PHOSPHORYLATION OF THE ALZHEIMER'S AMYLOID PRECURSOR PROTEIN MODULATES ITS RETROMER-MEDIATED RETRIEVAL FROM THE ENDOSOME TO THE TGN

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Introduction: Accumulation of Abeta peptide is central to AD. It results from proteolysis of APP by β- and γ- secretases and is associated with endocytic compartments. Although APP endosomal trafficking and sorting are predicted to modulate Abeta levels, the molecular mechanisms underlying endocytic APP retrieval to the trans-Golgi network (TGN) were to date not identified. The retromer complex and one of its putative sorting receptors SorLA are potential molecular players, but the formation of an APP/retromer-containing complex has not been elucidated.

Aims: To characterize the molecular components of endocytic APP retrieval to the TGN, and its regulation by APP phosphorylation.

Methods: The endocytic APP-GFP pathway was characterized by monitoring and modulating the trafficking and processing of APP-GFP S655 phosphomutants and one of the retromer components, VPS35.

Results: APP is present in clathrin-, Rab 5- and VPS35-endocytic vesicles targeted for the TGN. These vesicles often tubulate, supporting a retromer-mediated pathway. APP binds to the retromer subunit VPS35 with SorLA. Further, APP phosphorylation at S655, within the 653YTSI656 basolateral motif, enhances APP retrieval while decreasing APP lysosomal targeting. This leads to enhanced mature APP half-life and decreased Abeta production. VPS35 siRNA downregulation impairs both the phosphorylation-dependent APP retrieval to the TGN, and APP half-life.

Conclusions: APP S655 phosphorylation modulates its retromer-mediated endosomal to TGN retrieval and this adds to our understanding of APP targeting via a pathway whose misregulation is associated with the major late onset AD form. Consequences to CTF and AICD production will also be addressed.