Targeting mitochondrial and redox metabolism in PDAC

1- Therapy  
2- Prevention

Current projects
Future projects (ongoing development)
The role of mitochondria in cancer metabolism was ignored until recently.

Warburg’s effect: aerobic glycolysis (1924)
The role of mitochondria in cancer metabolism was ignored until recently

Warburg’s hypothesis (1956): mitochondria are dysfunctional in cancer cells

Current knowledge:

- Mitochondria are functional in most of cancer cells
- Mitochondrial metabolism is necessary for cancer cell proliferation and survival
- Mitochondria are involved in cancer therapeutic resistance
Mitochondria are functional in most of cancer cells

Reactive Oxygen Species (ROS)

Cairns RA et al. Nature Reviews Cancer 2011
Mitochondria are functional in most of cancer cells

In PDAC?

2014 LETTER

Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function

Andrea Viale1,2,*, Piergorgio Pettazzoni1,2,*, Costas A. Lyssiotis3, Haoqiang Ying1, Nora Sanchez1,2, Matteo Marchesini1,2, Alessandro Carugo1,2,*, Tessa Green1,2, Sahil Seth3, Virginia Giuliani3, Maria Kost-Alimova3, Florian Muller3, Simona Colla1, Luigi Neri1,2, Giannicola Genovesi1, Angela K. Deem1, Avnish Kapoor1, Wantong Yao1,2, Emanuela Brunetto4, Ya’an Kang4, Min Yuan5, John M. Asara6, Y. Alan Wang4, Timothy P. Heffernan7, Alec C. Kimmelman8, Huamin Wang9, Jason B. Fleming9, Lewis G. Cantley8, Ronald A. DePinho8 & Giulio F. Draetta1,2

Role in resistance

2015

MYC/PGC-1α Balance Determines the Metabolic Phenotype and Plasticity of Pancreatic Cancer Stem Cells

Patricia Sancho,1,2,*, Emma Burgos-Ramos,2 Alejandra Taver,3 Tony Bou Kheir1, Petra Jagust1, Matthieu Schoenhals1, David Barneda1, Katherine Sellers,5 Ramon Campos-Olives,3 Osvaldo Graña3, Catarina R. Viera3, Maria Yuneva3, Bruno Sainz, Jr.1,2 and Christopher Heeschen1,2,9

Cell Metabolism Article
Mitochondria are functional in most of cancer cells in PDAC?

2020 Cell Reports Medicine

**Article**

Targeting Mitochondrial Complex I Overcomes Chemoresistance in High OXPHOS Pancreatic Cancer

Rawand Masoud, Gabriela Reyes-Castellanos, Sophie Lac, Julie Garcia, Samir Dou, Laetitia Shintu, Nadine Abdel Hadi, Tristan Gicquel, Abdessamad El Kaoutari, Binta Dièmè, Fabrice Tranchida, Laurie Corimareche, Laurence Borge, Odile Gayet, Eddy Pasquier, Nelson Dusetti, Juan Iovanna, and Alice Carrier

2020 biomedicines

**Review**

Mitochondrial Metabolism in PDAC: From Better Knowledge to New Targeting Strategies

Gabriela Reyes-Castellanos, Rawand Masoud and Alice Carrier

2021 International Journal of Molecular Sciences

**Review**

Targeting Redox Metabolism in Pancreatic Cancer

Nadine Abdel Hadi, Gabriela Reyes-Castellanos and Alice Carrier

Heterogeneity

Targeting
Mitochondria are functional in most of cancer cells

Safety and tolerability of the first-in-class agent CPI-613 in combination with modified FOLFIRINOX in patients with metastatic pancreatic cancer: a single-centre, open-label, dose-escalation, phase 1 trial

Lancet Oncol 2017; 18: 770-78

Adapted from Reyes-Castellanos et al. Biomedicines 2020
Mitochondria are important for the function of TME cells surrounding cancer cells.
Mitochondria are dysfunctional in distant organs during cancer

CACHEXIA AS A MULTI-ORGAN SYNDROME
Our goal: Exploration of mitochondrial metabolism in PDAC

→ Considering tumor cells, TME cells, and distant organs
Thank you for your attention

“I don’t know where she gets all that energy.”
TUMOR MICROENVIRONMENT
FOCUS ON
THE NON-IMMUNE STROMA

Dr. Corinne BOUSQUET
Research Director, INSERM
Cancer Research Center of Toulouse
Typical feature: Fibrotic stroma - 80% of the tumor mass

PDAC

Unsupervised clustering of TME reconstructed from RNAseq (>10,000) across melanomas and carcinomas

TME RNAseq SIGNATURES ARE CONSERVED ACROSS CANCERS & PROGNOSTIC

Bagaev A, Cancer Cell 2021
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Bagaev A, Cancer Cell 2021

Moffit et al, Nature Genetics 2015
Puleo et al, Gastroenterology 2018
Maurer et al, Gut 2019
TME RNAseq SIGNATURES ARE CONSERVED ACROSS CANCERS & PROGNOSTIC

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Bagaev A, Cancer Cell 2021

TME signatures across melanomas and carcinomas:

- Liver Hepatocellular Carcinoma
- Lung Adenocarcinoma
- Lung Squamous Cell Carcinoma
- Ovarian Serous Cystadenocarcinoma
- Pancreatic Adenocarcinoma
- Phaeochromocytoma and Paraganglioma
- Prostate Adenocarcinoma
- Skin Cutaneous Melanoma
- Thyroid Carcinoma
- Uterine Corpus Endometrial
- Uterine Carcinosarcoma
- Uveal Melanoma

Tumor Mutational Burden:

- +
- ++
- +++

T cells:

- +
- ++
- +++

Suppressor cells:

- +
- ++
- +++

Fibroblasts:

- +
- ++
- +++

Tumor proliferation rate:

- +
- ++
- +++

STATE OF THE ART

Moffit et al, Nature Genetics 2015
Puleo et al, Gastroenterology 2018
Maurer et al, Gut 2019
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Response to immunotherapies (anti-PD1)
THERAPIES TARGETING THE NON-IMMUNE STROMA OF PDAC

To enhance drug delivery or block pro-tumor features by “normalizing” the non-immune stroma

But although promising in pre-clinical models, it resulted in insufficient clinical successes

Why?
1) Lack of patient stratification?
2) INTRA-TUMOR SPATIAL & CELL HETEROGENEITY

Different « subTME » spatially co-exist within a same tumor

« subTME » may evolve upon treatment

Grunwald, BioRxiv 2021

EXAMPLE OF CAFs

Different CAF subsets with different functions

Cell plasticity upon treatment (e.g. SHH inhibition): ↓myCAF but ↑iCAF

Elyada, Cancer Discov 2019
Dominguez, Cancer Discov 2019
Steele, Clin Cancer Res, 2021
TARGET THE NON-IMMUNE STROMA
IN ADDITION TO TUMOR & IMMUNE CELLS

• Understand the biology of the non-immune stroma to discover novel therapeutic targets (go beyond traditional tumor-centric studies and immuno-oncology efforts)
  = heterogeneity / plasticity along tumor progression & treatment
    * CAFs
    * Other stromal cells: Neural / Endothelial / adipose tissue
  = different cell interactions (& microbiome???)
  = learn from “omics” analyses (bulk/deconvolution, single cell/spatial
    Transcriptomics, translatomics, proteomics
    Multiplexed imaging
    Computational biology & AI)

on patient samples & clinical trials (ancillary studies)

Moncada, Nat Biotech 2020
de Vries, Front Oncol 2021
Lewis et al, Nature Methods 2021
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• Test combinatorial / serial drug protocols considering the triangular targets
  (tumor cells + immune + non-immune stroma)

• Develop integrated “Tumor-TME” preclinical platforms (e.g. microfluidic cancer-on-chips)
  Colombo, IJMS 2021
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  Colombo, IJMS 2021

• Find (bio)markers of drug response to stratify patients (depending on their TME types)

• Learn from other tumors = TME is conserved across cancers!
DECIPHER INTRA-TUMOR CELL & SPATIAL HETEROGENEITY

Data integration  
Computational biology  
Artificial intelligence

Moncada, Nat Biotech 2020  
de Vries, Front Oncol 2021  
Lewis et al, Nature Methods 2021

IMPROVE PRECLINICAL MODELS  
= TARGET VALIDATION & DRUG TESTING

GEMM  
PDX  
Humanized immunocompetent

Complex microfluidic Cancer-on-chip models

Colombo, IJMS 2021

LEARN FROM CLINICAL TRIALS  
ANCILLARY STUDIES