12-10-2014

Prostate Field Cancerization -- Thinking Outside the Tumor

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**Recommended Citation**

Shoshan, Dor and Bisoffi, Marco, "Prostate Field Cancerization -- Thinking Outside the Tumor" (2014). *Student Research Day Abstracts and Posters*. Paper 64.  
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**BACKGROUND**

- Prostate cancer is the second most common cancer in American men with about 230,000 new diagnoses and 30,000 deaths annually. Diagnosis by biopsy is hampered by a 30-50% false-negative rate due to small and easily missed cancer foci.
- **Field cancerization** denotes genetic and/or biochemical molecular alterations in phenotypically normal cells residing in histologically normal tissues adjacent to prostate tumors and may represent a temporal record of pathways underlying oncogenesis.
- Our previous research has shown that the key transcription factor early growth response 1 (EGR-1) is up-regulated at the mRNA level in field cancerized human prostate tissues excised 1 cm from visible tumor margins (Haaland CM et al. 2009; International Journal of Oncology 2009; 35:537-546).

**HYPOTHESIS and OBJECTIVE**

- We hypothesize that EGR-1 protein expression will be similarly elevated in cancerous and histologically normal adjacent tissues, which will support the concept of field cancerization. We further hypothesize that markers of field cancerization, such as EGR-1, could serve as biomarkers of disease and improve early cancer detection (diagnosis) at the time of biopsy.
- The objective of this project is to determine and compare the expression of EGR-1 protein in malignant and adjacent tissues using quantitative methods.

**EXPERIMENTAL METHODS**

**Tissue Source:** Human prostate tissues containing cancer cells (malignant) and matched adjacent tissues devoid of tumor cells (benign) from prostatectomies and matched biopsies were from the Cooperative Prostate Cancer Tissue Resource (CPCTR) supported through the University of New Mexico (UNM) Health Sciences Center. The PC-3 cell line was used for antibody control experiments. The present work is approved by Chapman University IRB protocol #1439512 under biosafety level 2 (BSL2) approved practices as per Institutional, State, and Federal laws.

**Immunofluorescence Microscopy:** Immunofluorescence (conventional) microscopy was performed using rabbit anti-human EGR-1 antibodies (Santa Cruz Biotechnology), unspecific control IgG, and goat anti-rabbit Alexa Fluor 488 (green) conjugated antibodies (Life Technologies) according to our previously published protocols (Jones AC et al. 2012; Prostate 2012; 72:1159-70). Fluorescent DAPI dye (blue) was used to visualize cell nuclei.

**Quantification:** Quantitative analysis (pixel densitometry) was performed using ImageJ (provided by the National Institutes of Health) and graphs were generated using Microsoft Excel and Jmpin software. Two signal acquisition modes were employed: Whole field analysis and region of interest analysis.

**SIGNIFICANCE of RESEARCH**

- **Markers of field cancerization:**
  - Have the potential to lower the persistently high false biopsy negative detection rate by expanding the target region.
  - May provide a target for repeat biopsy for patients with high serum prostate specific antigen (PSA) but negative biopsy.
  - Could improve clinical decision making, such as surgical intervention vs. active surveillance.

- **Biopsy cores (small circles)** miss the two small cancer loci (white irregular structures), while the field associated with the cancer loci (dashed circles) is detected by biopsies.

**RESULTS**

- Testing the specificity of the anti-EGR-1 antibody on PC-3 human prostate cancer cells.
- Representative immunofluorescent detection (green) of EGR-1 in two cases of malignant and benign tissues of prostatectomies and biopsies.
- Quantitative immunofluorescent data of EGR-1 in human malignant and benign prostate tissues from prostatectomies and biopsies by whole field and region of interest analyses.

**CONCLUSIONS and FUTURE RESEARCH**

- **EGR-1 protein expression** is similar in cancerous (malignant) and in histologically normal adjacent (benign) tissues from both prostatectomy and biopsy tissues. This supports the concept of field cancerization and indicates a potential organ-wide molecular change.
- Future research includes improvements at the conceptual and technical level:
  - Increasing the number of cases and including disease-free (age-matched) prostate tissues
  - Overcoming the autofluorescence of prostate tissue by the use of Alexa Fluor 633-conjugated 2nd antibodies (far red) and increasing the resolution of detection by confocal microscopy
  - Design studies towards the clinical exploitation of markers of field cancerization. In particular, we are interested in developing non-invasive assessment schemes using novel and upcoming technologies, including targeted nanoparticle imaging modalities.