Alzheimer's disease: insights into gamma-secretase

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γ-Secretase is critically involved in the production of amyloid β-peptide, the principal component of amyloid plaques in the brains of Alzheimer´s disease patients. γ-Secretase is a complex composed of Presenilin, Nicastrin, Aph1 and Pen2. The complex is assembled in the endoplasmic reticulum (ER) and is transported through the Golgi to its site of activity, the plasma membrane and endosomes/lysosomes. We previously proposed a mechanism of complex assembly control by which unassembled subunits are retained in the ER and only the fully assembled complex is permitted to leave the ER (Kaether et al, EMBO 23, 4738-48). Retention/retrieval of unassembled subunits requires specific signals and we have identified two such signals in PS1 and Pen2. We furthermore identified Rer1 as a protein that is involved in retention/retrieval of unassembled Pen2 to the ER. Direct binding of unassembled Pen2 to Rer1 is mediated by the first transmembrane domain of Pen2 and a conserved asparagine in this domain is required. Downregulation of Rer1 leads to increased surface localization of Pen2, whereas overexpression of Rer1 stabilises unassembled Pen2. Rer1 is the first identified interaction partner of mammalian transmembrane-based retention/retrieval signals.