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NLM Citation: Dean L, McEntyre J, editors. Coffee Break: Tutorials for NCBI Tools [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 1999-. The neighborhood of Alzheimer's amyloid precursor protein: new clues on Alzheimer's pathology from other proteins linked to amyloid plaque formation. 1999 Sep 15.
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

The neighborhood of Alzheimer's amyloid precursor protein

new clues on Alzheimer's pathology from other proteins linked to amyloid plaque formation

Created: September 15, 1999.

The identification of amyloid-rich plaques has long been a diagnostic tool for pathologists investigating Alzheimer's disease (AD). The plaques are formed through the accumulation and aggregation of beta-amyloid peptides derived from the amyloid precursor protein (APP; see figure) and are characteristically found in the brain parenchyma and around blood vessels. Although it is clear that APP plays a role in AD pathology, the normal function of APP is currently unknown.

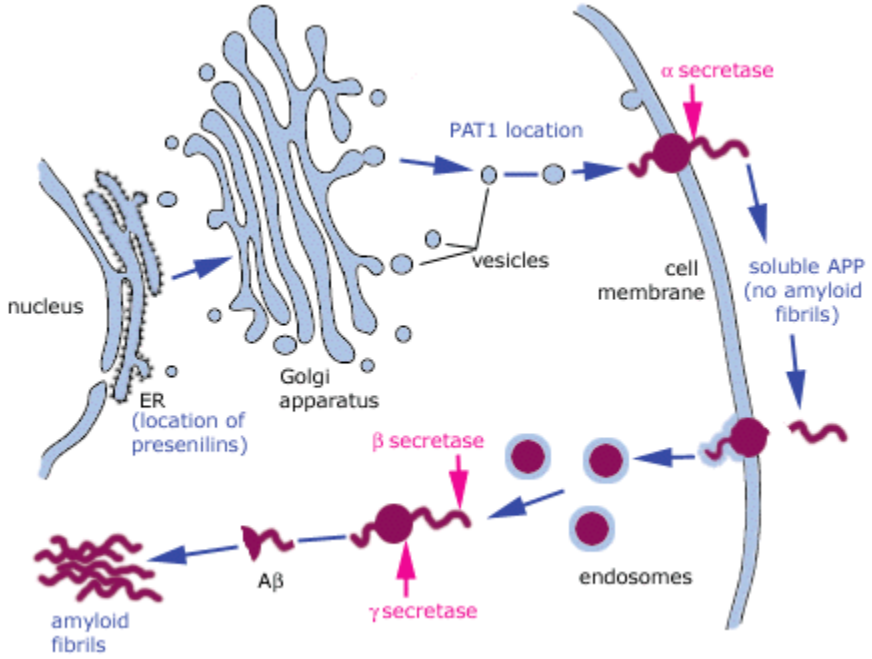
Mutations in APP itself are linked to only a small fraction of familial AD cases. However, more recently, mutations in two more genes have been linked to a much larger subset of familial AD cases, presenilin-1 (PS-1) and presenilin-2 (PS-2).

Similar to APP, the presenilins are also membrane-spanning proteins but are found mostly in the endoplasmic reticulum, whereas APP is found distinctly on the basolateral surface of cells. Mutations in the presenilins increase the production of beta-amyloid, suggesting that they influence the metabolism of APP in some way. This could be through a direct interaction but could also be a result of an indirect effect, perhaps on the trafficking of APP as it travels from its site of synthesis on the ribosome, via the endoplasmic reticulum and Golgi apparatus, to the cell surface, or as it is internalized from the cell surface for break down or recycling (see figure).

Several APP-interacting proteins have been reported recently, including the presenilins themselves and adaptor proteins, which could act as a scaffold for intracellular signalling molecules. Another protein, called PAT1, has also been found to bind to the cytoplasmic tail of APP. PAT1 appears to recognize and bind to a specific signal sequence, called the basolateral sorting sequence, which ensures that APP is transported to the basolateral membrane.

As it turns out, PAT1 bears more than a passing resemblence to kinesin light chain, found by searching the sequence database. Kinesins are motor proteins and help transport molecules around cells by connecting the cargo molecule (in this case, APP) to microtubules, which provide a network of "railroad tracks" on which to shuttle molecules around the cell. Combining this result with other experimental evidence, it seems likely that PAT1 plays a role in sorting and delivering APP to the right place in the cell.

Although the roles of APP, the presenilins, and other molecules implicated in AD still require significant investigation, the characterization of genes and proteins that are linked to amyloid plaque formation may help build a picture of the events that lead to AD. Not least, the identity of the enzymes that cleave APP and how the presenilins exert their effect on APP would provide insight into the most common neurodegenerative disease in the world.



The trafficking and metabolism of amyloid precursor protein (APP).
After synthesis on the ribosome, APP enters the endoplasmic reticulum (ER) and is transported via the Golgi apparatus to the cell membrane on the basolateral surface of the cell. The presenilins, which are thought to play a role in APP metabolism, reside mainly in the ER. PAT1, the subject of this article, may attach APP to the microtubules — the 'railroad tracks' of the cell — to assist in transporting APP to the membrane. The generation of the toxic beta-amyloid peptides requires that APP on the cell surface enters a cellular recycling program, after which two cleavages occur, one in the extracellular domain and one in the transmembrane domain. However, which enzymes carry out these cleavages, where in the cell they occur, and how the events are regulated, are not known. An alternative pathway to beta-amyloid formation involves another cleavage by an enzyme termed 'alpha-secretase', which is thought to be located near the plasma membrane. If this second pathway is triggered, beta-amyloid can not be formed, so amyloid plaques do not accumulate.

Search PubMed for APP and the presenilins.

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Find articles that discuss both amyloid precursor protein and the presenilins

Search PubMed for kinesin-related links to Alzheimer's disease.

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Are there other kinesin-related links to Alzheimer's disease?

Use BLAST to search for PAT1.

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What can PAT1 do for amyloid precursor protein?