Application of Genomic Profiling to Identify Factors that Contribute to Cancer Health Disparities

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“African-Americans have the highest death rates from all cancer sites combined, and from malignancies of the lung, colon and rectum, breast, prostate, and the cervix of all racial groups in the United States”

From the American Cancer Society
“While data suggest that access to quality care is a factor in cancer disparities, other factors also play a major role, including tumor biology and genetics”

From the AACR Health Disparity Meeting, Atlanta, 2007

  - More common among young African-American women

  - Risk alleles are more common among African-Americans

Gene expression analysis:
- 33 African-American (AA) patients
- 36 European-American (EA) patients

Tumors were matched for clinical parameters.

Analysis at gene and pathway level.
Differentially Expressed Genes

- 162 genes differently expressed (FDR ≤ 5%)
  - Several metastasis-related genes, e.g., CXCR4, MMP9, AMFR
- Differently expressed genes were not shared with the published list(s) of marker genes for prostate tumors

Marker genes in prostate cancer
Meta-analysis by Rhodes et al.
Cancer Res. 2002, 62, 4427-4433

80 marker genes – no overlap
Pathway Analysis: Differences In Immune Response

Significance of enrichment for genes in a pathway

Differently expressed genes

- Immune response
- Defense response
- Response to biotic stimulus
- Organismal physiological process
- Response to stimulus
- Response to pest/pathogen/parasite
- Humoral immune response
- Response to external biotic stimulus
- Humoral defense mechanism
- Response to stress
- Antigen processing
- Endogenous antigen via MHC class I
- Antigen presentation
- Antimicrobial humoral response (Vertebrata)
- Antimicrobial humoral response
- Endogenous antigen response
- Cell defense response
- Signal transduction
- Cell communication
- Apoptosis
## Two-Gene Classifier

### Genes
1. Crystalline Beta B2 (*CRYBB2*)
2. Phosphoserine Phosphatase-like (*PSPHL*)

### TUMOR (AA) vs. TUMOR (EA)

#### Test Set

<table>
<thead>
<tr>
<th>True/Predicted</th>
<th>African-American</th>
<th>European-American</th>
<th>Total</th>
<th>% Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>African-American</td>
<td>30</td>
<td>3</td>
<td>33</td>
<td>91%</td>
</tr>
<tr>
<td>European-American</td>
<td>2</td>
<td>34</td>
<td>36</td>
<td>94%</td>
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</tbody>
</table>

#### Blinded Independent Validation Set

<table>
<thead>
<tr>
<th>True/Predicted</th>
<th>African-American</th>
<th>European</th>
<th>Total</th>
<th>% Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>African-American</td>
<td>30</td>
<td>4</td>
<td>34</td>
<td>88%</td>
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<tr>
<td>European</td>
<td>0</td>
<td>5</td>
<td>5</td>
<td>100%</td>
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</table>
PSPHL (Phosphoserine Phosphatase-like)

- Advanced PCa
- Williams Beuren Syndrome

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Fold Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EA Tumor vs. non tumor</td>
<td>20</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AA Tumor vs. non tumor</td>
<td>84</td>
<td>0.009</td>
</tr>
<tr>
<td>Normal AA vs. EA</td>
<td>38</td>
<td>0.015</td>
</tr>
<tr>
<td>Tumor AA vs. EA</td>
<td>161</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Numerous interferon-regulated genes were found to be more highly expressed in tumors of African-American patients: A viral signature?

**Interferon γ**

Fold Change: 1.95

\[ P = 0.02 \]

**Indolamine 2,3-dioxygenase**

Fold Change: 2.03

\[ P = 0.03 \]
Conclusions

- Numerous genes were differently expressed in prostate tumors comparing African-American and European-American patients
  - Increased expression of metastasis-promoting genes in tumors from African-American men
  - A two-gene tumor signature differentiates between the two patient groups
- Indication of distinct tumor microenvironment
  - Differences in tumor immunobiology and presence of interferon $\gamma$ signature
- Immune-related differences could be predisposing to tumor progression and may affect therapy outcome
Future Course

• Examine immunobiology of tumors in African-American patients
  • Immune tolerance
    • Indoleamine 2,3-dioxygenase & tryptophan availability
    • Immune cell profiling of tumors (with A. Hurwitz)
  • Interferon $\gamma$ signature
    • Serum markers in case control study
    • Presence of viral sequences in tumors from viral infections (e.g., XMRV) or endogenous retroviruses (e.g., HERV-K) (with M. Linehan, H. Young, R. Silverman, N. Bannert, others)

• Investigate the function of *PSPHL*
  with Jun Luo, William Isaacs (JHU)
Contributors at NCI
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Intramural: Yi M, Stephens RM (both ABCC), Gillespie JW, Caporaso NE

Extramural
Yfantis HG (Baltimore VA Hospital), Loffredo CA (Georgetown University)
Tissue resource: NCI Collaborative Prostate Cancer Tissue Resource