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Science

Alzheimer's disease is neurodegenerative pathology, histologically characterized by the deposition of amyloid plaques, composed mainly by the amyloid β ($A\beta$) peptide, and intracellular tangles, composed by hyperphosphorylated tau proteins.

The $A\beta$ peptide derives from the (two steps) proteolytic amyloidogenic pathway of the amyloid precursor protein (APP).

The APP is previously cleaved by β -secretase, and subsequently by γ -secretase, releasing, as final reaction products, the $A\beta$ peptide and the APP intracellular domain (AICD).

The γ -secretase is a tetrameric complex that cleaves many type of I transmembrane proteins, including APP, Notch and syndecan 3. It is composed by nicastrin, (Nct), anterior pharynx defective 1 (Aph-1), presenilin enhancer 2 (Pen-2) and presenilin (PS) subunits: if the first three subunits are required for the stability and maturation of the secretase, the presenilin is the enzymatic core of the secretase. It is a multispanning membrane protein characterised by an aspartyl proteolytic activity. missense mutations in the PS genes (PS1 or PS2) are a major cause of familial Alzheimer's disease (FAD).

Recently has been noticed that APP, PS and Aph-1 proteins are characterised by the presence of a highly conserved GXXXG motif, respectively in the juxtamembrane/transmembrane, TM8 and TM4 domains.

The GxxxG motif is a frequently occurring sequence of residues that is known to favor helix-helix interactions in membrane proteins. It has been shown to promote close apposition and association of transmembrane (TM) domains.

Recently it has demonstrated that the proper orientation and dimerization of the APP transmembrane domains and the promotion of the $A\beta$ release are deeply influenced by the presence of the GxxxG motif.

The aim of this project is precisely to analyze the role of these particular TM motifs in i) the functional assembly of the gamma-secretase ii) the binding of the substrates to the gamma-secretase iii) the physiopathological consequence of this mechanism in terms of processing and particularly Abeta production.