Molecular mechanisms of neurodegeneration

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Title of project or programme

Molecular mechanisms of neurodegeneration

Principal Investigators of project/programme grant

Title	Forname	Surname	Institution	Country
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Source of funding information

Medical Research Council

Total sum awarded (Euro)

8486873.77

Start date of award

01-04-2005

Total duration of award in months

60

The project/programme is most relevant to

- Alzheimer’s disease and other dementias
- Parkinson’s disease
- Neurodegenerative disease in general

Keywords

Research abstract in English

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 parallel, we will use an unbiased approach making use of mutagenesis with ethyl N-nitrosourea, to identify disease modifiers. 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. We also wish to develop experimental systems by which to study the spreading of alpha-synuclein pathology between cells.

Lay Summary