

Actin regulation in mitochondrial DNA inheritance

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Research area: Organelle dynamics and inheritance

Project outline:

During oogenesis, purifying selection removes detrimental mtDNA mutations to keep the integrity of the mitochondrial genome in the next generation. We performed a genome-wide screen and identified several actin regulatory proteins that influence purifying selection, including sorting nexin 9 (SNX9). Recently, foci and larger comet-like assemblies of actin filaments have been observed at points of mitochondrial remodelling and are important for mitochondrial dynamics and quality control (e.g. mitophagy) (Kruppa et al, 2018, Hsieh & Wang 2019). In addition, SNX9-mediated mitochondrial-derived vesicles budding is demonstrated as an alternative form of mitophagy to maintain mitochondrial health (Towers et al, 2021).

This PhD project will probe the role of SNX9 and other actin regulators in mitochondrial and mtDNA dynamics. There are three aims: (1) Which actin regulatory pathways affect mtDNA purifying selection? This will be investigated using siRNA knockdowns of actin regulators in *Drosophila* oocytes and patient-derived human cells (Hansong Ma); (2) What is the relationship between SNX9 and other actin regulators and mitochondrial morphology? The localisation of endogenous SNX9 and other actin regulators to mitochondria will be determined in *Drosophila* oocytes and human cells (Hansong Ma, Jenny Gallop), and the effects of actin regulatory knockouts on mitochondrial morphology will be assessed by electron microscopy (in collaboration with Dr Luke Chao at Massachusetts General Hospital); (3) Do mtDNA copy number or mtDNA mutations affect actin polymerisation dynamics? An established cell-free assay will be used to investigate actin polymerisation dynamics at mitochondria harbouring different DNA content or mutations (Jenny Gallop).

BBSRC DTP main strategic theme: Understanding the rules of life