Tumor Endothelial cells as a Targetable Gateway That Modulates Access of Drugs to Cancer Cells

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Introduction

• Human endothelial cells (EC) lining the tumor vasculature of human prostate adenocarcinoma are preserved in primary xenografts of intact surgical remnant tissue.
• Androgen deprivation (AD) causes apoptosis in AR-expressing endothelial cells.
• Testosterone-deprivation (T-D) leads to a rapid loss of 40-60% of ECs resulting in de-endothelialization of the vasculature of primary xenografts.
• De-endothelialization is followed by re-endothelialization with human endothelial cells in the absence of T.
• This study determined the consequences of targeted perturbation of human prostate endothelium on access of chemotherapeutic agents to prostate cancer (CaP) cells.

Results

Compromised Endothelial Barrier Upon T-D

Fig 4. Increased tissue localization of Stasix® particles (platelets) in prostate tissue following T-D. Upper panel shows MRI signals. Lower panel shows IHC staining using the platelet specific marker CD42b. Platelets were injected via the tail vein on Day 3 post-T-D and allowed to circulate for 15 minutes. Stasix® particles were from Entegron, Inc., Research Triangle Park, NC. Imaging was performed by Dr. Christopher Lascolla, MD, Duke University Medical Center with a 3T Bruker MRI.

Fig 5. 5. Representative model and experimental strategy to study the consequences of targeted perturbation of human prostate endothelium on access of chemotherapeutic agents to prostate cancer (CaP) cells.

Experimental Procedures

• Fresh clinical prostate tissue and tissue transplanted onto “humanized” mice were used.
• Vasculature leakage was measured using MRI (contrast dye), MS (particles), IHC (lectins), and photoacoustic imaging (hemoglobin).
• Endothelium stabilized by 2 weeks after implantation. Removal of T-silastic tubing 3-7 days before subcutaneous (s.q.) transplantation with 8-10 pieces of fresh clinical prostate tissue. Over the initial 14 days after transplantation there was a burst of angiogenesis by the human endothelial cells resulting in a 5-10 fold increase in MVD. Endothelium stabilized by 2 weeks after implantation. Removal of T-silastic tubing (T-D) induced acute endothelial cell involution that can be monitored over the 14-17 days after T-D.

Transcriptomes were distinctive among cell types but similar in cells of the same cell type isolated from fresh tissue and tissue transplants. Specific gene sets each cell type expressed.

Summary of key findings

• T-D induced a “window” for increased access of therapeutics to prostate tissue.
• T-D increased tissue and cellular exposure to Cis-Pt.
• Cell type-specific enrichment was efficient.
• Transcripts were comparable within the same cell type isolated from fresh tissue and pre-T-D tissue transplant.
• T-D induced dynamic changes in transcripts in epithelial, endothelial and stromal cells.
• Transcripts evolved over the time after T-D.
• Transcripts of endothelial cells before and after T-D were different markedly.
• Profiles of uptake transporters and efflux pumps varied among cell types, and evolved in response to T-D.

Conclusions

• Primary tissue transplants provide a unique tool for analysis of the roles of targeted microvascular damage in organ-specific therapies.
• Evolution of the endothelial compartment and stromal compartment in response to androgen deprivation may be important to cancer biology and delivery of therapeutics.

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