BCHM 421/422 – 2020/2021

Project Outline: Mitochondria are best appreciated as the energy source for the cell, using acetyl-CoA to produce ATP. While mitochondria are typically drawn as oval-shaped tubes, these organelles are much more flexible, undergoing a constant cycle of fission to split into smaller units, or fusion to form a larger network. There have been huge advances over the last ten years on the roles and regulation of this pathway, which is termed mitochondrial dynamics. Overall, proper balance of both sides of mitochondrial dynamics appears essential to maintain metabolic function and prevent accumulation of organelle damage.

Several studies have suggested that mitochondrial fission is important for maintaining strong unregulated growth of cancer cells. On the other hand, less is known about roles of mitochondrial fusion in cancer. In this regard, we have been investigating mechanisms that coordinate mitochondrial fusion and the mitophagy recycling pathway. Now, we are further interested in identifying new strategies to target mitochondrial fusion to impair the growth or sensitize cancer cells to chemotherapy drugs.

Supervisor: Edmond Chan

Project title: Modulating mitochondrial dynamics to target breast cancer cells

Project goals: To identify the strongest regulatory genes of mitochondrial fission and fusion that target metabolism and growth using breast cancer cell models.

Experimental approaches: This project features molecular cell biology to study mitochondria. You will learn how to culture cancer cell models. These cell models will be treated with gene targeting approaches (shRNA or CRISPR-Cas9 genome editing) to target either mitochondrial fission or fusion pathways. Mitochondrial dynamics will be measured using microscopy. Cell growth and cell death pathways will be monitored in parallel using biochemistry and live cell imaging.

Key References:

Youle, RJ and van der Bliek, AM. (2012). Mitochondrial fission, fusion, and stress. Science, 337(6098), 1062-1065. www.ncbi.nlm.nih.gov/pubmed/22936770

Serasinghe MN et al (2015). Mitochondrial division is requisite to RAS-induced transformation and targeted by oncogenic MAPK pathway inhibitors. Mol Cell. 57(3): 521-36. doi: 10.1016/j.molcel.2015.01.003. www.ncbi.nlm.nih.gov/pubmed/25658204

Kashatus JA et al (2015). Erk2 phosphorylation of Drp1 promotes mitochondrial fission and MAPK-driven tumor growth. Mol Cell. 57(3):537-51. doi: 10.1016/j.molcel.2015.01.002. www.ncbi.nlm.nih.gov/pubmed/25658205

Examples of our cell biology work:

Nwadike C et al (2018). AMPK Inhibits ULK1-Dependent Autophagosome Formation and Lysosomal Acidification via Distinct Mechanisms. Mol Cell Biol. 38(10). pii: e00023-18. doi: 10.1128/MCB.00023-18. www.ncbi.nlm.nih.gov/pubmed/29507183

Gallagher LE et al (2017). Lysosomotropism depends on glucose: a chloroquine resistance mechanism. Cell Death Dis. 8(8):e3014. doi: 10.1038/cddis.2017.416. www.ncbi.nlm.nih.gov/pubmed/28837152

Suggested extended reading:

Vyas S et al (2016) Mitochondria and Cancer. Cell. 166(3):555-566. doi: 10.1016/j.cell.2016.07.002. www.ncbi.nlm.nih.gov/pubmed/27471965