Potential Role for STAT3 Inhibitors in Glioblastoma

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KEYWORDS

• Glioblastoma multiforme • STAT3 • Signal transducers and activators of transcription • Inhibitors

KEY POINTS

- Signal transducers and activators of transcription 3 (STAT3) is a transcription factor involved in cell differentiation, proliferation, and survival.
- In a variety of tumors, including glioblastoma multiforme (GBM), constitutive activation of STAT3 has been implicated as a critical mediator of tumorigenesis and progression.
- Constitutive activation of STAT3 in the GBM microenvironment drives angiogenesis, tumor cell proliferation, invasion, and immunosuppression.
- Targeting STAT3 affords an opportunity to intervene on multiple pro-oncogenic pathways at a single molecular hub.
- Clinical implementation of STAT3 blockade in GBM awaits the identification of safe and effective strategies for inhibiting STAT3 and the development of technologies that improve delivery of these agents to the CNS.

INTRODUCTION

Signal transducers and activators of transcription (STATs) are a family of transcription factors that are activated by membrane-bound receptors and subsequently translocate to the nucleus to promote expression of a variety of genes associated with cell survival, differentiation, and proliferation.[1] The STAT family includes 7 proteins (STATs 1, 2, 3, 4, 5a, 5b, and 6) with an array of functions but a common molecular structure that reflects a highly conserved mechanism of activation and signaling.[2] Given their established role in regulating cell survival and proliferation, it is not surprising that STATs have emerged as critical mediators of oncogenesis. In particular, STAT3 has been targeted for antineoplastic therapy because of its role as molecular conversion point for several pro-oncogenic processes, including disrupted growth regulation, apoptosis, angiogenesis, invasion, and modulation of the host immune system.[3] Furthermore, STAT3 is constitutively active in a wide variety of cancers and has generally been associated with poor prognosis, although this remains controversial.[4,5] Nevertheless, the preponderance of available data support a pro-oncogenic role for STAT3 and STAT3 blockade alone is sufficient to inhibit malignant transformation in some model systems.[6,7]

Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor. The current standard of care for GBM involves a tripartite treatment approach of cytoreductive surgery, targeted irradiation, and temozolomide.[8] Despite maximally aggressive therapy, the median survival for patients with GBM is only 14.6 months, with a 3-year survival rate of approximately 10%.[8] Hallmarks of GBM pathogenesis include the invasion of healthy brain tissue,[9] neovascularization,[10]

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local hypoxia and necrosis,[11] and local and systemic immunosuppression.[12,13] Several diverse cell populations have been implicated in GBM pathogenesis. For example, cancer stem cells have been identified as a distinct cell population in GBM and are thought to be largely resistant to standard therapies.[14,15] In addition, endothelial cells of tumor-associated vasculature have been reported to harbor the same mutations as bulk tumor cells[16] and may be derived from cancer stem cells.[17,18] Coordinated interactions among these diverse cell types dictate GBM behavior and susceptibility to therapeutics. In the case of cancer stem cells, evidence suggests that GBM stem cells in culture may be susceptible to radiation[19] but acquire radioresistance within the perivascular niche.[20]

The complexity of the tumor microenvironment presents a formidable challenge to the development of effective therapies. STAT3 has emerged as an appealing target for GBM therapy because it has been implicated in several pro-oncogenic processes. In addition, constitutive activation of STAT3 has been reported in GBM and may be associated with a poor prognosis.[21] Accordingly, targeting STAT3 affords a potential therapeutic focal point, allowing a single therapy to target multiple pro-oncogenic processes. Preclinical studies suggest that STAT3 blockade has antitumor activity in vitro[22] and in vivo.[23] However, more recent evidence indicates that the role of STAT3 may be more nuanced than initially appreciated, alternately having protumor or antitumor effects depending on the genetic profile of the tumor.[5] Here the authors review the potential role of STAT3 as a therapeutic target in GBM.

STAT3 SIGNALING PATHWAY

STAT3 is a member of the STAT family of cytoplasmic transcription factors, which transmit signals from the cell surface to the nucleus in response to extracellular cytokines, growth factors, hormones, and oncoproteins.[24,25] STAT3 contains an N-terminal domain, a coiled-coil domain, a DNA-binding domain, a linker domain, an Src Homology 2 (SH2) domain, and a transactivation domain.[26] The function of each of these domains is summarized in **Table 1**.

STAT3 exists as an inactive monomer and is activated by the phosphorylation of tyrosine 705 (Y^{705}) by Janus tyrosine kinases (JAK), membrane-associated tyrosine kinases, and nonreceptor tyrosine kinases.[26–31] Another major activator of STAT3 is interleukin-6 (IL-6). When IL-6 binds to the IL-6 receptor (IL-6r), the functional subunit (gp130) facilitates the formation of a STAT3 homodimer via phosphorylation of the cytoplasmic tails. The activated complex is then able to activate downstream JAK signaling proteins. The gp130 subunit of the IL6/IL6r complex also provides docking sites for STAT3 monomers using the SH2 domain.[32–34] Subsequently, STAT3 is phosphorylated by the JAK family of kinases leading to dimerization via phosphotyrosine interactions within the SH-2 domains. Following dimerization, STAT3 translocates to the nucleus where it binds to specific DNA promoters and regulates transcription.[35] STAT3 activation and signaling is reviewed in **Fig. 1**.

Table 1
STAT3 domains

Domain	Function
N-terminal	Stabilization of STAT3 dimers and STAT3-DNA interactions
Coiled-coil	Interaction with other proteins
DNA binding	Interaction with DNA strand
SH2	Dimerization
Transactivation	Interaction with transcriptional machinery

Increased activation of STAT3 results from the disruption of proteins that regulate STAT3 expression and activation. The critical regulators of STAT3 activity include IL-4,[36] IL-6,[37–40] epidermal growth factor receptor (EGFR),[41,42] fibroblast growth factor,[43] leptin,[44] MicroRNA-21,[45] PPARγ,[46] PIAS3,[47,48] PTPRD,[49] and SOCS3.[47] Furthermore, STAT3 activity is increased under conditions of hypoxia, infection, stress, and UV radiation.[50,51] Once bound to DNA, STAT3 influences the expression of genes involved in cell cycle regulation, apoptosis, migration, angiogenesis, and invasion via the activation of B-cell lymphoma 2 (Bcl-2), B-cell lymphoma-extra large (Bcl-xL), c-Myc, cyclin D1, Mcl-1, matrix metallopeptidase 9 (MMP9), and survivin.[52,53]

ROLE OF STAT3 IN ONCOGENESIS

Immune Evasion

GBMs have long been documented to suppress the immune system in patients, locally in the tumor microenvironment and systemically.[54] GBMs have evaded the immune system via several mechanisms. Patients with GBM have been shown to exhibit T-cell anergy, lymphopenia, impaired antibody production, impaired lymphocyte protein synthesis, and impaired lymphocyte responsiveness.[55–61] Thus, GBMs evade the immune system at the levels of antigen recognition and immune activation.

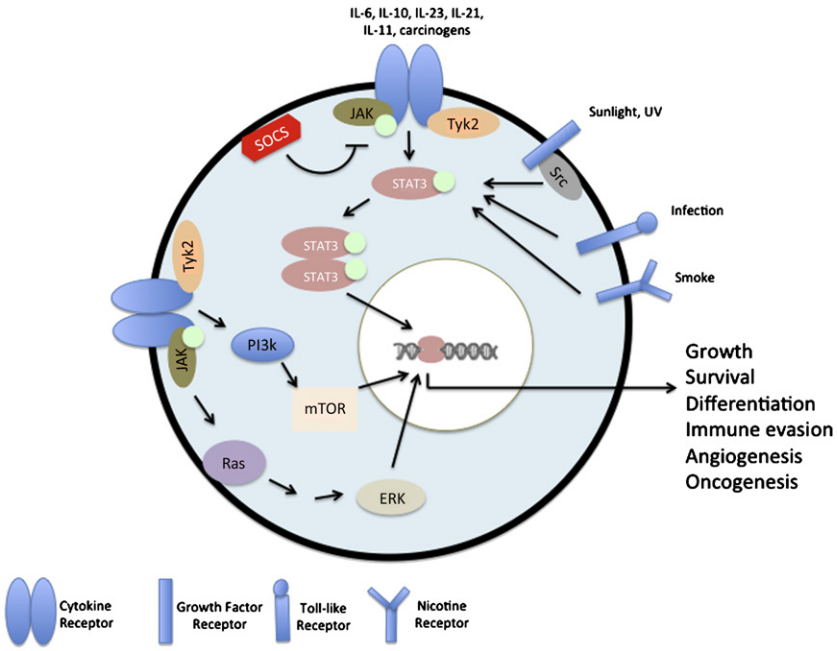

Fig. 1. Pathways involved in the activation of STAT3. STAT3 is activated when Tyrosine 705 is phosphorylated by various intracellular kinases, including JAK, Src, mTOR, and ERK. The activity of these kinases can be increased by various hormones, cytokines, and environmental factors acting at the extracellular surface.

STAT3 has been implicated as a key negative regulator of antitumor immune responses within the GBM microenvironment.[62] STAT3 activity in tumors has been shown to coordinate tumor immune evasion via multiple mechanisms. For example, STAT3 activity restricts immune surveillance by suppressing the release of proinflammatory cytokines and chemokines. Furthermore, constitutive activation of STAT3 in tumors cells has been shown to increase the secretion of soluble immunosuppressive factors,[63] such as IL-10, which negatively affects the Th1 immune response,[64] and vascular endothelial growth factor (VEGF), which feeds back to further activate STAT3 in immature dendritic cells. STAT3 expression in immature dendritic cells subsequently leads to the inhibition of dendritic maturation and activation[65] by suppressing the expression of major histocompatibility complex (MHC) class II, costimulatory molecules, and IL-12.[63] Because mature dendritic cells are the primary antigen presenting cells, STAT3-mediated inhibition of dendritic cell maturation effectively disrupts both the innate and adaptive immune responses. Conversely, inducible ablation of STAT3 in hematopoietic cells enhances dendritic cell maturation.[66]

In addition to inhibiting dendritic cell maturation, STAT3 seems to modulate multiple elements of innate and adaptive immunity. STAT3 is constitutively activated in natural killer cells, neutrophils, and macrophages present in the tumor stroma, and STAT3 ablation results in enhanced antitumor activity in these cell types and in T lymphocytes.[66] Thus, it seems that constitutive STAT3 activation in the tumor drives a feed-forward mechanism of constitutive STAT3 activation in tumor-interacting immune cells, which drives widespread immune suppression.[67]

STAT3 expression also plays a role in the proliferation and function of regulatory T (Treg) cells,[66] a population of CD4+ T cells that accumulates inside tumors[68] and has suppressive activity toward effector T cells and other immune cell types.[69] Treg cell activation and expansion has been repeatedly shown to require direct contact with dendritic cells residing in tumors.[70–74] Subsequently, Treg cells secrete transforming growth factor β (TGFβ), leading to the suppression of CD8+ T-cell activation.[73,75]

STAT3 activity has been associated with the expansion of a lineage of T-helper cells characterized by the expression of IL-17 (Th17 cells).[76] Several studies indicate that STAT3 is critical for Th17 expansion.[77–80] Although the role of Th17 cells in immune evasion has not been clearly established, emerging evidence suggests that skewing of the T-helper cell response toward Th17 differentiation mutes the antitumor Th1 response and facilitates tumor progression.[81]

Angiogenesis

Angiogenesis has been shown to play a critical role in GBM progression.[82] The formation of new blood vessels in GBM is mediated by the elevated expression of VEGF.[83] Accordingly, VEGF has emerged as a prominent antiangiogenesis target; bevacizumab, an antibody against VEGF, has been approved by the Food and Drug Administration as monotherapy for recurrent GBM.[84,85] Factors modulating VEGF-mediated angiogenesis, however, remain poorly understood; although patients typically exhibit radiographic regression on bevacizumab, an overall survival benefit has not been clearly demonstrated.[86] Although the development of resistance plays a role in progression on bevacizumab,[87] some investigators suggest that anti-VEGF therapy induces a more invasive tumor phenotype secondary to local hypoxia.[88]

STAT3 has been implicated as a downstream effector in the VEGF angiogenesis signaling pathway. Yahata and colleagues[89] demonstrated that exposing human endothelial cells to VEGF in vitro results in nuclear translocation of phosphorylated-STAT3 (p-STAT3) and that blocking STAT3 activity leads to a reduction in endothelial cell migration and tube formation. STAT3 has also been shown to localize to glioma endothelial cells.[90] Furthermore, hypoxia induces STAT3 activation and nuclear translocation and enhances endothelial tube formation and tumor cell migration in GBM cell lines.[91] STAT3 also acts reciprocally to upregulate VEGF expression.[90] Although the connection between STAT3 and VEGF has been most extensively studied in GBM cell lines, in vivo studies in other tumors have demonstrated a correlation between STAT3 activity, VEGF expression, and tumor progression.[92] Based on these data, blocking STAT3 in GBM may have potent effects as an antiangiogenesis therapy. Additional research is needed to determine if STAT3 blockade elicits similar escape mechanisms and induces the invasive phenotype observed with VEGF inhibitors.

Differentiation

GBMs are characterized by a high degree of molecular,[93] histologic, and phenotypic diversity, suggesting that the inciting events in GBM pathogenesis likely occur early in the process of glial differentiation.[94,95] Neural stem cells give rise to all components of the nervous system. Although GBM cells share few characteristics with differentiated glia, some of the defining characteristics of neural stem cells, such as migration[96] and milieu-dependent differentiation,[97] are hallmarks of gliomagenesis.

Evidence suggests that STAT3 may play a crucial role in normal and pathologic glial differentiation through interactions with the ciliary neurotrophic factor (CNTF).[98,99] Binding of CNTF to its receptor leads to the activation of JAK tyrosine kinases and subsequent phosphorylation of STAT3 and STAT1 via their SH2 domains.[100] Inhibition of STAT3 signaling in neural precursor cells has been shown to prevent the activation of the glial fibrillary acidic protein (GFAP) promoter and block glial differentiation.[98] STAT3-mediated glial differentiation may be disrupted in at least a subset of gliomas because of the epigenetic silencing of bone morphogenic protein receptor-1B.[101,102] Although much remains to be learned about the role of STAT3 activation in glial differentiation and gliomagenesis, available evidence indicates that GBMs may be able to capitalize on the protumorigenic effects of constitutive STAT3 activation without compromising their undifferentiated phenotype. Therefore, it may be reasonable to speculate that STAT3 activation can be therapeutically blocked with relative impunity regarding glial differentiation. Conversely, some studies indicate that STAT3 blockade may induce differentiation of GBM stem cells.[103] Future studies are needed to clearly elucidate the relationship between STAT3 activation, glial differentiation, and GBM pathogenesis.

Survival and Proliferation

STAT3 plays a central role in cell survival and cell cycle progression via its interactions with the gp130 subunit of the IL-6 receptor.[104] There seems to be 2 distinct pathways for IL-6–mediated survival and proliferation. Tyrosine 759 of gp130 has been shown to be critical for facilitating the S to G2 cell cycle progression but not for preventing apoptosis. Tyrosines in the YXXQ motif, however, induce antiapoptotic signaling via Bcl-2.[105] These data indicate that STAT3 may be especially important for preventing apoptosis and involved to a lesser degree in cell cycle progression in the IL-6–dependent survival and proliferation pathways.

STAT3 is also involved in several other antiapoptotic and mitogenic pathways. The oncogene v-Src has been shown to activate STAT3, representing a critical step in v-Src's modulation of cyclin D1, cyclin D2, cyclin E, and c-Myc expression.[106,107] STAT3 has also been shown to inhibit apoptosis via upregulation of Bcl-xL,[108] Mcl-1,[109] and survivin.[110] In addition, STAT3 disrupts p53 function by binding to the p53 promoter and subsequently inducing downregulation of p53 expression.[111] In vitro studies of STAT3

inhibitors have shown that STAT3 blockade leads to cell cycle arrest and the induction of apoptosis in a dose-dependent manner.[112] Furthermore, studies of STAT3 inhibitors in GBM xenograft models have demonstrated a significant impact on tumor growth.[113,114] Taken together, these studies indicate that STAT3 inhibitors may have in vivo antitumor activity independent of an antitumor immune response.

Invasion

GBMs are highly invasive, frequently infiltrating normal brain and precluding complete surgical resection. Although several factors are involved in GBM cell migration, STAT3 has recently emerged as a potential target for inhibiting invasion because STAT3 inhibitors have been shown to decrease the migratory behavior of GBM cells in vitro.[115] This result was observed regardless of PTEN expression. Although the precise mechanism is unknown, STAT3 has been observed to induce the expression of the proinvasive factors matrix metalloproteinase-2 (MMP-2) and fascin-1.[37,38] STAT3 may also play a role in HIF- and VEGF-mediated cell migration in response to hypoxia.[88,116] Studies in other tumor types suggest that blocking STAT3 and HIF together may increase the susceptibility to antineoplastic therapies working through separate mechanisms.[117] Because local tumor hypoxia has been shown to induce a more invasive phenotype,[88] STAT3 has been suggested as a potential biomarker of VEGF activity[118] and may represent a valuable target for augmenting anti-VEGF therapy.

Antitumor Activity of STAT3

Although most studies have highlighted STAT3′s role in oncogenesis, some evidence suggests that the role of STAT3 may be context dependent.[119] STAT3 has been shown to inhibit proliferation in leukemia cells,[120] prostate cells,[121] and melanoma cells.[122] Furthermore, STAT3 may actually promote differentiation in some contexts.[120,123] In GBM, an interest in STAT3′s antitumor activity first emerged from evidence suggesting that STAT3 can regulate gliogenesis by promoting the differentiation of cortical precursor cells into astrocytes.[98] STAT3′s antitumor properties were further explored by Iglesia and colleagues[5]; they noted that experimental ablation of STAT3 in PTEN mutations unexpectedly led to increased astrocyte proliferation, invasiveness, and tumorigenesis. This finding indicates that STAT3 may have a role in suppressing malignant transformation of astrocytes in the context of PTEN pathway disruption, and future STAT3-targeted therapies should take into consideration the genetic background of the tumor.

APPROACHES TO STAT3 INHIBITION

STAT3 overexpression is typically driven by an impairment of inhibitory molecules. Although several drugs have been shown to be active in vitro, significant challenges in the form of administration, toxicity, cell permeability, and nonselective activity have limited the translation of STAT3 inhibitors to clinical practice.

Preventing STAT3 Activation

One approach to preventing the activation of STAT3 is disrupting upstream tyrosine kinases. These include but are not limited to JAKs, growth factor receptors, and cytokines receptors. A fundamental challenge to this strategy is the multitude of signaling pathways that converge to activate STAT3. Efforts at disrupting the activation of STAT3 have targeted several kinases, including EGFR (head and neck squamous cell carcinoma), receptor tyrosine kinases (RTK; pancreatic cancer and non–small cell lung cancer), JAK (myelofibrosis and acute lymphoblastic leukemia), and SRC (head and neck squamous cell carcinoma). A summary of therapeutics targeting upstream kinases is presented in **Table 2**.

Monoclonal antibodies against EGFR have been used to block the interaction between VEGF and its receptor (cetuximab, panitumumab). Compounds have also been developed to target the tyrosine kinase activity of the EGFR (gefitinib, erlotinib, lapatinib). Although these drugs have shown efficacy in other tumors, GBM has demonstrated resistance to EGFR therapy, thought to arise from mutations of the extracellular domain of EGFR (preventing the efficacy of monoclonal antibody therapy), increases in cytoplasmic tyrosine kinase activity, or increased activity of parallel signaling pathways.[124]

Sorafenib, a tyrosine kinase inhibitor, has been shown to decrease GBM growth both in vitro and

Table 2
Therapeutics targeting STAT3 activation

Target	Drug
EGFR	Cetuximab, panitumumab
RTK	Gefitinib, erlotinib, lapatinib, sorafenib
JAK	AG490, LS-104, ICN1824, CEP-701, JSI-124
SRC	Dasatinib, AZD0530, bosutinib

in vivo.[125] Attempts at disrupting signaling through JAK proteins have been shown to be effective in vitro, with AG490 disrupting the IL-6 activation of STAT3 in U251 cell lines.[126] JSI-124 has also been shown to arrest cells in the G2/M phase and induce apoptosis in the U251 glioma cell line.[127] Finally, Liu and colleagues[128] reported that the introduction of adenovirus-vector carrying basic fibroblast growth factor siRNA decreased the activation of extracellular signal-regulated kinases 1/2 and JAK2 and decreased IL-6 secretion, leading to reduced STAT3 phosphorylation and decreased expression of the downstream molecules cyclin D1 and Bcl-xL.

Preventing Homodimerization of STAT3

After STAT3 is phosphorylated, it forms a functional homodimer via interactions between the SH2 domains. This complex allows for translocation of the homodimer complex to the nucleus, where STAT3 modulates gene expression. Efforts aimed at preventing STAT3 dimerization have been directed against the SH2 domain.[53,129–131] Using a pY-containing peptide, the first efforts at blocking the Y^{705} residue found that this strategy was able to inhibit the binding of STAT3 to DNA in vitro.[130,131]

The SH2 domain of STAT3 also interacts with upstream signaling proteins, including EGFR and the IL-6/IL6r complex. Attempts to disrupt the interaction between EGFR and SH2 have focused on preventing the phosphorylation of 2 tyrosine residues in the EGFR (Y^{1068} and Y^{1086}), which are required for recruiting STAT3 to the activated EGF-EGFR complex.[132] A phosphodecapeptide, which was synthesized based on the amino acids surround the Y^{1068} motif, has also been shown to inhibit the binding of STAT3 to DNA. Efforts targeted at disrupting the interaction between the gp130 subunit of the IL-6/IL-6r complex and STAT3 have also shown inhibition of STAT3 binding to DNA in vitro.[32] Therapies preventing the homodimerization of STAT3 in high-grade glioma are limited to in vitro studies. Kim and colleagues[133] reported that aspirin inhibited IL-6/STAT3 signaling in A172 cells. Tocilizumab, a humanized anti–IL-6r antibody decreased proliferation in U87MG cells.[134] Furthermore, STAT3 inhibition may effectively target tumor stem cells, which are frequently resistant to standard therapies; it has been shown to be a critical regulator of growth, proliferation, and maintenance of the GBM stem cell phenotype.[135] Villalva and colleagues[136] reported a small molecule inhibitor of STAT3, Stattic, was able to both block STAT3 activity in GBM stem cell lines as well as sensitize cells to temozolomide in vitro.

Table 3
Roles of STAT3 in oncogenesis and primary downstream mediators

Oncogenic Process	Mediators
Immune evasion	↑ IL-10, VEGF ↑ Treg expansion ↑ TGFβ ↑ Th17 differentiation ↓ MHC expression ↓ Dendritic cell maturation, IL-12 ↓ Costimulatory molecules
Angiogenesis	↑ VEGF ↑ Vascular tube formation
Invasion	↑ MMP-2, MMP-9 ↑ Fascin-1
Proliferation/survival	↑ Bcl-2 ↑ Bcl-xL ↑ Mcl-1 ↑ Survivin ↑ Cyclin D1, cyclin D2, cyclin E, ↑ C-myc
Differentiation	↑ GFAP

SUMMARY

STAT3 plays multiple roles in GBM tumorigenesis and has emerged as a promising therapeutic target. The putative roles of STAT3 in oncogenesis are summarized in **Table 3**. Blocking STAT3 activity in preclinical studies has been shown to inhibit angiogenesis, promote antitumor immune responses, and inhibit the invasion of normal brain tissue. Although several approaches have been developed to block STAT3 activity in vivo, no strategy has yet emerged as a viable candidate for clinical translation. In addition, emerging evidence suggests that the role of STAT3 in tumorigenesis may be more nuanced than initially appreciated, alternately exhibiting proneoplastic or antineoplastic activity depending on the genetic background of the tumor. Future research is needed to more clearly delineate the roles of STAT3 in GBM and develop effective strategies for targeting tumor-induced STAT3 activation.

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