Mechanisms and functions of lysosome positioning

Supervisory team:
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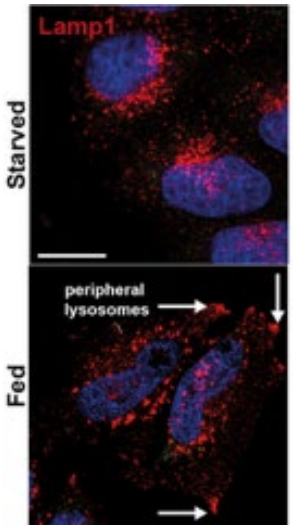
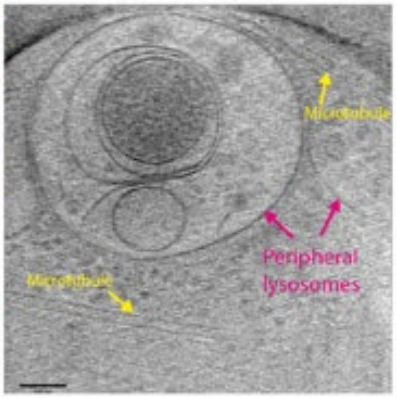
Project description:
Lysosomes are the main degradative organelle in the cell. They contain >60 acid-hydrolases to digest cargo delivered via membrane trafficking processes including endocytosis and autophagy. Lysosomes are also key regulators of cell metabolism; it has become increasingly clear that where lysosomes are within a cell is important for their functions.

Lysosome localisation is dynamic, adaptive and controlled by the molecular motors, kinesin and dynein, which coordinate with adaptor proteins to tether and transport lysosomes along microtubules. Distribution of lysosomes towards the cell periphery correlates positively with cell growth and is associated with changes in lysosome size, membrane composition, hydrolytic activity and cell signalling. For example, in response to nutrients, lysosomes are smaller, less acidic and enriched in the phospholipid, PI3P, which influences the recruitment of protein complexes, including the kinesin-adaptor protein FYCO1. The mechanisms leading to activation of kinesin after nutrient feeding are poorly understood.





Working between the labs of BC (lysosome biology) and MPD (intracellular transport). You will take a multi-disciplinary approach, using advanced imaging techniques, with molecular, cell and structural biology to investigate the molecular mechanisms and signalling pathways that control the nutrient-regulated subcellular localisation of lysosomes and its functional consequences.

The key objectives are:

Establish the basis for interaction between the kinesin-1-lysosome adaptor protein FYCO1 and its effect on regulation of the motor. Guided by AlphaFold3 modelling, you will carry out assays to establish and map the binding interfaces defining motor-cargo complexes between these protein complexes and determine how they control motor activity.

Characterise the subpopulation of lysosomes that FYCO1 transports. You will characterise the lysosomal pool decorated by FYCO1, including assessment of their size, hydrolytic activity and pH. Proteomics and candidate-approach analysis of isolated FYCO1-positive lysosomes will identify their lipid and protein composition. You will investigate the mechanisms that couple nutrient status with FYCO1-dependent lysosome distribution by manipulating the expression or activity of proteins required to sense nutrients (notably components of mTORC1 pathway).

Investigate the ultrastructural of lysosomes and their associated residing at the cellular periphery. You will use new tools developed by MPD to promote peripheral lysosomal transport and couple those with cryo-electron tomography

(Cryo-ET) to examine lysosomes at the edge of the cell in their native state. This will reveal new insights into their architecture and composition, and develop a new platform for the in situ study of other proteins associated with regulating nutrient-dependent lysosome positioning and its functional consequences.

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.