Elucidating the Mechanism of Amyloid Formation by Human Lysozyme

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Title of project or programme

Elucidating the Mechanism of Amyloid Formation by Human Lysozyme

Principal Investigators of project/programme grant

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Source of funding information

Biotechnology and Biological Sciences Research Council

Total sum awarded (Euro)

559041.33

Start date of award

01-07-2007

Total duration of award in months

43

Breadcrumb to current pageMain content Search our Database Major Programmes or research grants Title of project or programme Elucidating the Mechanism of Amyloid Formation by Human Lysozyme Principal Investigators of project/programme grant Title Forname Surname Institution Country PI 1 Professor Christopher Dobson University of Cambridge United Kingdom PI 2 Professor Carol Robinson University of Oxford United Kingdom PI 3 PI 4 PI 5 PI 6 Address of institution of lead PI Institution University of Oxford, Department of Chemistry Street Address 12 Mansfield Road City Oxford Postcode OX1 3TA Country United Kingdom Source of funding information Biotechnology and Biological Sciences Research Council Total sum awarded (Euro) 559041.33 Start date of award 01-07-2007 Total duration of award in months 43 The project/programme is most relevant to

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

Keywords

Research abstract in English

The overall objective of this study is to understand how soluble proteins convert into amyloid fibrils. We intend to achieve this aim by determining the structural features of the transient species which are populated throughout fibril formation, and to gain an understanding of the dynamic interactions between these states in unprecedented detail. In this study, we will generate mutational lysozyme variants to vary the population of the transient species. We will also employ naturally occurring (i.e. chaperones) and engineered biomolecules (i.e. antibody fragments) that interact with species along the aggregation pathway to try and trap these species for analysis. Once methods are established to populate these species, we will study the system under fibril forming conditions and in a time dependent manner, using an array of established biophysical techniques, in particular exploiting recent advances in NMR spectroscopy and nanospray mass spectrometry. We have established NMR relaxation techniques that probe the structures and stabilities of transient protein folding intermediates with populations as low as 1% that are in dynamic equilibrium with other states. We have also developed mass spectrometry methods for detecting protein assemblies exceeding 1 MDa in size, along with procedures that enable us to define both the stoichiometric and topological arrangement within such complexes. We shall use both these approaches to probe the nature and populations of oligomeric intermediates in lysozyme aggregation, along with similar studies of the species formed on interaction with other macromolecules. These complementary spectroscopic methods, along with our established ability to use theoretical and computational techniques for interpreting these types of data gives us an unrivalled opportunity to define the structural and dynamic character of fibril formation by a globular protein and to explore the manner in which such a process can be controlled or inhibited.

Lay summary

Our bodies contain some 100,000 proteins that enable or regulate essentially every chemical or biochemical process on which our lives depend. Under normal circumstances these proteins remain in their soluble functional states, but under other circumstances, for example as a result of mutations or even the impairment of regulating processes, they can form large insoluble aggregates that are non-functional and even toxic. This process is of great importance because it is the underlying origin of a range of debilitating human disorders, including neurodegenerative conditions such as Alzheimer’s disease, the transmissible spongiform encephalopathies (such as CJD, the human analogue of ‘mad cow disease’), type 2 (late onset) diabetes and systemic pathologies in which large quantities, sometimes kilograms, of protein are deposited in vital organs such as the kidney, heart and liver. In each of these diseases, a single protein undergoes a structural transition, often resulting in the formation of thread-like aggregates known as amyloid fibrils. Many of these diseases are linked to the ageing process, and as a large fraction of the world’s population lives to ages unprecedented in human history, these diseases are emerging as among the most feared and debilitating in the modern world. In recent years, much research has focused on understanding what causes proteins to misfold and form amyloid structures, and on the specific mechanism by which such transitions occur.

Nevertheless, as a result of structural heterogeneity, low populations and a transient nature, obtaining detailed information about this process has presented a formidable challenge. The primary objective of this study is to elucidate structural information of the different species that are populated along the aggregation pathway of human lysozyme. As well as being associated with a systemic amyloid disorder, lysozyme is one of the most highly studied of all proteins providing a unique opportunity to probe the difference between normal and aberrant behaviour at atomic resolution. By studying species populated under fibril forming conditions, we will be able to begin to understand not only the structures of intermediate species, but also the dynamics of the conversion between the different states involved in fibril formation. These studies should generate a sufficiently profound understanding of the distinctive differences between species involved in normal and aberrant folding behaviour to contribute significantly to the identification of novel strategies through which rational therapeutic intervention could lead to prevention or treatment, not just of this specific disease, but also perhaps the entire family of protein misfolding disorders.