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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

Poorly differentiated
Aggressive; poor prognosis
Difficult to treat

Mechanisms
Embryonic gene expression
Epithelial mesenchymal transition
Cell autonomous pathways
High % of ‘cancer stem cells’
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
  - VEGF-R
  - Tumor Formation Progression

- Endothelial Cell
  - VEGF-R
  - Angiogenesis

- Macrophage
VEGF and VEGF Tyrosine Kinase Receptors

Vasculogenesis and angiogenesis

Lymphangiogenesis

- Sunitinib
- Sorafenib
- Vandetanib
- Vatalanib
- Axitinib
- Semaximab
- AMG 706

IMC-18F1

VEGF-R

R

NRP

AFlibercept

VEGF-B

PIGF

Bevacizumab

HuMV833

IMC-1121B
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
VEGF/NRP2 Signaling Contributes to Tumor Initiation

Defined a Signaling Pathway That Can Be Targeted for Therapy

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

VEGF

NRP2 α6β1 Integrin

FAK

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; Brca1 f/f p53 f/f; TgWAP-Cre

Karl Simin (*PLoS Genetics*)

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**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

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 growth](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.