Hijacking Host Cell Organelles: How do obligate intracellular pathogens tether host organelle membranes?

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Project description:

Organelles such as the ER, mitochondria, and peroxisomes need to be able to communicate and exchange metabolites. This cooperation is facilitated by interactions between specific proteins on organelle membranes to form contact sites. These are fundamental to cell function and in human cells disruption of these contact sites is associated with disease including Alzheimer's, Parkinson's, and Diabetes.

However, emerging data suggests that these contact sites can be exploited by intracellular pathogens. For example, Chlamydia trachomatis and norovirus, bind to these contact site proteins to establish direct contact with the host ER, potentially allowing them to acquire host lipids. However, the mechanistic details of this process, the impact on the host and prevalence of this phenomenon is poorly understood.

This project will explore organelle contact site hijacking using microsporidia and human cells as a model host-parasite system. These eukaryotic intracellular parasites have small genomes and highly scaled-back metabolic capabilities, making them highly dependent on the host, importing resources that they cannot make themselves. They are particularly lacking in lipid biosynthesis pathways and our hypothesis is that microsporidia access host lipids, by forming membrane contact sites with host organelles such as the ER, mitochondria and peroxisomes.

Specifically this project aims to: 1) identify machinery involved in microsporidia-host organelle interactions. 2) predict which lipid species are required by microsporidia. 3) understand how lipids are transferred between host and microsporidia.

To achieve this the student will integrate a broad range of methodologies including: cell culture, generation of stable cell lines and infection of human cells with microsporidia, bioinformatic analysis, molecular cloning approaches, Western blotting, protein biochemistry and mass spectrometry, epifluorescence and electron microscopy, lipid synthesis and Raman spectroscopy.

This approach, which incorporates a variety of cutting edge techniques means that the PhD student will receive training by a cross disciplinary team, providing a well-rounded PhD training and an excellent basis for starting a research career. Outcomes of the study will lead to a better understanding of the fundamentals of membrane contact sites and mechanisms of pathogenesis in intracellular parasites. Understanding host-pathogen interactions are important across a broad range of disciplines, including human disease, animal health and welfare, and optimisation of agriculture and aquaculture, and this PhD would suit a student interested in those areas. It will also generate a valuable set of tools for studying parasite host-organelle interactions and lipid exchange in parasites more broadly.