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Review

Calling in SYK: SYK's dual role as a tumor promoter and tumor suppressor in cancer

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ABSTRACT

SYK (spleen tyrosine kinase) is well-characterized in the immune system as an essential enzyme required for signaling through multiple classes of immune recognition receptors. As a modulator of tumorigenesis, SYK has a bit of a schizophrenic reputation, acting in some cells as a tumor promoter and in others as a tumor suppressor. In many hematopoietic malignancies, SYK provides an important survival function and its inhibition or silencing frequently leads to apoptosis. In cancers of non-immune cells, SYK provides a pro-survival signal, but can also suppress tumorigenesis by restricting epithelial–mesenchymal transition, enhancing cell–cell interactions and inhibiting migration.

1. Introduction

The autonomous growth of cancer cells is driven by an array of mutations, amplifications, rearrangements and modifications affecting hundreds of distinct genes. Only a limited number of these genes express proven, effectively druggable targets. Prominent among these are protein kinases, important components of the signal transduction machinery of eukaryotic cells that regulate the interactions of the cell with its environment and control such processes as energy metabolism, cell cycle progression, cytoskeletal rearrangement, gene expression and apoptosis. Tyrosine-protein kinases, which account for 17% of the human kinome, are particularly attractive drug targets due to their intimate involvement with the regulation of cell proliferation and survival and their frequent association with tumorigenesis [1,2]. Thus, a number of therapeutic agents targeted against tyrosine kinases including imatinib (Gleevec) for the inhibition of BCR-ABL, gefitinib (Iressa) and erlotinib (Tarceva) for targeting activated mutants of the epidermal growth factor receptor (EGFR) and trastuzumab (Herceptin) for the inhibition of human epidermal growth factor receptor-2 (HER2) are important components of the oncologist's armamentarium [1]. While a role in malignant transformation for many tyrosine kinases is well documented, the ability of others to modulate the growth properties of cancer cells is less well understood. SYK (spleen tyrosine kinase) is a prime example since both tumor promoting and tumor suppressing roles for this enzyme have been described.

SYK was originally isolated by our group from bovine thymus [3,4] and by the Yamamura group from porcine spleen [5]. These tissue sources are consistent with expression analyses, which confirm that SYK is expressed at highest levels in cells of hematopoietic origins [6–8]. SYK functions as an essential component of the signaling machinery of multiple receptors in the immune system that play important roles in distinguishing self from nonself [9]. SYK contains a tandem pair of SH2 (Src homology 2) domains at the N-terminus that are separated from each other by a linker A region [10]. A longer linker B region separates the SH2 domains from the catalytic domain. Structural analyses indicate that hydrophobic residues in linker A, linker B and the catalytic domain interact to restrict SYK to a largely autoinhibited conformation [11]. SYK is activated when it is recruited to an immune recognition receptor through the binding of its SH2 domains to a doubly phosphorylated immunoreceptor tyrosine-based activation motif or ITAM, a sequence of amino acids found on most SYK-coupled receptors [12]. ITAMs consist of two sets of YXXL/I sequences separated by 6–10 amino acids. Examples of receptors possessing ITAM-containing components include the B cell receptor for antigen (BCR); receptors for IgE (FcεRI), IgG (FcγRIIa) and IgA (FcαRI), the collagen receptor of platelets (GPVI) as well as NK cell activating receptors and integrins that signal through associated DAP12 or FcRγ components. Following receptor engagement and clustering, a member of the Src-family of tyrosine kinases catalyzes the phosphorylation of the more N-terminal tyrosine within the ITAM to initiate the recruitment of SYK to the receptor [9,13]. Phosphorylation of the second ITAM tyrosine, likely by SYK, completes the

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formation of the receptor-SYK complex. Binding to dually phosphorylated ITAMs relieves autoinhibition to activate SYK [11], which then catalyzes the phosphorylation of protein substrates primarily on tyrosines located in sites rich with acidic amino acids [13] (however, recent evidence has shown that SYK also has the ability to phosphorylate some proteins on serine [14,15]). SYK itself has multiple tyrosines that become phosphorylated that regulate its activity and its ability to participate in protein–protein interactions [13]. Substrates for SYK consist of adaptor/scaffolding proteins such as BLNK, SLP76 and LAT, and multiple regulatory enzymes that include lipid kinases, phospholipases and guanine nucleotide exchange factors [9,13]. These phosphorylations serve to couple liganded receptors to the activation of signaling cascades that include the PI3K/AKT/mTOR, Ras/ERK, PLCγ/NFAT, and IKK/NFκB pathways. These, in turn, are important modulators of metabolism and gene transcription that determine the physiological responses of an immune cell to receptor engagement. The critical involvement of SYK in the activation of immune cells has made it a popular target for anti-inflammatory therapeutics directed against such diseases as allergic asthma, rheumatoid arthritis, lupus erythematosus and thrombocytopenic purpura [16].

In addition to SYK's presence in most hematopoietic cells, there are multiple reports of SYK in various cell types outside of the immune system, particularly in epithelial cells from a variety of organs [17,18] where it is present generally at much lower levels [6–8]. For example, SYK is present in epithelial cells of the breast at levels at least 6-fold lower than in infiltrating immune cells [19]. However, *Syk* haploinsufficient mice exhibit increased ductal outgrowth, suggesting an important role for SYK in tissue homeostasis in the breast [20]. There also are many examples of individual cell lines that are not of hematopoietic origin that have levels of SYK mRNA as high as or even higher than those found in lymphoid cell lines [8].

2. SYK as a tumor promoter

2.1. SYK and cell survival signaling downstream of the BCR in hematopoietic malignancies

Much of the attention on SYK as a promoter of cancer cell growth has focused on malignancies of B cell origins and the role of tonic or chronic signaling from the BCR in the maintenance of tumor cell viability. During the course of B cell development in the bone marrow, successful rearrangement of the immunoglobulin heavy chain locus yields a pre-B cell receptor that contains the heavy chain, surrogate light chains and an associated heterodimer of CD79a and CD79b, which are the signaling subunits that contain the ITAM sequences [21]. Successful gene rearrangement and receptor assembly are required for cells to survive the pro- to pre-B cell transition through signals sent from the pre-BCR via SYK. Consequently, SYK-deficient B cell precursors largely fail to progress to the pre-B cell stage of development [22]. Those that do make the transition, mainly through the expression of low levels of the SYK-family kinase, ZAP-70, fail to progress further to become mature B cells [23]. This latter transition requires rearrangement of the light chain locus and the production and expression at the cell surface of a mature B cell receptor, again associated with the CD79a and CD79b signaling components. At this stage of development, SYK is again required for cell survival and is thought to be activated by tonic signaling (i.e., signaling in the absence of antigen) from the assembled BCR complex [21]. In fact, sustained BCR expression and tonic signaling are required for the continued survival of mature B cells [24]. Signaling through the BAFF (B cell-activating factor) receptor, a tumor necrosis factor (TNF)-family receptor required for follicular B cell survival, also co-opts SYK, the BCR and its ITAMs as part of its mechanism to promote cell survival [25].

In a mouse model of non-Hodgkin lymphoma, mice bearing both a c-Myc oncogene driven by an immunoglobulin enhancer (Eμ-*MYC*) and a HEL specific BCR (BCR^{HEL}) develop lymphoid tumors that are reliant on tonic BCR signaling for survival [26]. Further introduction of a soluble hen egg lysozyme transgene to generate an Eμ-MYC/BCR^{HEL}/sHEL mouse results in the appearance of more aggressive tumors that are chronically activated through the BCR and resemble Burkitt's lymphoma. This supports the concept that either tonic or chronic signaling through the BCR contributes to tumorigenesis. In both tumor types, the silencing of SYK expression induces apoptosis and inhibits tumor formation in mice.

A prime example of a role for SYK and the BCR in tumorigenesis is B cell chronic lymphocytic leukemia (B-CLL). B-CLL arises due to the clonal expansion of phenotypically mature B cells. B-CLL cells are typically BCR positive and fall into two general classes: an indolent form with mutated immunoglobulin variable heavy chain region (IgV_H) genes and a clinically aggressive form with unmutated IgV_H genes that also express the SYK-family kinase, ZAP-70 [27]. ZAP-70 is not normally found in B cells and its ability to enhance tumorigenesis in B-CLL does not require it to be catalytically active, suggesting a scaffolding function for the enzyme [28]. Cells of both classes are characterized by the presence of elevated levels of constitutively active SYK [29]. Whether SYK activation occurs due to BCR engagement by an unknown antigen through chronic signaling—the IgM repertoire of B-CLL samples is less polymorphic than one would expect from random gene rearrangements—or from ligand-independent tonic signaling from the assembled BCR complex is not completely clear, although either mechanism may drive tumor development [30].

The inhibition of SYK activity or the silencing of SYK expression in both indolent and aggressive B-CLL triggers apoptosis by the conventional mitochondrial/caspase 3 pathway [29,31,32]. The highly malignant, unmutated class of cells is particularly dependent on the activity of SYK for survival [31]. In a phase 1/2 clinical trial of the SYK inhibitor fostamatinib, 55% of human patients with B-CLL had a positive response to therapy [33]. Cells from treated patients exhibited a reduced profile of BCR-mediated activation events including decreased expression of NF-κB and c-Myc target genes, reduced activation of BTK (a tyrosine kinase activated downstream of SYK), lowered levels of MYC and JUNB, and decreased expression of cell surface activation markers, all consistent with an inhibition of BCR signaling [34].

BCR-dependent signaling also is involved in diffuse large B cell lymphoma (DLBCL). DLBCL is a heterogeneous collection of malignancies, a subset of which are BCR positive, display gene expression signatures consistent with anti-IgM-activated B cells and are reliant for survival on the expression of components of the BCR complex [35]. Many DLBCL cell lines exhibit tonic or chronic signaling from the BCR that results in the constitutive phosphorylation of SYK on activation loop tyrosines [36]. An evaluation of 61 DLBCL tumor samples from human patients found that 44% had elevated levels of phosphorylated SYK; and this phosphorylated SYK was localized to the plasma membrane where BCR complexes are found [37]. A fraction of primary DLBCL samples exhibit increases in *SYK* gene copy number, which correlates with increased protein expression [38]. BCR-dependent DLBCL cells also frequently overexpress the transcriptional repressor, BCL6, which downregulates the expression of PTPROt, a receptor-type protein tyrosine phosphatase and negative regulator of SYK-dependent BCR-signaling [39]. Thus, a decrease in PTPROt expression enhances tonic signaling from the BCR [40]. The SYK inhibitors R406 and PRT318 are cytotoxic or cytostatic for most BCR-positive DLBCL cells [36,37]. The knockdown of SYK by siRNA arrests cell cycle progression in PRT318-sensitive DLBCL cell lines, which phenocopies the effects of the SYK inhibitor [37]. Consistent with these observations, a positive response rate of 22% for DLBCL patients was observed in a clinical trial of fostamatinib [33].

The constitutive activation of SYK also has been reported in other B cell-derived malignancies including follicular lymphoma (FL) [41], mantle cell lymphoma (MCL) [42] and marginal zone lymphoma (MZL) [43]. Primary FL cells are hyperresponsive to BCR engagement as compared to tumor-infiltrating, but nonmalignant B cells [44]. In

MCL, a rare but deadly form of non-Hodgkin lymphoma, SYK is frequently overexpressed due to gene amplifications in both cell lines and primary tumor samples [42]. In splenic MZL, SYK expression also is upregulated [43], potentially due to the downregulation of miR-27b and miR-377 microRNAs, which are predicted to modulate *SYK* gene transcription [45]. In both FL and MCL, the SYK inhibitor, piceatannol, is toxic to cells expressing constitutively active, phosphorylated SYK.

In summary, the accumulating evidence indicates that SYK is clearly an important mediator of tonic and chronic signaling through the BCR in multiple B cell-derived lymphomas where it plays a major role to support cell survival.

2.2. SYK and cell survival signaling downstream of receptors other than the BCR in hematopoietic malignancies

A role for SYK in supporting tumor cell growth is not restricted to cells expressing ITAM-containing components of the BCR complex. In B cell acute lymphocytic leukemia (B-ALL) a large percentage of malignant cells are derived from pro-B cells that lack pre-BCR or BCR complexes. However, these tumor cells survive and develop many characteristics of pre-B cells even in the absence of the pre-BCR [46]. Interestingly, most B-ALL cells and primary isolates from patients still have elevated levels of constitutively active, phosphorylated SYK and their growth both in culture and in tumor xenografts is attenuated by inhibitors of SYK activity [46–48]. The expression of SYK can be detected in 94% of peripheral T cell lymphomas (PTCLs) and immunoblotting experiments indicate that the kinase is constitutively phosphorylated in these cells [49]. The signals that act upstream of SYK to enhance its activity in B-ALL and PTCL remain to be identified, although the T cell antigen receptor (TCR) is a clear suspect in PTCL [50].

In some lymphoid cancers, ITAM-containing proteins other than components of the BCR-signaling complex support the activation of SYK to promote cancer cell survival. During the latent stage of infection, Epstein–Barr virus (EBV) expresses the integral membrane protein LMP2A [51]. LMP2A interacts with both Lyn and SYK, the latter through an N-terminal ITAM that, when phosphorylated, stably associates with SYK's tandem pair of SH2 domains. These interactions inhibit signaling through the BCR and prevent lytic replication. Interestingly, LMP2A serves as a surrogate BCR to promote B cell differentiation even in the absence of cell surface immunoglobulins by providing the tonic signals required for B cell survival [52]. Thus, B cells expressing LMP2A can populate lymphoid organs even in Rag-1-deficient mice. While EBV infections are nearly universal in adults, these are effectively controlled by a cytotoxic T cell response. However, EBV infections uncontrolled by adaptive immune responses in immunocompromised individuals can result in EBV+ post-transplant lymphoproliferative disorder (PTLD). The resulting mainly B cell-derived lymphomas are characterized by the appearance of constitutively active SYK [53]. Most are dependent on SYK expression and activity for survival as both siRNAs directed against SYK mRNA and the SYK inhibitor R406 induce apoptosis in these cells.

In acute myeloid leukemia (AML), integrins can function upstream of SYK to enhance its activity and support tumor cell growth. AML arises from the enhanced proliferation and defective differentiation of progenitor cells of the myeloid lineage and thus does not typically express components of the BCR complex. An investigation of the sensitivity of AML cells to inhibitors of EGFR (which is not expressed in AML), coupled with a siRNA screen, identified SYK as a key player in AML pathogenesis [54]. Both siRNAs and inhibitors targeting SYK decrease proliferation and induce differentiation of AML cell lines and primary AML blasts and inhibit the growth of AML xenografts in mice [54]. One clue to the upstream activator of SYK in AML came from a shRNA-based screen that identified β3-integrin (ITGB3) as an important factor supporting the proliferation and inhibiting the differentiation of AML [55]. Downregulation of ITGB3 expression by RNA interference decreases the level of phosphorylated and activated SYK and mimics the effects of SYK inhibitors on AML proliferation and differentiation. Another clue came from a mass spectrometric-based analysis of SYK-interacting proteins in AML cells that identified Mac-2 (β2αM integrin) and FcγRI as key SYK-binding partners [56]. The engagement of either receptor is coupled to the activation of SYK. Interestingly, the knockdown of CD18 (β2-integrin) or of the FcRγ chain attenuates the SYK-dependent proliferation of AML cell lines. In both neutrophils and macrophages, the integrin-mediated activation of SYK requires the expression of either DAP12 or FcRγ (FCER1G) [57], both of which contain ITAM sequences that, when phosphorylated, associate with SYK. The constitutive phosphorylation of the FcRγ ITAM and its association with SYK were observed in AML cells, suggesting its role in the tonic activation of SYK [56].

Approximately 1/3 of patients with AML have mutations in the *FLT3* gene that result in the expression of a constitutively active receptor tyrosine kinase. In these cells, a role for SYK also has been implicated [58]. Active, phosphorylated FLT3 physically associates with SYK through its more C-terminal SH2 domain and SYK, in turn, enhances the activity of FLT3 by phosphorylation. This cooperative activation of both kinases leads to an increase in the expression of MYC and MYC target genes.

2.3. SYK fusion proteins in hematopoietic malignancies

An alternative way to generate tonic, SYK-dependent signals is through gene rearrangements and the production of constitutively active fusion proteins. Data generated from next generation sequencing indicates that SYK is rarely mutated in any type of cancer [59]. Thus, point mutations in SYK do not appear to be important drivers of tumorigenesis. However, chromosomal translocations involving the *SYK* gene have been detected and these can result in the production of fusion proteins that promote myeloproliferative or lymphoproliferative diseases. For example, a fusion protein in which the dimerization domain of the *TEL* gene product is fused to SYK results in an active kinase that promotes a myeloproliferative disorder [60]. Constitutive activation requires the TEL oligomerization domain and results in the phosphorylation on tyrosine of the fusion protein. The oligomerization of TEL-SYK through the TEL domain likely mimics the activation of SYK that occurs during the clustering of the receptors with it associates. This stimulates SYK autophosphorylation on sites that modulate its activity and promote its interactions with downstream effectors that bear SH2 or functionally related domains [13].

A fusion protein that contains the N-terminal Tec and PH homology domains of the tyrosine kinase ITK fused to most of linker B and the catalytic domain of SYK is found frequently in nonspecific PTCLs. The resulting fusion protein is constitutively active and its expression leads to the phosphorylation of downstream adaptor and effector proteins [61,62]. Unlike TEL-SYK, ITK-SYK expression selectively leads to T cell lymphoproliferative diseases, perhaps due to a requirement for the expression of SLP-76, which is critical for ITK-SYK activation and the subsequent phosphorylation of either SYK or ZAP-70, which then play important adaptor functions downstream of activated TEL-SYK perhaps similar to the role played by ZAP-70 in B-CLL [63]. Expression of neither the TEL-SYK nor ITK-SYK fusion protein alone is likely to be sufficient for full B or T cell transformation as recent mouse models indicate that additional genetic changes are required to overcome SYK-induced, Blimp-1-mediated terminal differentiation [64].

2.4. SYK and ITAM-signaling in non-hematopoietic malignancies

The inappropriate activation of SYK through the abnormal expression of ITAM-containing proteins can contribute to cell transformation in non-hematopoietic cells. For example, mouse mammary tumor virus (MMTV), which causes adenocarcinomas in mice, expresses an *env* gene product that, when expressed in mammary epithelial cells, induces morphological changes consistent with transformation [66]. The Env protein contains an ITAM sequence through which it associates

with SYK. Env-induced transformation requires the conventional pair of ITAM tyrosines and is blocked by the SYK inhibitor, piceatannol. Similarly, the ITAM of LMP2A, which contributes to cancer cell survival in PTLD, also influences the physical properties of EBV-induced nasopharyngeal carcinoma cells [67]. LMP2A associates with SYK via its ITAM and enhances motility in a manner dependent on the conserved ITAM tyrosines and on the expression and activity of SYK. The ectopic expression of LMP2A in keratinocytes also promotes cell migration in an ITAM- and SYK-dependent manner by inducing the translocation of αV-integrin to the membrane [68]. The gene for C35 (C17orf37), which is located on the *HER2* amplicon, is increased in expression with *HER2* gene amplification in human breast cancer [69]. C35 also has an ITAM and its expression in mammary epithelial cells induces invasive growth and triggers an epithelial-to-mesenchymal transition (EMT) as characterized by a loss of E-cadherin. This activity requires both the C35 ITAM sequence and SYK. It is interesting that, in many of these same cell types, the expression of SYK in the absence of ITAM-containing effectors like Env, LMP2A and C35 actually inhibits cell motility and EMT (see below). Thus, these aberrantly expressed, ITAM-containing molecules may sequester SYK away from its normal interacting partners within the cell in much the same way that LMP2A expression inhibits BCR signaling in EBV+ B cells. They potentially could localize active SYK near a particular set of substrates whose phosphorylation alters cellular growth properties.

2.5. SYK and cell survival signaling in non-hematopoietic malignancies

Oncogenic mutations in K-Ras are seen frequently in adenocarcinomas of the pancreas, lung and colon. A recent analysis compared gene expression profiles of lung and pancreatic cancer cells dependent on the expression of oncogenic K-Ras for survival to tumor cells not dependent on K-Ras [70]. Interestingly, *SYK* is the gene most commonly expressed in K-Ras-dependent (or K-Ras addicted) cells that is missing from K-Ras-independent cells. Accordingly, SYK protein levels are relatively high in K-Ras addicted cells. In these cells, the knockdown of SYK expression or inhibition of SYK activity results in caspase 3 activation and cell death. The expression in many cells of oncogenes like K-Ras induces apoptosis unless cells acquire additional anti-apoptotic measures [71]. Thus, it is likely that the pro-survival activity of SYK protects these cells from K-Ras-induced apoptosis.

A similar pro-survival role for SYK is seen in retinoblastoma [72]. Whole genome sequencing of retinoblastoma cells reveals no significant mutations in any oncogenes or tumor suppressor genes other than *RB1*. However, many epigenetic changes in gene methylation are observed, including reduced methylation of the *SYK* gene promoter. As a consequence, SYK is expressed in both retinoblastoma orthotopic xenografts and cell lines, but is actually absent from normal retina. Both the application of SYK inhibitors and knockdown of SYK expression by shRNA result in a dramatic increase in mitochondrial-based apoptosis. The addition of a SYK inhibitor to the chemotherapeutic regimen used to treat retinoblastoma in a mouse model significantly improves outcomes, clearly suggesting SYK as a promising therapeutic target for the treatment of childhood retinoblastoma [72]. Thus, the expression of SYK can protect cancer cells from the pro-apoptotic consequences of either the loss of Rb or the expression of activated K-Ras.

For many tissues—including brain, colon, kidney and ovary—the levels of SYK mRNA are, in general, higher in cancerous than in normal tissues [8], suggesting possible roles for the kinase in tumorigenesis in many cell types outside of the immune system. In ovarian cancer, for example, the expression level of SYK increases with tumor grade [73]. Tumors of low malignant potential have lower levels of SYK, intermediate levels are present in grade 1 tumors, and the highest levels are found in aggressive grade 3 cancer cells. The silencing of SYK expression markedly inhibits anchorage-independent growth and induces apoptosis in SYK-expressing ovarian cancer cells. An analysis of genes co-expressed in small cell lung cancer (SCLC) reveals SYK as a potential oncogenic driver [74]. An examination of primary tumor samples found SYK present in 11 of 33 SCLC tissues at levels much higher than those in normal alveolar epithelium. Also, a large majority of SCLC cell lines overexpress SYK mRNA [75]. The silencing of SYK expression by siRNA decreases cell growth and increases apoptosis in SYK-positive SCLC cells. Similarly, SYK is frequently found in squamous cell carcinomas of the head and neck (SCCHN) where its expression enhances cell migration [76]. Interestingly, elevated SYK expression is also observed in SCCHN patient tissues where it correlates with increased metastases to the lymph nodes and with a poor patient survival.

2.6. Mechanisms of SYK-dependent survival signaling

A fundamental hallmark of a cancer cell is its ability to resist apoptosis [77], a capability enhanced by the expression of Syk (Fig. 1). Signaling through PI3K and AKT, known mediators of pro-survival signaling, is thought to underlie SYK's role as a promoter of tumorigenesis in many tumors. In normal B cells, SYK couples the antigen receptor to the activation of the PI3K/AKT pathway [78,79]. The activation of PI3K generates phosphatidylinositol 3,4,5-trisphosphate (PIP3), a membrane anchor for and activator of the serine/threonine kinase, AKT. Activation of PI3K and AKT in response to BCR-signaling is essential for the BCR- and SYK-dependent tonic signaling that promotes cell survival in normal B cells as the death of mature B cells resulting from the induced deletion of the BCR can be rescued by expression of a constitutively active form of PI3K or by deletion of PTEN [80].

AKT is a pleiotropic kinase that controls survival signaling through the phosphorylation of multiple downstream substrates that play key roles in regulating the activity and/or expression of pro- and/or anti-apoptotic proteins. Multiple mechanisms are operative in different tumor cell types. An important downstream target of pro-survival signaling in B-CLL is MCL-1, an anti-apoptotic member of the Bcl-2 family of cell death regulatory proteins [81]. The silencing of MCL-1 by RNA interference leads to cell death, indicating its importance as a downstream target of survival pathways [82]. B-CLL cells in general exhibit a SYK-dependent increase in the basal state of phosphorylation of AKT. Activated AKT phosphorylates and inhibits glycogen synthase kinase 3 (GSK3), a negative regulator of MCL-1 protein stability. GSK3 targets

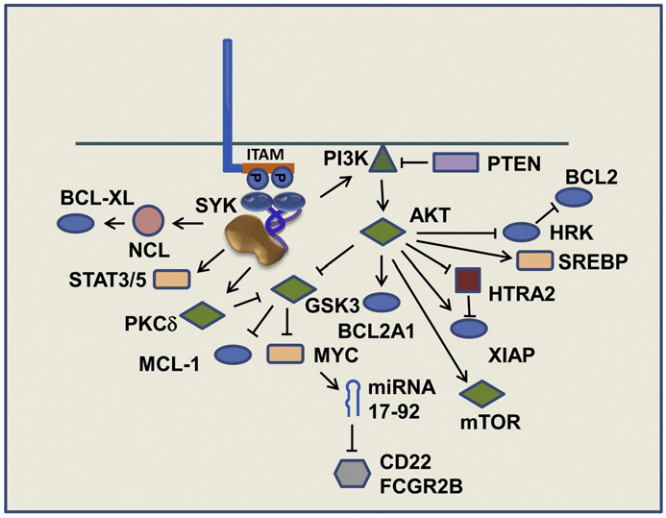

Fig. 1. Mechanisms of SYK-promoted cell survival. SYK promotes the coupling of ITAM-bearing receptors to pro-survival pathways via the modulation of protein kinase activity ( ) leading to changes in the level of key regulators of apoptosis ( ) including increases in the production of anti-apoptotic proteins such as BCL-XL, MCL-1, BCL2A1, and XIAP; and a decrease in the pro-apoptotic protein HRK. SYK can also promote the activation of transcription factors ( ) such as STAT3, STAT5 and SREBP and enhance MYC-induced expression of microRNAs targeting ITIM-containing proteins such as CD22 and FCGR2B.

MCL-1 for destruction by phosphorylating it on Ser-159, which stimulates its ubiquitination by the Fbw7-containing Skp1-Cullin-F-box complex (SCF) to trigger subsequent proteasomal degradation [83]. Interestingly, PKCδ also is a downstream target of activated SYK in B-CLL cells [29]. Active PKCδ promotes the activation of AKT and also functions independently of AKT to inactivate GSK3 and stabilize MCL-1. This provides an alternative mechanism by which the level of MCL-1 can be regulated even in subsets of B-CLL cells in which AKT is not demonstrably activated. Thus, the treatment of cells with inhibitors of SYK results in the downregulation of MCL-1 at the level of protein stability due to an AKT and/or PKCδ-mediated inhibition of GSK3. In retinoblastoma, the expression of SYK also protects MCL-1 from degradation [72], indicating that this mechanism is likely to be operative in multiple tumor types.

Activation of the PI3K/AKT pathway also is an important promoter of cell survival in DLBCLs, although the consequences of activation vary with tumor type. In BCR-dependent DLBCLs exhibiting high levels of activated NF-κB, the inhibition of SYK or PI3K attenuates the transcription of NF-κB-regulated genes that include *BCL2A1*, a gene that codes for an anti-apoptotic member of the BCL-2 family [38]. In contrast, in BCR-dependent cells with low levels of NF-κB, BCR signaling represses the expression of HRK, a BH3 domain-only pro-apoptotic protein [38]. Inhibitors of either SYK or PI3K enhance the expression of HRK, which then promotes apoptosis through its interactions with anti-apoptotic proteins such as BCL-2 and Bcl-xL [38,84].

The expression of LMP2A in EBV-infected cells promotes cell survival through the SYK-dependent, constitutive activation of PI3K/AKT, which enhances the expression of the anti-apoptotic protein, BCL-XL (BCL2L1) [85], and protects EBV+ Burkitt's lymphoma cells from MYC-induced apoptosis [86]. In EBV+ B cell lymphomas, the inhibition of SYK also results in the degradation of the caspase 3 inhibitor, XIAP [87], due to a decrease in the AKT-dependent inhibition of HTRA2, a protease for which XIAP is a known substrate [52].

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase and well known regulator of tumor growth and proliferation that is activated downstream of the PI3K/AKT pathway [88]. In AML, inhibitors or shRNA targeting SYK suppress the activity of mTOR, which is constitutively active in untreated cells [89]. Combinations of SYK inhibitors with inhibitors of PI3K or mTOR synergize to induce AML cell differentiation.

Interesting positive feed-forward signals also can be stimulated through the PI3K/AKT pathway to enhance the efficiency of BCR-signaling in some tumor cells. The BCR-mediated activation of SYK and PI3K/AKT in DLBCLs activates the transcription factor SREBP, a key regulator of genes required for cholesterol biosynthesis [38]. The resulting increased expression of enzymes of the cholesterol anabolic pathway elevates plasma membrane cholesterol, which enhances BCR-signaling by promoting receptor clustering within cholesterol-rich membrane microdomains or lipid rafts. Additionally, the SYK-dependent activation of AKT and consequent inhibition of GSK3 increase the intracellular level of MYC, whose degradation is enhanced when phosphorylated by GSK3. MYC activates the miR17-92 cluster of microRNAs, which enhance BCR signaling by downregulating the expression of inhibitory proteins including CD22 and FcγRIIb (FCGR2B) [90]. Both CD22 and FcγRIIb contain within their cytoplasmic tails immunoreceptor tyrosine-based inhibitory motifs (ITIMs). ITIMs, when phosphorylated on tyrosine, bind negative regulators of BCR signaling including the lipid phosphatase SHIP1 and the tyrosine phosphatase SHP-1 [91]. Thus, either enhanced expression of MYC or of the miR17-92 cluster reduces the expression of ITIM-containing proteins to promote the BCR-dependent activation of downstream signaling effectors that include SYK, PI3K and AKT.

SYK also is tied to pro-survival pathways not directly associated with increased activity of the PI3K/AKT pathway. In multiple cell types including DLBCL, Burkitt's lymphoma, and breast carcinoma, an interaction of SYK with nucleolin (NCL) promotes the binding to NCL of the mRNA coding for the anti-apoptotic protein, BCL-XL, but not the alternatively spliced message coding for the smaller pro-apoptotic protein, BCL-XS [92]. This interaction with NCL stabilizes the BCL-XL transcript from being degraded in response to oxidative or genotoxic stress. SYK also influences the activity of signal transducer and activator of transcription (STAT) proteins, transcription factors that are activated through phosphorylation on tyrosine. Of the many STAT proteins, STAT3 and STAT5 in particular are key regulators of tumor cell survival [93]. Proteomic analyses of SYK-interacting proteins in AML identified both STAT3 and STAT5 as direct binding partners of SYK [56]. Both are constitutively activated and phosphorylated in AML cells in which tonic signaling and SYK activation are mediated by integrins and FcRγ. The expression of constitutively active forms of STAT3 or STAT5 rescues AML cells from the anti-proliferative effects of inhibitors of SYK activity or expression. Similarly, the expression in cells of the TEL-SYK fusion protein results in the phosphorylation of STAT5 [94], while STAT3 is phosphorylated in both B-CLL and B-ALL cells through a SYK-dependent pathway [31,95]. Interestingly, the activation of STATs occurs via pathways independent of Janus kinases (JAKs), the canonical upstream regulators of STAT activity. Finally, in ovarian cancer cells, SYK promotes cell survival by inhibiting the expression of C-JUN [73]. Consequently, apoptosis triggered by a loss of SYK is partially rescued by inhibitors of JNK, the upstream activator of C-JUN.

3. SYK as a tumor suppressor

3.1. SYK and tumor suppression in B-ALL

The vast bulk of the evidence from studies on tumor cells of hematopoietic origins indicates that the presence of SYK and its activation are important for cell survival and, as such, promotion of tumor growth with one notable exception. The abnormal alternative processing of *SYK* mRNA leads to a dramatic reduction in SYK expression and activity in childhood CD19+CD10- pro-B cell ALL that likely arrests cellular maturation at the pro-B cell to pre-pre-B cell transition. This is a rare example where a loss of SYK contributes to malignant progression in a B cell-derived cancer [96].

3.2. SYK and tumor suppression in carcinomas

Defining a precise role for SYK in carcinomas, cancers derived from epithelial cells, has been a complicated process. In some cell and tissue types, SYK appears to be associated with a malignant phenotype as discussed above. However, for many tumor types, SYK is encountered frequently in well or moderately differentiated carcinomas, but it is absent from poorly differentiated and invasive cells. Its knockdown in more well differentiated cancers enhances invasive growth behaviors while its re-expression in highly malignant cancer cells retards motility and inhibits metastasis. Thus, SYK is frequently described as a tumor suppressor in many epithelial cell-derived cancers.

An inverse relationship between SYK expression and tumor progression was first described by Mueller and co-workers studying a role for the kinase in mammary carcinogenesis [97]. At both the mRNA and protein levels, SYK is present in normal mammary gland epithelial cells and in breast cancer cells of low metastatic potential, but is absent from highly invasive, malignant cell lines. In patient samples, the loss of SYK during tumor development is progressive with levels of the kinase reduced in ductal carcinoma in situ (DCIS) and lost in invasive breast cancer [19,98]. Distant metastases are more frequently encountered in breast cancer patients with reduced levels of SYK mRNA [99]. The loss of SYK is a consequence of both the methylation of CpG islands in the *SYK* promoter and allelic loss. The *SYK* promoter is frequently hypermethylated in primary breast tumors, but unmethylated in adjacent normal breast tissue [100]. Heterozygotic loss of the *SYK* gene is frequent in invasive ductal carcinoma (IDC) and in DCIS located adjacent to IDC [19]. Consequently, *Syk* haploinsufficient mice exhibit an increased risk of mammary tumors [20].

A similar asymmetric distribution of SYK between well and poorly differentiated cancer cells is seen in a number of different tumor tissues. SYK is present in normal ducts and ductules in the pancreas and in well differentiated malignant ducts, but is lost as pancreatic ductal adenocarcinoma (PDAC) cells progress through moderately differentiated to poorly differentiated [101]. Similarly, SYK is present in differentiated PDAC cell lines, but is absent from less differentiated lines. Interestingly, the pancreatic and lung cancer cells dependent on K-RAS (and SYK) for survival have a more epithelial morphology while K-RAS-independent cells that lack SYK have a mesenchymal morphology [70]. Decreases in the expression of SYK in more malignant, invasive tumor cells due to epigenetic silencing are also seen in bladder cancer [102], colorectal cancer [103], melanoma [104,105], gastric cancer [106,107], nasopharyngeal cancer [108], and hepatocellular carcinoma (HCC) [109]. Interestingly, SYK levels are controlled also at the protein level by CHK1, which is frequently overexpressed in HCC. CHK1 phosphorylates SYK on Ser-295 promoting its ubiquitination and proteasomal degradation [110].

Carcinomas at the primary tumor site generally have an epithelial morphology, are tightly packed, and are characterized by the expression of E-cadherin located at the sites of fixed cell–cell junctions. The process by which cancer cells leave the primary tumor to enter the circulation and travel to distant sites requires a transition to a mesenchymal phenotype characterized by a loss of cell polarity, increased motility, and enhanced invasive properties [111]. This epithelial-to-mesenchymal transition (EMT) is crucial for embryogenesis and organ development, but cancer cells use this process to initiate invasion and metastasis. Variances in the expression of SYK in poorly versus well or moderately differentiated tumor cells likely reflect intrinsic effects of the kinase on the differentiation and physical properties of these cells that include the regulation of EMT. The expression in immortalized, but nontransformed, MCF10A breast epithelial cells of a shRNA targeting SYK increases cell motility, invasion, and growth in soft agar and induces a more fibroblast-like morphology characteristic of EMT [20]. Analysis of changes in gene expression resulting from the silencing of SYK expression confirms the loss of epithelial gene products and the increased expression of genes characteristic of mesenchymal cells. Similarly, a catalytically inactive form of SYK expressed in MCF7 cells acts as a dominant negative mutant to increase tumorigenesis in a mouse xenograft model [97]. Comparable results are observed in K-Ras addicted pancreatic carcinomas where the knockdown of SYK expression leads to a loss of E-cadherin expression, a characteristic feature of EMT [70]. Interestingly, *SYK* is included in the EMT core gene signature as a gene reduced in expression in breast cancer cells undergoing EMT in response to multiple EMT-inducing transcription factors [112]. Thus, SYK is a negative regulator of the EMT process, which likely explains much of its differential expression in well versus poorly differentiated tumors.

The ability of SYK to enhance and support the growth properties of cells with an epithelial phenotype likely underlies its growth inhibitory effects when re-expressed in more malignant, invasive mesenchymal cells that normally lack SYK. The re-introduction of SYK into highly invasive breast carcinomas reduces cell motility [113], invasive growth [97] and slows tumor growth and inhibits metastases in animal xenograft models [97]. Similar reductions in cell migration and invasion are seen when SYK is re-expressed in SYK-negative hepatocellular carcinoma [109], colorectal cancer [103], melanoma [104,105] and pancreatic adenocarcinoma [101]. Gene expression analyses of SYK-negative Panc1 cells identified significant changes in the expression of over 2000 genes resulting from the re-expression of SYK [101] including genes such as MMP2 that are required for invasive growth. Panc1 cells in which SYK is re-expressed develop a more differentiated phenotype and have increased cell–cell interactions [101], which is consistent with the ability of SYK to enhance cell–cell interactions in breast cancer cells [113]. Rapid changes in the physical properties of cancer cells expressing SYK can be observed upon the application of inhibitors of the kinase [113]. Thus, the negative effect of SYK on the growth properties of metastatic tumor cells is likely a product both of SYK-dependent changes in gene expression and the more direct effects of phosphorylation of modifiers of cytoskeletal dynamics [114,115]. For example, SYK can catalyze the phosphorylation of cytoskeletal proteins such as α-tubulin, cortactin, E-cadherin, α-catenin and MAP1B [113–117]. SYK also is recruited to the centrosome where multiple substrates are located [118,119]. It is this ability of SYK to enhance adhesion and negatively affect motility and invasion that explains its absence from highly aggressive tumor cells and underlies its classification as a tumor suppressor in certain tumor cell types.

As carcinoma cells progress to a more highly invasive phenotype, the suppression of SYK expression and activity likely requires the upregulation of additional mechanisms for survival. For example, many K-Ras-independent carcinomas are deficient in PTEN [70] and have high levels of active AKT, which promotes cell survival. Interestingly, a fraction of primary DLBCL samples exhibit increases in the *SYK* gene copy number while a distinct subset exhibits a loss of *PTEN* [38], suggesting that both mechanisms may independently promote cell survival.

3.3. Alternative splicing of SYK

Transcription of the *SYK* gene gives rise to two alternatively spliced products: full-length SYK, which is sometimes referred to as Syk(L), and the shorter gene product SYKB, also referred to as Syk(S). SYKB lacks a stretch of 23 amino acids in linker B, referred to as the linker insert or DEL [120], and is intrinsically less active as compared to SYK in coupling the BCR to intracellular signaling [121]. Growing evidence indicates that SYK and SYKB have different effects on the growth properties of cancer cells. SYKB is found, along with SYK, in many breast cancer cell lines in which the *SYK* gene is not silenced, but is missing from normal breast epithelial cells [120]. Interestingly, unlike full-length SYK, the ectopic expression of SYKB in highly invasive breast cancer cells fails to reduce cell invasiveness [120]. Similarly, the expression pattern of SYK versus SYKB varies in HCC. SYK levels are down-regulated in HCC tumor samples as compared to normal liver tissue, but SYKB levels are actually higher in HCC [122]. Since the phosphorylation site on SYK for CHK1 is located in the DEL sequence, elevated levels of CHK1 also lead to the selective loss of the full-length kinase while not affecting the level of SYKB [110]. The re-expression of SYK, but not SYKB in SYK-negative HCC cells inhibits cell growth in vitro and tumor growth and metastasis in vivo [122]. In fact, the expression of SYKB moderately enhances tumor cell growth and promotes the formation of lung metastases in mice. Of the two splice isoforms, SYKB is found preferentially in poorly differentiated HCC cells where its presence correlates with increased features of cells having undergone EMT. In fact, the expression of SYKB is a significant indicator of poor prognosis in HCC patients [122]. Thus, SYKB lacks the tumor suppressive activities of SYK, and its expression may actually contribute to a more highly transformed phenotype.

Even in cells where the overall effect of the elevated expression of SYK enhances tumorigenesis, differences exist in the properties of the two splice isoforms. An analysis of alternative splicing and its contributions to tumor cell survival identified splicing of the *SYK* transcript as a major contributor to ovarian cancer cell survival [73]. In this system, the induction of SYK promotes cell survival, while the manipulation of *SYK* gene splicing to decrease SYK and increase SYKB induces apoptosis. While the level of expression of SYK selectively reduces the expression of C-JUN to inhibit apoptosis, SYK-dependent changes in anchorage-independent growth are more a product of the total level of SYK isoforms expressed. Interestingly, the treatment of cells with EGF selectively promotes the expression of the full-length kinase to promote cell survival.

The differential effects of SYK and SYKB on the properties of cancer cells are generally attributed to differences in their respective localizations within the cell. Cellular fractionation and immunofluorescence studies indicate that SYK is present in both the nucleus and cytoplasm, but SYKB is confined to the cytoplasm [73,120,122]. SYK, but not SYKB, can enter the nucleus where it interacts with histone deacetylases and the transcription factor Sp1 to repress the transcription of Sp1-

Table 1
Cancer cells in which SYK functions as a tumor promoter.

Cancer type	Observation	Reference
B-cell lymphocytic leukemia (B-CLL)	Constitutively active SYK Inhibition of SYK induces apoptosis.	[28,31,32]
Diffuse large B-cell lymphoma (DLBCL)	Constitutively active SYK, gain in gene copy number Inhibition of SYK induces apoptosis or cell cycle arrest.	[36–38]
Follicular lymphoma (FL)	SYK inhibition induces apoptosis.	[41]
Mantle cell lymphoma (MCL)	SYK overexpressed due to gene amplification Inhibition induces apoptosis.	[42]
Marginal zone lymphoma (MZL)	SYK expression is upregulated.	[43]
B-cell acute lymphocytic leukemia (B-ALL)	Constitutively active SYK SYK inhibitors block cell and tumor growth.	[46–48]
Peripheral T cell lymphoma (PTCL)	Constitutively active SYK TEL-SYK fusion protein	[49,62]
EBV + post-transplant lymphoproliferative disorder (PTLD)	LMP2A-mediated SYK activation SYK inhibition induces apoptosis.	[53]
Acute myeloid leukemia (AML)	Integrin-mediated SYK activation SYK inhibition decreases proliferation and induces differentiation.	[54–56]
Nasopharyngeal carcinoma	LMP2A-mediated SYK activation	[65]
HER2-positive breast cancer	C35-mediated SYK activation	[67]
Pancreatic cancer	K-Ras dependent cells Silencing SYK results in apoptosis.	[68]
Lung cancer	K-Ras dependent cells Silencing SYK results in apoptosis.	[68]
Retinoblastoma	SYK expressed in cancer cells, but not normal retina SYK inhibition induces apoptosis.	[70]
Ovarian cancer	SYK expression increases with tumor grade. SYK inhibition induces apoptosis.	[71]
Small cell lung cancer (SCLC)	Elevated SYK expression in tumors Silencing SYK promotes apoptosis.	[72,73]
Squamous cell carcinoma of the head and neck (SCCHN)	Elevated SYK expression enhances motility.	[74]

regulated oncogenes such as CCD1 (cyclin D1) and FRA1 (FOSL1) [123]. Consistent with such a mechanism, the appearance of SYK in the nucleus is of positive prognostic significance in gastric cancer [107].

The basis of the differential localization of SYK and SYKB is not entirely clear. The DEL region resembles a bipartite nuclear localization signal (NLS) and the replacement of basic amino acids within this sequence results in the exclusion of SYK from the nucleus [120]. However, the replacement of Y290 (based on the murine Syk numbering system) with a phenylalanine has the same effect, but this change actually converts the DEL into a nuclear export sequence (NES) [124]. Attachment of the entire linker B region, but not the DEL sequence, to a heterologous protein can deliver it into the nucleus [120]. However, this activity maps to a region located near the C-terminal end of the linker, well removed from the DEL, which is located in the N-terminal one-third of linker B [124]. The localization of full-length SYK itself also is subject to regulation as integrin clustering, BCR engagement and PKC activation result in a translocation of SYK out of the nucleus [113,124]. Regardless of the mechanism, it is clear that an analysis of changes in the levels of total SYK plus SYKB mRNA and/or total SYK plus SYKB protein (e.g., as measured by immunofluorescence microscopy) can be misleading when assessing the potential involvement of SYK in modulating the growth properties of a particular cancer type.

4. Conclusions

The ability of SYK to function as either a promoter (Table 1) or suppressor (Table 2) of malignant cell growth appears to be highly dependent on the cell type and its stage of differentiation, the relative levels of the two SYK isoforms that are expressed, the mechanisms acting upstream of the kinase that lead to its activation, and the biological role

Table 2
Cancer cells in which SYK functions as a tumor suppressor.

Cancer type	Observation	Reference
Childhood $CD19^{+}CD10^{-}$ pro-B-ALL	SYK loss leads to malignancy.	[94]
Breast cancer	Decreased SYK correlates with invasion, metastasis and tumor grade. Promoter methylation and allelic loss SYK re-expression inhibits motility and metastasis. Silencing SYK induces EMT.	[20,95–98]
Pancreatic ductal adenocarcinoma	Loss of SYK in less differentiated tumor cells Silencing SYK induces EMT.	[68,99]
Bladder cancer	Decreased expression of SYK, epigenetic silencing	[100]
Colorectal cancer	Decreased expression of SYK, epigenetic silencing Re-expression reduces migration and invasion.	[101]
Melanoma	Decreased expression of SYK, epigenetic silencing Re-expression reduces migration and invasion.	[102,103]
Gastric cancer	Decreased expression of SYK, epigenetic silencing Change in nuclear localization	[104,105]
Nasopharyngeal cancer	Decreased expression of SYK, epigenetic silencing	[106]
Hepatocellular carcinoma	Decreased expression of SYK, epigenetic silencing CHK1-mediated degradation SYK re-expression inhibits motility and invasion. SYKB promotes metastasis.	[107,108,120]
Ovarian cancer	SYK promotes cell survival while SYKB induces apoptosis.	[71]

played by the kinase. The expression of SYK in cancer cells affects their growth properties primarily through three mechanisms: 1) The presence of SYK promotes cell survival by stabilizing at both the protein and mRNA level the expression of anti-apoptotic proteins. This activity underlies many of the tumor promoting activities of the kinase. 2) The presence of SYK alters gene expression to affect cellular differentiation programs that regulate EMT. This requires that SYK has the capacity to transit from the cytoplasm into the nucleus. This activity likely explains the differential expression of SYK between cancer cells of epithelial versus mesenchymal phenotypes. 3) As a consequence of its catalytic activity, the presence of SYK alters cytoskeletal dynamics to affect cell–cell and cell–matrix adhesion and cell motility. This activity likely underlies many of the tumor suppressive activities of the kinase when re-expressed in mesenchymal cells. However, the latter two functions of SYK can be corrupted by the elevated or abnormal expression of molecules bearing ITAM sequences that result in the aberrant sequestration and relocalization of the kinase. This dual role for SYK is likely to be a complicating factor in the development of SYK inhibitors for therapeutic purposes as it will be important to know the exact role being played by the kinase in the tumor cells being targeted.

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