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Structural characterisation of the retromer complex and associated sorting nexins

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Retromer is a peripheral membrane protein complex that plays a critical role in a broad range of physiological, developmental and pathological processes including Wnt signalling, toxin transport and amyloid production in Alzheimer's disease. The mammalian retromer complex consists of a core 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 molecular and functional diversity of retromer and the identification of new interacting proteins has revealed that the role of retromer extends to 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 β -2-adrenergic receptor.

Using the MX and SAXS/WAXS beamlines at the Australian Synchrotron, we have acquired structural data to determine how the core cargo recognition sub-complex assembles and to characterise the retromer-associated sorting nexins. We are using this information in combination with biochemical and biological studies to understand retromer-mediated endosomal protein sorting and how this fascinating protein complex contributes to a diverse set of cellular processes.

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