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Prostate Field Cancerization -- Thinking Outside the Tumor


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PROSTATE FIELD CANCERIZATION – THINKING OUTSIDE THE TUMOR

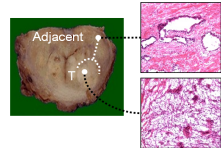


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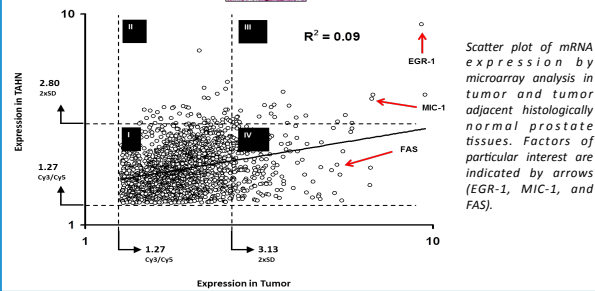
Schmid College of Science and Technology, Biological Sciences/Biochemistry and Molecular Biology, Chapman University, Orange, CA
17th Annual Chao Family Comprehensive Cancer Center Scientific Retreat

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 1cm from visible tumor margins (Haaland CM et al. 2009; International Journal of Oncology (2009); 35:537-546).



Tissue resection and H&E histology of tumor (T) and histologically normal adjacent prostate tissue removed at 1 cm from the tumor margin.



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

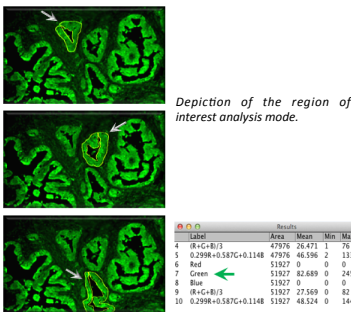
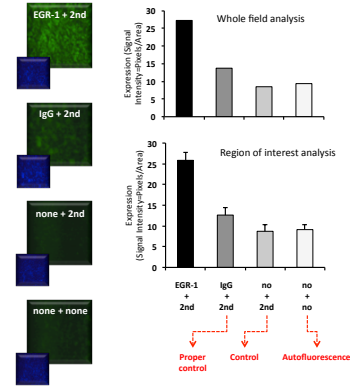
Tissue Samples: Human prostate tissues containing cancer cells (malignant) and matched adjacent tissues devoid of cancer cells (benign) from prostatectomies and matched biopsies were from the Cooperative Prostate Cancer Tissue Resource (CPCTR) procured through the University of New Mexico (UNM) Health Sciences Center. The PC-3 cell line was used for antibody control experiments. The present work is approved by Chapman University IRB protocol #1415H024 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.

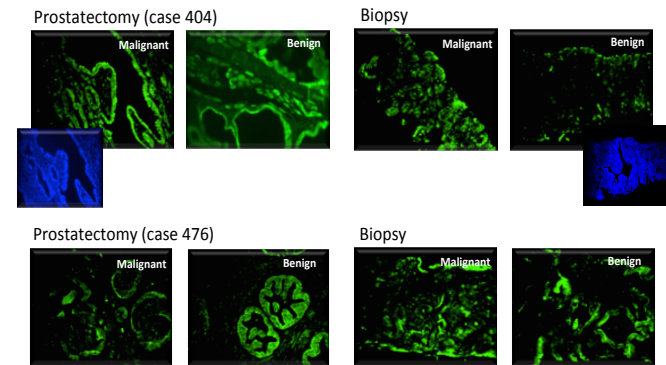
Quantification: Quantitative analysis (pixel densitometry) was performed using ImageJ64 (provided by the National Institutes of Health) and graphs were generated using Microsoft Excel and Jupyter software. Two signal acquisition modes were applied: Whole field analysis and region of interest analysis.

RESULTS

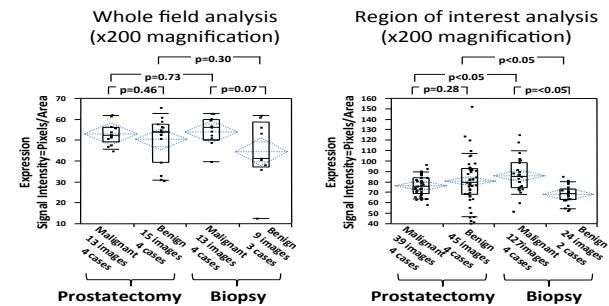
Testing the specificity of the anti-EGR-1 antibody on PC-3 human prostate cancer cells.



Representative immunofluorescent detection (green) of EGR-1 in two cases of malignant and benign tissues of prostatectomies and biopsies.



Quantitative immunofluorescence data of EGR-1 in human malignant and benign prostate tissues from prostatectomies and biopsies by whole field and region of interest analyses.

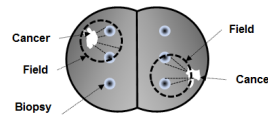


SIGNIFICANCE of RESEARCH

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.



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 prostatic tissues 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

ACKNOWLEDGEMENTS

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