Contribution ID: **42** Type: **Poster Presentations**

Targeting transthyretin amyloidosis: Neutron and X-ray diffraction analysis of a pathogenic protein

Tuesday, 17 November 2015 18:32 (2 minutes)

Transthyretin (TTR) amyloidosis is the most common hereditary form of amyloidosis that is characterised by extracellular deposition of insoluble amyloid fibrils derived from misfolded protein in one or more organ systems in the body. It is an irreversible and progressive disease and is fatal within 10 years of onset. Autosomal dominant mutations in the TTR gene 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. [1,2]

Up to date, around 200 X-ray crystal structures are available for TTR, but there is no consistent model to conclude the molecular assembly of the fibril building blocks and the triggering factors for this process. 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. Looking at the differences in hydrogen bonding, protonation states and hydration of two TTR mutants – S52P and T119M, which play opposite roles in the protein stability, will provide key insights into how they destabilise the tetramer and promote amyloidotic aggregation. Neutron analysis of the TTR in complex with various ligands will also provide useful information for improved drug design for the treatment of TTR amyloidoses.

References

[1] - A.M. Damas, M.J. Saraiva, J. Struc. Biol. 130, 290-299 (2000).
[2] - L.H. Connors, A. Lim, T. Prokaeva, V.A. Roskens, C.E. Costello. Amyloid 10, 160-184 (2003).

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Session Classification: Poster Session

Track Classification: Main