retrieval of the alzheimer's amyloid precursor protein from the endosome to the TGN occurs via the retromer and is dependent on protein phosphorylation

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In cells, retrograde transport of several transmembrane proteins from endosomes to the trans-Golgi network (TGN) occurs via Rab 5-containing endosomes, mediated by clathrin and the recently characterized retromer complex. This complex and one of its putative sorting receptor components, SorLA, were reported to be associated with late onset Alzheimer's disease (AD). Researchers at the Centre for Cell Biology are able to show for the first time the formation of an APP (Alzheimer's Amyloid Precursor Protein) – and retromer-containing protein complex. Thus providing a physiologically significant means of APP retrieval from the endosome to the TGN. Furthermore, protruding tubules near the TGN containing APP, were shown to occur, again supporting an association with a retromer-mediated pathway.

From a regulatory perspective, mimicking APP phosphorylation at residue S655, within the APP 653YTSI656 basolateral motif, enhances APP retrieval via a retromer-mediated process. Additionally, the phosphomimetic APP S655E displays decreased APP lysosomal targeting, enhanced mature half-life, and decreased tendency towards Abeta production. VPS35 downregulation impairs the phosphorylation dependent APP retrieval to the TGN, and decreases APP half-life.

In essence, we reported for the first time the importance of APP phosphorylation on S655 in regulating its retromer-mediated sorting to the TGN or lysosomes. Significantly, the data are consistent with known interactions involving the retromer, SorLA and APP. Further, these findings add to our understanding of APP targeting and potentially contribute to our knowledge of sporadic AD pathogenesis representing putative new targets for AD therapeutic strategies.