EXO-METABOLOMICS FINGERPRINT OF BLADDER CANCER PROGRESSION USING ^{1}H-NMR

Invasive and non-invasive tumour cells show two different metabolisms

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Introduction

- Urothelial bladder cancer (UBC) is the most common tumor of the urinary system.
- Divided into low-grade non-muscular invasive bladder cancer (**NMIBC**) and high-grade muscular invasive bladder cancer (**MIBC**).
- Problem: **lack of prognostic markers** that can anticipate the progression of the cancer.

Aim

Investigate the correlation between different risks of progression and cells metabolism, in order to provide new prognostic markers for in vivo analysis.

In this study, we used ^{1}H-NMR to characterize the intake of nutrients and the excretion of products in the extracellular medium of three urothelial bladder cancer cell lines (UBCcls).

Methods

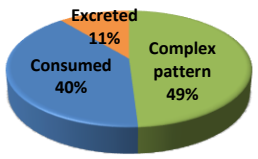
Cells were grown in RPMI culture medium for 1, 2 or 3 days in separated containers.

Cellular model that may represent different types of tumors [1, 2, 3]

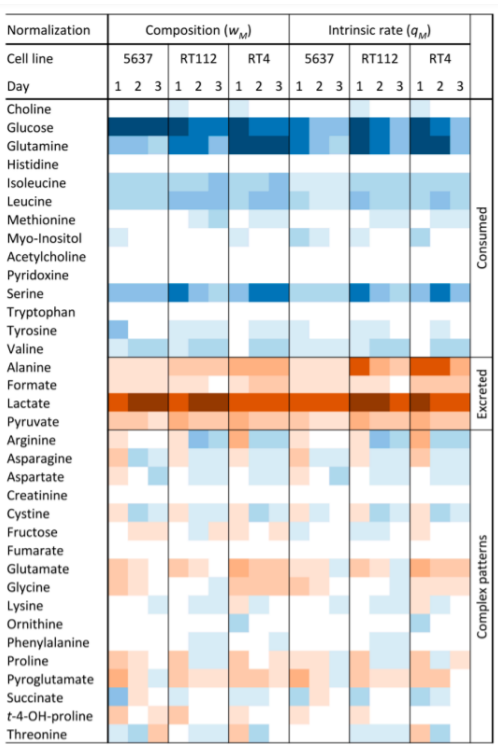
UBCcls	Genetic alteration	Genetic instability	Model	Risk of progression
5637	TP53 mut	++	Aggressive	High
RT112	TP53/FGFR3 mut	+	Non-aggressive	Unknown
RT4	FGFR3 mut	+	Non-aggressive	Low

Results: Exo-metabolomic profile

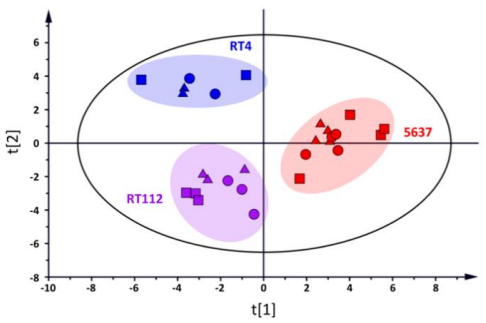
Consumed:
- Glucose
- Glutamine
- Serine
- BCAAs
- Arginine



Excreted:
- Lactate
- Alanine
- Pyruvate
- Formate

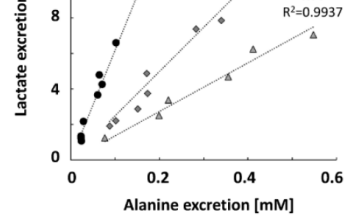


OPLS-DA separation due to pyruvate and serine metabolisms, arginine, glutamine, and BCAAs.



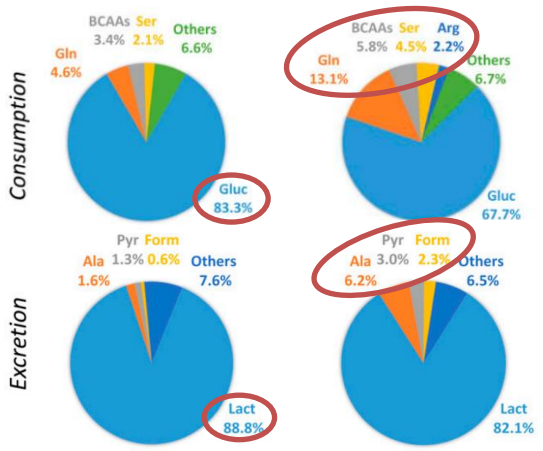
Good predictive power (Q2 =0.868) and highly significant (CV-ANOVA=8.0E-05).

Lactate/Alanine: Degree of glycolysis and OxPhos

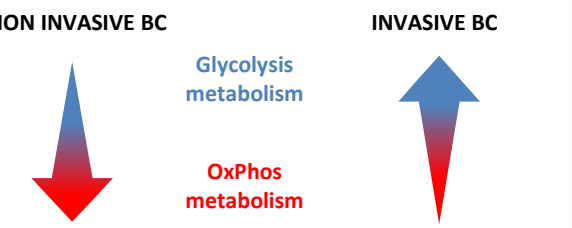


<u>Invasive cells</u> consume almost exclusively glucose and excrete lactate

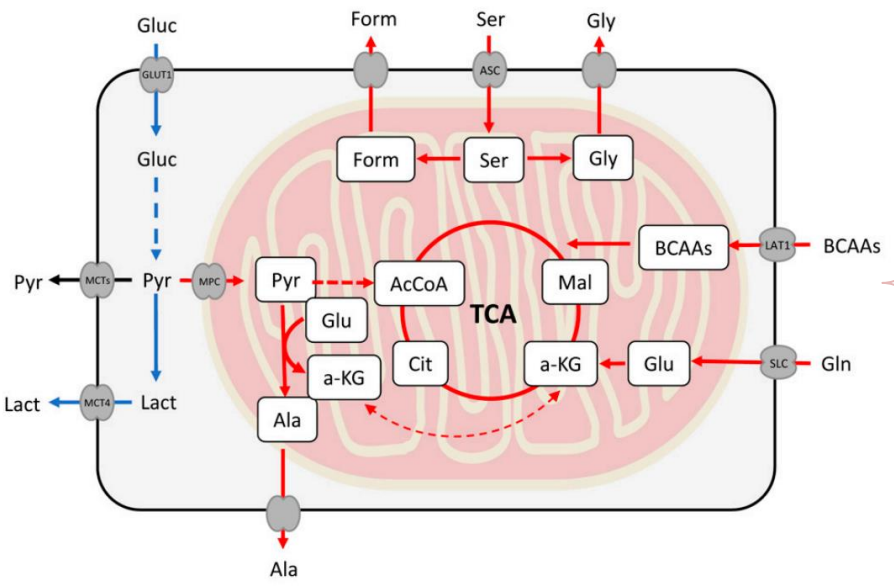
<u>Non-invasive cells</u> show mitochondrial activity



Differently regulated biochemical pathways in the UBCcls

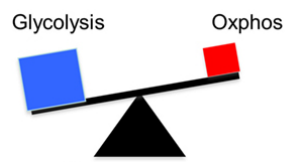


The Interplay between Oxidative Phosphorylation and Glycolysis as a Potential Marker of Bladder Cancer Progression

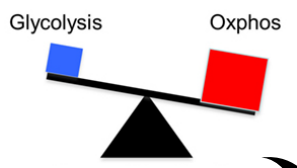


<u>Two classes of cancer metabolism</u>

- **INVASIVE CANCER**
- **LOW OXIDATIVE METABOLISM**
- **HIGH RISK OF PROGRESSION**
- **MUTATION OF TP53 GENE**



- **NON INVASIVE CANCER**
- **ACTIVE OXIDATIVE METABOLISM**
- **LOW RISK OF PROGRESSION**
- **MUTATION OF FGFR3 GENE**



<u>First time the importance of oxidative phosphorylation for BC cells has been observed</u>.

References

1 - Earl et al. The UBC-40 Urothelial Bladder Cancer cell line index: a genomic resource for functional studies. BMC Genomics 16, (2015)
2 - Simabuco et al. p53 and metabolism: from mechanism to therapeutics. Oncotarget 9 (34), 23780-23823. (2018)
3 - Frattini et al. A metabolic function of FGFR3-TACC3 gene fusions in cancer. Nature, 553,222-227 (2018).