Autophagy and the integrated stress response in neurodegeneration: how endomembrane trafficking shapes human neuronal/glial interactions during stress

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Project description:
The causes of the insidious decline in neuronal functional and the sustained loss of neuronal viability that underpin diverse types of ageing-associated brain degeneration are broad and multifaceted. There are, however, several unifying features, such as failing mitochondrial function, aberrant endocytic trafficking, and ineffective autophagy stress responses. Autophagy is a cytoplasmic quality control system responsible for the selective isolation, delivery, and lysosomal degradation of misfolded proteins/aggregates and damaged/redundant organelles (including mitochondria). It is controlled by the protein products of a dedicated set of autophagy associated genes (ATG genes), whose roles and regulation in non-neuronal cell-types are well understood. Crucially, despite the general acceptance that autophagy protects against the onset and progression of diverse neurodegenerative conditions, little is known about how neuronal autophagy is regulated throughout the lifespan.

Accumulating evidence describes how the autophagy machinery can engage with other regulatory pathways needed for sustained cellular health. For example, we and others have found that some core autophagy proteins interact with key regulators of the endocytic pathway [e.g., Baines et al., 2022]; meanwhile, we have described how human ATG8 proteins can moonlight as co-factors to influence transcriptional control in stressed neurons [Jimenez-Moreno et al. 2019]. This project will examine how autophagy shapes human iPSC-derived neuronal and glial (astrocytes, microglia) responses following insults known to engage the so-called "integrated stress response"—a conserved regulatory pathway for the upregulation cell stress responsive genes. Studies will include: (i) how mutations in endocytic regulators identified as drivers of neuronal disruption in ageing-associated human diseases influence autophagy, neuronal physiology, and glial stress responses; (ii) how the autophagy system directly influences the integrated stress response in neurons and glia through interactions with key drivers of adaptive protein expression; (iii) how manipulation of the integrated stress response in neurons and glia shapes neuroinflammatory signalling through altered cytokine and chemokine expression and release.

References: Baines et al., (2022) The ATG5 interactome links clathrin-mediated vesicular trafficking with the autophagosome assembly machinery. Autophagy Reports 1: 88-118 Jiménez-Moreno, et al., (2019) LIR-dependent LMX1A/LMX1B autophagy crosstalk shapes human midbrain dopaminergic neuronal resilience. bioRxiv https://doi.org/10.1101/636712

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.