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). 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 that represses receptor signaling. As one example relevant for lung cancer, c-Src cooperates with multiple receptor tyrosine kinases to modulate intramolecular interaction leading to a closed conformation of the catalytic activity of SRC. SRC cooperates with 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. 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. Conversely, Stat1 is thought to play a tumor-suppressor role through anti-growth, pro-death, and enhanced immune recognition of tumor cells. 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.

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. Stat3 also regulates genes important in cell-cycle progression, such as Myc and cyclin D1, which act to drive cells through the G1/S cell-cycle check point. Stat3 has been shown to play an important role in tumor angiogenesis by up-regulating VEGF and HIF1α. Inhibiting Stat3 in tumor cells increases the expression of pro-inflammatory cytokines that activate innate immune responses in dendritic cells and result in antitumor immune responses in dendritic cells and result in antitumor

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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 in37).

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 p130Cas 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 1α (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.

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