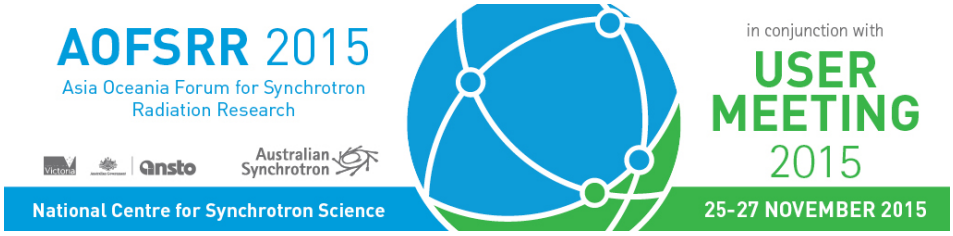

Contribution ID : **134** Type : **Poster**

STRUCTURAL CHARACTERISATION OF THE RETROMER COMPLEX AND ASSOCIATED SORTING NEXINS

Friday, 27 November 2015 13:30 (45)

Retromer is a protein complex that plays a central role in endosomal traffficking. Recently, retromer dysfunction has been linked to several neurological disorders including Alzheimer's and Parkinson's diseases. The classical mammalian retromer complex consists of a heterotrimeric cargo recognition sub-complex (VPS26, VPS29 and VPS35) associated with a dimer of proteins from the SNX–BAR sorting nexin family that drives membrane deformation and tubulation. By recruiting the cargo-selective sub- complex to the forming tubules, the SNX–BAR coat complex mediates the retrograde transport of proteins from endosomes to the trans-Golgi network. Recent studies, however, have highlighted the functional diversity of retromer and identification of new interacting proteins has revealed that the role of retromer extends to aspects of endosome-to-plasma membrane sorting and regulation of signalling events. Emerging evidence indicates that cargo specificity is mediated by specific sorting nexins. These include SNX3, involved in the trafficking of the Wntless/MIG-14 protein, and SNX27, a PX-FERM protein that mediates the retrieval of the β2-adrenergic receptor. We have acquired crystallographic and small angle scattering data to determine how the core cargo recognition sub-complex assembles and to characterise the retromer-associated sorting nexins. We are using this structural information in combination with biochemical and biological studies in a synergistic approach to understand retromer-mediated endosomal protein sorting. The retromer complex is conserved across all eukaryotes and we are also currently exploring the structure and function of these proteins in zebrafish and *Chaetomium thermophilum*.

Keywords

retromer, sorting nexin, small angle scattering, x-ray crystallography

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Session Classification : Poster Session 2

Track Classification : Structural Biology