Poster Presentation

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Unravelling transthyretin amyloidosis by neutron crystallography

Ai Woon Yee[1], Martine Moulin[1], Matthew Blakeley[2], Jonathan Cooper[3], Michael Haertlein[1], Edward Mitchell[4], Trevor Forsyth[1]
[1]Life Sciences Group, Institut Laue-Langevin, Grenoble, France, [2]Large-Scale Structures Group, Institut Laue-Langevin, Grenoble, France, [3]Laboratory of Protein Crystallography, Drug Discovery Group, Wolfson Institute for Biomedical Research, UCL, London, United Kingdom, [4]Business Development Unit, European Synchrotron Radiation Facility (ESRF), Grenoble, France
E-mail: yee@ill.fr

Human transthyretin (TTR) is a 55 kDa homotetramer plasma transport protein for thyroxine T4 and for retinol, through the association with retinol binding protein, in the blood and cerebrospinal fluid. TTR mutants have been implicated in familial amyloid polyneuropathy (FAP), a life-threatening multisystem disorder characterised by extracellular depositions of amyloid fibrils. It is an irreversible and progressive disease and is fatal within 10 years of onset. There are currently more than 80 pathogenic mutations reported for TTR. These mutations alter the protein stability leading to tetramer dissociation and favouring an abnormal monomeric structure, which in turn polymerises into unknown intermediates and finally into amyloid fibrils.

The crystal structures for a large number of stabilising and destabilising mutants have been solved using X-ray over the years. However they have been found to be strikingly similar, thus suggesting that gross structural differences cannot explain the wide phenotypic variations between mutated TTRs. Neutron protein crystallography is a powerful tool that strongly complements X-ray structural studies by revealing key details of hydrogen atom interactions within the protein. We have collected high-resolution neutron data from two TTR mutants – S52P, a highly unstable mutant, and T119M, a superstable mutant that is resistant to amyloid formation. By comparing the structures of the mutants with that of the WT, we have identified key water molecules in each monomer, explaining higher stability of monomer A. We have also been able to locate specific regions in the S52P structure which are highly destabilised, based on the susceptibility to H/D back-exchange. Combining neutron crystallography, native mass spectrometry and other biochemical analyses, we have gained new insights into TTR tetramer stability and amyloid formation mechanism.

[1] Haupt et al. (2014). IUCrJ 1, 429-438.
[2] Yee et al. (2017). PhD thesis, Keele University, UK.

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