Structural Basis of Serpin Polymerisation

https://neurodegenerationresearch.eu/survey/title-of-pistructural-basis-of-serpin-polymerisation/

Title of project or programme

Title of PI Structural Basis of Serpin Polymerisation

Principal Investigators of project/programme grant

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- United Kingdom

Source of funding information

Medical Research Council

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571715.42

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01-03-2009

Total duration of award in months

36

The project/programme is most relevant to

- Neurodegenerative disease in general

Keywords

Research abstract in English

Ordered and stable protein association is the molecular basis behind several important diseases including Alzheimer's, Huntington's, Parkinson's, and the prion encephalopathies, although the precise molecular mechanisms are unknown. A family of proteins known as the serpins also form stable intermolecular linkages resulting in protein accretion and diseases, such as dementia, cirrhosis and thrombosis. Because the serpins are structurally and functionally well characterised they have become the model for understanding the entire family of conformational diseases. Serpins utilise a thermodynamically-driven beta-sheet expansion mechanism for their function as protease inhibitors,

and it is believed that a similar intermolecular beta-sheet expansion mechanism accounts for the stability of the serpin polymers. We have recently solved a crystal structure of a stable serpin dimer that revealed a large-scale domain swap including two strands of the central A beta-sheet (strands 4 and 5). In this grant we will determine if this unexpected mechanism is the molecular basis behind pathogenic serpin polymerisation by investigating the following hypotheses: i) linear serpin polymers exchange strands 5 and 4A, and that flexibility between protomers is conferred by some local unfolding; ii) the s4A/s5A domain swap we observe in our crystal structure is the general pathological mechanism behind serpin polymerisation and the resulting serpinopathies; and, iii) the polymerogenic monomeric state, M*, is formed by the release of strand 5 from beta-sheet A. We will employ a combination of biochemical and structural techniques using serpins antithrombin (AT) and alpha-1-antitrypsin (alpha1AT) to achieve the following three aims: 1) To determine the crystal structure of open AT polymers. 2) To determine if alpha1AT polymerises in cells using the s4A/s5A mechanism. 3) To determine the structure of the M* state. Successful completion of the aims will reveal the structural basis of serpin polymer formation and propagation, and allow the development of strategies to slow, prevent and even reverse serpin polymerisation.

Lay summary
In which category does this research fall?

- Basic research