Machinery and Mechanisms of Endosomal Protein Sorting – A key Pathway Associated with Alzheimer Disease

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Country

United Kingdom

Title of project or programme

Machinery and Mechanisms of Endosomal Protein Sorting - A key Pathway Associated with Alzheimer Disease

Source of funding information

MRC

Total sum awarded (Euro)

€ 1,025,564

Start date of award

01/12/2013

Total duration of award in years

4.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords
Research Abstract
The goal of the proposed research is to identify and characterise genes encoding endosomal protein sorting machinery. The genes that function at endosomes will be tested for a role in

regulating the localisation and processing of amyloid precursor protein (APP). Those genes are likely to be most relevant for Alzheimer disease (AD). The endosome-to-Golgi retrieval pathway has been shown to play a key role in mediating the localisation and processing of APP. This occurs through the association of APP with the Vps10-domain containing protein SorL1. The SorL1 protein is a cargo protein for the retromer complex and requires retromer for its retrieval from endosomes to the Golgi. Loss of SorL1 or retromer function increases processing of APP to the neurotoxic Abeta peptide that is causal in AD. A genome-wide siRNA screen for genes required for endosome-to-Golgi retrieval has been performed in the SEAMAN lab and has identified 88 genes required for endosome-to-Golgi retrieval including SFT2D2, ZDHHC5 and GRINA. The specific functions of the STF2D2, ZDHHC5 and GRINA proteins will be investigated and proteins that function with them identified by native immunoprecipitation and GST-pulldown experiments. The requirement for the 88 endosome-to-Golgi retrieval genes in regulating APP localisation and processing will be determined and the role of these genes in regulating SorL1 localisation investigated in neuronal cells. Genes identified through the siRNA screen as enhancing endosome-to-Golgi retrieval when silenced will be validated and their role in regulating APP processing determined. Additionally a small molecule screen to identify modulators of endosome-to-Golgi retrieval, both positive and negative, will be performed using an antibody-uptake assay in a high throughput format. Those compounds that affect endosomal protein sorting will be characterised with respect to APP processing and effects on the endo-lysosomal system.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United Kingdom

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A