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

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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’

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
- Macrophage

Tumor Formation Progression
Angiogenesis
VEGF and VEGF Tyrosine Kinase Receptors

Vasculogenesis and angiogenesis

Lymphangiogenesis

- Sunitinib
- Sorafenib
- Vandetanib
- Vatalanib
- Axitinib
- Semaximab
- AMG 706
NEUROPILIN-1 & 2

Bind two structurally distinct ligands: Semaphorins and VEGFs

NRPs mediate axon guidance, angiogenesis

NRPs Function as Co-Receptors

Michael Klagsbrun (Childrens Hospital)
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
Defined a Signaling Pathway That Can Be Targeted for Therapy

VEGF/NRP2 Signaling Contributes to Tumor Initiation

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)

(Generentech Anti-NRP2B)
Prostate Cancer: NRP2 Expression is Induced by PTEN Loss and Correlates with Gleason Grade

**A.** Wild-type vs. PTEN<sup>pc1/-</sup>

**B.** Benign vs. AdCA

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 time for different treatments including Control, Anti-IGF-1R, Anti-NRP2, and 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.