The α, β, γ's of Alzheimer's Disease

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Alzheimer's Disease (AD) is a progressive neurodegenerative disease characterized by memory loss, reasoning impairment, and muscle rigidity and weakness. It is the eighth highest cause of death in the United States, affecting primarily the elderly population. All AD patients have in their brains intracellular protein aggregates called neurofibrillary tangles (NFTs) and extracellular protein deposits named β-amyloid plaques in common. There are two main categories of AD, familial and sporadic. Sporadic, while not fully understood is hypothesized to arise during an individual's life from environmental factors or spontaneous gene mutations. This review focuses on the familial, or inherited, type of AD. Currently evidence of three gene mutations are associated with the familial type: presenilin1, presenilin2, and the amyloid precursor protein (APP). Tau protein hyperphosphorylation leading to NFT formation, and APOE allele type are also integral parts of AD. Each mutation plays a very different role in the progression of AD. The β-amyloid plaques are a result of proteolytic cleavage of APP. The processing of APP is carried out by three secretases regulated by the presenilin genes. Current research focuses on the effects of various combinations of APOE alleles on AD susceptibility, cleavage of APP by α, β, and γ secretases, and the use of immunizations and drug therapy to the combat the fatal disease.

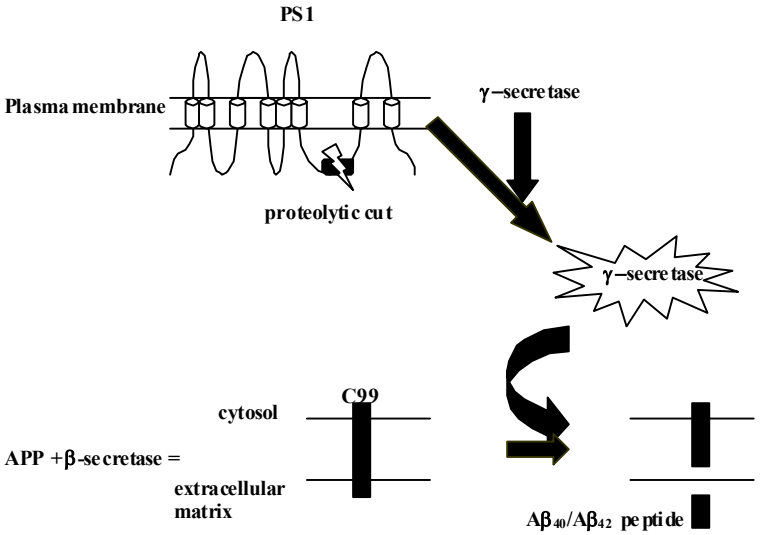

Figure2: Aβ formation. The proposed pathway for Aβ peptide formation via proteolytic cleavage by γ-secretase in AD patients. It is known that cleavage of the transmembrane protein PS1 at the site indicated is necessary for the secretase's activation; however it is not known whether γ-secretase is an enzyme different from PS1 or if γ-secretase is actually PS1.