Mitochondrial ubiquitin dynamics and apoptotic cell death.

https://www.neurodegenerationresearch.eu/survey/mitochondrial-ubiquitin-dynamics-and-apoptotic-cell-death/

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United Kingdom

Title of project or programme

Mitochondrial ubiquitin dynamics and apoptotic cell death.

Source of funding information

MRC

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€ 757,790

Start date of award

03/05/2016

Total duration of award in years

3.0

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords
Research Abstract

Mitochondria play an important role in the orchestration of apoptotic cell death. Synthetic BH3-mimetics promote apoptosis and have shown some success in the clinic. However, additional approaches are required to improve their efficacy and overcome resistance. Mitochondrial dysfunction has been linked to neurodegeneration, in particular to Parkinson’s disease (PD), which is characterised by the loss of dopaminergic neurons from the substantia nigra. Two PD-

associated genes, the ubiquitin E3-ligase Parkin and PINK1 are involved in the safe disposal of damaged mitochondria by mitophagy. Depletion of the unique mitochondrial deubiquitylase (DUB), USP30, has been shown to promote mitophagy in cells with defective Parkin or PINK1 and rescue motor function and dopamine levels in a corresponding fly model. We have recently shown that USP30 depletion also sensitises cancer cells to BH3-mimetics, expanding the clinical potential of a future USP30 inhibitor. We will generate CRISPR/CAS9 dependent knock-out and/or catalytically inactive knock-in cell lines and use a range of proteomic and cell biological approaches to a) identify new substrates of USP30 and explore its role in Parkin-independent mitophagy, b) explore the synergism between USP30-silencing and a toolkit of BH3-mimetics within a panel of cell lines and c) elucidate the mechanism of action of USP30 in modulating apoptotic cell death. Whilst this proposal is focused on USP30 as the preeminent mitochondrial DUB, we will in parallel evaluate USP9X and USP24, two DUBs which have been proposed to stabilise MCL1, thus contributing to a major mechanism of resistance to BH3-mimetics.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United Kingdom

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

Database Tags:
N/A