STAT3 Signaling Regulates Crosstalk between the Tumor and Its Immune Microenvironment

Cartoons courtesy of Hua Yu, Ph.D./members of Yu and Jove labs
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STAT3 and the Tumor-Inflammatory milieu

- Constitutively activated in many tumors (especially melanoma)
- Activation mediated in part by Src activation
- Promotes growth, survival, angiogenesis, anti-inflammatory, immunosuppressive effects
- Blockade leads to apoptosis of tumor cells, immunostimulation, anti-angiogenesis
  - Dominant negative mutation in hematopoietic cells
  - Small-molecule inhibitor of STAT phosphorylation
STAT3 Signaling in Tumor and Inflammatory cells

Oncogenic Signals Or Hypoxia

↑ Immune suppressing factors
↓ Immunologic danger signals

Immune cells

STAT3↑

Gene Expression

Tumor Microenvironment

Tumor cells

Tumor Survival

Immune Evasion

Angiogenesis
Molecules that mediate STAT3 effects in tumor/ inflammatory/ immune/pro-angiogenic milieu

- VEGF
- IL-10
- bFGF
- HGF
- HIF-1
- MMPs

Angiogenesis

- EC
- Gr1+ CD11b+
- VEGF
- bFGF
- HGF
- IL-10

- Stat3
- Tumor Stat3

- HIF1
- MMP2
- MMP9

- VEGF
- IL-10
- Treg
- Tumor Stat3
- Stat3

- Nk
- MΦ
- DC
- Mcl-1
- Cyclin D1/2
- c-Myc
- Bcl-XL
- Survivin
- p53
Stat3 activation in immune cells protects tumor from immunotherapy

Kortylewski et al, Nat Med 2005
Can STAT3 inactivation in tumor cells facilitate immunotherapy?

Tumor cells

- P-STAT3
- STAT3

- Impaired DC maturation, activation
  - IL-10
  - VEGF
  - ???
  - DC maturation, activation

- Tolerant T cells
- Activated T cells

- Tumor cells
  - TNF
  - IP-10
  - IL-6
  - RANTES

Adapted from Gamero, Young, Wiltrout Cancer Cell 2004