Structural insights into the cargo binding specificity of the retromer complex

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Retromer is a protein coat that mediates endosomal protein sorting and trafficking. It assembles on endosomes and forms tubular vesicles that return specific transmembrane proteins to the plasma membrane or to the *trans*-Golgi network. Therefore, the rescued cargo proteins avoid the lysosomal degradation pathway. Retromer's cargo includes cellular transmembrane proteins such as, signaling receptors, ion channels, transporters or enzymes. Defects in retromer impair various cellular processes and underlie some forms of Alzheimer's disease and Parkinson's disease. The retromer complex comprises a VPS26-VPS29-VPS35 heterotrimer and various combinations of sorting nexin (SNX) proteins that contribute to membrane recruitment and formation of recycling tubules. We published recently an X-ray crystallographic analysis of a four-component complex comprising the VPS26 and VPS35 subunits of retromer, the sorting nexin SNX3, and a recycling signal from the divalent cation transporter DMT1-II. This analysis identifies a binding site for canonical recycling signals at the interface between VPS26 and SNX3. To further analyse the cargo binding we have solved the structure of retromer with other cargo proteins. These interactions have been validated by isothermal titration calorimetry and mutational analysis. The results presented here reveal the molecular details of the cargo binding specificty of the retromer complex for the canonical recycling signal.

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