REVIEW

GENETIC BASIS OF NEURODEGENERATION IN FAMILIAL ALZHEIMER’S DISEASE

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Alzheimer’s disease (AD), the most common form of dementia, is characterized by two types of brain lesions, referred to as senile plaques and neurofibrillary tangles. Moreover, neuronal cell loss and synaptic degeneration appear in affected regions of the brain. A series of endoproteolytic cleavages of the amyloid precursor protein (APP) controlled by α-, β-, and γ-secretases leads to a formation of non-amyloidogenic (the α-secretase pathway) and amyloidogenic (the β-secretase pathway) products which are essential for neurodegeneration. According to the “amyloid cascade hypothesis”, the accumulation of amyloid β (Aβ) peptides in the brain is a primary event in the pathogenesis of AD. One of the strong pieces of evidence supporting this hypothesis was the identification of pathogenic mutations within APP, presenilin 1 and presenilin 2 genes responsible for familial autosomal dominant AD. These mutations affect APP processing causing overproduction of Aβ42. Finding specific inhibitors of the Aβ42 generation is a major goal of AD drug development programs now and the key challenge for the treatment of the most devastating disease of human brain.

Key words: Alzheimer’s disease, amyloid precursor protein, β-amyloid, mutation, neurodegeneration, presenilins, secretases