

EDITORIAL

Ironing out the Wrinkles in Misfolded Proteins

The process by which proteins gain their structure is known as protein folding and occurs as the polypeptide chain is being formed within the cell. As proteins control key cellular processes, aberrations in their folding will have deleterious consequences. As such, when proteins do not fold into their normal shape properly, they are said to misfold. Proteins can misfold for a variety of reasons such as a result of changes to the cellular environment as the protein is folding, or genetic mutations leading to amino acid alterations in the polypeptide chain. Protein misfolding is well known to many biochemists as the precipitate that forms when working with their favourite protein, more often than not at some crucial stage of the experiment! Aggregation of misfolded proteins can lead to either ordered or disordered structures – the pathways for which depend on the protein itself and the conditions in which it is misfolding. The most commonly recognised ordered structure is that of the amyloid fibril, which is associated with a number of pathological conditions.

Protein misfolding diseases are a diverse group of disorders associated with the incorrect folding of particular proteins by the cell. Diseases in which amyloid deposits form account for a number of common conditions affecting humans that range from heart disease to neurodegenerative disorders such as Alzheimer's and Parkinson's disease. In terms of the amyloid-related diseases, there are over 20 proteins which are known to form amyloid *in vivo*. The same structure – the amyloid fibril – is formed from these disease-associated proteins, which share no similarity in normal structure or function. Amyloid fibrils share a common morphology (cross β -structure) and are characterised using electron microscopy and their binding to dyes such as Congo red and thioflavin T. The drastic change in conformation to the common β structure of amyloid by these proteins has led

to the proposition that amyloid fibrils can form from any protein given the right conditions. The pathological consequences of the amyloid disorders range from the physical impairment of organ activity due to the proteinaceous deposits to a toxic effect of the misfolded proteins. The latter case is under intense study at present in a number of neurodegenerative disorders, where it is believed small, soluble, oligomeric forms of the offending protein, which form on the folding pathway to become amyloid, are the more toxic, disease-causing protein species. This then puts amyloid deposits as a potential defense mechanism for the cell to immobilise these toxic molecules. While amyloid-related diseases are perhaps the best known protein misfolding disorders, there are other classes of proteins that form aggregates in which amyloid is not the result, such as in the serine protease inhibitor (serpin) family of proteins.

There are many laboratories in Australia working on protein misfolding diseases and this topic has been the focus of two recent symposia held in Melbourne in 2006 and in Queensland in 2007. This Showcase on Research begins with an article by Heath Ecroyd and John Carver, who provide an overview of amyloid fibril formation and highlight the potential for molecular chaperone proteins to inhibit this process. Danny Hatters brings us up to date on research on Huntington's disease and other disorders. The aggregation of serpin proteins is covered by Anja Knaupp and Stephen Bottomley. Finally, Antony Cooper describes his work on using a yeast model system to study the aggregation and toxicity of α -synuclein, which is implicated in Parkinson's disease. These articles show some of the breadth of research in protein misfolding being carried out and with most, the question of what particular misfolded form of the protein is killing the cell, and how, is the key question to be addressed.

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Cover Illustration

Amyloid fibrils formed from a protein containing a polyglutamine repeat.

Image courtesy of Stephen Bottomley, Department of Biochemistry and Molecular Biology, Monash University.

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