expression and localization of SYK in the nucleus of breast cancer cells have been correlated with the repression of invasive tumor growth (Wang 2003).

Function

The SYK protein is known to have an important role in adaptive immune receptor signalling with recent reports indicating its mediation of other diverse biological functions, including cellular adhesion, innate immune recognition, osteoclast maturation, platelet activation and vascular development (Mócsai 2010). The protein is also involved in

coupling activated immunoreceptors to downstream signaling events that mediate diverse cellular responses, including proliferation, differentiation, and phagocytosis.
SYK plays a critical role in the transition of pro-B cells into pre-B cells (Turner 1995). SYK is greatly involved in signal transduction initiated by the classic immunoreceptors, including BCRs, Fc receptors, and the activating natural killer receptors (Tohyama 2009; Berton 2005; Crowley 1997). SYK is associated mainly with ITAM dependent pathways and affects early development and activation of various cells including B cells, mast cell degranulation, neutrophil and macrophage phagocytosis, as well as platelet activation (Zhou 2006; Tohyama 2009; Mócsai 2010). SYK-mediated phosphorylation of various adaptor proteins leads to the activation of downstream pathways that execute phagocytosis. SYK is important in complement-mediated phagocytosis resulting from the binding of C3bi-coated particles to complement receptor 3 (Tohyama 2009; Tohyama 2006). SYK is known to play a major role in the development of signal transduction events initiated after high-affinity IgE receptor (FCER1A) aggregation (Wong 2004; Matsubara 2006), mast cell activation, degranulation, and cytokine production (Matsubara 2006; Masuda 2008). It is anticipated that SYK activation coupled with platelet activation and aggregation may assist in lymphatic vessel development and their separation from blood vessels (Mócsai 2010, Turner 1995). SYK is claimed to have a role in osteoclast differentiation and osteoclast function (Tohyama 2009, Mócsai 2010). SYK has been found to have a major role in pre T-cell receptor (TCR) signalling. This is known to occur during the transition from the double negative 3 (DN3) to the DN4 stage of early thymocyte development (Palacios 2007). In vivo studies have shown that SYK is required for firm leukocyte adhesion to inflamed endothelium (Frommhold 2007) and development of vasculopathy reaction (Hirahashi 2006). The innate immune system uses pattern recognition receptors (PRRs) to detect pathogen-associated molecular patterns (PAMPs) and activate immune responses. SYK has been found to be a key component of these pathways and increased evidence points to the involvement of SYK-coupled PRRs in innate recognition of bacteria, with CLEC7A, CLEC6A and CLEC4E all implicated in sensing of mycobacterial PAMPs (Geijtenbeek 2009). SYK is presumably also involved in signalling PRR-mediated recognition of certain viruses.
The role of ZAP70 in B cells have been investigated, but is poorly understood possibly due to the functional redundancy between SYK and ZAP70 (Fallah-Arani 2008). Toyabe et al displayed the ability of a T cell subpopulation to express high levels of SYK and partially compensate for loss of T-cell functions in patients with deficiency of ZAP70 (Toyabe 2001).

Homology

Both ZAP-70 and SYK are dependent upon a Src-family protein tyrosine kinase for association with the phosphorylated zeta-chain. Thus, the differential expression of these kinases suggests the possibility of different roles for ZAP70 and SYK in TCR signaling and thymic development (Palacios 2007). Activation of PTKs is an important mechanism in the transduction of signals from multi-subunit immunoreceptors, including the B and T cell receptors for antigen and the widely distributed receptors for the Fc portion of immunoglobulins (Paolini 2001). ZAP70 is expressed in T cells, natural killer cells and thymocytes, whereas SYK is present in all hematopoietic cells. Both ZAP70 and SYK are reported to be activated after TCR stimulation.
Nonetheless, ZAP70 activation is known to require presence of Lck or another associated Src family PTK, while SYK is independent of Lck to undergo phosphorylation (Chan 1994, Couture 1994, Kolanus 1993). Regardless of its presence in all thymocyte subsets, SYK expression is downregulated three- to fourfold in peripheral T cells and, contrary to ZAP70, SYK expression is 12- to 15-fold higher in peripheral B cells compared to peripheral T cells (Chan 1994).
Another study showed functional homology in antigen receptor signaling by demonstrating that expression of ZAP70 in SYK-B cells reconstitutes BCR function (Kong 1995). Another feature that distinguish ZAP70 from SYK is its greater dependency on Src kinases for activation and its ability to phosphorylate and promote the auto-activation of the downstream MAPK p38 (reviewed in Au-Yeung 2009).

Mutations

The development of B cells proceeds through a well-characterized set of stages defined by the extent of antigen receptor rearrangement and the expression of particular cell surface markers. When mice deficient for recombination-activating gene 1 (RAG1) were reconstituted with fetal liver from SYK-deficient embryos, the pool of pre-B cells formed was reduced. This suggests that SYK is required for the proper signalling from the pre-BCR to generate or maintain the pool of pre-B cells. Indeed, it has been shown that SYK is an essential transducer of BCR signals required for the transition of immature into recirculating B cells (Turner 2000). Moreover, SYK-deficient mice die due to embryonic and perinatal death (Turner 1995; Cheng 1995).

Epigenetics

SYK can also be inactivated by epigenetic modifications (i.e. hypermethylation)

Implicated in

t(5;9)(q33;q22)

Disease

found in Peripheral T-cell lymphoma (Streubel et al. 2006).

Hybrid/Mutated gene

N-terminal ITK (bp 1-577) fused in frame with C-terminal SYK cDNA

t(9;12)(q22;p12)

Disease

found in a case of myelodysplastic syndrome (Kuno et al. 2001).

Oncogenesis

ETV6-SYK is constituvely tyrosine phosphorylated

Breast cancer

SYK mRNA and protein expression in a panel of well-characterized breast cancer cell lines, normal mammary gland tissue, and a normal breast epithelial cell line has been investigated by Coopman et al (Coopman 2000). They readily detected SYK expression in normal mammary tissue and epithelium, as well as in non-invasive breast carcinoma cell lines. SYK expression was however observed to be reduced or absent in the invasive breast tumor cell lines. Hypermethylation of the SYK locus during breast cancer progression was found to cause a loss of SYK protein expression in highly invasive and metastatic human mammary carcinomas (Coopman 2000,Yuan 2001). Moreover, Wang et al have shown that full-length SYK can enter the nucleus and thereby suppress invasion (Wang 2003). The sequences confined to a region of the SYK molecule near the junction of the linker B and catalytic domain were determined to be responsible for its distribution between the nucleus and cytoplasm (Zhou 2006). It was further demonstrated that the distribution of SYK between the nucleus and cytoplasm was regulated by signals sent downstream from the activated BCR and require the receptor-mediated activation of protein kinase C (PKC) and the induction of new protein synthesis.

Colon carcinoma

Expression of the SYK gene in human colon carcinoma cells is known to be suppressed in a p53-dependent manner, an indication that loss of p53 function during tumorigenesis can lead to deregulation of SYK activity (Okamura 1999). As reviewed recently by Krisenko et al,the levels of SYK mRNA in many cancerous tissues, including colon, are higher than in normal corresponding tissue (Krisenko 2015).

Gastric cancer

An inverse correlation between nuclear SYK and lymph node metastasis was observed in gastric cancer patients (Wang 2004).

Ovarian cancer

Ovarian tumors of low malignant grade have low levels of SYK compared to aggressive grades, which have the highest levels (Prinos 2011). Interestingly, when SYK expression was silenced, anchorage-independent growth was inhibited, and apoptosis was induced in SYK-expressing ovarian cancer cells.

Lung cancer

Primary tumors of small cell lung cancer (SCLC) was examined and found to express higher levels of SYK compared to normal alveolar epithelium (reviewed by Krisenko 2015).

Chronic lymphocytic leukemia (CLL)

Both SYK and ZAP70 are present in CLL in B cells and may compete in facilitating BCR signaling (reviewed in Au-Yeung 2009). CLL fall into two classes, an indolent milder form and an aggressive form that is particularly dependent on SYK activity for survival (Buchner 2009).

Diffuse large B-cell lymphoma (DLBCL)

DLBCL can exhibit tonic or chronic signaling from the BCR that results in constitutive phosphorylation of SYK on activation loop tyrosines (Chen 2008). In a study from 2011 by Cheng et al, 44% of DLBCL samples showed elevated levels of phosphorylated SYK (Cheng 2011).

Follicular lymphoma (FL)

Constitutive activation of SYK has been reported in FL, were primary cells are hyperresponsive to BCR engagement as compared to nonmalignant B cells (Leseux 2006; Irish 2006).

Mantle cell lymphoma (MCL)

Constitutive activation of SYK has been reported in MCL as well, with a frequent overexpression of SYK due to gene amplification in both cell lines and primary tumors (Rinaldi 2006).

Marginal zone lymphoma (MZL)

Ruiz-Ballesteros reported upregulation of SYK in splenic MZL, potentially due to downregulation of microRNAs predicted to modulate SYK gene transcription (Ruiz-Ballesteros 2005).

B cell acute lymphocytic leukemia (B-ALL)

B-ALL cells are derived from pro-B cells that lack pre-BCR or BCR complexes, but still these cells have elevated levels of constitutively active phosphorylated SYK (Perova 2014).

Rheumatoid arthritis (RA)

It is likely that SYK is widely expressed in a range of haemopoietic cell lineages in RA synovium. Inhibition of Syk suppresses both inflammation and bone erosion in animal models of RA (Singh Najjar 2014). Indeed, Syk has been shown to be necessary for emerging pathology in several animal models of arthritis.

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