"It is widely believed that the cascade of events leading to [β-]amyloid accumulation is at the root of AD pathogenesis and the ensuing dementia."

Roher A., 2003[7]

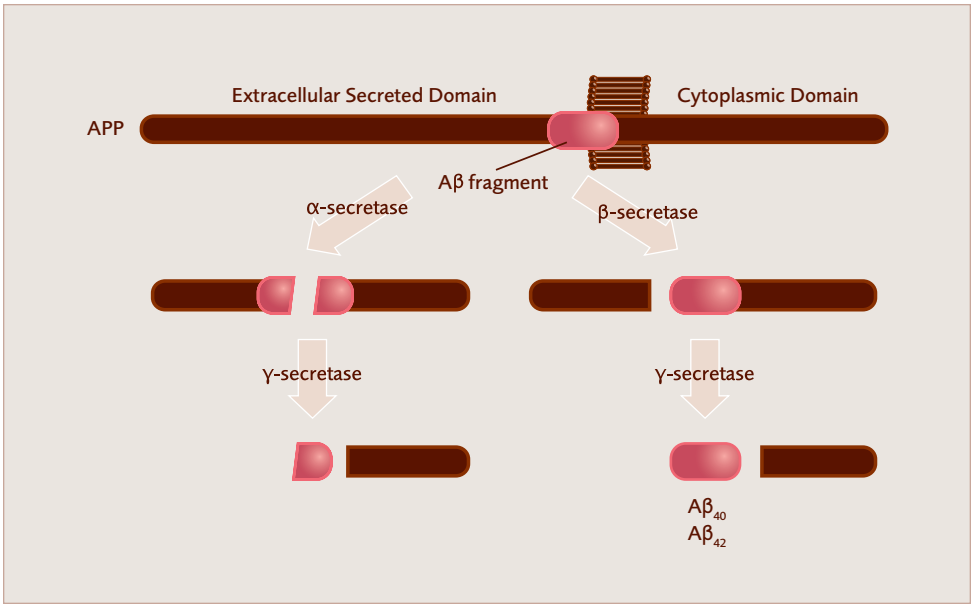
Understanding the β-amyloid pathway

There has been a long-standing difference of opinion about whether the Aβ plaques are a cause of AD, or merely the result of the degeneration of neuronal tissue.

Elucidation of the biochemistry of Aβ synthesis and clearance has, however, provided evidence for a causative role for Aβ in AD. A great deal of evidence for such a role for Aβ has also come from the field of genetics. Transgenic mice with a mutant form of the human APP gene show both Aβ deposits and behavioral abnormalities[8]. Down's syndrome patients, who carry an extra copy of the APP gene (which is located on chromosome 21), show Aβ deposition as early as age 12, and often develop dementia by their mid-thirties[8]. In a small number of AD cases (1-2%), the disease is known to be directly associated with specific genetic mutations[3]. Mutations resulting in AD have been identified on three separate genes—the APP gene on chromosome 21 (10 mutations), the presenilin 1 (PS1) gene on chromosome 14 (90+ mutations) and the PS2 gene on chromosome 1 (6+ mutations)—each of which directly affects different points along the pathway that leads to the production of Aβ[9]. The APP gene is responsible for the production of amyloid precursor protein (APP), while it is now believed that γ-secretase, mediates the final step in Aβ synthesis[2]. This genetic "smoking gun" reinforces the primary role of Aβ in the pathogenesis of AD, a role that has become increasingly recognized by the research community.

Further evidence has come from studies of the polymorphic apoE gene. The most common apoE genotype (apoE3) plays a role in cholesterol metabolism and is believed to be involved in clearing Aβ from the brain[10]. The presence of apoE4 alleles is associated with higher levels of Aβ within the brain, suggesting impaired clearance of Aβ in the presence of apoE4 protein. People with one or both apoE4 alleles have been shown to be at higher risk of AD. This again indicates a direct link between Aβ levels and AD[11].

Figure 4: APP and its cleavage



Understanding the β-amyloid pathway

It is not known whether the accumulation of Aβ precedes the pathological intercellular formation of hyperphosphorylated tau. However, there is increasing supporting evidence, that in AD, the tau alteration follows amyloid plaque formation and deposition rather than the other way around[11]. This is supported by animal studies where transgenic mice (APP + tau) developed neurofibrillary tangles (NFT) as a consequence of Aβ deposition. Additionally, in families with tau mutations, widespread NFT were observed in the absence of amyloid deposits—meaning that high levels of intercellular tau will not necessarily lead to Aβ plaque formation.

Aβ production

Aβ production begins with amyloid precursor protein (APP), a transmembrane protein found in healthy neurons, believed to be neuroprotective. APP is initially cleaved by either α-secretase or β-secretase, and then by γ-secretase. The more common peptide end products of the α-secretase pathway are soluble and do not result in the formation of Aβ. Among the final products of the β-secretase pathway, however, are several β-amyloid variants, $Aβ_{40}$ and $Aβ_{42}$, consisting of 40 and 42 amino acids respectively (Figure 4). The less common $Aβ_{42}$ is more toxic than $Aβ_{40}$, and has a tendency to aggregate more rapidly into small clusters, or oligomers and ultimately into fibrils and plaques (Figures 3–6). The oligomers are believed to be very toxic to neurons. Several mechanisms of cell damage have been proposed, e.g. activation of apoptosis, depletion of presynaptic APP leading to loss of synaptic transmission, hyperphosphorylation of tau protein causing microtubule collapse, and stimulation of microglia, eliciting a strong inflammatory response[6].