BCHM 421/422 Project – 2023-24

Project Title: Targeting mitochondria inner membranes to inhibit cancer metabolism

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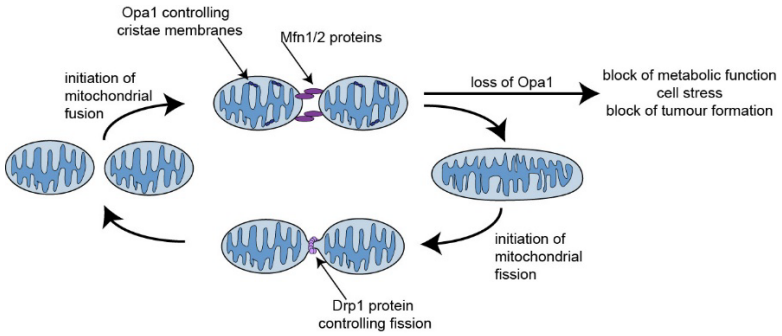
Project Outline: Mitochondria are recognised as the major cellular energy source, metabolising acetyl-CoA to produce ATP. However, mitochondria have wider roles coordinating cell metabolism and this overall function is intimately interrelated to the control of cell growth and death, as reviewed in (Vyas et al. 2016). Since mitochondria form central hubs for cell regulation, they have been proposed to form critical targets that could be inhibited to block the growth of cancer, as we recently discussed (Punter et al. 2022).

Our lab has recently become interested in the pathways that control mitochondrial dynamics, which are composed of a balance of membrane fission and fusion events. Contrary to standard depictions, mitochondria are constantly undergoing cycles of fission (to split the organelle into smaller units), or fusion (to form a larger network), as reviewed in (Youle and van der Bliek 2012). The coordinated actions of fission and fusion are important to maintain the overall health of mitochondria and we have recently studied how nutrient signals can fine-tune levels of mitochondrial fusion (Abdullah et al. 2022).



Here, we are interested in using this knowledge to better understand how mitochondrial fusion can be targeted to inhibit cancer cells. Our preliminary studies have indicated that targeting of the protein Opa1 (optic atrophy 1), which controls fusion of the mitochondrial inner membrane (aka. cristae membranes), effectively reduces tumorigenic potential of breast cancer cells. Our ongoing work aims to define the cell stress and metabolic pathways that are dependent on Opa1. Interestingly, other recent reports have highlighted that the mitochondrial cristae can also be important in the control of mitochondrial DNA, cellular inflammation and resistance to anti-apoptosis drugs (Chen et al. 2019, He et al. 2022).

Project Goals: Our primary questions are whether there are better ways of inhibiting mitochondria to kill cancer cells and what are the underlying mechanisms. The goal of this project is to determine if targeting of other mitochondrial fusion factors (such as the mitofusin proteins Mfn1/2) or regulators of cristae maintenance can offer better inhibitory effects on cancer cell, relative to loss of Opa1.

Experimental Approaches:

You will learn how to culture cancer cells. Mitochondrial regulators will be genetically targeted in these cell models. We will study cell metabolism and related stress response pathways by western-blot analysis with parallel microscopy based analysis of mitochondrial dynamics. In addition, we will test effects of mitochondrial fusion in cancer growth assays. Findings could suggest potential targets to modulate mitochondrial function and reduce growth in cancer.

Keywords:

Mitochondria	Cell metabolism
Cancer biology	Cell growth

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