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Targeting transcription factor STAT3 for cancer prevention and therapy

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ABSTRACT

Signal Transducers and Activators of Transcription (STATs) comprise an important class of transcription factors that have been implicated in a wide variety of essential cellular functions related to proliferation, survival, and angiogenesis. Among various STAT members, STAT3 is frequently overexpressed in tumor cells as well as tissue samples, and regulates the expression of numerous oncogenic genes controlling the growth and metastasis of tumor cells. The current review briefly discusses the importance of STAT3 as a potential target for cancer therapy and also provides novel insights into various classes of existing pharmacological inhibitors of this transcription factor that can be potentially developed as anti-cancer drugs.

Contents

Abbreviations: CML, chronic myelogenous leukemia; DBD, DNA-binding domain; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; HNSCC, head and neck squamous cell carcinoma; HCC, human hepatocellular carcinoma; IGFR, insulin-like growth factor receptor; IL, interleukin; IFN, interferon; JAK, Janus activated kinases; MM, myltiple myeloma; NSCLC, non-small cell lung cancer; PIAS, protein inhibitor of activated STATs; PDGFR, platelet-derived growth factor receptor; RTK, receptor tyrosine kinases; STAT, signal transducers and activators of transcription; Src, protein tyrosine kinase; STAT3i, STAT3 inhibitor; SOCS, suppressor of cytokine signaling; VEGF, vascular endothelial growth factor.

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1. Introduction

Signal Transducers and Activators of Transcription (STATs), a family of transcription factors, were first discovered in 1994 during the evaluation of the molecular pathways involved in interferon (IFN)-triggered gene regulation (Darnell, 1996; Siveen, Nguyen, et al., 2014; Siveen, Sikka, et al., 2014). A total of seven STAT proteins, STAT1, -2, -3, -4, -5a, -5b, and -6, have been identified till date in mammalian cells (Ihle, 2001; Subramaniam et al., 2013a; Sethi et al., 2014; Siveen, Nguyen, et al., 2014; Siveen, Sikka, et al., 2014) (Fig. 1), and have been found to mediate pleiotropic cellular functions including those related to cellular proliferation, survival, and angiogenesis (Xiong et al., 2014).

Generally, STATs are localized in the cytoplasm in an inactive state, and stimulation by diverse cytokines as well as growth factors can trigger their subsequent dimerization and activation (Mohan et al., 2014; Siveen, Sikka, et al., 2014; Dai et al., 2015; Lee et al., 2015). Consequently, phosphorylation at tyrosine residues on the cytoplasmic domain of the dimerized receptors by activated upstream kinases (called Janus activated kinases—JAKs) creates a dock for the SH2 domain of STAT proteins. Docked STAT proteins are subsequently activated via phosphorylation of specific tyrosine residues at their C-terminus by nearby JAKs. Activated STAT monomers forms homo- or hetero-dimers and translocate to the nucleus. Nuclear STAT dimers bind to specific sequences in the promoters of target genes to regulate gene transcription (Fig. 2) (Darnell et al., 1994; Aittomaki & Pesu, 2014; Mohan et al., 2014; Siveen, Sikka, et al., 2014; Dai et al., 2015; Lee et al., 2015). Besides JAKs, other tyrosine kinases that can activate STATs includes Src family members and growth factor receptors such as epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR) (Mohan et al., 2014; Siveen, Sikka, et al., 2014; Dai et al., 2015; Lee et al., 2015; Santoni et al., 2015).

2. STAT3 signal transduction cascade

STAT3 is a member of the STAT seven-member family that regulates gene transcription through relaying signals from activated plasma membrane receptors to the nucleus (Leeman et al., 2006; Quesnelle et al., 2007; Subramaniam et al., 2013a; Sethi et al., 2014; Siveen, Nguyen, et al., 2014; Siveen, Sikka, et al., 2014). Similar to other STAT family proteins, STAT3 contains a domain, an N-terminus containing the dimerization domain, a coiled-coil domain necessary for protein interactions, an SH2 domain essential for recruitment to receptors, a conserved tyrosine residue at position 705 (Tyr-705), and a central DNA binding domain (Xiong et al., 2014) (Fig. 1). Originally identified as an acute phase response factor activated by the interleukin (IL)-6 family of cytokines (Minami et al., 1996), further studies have demonstrated that STAT3 can also be activated by a diverse range of cytokines in addition to the IL-6 family (Takeda et al., 1997; Mohan et al., 2014; Siveen, Sikka, et al., 2014; Dai et al., 2015; Lee et al., 2015). Activation and inactivation of STAT3 are strictly regulated to prevent unscheduled gene regulation that may elicit a host of human diseases. STAT3 activation is achieved through phosphorylation of Tyr-705 by receptor tyrosine kinases (RTK) such as EGFR, PDGFR, fibroblast growth factor receptor (FGFR), insulin-like growth factor receptor (IGFR), receptor-associated kinases such as JAK, and non-receptor kinases such as Src and Abl (Mohan et al., 2014; Siveen, Sikka, et al., 2014; Xiong et al., 2014; Dai et al., 2015; Lee et al., 2015; Mali, 2015).

However, within the STAT3 C-terminus lies another phosphorylation site, serine 727 (Ser-727), whose phosphorylation also demonstrated gene regulation following nuclear translocation (Sakaguchi et al., 2012). Peak STAT3 phosphorylation occurs within 15–60 min of exposure to a cytokine and declines several hours thereafter (Subramaniam et al., 2013b). STAT3 signaling is negatively regulated by dephosphorylation of Tyr-705. Additionally, inactivation can also occur through two pathways: (1) Suppressor of cytokine signaling (SOCS) family of inhibitors; and (2) protein inhibitor of activated STATs (PIAS). STAT3 is inhibited at a transcriptional level through the SOCS family of inhibitors while PIAS1 inhibits STAT3 by preventing binding of STAT3 to DNA (Junicho et al., 2000; Flowers et al., 2005; Li et al., 2015).

Interestingly, unlike other STATs, STAT3 can enter the nucleus independent of its phosphorylation. Activated STATs shuttle more rapidly but inactivated STATs may also translocate into the nucleus through its direct interaction with nuclear pore proteins (i.e. nucleoporins) such as Nup153 and NUP214 (Pranada et al., 2004; Herrmann et al., 2007). In 2004, using fluorescence localization after photobleaching (FLAP), Pranada et al. demonstrated nucleocytoplasmic shuttling of STAT3 to be a dynamic process independent of Tyr-705 phosphorylation and cytokine stimulation (Pranada et al., 2004). Conversely, the karyopherin family of transport proteins, referred to as importins or exportins, mediate nuclear translocation of activated STATs (Reich & Liu, 2006). Nonetheless, nuclear accumulation of activated STAT3 is strongly dependent on Tyr-705 phosphorylation coupled with enhanced nuclear import and reduced nuclear export (Pranada et al., 2004).

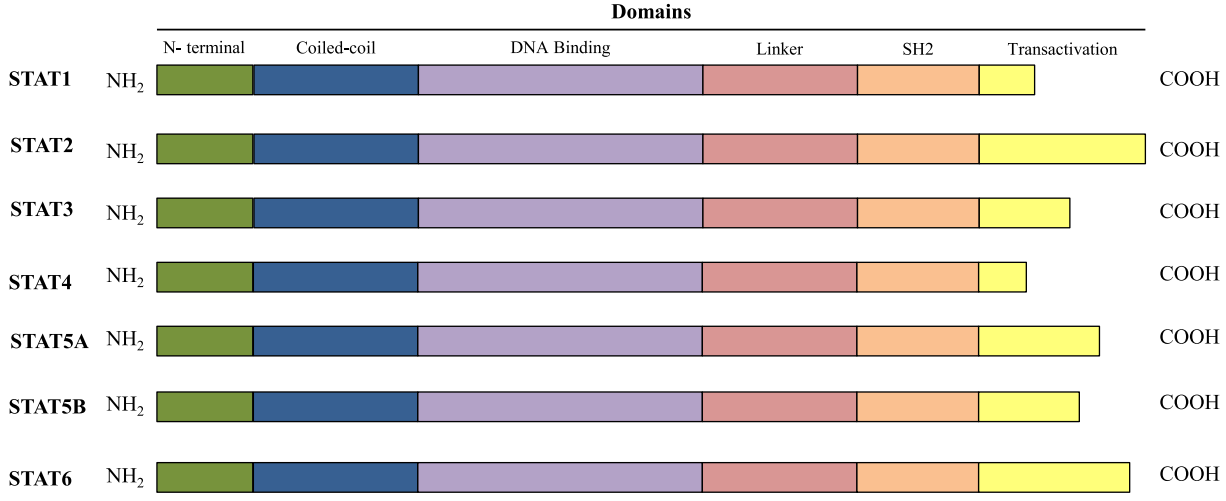

Fig. 1. STAT family of proteins. Linear representation of the domain structures of the seven signal transducer and activation of transcription (STAT)-family proteins: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. The N-terminal domain mediates interaction between STATs, promoter binding, and assembly of transcription machinery. The coiled-coil domain facilitates interactions with regulatory proteins and transcription factors. The DNA-binding domain makes direct contact with STAT-regulated gene promoters, with a consensus core sequence of TT(N4–6)AA. The SH2 domain mediates dimerization via interaction with phosphorylated Tyr705 of another STAT monomer. The transactivation domain is responsible for transcriptional activation of target genes. The transactivation domain of some STATs may contain a serine residue that has been demonstrated to regulate transcriptional activity.