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MITOCHONDRIAL REPROGRAMMING IN CANCER

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Tumours must overcome numerous metabolic challenges to thrive in nutrient-deprived microenvironments and to evade therapeutics. Mitochondria are dynamic organelles that provide the metabolic flexibility and plasticity demanded by cancer cells. Our overall objectives are to understand how mitochondria are reprogrammed at different stages of tumorigenesis and to reveal metabolic vulnerabilities in cancer by targeting mitochondrial metabolite transporters.

Intracellular biochemical reactions are compartmentalised to optimise energy efficiency and cellular adaptation to the environment. Essential metabolites, including amino acids and nucleotides, are transported both in and out of mitochondria under the control of dedicated solute carrier proteins. These metabolite transporters sit in the impermeable inner mitochondrial membrane and couple the metabolic reactions of the cytosol with the mitochondrial matrix. Mitochondrial solute carriers therefore represent crucial sites of cellular metabolic control that help govern tumour growth, survival and metastasis (Figure 1). This year, we studied how mitochondrial transport of amino acids and nucleotides is regulated in cancer. Our results have helped define the cellular contexts in which mitochondrial uptake of certain amino acids and nucleotides are essential for metabolic control with broad implications for epigenetic and innate immune signalling in cancer.

One of our specific goals is to understand how the mitochondria transport and metabolise nucleotides. Nucleotides are essential building blocks for the synthesis of mitochondrial DNA and RNA and we recently found that blocking mitochondrial nucleotide supply can suppress cancer cell growth (Grotehans *et al.*, 2023, *EMBOJ*). However, post doc Vanessa Xavier noticed that the inhibition of mitochondrial ribonucleotide supply also limits the build-up of mitochondrial double-stranded RNA (dsRNA) in cancer cells.

Mitochondrial double-stranded RNA in cancer

Mitochondrial dsRNA arises upon the hybridisation of long polycistronic mitochondrial RNA transcripts. Analogous to viral dsRNA, mitochondrial dsRNA is a potent immunogen when exposed to cytosolic dsRNA receptors and can drive inflammation. Therefore, mitochondrial dsRNA homeostasis is carefully regulated in healthy tissue to prevent aberrant innate immune signalling. Vanessa characterised the spatial distribution of dsRNA within mitochondria and found that mitochondrial dsRNA accumulated in proliferating cancer cells. This build-up of mitochondrial dsRNA was dependent on cell cycle progression and mitochondrial pyrimidine nucleotide salvage (Figure 2A). Next, Vanessa teamed up with Prof. John Le Quesne and the Deep Phenotyping team to search for evidence of mitochondrial dsRNA in the tumours of lung cancer patients. Using multiplex imaging of a patient tumour tissue microarray, they indeed detected an increase of dsRNA in malignant lung adenocarcinoma cells (Figure 2B,C). This work illuminated a link between mitochondrial dsRNA homeostasis and cellular proliferation in tumours (Xavier *et al.*, 2024, *Life Sci. Alliance*). The accumulation of mitochondrial dsRNA could be a novel marker of cell malignancy, and it will be important to determine how mitochondrial dsRNA influences tumour immunogenicity in future studies.

Publications listed on page 123

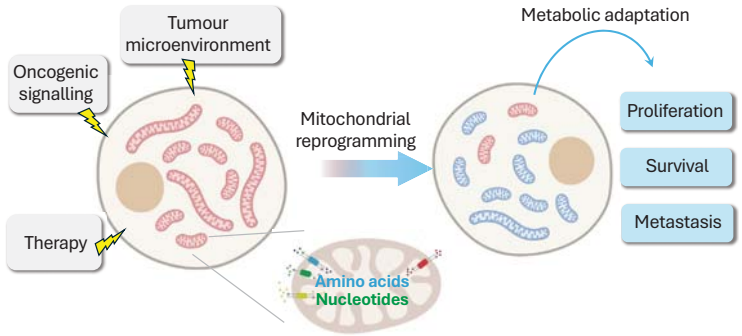

Figure 1. Mitochondrial reprogramming in cancer
Multiple mechanisms drive mitochondrial reprogramming during tumour development. Mitochondrial solute carriers support mitochondrial metabolic adaptation by transporting key metabolites including amino acids and nucleotides across the inner mitochondrial membrane.

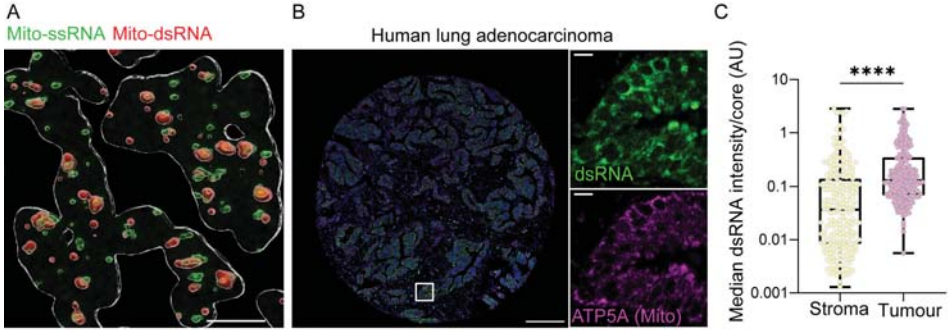

Figure 2. Cancer cells accumulate mitochondrial double-stranded RNA
A Super-resolution imaging of mitochondrial single-stranded (ss)RNA and double-stranded (ds)RNA foci in U2OS cells. **B** Mitochondrial dsRNA detected in a core from lung adenocarcinoma tissue microarray (TMA) by multiplex imaging using antibodies raised against dsRNA and ATP5A (mitochondrial protein). **C** Median dsRNA intensity in stroma and tumour regions per core of the TMA (N=233 cores with stroma, N=221 cores with tumour). This figure was adapted from Xavier *et al.*, 2024 *Life Sci. Alliance. DOI: 10.26508/lsa.202402764.*