STAT3
The Oncogenic Signaling Hub
STAT3 is an Oncogene

- STAT3 is a member of the Signal Transducers and Activators of Transcription protein family
- STAT3 is one of the drivers in the JAK/STAT pathway
- STAT3 is a transcription factor and an oncogene
- STAT3 is a key factor in multiple pathways
- STAT3 confers stemness characteristics in tumor cells

JAK, Janus kinase.

Stemness Characteristics Have Multiple Outcomes

Cancer Stem Cells are a subset of cells existing within a tumor with high tumor-initiating capabilities.

**Tumorigenesis**
due to unregulated self-renewal and differentiation.

**Metastasis**
due to EMT-mediated increase in migration and invasiveness.

**Resistance**
due to activation of multiple resistance-mediating genes.

Acquisition of transient stemness increases ability to metastasize.

Innate resistance to conventional chemo- and radiotherapies may underlie tumor recurrence.

EMT, epithelial-mesenchymal transition.
Key Stemness Pathways May Drive Malignancy

- Several signaling pathways have been identified that can result in stemness characteristics
- Dysregulation or activation of these pathways may drive tumor growth

JAK, Janus kinase; STAT, signal transducer and activator of transcription.

Cancer Stem Cells: Stemness Characteristics

- Ability to self-renew and differentiate
- Convey tumorigenicity
- Play a key role in metastasis
- Show innate resistance to multiple conventional therapies
- Have dysregulated stemness signaling pathways

Cells with these properties have “Stemness” characteristics

*Bulk tumor cells.

STAT3 is a Transcription Factor

STAT3 has many ligand activators: cytokines, growth factors\(^1\)...

Inactive state in cytoplasm\(^2\)

Ligand binds to its cell surface receptor which is then phosphorylated\(^1,2\)

Phosphorylated STAT3 forms a dimer\(^1,2\)

Dimer translocates to nucleus\(^1,2\)

Binds to DNA and activates transcription\(^1,2\)

STAT3 transcribes many genes\(^1\)

Activated JAK catalyzes phosphorylation of STAT3\(^3\)

JAK, Janus kinase; STAT, signal transducer and activator of transcription.
STAT3 Function in Normal Cells

- STAT3 is critical for embryonic development\(^1\)
- STAT3 activation in normal cells is tightly regulated and transient, initiating its own repression via negative feedback loops\(^1\)\(^-\)\(^3\)

**Embryogenesis\(^1\)**

**Innate Immunity\(^3\)**
- Neutrophils

**Organogenesis\(^4\)\(^-\)\(^6\)**

**Adaptive Immunity\(^3\)**
- B cells
- T cells

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STAT, signal transducer and activator of transcription.
STAT3 is Activated in Multiple Cancers

High levels of activated STAT3 has been identified \textit{in vitro} and \textit{in vivo} in multiple cancer types\textsuperscript{1-3}

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STAT, signal transducer and activator of transcription.
Multiple Upstream and Downstream Factors can Activate STAT3

STAT3 has many upstream activators that drive its activation, primarily through the JAK/STAT pathway

**Growth Factors**
- EGF
- TGF-α
- PDGF
- IGF-1
- M-CSF
- GM-CSF

**Pro-inflammatory Cytokines**
- IL-6
- IL-5
- IL-9
- TNF-α
- IL-22
- IL-12

**Other Factors**
- Src
- Ras
- cadherin
- TLR
- G-protein coupled receptors

**Activated STAT3 “crosstalks” with downstream stemness signaling pathways to confer stemness characteristics**

*Scr, TLR, Ras, and G-protein coupled receptors can activate STAT via non-JAK mechanisms.

EGF, epidermal growth factor; GM-CSF, granulocyte macrophage colony-stimulating factor; IGF, insulin-like growth factor; JAK, Janus kinase; M-CSF, macrophage colony-stimulating factor; PDGF, platelet-derived growth factor; STAT, signal transducer and activator of transcription; TGF-α, transforming growth factor alpha; TLR, toll-like receptor; TNF-α, tumor necrosis factor alpha.

STAT3 Drives Stemness Characteristics

Multiple mechanisms can cause STAT3 to become constitutively activated, leading to dysregulation of stemness pathways

- ↑ Epigenetic dysregulation
- ↓ SOCS ↑Cytokines
- ↓ PIAS
- ↑ Gain-of-function mutations

PIAS, proteins that inhibit activated STATs; SOCS, suppressors of cytokine signaling; STAT, signal transducer and activator of transcription.

STAT3 Drives Tumorigenicity

STAT3 activation drives CSC renewal both directly and via upregulation of other stemness pathways.

* Bulk tumor cells.
CSC, cancer stem cell; JAK, Janus kinase; STAT, signal transducer and activator of transcription.

STAT3 Drives Metastasis

Epithelial-Mesenchymal Transition (EMT) is a critical step in metastasis

Activated STAT3 modulates the expression of several EMT-related transcription factors

Twist, Snail, ZEB1

MMP9

Epithelial-Mesenchymal Transition

Epithelial cell → Mesenchymal cell

Epithelial cells acquire fibroblast-like properties

↑ Twist, Snail and ZEB1 suppress E-cadherin

↓ E-cadherin causes loss of cell-cell adhesion

↑ MMP9 breaks down extracellular matrix

Changes result in increased migration and invasiveness

Cancer Stem Cell

non-Stem Cancer Cells*

Bulk tumor cells.
EMT, epithelial-mesenchymal transition; MMP9, matrix metalloproteinase 9;
STAT, signal transducer and activator of transcription.

STAT3 Drives Resistance

Tumor-associated fibroblasts in the microenvironment release IL-6

IL-6 and NANOG activate STAT3

NANOG

STAT3 increases expression of ABC transporters

^{1,2} \uparrow MDR-1 \uparrow MRP

Activated STAT3 increases expression of drug efflux pumps driving resistance

ABC, ATP-binding cassette; MDR-1, multidrug resistance gene-1; MRP, multidrug resistance-associated protein; STAT, signal transducer and activator of transcription.

STAT3 Reduces Apoptosis

Activated STAT3 enhances cell survival pathways in tumor cells

- Apoptotic pathways are intrinsically regulated by the Bcl-2 family and the Inhibitors of Apoptosis family (IAPs), eg, survivin\textsuperscript{1,2}
- Activated STAT3 upregulates antiapoptotic genes and pathways\textsuperscript{1,3}
- Survival pathways confer chemo- and radioresistance\textsuperscript{1,2}

*Bulk tumor cells.
STAT, signal transducer and activator of transcription.
STAT3 is Continually Activated via Immune Response

In response to tumors, immune cells are recruited to destroy tumor cells.

STAT3 activated in tumor cells

Activates STAT3 in immune cells

Positive Feedback Loop

Receptor

JAK

JAK

Dendritic cell

Neutrophil

Macrophage

Immune cells release cytokines

IL-6

IL-6

IL-6

JAK, Janus kinase; STAT, signal transducer and activator of transcription.

....but STAT3 activation in these cells causes a positive feedback loop

STAT3 suppresses anti-tumor immunity by activating in immune cells, decreasing anti-tumor immunity and enhancing immunosuppression via several mechanisms. STAT3, shown in the diagram, activates multiple pathways:

- Increased expression of immunosuppression factors (↑IL-10, VEGF, TGFβ, IL-23)
- Activates Wnt pathway
- Blocks T-cell recruitment to microenvironment

TH1 immune response suppressed

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**Reference:**
STAT3 Plays a Role in Angiogenesis

- STAT3 is a direct transcriptional activator of VEGF
- STAT3 also induces expression of hypoxia-inducible factor 1α (HIF1α)
- Together, STAT3 and HIF1α maximize expression of VEGF

*Bulk tumor cells.
STAT, signal transducer and activator of transcription; VEGF, vascular endothelial growth factor.
Overactivation of STAT3 Correlated with Poor Outcomes

- High levels of activated STAT3 in clinical samples correlated with poor prognosis in multiple cancers\(^1-^6\).

- The clinical pathologic significance of STAT3 has been demonstrated in gastric\(^3-^5\), colorectal\(^6\), and bone\(^7\) cancer.

- Differences in survival have been reported between patients with high levels of activated STAT3 versus low levels\(^3-^7\).

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**Gastric cancer survival\(^5\)**

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<th>Percent survival</th>
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**Osteosarcoma survival\(^7\)**

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<th>Time (months)</th>
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\(^{p=0.044, N=48}\) \(^{p=0.0098, N=23}\)

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**References**


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STAT, signal transducer and activator of transcription.
STAT3 is an Oncogenic Signaling Hub

- STAT3 is an oncogene that drives cancer cell stemness via multiple pathways.
- STAT3 dysregulation drives tumorigenicity, metastasis, and resistance and also suppresses anti-tumor immunity.

STAT, signal transducer and activator of transcription.
STAT3 is a Potential Therapeutic Target

- STAT3 is an integral part of multiple pathways involved in perpetuating stemness characteristics in cancer cells
- Downstream effects of STAT3 can create a positive feedback loop resulting in continuous activation of STAT3, enhancing “crosstalk” with other stemness pathways
- Stemness pathways help drive malignancy in cancers by increasing unregulated proliferation, tumor initiation, metastasis, and resistance
- In normal development, STAT3 is critical for early embryonic development and some organogenesis, before becoming essentially dormant during adult life
- Persistently activated STAT3 has been identified in multiple cancer types
- Therefore, STAT3 is a potential research target for the treatment of multiple cancers

STAT, signal transducer and activator of transcription.
References