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Association of STAT3 Signalling Pathway in Microenvironment of Glioma Tumors

Rutu Shah[1], Nidhi Gondaliya[2], and Trupti Trivedi*[3]

[1]Department of Life Science, Gujarat University, Ahmedabad-380009, Gujarat, India and Cancer Biology Department, The Gujarat Cancer and Research Institute, Civil Hospital Campus, Asarwa, Ahmedabad-380 016, Gujarat, India, rutu.shah@gcriindia.org
[2]Department of Life Science, Gujarat University, Ahmedabad-380009, Gujarat, India, nidhi.gondaliya@gujaratuniversity.ac.in
*[3] Cancer Biology Department, The Gujarat Cancer and Research Institute, Civil Hospital Campus, Asarwa, Ahmedabad-380 016, Gujarat, India, trupti.trivedi@gcriindia.org

Abstract: **This article presents a comprehensive literature review regarding the function of the Signal Transducer and Activator of Transcription 3 (STAT3) signalling pathway in the advancement of gliomas and its impact on glioma microenvironment. The STAT3 pathway is essential in gliomas as it regulates vital biological processes, including cell survival, tumor proliferation, immune suppression, and the modulation of the tumor microenvironment (TME). This article emphasizes the mechanisms through which STAT3 contributes to the aggressive characteristics of gliomas, such as its role in promoting tumor growth, facilitating immune evasion, and mediating resistance to standard treatments like chemotherapy and radiation. The dual function of STAT3 in both advancing tumor progression and inhibiting anti-tumor immune responses highlights its potential as a target for therapy. Moreover, targeting the STAT3 pathway may provide promising approaches to enhance outcomes for glioma patients by boosting anti-tumor immunity and overcoming resistance to treatment. Consequently, ongoing research into STAT3 signalling within the glioma TME is crucial for the development of advanced therapies that could significantly improve the management of glioma patients.**

Index Terms: **Glioma, STAT3, Immune suppression, Tumor microenvironment, Therapeutic resistance**

I. INTRODUCTION

Gliomas are a diverse group of primary malignant brain tumors, originating from glial cells and representing the most common brain tumor within the central nervous system (CNS) (1). These tumors represent a significant risk to the public health system globally, including India where rising prevalence of CNS tumors present substantial challenges in managing glioma patients due to its high level of morbidity and mortality (2). Due to the highly invasive growth pattern of glioma tumors, complete surgical resection remains a significant challenge. Moreover, the high tumor heterogeneity and presence of glioma stem cells (GSCs) complicate the response to therapy (3). Despite advancements in treatment options such as surgery, radiation, and chemotherapy, these tumors remain difficult to treat and are associated with poor survival outcomes (4-5).

For glioma patients, current treatment protocols focus on surgical resection followed by chemo radiotherapy, with temozolomide (TMZ) being the standard chemotherapeutic agent (6). However, most patients eventually develop resistance to TMZ (7). Although immunotherapies and biomarker-driven treatments are being explored for many cancers. However, for glioma tumors are still lacking, especially against the molecular mechanisms that drive tumor progression and immune evasion (8). Worldwide, tumor recurrence and treatment resistance continue to be major issues (9). Hence, advancing in cancer treatment strategies implicates a deeper understanding of the complex molecular interactions between glioma cells, immune cells, and the tumor microenvironment (TME). Such insights will pave the way for the development of integrated, personalized therapies aimed at

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improving clinical outcomes and enhancing the quality of life for glioma patients (10).

In this regards, identifying the primary signalling molecules that contribute to gliomagenesis is essential for enhancing clinical treatment approaches and patient outcomes. Signal Transducer and Activator of Transcription 3 (STAT3) signalling pathway is a fascinating target for cancer treatment because of its critical role in tumor development and progression (11-12). Under normal physiological conditions, STAT3 is involved in essential cellular processes, including cell growth, differentiation, and survival. Its activation in healthy tissues is typically transient and tightly regulated (13). In the context of several cancers and particular in gliomas, STAT3 functions as a key oncogenic driver that becomes persistently and aberrantly activated. Due to this dysregulation, STAT3 promotes abnormal cell proliferation, cell survival, metastasis, immune invasion and it is vigorously associated with poor prognosis of cancer patients (14-15).

The glioma TME is a highly complicated and heterogeneous environment that composed of various cell types, including tumor cells, tumor cells infiltrating immune cells, Cancer-Associated Fibroblasts (CAFs), smooth muscle cells, and endothelial cells (16-17). Whenever, this highly intricate environment supports tumor survival and contributes to treatment resistance by adopting an immunosuppressive niche in gliomas (18-19). A key signalling molecule, STAT3 plays an eventual role in the immunosuppressive landscape for glioma tumors by suppressing immune responses and influence anti-tumor immune activity through the upregulating immunosuppressive molecules, which is involved in decreasing the effectiveness of cancer therapies (20-21-22-23). Central involvement of STAT3 in tumor development and immune evasion has established as a promising targets for therapeutics strategies (20).

II. TUMOR MICROENVIRONMENT IN GLIOMA

The brain TME, predominantly in gliomas, exhibits distinct biological and structural features compared to other cancers (24). Glioma TME plays a dual role: supporting tumor advancement through immune evasion, increased invasiveness, resistance to cell death, and insensitivity to standard treatments, while simultaneously presenting itself as a promising therapeutic target due to its complex and dynamic nature (25). Glioma cells engage in continuous interactions with stromal and immune cells, releasing a spectrum of cytokines and chemokines that actively reduce anti-tumor immunity (26). These secreted factors lead to reduced expression of Major Histocompatibility Complex (MHC) molecules, induce T cell unresponsiveness and death, suppress natural killer (NK) cell activity, and promote the recruitment of regulatory T cells (Tregs) and immature dendritic cells (DC), collectively establishing a pro-tumoral niche (18). Instead of mounting effective anti-tumor responses, these cells often adopt immunosuppressive phenotypes, characterized as M2-like macrophages, which secrete cytokines and growth factors that inhibit cytotoxic immune cells and promote tumor cell proliferation, blood vessel formation, and tissue remodeling (27-28).

At the molecular levels, oncogenic STAT3 signalling pathway is pivotal in promoting immunosuppression within glioma TME (29). It serves as an essential mediator that intricately associates tumor cells and immune cells, thereby reinforcing the immunosuppressive characteristics of the TME, which is facilitates tumor progression and humpers anti-tumor immunity (30).

In this complex milieu of gliomas, STAT3 functions as a crucial molecular hub, triggered by a various extracellular signals including cytokines, growth factors, and hormones (31-32). Once activated, STAT3 moves to the nucleus, where it influence the expression and transcription genes related to immune evasion, thereby creating an immunosuppressive TME that facilitates tumor proliferation and inhibit immune response (33-34). Prolonged activation of STAT3 enhances the expression of immunosuppressive factors, facilities the maintenance of GSCs and hampers antigen presentation, thus impairing the anti-tumor immune response (35-36). Furthermore, the activation of STAT3 has been demonstrated to considerably affect the immune environment and impact the overall prognosis of glioma patients (37).

Therefore, exploring the relationship between the TME, particularly certain elements and tumors as well as intervening in this interaction presents considerable therapeutic opportunities for altering tumor immunosuppression (38). Current research is exploring strategies that combine immune checkpoint blockade with additional therapies targeting the TME to enhance treatment effectiveness (39). These strategies include integrating immune checkpoint inhibitors (ICIs) with anti-angiogenic agents, STAT3 inhibitors, oncolytic viruses, and vaccines, all aimed at improving treatment outcomes. These multifaceted approaches seek to transform the TME from a tumor-promoting to a tumor-suppressing environment (40).

Preclinical studies are investigating inhibitors that target STAT3 signalling to restore immune function and enhance tumor sensitivity to current therapies (41). Therefore, selectively targeting STAT3, along with other immunosuppressive pathway molecules within the TME, is emerging as a promising strategy to restore anti-tumor immunity and improve outcomes in glioma treatment (38).

III. STAT3 SIGANLLING PATHWAY IN GLIOMA

In mammals, STAT family consists of seven members STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6, each encoded by distinct genes and act as cytoplasmic transcription factors (42). STAT proteins are activated in response to a broad range of extracellular stimuli, including approximately 50 known signalling molecules such as interferons, interleukins, growth factors, and hormones. Once activated, they translocate into the nucleus where they regulate the expression of genes critical to several fundamental biological processes, including cellular proliferation, differentiation, immune responses, development, and apoptosis (43-44-45).

The STAT3 gene is located on the long arm of human chromosome 17, at cytogenetic band 17q21 (46). It encodes a protein with a molecular mass of approximately 92 kDa and a length of 770 amino acids. The STAT3 protein comprises several well-defined structural domains: The N-terminal domain (involved in dimer stabilization), the coiled-coil domain (CCD) which facilitates protein-protein interactions, the DNA-binding domain (DBD) crucial for gene transcription, and the SH2 (Src Homology 2) domain responsible for phosphotyrosine binding and dimerization. The protein also includes a C-terminal transactivation domain (TAD), which regulates transcriptional activity. A helical linker domain, spanning residues 500–575, connects the DNA-binding and SH2 domains. STAT3 activation primarily occurs through phosphorylation at two key residues: tyrosine 705 (Y705), which is essential for dimerization and nuclear translocation, and serine 727 (S727), which modulates maximal transcriptional activity (47- 48) (Figure 1).

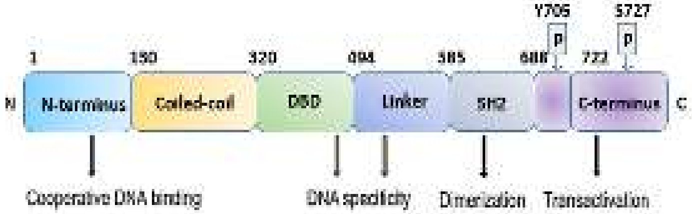

Figure 1: Schematic and functional architecture of the STAT3 protein

Predominantly, STAT3 plays a pivotal role in inflammation, tissue regeneration, cell growth, and cellular differentiation. Its function is especially important in the nervous system, where it contributes to brain development and the differentiation of astrocytes (49). Unusually, the function of STAT3 in cancer, mainly in gliomas, is highly context-dependent. It can function either as an oncogene promoting tumor growth or, in some contexts, as a tumor suppressor, depending on the specific genetic and molecular landscape of the tumor (50). In gliomas, STAT3 is frequently found to be constitutively activated, supporting the maintenance of cancer stem cell (CSC) properties, enhancing tumor invasiveness, and contributing to immune evasion mechanisms (51-52) and it is also stimulating tumor progression by regulating cell cycle-related genes, inhibiting programmed cell death (apoptosis), and fostering cellular proliferation and invasive behaviour (53-54).

STAT3 becomes activated upon the engagement of cytokines like interleukin-6 (IL-6) with its co-receptor gp130. This interaction leads to the activation of Janus kinases (JAKs), which phosphorylate STAT3 at Y705. Phosphorylated STAT3 then dimerize via its SH2 domains, translocate to the nucleus, and binds to specific DNA response elements to regulate the transcription of target genes (55-56). These target genes are involved in key cellular functions such as survival, proliferation, inflammation, and angiogenesis (57) (Figure 2).

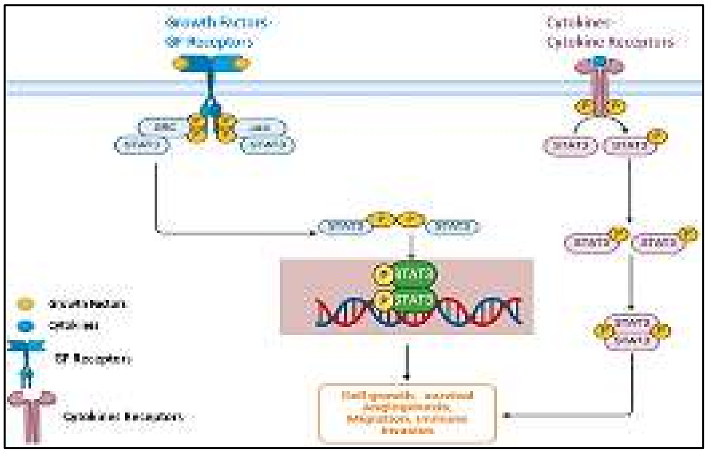

Figure 2: Regulation of Target Gene Transcription through the STAT3 Signaling Pathway

In gliomas, persistent STAT3 signalling promotes resistance to radiotherapy and chemotherapy by stimulating angiogenesis through the upregulation of vascular endothelial growth factor (VEGF) and hypoxia-inducible factor 1-alpha (HIF-1α) (58), and by enhancing tumor cell invasiveness via the activation of matrix metalloproteinase such as MMP-2 and MMP-9 (59). Moreover, STAT3 activation supports tumor cell survival by inducing the expression of anti-apoptotic and cell cycle-related genes, including survivin, BCL-XL, Cyclin D1, MYC, and MCL1 (60) (Figure 3).

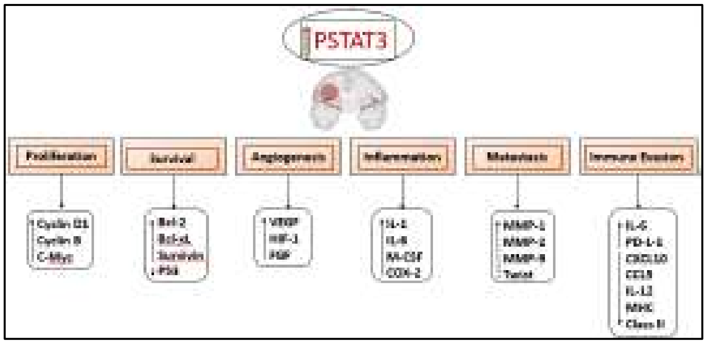

Figure 3: Constitutively Activated STAT3: Activate Downstream Targets

Under normal physiological conditions, STAT3 activity is tightly regulated through negative feedback mechanisms to prevent over activation. These include dephosphorylating by protein tyrosine phosphatases (PTPs), inhibition by suppressors of cytokine signalling (SOCS), and modulation by protein inhibitors of activated STATs (PIAS) (61-62). However, in gliomas and other cancers, these regulatory pathways are often disrupted, resulting in unchecked STAT3 activation that drives tumor progression, stemness, and immune evasion (63-64).

STAT3 also contributes significantly to the formation of an immunosuppressive TME. It induces the expression of immunosuppressive cytokines and immune checkpoint molecules, including IL-6, IL-10, PD-1, PD-L1, TGF-β, and VEGF. At the same time, it suppresses immune-stimulatory factors such as CD80, CD86, CXCL10, CCL5, MHC class II, TNF-α, IFN-β, and IL-12, this dual regulation helps tumors evade immune detection and promotes an environment conducive to tumor growth (64). Chronic activation of STAT3 is a hallmark of many cancers and contributes significantly to therapy resistance, glioma progression, and immune suppression (65). STAT3 represents a compelling therapeutic target (66). Strategies to inhibit STAT3 either by blocking its activation, dimerization, or DNA-binding activity hold promise for suppressing tumor growth, restoring anti-tumor immune responses, and improving outcomes for patients with gliomas and other STAT3-driven cancers (67).

IV. STAT3 SIGNALLING MEDIATED TME IN GLIOMA

The TME is a complex and heterogeneous system where intricate cross-talk, particularly involving STAT3 activation in tumor cells and other cell populations, tightly controls immune evasion and fosters tumor progression (68). The TME's pivotal role in cancer progression and therapy resistance, especially in immunotherapy, is increasingly evident (69). STAT3 stands out as a critical regulator influencing tumor growth, immune evasion, and treatment resistance (60). The excessive activation of STAT3 enhance tumor-promoting effects by altering the expression of downstream molecules, consequently facilitating increased cell proliferation, cell survival, angiogenesis, and immune evasion (70). Overall, it is crucial in the immunoediting process within the TME, enabling the shift from immune surveillance to immune evasion (71). STAT3 is essential in modulating the immune cells in this context, positioning it is a key focus for cancer research and cancer therapies (72).

In specific, Myeloid-Derived Suppressor Cells (MDSCs) represent a significant population of immune cells regulated by STAT3. These immunosuppressive myeloid cells proliferate and accumulate within the TME, where their activation plays a crucial role in immune suppression (73). STAT3 is vital for the differentiation, survival, and proliferation of MDSCs, while also inhibiting their maturation in to the fully functional myeloid cells. Concurrently inhibiting their maturation abilities, the build-up of immature MDSCs, which release various cytokines that impair T cell activity and suppress the immune response (70). Furthermore, STAT3 encourages the polarization of macrophages towards the M2 phenotypes, which is linked to tumor promoting activities, including the secretion of pro-tumor cytokines such as IL-10 AND TGF- β (74).

Moreover, dendritic cells (DCs), which are essential for the ignition of adaptive immune responses, are significantly affected by the activation of STAT3. As antigen presenting cells, DCs are precarious in priming T cell mediated immune responses (75). Conversely, the activation of STAT3 within DCs hinders their maturation and functionally, thereby diminishing their capacity to effectively activate T cells. Precisely, STAT3 reduces the expression of co stimulatory molecules and key maturation markers that are important for the DCs functions (76). Besides, STAT3 inhibits the production of vital pro inflammatory cytokines such as IL-12 and TNF-α, which are necessary for the activation of cytotoxic T cells by DCs. As well STAT3 obstructs the secretion of important chemokines like CCL5 and CCL9, which are indispensable for the recruitment of immune cells to the tumor site (64). These cumulative effects further impede the ability of DCs to elicit a strong immune response against tumors. This dysfunction of DCs establishes a positive feedback loop, where tumor-derived factors such as IL-6, IL-10, and VEGF perpetuate the activation of STAT3 in DCs, thereby intensifying immune suppression with in TME (77).

Regulatory T cells (Tregs), represent another important subset of immune cells within the TME that are significantly influenced by STAT3. These specialized CD4+ T cells are responsible for supressing T cell-mediated cytotoxicity and maintaining immune tolerance. STAT4 act as a vital cofactor for FOXP3, the transcription factor that governs the development and function of Tregs. Upon activation, STAT3 promotes the differentiation and expansion of Tregs, which contributes to the formation of an immunosuppressive TME (78). Cytokines associated with tumors, such as IL-10 and TGF- β, further activate STAT3 in tumor infiltrating DC, leading to the suppression of cytotoxic CD8+ T cell function, which is essential for effective anti-tumor immunity. Additionally, the activation of STAT3 hampers the CXCR3/CXCL10 axis, crucial for the recruitment of CD8+ T cells to the tumor site (79). As a consequence, Tregs turn out to be significant barrier to anti-tumor immunity, allowing tumors to evade immune surveillance and continue their growth (80).

Another immune cell type affected by STAT3 in the TME is the cancer-associated fibroblasts (CAFs). CAFs serve as crucial stromal cells in the TME, playing a significant role in tumor progression and immune evasion. The activation of STAT3 in CAFs by molecules such as leukaemia inhibitory factor (LIF) results in the release of cytokines and growth factors that promotes the tumor growth, including the IL-6, TGF-β, VEGF, and CCL2, which facilitate tumor progression, immune suppression and metastasis. Contribute to tumor progression, immune suppression, and metastasis (81). These cytokine molecules not only aid the tumor directly but also modify the behavior of immune cells, thereby enhancing the immunosuppressive milieu. Particularly, the cytokines released by CAFs can established a paracrine feedback loop, triggering STAT3 activation in adjacent tumor and immune cells, which intensifiers the immunosuppressive signals within the TME This process further enhances the tumors ability to escape immune detection and evade the tumor developments (70).

Natural killer (NK) cells, along with MDSCs, Tregs, DC and CAFs, are integral to the immune defence against tumors. However, the activation of STAT3 negatively impact on NK cells development, activation and cytotoxicity, hereby diminishing their capacity to effectively target and destroy the tumors cells. Cytokines like IL-6 trigger both the STAT3 and NF-κB pathways concurrently, establishing a feedback mechanism that perpetuates the TME and encourages tumor proliferation (82). Moreover, STAT3 activation improves the function of the Aryl Hydrocarbon Receptor (AHR), which recruits tumor-associated macrophages (TAMs), further suppressing the immune response and aiding tumor progression (83).

Recognizing the pivotal function of STAT3 in modulating immune suppression and facilitating the tumor progression, it has emerged as a significant target for cancer treatment (84). Clinical trials are investigating STAT3 inhibitors, especially in conjugation with therapies that re-establish immune activity, as possible intervention for gliomas and various other malignancies (85). Through hindering STAT3, these therapies target to fortifying the immune response, reactivating cytotoxic T cells, and improving the effectiveness of immunotherapies. Research Studies indicate that inhibition of STAT3 in CD8+ T cells boosts their anti-tumor efficacy, yielding encouraging outcomes for cancer immunotherapy (79). Furthermore, the combination of STAT3 inhibitors with immune checkpoints inhibitors, like combining STAT3 inhibitors with immune checkpoint inhibitors such as anti-PD-1 or anti-CTLA-4, is presently under investigation in clinical trials to enhance the immune response and patients (86).

Consequently, STAT3 serve as a vital mediator in immune evasion and tumor development within the TME. By focusing on this pathway, there is potential to counteract immune suppression, enhance anti-tumor immunity, and increase the effectiveness of current cancer treatments, eventually resulting in better clinical outcomes for patients with gliomas and other malignancies.

CONCLUSION

The management of gliomas remains significant challenges due to its aggressive characteristics and the persistent activation of STAT3 signalling, which contributes to tumor proliferation, immune evasion and treatment resistant. Nevertheless, STAT3 serve as a promising biomarker for early diagnosis and a potential target for therapeutic strategies. The development of selective STAT3 inhibitors, combined with innovative therapies, has the potential to not only inhibit the tumor growth but also reinstates anti-tumor immunity, thereby reprogramming the TME. By optimizing treatments methodologies and incorporating new managements strategies, there is optimism for considerably improved patient outcomes, leading to enhanced survival rates and a better quality of life for individuals diagnosed with glioma tumors.

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