SRC and STAT Pathways

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Members of the Src family of protein tyrosine kinases (SRC) can link signaling initiated by growth factor, integrin, and cytokine receptors on the surface of cells to their downstream effector signaling cascades (Figure 1).[1] Each protein consists of an amino-terminal domain that can be myristoylated, an SH2 and SH3 domain, a tyrosine kinase domain, and a negative regulatory element at the carboxy-terminus. When activated by receptor tyrosine kinases through SH2 binding, SRC is autophosphorylated at tyrosine 419. Phosphorylation of tyrosine 527, however, promotes an intramolecular interaction leading to a closed conformation and inactivation of the catalytic activity of SRC. SRC cooperates with multiple receptor tyrosine kinases to modulate signaling.[2] As one example relevant for lung cancer, c-Src cooperates with the epidermal growth factor receptor (EGFR), and Src-kinase activity is required for transformation by EGFR.[1–5] Phosphorylation of EGFR by c-Src modulates receptor function and allows for EGF-induced promotion of cell growth, survival, and angiogenesis.[6,7]

SRC signaling can result in activation of downstream signaling pathways that control cellular proliferation, survival, invasion and metastasis, and angiogenesis (Figure 1). SRC signaling can allow for enhanced cellular proliferation by up-regulating genes important in cell cycle progression, such as Myc, $p21^{WAF1/CIP1}$, cyclin D, $p27^{Kip1}$ and cdc2.[8,9] SRC protect cells against apoptosis induced by loss of cell adhesion (anoikis), and PI3K/Akt and Stat3 are key downstream survival cascades regulated by SRC. SRC promotes tumor cell invasion and metastasis by affecting cell adhesion, invasion, and motility.[10] c-Src can regulate both focal adhesions and adherens junctions necessary for invasion of tumor cells by activation of downstream focal adhesion kinase (FAK), $p130^{Cas}$, and paxillin.[10] VEGF and HIF1α are downstream targets for c-Src, and small molecule inhibitors of SRC can negatively regulate VEGF and inhibit angiogenesis.[11–15]

Increased SRC activity is found in human tumors, including lung cancer, resulting from diverse mechanisms including tyrosine phosphatase-mediated dephosphorylation of Tyr 527, increased SRC protein levels, increase in upstream receptor tyrosine kinase activity, or loss of negative regulatory proteins.[10,16,17] Small molecule inhibitors of SRC have antitumor properties through negatively regulating cell proliferation, survival, angiogenesis, and invasion.[18–20] A number of small-molecule oral SRC tyrosine kinase inhibitors such as dasatinib (BMS-354825), SKI-606, and AZD-0530 have entered early phase clinical trials.

STAT SIGNALING PATHWAYS

Signal transducers and activators of transcription (STAT) proteins are a family of cytoplasmic transcription factors with similar structure that are activated by tyrosine kinase signals.[21–24] STATs are activated when critical tyrosine residues become phosphorylated by protein tyrosine kinases, including membrane-bound growth factor receptors, such as EGFR, and non-receptor tyrosine kinases such as SRC and JAK. Once critical tyrosine residues on STAT proteins become phosphorylated, two monomers dimerize, translocate to the nucleus, and subsequently bind to cognate sequences contained within gene promoters where they cooperate with other transcriptional proteins to regulate gene expression. After activation of STAT-dependent genes, STAT activity is down-regulated through a number of mechanisms. Either gain of function mutations in upstream tyrosine kinases or loss of negative feedback mechanisms can contribute to STAT activation and oncogenesis.

Stat3 and Stat5 regulate basic biological processes important in tumorigenesis, including cell cycle progression, apoptosis, tumor angiogenesis, invasion and metastasis, and tumor cell evasion of the immune system.[23] Conversely, Stat1 is thought to play a tumor-suppressor role through anti-growth, pro-death, and enhanced immune recognition of tumor cells.[22] Numerous studies have shown constitutive activation of Stat3 and Stat5 in a diverse group to tumors from cancer patients, including lung cancer, and multiple studies have shown that inhibition of Stat3 or Stat5 activation results in growth suppression and apoptosis.[18,23,25]

Stat3 can up-regulate pro-survival genes such as Bcl-2, Bcl-xL, Mcl-1, survivin, and Akt while Stat3 can repress the pro-death genes TRAIL and p53.[23,26,27] Stat3 also regulates genes important in cell-cycle progression, such as Myc and cyclin D1, which act to drive cells through the G_1/S cell-cycle check point.[8,28] Stat3 has been shown to play an important role in tumor angiogenesis by up-regulating VEGF and HIF1α.[29,30] Inhibiting Stat3 in tumor cells increases the expression of pro-inflammatory cytokines that activate innate immune responses in dendritic cells and result in antitumor

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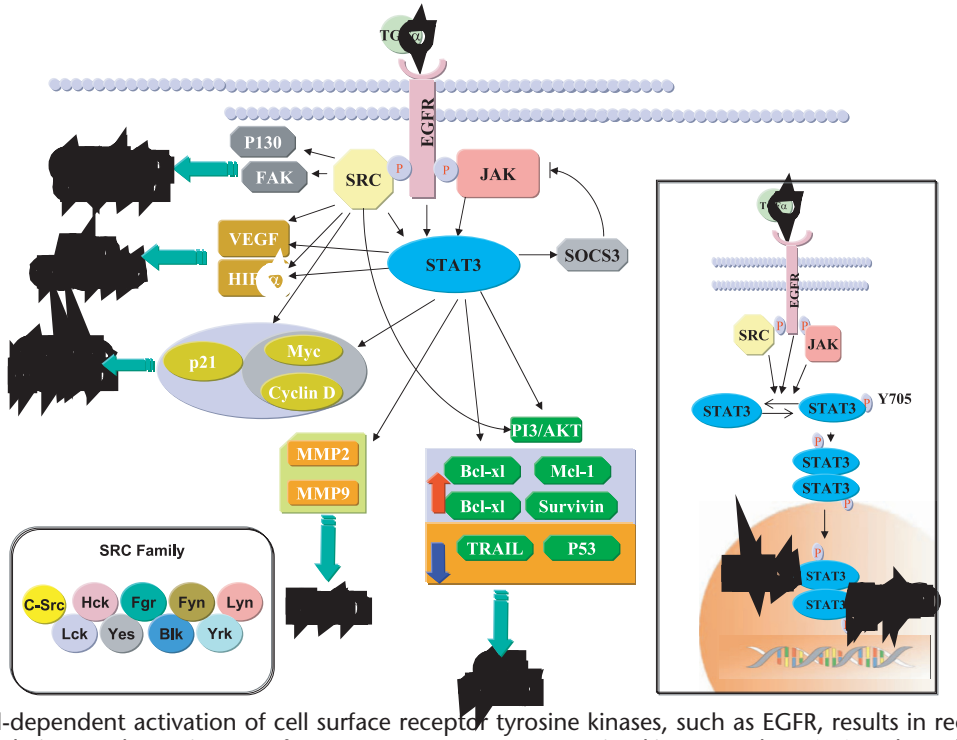

FIGURE 1. Ligand-dependent activation of cell surface receptor tyrosine kinases, such as EGFR, results in receptor dimerization, autophosphorylation, and recruitment of accessory non-receptor tyrosine kinases such as SRC and JAK family members. SRC family proteins (*left lower inset*) can activate a number of downstream proteins through tyrosine phosphorylation. Downstream proteins activated by SRC signaling include $p130^{Cas}$ and FAK (cell adhesion and invasion), PI3K/Akt (cell survival), and VEGF and HIF1α (angiogenesis). SRC signaling can also regulate cell cycle proteins such as c-Myc, cyclin D, and p21 through transcriptional and post-translational mechanisms. Tyrosine kinase activity of EGFR, SRC, and JAK proteins leads to tyrosine phosphorylation of Stat3 monomers, dimer formation, nuclear translocation, DNA binding, and transcription of Stat3-dependent genes (*right lower inset*). Activated Stat3 up-regulates a number of genes involved in the hallmarks of cancers, such as vascular endothelial growth factor (VEGF) and hypoxia inducible factor 1 α (HIF1α) (angiogenesis), c-Myc and cyclin D1 (cell cycle progression), and matrix metalloproteinases such as MMP2 and MMP9 (invasion). Stat3 plays a major role in controlling tumor cell survival by up-regulating Bcl-2 survival genes (Bcl-2, Bcl-xL, Mcl-1), the IAP member survivin, and Akt1 while repressing pro-death genes TRAIL and p53. Stat3 activates SOCS3 that negatively regulates JAK activity and hence is a negative feedback mechanism for Stat3 activation.

T-cell responses.[31,32] Finally, Stat3 has been implicated in the control of tumor cell invasion and metastasis through direct regulation of matrix metalloproteinase gene products and other genes implicated in tumor cell migration and invasion.[33–35]

Given the important role of Stat3 in cancer, a large effort is currently underway to develop novel inhibitors of Stat3 as well as Stat5.[22,36,37] Indirect approaches include inhibition of hyperactive upstream tyrosine kinase signals from upstream ligand-receptor interactions or aberrant receptor and non-receptor protein tyrosine kinases such as EGFR, SRC, and JAK. A direct approach involves direct targeting of STAT proteins through novel peptides, peptidomimetics, non-peptide analogues, peptide aptamers, platinum (IV) complexes, G-rich oligodeoxynucleotides, decoy oligonucleotides, antisense oligonucleotide, and siRNA approaches (reviewed in[37]).

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ERRATUM

Garfield DH, Cadranel JL, Wislez M, Franklin WA, Hirsch FR. The Bronchioloalveolar Carcinoma and Peripheral Adenocarcinoma Spectrum of Diseases. *J Thorac Oncol* 2006;1:344–359.

In the article that appeared on page 344 of the May 2006 issue, the author line and the Table of Contents should have listed the authors as follows: David H. Garfield, MD, Jacques L. Cadranel, MD, PhD, Marie Wislez, MD, PhD, Wilbur A. Franklin, MD, and Fred R. Hirsch, MD, PhD. This article was printed with a number of other errors. Please refer to the journal web site at www.jto.org for the final corrected version of this article. The citation for this article remains the same. The Editor regrets these errors.

