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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

\[ \text{Poorly differentiated} \]
\[ \text{Aggressive; poor prognosis} \]
\[ \text{Difficult to treat} \]

**Mechanisms**

- Embryonic gene expression
- Epithelial mesenchymal transition
- Cell autonomous pathways
- High % of ‘cancer stem cells’
Cancer Stem Cells and Tumor Differentiation

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 ANGIÖGENIC FACTOR

Tumor Cell

VEGF-R

VEGF

Endothelial Cell

VEGF-R

Macrophage

Tumor Formation Progression

Angiogenesis
VEGF and VEGF Tyrosine Kinase Receptors

Vasculogenesis and angiogenesis

Lymphangiogenesis

- Sunitinib
- Sorafenib
- Vandetanib
- Vatalanib
- Axitinib
- Semaximab
- AMG 706
NEUROPILEN-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-NRP2β)
Prostate Cancer: NRP2 Expression is Induced by PTEN Loss and Correlates with Gleason Grade

- **Pathology**
  - 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%)

- **Fold Change (Log Scale)**
  - G3-AdCa

- **c-Jun**: Induced by PTEN loss and regulates NRP2 expression

Experiments show that NRP2 levels are induced in prostate cancer cells with PTEN loss and correlate with Gleason grade. Additionally, 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

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

Tumor Volume

Graph showing tumor volume over Days with different treatments.
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.