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Exploring EGR-1 as a Master Regulator of Prostate Field Cancerization

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BACKGROUND

Demographics of prostate cancer:

- **2nd leading cause of cancer-related death of men in USA**
- **30,000 men die each year (one death every 17 minutes)**
- **80% men before the age of 80 are diagnosed**
- **233,000 men are diagnosed each year** [1]

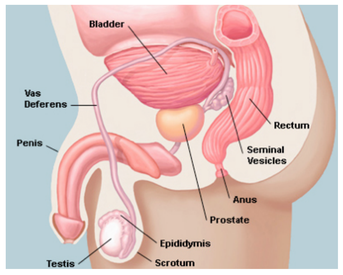

Figure 1. The prostate is a walnut sized gland found in males that is located below the bladder.

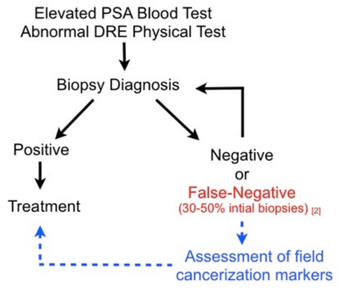

Figure 2. Improved dianosis of prostate cancer involves markers of field cancerization.

Field Cancerization: Molecular alterations in structurally intact cells residing in histologically normal tissues adjacent to tumors [3]

Significance: Increase clinically informative area as it pertains to prostate biopsies for confirmatory diagnosis of cancer [4]

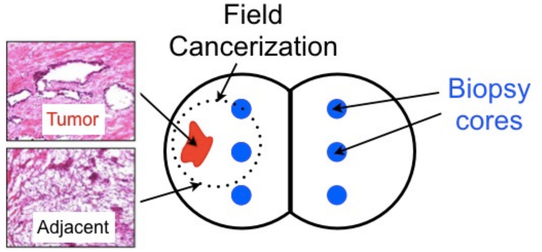

Figure 3. Avoiding false negative biopsies through the use of markers of field cancerization. (A) Biopsy cores (blue circles) miss the tumor foci (red irregular structure). (B) The field associated with the tumor (dotted circle) is detected by the biopsies (blue circles).

Function

- Our lab identified four protein factors as markers of field cancerization [5,6]

FAS	controls cell survival and apoptosis
MIC-1	controls cell inflammation
PDGF-A	controls cell survival, growth, and apoptosis
EGR-1	controls cancer cell metabolism

QUESTION

Is EGR-1 a master regulator of prostate field cancerization?

PURPOSE: understand field cancerization on the molecular level by identifying function pathways

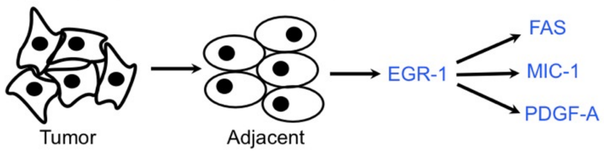

Figure 4. Tissues adjacent to tumors may undergo morphological changes leading to molecular alterations that are in complete absence of any cytological or histological change. These molecular alterations can involve changes in expression for several protein factors: early growth response 1 (EGR-1), the lipogenic enzyme fatty acid synthase (FAS), and the secreted growth factors platelet derived growth factor A (PDGF-A) and macrophage inhibitory cytokine 1 (MIC-1). As a key transcription factor, we hypothesis EGR-1 is a master regulator of FAS, MIC-1, and PDGF-A.

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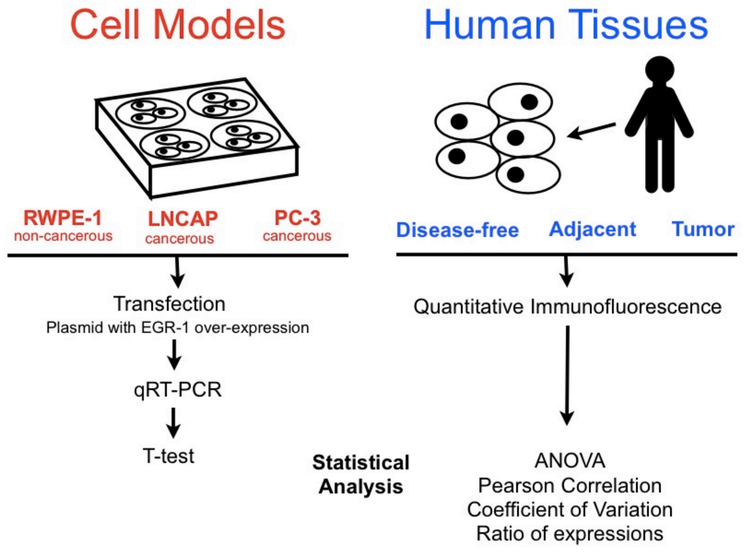
METHODS



RESULTS: Cell Models

- **EGR-1 is a regulator of FAS, MIC-1, and PDGF-A expression**
- EGR-1 down-regulated FAS and MIC-1 expression by 70% and 30% in PC-3 cells (p=0.005, p=0.015)
- EGR-1 up-regulated PDGF-1 expression by 110-fold in PC-3 cells (p=0.004)

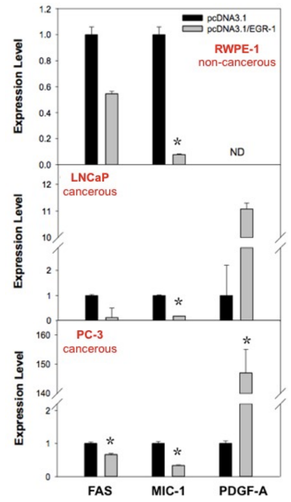


Figure 8. qRT-PCR results show the effect of EGR-1 over expression on FAS, MIC-1, PDGF-A mRNA expression in cell models: RWPE-1, LNCaP, and PC-3.

RESULTS: Human Tissues

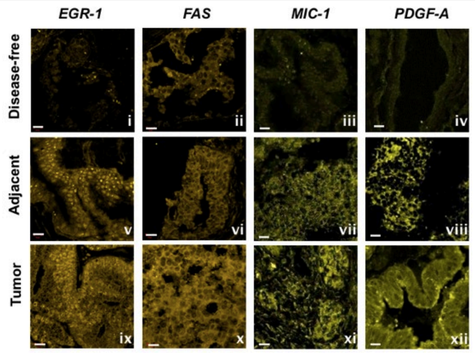


Figure 5. Representative immunofluorescence image.

- EGR-1, FAS, MIC-1, and PDGF-A have greater expression in adjacent tissue, which can be a molecular mechanism of field cancerization
- Ratio of either FAS, MIC-1, and PDGF-A to EGR-1 expression
- High ratios suggest a potential regulatory role of EGR-1
- **EGR-1 is regulator of FAS, MIC-1, and PDGF-A expression**
- Ratio of MIC-1 to EGR-1 expression increased significantly in adjacent and tumor tissues ($p<0.05$)

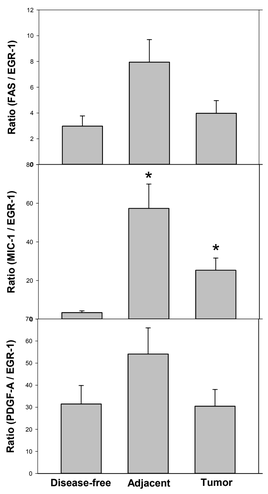


Figure 6. The ratio of either FAS, MIC-1, or PDGF-A to EGR-1 expression in disease-free compared to adjacent and tumor tissues determined a potential regulatory function of EGR-1.

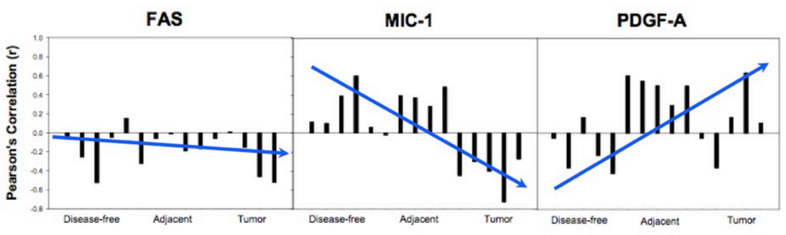


Figure 7. Pearson's correlation (r) shows the association between high EGR-1 expression and FAS, MIC-1, and PDGF-A expression in disease-free, adjacent, and tumor tissues. General trends of EGR-1 regulation of FAS, MIC-1, and PDGF-A expression are represented by blue arrows.

SUMMARY

	Cell Models			Human Tissues		
	RWPE-1 Non-cancerous	LNCaP Cancerous	PC-3 Cancerous	Disease-Free	Adjacent	Tumor
FAS			↓ 70% p=0.005			↘ r =0.66 p =0.043
MIC-1	↓ 10% p=0.004	↓ 20% p=0.0007	↓ 30% p=0.015			↓ r =0.78 p =0.008
PDGF-A			↑ 110-fold p=0.004		↗ r =0.59 p=0.01	↑ r =0.9 p=0.004

CONCLUSIONS

- **EGR-1 is regulator of FAS, MIC-1, and PDGF-A expression**

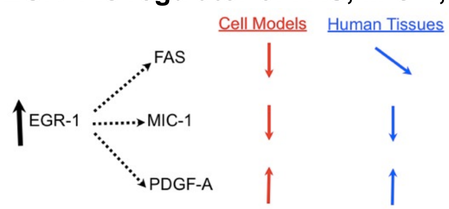


Figure 9. Elevated EGR-1 expression results in up-regulated FAS and MIC expression and down-regulated PDGF-A expression in cell models and human tissues. Vertical arrows indicated strong regulation, while slanted arrows represent moderate regulation.

- This novel analysis between cell models and human tissues is helpful identifying pathways in prostate field cancerization
- EGR-1, FAS, MIC-1, and PDGF-A are markers that can lead to improvements in prostate field cancerization

ACKNOWLEDGEMENTS

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