PANCREAS CANCER MODELING: A METABOLIC APPROACH

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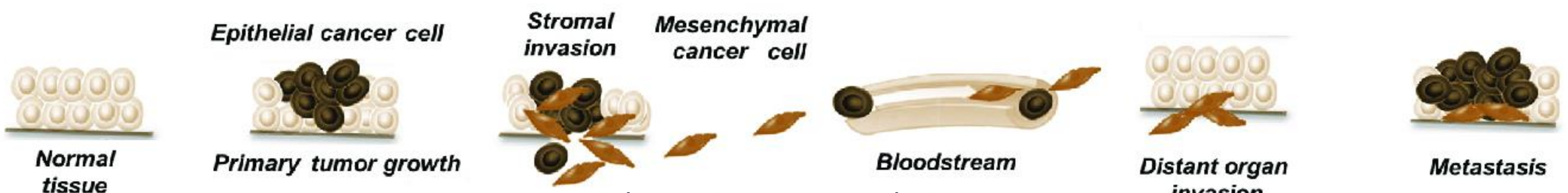
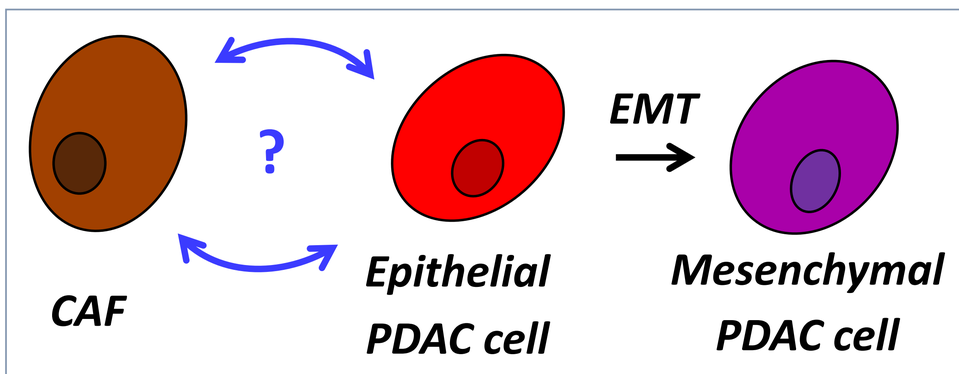
Pancreatic ductal adenocarcinoma, (PDAC), is the most common pancreatic cancer type. It has a high lethality with a survival rate of 5%. In the tumor, Epithelial PDAC cells are surrounded by cancer associated fibroblast (CAF) that confers a limited nutrient and oxygen resources. To survive to this poor intake, epithelial PDAC cells have adapted their metabolism. It is also known that some of those cells can undergo epithelial-mesenchymal transition (EMT), become mesenchymal cancer cells and invade distant organs to form malignant metastases.



Schematic cancer evolution

3 MODELS + COMMUNICATIONS

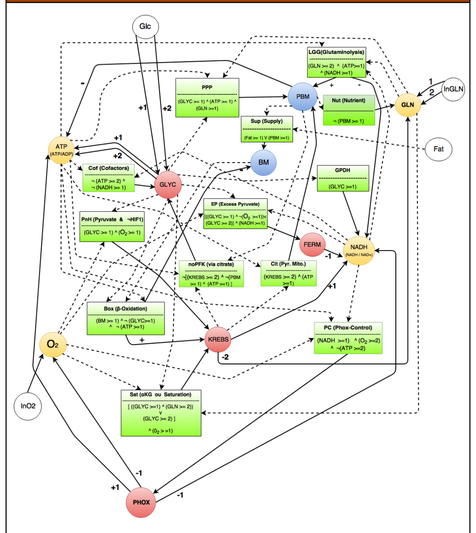


Relationship between models

- Metabolism shifts between CAF, epithelial and mesenchymal PDAC cells
- Limitation on observability
  - ➔**1 model to each cell type**
- Connection between Epithelial PDAC and CAF cells which promotes EMT transition
  - ➔ **hypothesis on communications between cells**

METHODOLOGY

CAF



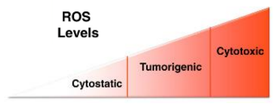
*Energetic metabolism regulatory network**

*R.Khooderam, G.Bernot, J-Y Trosset In advances in Systems and Synthetic biology

Epithelial PDAC cell

Existing model enrichment :

- Interest in Ros marker of cancer



- Kras mutation causes cancer behaviour

Coupling cells

- Knowledge only on cell supernatants
- Need to make assumption about messenger direction and nature

Mesen. PDAC cell

- Add the best representative pathways

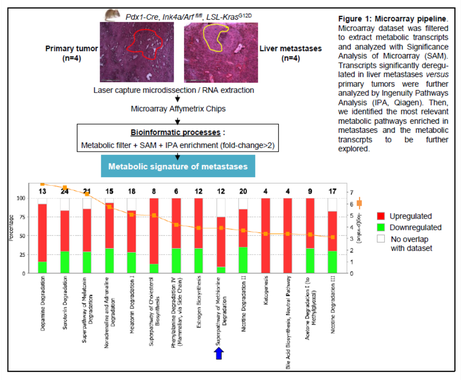
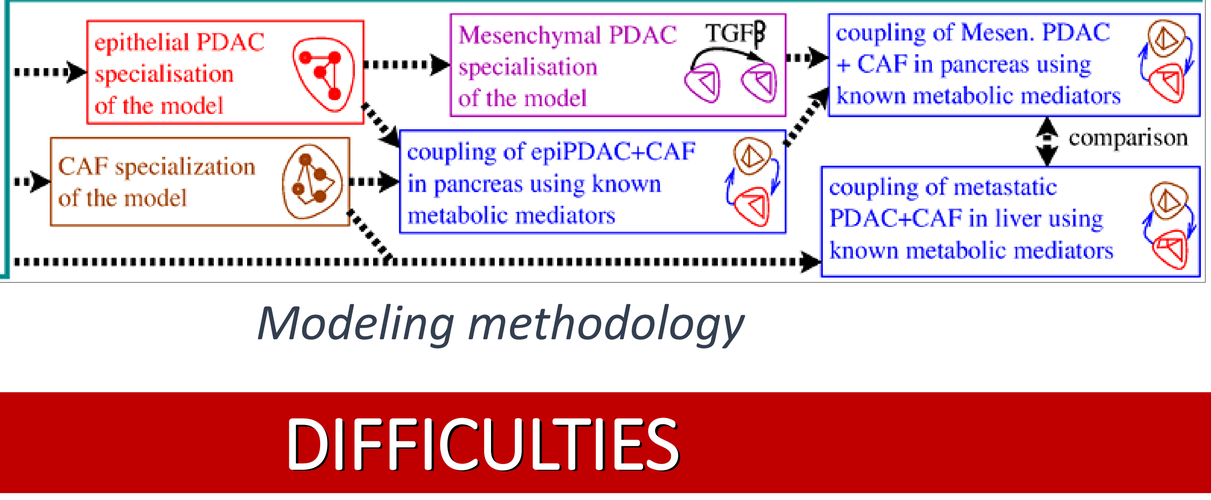


Figure 1: Microarray pipeline. Microarray dataset was filtered to extract metabolic transcripts and analyzed with Significance Analysis of Microarray (SAM). Transcripts significantly deregulated in liver metastases *versus* primary tumors were further analyzed by Ingenuity Pathways Analysis (IPA, Qiagen). Then, we identified the most relevant metabolic pathways enriched in metastases and the metabolic transcrpts to be further explored.

Microarray pipeline: relevant transcripts expression in mesenchymal PDAC cells

Preliminary results	Biological information all along the project
Identified metabolic signatures of mouse metastatic PDAC Biological knowledge at molecular level and literature Generic mathematical model of energy metabolism and biomass production	Constant dialog between biologists and modelers + New bioinformatics data on mouse and human metabolic signatures and signaling molecules



Modeling methodology

DIFFICULTIES

- ➢ Non-regression tests of known temporal properties are mandatory when modifying regulatory graph (huge number of imbricated feedback loops)
- ➢ Develop a methodology to extract as much information as possible from the comparison of two close models (Epithelial PDAC cell and mesenchymal PDAC cell)

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