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Project #2 Outline: Mitochondria are mainly considered as the central energy source for the cell, using acetyl-CoA to produce ATP. While mitochondria are typically drawn as oval-shaped tubes with internal cristae, these organelles are much more fluid and dynamic (for a good general review see: (Youle and van der Bliek 2012)). In fact, mitochondria are constantly undergoing cycles of fission (to split into smaller units), or fusion (to form a large network). In normal cells, there is a coordinated balance of fission and fusion to help maintain a healthy pool in the cell.

Here, we are interested in studying mitochondrial fission and fusion and how this cycle is subverted when the cell becomes infected by pathogens such as RNA genome coronaviruses. Interestingly, one innate cell immunity pathway is coordinated by the mitochondrial anti-viral signalling protein (MAVS) (Seth et al. 2005). MAVS is localised on the mitochondrial outer membrane and becomes activated following viral infection to drive a coordinated cytokine response. It remains unclear how mitochondrial dynamics is reprogrammed during coronavirus infection and how imbalance of mitochondrial fission (or fusion) modulates MAVS-mediated anti-viral function. To further explore, we will study genes of the SARS-CoV2 virus that underlies the current COVID-19 pandemic (as general review, see (Cevik et al. 2020)). A recent study has been able to jumpstart the research by mapping the interactome (protein interaction network) for all SARS-CoV2 genes using mass spectrometry proteomics approaches (Gordon et al. 2020). Also, earlier work has suggested that the open-reading frame 9b (Orf9b) of a related coronavirus locates onto the mitochondria during infection to suppress MAVS anti-viral responses (Shi et al. 2014). More recently, cell metabolic stress (sensed via the AMPK pathway) was shown to modulate the mitochondrial fission factor (Mff) to impair MAVS and anti-viral signalling (Hanada et al. 2020).

All these emerging results suggest a number of antiviral pathways that may be exploited upon SARS-CoV2 infection but details remain unclear. This project aims to further roles for key SARS-CoV2 fusion proteins in the regulation of mitochondrial dynamics regulators (Opa1, Mitofusin1 and 2) and MAVS anti-viral cytokine responses. Findings could highlight mechanisms centred around mitochondria that are critical for SARS coronavirus infection. Insights from this work could suggest potential strategies to help target the current COVID19 pandemic or improve our understanding of virus-host interactions to help navigate future virus-based threats.

Supervisor: Edmond Chan

Project title: Mechanisms of SARS-CoV2 in the subversion of mitochondrial anti-viral immunity

Keywords:	Mitochondria	Cell biology
	Virus	Cell immunity

Project goals: To define the SARS-CoV2 genes that control mitochondrial dynamics and mitochondria-based antiviral signalling.

Experimental approaches: You will learn how to culture mammalian cells. These cell models will be transfected with gene plasmids constructs to express a subset of viral proteins. Effects on mitochondrial dynamics will be measured by western-blot analysis of cell signalling and compared with parallel microscopy based analysis of mitochondrial dynamics. Anti-viral gene expression responses will be monitored following treatments that mimic cell stress from viral infection.

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