Investigating the Mitochondrial Basis of Neuronal ageing

Supervisory team:
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Project description:

The exact cellular biological mechanisms of age related cognitive decline are poorly understood. Brain ageing is caused by accumulated damage that leads to neuronal dysfunction, tissue failure, and ultimately death. A number of ageing theories have been proposed which have been centred around the gradual damage of the energy generating organelle the mitochondria. How mitochondrial function declines with age has been long debated. Age has been associated with decreased oxidative function, accumulation of mitochondrial DNA mutations, decreased dynamics (fission/ fusion/ transport), lipid compositions changes and build-up of reactive oxygen species (ROS). Currently we don't know which age-related mitochondrial change is the driving force for other mitochondrial perturbations and exactly what age related mitochondrial change is the major contributor to the ageing brain. Our work has previously shown that mitochondrial dynamics are significantly altered by age (Smith et al., 2019 Neuron & Lin T-H et al., 2021 PNAS) and this project will investigate mechanisms behind this processes.

The student will use Drosophila techniques to look at the effect of several mitochondrial perturbations on specifically neuronal ageing. Genetic approaches will be used analyse the effect of mitochondrial DNA mutations, trafficking deficits or ROS, on lifespan, behaviour, metabolism shifts, lipid profiles and neuronal physiology. We also have a large tool set to enable us to determine mitochondrial health and function in vivo at different ages using confocal imaging techniques (Smith et al., 2019 Neuron & Lin T-H et al., 2021 PNAS).

Mitochondria and peroxisome metabolism is tightly linked. Substrates for peroxisomal β-oxidation, are altered in the ageing brain. The student will investigate whether loss of peroxisomal function contributes to neuronal ageing and conversely whether enhanced peroxisome transportation in vivo will improve age related phenotypes.

The PhD student will also have the opportunity to learn how to generate and analyse large bioinformatics data sets. Dissected brain samples from our aged v's young animals will be processed for untargeted lipidomic and metabolomic analysis. Using this unbiased and data driven approach, we will be able to genetically inhibit or overexpress several select enzymes involved in uncovered dysregulated pathways.

With this multi-disciplinary approach we aim to unravel new fundamental biological mechanisms, to understand the mechanisms of neuronal ageing, and to specifically determine what mitochondrial and peroxisomal changes impact function.