Pathobiology of alpha-1-antitrypsin deficency and the serpinopathies

https://neurodegenerationresearch.eu/survey/pathobiology-of-alpha-1-antitrypsin-deficency-and-the-serpinopathies/

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Country

United Kingdom

Title of project or programme

Pathobiology of alpha-1-antitrypsin deficency and the serpinopathies

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MRC

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07/10/2013

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2.7

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords
Research Abstract

We have used a wide range of techniques to show that naturally occurring mutations in members of the serine proteinase inhibitor (serpin) superfamily result in abberant conformational transitions to cause disease. The most common of these is the sequential linkage between the reactive centre loop of one molecule and beta-sheet A of another. This process of loop-sheet polymerisation results in the retention of ordered serpin polymers within the cell of synthesis. Polymerisation of mutants of antitrypsin, antithrombin, C1 inhibitor and

antichymotrypsin cause cirrhosis, thrombosis, angioedema and emphysema respectively. Perhaps most striking is our description of the same process in a neurone specific serpin, neuroserpin, to cause a novel dementia that we have called Familial Encephalopathy with Neuroserpin Inclusion Bodies (FENIB). A central feature of these conditions is a genotype-phenotype correlation that can be explained by the rate of intracellular polymerisation. In view of their common mechanism we have grouped these diseases of the serpins together as the serpinopathies and have used them as a paradigm for a broader class of disorders that we have called the conformational diseases. The serpinopathies provide a structurally defined model of protein aggregation in association with disease. We propose to use the small molecules, crystal structures, cell lines, monoclonal antibodies, fly models and the genetic screen that were generated in the last programme grant to address the following specific questions: (i) what are the conformational transitions underlying the serpinopathies? (ii) what is the effect of small molecules that block the polymerisation of alpha-1-antitrypsin? (iii) what is the cellular response to the retention of ordered serpin polymers within the endoplasmic reticulum? (iv) can we prepare monoclonal antibodies to latent alpha-1-antitrypsin and neuroserpin in order to define their role in disease? (v) what is the role of polymers in lung disease in alpha-1-antitrypsin deficiency? These studies, although focused on alpha-1-antitrypsin and neuroserpin, are applicable to many of the mutations in serpins that underlie the serpinopathies. The long-term aim of our work is to understand mechanisms of disease caused by the serpinopathies (from pathological conformational transitions to pathways of cell toxicity) so that we can develop novel therapeutic strategies to treat the associated clinical syndromes.

Lay Summary
Further information available at:

Types:
Investments > €500k

Member States:
United Kingdom

Diseases:
Alzheimer's disease & other dementias

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2016

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