Molecular and Cellular Profiling of Mitochondrial Solute Carriers in Cancer

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INTRODUCTION:

Mitochondrial Solute Carriers (MSCs, SLC25 family) are proteins mediating the transport of solutes across the inner mitochondrial membrane. Albeit several MSCs are quantitatively and qualitatively altered in distinct pathological conditions , their gene expression profiles have never been systematically screened across cancers.

AIM OF THE PROJECT :

The project has two main aims, i.e., contributing to understanding the role of MSCs in the disease mechanism of cancer cells and identifying potential MSC targets for cancer therapy.

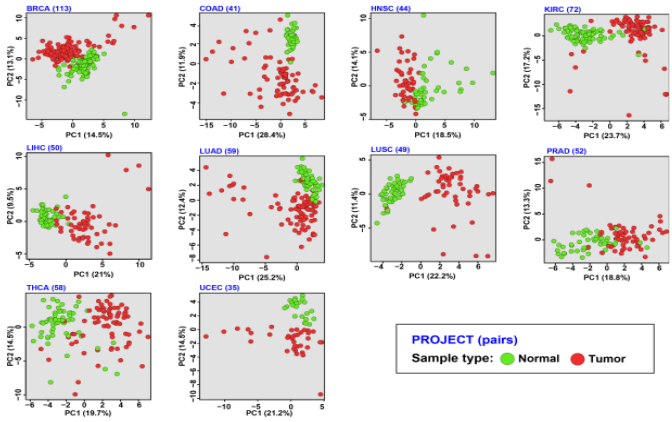

Figure 1 - Principal component analysis (PCA) of the expression profiles of Mitochondrial Solutes Carriers (MSCs). PCA of matched normal/tumor samples, each dot represents a single sample.

METHODS:

- Bioinformatic analysis of RNA-seq data (TCGA).
- Multivariate analysis (Principal Component Analysis, PCA).
- Correlation networks (co-expression and mutual exclusivity).

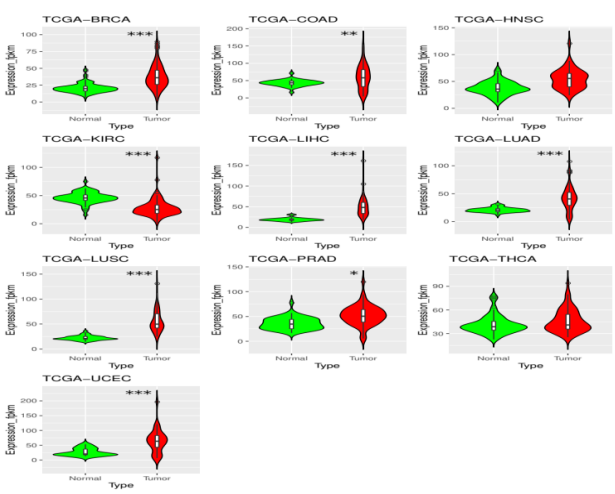

Fig.2- Distribution of *SLC25A39* expression values in all the samples of the TCGA tumor types.

We leveraged the heterogeneity of MSC expression to identify co-expression and mutual exclusivity patterns across tumor types, performing over 92,000 correlation analyses. In colorectal cancer, two mutually exclusive MSC groups emerged, with SLC25A39 and its paralog SLC25A40 showing a clear exclusivity **(Fig.3)**.

RESULTS:

We analyzed RNA-seq data from 10 tumor types in TCGA, including matched tumor and healthy tissues, to extract MSC gene expression profiles. PCA revealed that MSCs effectively distinguish between tumor and healthy samples **(Fig.1)**.

Among the MSCs, SLC25A22 and SLC25A39 are overexpressed in 7 out of 10 tumor types analyzed. Notably, SLC25A39 emerges as a novel cancer-related gene, with recent studies showing its role in transporting glutathione into mitochondria.

SLC25A39 expression in tumor samples shows greater heterogeneity than in healthy tissues—a pattern common to MSCs across all 33 TCGA cancer types **(Fig.2)**.

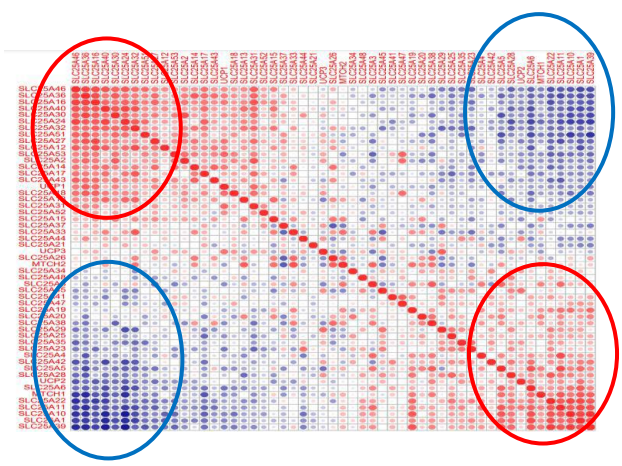

Fig.3 2809 MSC-pairs in colorectal cancer shows two groups (circuits 1 and 2): in red co-expressed MSC and in blue mutually-exclusive MSCs.

CONCLUSIONS:

In this first year we found that the expression of MSC-coding genes discriminates tumors from the matched healthy tissues and that two MSCs, SLC25A22 and SLC25A39, are over-expressed in seven out of ten different tumor types. We also verified that the expression of the two close paralogs SLC25A39 and SLC25A40, possibly transporting GSH, are mutually exclusive in different tumor samples of the same tumor type .