Modeling prostate cancer in mice

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Modeling molecular pathways of prostate cancer progression

Initiation: Inflammation, Oxidative/DNA damage, Telomere shortening

Progression: Senescence, Re-activation of developmental signaling pathways

Treatment: Castration-resistance, EMT

Processes:
- NKKX3.1 down-regulation
- MYC overexpression
- PTEN inactivation
- ERK/MAPK activation
- p53
- EZH2 overexpression

Genes:
- TMPRSS2-ERG fusion

(Shen and Abate-Shen, 2010)
Translational opportunities for mouse models of prostate cancer

Distinguish indolent from aggressive cancer

- Avoid over-treating men with low risk cancer

Identify molecular processes of malignancy

- Improve diagnosis and treatment of lethal cancer
Modeling molecular pathways of prostate cancer progression

(Shen and Abate-Shen, 2010)
Mouse models of prostate cancer

Low grade PIN (N model)

Cancer/CRPC with no mets (NP model)

Cancer/CRPC with infrequent metastases (NPB model)

Cancer/CRPC with frequent metastases (NPK model)
Conservation of molecular pathways of NPK mouse model with human prostate cancer

UP-regulated in malignancy

DOWN-regulated in malignancy

Human malignancy signature

Aytes, et al. PNAS (2013)
From mice to man:
Systems approaches for cross species analyses

(Collaboration with Michael Shen and Andrea Califano)
From mice to man: Cross species analyses of malignant cancer

Strategy:
• Mouse and human prostate cancer interactomes
• Demonstrate conservation of their activities
• Identify synergistic master regulators
• Functional and clinical validation

Assemble mouse and human prostate cancer interactomes

Human Interactome

- Human prostate cancer
  - Normal
  - Primary tumors
  - Metastases

Dataset: 185 GEPs

Mouse interactome

- Prostate cancer GEMMs
  - Normal
  - LG-PIN
  - HG-PIN/Cancer
  - CRPC
  - Metastases

Dataset: 384 GEPs

Drug perturbations
- Hormone signaling
- Signaling pathways
- Kinase inhibitors
- Other pathways

Mice from: Sawyers, Van Dyke, Foster, Williams
Cross-species integration of prostate cancer regulatory networks
Identification of conserved master regulators
Conserved master regulators of malignancy

Human

Indolent  Aggressive

Mouse

Indolent  Aggressive

DA DE

13323  CHAF1A
411  TRIB3
511  FOXM1
578  CENPF
5867  PSRC1
3173  TSFM
3060  ASF1B

DA DE

445
1267
717
15953
9114
13359
19222
FOXM1 and CENPF are predicted to be synergistic master regulators.
Functional synergy of FOXM1 and CENPF
FOXM1 and CENPF synergize to promote tumor growth
Clinical synergy of FOXM1 and CENPF: Kaplan Meier based on protein expression

TMA with >900 primary tumors each with extensive clinical outcome data (MSKCC)
Summary: Cross species analysis of master regulators of malignancy

• Cross-species interactomes to integrate data from mouse and man to identify master regulators of malignancy
• Broadly relevant for informing cancer phenotypes and therapeutic response
From mice to man: Cross species analyses of drug response

Strategy:
- Predict drugs that inhibit the FOXM1-CENPF in vivo
- Evaluate potential drug synergy
- Validate drug synergy/response in vivo
- Determine mechanism of drug synergy

Mitrofanova, Aytes... Shen, Abate-Shen, Califano. (in prep)
Predicting drugs that inhibit FOXM1-CENPF
Predicting drugs that work together

<table>
<thead>
<tr>
<th>Rapamycin</th>
<th>PD0325901</th>
<th>Bay11–7082</th>
<th>LY294002</th>
<th>MDV3100</th>
<th>WP1066</th>
<th>MK2206</th>
<th>Imatinib</th>
<th>Dasatinib</th>
<th>Sorafenib</th>
<th>Testosterone</th>
<th>Docetaxel</th>
<th>Calcitriol</th>
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Rapamycin and PD0325901 inhibit FOXM1-CENPF in vivo
Rapamicin and PD0325901 revert the mouse malignancy signature

Reversion signature
Rapamycin and PD0325901 revert human malignancy signatures

Reversion signature
Master regulators of drug response
Master regulators of the drug response are predictive of outcome in human cancer

<table>
<thead>
<tr>
<th></th>
<th>% Cases</th>
<th>mRNA Upregulation</th>
<th>mRNA Downregulation</th>
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<tr>
<td>TOP2A</td>
<td>43%</td>
<td></td>
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<tr>
<td>WHSC1</td>
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<tr>
<td>MCM4</td>
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<td></td>
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<tr>
<td>CENPF</td>
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</tr>
<tr>
<td>BRCA1</td>
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<td></td>
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<tr>
<td>MCM2</td>
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<tr>
<td>FOXM1</td>
<td>32%</td>
<td></td>
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<tr>
<td>UHRF1</td>
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<td></td>
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<tr>
<td>ASF1B</td>
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<tr>
<td>BLM</td>
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<td></td>
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<tr>
<td>CCNA2</td>
<td>32%</td>
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<td>E2F1</td>
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<tr>
<td>SUV39H1</td>
<td>8%</td>
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<td>MYBL2</td>
<td>19%</td>
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<tr>
<td>CRY2</td>
<td>14%</td>
<td></td>
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</table>

Sboner dataset

Log Rank p-value = 2.63 X 10^-5
Summary:

Cross species interrogation of drug response

• Cross-species integration of preclinical data from mouse and man to study drug response *in vivo*

• Valuable approach for predicting drug response *in vivo* and for evaluating the mechanism of action
Translational opportunities for mouse models of prostate cancer

Distinguish indolent from aggressive cancer

- Avoid over-treating men with low risk cancer

Identify molecular processes of malignancy

- Improve treatment for lethal prostate cancer
Modeling cancer initiation in mice

Loss of the Nkx3.1 leads to precancerous lesions (PIN)
Nkx3.1 mutant mice model indolent prostate cancer
Biomarkers of indolent prostate cancer

Strategy:

• Molecular signature of aging and senescence
• GSEA to identify an “indolence signature”
• Decision tree learning to identify 3-gene panel
• Validation on TMAs and biopsies

Irshad, Bansal... Benson, Shen, Califano, Abate-Shen. Cancer Cell (Sci Trans Med)
Indolent prostate cancer is enriched for a molecular signature of aging and senescence.
Validation on low Gleason score prostate cancer

Taylor dataset

Validates the hypothesis and the indolence signature
Decision tree learning model to identify 3-gene panel
3-gene panel distinguishes indolent lesions on biopsy samples from patients on active surveillance.
Summary II: Biomarkers of indolent prostate cancer

- Biomarker to help stratify low-Gleason score prostate cancer
- Now validating in retrospective and prospective studies
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