Anabolic metabolism and pro-survival signaling are engaged to rescue the phenotype of electron transport chain dysfunction in a cybrid cell model

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Mitochondria perform crucial roles in energy transduction and apoptosis making them a major site for life and death of the cell. Despite this apparent importance, mitochondria are inherently prone to stress and recent literature has highlighted the importance of mitochondrial stress signaling to promote cell survival. We postulate that back and forth signaling between the mitochondria and rest of the cell is paramount for cell survival, and that the breakdown of this communication potentiates ageing and age-related complex diseases.

We aimed to explore these ideas by performing metabolic characterisation and investigating stress signaling in a cybrid model of mitochondrial dysfunction. Four xeno-mitochondrial cybrid cells were used to model mitochondrial stress. These possess a *Mus musculus* nuclear genome and mitochondrial genomes of: *Mus musculus* (Mm), *Mus dunni* (Md), *Mus pahari* (Mp) and *Rattus norvegicus* (Rn) giving a control (Mm), and a respective, ascending increase in evolutionary divergence between nuclear and mitochondrial genomes, resulting in electron transport chain dysfunction.

When cultured in glucose containing DMEM, oxygen consumption rate was decreased by 39%, 61% and 73% for Md, Mp and Rn respectively compared with Mm. Despite these marked changes in oxidative phosphorylation, there were no differences between cell lines in cell viability (by resazurin reduction), cell proliferation or cellular ATP levels (by luminescence). The large reduction in catabolic, oxidative metabolism was associated with a shift towards anaerobic glycolysis and channelling of substrates through anabolic metabolism. This metabolic phenotype is reminiscent of that observed in cancer cells, and we interestingly concomitantly observed activation of pro-survival signaling kinases Akt and AMPK as well as their downstream targets GSK3β and ACC by western blotting.

These results suggest that at least *in vitro*, cells can compensate for a loss of oxidative metabolism through a metabolic-signaling axis and this model may provide an important insight of how metabolic reprogramming may not only support the rapid growth of cancer cells, but also contribute to pro-tumourigenic signaling.