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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

**Diagram:**

- Tumor Cell
  - Tumor Formation Progression
  - VEGF-R
- Endothelial Cell
  - Angiogenesis
  - VEGF-R
- Macrophage
  - VEGF

**Legend:**

- VEGF: Vascular Endothelial Growth Factor
- VEGF-R: Vascular Endothelial Growth Factor Receptor
- Tumor Cell
- Endothelial Cell
- Macrophage
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
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.

**Prostate Cancer NRP2 Expression**

**Graph 1:**
- NRP2 levels (qPCR) across different conditions: Normal, PIN, AdCa (G3), AdCa (G5)
- Comparison of PTEN and NRP2 expressions
- Pathology: Normal, Gleason grade 3, Gleason grade 5
  - Normal: 11 cases, 0% NRP2 expression
  - Gleason grade 3: 36 cases, 14% NRP2 expression
  - Gleason grade 5: 21 cases, 76% NRP2 expression

**Graph 2:**
- Fold Change (Log Scale) of PTEN and NRP2 across different conditions
- Pathology: G3-AdCa

**Graph 3:**
- Western Blot of PTEN, NRP2, and Actin in PC-3 and C4-2 cells
- Comparison of NRP2 promoter luciferase relative change
  - sh-GFP, sh-c-Jun
  - PTEN-/-, wild-type

**Images:**
- **A.** Wild-type vs. PTEN-/-
- **B.** Benign vs. AdCA
VEGF/NRP2 Signaling Represses IGF-1R Signaling in Prostate Cancer

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

Tumor Volume

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