Update on Pancreatic Cancer Research

Andrew D. Rhim, MD
University of Michigan
Pancreatic Cancer Action Network
Educational Seminar
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Agenda

1. Review how basic research can be translated into real world solutions for our patients
2. Describe some of the tools we use to understand the disease in the laboratory
3. Present selected landmark studies in our field and illustrate how this work might impact our patients
4. Share our view for the future
Basic Research

- Focus on fundamental understanding of disease and basic biological processes that may be relevant in PDAC
- Tools: in vitro tissue culture, mouse models

Translational Research

- Focus on exploiting our new understanding of basic biology for potential application to our patients
- Validation of important findings in patients
- Tools: patient samples, computational

Clinical Research/Trials

- Evaluation of new assays and treatments for clinical benefit

Basic Science → Patient Impact

- What are the earliest events when a pancreas cell turns into a cancer cell? → Early Diagnosis
- What is required for PDAC to develop? → Chemoprevention
- What do PDAC cells require to survive? → Treatment
Tools of the Trade

Basic Science Tools

- Tissue Culture
  - Cheap and fast
  - Easy to manipulate
  - Artificial environment
Basic Science Tools

• Mouse models
  – Transplant models
  – Human xenograft
  – Genetically engineered

Genetically Engineered Mouse Models of PDAC
Early Pancreatic Cancer Biology

When do pancreatic cancer cells leave the pancreas?

GEMMs can also be used to study early stage PDAC

Rhim et al., Cell 2012
Robust Fluorescent Labeling of Pancreas

>95% of all pancreatic epithelial cells are labeled fluorescent

PKCY 3wk 8-10wk 16-20wk

“Normal” PanIN PDAC
Circulating green fluorescent cells can be detected in mice with PanIN and PDAC

- Pdx-Cre; RosaYFP (Labeled wt control)
- PanIN (PKCY 2.5mo)
- PDAC – 1.0cm tumor (PKCY 4.5mo)

Circulating pancreatic cells detected in PDAC and PanIN mice
Geometrically Enhanced Differential Immunocapture (GEDI)

- Pancreas epithelial cells express specific cell surface proteins that normal blood cells do not.
- The walls and “bumpers” of a microfluidic chip are coated with antibody:
  - Red and white blood cells flow through.
  - Rare pancreas cells will bind to the chip.

Credit: Brian Kirby, Ph.D. Cornell University
GEDI can be used to isolate human circulating tumor cells

Identification of Circulating Pancreas Cells using GEDI

Red: CD45
Green: Pdx-1
Blue: DAPI
Evidence of pancreas cell dissemination in the absence of pancreatic tumor

Next Steps

- Can counting CPCs be used to determine true pancreatic cancer risk in high-risk patients
  - Family history
  - Other cancer syndromes
- Using CPCs as a “liquid biopsy” of worrisome pancreas lesions that cannot be detected on current clinical tests
Early Pancreatic Cancer Biology

Can PanIN lesions be ablated?

A model for preclinical PDAC prevention (or PanIN treatment) studies

Start Chemoprevention Trial

Effect on PanIN?

Tumor latency changed?

PKCY 3wk

8-10wk

16-20wk

“Normal”

PanIN

PDAC

D  E  F
Gamma secretase inhibition (MRK-003) prevents PanIN progression

Plentz, Rhim et al. Gastro 2009

Similar chemopreventive effects with anti-IL6

Zhang, Rhim et al. Cancer Res 2013
Pancreatic Tumor Biology

What is required for pancreatic cancer cells to grow and spread?

Cancer is a Genetic Disease

- Mutations and alterations in specific oncogenes and tumor suppressor genes alter cell biology
- Cancer cells have numerous mutations to add-up to a dangerous situation
- As recent as the early 2000s, it had been difficult and expensive to identify all cancer-related DNA alterations
Advances in sequencing are changing cancer research and care

Genomic profiling of human PDAC

Table 1 | Mutations in pancreatic ductal adenocarcinoma (n = 99)

<table>
<thead>
<tr>
<th>Mutation class</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missense</td>
<td>1,684</td>
</tr>
<tr>
<td>Nonsense</td>
<td>99</td>
</tr>
<tr>
<td>Splice site</td>
<td>89</td>
</tr>
<tr>
<td>Insertion/deletion</td>
<td>144</td>
</tr>
<tr>
<td>Non-silent</td>
<td>2,016</td>
</tr>
<tr>
<td>Silent</td>
<td>611</td>
</tr>
</tbody>
</table>

Table 2 | Significantly mutated genes in pancreatic ductal adenocarcinoma

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Gene name and protein function</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS</td>
<td>Oncogene; GTPase; activation of MAPK activity</td>
</tr>
<tr>
<td>TP53</td>
<td>Tumour suppressor p53; DNA damage response</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>Cyclin-dependent kinase inhibitor 2A; G1/S transition of mitotic cell cycle; tumour suppressor</td>
</tr>
<tr>
<td>SMAD4</td>
<td>Mothers against decapentaplegic homologue 4; BMP signalling pathway</td>
</tr>
<tr>
<td>MLL3</td>
<td>Myeloid/lymphoid or mixed-lineage leukaemia protein 3; DNA binding; regulation of transcription</td>
</tr>
<tr>
<td>NRAS</td>
<td>Transforming growth factor &amp; receptor type II; regulation of growth</td>
</tr>
<tr>
<td>ARID1A</td>
<td>AT-rich interactive domain-containing protein 1A; DNA/HSF complex; chromatin modification</td>
</tr>
<tr>
<td>ARID2</td>
<td>AT-rich interactive domain-containing protein 2; chromatin modification</td>
</tr>
<tr>
<td>EPC1</td>
<td>Enhancer of polycomb homologue 1; histone acetylation</td>
</tr>
<tr>
<td>FAT1</td>
<td>Alpha telangietatic mutated; DNA damage response</td>
</tr>
<tr>
<td>SP2</td>
<td>Splicing factor 2B polypeptide 1; nuclear mRNA splicing</td>
</tr>
<tr>
<td>JAM2</td>
<td>Zinc finger imprinted 2; regulation of transcription</td>
</tr>
<tr>
<td>MAPK14</td>
<td>Dual specificity mitogen-activated protein kinase 14; Toll-like receptor signalling pathway</td>
</tr>
<tr>
<td>PAK1</td>
<td>Serine/threonine-protein kinase 1A; non-selective protein kinase 4; sodium channel activity</td>
</tr>
<tr>
<td>FGFR4</td>
<td>Serine/threonine-protein kinase 4; non-selective protein kinase 4; sodium channel activity</td>
</tr>
<tr>
<td>MAPK14</td>
<td>Serine/threonine-protein kinase 4; non-selective protein kinase 4; sodium channel activity</td>
</tr>
</tbody>
</table>

Jones et al, Science 2009
Biannkin and ICGC, Nature 2012
Yachida et al., Nature 2010
Genome-based Personalized Cancer Therapeutics

• Each patient’s tumor has a different collection of genomic alterations
  – Some are very common
  – Others are unique, and impact specific biological pathways

• If we can identify which pathways are most affected in an individual’s tumor, we might be able to customize cancer therapy
  – PanCAN Know Your Tumor Initiative
Challenges in Personalized Therapy

• Heterogeneity
  – Cancer cells can diverge widely based on location within the tumor

• Targets
  – We don't have drugs to target all of the possible pathways affected by mutations

• Biology
  – We don’t know the full effects of all possible mutations
    • Understanding the downstream effects of genetic alterations might allow us to identify new targets and design new drugs in response

Kras mutations induce changes in cell metabolism

• Mutations in Kras codon 12 are common in PDAC
  – Hard to drug

• Kras mutations lead to alterations in metabolism

• Exploration of these metabolic changes have uncovered a new vulnerability in PDAC cells
  – New drugs in pipeline

Son and Lyssiotis et al., Cell 2013
Pancreatic Tumor Biology

What is the role of tumor microenvironment in pancreatic cancer?

Hallmarks of [most] PDAC:
• Differentiated ductal pathology
• Large amounts of stroma
  – Immune cells
  – Myofibroblasts
  – Matrix
Pancreatic tumors have limited blood flow

Olive et al., Science 2009

Modulating intratumoral pressure can enhance drug delivery

Provenzano et al., Cancer Cell 2012
Pancreatic Tumor Biology

How does pancreatic cancer evade the immune system?
Cancer evades the immune system in multiple ways

• Many types of immune cells
• Lots of cross-talk
  – Some cells encourage NK and T-cells to destroy
  – Some cells and signals prevent attack
• If we can understand this biology, we might be able to design ways for the immune system to attack cancer cells

Some immune cells protect tumors from the immune system

Rhim et al Cancer Cell 2014  Beatty et al., Science 2011
First positive clinical trial to feature immune-reeducation in PDAC

Beatty et al., Science 2011

Immune cell engineering to treat PDAC

- Extract T-cells from patient
- Genetically modify T-cells to activate and engineer an anti-cancer response
- Reinject T-cells into patient
- Future: combine with other therapies designed to further activate and disinhibit T-cells

UPenn; Stromnes, et al., Cell 2015
An age of enlightenment for pancreatic cancer

• Based on:
  – Acknowledgement of the idiosyncratic nature of PDAC
  – Advances in our basic understanding of biology and disease

• Catalyzed by:
  – Disruptive technologies
    • GEMMs
    • Deep sequencing
    • Microfluidics
    • Ex vivo immune cell engineering

• Manifested as:
  – Early biomarkers and diagnostics
  – Targeted therapies

Joseph Wright 1766, “A Philosopher Giving A Lecture at the Orrery”