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Amyloid Aggregates, Presenilins, and Alzheimer's Disease

Ralf Baumeister* and Stefan Eimer

Alzheimer's disease is today the most common cause of neurodegenerative death in the western world. The disease is characterized by two fundamental events, the accumulation of insoluble fibrillar aggregates of β-amyloid peptide (Aβ) and the degeneration and death of neurons in the brain regions that are concerned with learning and memory processes. Abnormal protein deposition is also a shared characteristic of other age-related neurodegenerative disesases, such as Parkinson's disease, Huntington's disease, and the Prion diseases. There is increasing evidence that the mechanism of this aggregation may be similar in each of these diseases.[1] Several recent studies have advanced our understanding considerably of the molecular and cellular mechanisms that cause the disease. The purpose of this article is to summarize recent results.

The Biochemistry of APP Processing and Amyloid Aggregation

The central role in the pathogenesis of Alzheimer's disease is played by a small, 40 – 42 amino acid long, four kDa peptide called Aβ. Aβ is derived from the 695 – 770 amino acid long amyloid precursor protein (APP) by various proteolytic steps that are thought to take place in several intracellular compartments[2] (Figure 1). The detailed mechanism of Aβ production from APP, the exact localization of the three proteases involved, and the functions of Aβ and APP are not yet understood (for review articles see refs. [3, 4]). The 40 amino acid peptide Aβ40 is the predominant form that is produced during the metabolism of APP. Under pathological conditions the production of a 42 amino acid variant (Aβ42), normally a minor product, is enhanced.

Aβ40 is kinetically inert for several days in solution. In the disease state it is converted into a fibrous form, which is relatively resistant to chemical denaturing or proteolytic digestion.[5] This conversion is mediated by a change in the three-dimensional structure of Aβ40 and results in an increase in the hydrophobicity of the peptide. The peptide then aggregates and forms an ordered fibrillar morphology. The structural properties of the Aβ aggregates suggest that, in contrast to amorphous precipitates, their formation is seeded and involves polymerization from a nucleus.[1, 6] This process is very slow because of the high entropy of intermolecular interactions.[6] For this reason, the sporadic forms of Alzheimer's disease, which comprise the fast majority of clinical cases, occur late in life (usually between the ages of 75 and 85), although Aβ can be detected much earlier. Another Aβ variant, Aβ42, is more hydrophobic and may produce the pathogenic seed in the development of the disease.[6] Aβ42 is highly aggregable and is the predominant form of Aβ in senile plaques.[2] Overexpression of APP increases the amount of Aβ40 and Aβ42 and results in faster aggregation.[7] It is in this context interesting to note that patients with Down's syndrome, who have an additional copy of chromosome 21 on which the APP gene is located, invariantly develop symptoms of Alzheimer's disease and develop them significantly earlier.[3]

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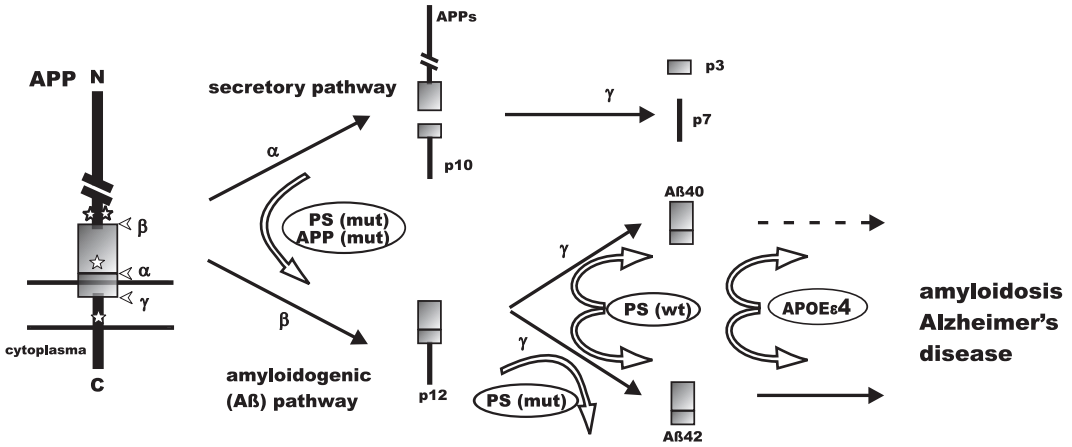

Figure 1. Flowchart of APP metabolism. The factors that affect the processing of APP and the onset of the disease are shown. Left: Schematic representation of APP with the relative positions of mutations indicated by asterisks. The position of the Aβ region is shown by a box. p3, p7, p10, p12 = APP cleavage products with molecular weights of 3, 7, 10, and 12 kDa size, respectively; α, β, γ = secretases involved in the cleavages; mut: mutation; wt = normal type.

Modulators of Aggregation

The first susceptibility gene identified for the common, sporadic form of Alzheimer's disease was the *apoe* gene, which encodes a protein involved in cholesterol transport.[8] People with a particular variant of the APOE protein (the ε4 isoform), have an increased risk of developing sporadic late-onset Alzheimer's disease.

Convincing evidence that the *apoe* gene directly affects Aβ deposition was provided by Paul's research group.[9] They crossed transgenic mice overexpressing a human APP variant, which exhibits strong Aβ and amyloid deposition, with *apoe*-knock-out mice. The progeny from this cross showed a dramatic reduction of Aβ deposits, which indicates that the main contribution of the APOE protein is to promote Aβ fibril formation. Another recent report suggests that other polymorphisms in the transcriptional regulatory region of the *apoe* gene might also be associated with an increased risk of Alzheimer dementia, even in the absence of the ε4 isoform.[10]

The APOE protein may be considered a modifier of Alzheimer's disease since APOE variants do not result in an earlier onset of the disease but promote the late stages of the disease. In contrast, mutations in the three identified loci on chromosomes 2, 14, and 21 cause an heritable form of the disease (FAD, familial Alzheimer's disease) that generally leads to an earlier onset and faster progression of the disease relative to the sporadic cases. All mutations have been shown to promote the seeding of amyloid aggregates. The first gene identified encodes APP itself.[2, 11] The various mutations affect the overproduction of Aβ42 or an overall increase in Aβ secretion. However, these mutations are rare and were found only in a small patient group worldwide. The vast majority of FAD cases correlate with two genes, which encode transmembrane proteins, which been designated presenilin-1 (PS1) and presenilin-2 (PS2). Mutations in PS1 and PS2 are responsible for the most aggressive clinical forms of Alzheimer's disease, with a mean age of onset of approximately 45 and 52 years, respectively. Recent research on the function of the presenilins provides an important clue to understanding the mechanism of the disease.

Presenilin Mutants and Amyloid Formation

PS1 and PS2 encode proteins of 467 and 448 amino acids, respectively, which are about 67 % identical in their primary sequence.[12] The presenilins are highly conserved in evolution, and have been identified in nematodes (*Caenorhabditis elegans*), fruit flies (*Drosophila*), clawed frogs (*Xenopus*), Zebrafish, and mammals.[13] Several research groups have recently analyzed the topology of PS1[14, 15] and its *C. elegans* homologue SEL-12.[16] The amino and carboxy termini of both proteins have a cytoplasmic localization and is followed by six transmembrane (TM) domains and a large, hydrophilic loop, which again protrudes into the cytoplasma of the cell (Figure 2). It is very likely that the other presenilins adopt similar structures based on the sequence conservation.

The phenotypes associated with mutations in the presenilin genes are most informative for understanding their function in the nervous system. To date, more than 35 mutations in the PS1 gene and two mutations in the PS2 gene have been isolated from FAD patients, which supports the key role of the presenilins in the mechanism of the disease.

With the noteworthy exception of PS1Δ10, a splice variant which eliminates exon 10 (but results in a mutation of a highly conserved serine to cysteine at the splice site in TM6), all mutations that have been isolated from patients are single amino substitutions. No mutations have so far been isolated from FAD patients that result in frameshifts or premature translational stops and cause truncations of the carboxy terminal. This suggests that severe structural or functional defects cannot be tolerated in the presenilins. The embryonic lethality of presenilin-knock-out mice supports this view. One plausible explanation would be that the FAD mutations cause subtle defects, since they do not have embryonic phenotypes. More than 80 % of the mutations occur in amino acids that are conserved in presenilins of different species.[17] The local-

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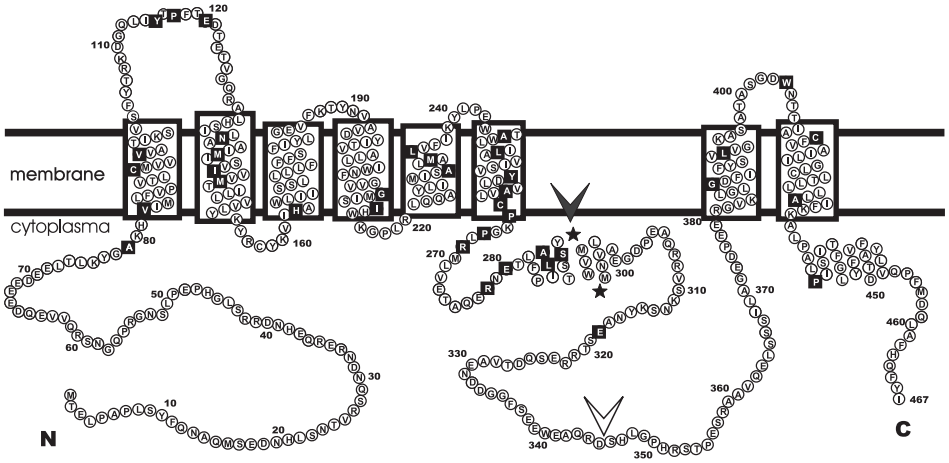

Figure 2. The structure of PS1. The eight transmembrane domain model of PS1 structure is depicted as suggested by Li et al.[16] Putative TM domains are boxed. Sites of proteolytic cleavage by presenilinase (black arrowhead, exact position: black asterisk) and caspase (white arrowhead) are indicated. Positions of FAD mutations in PS1 are boxed.

ization of these mutations suggests that TM2 and the two large hydrophilic loops are most critical for PS1 function.

Proteolytic Processing of Presenilins

Only a minor amount of the endogenous presenilin proteins can be isolated as full-length proteins. The most abundant fragments identified are an approximately 27–28 kDa amino-terminal fragment (NTF) and an approximately 18–20 kDa carboxy-terminal fragment (CTF).[12] PS2 is proteolytically cleaved into two stable cellular polypeptides of about 20 kDa and 34 kDa.[18] The cleavage in the large cytoplasmic loop is obviously tightly regulated, since overproduction of PS results in the accumulation of the full-length protein, but not of the proteolytic fragments. The resulting fragments are very stable and interact with one another. Since they are found in complexes with a higher molecular weight, they probably bind other currently unidentified proteins as well. Considerable effort was made to identify whether presenilinase cleavage is a functional requirement,[19] a stable degradation intermediate,[20, 21] or even a preparation artifact.[22] This question has not yet been fully resolved. Lack of cleavage is probably not a central feature of pathogenesis in FAD patients, since little, if any, full-length PS1 is observed in brain tissue of patients carrying PS1 mutations.[23]

The presenilins PS1 and PS2 are also proteolytically processed by proteases of the caspase superfamily (proteins that take part in programmed cell death, apoptosis).[18] This process generates a larger NTF and a smaller CTF if full-length presenilin is the substrate, or only a smaller CTF if the conventional CTF is the substrate (Figure 2). There was a lot of excitement last year when Tanzi's research group reported that the PS2 mutation N141I enhances the intracellular concentration of the alternative CTF derived by caspase-cleavage.[24] It was postulated that apoptosis-mediated cleavage may be required for the effect of mutant PS proteins on abnormal Aβ processing. Indeed, a functional involvement of PS in apoptosis had been reported before. However, a combined effort of three research groups showed recently that the inhibition of caspase cleavage does not affect Aβ generation. Moreover, mutation of the caspase cleavage site prevented the apoptotic proteolysis, but did not affect the biological activity of human PS1 and PS2 in *C. elegans*.[25]

Presenilins and the Metabolism of APP

Mutant presenilin proteins, like mutant APP itself, affect proteolytic processing of APP (Figure 1). Mutations in all three genes enhance the processing pathway that results in an increased production of the 42 amino acid variant Aβ42, whereas Aβ40 levels are not affected.[12] Since this variant aggregates much faster than Aβ40, these results strongly support the model of Aβ42 being the key component involved in the disease mechanism. All PS1 and PS2 mutations analyzed to date increase the Aβ42 levels significantly. These results strongly support the central role of Aβ formation and presenilin function in the disease mechanism.

How are the presenilins involved in the proteolytic processing of APP? It has long been thought that proteolysis of APP mostly occurs at or near the cytoplasmic membrane (the non-amyloidogenic or secretory pathway, upper part in Figure 1) or during reinternalization (Aβ generating pathway, lower part in Figure 1).[26] In contrast, the presenilins are located mostly in the membranes of the endoplasmic reticulum (ER) and the early Golgi apparatus. However, last year several research groups identified intracellular Aβ formation and showed that the ER is the first compartment where Aβ42 accumulates.[27–29] These results also suggest that the proteolytic cleavage at the carboxy terminus of Aβ40 and Aβ42 are accomplished by different enzymes and/or by a different intracellular localization of the enzyme(s) involved. These data provoked an exciting new model that explained how the presenilin can affect APP processing. The localization of the presenilin in the ER and Golgi membranes suggests that they are in a perfect position to control the transport and/or trafficking of APP. There is indeed support for such a role: the presenilin SPE-4 in the nematode *C. elegans* controls the sorting and protein trafficking in specialized organelles.[30] In addition, several recent publications report that there may be direct binding of PS1 and PS2 to the immature form of APP in

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the ER.[31, 32] Although these interactions, identified through co-immunoprecipitation studies and in the yeast-two-hybrid system, nicely fit into this model, attempts to reproduce these results in other research groups have failed.[33] Nevertheless, the generally observed increase in Aβ42 production in the presence of presenilin mutants indicates that APP and presenilins at least interfere functionally.[34] It came as a big surprise that in cells of PS1-knock-out mice the Aβ40 and Aβ42 levels dropped by 80%, whereas neurons in FAD patients have increased levels of Aβ42.[35] Although the subcellular localization of these fragments could not be determined, the most obvious interpretation is that the presenilins themselves have protease (γ-secretase, see Figure 1) activity or may regulate the activity of this protease. However, these results are also compatible with PS1 having a role in the intracellular compartmental transport of membrane proteins. In accordance with the latter model a lack of PS1 could redirect APP sorting and transport from the ER through compartments that lack γ-secretase activities. It is puzzling to see that both Aβ40 and Aβ42 are equally affected by PS mutants. Additional work is clearly required to solve these discrepancies, and eventually the presenilins might even serve as a therapeutic target for Alzheimer's disease. A significant decrease of presenilin activity, accomplished by either reducing the expression levels or by interfering with the processing, is suggested to reduce the Aβ production and, thus, the aggregation of plaque formation in the brain.

Biological Function of Presenilins

To fully understand the role of presenilins in Alzheimer's disease it is essential to know more about their biological function. The few data we have are derived from work carried out on the nematode *C. elegans* and in mice. The SEL-12 mutants *C. elegans* suggest that the presenilins play a role in the signal transduction of the Notch transmembrane receptor, a pathway through which adjacent cells communicate.[36] The human presenilins are also linked to the Notch pathway, since human PS1 and PS2 are functional in *C. elegans*[20, 21] and Notch activity is strongly reduced in PS1-knock-out mice.[37, 38] It is not clear, at this point, whether the PS proteins function in the signaling pathway or activity of Notch, or, at an earlier step, in the sorting and transport of Notch from the ER to the membrane. Since SEL-12 mutations seem to influence the function of other secreted transmembrane proteins as well,[39] which supports the latter model, we suggest that the PS proteins play a more general role in the cell.

Outlook

Significant progress has been made in the past couple of years to understand the molecular and genetic basis of Alzheimer's disease and FAD. The fundamental importance of Aβ42 and the presenilins as key players in the disease mechanism has been substantiated. Work in the following years will most likely concentrate on the identification of new genes and interactors to close the remaining gaps in the story. The nematode *C. elegans* model as a biological assay system to identify additional components required for presenilin function, and the availability of several mouse models for Aβ aggregation will provide additional clues and maybe targets for therapeutic intervention in the near future.

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