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Signal Transducer and Activator of Transcription-3, Inflammation, and Cancer:

How Intimate Is the Relationship?

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Abstract

Signal transducer and activator of transcription-3 (STAT-3) is one of six members of a family of transcription factors. It was discovered almost 15 years ago as an acute-phase response factor. This factor has now been associated with inflammation, cellular transformation, survival, proliferation, invasion, angiogenesis, and metastasis of cancer. Various types of carcinogens, radiation, viruses, growth factors, oncogenes, and inflammatory cytokines have been found to activate STAT-3. STAT-3 is constitutively active in most tumor cells but not in normal cells. Phosphorylation of STAT-3 at tyrosine 705 leads to its dimerization, nuclear translocation, DNA binding, and gene transcription. The phosphorylation of STAT-3 at serine 727 may regulate its activity negatively or positively. STAT-3 regulates the expression of genes that mediate survival (survivin, bcl-xl, mcl-1, cellular FLICE-like inhibitory protein), proliferation (c-fos, c-myc, cyclin D1), invasion (matrix metalloproteinase-2), and angiogenesis (vascular endothelial growth factor). STAT-3 activation has also been associated with both chemoresistance and radioresistance. STAT-3 mediates these effects through its collaboration with various other transcription factors, including nuclear factor-κB, hypoxia-inducible factor-1, and peroxisome proliferator activated receptor-γ. Because of its critical role in tumorigenesis, inhibitors of this factor's activation are being sought for both prevention and therapy of cancer. This has led to identification of small peptides, oligonucleotides, and small molecules as potential STAT-3 inhibitors. Several of these small molecules are chemo-preventive agents derived from plants. This review discusses the intimate relationship between STAT-3, inflammation, and cancer in more detail.

Keywords

STAT-3; inflammation; cancer; chemoresistance

Introduction

Signal transducer and activator of transcription (STAT)-3 is one of the members of a family of transcription factors. It was first identified in 1994 as a DNA-binding factor that selectively binds to the IL-6-responsive element in the promoter of acute-phase genes from

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Conflicts of Interest
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IL-6-stimulated hepatocytes.[1] STAT-3 was also independently identified as a DNA-binding protein in response to epidermal growth factor.[2] The gene that encodes STAT-3 is located on chromosome 17q21. The 92-kDa protein is 770 amino acids long with sequential N-terminal coiled-coil domain, DNA-binding domain, a linker, SH2 domain, and C-terminal transactivation domain. The latter contains a tyrosine residue at position 705 and a serine residue at position 727, which undergoes phosphorylation when activated (Fig. 1).

STAT-3 is activated by many cytokines and growth factors, including epidermal growth factor,[3] platelet-derived growth factor,[4] and IL-6[1] as well as by oncogenic proteins, such as Src[5] and Ras[6] (Table 1). In addition numerous carcinogens, such as cigarette smoke[7] and tumor promoters, have been identified that can activate STAT-3.[8,9]

The activation of STAT-3 is regulated by phosphorylation of tyrosine 705 by receptor and nonreceptor protein tyrosine kinases (Table 2). These include epidermal growth factor receptor (EGFR) kinase,[92] Src,[5] Janus-activated kinases (JAK),[93–95] and extracellular signal-regulated kinase (ERK).[96] The phosphorylation of STAT-3 in the cytoplasm leads to its dimerization, translocation into the nucleus, and DNA binding; as a result genes that regulate cell proliferation, differentiation, and apoptosis are expressed. In addition, numerous serine kinases have been implicated in the phosphorylation of STAT-3 at serine 727. These include protein kinase C (PKC),[97] mitogen-activated protein kinases, and CDK5.[98] PKC-ε has been shown to interact with STAT-3 directly and phosphorylate serine 727,[99] which maximizes its transcriptional activity.[100,101]

Besides phosphorylation on tyrosine and serine sites within the carboxyl-terminal region, STAT-3 is also acetylated on a single lysine residue 685 by histone acetyltransferase p300[142] (Table 2). STAT-3 acetylation is reversible by type I histone deacetylase (HDAC). The acetylation of STAT-3 was found to be critical for it to form stable dimers, which are required for cytokine-stimulated DNA binding and transcriptional regulation.

STAT-3 activation is negatively regulated through numerous mechanisms (Table 2). These involve the suppressors of cytokine signaling (SOCS),[136] protein inhibitor of activated STAT (PIAS),[105] protein phosphatases,[173] and ubiquitination-dependent proteosomal degradation[174] (Table 2). The SOCS proteins were shown to bind to the JAK activation loop as pseudosubstrate inhibitors through their SH2 domain, thereby blocking subsequent signaling that requires phosphorylation and activation of STAT-3.[175] Eight SOCS proteins with similar structures have been identified so far.[176] SOCS-3 negatively regulates the gp130-STAT-3 pathway in mouse skin wound healing, suggesting that STAT-3 is required for wound healing.[177] Different SOCS family members, however, have distinct mechanisms of inhibition of JAK/STAT signaling. Recently, the involvement of SOCS-1 in carcinogenesis has been reported.[178] Frequent hypermethylation in CpG islands of the functional SOCS-3 promoter correlates with its transcription silencing in cell lines (lung cancer, breast cancer, and mesothelioma) and primary lung cancer tissue samples.[179–181] Restoration of SOCS-3 in lung cancer cells where *SOCS-3* was silenced by methylation resulted in the downregulation of active STAT-3, induction of apoptosis, and growth suppression.[181] Methylation silencing of SOCS-3 is an important mechanism of constitutive activation of the STAT-3 pathway in cancer pathogenesis.[178,179]

In contrast to SOCS, the PIAS-3 are nuclear factors that are able to interact with phosphorylated STAT-3 and block transcription.[105] Smad4 has been shown to suppress the tyrosine phosphorylation of STAT-3 in pancreatic cancer cells.[182]

STAT-3 activation is also negatively regulated by various protein tyrosine phosphatases, including CD45,[123] PTEN,[124] SHP-1,[183] SHP-2[184] (Table 2).

The ubiquitin-proteasome pathway is responsible for selective degradation of shortlived cellular proteins and is critical for the regulation of many cellular processes. STAT-3 has been shown to undergo degradation through this pathway.[174,185,186] In IL-6-dependent KT-3 cells, the transcription factor was found to be conjugated by exogenous biotinylated Ub and degraded in a proteasome-dependent manner.[174] Additionally, caspases have been found to directly cleave STAT-3.[187] STAT-3 cleavage was accompanied by reductions in STAT-3–DNA binding, STAT-3-driven reporter protein (luciferase) activity, and the expression of selected STAT-3-dependent genes and correlated with increased sensitivity to apoptotic stimuli.

The ablation of STAT-3 leads to embryonic lethality,[188] and tissue-specific ablation of the transcription factor yields important defects in hepatocytes,[189] macrophages,[190] keratinocytes,[191] and thymic or mammary epithelial cells.[192]

STAT-3 is an oncogenic protein that is constitutively activated in many human cancers. For instance, in 30–60% of primary breast cancers, STAT-3 is constitutively active.[193] Constitutive activation of STAT-3 has also been reported in several other primary cancers, in tumor cell lines, and in many oncogene-transformed cells. Inactivation of STAT-3 in most of these cell lines leads to inhibition of cell proliferation. The critical role of this factor in cancer is indicated by the fact that β4 integrin actively contributes to the initiation, growth, and invasion of ErbB2-induced mammary tumors in transgenic mice by promoting the activation of STAT-3.[194] The evidence below shows that STAT-3 activation is intimately connected with all aspects of tumorigenesis.

STAT-3 Activation Mediates Inflammation

Several lines of evidence suggest that STAT-3 is a mediator of inflammation.[195] First, STAT-3 was initially discovered as an acute-phase response protein, thus suggesting its link to inflammation. Second, most proinflammatory agents have been shown to activate this factor. IL-6 is a major mediator of inflammation and mediates its effects through the activation of the STAT-3 pathway.[2] Similarly, tumor promoters, lipopolysaccharides, and cigarette smoke can activate the STAT-3 pathway.[7,196] Third, the DNA binding for STAT-3 in the promoter of acute-phase proteins was found to compete with that of NF-κB, another pro-inflammatory transcription factor.[139] Fourth, STAT-3 has been shown to regulate NF-κB recruitment to the IL-12p40 promoter in dendritic cells.[197] Fifth, recently it was shown that IL-11 and its glycoprotein 130 (gp130) receptor in inflammation-associated gastric epithelial cell oncogenic transformation is mediated by and dependent on increased activation of STAT-3.[198] Sixth, in some cell types IL-6-induced STAT-3 activation has been shown to be dependent on cyclooxygenase 2, a pro-inflammatory enzyme.[199] All this evidence supports the role of the STAT-3 pathway in inflammation.

STAT-3 Activation Can Transform Cells

The transformation of cells by various oncogenes, protein tyrosine kinases, and viruses accompanies the activation of STAT-3.[200] Yu *et al.* showed that transformation of cells by src protein kinase is mediated through the activation of STAT-3.[5,201] Similarly the transformation of T cells by human T-cell lymphotropic virus I was also mediated through the activation of STAT-3.[95] Hepatitis C virus core protein has also been shown to transform the cells through activation of STAT-3.[30] The STAT-3 activation is induced by v-Fps; by polyoma virus middle T antigen, which activates Src family kinases; and by v-Sis, which acts as a ligand for the platelet-derived growth factor receptor.[92] STAT-3 signaling is also required for hepatocyte growth factor/scatter factor-Met-mediated tumorigenes.[202] Moreover, a constitutively activated form of STAT-3 induces cell transformation, growth in

soft agar, and tumors in nude mice, further confirming the importance of the activated form detected in tumors. Thus, STAT-3 is considered an oncogene.[203]

STAT-3 Activation Can Suppress Apoptosis

Evidence indicates that oncogenic transformation of the cells leads to activation of STAT-3, which then provides the survival signal. Conditional inactivation of STAT-3 shows that it has proapoptotic functions during mammary gland involution.[192] In most cells, STAT-3 activation can suppress apoptosis. These effects are mediated through the expression of various cell survival gene products that are regulated by STAT-3. These include bcl-xl,[204,205] bcl-2,[206] survivin,[207] Mcl-1,[208] and cIAP2.[209] Additionally, most tumor cells that exhibit constitutive activation of STAT-3 also express these cell survival gene products.[210,211] Thus, suppression of STAT-3 activation can suppress the expression of all these cell survival gene products and potentiate apoptosis.[212] The downregulation of STAT-3 also leads to expression of fas protein, which can promote apoptosis.[213]

STAT-3 Activation Can Lead to Cellular Proliferation

STAT-3 activation has also been linked with proliferation of tumor cells. This effect of STAT-3 is mediated through its ability to induce the expression of cyclin D1.[214] STAT-3 has also been shown to upregulate the expression of several growth-promoting genes, such as myc[215] and pim-1.[216] The proapoptotic factors, such as Fas, are downmodulated by STAT-3 activation.[213] There are other reports, however, which suggest that this transcription factor can activate the expression of the cell cycle inhibitor p21(waf1),[217] suggesting that STAT-3 can also block cell cycle progression and prevent abnormal cell proliferation. During cellular transformation, however, phosphatidylinositol 3-kinase/Akt pathway was found to inhibit the transcriptional activation of the p21(waf1) gene by STAT-3 proteins without altering the regulation of the myc promoter.[218]

STAT-3 Activation Can Mediate Cellular Invasion

Numerous reports indicate STAT-3 activation plays a major role in tumor cell invasion, and inhibition of STAT-3 reduces invasion.[182,219–221] STAT-3 activation regulates the expression of matrix metalloproteinase (MMP)-2 and MMP-1, which then mediate tumor invasion and metastasis.[222,223] STAT-3 upregulates the transcription of MMP-2 through direct interaction with the MMP-2 promoter. Furthermore, blockade of activated STAT-3 in highly metastatic cells significantly suppresses the invasiveness of the tumor cells, inhibits tumor growth, and prevents metastasis in nude mice. Also, overexpression of phosphorylated STAT-3 correlates with the invasion and metastasis of cutaneous squamous cell carcinoma.[224] STAT-3, however, is also known to upregulate tissue inhibitors of metalloproteinase (TIMP)-1, a cytokine known to block metalloproteinases and decrease invasiveness in certain cancer cell types.[225] STAT-3 also controls the expression of the *MUC1* gene, which can mediate tumor invasion.[226] Thus, STAT-3 mediates tumor invasion through numerous mechanisms.

STAT-3 Activation Can Mediate Angiogenesis and Metastasis

One of the first pieces of evidence to suggest that STAT-3 is linked with angiogenesis was from granulocyte-macrophage colony-stimulating factor-induced angiogenetic activity in chick chorioallantoic membrane.[227] It was shown that constitutive STAT-3 activity upregulates vascular endothelial growth factor (VEGF) expression and tumor angiogenesis.[228] Most tumor cells that exhibit constitutively active STAT-3 also express VEGF.[229,230] Thus, downmodulation of STAT-3 activation can suppress the expression of VEGF and inhibit angiogenesis. Indeed, Li *et al.* found an inhibition of growth and

metastasis of human hepatocellular carcinoma by antisense oligonucleotide targeting of STAT-3.[231] The metastasis of human melanoma to brain was also linked to STAT-3 activation.[232] Besides VEGF, it has been shown that TWIST, another mediator of tumor metastasis, is regulated by STAT-3.[233]

Role of STAT-3 in Carcinogenesis

STAT-3 can mediate both the tumor initiation and the tumor promotion phases of carcinogenesis. While deletion of STAT-3 suppressed skin carcinogenesis,[9] forced expression enhanced malignant progression.[234,235] STAT-3-deficient mice were completely resistant to skin tumor development when 9,10-dimethylbenz-[a-]anthracene was used as the initiator and 12-*O*-tetradecanolyphorbol-13-acetate as the promoter.[9] Activation of STAT-3 has also been shown to be an early event in tobacco-chewing-mediated oral carcinogenesis in human samples.[32] The activation of STAT-3 has also been linked with hepatocarcinogenesis, as suggested by SOCS-3 deficiency in mice.[236]

Role of STAT-3 in Chemoresistance and Radioresistance

Activation of STAT-3 has been linked with resistance of tumor cells to chemotherapeutic agents.[80,237] Work from our laboratory and others have shown constitutive activation of STAT-3 in multiple myeloma can mediate chemoresistance.[238] This is mediated through the upregulation of antiapoptotic gene products regulated by STAT-3, as shown in metastatic breast cancer cells.[239] Thus, downmodulation of STAT-3 can overcome chemoresistance.[85]

The resistance of tumor cells to γ radiation has also been associated with STAT-3 activation. STAT-3-deleted B cells are highly susceptible to irradiation.[240] *In vivo* experiments with gene-targeted mice showed that IL-6 and, to a lesser extent, IL-10 are the relevant stimuli that combine with B-cell receptor (BCR) ligands to promote B-1 cell radioresistance. STAT-3 promotes cell survival in response to selected growth factors and is activated by combined BCR cross-linking and IL-6 (IL-10). Importantly, STAT-$3^{-/-}$ B-1 cells become susceptible to irradiation, indicating that STAT-3 activation by BCR accounts for the inherent radioresistance of peritoneal B-1 B cells. Kim *et al.* showed that DN-STAT-3 and DN-survivin together result in the greatest radiosensitization of MDA-MB-231 (breast cancer cell line), decreasing angiogenesis, and cell survival.[241]

Chemopreventive Agents Inhibit STAT-3 Activation

Several natural agents known to be chemo-preventive are quite effective in suppressing STAT-3 activation (Table 1). These include curcumin,[73,242] resveratrol,[85] ursolic acid,[87] guggulsterone,[80] capsaicin,[69] cucurbitacin,[72] indirubin,[81] flavopiridol,[77] epigallocatechin gallate,[75] CDDO-Me (methyl-2-cyano-3,12-dioxooleana-1,9-dien-28-oate),[70] emodin,[76] silibinin,[86] and chalcone.[71] How these phytochemicals suppress STAT-3 activation has been investigated. For instance, guggulsterone, ursolic acid, and capsaicin have been shown to transcriptionally upregulate the expression of SHP2, which leads to inactivation of STAT-3.[69,80,87] Other mechanisms have also been described. For instance, luteolin has been shown to promote the degradation in STAT-3 in human hepatoma cells.[243] Indirubin was found to inhibit STAT-3 activation through inhibition of Src kinase activity.[81]

Conclusions

This description, overall, shows that STAT-3 activation plays a very intimate role in tumorigenesis. Inhibitors of the STAT-3 pathway thus have enormous potential in the treatment of cancer. Whether STAT-3 can be exploited as a prognostic factor in human cancers remains to be examined.

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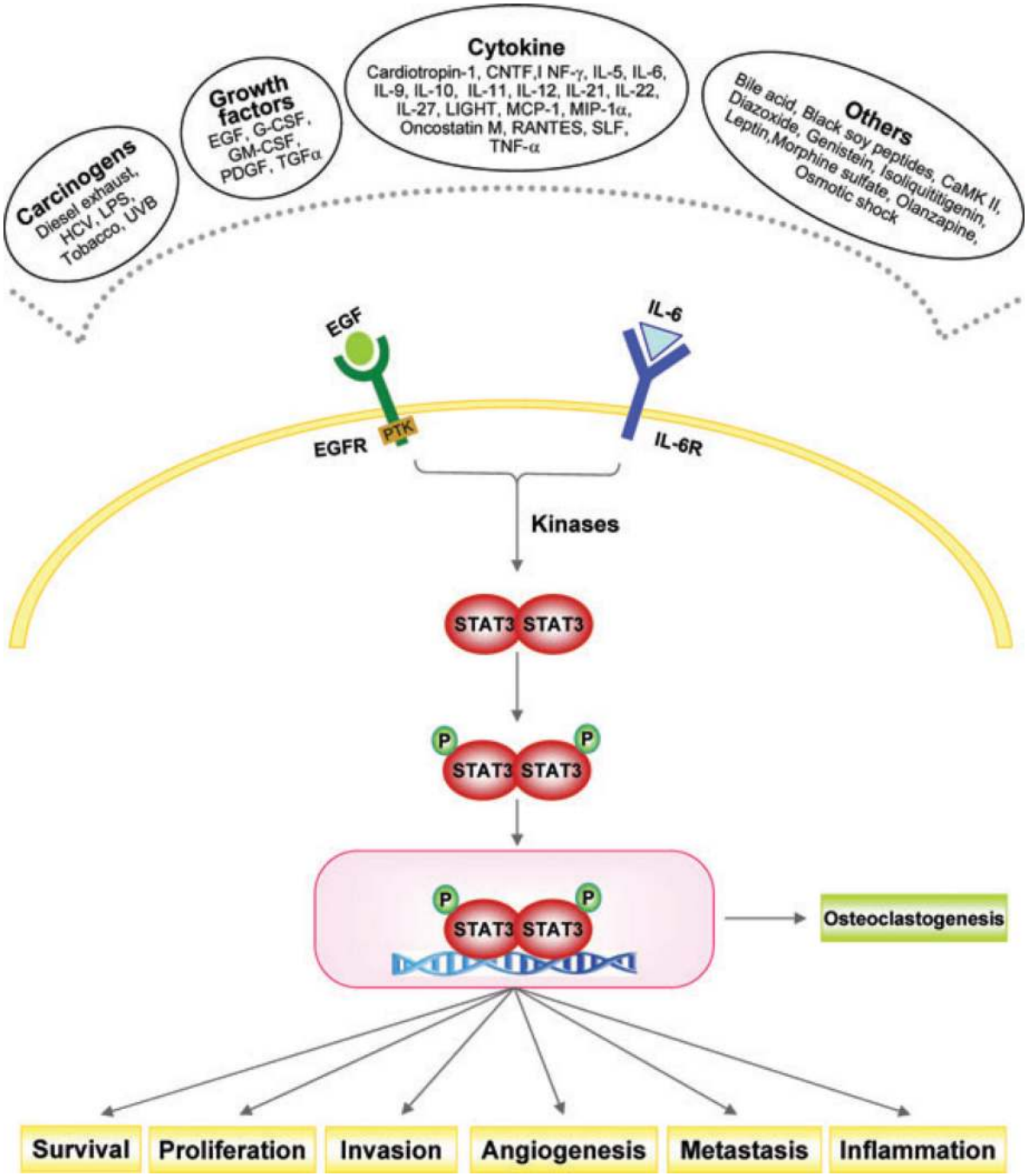

Figure 1.
Signaling pathway leading to signal transducer and activator of transcription (STAT)-3 activation (see text for definitions of abbreviations).

TABLE 1

Activators and Inhibitors of Signal Transducer and Activator of Transcription (STAT)-3

Activators	*Others*	• Sodium salicylate[64]
Cytokines	• Bile acids[34]	• Statin[65]
• Cardiotrophin-1[10]	• Black soy peptides[35]	• T40214[66]
• CNTF[11]	• CaMKIIg[36]	• UCN-01[67]
• IFN-γ[12]	• Diazoxide[37]	• WP-1034[68]
• IL-5[13]	• Genistein[38]	*Natural*
• IL-6[2]	• Isoliquiritigenin[39]	• Caffeic acid[49]
• IL-9[14]	• Leptin[40]	• Capsaicin[69]
• IL-10[15]	• Morphine sulfate[41]	• CDDO-Me[70]
• IL-11[16]	• Olanzapine[42]	• Chalcone[71]
• IL-12[17]	• Osmotic shock[43]	• Cucurbitacin[72]
• IL-21[18]	**Inhibitors**	• Curcumin[73]
• IL-22[19]	Synthetic	• Deoxytetrangiomycin[74]
• IL-27[20]	• AG 490[44]	• EGCG[75]
• LIGHT[21]	• Atiprimod[45]	• Emodin[76]
• MCP-1[22]	• Auranofin[46]	• Flavopiridol[77]
• MIP-1α[23]	• Aurothiomalate[47]	• Galiellalactone[78]
• Oncostatin M[24]	• BMS-354825[48]	• Genistein[79]
• RANTES[23]	• CADPE[49]	• Guggulsterone[80]
• SLF[25]	• Stattic[50]	• Indirubin[81]
• TNF-α[26]	• Dobesilate[51]	• Magnolol[82]
Growth Factors	• Ethanol[52]	• Parthenolide[83]
• EGF[2]	• NCX-4016[53]	• Piceatannol[84]
• G-CSF[27]	• Nelfinavir[54]	• Resveratrol[85]
• GM-CSF[13]	• PDP[55]	• Silibinin[86]
• PDGF[4]	• Platinum compounds[56]	• Ursolic acid[87]
• TGF-α[28]	• PS-341[57]	*Others*
Carcinogens	• Y(p)LPQTV[58]	• EKB569[88]
• Diesel exhaust particles[29]	• R115777[59]	• GQ-ODN[66]
• HCV[30]	• S31-M2001[60]	• Retinoic acid[89]
• LPS[31]	• S-3I-201[61]	• Rituximab[90]
• Tobacco[32]	• SCH66336[62]	• STA-21[91]
• UVB[33]	• SD-1029[63]	• TKS 050[79]

CaMKII, calmodulin-dependent protein kinase II; CAPDE, caffeic acid phenyl ethyl ester; CDDO-Me, methyl-2-cyano-3,12-dioxooleana-1,9-dien-28-oate; CNTF, ciliary neurotrophic factor; EGCG, (−)-epigallocatechin-3-gallate; EGF, epidermal growth factor; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; GQ-ODN, G-quartet oligodeoxynucleotide; HCV, hepatitis C virus; IFN-γ, interferon gamma; IL, interleukin; LIGHT, lymphotoxin homologue, inducible and competes with HSV glycoprotein D for HveA and is expressed on T lymphocytes; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein 1; MIP-1α, macrophage inflammatory protein-1-α; PDGF, platelet-derived growth factor; PDP, phosphododecapeptides; PS-341, bortezomib; RANTES, regulated on

activation normal T cell expressed and presumably secreted; SLF, steel factor; TGF-α, transforming growth factor α; TKS 050, N-{4-[(3,4-dichloro-6-fluoro-phenyl)amino]-quinazoline-6-yl}-2-chloroacetamide; TNF-α, tumor necrosis factor α; UVB, ultraviolet B radiation.

TABLE 2

Intracellular Modulators of STAT-3 Activity

Protein kinases

- JAK1 and JAK2 phosphorylate STAT-3.[2,93,94]
- Src kinase family of kinases (Src, Hck, Lyn, Fyn, and Fgr) binds STAT-3 and induces tyrosine phosphorylation.[5,102]
- Bcr-Abl induces tyrosine phosphorylation and DNA-binding activity of STAT-3.[103]
- JAK3 binds CD40 and phopshorylates STAT-3.[104]
- ERK binds STAT-3 and phosphorylates at ser 727, which negatively regulates Tyr 702 phosphorylation.[105]
- Fes binds and induces tyrosine phosphorylation of STAT-3.[106,107]
- PKCδ binds STAT-3, induces Ser727 phosphorylation, and inhibits its activity.[97,108,109]
- p94 (fer) binds and causes the tyrosine phosphorylation of STAT-3.[110]
- mTOR or p70 S6 kinase activated by PI3K/AKT mediates the serine 727 phosphorylation of STAT-3 by CNTF.[101]
- IRAK1 binds and causes the Ser 727 phosphorylation of STAT-3.[111]
- CDK9 binds STAT-3 and leads to human γ-fibrinogen gene expression.[77,112]
- ZIP kinase binds STAT-3 in the nucleus and enhances its transcriptional activity via phosphorylation of Ser727.[113]
- TGF-β-activated kinase 1 (TAK1) binds STAT-3 and increases ser 727 phosphorylation.[114]
- NIK binds STAT-3 in response to LIGHT.[21]
- Protein kinase C-ε binds and phosphorylates STAT-3 at Ser727.[99]
- Bruton's tyrosine kinase binds STAT-3 and prevents its activation.[115]
- Peptidyl-prolyl cis/trans isomerase 1 (Pin1) binds STAT-3, induces ser 727 phosphorylation, and enhances its activity.[116]

Protein phosphatases

- SHP-1 and SHP-2 prevents the phoshporylation of STAT-3 by negatively regulating JAK activity.[117]
- LMW-PTPase is negative regulator of STAT-3 phosphorylation.[118]
- Protein phosphatase 2 A translocates to nucleus and dephosphorylates STAT-3 at serine 727.[119,120]
- Protein-tyrosine phosphatase D1 activates STAT-3 through interaction with Etk.[121]
- Cytosolic isoform of PTPε inhibits STAT-3 activation by inactivating JAKs.[122]
- CD45 directly dephosphorylates and binds to JAKs.[123]
- PTEN is a negative regulator of STAT-3 activation through inhibition of PI3K/AKT pathway.[124,125]
- PTP1 B is a negative regulator of JAK2.[126]
- T-cell PTP inhibits IL-6-induced tyrosine phosphorylation and activation of STAT-3.[127]
- LMW-DSP2 regulates IL-6/LIF-mediated signaling through dephosphorylation of Jaks and STAT-3.[128]
- Receptor protein tyrosine phosphatase T dephosphorylates STAT-3.[129]

Viral proteins

- EZI, a novel nuclear zinc finger protein, binds nuclear STAT-3 and augments its activity.[130]
- Kaposi sarcoma-associated viral cyclin K binds nuclear STAT-3 and inhibits its activity.[131]
- Herpes virus saimiri subgroup A strain 11 (STP-A11) binds STAT-3 and increases its transcriptional activity.[132]
- Kaposi's sarcoma-associated herpes virus (KSHV)-encoded latency-associated nuclear antigen (LANA) binds STAT-3 and enhances its transcriptional activity.[133]

Others

- c-Jun binds STAT-3 β and enhances promoter activity.[134]
- IFNAR-1 chain binds to STAT-3 directly and enhances its activity.[135]
- SOCS family of proteins binds JAK and negatively regulates JAK-STAT pathway.[136]
- Glucocorticoid receptor binds to STAT-3 and forms a transactivating/signaling complex.[137]
- Protein inhibitor of activated STAT (PIAS)-3, an E3 ligase, binds STAT-3 and blocks its DNA-binding and gene expression.[105]
- SSI-1 [(for STAT-induced STAT inhibitor/SOCS)-1] binds Jak2 and Tyk2, and negatively regulates STAT-3 activation.[138]
- STAT-3 binds NF-κB p65 and inactivates its transcriptional activity.[139–141]
- CREB-binding protein (CBP)/P300 binds STAT-3, induces acetylation at Lys 685, and induces dimerization.[142–145]
- STAT-3-interacting protein, StIP1, binds STAT-3 and prevents nuclear translocation.[146]
- EGFR binds STAT-3 and stimulates its activity.[92,147]
- IL-2 receptor β chain binds to STAT-3.[148]
- Cyclin-dependent kinase inhibitor p21 binds to STAT-3 and inhibits its activity.[149]
- Cyclin D1 binds to nuclear STAT-3 and inhibits its activity.[150]
- Co-activator NcoA/SRC1a binds to STAT-3 through 752–761 region, phosphorylates ser 727, and enhances its activity.[151,152]
- Grb2 binds STAT-3 and inhibits its interaction with EGFR.[55,147,153]
- Rac1 GTPase binds and stimulates STAT-3 phosphorylation at tyrosine and serine residues.[154]
- MyoD binds STAT-3 and inhibits its activity.[155]
- Promyelocytic leukemia protein (PML) binds STAT-3 and inhibits cell proliferation.[156]
- GRIM-19 binds STAT-3 and negatively regulates its activity.[157]
- Prothymosine-α binds STAT-3 and enhances its activity.[158]
- PPARγ binds STAT-3 and inactivates its transcriptional activity.[159]
- Osteospecific transcription factor Runx2 binds nuclear STAT-3 and inhibits its activity.[160]
- Proline-, glutamic acid-, and leucine-rich protein-1 (PELP1) is a novel estrogen receptor co-activator that binds to STAT-3 in the nucleus and increases its activity.[161]
- PAX3-FKHR binds STAT-3 and its transcriptional activity.[162]
- A Ras homologue member I (ARHI) binds STAT-3 and inhibits its activity.[163]
- Histone deacetylase (HDAC)-1 binds STAT-3 and induces deacetylation.[142]
- SP1 binds STAT-3 and increases its transcriptional activity.[164]
- HIF-1α and p300 binds to STAT-3 and leads to VEGF expression.[165]
- Importin α5 and α7 bind to STAT-3 and enhance its activity.[166]
- G-CSFR phosphotyrosine peptide ligands pY704VLQ and pY744LRC bind to STAT-3.[167]
- Duplin, a negative regulator of Wnt signaling, binds STAT-3 and inhibits its DNA-binding activity.[168]
- Daxx binds STAT-3 in the nucleus and downregulates its transcriptional activation.[133]
- Unphosphorylated STAT-3 accumulates in response to IL-6 and activates transcription by binding to NF-κB.[169]
- Nescient helix-loop-helix 2 interacts with STAT-3 to regulate transcription of prohormone convertase 1/3.[170]
- Kruppel-associated box zinc-finger protein (KAP) 1 binds STAT-3 and regulates its transcriptional activity.[171]
- Binder of ADP-ribosylation factor-like two (BART) augments STAT-3 activity by keeping it in the nucleus.[172]

CDK9, cyclin-dependent kinase 9; CNTF, ciliary neurotrophic factor; DSP, dual specificity phosphatase; EGFR, epidermal growth factor receptor; G-CSFR, granulocyte colony-stimulating factor receptor; HIF-1α, hypoxia-inducible factor 1 subunit α; IFNAR-1, interferon (α, β, and ω) receptor 1; IRAK1, interleukin-1 receptor-associated kinase 1; JAK, Janus kinase; LMW, low molecular weight; PKC, protein kinase C; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; NIK, NF-κB-inducing kinase; PPARγ, peroxisome proliferator-activated receptor γ; PTEN, phosphatase and tensin homologue; PTP, protein tyrosine phosphatase; SOCS, suppressors of cytokine signaling; STAT, signal transducers and activators of transcription; EZI, endothelial cell-derived zinc finger protein; ZIP, leucine zipper kinase; GRIM-19, gene associated with retinoid-IFN-induced mortality-19; MyoD, myogenic differentiation; PAX3-FKHR, paired box 3-FKHR-Forkhead (Drosophila) homolog 1 (rhabdomyosarcoma).