Molecular mechanisms of neurodegeneration

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Principal Investigators

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Country

United Kingdom

Title of project or programme

Molecular mechanisms of neurodegeneration

Source of funding information

MRC

Total sum awarded (Euro)

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Start date of award

01/10/2011

Total duration of award in years

5.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias|Parkinson's disease & PD-related disorders

Keywords
Research Abstract

Considerable progress has been made in characterizing the molecular neuropathology of dementias and movement disorders. Most cases of disease associated with pathological filament formation are now accounted for by either tau or alpha-synuclein deposits. The discoveries of mutations in the tau gene in inherited forms of frontotemporal dementia and the alpha-synuclein gene in inherited forms of Parkinson’s disease have established that the pathway leading from soluble to filamentous protein, be it tau or alpha-synuclein, is central to the aetiology and pathogenesis of these familial cases of disease. The same is probably true of

the much more common sporadic diseases, such as Alzheimer’s disease, Parkinson’s disease, dementia with Lewy bodies, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration and Pick’s disease. A detailed understanding of the mechanisms underlying the assembly of tau and alpha-synuclein into abnormal filaments could provide novel targets for putative drugs It is therefore important to understand as much as possible about these mechanisms. In the future, the mouse line transgenic for human P301S tau will be used to identify genetic and pharmacological modifiers (enhancers and suppressors) of the neurodegenerative phenotype. This will lead to a comprehensive test of the hypothesis that hyperphosphorylation is important for the assembly of tau into filaments and neurodegeneration. We are in the process of investigating the relevance of individual phosphorylation sites by producing lines of transgenic mice with mutations in these sites. We will assess the relevance of individual protein kinases by using knock-out mice and specific protein kinase inhibitors. The proposed work is based on the hypothesis that the hyperphosphorylation of tau contributes directly to disease. In addition, we have recently shown that experimental tauopathy can be transmitted and that it spreads between adjacent brain regions in a tau-dependent manner. This work has opened up new avenues for the understanding of tauopathy. In the future, we will pursue a similar strategy with respect to alpha-synuclein and its involvement in neurodegeneration. This field is younger and much remains to be learned. We are concentrating on understanding the mechanisms by which alpha-synuclein assembles into filaments and on developing transgenic mouse models for the human alpha-synucleinopathies.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United Kingdom

Diseases:
Alzheimer's disease & other dementias, Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

Database Tags:
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