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# STAT3: A target for many human cancers

50-100% Stat3 activation in

## Solid Tumors
- Prostate cancer: STAT3
- Non-small Cell Lung cancer: STAT3
- Breast cancer: STAT3, STAT5
- Head and Neck cancer: STAT3
- Melanoma: STAT3
- Ovarian cancer: STAT3
- Pancreatic cancer: STAT3
- Glioma: STAT3
- Stomach Cancer: STAT3
- Cervical Cancer: STAT3

## Blood Tumors
- Multiple Myeloma: STAT3
- Acute Myelogenous Leukemia (AML): STAT3, STAT5
- Chronic Myelogenous Leukemia (CML): STAT5
- Burkitt’s Lymphoma: STAT3
- Non-Hodgkins Lymphoma: STAT3
- Cutaneous T cell Lymphoma: STAT3
Importance of Stat3 in Cancer Therapy
Multiple roles of STAT activation in tumor cells

H. Yu and R. Jove

Nature Reviews | Cancer
Role of Stat3 in Oncogenesis and the Tumor Microenvironment

Proliferation and survival

- ↑ Myc
- ↑ Cyclin D1/D2
- ↑ BCL-X_L ↓ p53
- ↑ MCL-1 ↓ Stat1
- ↑ Survivin ↓ IFNs

Angiogenesis

- ↑ bFGF ↓ IFNγ
- ↑ HGF ↓ IL-12
- ↑ VEGF ↓ IP-10
- ↑ HIF-1 ↓ Stat1
- ↑ MMP-2 ↓ IFNβ
- ↑ MMP-9 ↓ p53

Immunosuppression

- ↓ IFNβ
- ↓ IFNγ
- ↑ IL-10 ↓ IL-12
- ↑ TGFβ ↓ TNFα
- ↑ VEGF ↓ IP-10
- ↑ IL-6 ↓ RANTES
- ↑ IL-6 ↓ MHC II
- ↑ Foxp3 ↓ CD80
- ↓ CD86
- ↓ Stat1
Gene Therapy with a DN Stat3 Involves “Bystander Effects”

Stat3 Is Critical for Tumor Angiogenesis

Critical Role of Tumor Stat3 Activity in Immune Evasion

Wang, Niu, Kortylewski and Burdelya et al, Nature Medicine; Jan 2004
Burdelya and Kujawski et al, J. Immunol, Jan 2005
Yu and Jove, Nature Reviews Cancer, Feb 2004
Stat3 Activity in Immune Cells Mediates Immune Suppression

Stat3 mediates the crosstalk between tumor and immune cells:

Stat3 targeting: beyond tumor cells

Tumor microenvironment

VEGF
IL10
IL6
IL23

DCs, Tregs
Macrophages
NK cells, Granulocytes

Alter tumor Environment

Immunity

Anti-angiogenesis

Endothelial cells

Stat3

Stat3

Stat3
Crosstalk between tumor cells and endothelial cells: role of Stat3
Crosstalk between tumor cells and endothelial cells: role of Stat3

Maciej Kujawski and Andreas Herrmann et al

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[Graphs showing the relationship between different cell types and the effect of Stat3 siRNA on tube formation.]
CpG-Stat3siRNA: Targeted delivery, DC activator and Stat3 inhibitor into a single agent.
Genetic ablation of Stat3 in immune cells: drastic improvement of immunotherapy

Stat3+/+  Stat3−/−

Day 0  Day 3

Stat3+/+  CpG i.t.  Stat3+/+


Stat3−/−  −−  +CpG  +Rat IgG

Tumor volume [mm³]

Days
Enhancing CpG antitumor immunity by a small-molecule Stat3 inhibitor

B16 tumor

Primary tumor site

Secondary tumor site
Targeting Stat3 for Cancer Therapy

**Immune inhibitors**
- CTLA-4
- B7-H1
- B7-H4
- IDO
- PD-1
- SOCS1
- IL-10
- TGF-β
- COX2

**Immune activators**
- Dendritic cell vaccines
- Modified tumor cell vaccines
- Engineered T cells
- CpG ODNs
- LIGHT
- Tumor-associated antigens (Peptides)
- Cytokine or chemokine administration

Adapted from: Yu et al. *Nature Reviews Immunology* 7, 41–51 (January 2007)