Antiangiogenesis - Immune Therapy Combinations

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Overview

• Effect of VEGF on antitumor immune response
  - Antigen presentation
  - Effector mechanisms
  - Ying and yang and immunity and angiogenesis in tumors

• Effect of VEGF blockade on immune therapy

• Multifunctional tool opportunities
VEGF mediates immature DC development through VEGF-R2 and blocks DC maturation through VEGF-R1.
VEGF impairs DC maturation mainly through VEGF-R2

Huang et al, Blood, 2007
VEGF collaborates with beta-defensin to induce vascular leukocytes

Discovery of mouse vascular DCs

CD11c

Matrigel

Conejo-Garcia et al., Nature Med. 2004
Vascular DCs enhance tumor vascularization and growth

Conejo-Garcia et al., Nat Med 2004
Discovery of Human Vascular DCs

Conejo-Garcia et al., *Blood*. 2005
Transdifferentiation of DC precursors into endothelial-like vascular leukocytes

Coukos et al, BJC 2007
VEGF induces MDSCs through VEGF-R2

Huang et al, Blood, 2007
Alternatively activated DC produce VEGF and promote angiogenesis

Riboldi et al, J Immunol 2005
COX-2 suppression enhances the efficacy of vaccination

Basu et al, J Immunol 2006
Plasmacytoid DC produce VEGF and promote angiogenesis

Curiel et al, Ca Res 2004
VEGF blockade improves vaccine therapy

Gabrilovich et al, Clin Cancer Res. 1999
VEGF blocks T cell adhesion on endothelium

Bouzin et al, J Immunol 2007
VEGF blockade induces antitumor immune response, increases T cell homing and improves vaccine therapy.

Manning et al, Clin Ca Res, 2007
VEGF-R1 and R2 blockade improves immune therapy and reduces Treg

Li et al, Clin Ca Res, 2006
ET_{BR} blockade enhances tumor vaccine

Buckanovich et al, submitted
ETBR blockade enhances tumor vaccine by increasing T cell homing to tumor

Buckanovich et al, submitted
VEGF blockade improves DC maturation in patients with solid tumors

Fricke et al, Clin Ca Res, 2007
Vaccine + VEGF blockade moves to the clinic

• Sipuleucel-T (APC loaded with recombinant prostatic acid phosphatase/GM-CSF fusion protein) i.v. on weeks 0, 2, and 4 + bevacizumab 10 mg/kg i.v. on Weeks 0, 2, 4, and every 2 weeks thereafter until toxicity or disease progression in androgen-dependent prostate cancer patients who had received prior definitive therapy with nonmetastatic, recurrent disease as manifested by a rising PSA.

• 22 patients treated, 3 patients responded with PSA ↓ >25%, 1 patient with PSA ↓ >50%.

Rini et al, Cancer 2006
Integrative Model of Immune Response and VEGF Interactions

Predominance of angiogenesis

T cells → IRN-γ → Suppression → VEGF → Angiogenesis

DC → MIG → Growth
Integrative Model of Immune Response and VEGF Interactions

Predominance of antitumor immune response

- DC
- IFN-γ
- T cells
- MIG
- Apoptosis
- Activation

Antiangiogenesis
Thrombosis
Successful tumor immunotherapy suppresses tumor vascularization

Qi and Blankenstein, Immunity 2000
Multifunctional tool opportunities

- Angiogenesis-targeting immunotherapy
- Thalidomide and analogs (antiangiogenic/anti-inflammatory and Th1 costimulatory)
- ET_{B}R inhibitors
- STAT3 inhibitors?
- COX-2 inhibitors?
- Sorafenib?
- Sunitimib?
Vaccination against tumor and angiogenesis targets produces synergism

**Angiogenesis/Vascular Targets**

- Mixed endothelial cells
- VEGF
- VEGF-R2
- VEGF-R1
- FGF-2
- FGF-R1
- Tie-2
- Endoglin (CD105)
- Integrin β3
- Calreticulin
Thalidomide and analogs

Thd and IMiDs:

- Inhibit TNF-α, IL-1β, 6, 12, and GM-CSF
- Costimulate primary human T lymphocytes inducing proliferation, Th1 polarization, cytokine production, and cytotoxic activity.

Dredqe et al, J Immunol 2002
STAT3 Inhibition

Survival:
↑ BCL-X<sub>L</sub>
↑ MCL-1
↑ Survivin
↓ p53

Proliferation:
↑ Myc
↑ Cyclin D1/D2
↓ p53

Angiogenesis and metastasis:
↑ VEGF
↑ HIF-1
↑ MMP-2
↓ p53

Immune evasion:
↑ Immunosuppressive factors
↓ Pro-inflammatory cytokines
↓ Pro-inflammatory chemokines

CD1<sup>11</sup>b<sup>+</sup>CD80<sup>+</sup> CD1<sup>11</sup>b<sup>+</sup>CD86<sup>+</sup>

% Gated cells

Unstimulated
WP1066

Hussain et al, Cancer 2007
Conclusions

• Tumor VEGF suppresses antitumor immune response
• Immune tolerance may increase, while immune activation may suppress tumor angiogenesis
• VEGF blockade enhances immune therapy
• Novel targets are available for therapy (ETB\textsuperscript{B}R)
• Novel functions discovered for existing drugs generate opportunities for combinatorial biologic therapy with multifunctional tools