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MYOFERLIN CONTROLS MITOCHONDRIAL STRUCTURE AND METABOLISM IN PANCREATIC DUCTAL ADENOCARCINOMA, AND AFFECTS TUMOR AGGRESSIVENESS

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Introduction Pancreatic ductal adenocarcinoma (PDAC) is the most common type of pancreatic cancer, and the third leading cause of cancer related death. Therapeutic options remain very limited and are still based on classical chemotherapies. Cell fraction can survive to the chemotherapy and is responsible for tumor relapse. It appears that these cells rely on oxydative phosphorylation (OXPHOS) for survival.

Myoferlin, a membrane protein involved in cell fusion was recently shown by our laboratory to be overexpressed in pancreatic cancer.

Material and methods We used pancreatic cancer cell lines depleted in myoferlin to assess mitochondrial function with an extracellular flux analyser. Pancreas cancer samples from the institutional biobank with matched PET scan data were used to correlate myoferlin abundance and glycolysis.

Results and discussions In the present study, we discovered that myoferlin was more expressed in cell lines undergoing (OXPHOS) than in glycolytic cell lines. In the former cell lines, we showed that myoferlin silencing reduced OXPHOS activity and forced cells to switch to glycolysis. The decrease in OXPHOS activity is associated with mitochondrial condensation and network disorganization. An increase of Dynamin-related protein (DRP)-1 phosphorylation in myoferlin-depleted cells led us to suggest mitochondrial fission, reducing cell proliferation, ATP production and inducing autophagy and ROS accumulation. Electron microscopy observation revealed mitophagy, suggesting mitochondrial alterations.

To confirm the clinical importance of myoferlin in PDAC, we showed that low myoferlin expression was significantly correlated to high overall survival. Myoferlin staining of PDAC sections was negatively correlated with several 18FDG PET indices indicating that glycolytic lesions had less myoferlin. These observations are fully in accordance with our in vitro data.

Conclusion As the mitochondrial function was associated with cell chemoresistance, the metabolic switch induced by myoferlin silencing could open up a new perspective in the development of therapeutic strategies. Among them, targeting functional domains (C2, Dysf, ...) of myoferlin should be a priority.

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UNCOUPLING FOXO3A MITOCHONDRIAL AND NUCLEAR FUNCTIONS IN CANCER CELLS UNDERGOING METABOLIC STRESS AND CHEMOTHERAPY

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Introduction While aberrant cancer cell growth is frequently associated with altered biochemical metabolism, normal mitochondrial functions are usually preserved and necessary for full malignant transformation. The transcription factor FoxO3A is a key determinant of cancer cell homeostasis, playing a dual role in survival/death response. We recently described a novel mitochondrial arm of the AMPK-FoxO3A axis in normal cells upon nutrient shortage.

Material and methods After extensive characterisation of mitochondrial FoxO3A function *in vitro* in several cell lines and tumours, we generated FoxO3A-knockout cancer cells with the CRISPR/Cas9 system and reconstituted FoxO3A expression with wild-type or mutant vectors.

Results and discussions Here we show that in metabolically stressed cancer cells, FoxO3A is recruited to the mitochondria through activation of MEK/ERK and AMPK which phosphorylate serine 12 and 30, respectively, on FoxO3A N-terminal domain. Subsequently, FoxO3A is imported and cleaved to reach mitochondrial DNA, where it activates expression of the mitochondrial genome to support mitochondrial metabolism and cell survival. Using FoxO3A^{-/-} cancer cells generated with the CRISPR/Cas9 genome editing system and reconstituted with FoxO3A mutants being impaired in their nuclear or mitochondrial subcellular localization, we show that mitochondrial FoxO3A promotes survival in response to metabolic stress.

In cancer cells treated with chemotherapeutic agents, accumulation of FoxO3A into the mitochondria promoted survival in a MEK/ERK-dependent manner, while mitochondrial FoxO3A was required for apoptosis induction by metformin.

Conclusion Elucidation of FoxO3A mitochondrial vs. nuclear functions in cancer cell homeostasis might help devise novel personalised therapeutic strategies to selectively disable FoxO3A pro-survival activity and manipulate cellular metabolism to counteract cancer initiation and progression.

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CATECHOL-O-METHYLTRANSFERASE: A DUAL-ROLE PLAYER IN DIFFERENT BREAST CANCER SUBTYPES?

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Introduction Catechol-O-methyltransferase (COMT) plays an essential role in detoxification of catechols by transferring the methyl group from S-adenosyl-L-methionine to the substrate. In breast cancer, it catalyses methylation of oestrogen metabolites to block their oestrogenicity which prevents their oxidation to carcinogenic quinones. In this study we investigated whether its tumour suppressor role is limited to oestrogen receptor dependent breast cancer, or whether it has a general validity.

Material and methods A differential cell surface proteomics analysis with SILAC-LC-MS quantification was performed on MDA-MB-231 breast cancer cell line and its clone selected for higher migration capacity. Analysis of migration and invasiveness of MCF7 cells stably transfected with COMT was performed using Transwell assay. The protein-level expression of COMT in different breast cancer subtypes was determined by