Tissue biomarkers in pancreatic ductal adenocarcinoma

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Challenges associated with tissue biomarker in pancreatic ductal adenocarcinoma

Tumor cells are rare in PDAC....
Challenges associated with tissue biomarker in pancreatic ductal adenocarcinoma

... and this is even worse in fine needle biopsies!
DNA-based biomarker in pancreatic ductal adenocarcinoma

TCGA, Cancer cell 2017
DNA-based biomarker in pancreatic ductal adenocarcinoma

Pishvaian et al. Lancet oncol. 2020

+ KRAS G12C targeting therapy

*POLO trial
DNA-based biomarker in pancreatic ductal adenocarcinoma

Ideal word: large NGS panel for all

Minimal work up:
- KRAS seq, WT → look for fusion transcripts
- BRCA1/2 seq → Pt/olaparib/genetic counselling
RNA-based biomarker in pancreatic ductal adenocarcinoma

How many subtypes?
Is it always back and white or a gradient?
RNA-based biomarker in pancreatic ductal adenocarcinoma

Aung et al. Clin can res 2018
RNA-based biomarker in pancreatic ductal adenocarcinoma

GemPred: RNA-based signature to predict response to gemcitabine in PDAC

More signatures to come?

Nicolle et al. Ann oncol 2021
RNA-based biomarker in pancreatic ductal adenocarcinoma

RNA signatures have a strong prognostic/predictive value

- RNAseq in routine practice is challenging
- Signature determination is complex in highly contaminated samples
- Methylation-based signatures?

Transform these signatures into routine-ready tools

AI-based

Tumor detection

Molecular subtype determination

Saillard et al. unpublished
RNA-based biomarker in pancreatic ductal adenocarcinoma

RNA signatures have a strong prognostic/predictive value

- RNAseq in routine practice is challenging
- Signature determination is complex in highly contaminated samples
- Methylation-based signatures?

Transform these signatures into routine-ready tools

IHC-based

Marker #1

#2 #3 #5

Full classical Intermediate tumors Basal-like

#4 #6

Adenosquamous (squamous component)

Red IHC: classical marker
Brown IHC: basal-like marker

Delecourt et al. unpublished
Protein-based biomarker in pancreatic ductal adenocarcinoma

- SO MANY PROGNOSTIC MARKERS....
  - None used

- No predictive marker in routine practice
  - hENT1/CDA for gemcitabine
  - SLFN11 for irinotecan...
Tissue biomarkers in pancreatic ductal adenocarcinoma

Jerome Cros
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Key messages:

- Adequate sampling is key to biomarker determination in PDAC

- Should all patients have at least a KRAS and BRAC1/2 seq?

- RNA-based signature may help stratify patients if they can be robustly determined
WHAT CAN WE LEARN FROM THE BLOOD?

CIRCULATING TUMOR CELLS (CTCs) IN PANCREATIC CANCER

LIQUID BIOPSY

Dr. Catherine Alix-Panabières
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Real-Time Liquid Biopsy

- Metastases evolve many years after primary tumor resection and can harbor unique genomic alterations.

- Biopsy of metastases is an invasive and sometimes dangerous procedure.

- Intra-patient heterogeneity of metastases at different sites.

- CTC/ctDNA might reveal representative information on metastatic cells located at different sites.

**Drug Resistance?**

<table>
<thead>
<tr>
<th>CTCs</th>
<th>Treatments</th>
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<tr>
<td><strong>Proteins</strong></td>
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<td>ER+</td>
<td>Endocrine therapy</td>
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<td>Her2/neu</td>
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<td><strong>DNA Mutations</strong></td>
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<td>KRAS mutations</td>
<td>EGFR targeted therapies</td>
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<td>PIK3 mutations</td>
<td>HER2/neu targeted therapies</td>
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</tbody>
</table>
Tumor-proximal liquid biopsy to improve diagnostic and prognostic performances of circulating tumor cells

Etienne Buscall, Laurence Chiche, Christophe Laurent, Véronique Vendrely, Quentin Denost, Jérôme Denis, Matthieu Thumerel, Jean-Marc Lacorte, Aurélie Bedel, François Moreau-Gaudry, Sandrine Dabernat, Catherine Alix-Panabières ... See fewer authors
LIQUID BIOPSY AND PORTAL VEIN

LOCALIZED PANCREATIC CANCER

300 CTCs and clusters/7.5 ml portal blood

Portal blood

Peripheral blood

0 CTCs/7.5 ml peripheral blood

Buscail, Alix-Panabières et al. CANCERS 2019
CANCER DISCOVERY REVIEW 2021

Liquid Biopsy: From Discovery to Clinical Application

Catherine Alix-Panabières¹ ² and Klaus Pantel³
Presence of CTCs from resected, locally advanced, or metastatic tumours was associated with poor PDAC patient prognosis, an increased number of metastases and an increased likelihood of relapse.
Clinical prospects of liquid biopsies

Catherine Alix-Panabières and Klaus Pantel

CTCs
ctDNA
miRNA
Evs (exosomes)
Proteins
Immune cells
Tumor-educated platelets
Clinical prospects of liquid biopsies

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CANCER DISCOVERY REVIEW 2021

Liquid Biopsy: From Discovery to Clinical Application

Catherine Alix-Panabières1,2 and Klaus Pantel3
High Clinical Value of Liquid Biopsy to Detect Circulating Tumor Cells and Tumor Exosomes in Pancreatic Ductal Adenocarcinoma Patients Eligible for Up-Front Surgery

Etienne Buscail, Catherine Alix-Panabières, Pascaline Quincy, Thomas Cauvin, Alexandre Chauvet, Olivier Degrandi, Charline Caumont, Séverine Verdon, Isabelle Lamrissi, Isabelle Moranvillier, Camille Buscail, Marion Marty, Christophe Laurent, Véronique Vendrely, François Moreau-Gaudry, Aurélie Bedel, Sandrine Dabernat, and Laurence Chiche
Can we assess the preparation of the pre-metastatic niches in PDAC?
To push liquid biopsy into widespread use, more intervention studies are needed;

To develop an algorithm that can combine different circulating biomarkers to obtain a precise tumour profile;

To define guidelines and SOP for liquid biopsy: technical variability in the pre-analytical and analytical steps

→ Big consortium to achieve these goals: ELBS
### MILESTONES IN CANCER 2000-2020

**2000**
- Malignant cell precursors identified in tumors

**2001**
- Mechanisms of resistance to targeted treatment (MILESTONE 1)
- Nobel Prize awarded for “discovery of key regulation of the cell cycle”

**2003**
- Epidemiological link between cancer and obesity

**2004**
- First angiogenic drugs gain FDA approval
- First antiangiogenic drug approved for cancer treatment

**2005**
- Liquid biopsies for non-invasive diagnosis and monitoring of patients (MILESTONE 2)
- HPV vaccines to prevent cervical cancer (MILESTONE 3)

**2006**
- Ovarian carcinoma-induced spontaneous in germline-tissue cancer (MILESTONE 4)
- Metabolic adaptations in cancer (MILESTONE 5)

**2008**
- First-tier analysis published by The Cancer Genome Atlas
- First cancer whole-genome sequence (MILESTONE 6)
- Description of colorectal cancer organoids

**2010**
- IDH1 mutations leading to the generation of 2-hydroxyglutarate
- Immune checkpoint inhibitors from bench to bedside (MILESTONE 7)
- Engineering T cells to kill cancer cells (MILESTONE 8)

**2011**
- Use of screening to decrease mortality from lung cancer
- Clearance of senescent cells by the immune system

**2012**
- Epigenetic drivers of tumor initiation and progression (MILESTONE 9)
- Chromatin diversity of tumor cells as a basis for cancer progressions and novel treatments (MILESTONE 10)

**2013**
- Full-length single-cell RNA sequencing of individual tumor cells
- Anti-tumor role of metabolically deplete cells
- Targeting ‘drugable’ non-kinase proteins (MILESTONE 12)
- Gut microbiome influences on anti-tumor immune responses (MILESTONE 13)

**2015**
- The ‘big bang theory’ of cancer evolution is proposed
- Driver mutations found in healthy tissue
- First FDA approval for a combination of immunotherapies
- First FDA approval for an anti-PI3K inhibitor

**2017**
- Potential of artificial intelligence in cancer diagnosis and monitoring (MILESTONE 14)
- First FDA approval of a treatment on the basis of tumor genetics alone
- First inhibitor of mutant KRas approved for clinical use

**2018**
- Nobel Prize awarded for “discovery of cancer therapy by inhibition of negative immune regulation”

**2019**
- Clinical trial of CAR T cells to target B cell malignancies in patients with multiple myelomas
- Nobel Prize awarded for “discovery of how cells sense and adapt to oxygen availability”

**2020**
- Pan-cancer analysis of whole genomes
- Clinical trial of CAR T cells targeting CAR-Natural Killer cells in patients with CD19+ cancers
In homage to Bertrand Kamal
SUMMARY

Dr. Florence Le Calvez-Kelm

- The shorter the amplicon size, the higher the mutant allelic fraction.
- The specific biological fragmentation characteristics of ctDNA should be taken into account when performing liquid biopsies based assays.
- Enrichment of short cfDNA molecules should increase the ability to detect tumour-derived mutations in liquid biopsy.

Dr. Jérôme Cros

- Adequate sampling is key to biomarker determination in PDAC
- Should all patients have at least a KRAS and BRAC1/2 seq?
- RNA-based signature may help stratify patients if they can be robustly determined (strong prognostic/predictive value)