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Apolipoproteins and amyloid fibril formation in disease

Several diseases, including Alzheimer's, Parkinson's, diabetes type II and atherosclerosis are associated with the protein misfolding and the deposition of amyloid fibrils. Our work has focused on amyloid fibril formation by apolipoproteins (Fig. 1) where we are developing strategies to inhibit amyloid fibril formation as a general and effective way to treat amyloid-related disease.

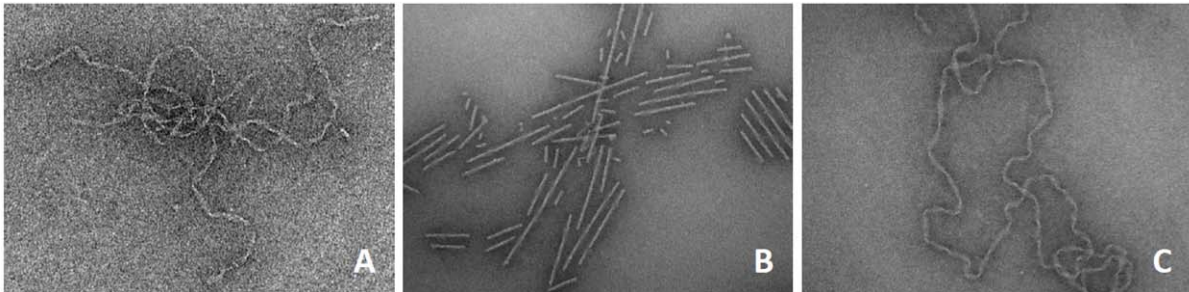


Fig 1: Transmission electron micrographs of amyloid fibrils formed by (A) oxidized apoA-I, (B) apoC-II in the presence of micellar phospholipid and (C) lipid-free apoC-II.

The structure of amyloid fibrils

Amyloid fibrils have increased β -structure relative to the non-fibrillar form and interact with Congo Red and thioflavin T (ThT). X-ray Diffraction patterns indicate a common cross β -structure with strands in adjacent β -sheets oriented at right angles to the long axis of the fibril. Our NMR and spectroscopic studies have been used to generate a simple 'G-like' structural model for apoC-II amyloid fibrils (1).

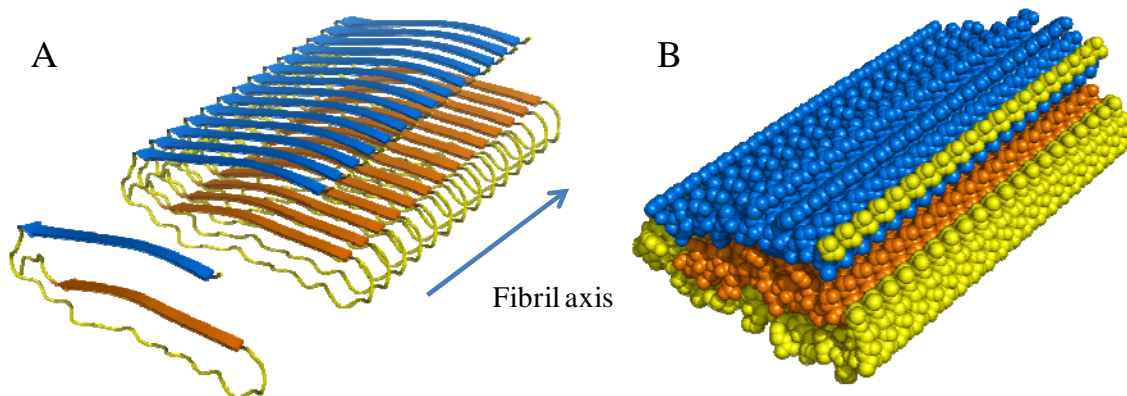


Fig 2. Structural model for apoC-II amyloid fibrils. (A) ApoC-II monomer adopts a 'letter G-like' β -strand-loop- β -strand structure. Each monomer contributes to each of the two β -sheets, giving rise to a parallel, in-register structure. (B) A space-filled view.

Inhibition of amyloid fibril formation

Our strategy for the development of inhibitors of amyloid fibril formation that takes advantage of the observation that amyloid fibrils are invariably composed of a single type of protein subunit. This implies that the assembly process has a high degree of specificity such that specific small molecules could block or reverse amyloid fibril formation. Our recent work involved the screening of a range of small molecules for their effects on amyloid fibril formation by apoC-II and lead to the identification of several activators and inhibitors (2-4). The mechanism of action of these modulators has now been characterised in terms of a simple kinetic model (Fig 3).

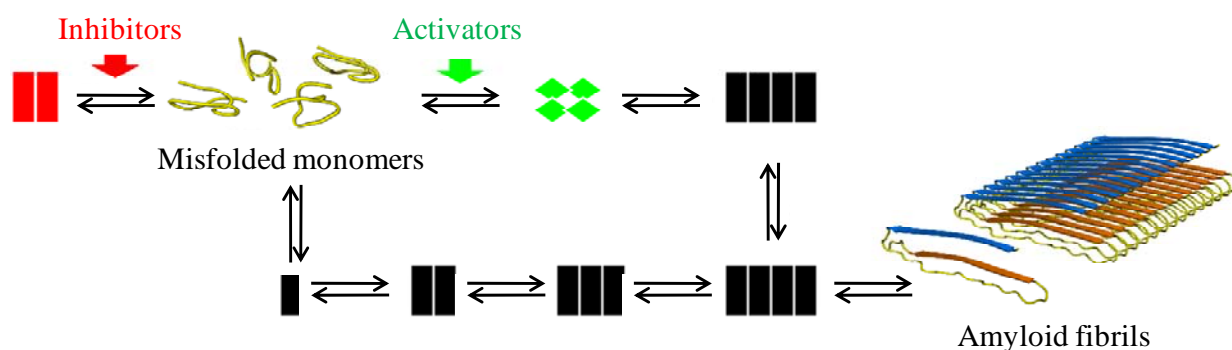


Fig 3. Kinetic model for the effects of activators and inhibitors on apoC-II amyloid fibril formation. Activators promote on-pathway tetrameric intermediates with increased β -structure while inhibitors stabilize non-amyloidogenic α -rich dimers.

Projects: Control of protein misfolding by metabolites

Our present work (in collaboration with Dr Mike Griffin) is to identify biological metabolites that modulate the misfolding and self-assembly of proteins to form amyloid fibrils. We believe that high affinity metabolites, play hitherto unrecognised roles in protein folding and assembly with the potential to modulate aberrant protein misfolding and disease.

Projects are available where the following specific aims:

Aim 1: To screen the metabolome for metabolites that regulate protein misfolding and fibril formation

Aim 2: To characterize high affinity, small molecule modulators of protein misfolding and self-assembly

Aim 3: To determine the effect of protein folding modulators on fibril morphologies.

Recent publications

1. Teoh, C. L., Pham, C. L., Todorova, N., Hung, A., Lincoln, C. N., Lees, E., Lam, Y. H., Binger, K. J., Thomson, N. H., Radford, S. E., Smith, T. A., Muller, S. A., Engel, A., Griffin, M. D., Yarovsky, I., Gooley, P. R., and Howlett, G. J. (2011) A structural model for apolipoprotein C-II amyloid fibrils: experimental characterization and molecular dynamics simulations, *J Mol Biol* 405, 1246-1266.
2. Ryan, T. M., Griffin, M. D., Teoh, C. L., Ooi, J., and Howlett, G. J. (2011) High-affinity amphipathic modulators of amyloid fibril nucleation and elongation, *J Mol Biol* 406, 416-429.
3. Ryan, T. M., Teoh, C. L., Griffin, M. D., Bailey, M. F., Schuck, P., and Howlett, G. J. (2010) Phospholipids enhance nucleation but not elongation of apolipoprotein C-II amyloid fibrils, *J Mol Biol* 399, 731-740.
4. Ryan, T. M., Howlett, G. J., and Bailey, M. F. (2008) Fluorescence detection of a lipid-induced tetrameric intermediate in amyloid fibril formation by apolipoprotein C-II, *J Biol Chem* 283, 35118-35128.