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Hira Lal Goel  
*University of Massachusetts Medical School*

*Et al.*

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Therapeutic Approaches to Aggressive Carcinomas Based on a Novel VEGF/Neuropilin Autocrine Pathway

Hira Lal Goel and Arthur M. Mercurio

Department of Cancer Biology
**Biology of High-Grade Carcinomas**

- **Triple-Negative Breast Ca**
- **High Gleason Grade Prostate Ca**

**Mechanisms**
- Embryonic gene expression
- Epithelial mesenchymal transition
- Cell autonomous pathways
- High % of ‘cancer stem cells’

**Properties**
- Poorly differentiated
- Aggressive; poor prognosis
- Difficult to treat
Frequency of cancer stem cells increases with tumor grade—poorly differentiated carcinomas harbor relatively high frequency of cancer stem cells. *Pece et al., Cell 2010*

**Autocrine Signaling Pathways** Sustain the Function of Cancer Stem Cells and the Distinct Characteristics of Poorly Differentiated Carcinomas & Are Prime Targets for Therapy

**Vascular Endothelial Growth Factor (VEGF)**
VEGF IS MUCH MORE THAN AN ANGIOGENIC FACTOR

Tumor Cell

Endothelial Cell

VEGF

VEGF-R

Angiogenesis

Tumor Formation Progression

Macrophage
VEGF and VEGF Tyrosine Kinase Receptors

Vascularogenesis and angiogenesis

Lymphangiogenesis

- Bevacizumab
- HuMV833
- IMC-1121B
- Sunitinib
- Sorafenib
- Vandetanib
- Vatalanib
- Axitinib
- Semaximab
- AMG 706

VEGF-R1, NRP₁/₂, R₂, R₃, NRP₂
NEUROPILIN-1 & 2

Bind two structurally distinct ligands: Semaphorins and VEGFs

NRPs mediate axon guidance, angiogenesis

NRPs Function as Co-Receptors
Neuropilin-2 Expression is Highly Enriched in Breast Tumor Stem Cells

**CD44+/CD24-** (Stem Cell Properties)

Formation of Mammospheres from Human Breast Ca Biopsy is Inhibited by NRP2 Ab
VEGF/NRP2 Signaling Contributes to Tumor Initiation

Defined a Signaling Pathway That Can Be Targeted for Therapy

FAK Inhibitors in Clinical Trials

Therapeutic Abs Exist

Bmi-1: Polycomb group transcriptional repressor
Represses p16/INK4A
Implicated in the self-renewal function of stem cells
Implications of VEGF/NRP2 Signaling for Breast Cancer Therapy

Bevacizumab (Avastin) (Not effective-FDA)
Does Not Inhibit VEGF/NRP2

Targeting NRP2 Directly Humanized Ab Available

FAK Inhibitor (VS-6030) In Clinical Trials
Implications of VEGF/NRP2 Signaling for Breast Cancer Therapy

Transgenic Mouse Model of Triple Negative Breast Cancer
TgMFT121; Brca1f/f p53f/f; TgWAP-Cre
Karl Simin (PLoS Genetics)

NRP2 Ab Treatment Reduces Tumor Formation

NRP2 AB Treatment Causes Stasis of Established Tumors (SUM1315)

(Genentech Anti-NRP2β)
Prostate Cancer: NRP2 Expression is Induced by PTEN Loss and Correlates with Gleason Grade

- NRP2 levels (qPCR) are shown for different conditions: Normal, PIN, AdCa (G3), AdCa (G5).
- Pathology table:
  - Normal: 11 cases, NRP2 expression 0 (0%).
  - Gleason grade 3: 36 cases, NRP2 expression 5 (14%).
  - Gleason grade 5: 21 cases, NRP2 expression 16 (76%).

- c-Jun is induced by PTEN loss and regulates NRP2 expression.

- Graph showing fold change in NRP2 and PTEN expression.

- Images showing wild-type and PTEN^Pc1-1 prostate tissues.

- Images showing benign and AdCa prostate tissues.

- Graph showing NRP2 promoter luciferase relative change with c-Jun shRNA.

- c-Jun is induced by PTEN loss and regulates NRP2 expression.
VEGF/NRP2 Signaling Represses IGF-1R Signaling in Prostate Cancer

Implications for Therapy?
Combined NRP2 and IGF-1R Inhibition of Prostate Tumor Growth

![Graph showing tumor volume over days with different treatments: Control, Anti-IGF-1R, Anti-NRP2, Anti-NRP2 + Anti-IGF-1R.](image)
SUMMARY

• Autocrine VEGF signaling in tumor cells contributes to de-differentiation and function of tumor initiating/stem cells

• NRP2 is the nexus of a signaling pathway that promotes de-differentiation and sustains tumor initiating/stem cells

• Anti-NRP2 therapy is worth pursuing, especially for high-grade cancers. Therapeutic Abs are available.