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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

<table>
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<tr>
<th>Characteristics</th>
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<td>Poorly differentiated</td>
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<tr>
<td>Aggressive; poor prognosis</td>
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<tr>
<td>Difficult to treat</td>
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**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
VEGF and VEGF Tyrosine Kinase Receptors

[Diagram showing interactions between VEGF and VEGF receptors, including targets and inhibitors such as Afibercept, PIGF, IMC-18F1, VEGF-R1, NRP1/2, R2, R3, and NRP2.]

Vasculogenesis and angiogenesis

Lymphangiogenesis

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

Other compounds:
- Bevacizumab
- HuMV833
- IMC-1121B
NEUROPIILIN-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

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-NRP2<sup>B</sup>)
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

VEGF

NRP2

α6β1 Integrin

FAK

Bmi-1

IGF-1R

De-Differentiation
TUMOR INITIATION

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

![Graph showing tumor growth inhibition with different treatments.]

- Control
- Anti-IGF-1R
- Anti-NRP2
- Anti-NRP2 + Anti-IGF-1R

Tumor Volume

Days

Tumor volume (mm³)
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.