Machinery, motifs and mechanisms of endosome-to-Golgi retrieval

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Title of project or programme

Machinery, motifs and mechanisms of endosome-to-Golgi retrieval

Principal Investigators of project/programme grant

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- United Kingdom

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Medical Research Council

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The project/programme is most relevant to

- Alzheimer’s disease and other dementias

Keywords

Research abstract in English

Protein localisation to the compartments that comprise the secretory and endocytic pathways is determined by intrinsic information in membrane proteins (i.e. sorting motifs) and extrinsic machinery (e.g. coat proteins) that recognise the sorting motifs. Endosome-to-Golgi retrieval is a vital pathway

that functions to recycle lysosomal hydrolase receptors (e.g. the cation-independent mannose 6-phosphate receptor – CIMPR) from endosomes to the Golgi and is required for the pathogenic action of Shiga toxin, a bacterial protein that is a causative agent in Shigellosis. Recently endosome-to-Golgi retrieval has been implicated in regulating the localisation and proteolytic processing of the amyloid precursor protein (APP) and therefore has a role in the development of Alzheimer's disease (AD).

The main aim of this proposal is to understand the molecular mechanisms of endosome-to-Golgi retrieval. These studies will therefore be of significant importance in determining the underlying causes of complex pathologies such as AD.

To understand this pathway, we must first identify the components that function in endosome-to-Golgi retrieval. This will be accomplished by an siRNA screen of ~22,000 human genes. Through our studies on the retromer complex, which is essential for the endosome-to-Golgi retrieval of the CIMPR, we have developed a simple and robust microscopy-based assay for evaluating the endosome-to-Golgi retrieval of a reporter protein. Genes identified as acting in endosome-to-Golgi retrieval will be phenotypically grouped based upon criteria such as effects upon the localisation of retromer or morphology of the Golgi and, in collaboration with Dr. Olav Andersen, will be analysed for effects upon the processing of APP. Additionally, genes functioning in endosome-to-Golgi will be investigated for AD-linked single nucleotide polymorphisms (SNPs) and other mutations through a collaboration with Peter St. George Hyslop and mutations identified will be investigated for effects on endosome-to-Golgi retrieval.

In conjunction with the siRNA screen, we will generate a library of CD8-reporter proteins to identify novel sorting motifs that function in protein localisation to the Golgi or post-Golgi endocytic compartments. Sorting motifs that specify localisation to the Golgi or endosomes will be examined for their ability to promote the membrane association/stability of the Golgi-associated, -ear containing, ARF-binding (GGA) proteins and retromer. Finally we will investigate the interaction between the retromer complex and Strumpellin, a protein mutated in hereditary spastic paraplegia (HSP), to determine the role of retromer in HSP and will examine the function of retromer in regulating the membrane trafficking and signalling activity of the BMP receptor.

Lay Summary