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Review

The Role of STAT3 in Cancer Development and Progression

Gökçen Kılınç[1], Oytun Erbaş[2]

ABSTRACT

The signal transducer and activator of transcription 3 (STAT3) is a key member of the STAT family found in the cytoplasm of most mammalian cells. STAT3 is a transient event in normal tissues, but it is activated inappropriately in cancer tissues and is triggered by certain cytokines. This continuous activation regulates the production of downstream proteins implicated in cancer initiation, development, and metastasis. Understanding STAT3 regulation and creating inhibitors targeting the STAT3 pathway are viable cancer treatment strategies. This review addresses the history, scientific advances, and future of the STAT3 pathway in cancer, including STAT3 regulation mechanisms, STAT3-induced cancer hallmarks, new inhibitors, and novel pharmaceutical delivery platforms.

Keywords: Angiogenesis, cancer stem cells, metastasis, STAT3, oncogenic signaling, tumorigenesis.

Signal transducer and activator of transcription (STAT) proteins are latent cytoplasmic transcription factors with seven members: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. STAT3 is involved in several fundamental cell activities, including cell proliferation, survival, differentiation, regeneration, immunological response, and cellular respiration. STAT3 can be tightly controlled by upstream signaling molecules including Janus kinase (JAK) and epidermal growth factor receptor.[1] It then localizes to the nucleus of cells and binds to target DNA, regulating the production of subsequent proteins. However, in addition to its normal cell activities, STAT3 activation in the tumor microenvironment (TME) is considered an oncogenic event. High phospho-STAT3 expression is linked to a poor prognosis in cancer patients, including non-small cell lung cancer, gastric cancer, and colorectal cancer. Constitutive activation of STAT3 plays an important role in tumor formation, development, metastasis, and recurrence.[1,2]

These are highly linked to cancer hallmarks and result in poor patient outcomes. Thus, the STAT3 pathway is a prospective target for cancer therapy.[2]

Also, STAT3 has a significant function in cervical cancer. STAT3 can downregulate LC3B, the most likely autophagy biomarker that may promote or inhibit cancer growth. However, the significance of STAT3 in cervical cancer autophagy is unknown.[3]

STAT3 AS AN ONCOGENE

Aberrant activation of the STAT3 transcription factor has been observed in a wide range of cancers, and a strong scientific basis now classifies this protein as an oncogenic driver. Consequently, It is considered a viable target in cancer therapy. For its inhibition to result in an effective therapeutic approach, a target tumor population defined by particular and detectable changes is required. STAT3's classical activation paradigm is based on constitutive phosphorylation at its 705 tyrosine site, which leads to dimerization, nuclear translocation, and the activation of cancer genes.[4]

As a result, cancers that exhibit this phosphorylated form are likely to be STAT3-dependent and vulnerable to existing treatments that target this dimeric form. However, recent research has shown

[1]University of George Emil Palade, Faculty of Medicine, Târgu Mureş, Romania
[2]ERBAS Institute of Experimental Medicine, Illinois, USA & Gebze, Türkiye

Correspondence: Gökçen Kılınç. University of George Emil Palade, Faculty of Medicine, Târgu Mureş, Romania

E-mail: gokcenkilinc1@gmail.com

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that STAT3 can function as an oncogene without tyrosine phosphorylation. This indicates that diverse transcription factor variations significantly impact tumor growth and treatment resistance. This complicates STAT3's classification as an oncogene and a potential prognostic and predictive biomarker. The requirement to target a specific tumor type suggests that future clinical research should use a precise definition of STAT3 activity. This will allow tumors addicted to this oncogene to be reliably identified, providing a strong foundation for patient classification. Complex cell signaling pathways are interrelated, integrating information that affects activities like protein synthesis, cell proliferation, differentiation, and cell death.[5]

STAT3 is a critical component in various carcinogenic signaling pathways, and it is the most closely connected to cancer among the seven STAT protein family members. In contrast to the transient physiological STAT3 signaling observed in normal cells, it is continuously active in many malignancies, and in many human cancer models, in-vitro STAT3 reduction induces growth inhibition and apoptosis. STAT3 Tyrosine 705 (Y705) phosphorylation activates the canonical pathway, which promotes malignant transformation by increasing cell proliferation, angiogenesis, and immune evasion.[4,6] Aside from that, STAT3 has been demonstrated to regulate mitochondrial respiration, which is activated by non-canonical signaling via the phosphorylation of STAT3's Serine727 residue. The cytokine and growth factor-rich tumor microenvironment, tyrosine kinase overexpression, and epigenetic modulation of negative STAT3 regulators are the primary processes behind its activation.[7–9]

Pathway Regulators and Mechanisms of Activation

STAT3 is a 770-amino acid protein with six functionally conserved domains: the amino-terminal domain, the coiled-coil domain, the DNA-binding domain, the linker domain, the SRC homology-2 domain, and the carboxyl-terminal transactivation domain. SRC homology-2 is the most conserved STAT domain and plays an important role in signaling by binding to particular phosphotyrosine patterns. In an unstimulated cell, negative modulators closely regulate STAT3 to keep it inactive in the cytoplasm. These modulators include members of the protein inhibitor of activated STAT and suppressor of cytokine signaling families, protein tyrosine phosphatases (SHP1, SHP2, PTPN1, PTPN2 PTPRD, PTPRT, and DUSP22), and ubiquitin enzymes.[10,11]

STAT3 is activated primarily by direct phosphorylation at tyrosine (705) and serine (727) residues induced by its upstream ligands, which include Janus kinases (JAKs), tyrosine kinases, cytokines, and several non-receptor tyrosine kinases such as SRC and ABL; phosphorylation induces dimerization of STAT3 proteins, followed by nuclear translocation, DNA binding, and, eventually, execution of their nuclear functions.[11]

STAT family proteins are ligand-dependent transcription factors that stimulate fast gene expression.[12] They were originally identified in the last 30 years. More than 40 polypeptide ligands, including cytokines, JAK kinases, and growth factors, have been linked to STAT phosphorylation. STAT3, a key member of the STAT family, regulates cell proliferation, differentiation, and death by tyrosine phosphorylation in response to epidermal growth factor, interleukin (IL)-6, and other stimuli after DNA binding. JAK activates STAT3 molecules, which dimerize primarily through the SH2 domain using TDAs to generate reciprocal pY-SH2 connections. Then, phosphorylated STAT3 can enter the nucleus and bind to particular DNA, activating downstream protein gene expression.[13,14]

STAT3 in Inflammation-Induced Carcinogenesis

As previously stated, the IL-6-JAK-STAT3 pathway is an important mediator of cancer inflammation that is initiated by genetic changes in transformed cells (intrinsic pathway), but it is also important for inflammatory conditions caused by environmental and other aetiological factors associated with increased cancer risk (extrinsic pathway). Several infectious agents known to cause inflammation-induced cancer activate STAT3 and are most likely reliant on it for their carcinogenic activity. For example, *H. pylori* infection, which has been linked to stomach cancer, activates STAT3 in host cells via the cytotoxin-associated gene A. Many tumor viruses, including *hepatitis B virus, human papillomavirus, human T-lymphotropic virus type 1,* and *Epstein-Barr virus*, activate STAT3 through different methods. A human enterotoxigenic strain of *Bacteroides fragilis* has been proven to cause colitis in both mice and humans; enterotoxigenic strain of *Bacteroides fragilis* colonization of mice results in STAT3 activation in the colon, which significantly promotes colon carcinogenesis. Both lipopolysaccharide (which mimics bacterial infection) and live bacteria activate STAT3, leading to the generation of IL-1β and IL-6, key mediators of inflammation-induced malignancy. [15,16]

STAT3 AND STEM CELLS

Stem cells are distinguished by their ability to self-renew and generate progenitor cells, which can then divide and specialize into the various types of cells seen in a given tissue. There are two types of naturally occurring stem cells: embryonic stem cells, which are separated from the inner cell mass of blastocysts, and adult stem cells, which can be found in a variety of tissues. Embryonic stem cells are considered totipotent and can give rise to all cell types in the organism, but adult stem cells are pluripotent and exhibit lineage restriction based on the tissue in which they dwell. The other form of stem cell is induced pluripotent stem cells, which can be created from adult cells.[14]

STAT3 Maintains the Cancer Stem Cells

Cancer stem cells (CSCs) are important to cancer growth and progression. CSCs are self-renewing and can produce a wide range of tumor cells, resulting in tumor heterogeneity. Furthermore, CSCs are responsible for cancer development, metastasis, and drug resistance. STAT3 is critical in the tumor inflammatory environment because it raises reactive oxygen species (ROS) levels, resulting in DNA damage and oncogene activation.[17] This suggests that STAT3 activation is also important in CSC regulation. Recent research has shown that STAT3 activation is necessary for several cancer types, including prostate, breast, hepatocellular carcinoma, colorectal cancer, and glioblastoma. STAT3 activation by IL-6 or ROS increases prostatic CSCs' self-renewal capacity. Furthermore, glioma-associated human mesenchymal stem cells (GA-hMSC) stimulate glioma stemness via the IL-6/gp130/STAT3 signaling pathway. High levels of aldehyde dehydrogenase activity in endometrial cancer activate CSCs via the IL-6/JAK1/STAT3 signaling pathways. Inhibiting these systems significantly decreased tumor cell growth.[18–20]

Activated STAT3 in CSCs required the expression of pluripotent stem cell markers Oct3/4 and Nanog. These signaling pathways upregulate CSC markers such as CD44, which enhances CSC characteristics. Furthermore, high levels of the CSC marker CD133 are associated with a poor prognosis and tumor development in hepatocellular carcinoma. On the contrary, inhibiting CD133 caused cell cycle arrest and tumor suppression via down-regulating cytokine-related genes. Treatment with sorafenib and nifuroxazide inhibited STAT3 activation and CD133 expression. Recent research has shown that vascular endothelial growth factor enhances self-renewal capability via the VEGFR2/STAT3 signaling pathway, upregulating Myc and Sox2 expression. In CD133+ cells originating from thyroid carcinoma, highly active STAT3 corresponds with enhanced self-renewal and radiochemist resistance. Due to the significance of STAT3 in preserving CSC features such as self-renewing capacities in carcinogenesis, blocking this signaling pathway may eradicate CSCs and help prevent cancer.[6]

TUMOR MICROENVIRONMENT

Tumor cells are well known for modifying and adapting to their environment. Constitutive STAT3 activation promotes tumor growth via the oncogenic signaling pathway, interacting with tumor cells and their surroundings. STAT3 activation goes awry, recruiting immune cells and compromising their roles to benefit tumor cells. Furthermore, STAT3 is a negative regulator of T helper 1 cells, which suggests that inhibiting STAT3 activity stimulates the production of proinflammatory cytokines. Hypoxic stress is induced in tumor tissue, inducing hypoxia-inducible factors. STAT3 modulates hypoxia-inducible factor 1 alpha stability and activity, leading to increased production of cytokines, chemokines, and growth factors that promote cancer formation. Furthermore, in response to surrounding tumor cells, stromal cells upregulate their C-X-C motif chemokine ligand 12 (CXCL12) receptors, increasing tumor cells' spreading potential.[21] Furthermore, STAT3 activation enhances the polarization of tumor-associated macrophages into the M2 phenotype and the production of programmed cell death ligand-s1, both of which boost tumor growth. STAT3 activation inhibition has anti-tumor properties because it suppresses macrophage polarization. Furthermore, activating STAT3 in endothelial cells promotes the expression of cell adhesion molecules, which is critical for tumor dissemination. Tumor cells can avoid an immune response by manipulating their immunological surroundings. STAT3 activation enhances tumor growth factor beta, vascular endothelial growth factor, and myeloid-derived suppressor cell proliferation while suppressing natural killer cell activity, enabling tumor cells to dodge immune response. STAT3 inhibitors have been shown to diminish immunosuppressive responses, which increase immune cell anticancer activity.[6,22]

STAT3-Associated Affected Systems

Cardiovascular disease: New evidence reveals that STAT3 signaling plays a role in cardiovascular health, particularly in myocardial infarction and heart

failure. As part of the healing process following cardiac damage, STAT3 is activated, impacting fibrosis, inflammation, and cardiomyocyte survival. Maladaptive cardiac remodeling may result from dysregulated STAT3 signaling.[23,24]

Clinical applications of STAT3: By promoting the healing processes and lowering pathological fibrosis, STAT3 as a therapeutic target may aid in the treatment of heart failure or myocardial infarction.[23,25]

Clinical trials are focusing on small compounds that can selectively modify STAT3 activity to balance the favorable and negative consequences of its activation in cardiovascular disorders. Furthermore, the JAK/STAT3 signaling pathway has recently received attention for its role in the occurrence and progression of cardiac fibrosis, and activation can stimulate the proliferation and activation of cardiac fibroblasts as well as the creation of extracellular matrix proteins, ultimately leading to cardiac fibrosis.[25]

Fibrotic disease: STAT3 is strongly implicated in fibrosis, a condition in which excessive scar tissue forms in organs such as the liver, kidney, and lungs. STAT3 activation encourages fibroblast proliferation and the synthesis of extracellular matrix components, which leads to organ fibrosis in conditions such as liver cirrhosis, idiopathic pulmonary fibrosis, and chronic kidney disease.[26,27]

Clinical uses for treating fibrosis: reversing or slowing the evolution of fibrotic illnesses may be possible by blocking STAT3 activation. The potential of selective STAT3 inhibitors or substances that target upstream signaling in the TGF-β/suppressor of the mother against the decapentaplegic pathway to lessen fibrosis in lung, kidney, and liver disorders is being investigated.[28–30]

Hyper-IgE syndrome: commonly known as Job's syndrome, is a rare primary immunodeficiency illness marked by elevated serum immunoglobulin E, recurrent skin and lung infections, and several other clinical characteristics. Autosomally dominant hyper-IgE syndrome is frequently caused by STAT3 mutations. It is essential for the generation and activity of T helper 17 cells, which are responsible for immune responses to external infections. Its mutations influence the development of other immune cells, such as T regulatory cells and dendritic cells, which contribute to immunological dysregulation. They also impede T helper 17 cell differentiation, which results in a compromised immune defense against infections.[31,32]

In conclusion, when the relationship between STAT3 and cancer is examined, it is understood that it is a very complex and multifaceted relationship. STAT3 is a transcription factor that plays a role in processes that include functions such as cellular proliferation, survival, differentiation, and immune modulation. Abnormal activation is common in tumorigenesis and affects the stages of formation, development, spread, and recovery of tumors. Chronic STAT3 activation can occur with mutations, overexpression of upstream signaling molecules, or paracrine and autocrine pathways within the TME. Since STAT3 makes important contributions to the progression of the neoplastic process in the medical field, it may be used as a treatment method in the future. Preliminary clinical studies have yielded successful results in inhibiting the STAT3 signaling pathway using inhibitors, peptide-based inhibitors, and monoclonal antibodies. However, although it maintains its normal functions in non-cancer cells, there are still some difficulties in effectively targeting STAT3.

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