Chapter 1
Molecular Neuropathology of Alzheimer Dementia and Therapeutic Approaches

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Alzheimer's disease (AD) is a neurodegenerative disorder of the central nervous system characterized by progressive loss of neurons in limbic and association cortices affecting almost all cognitive functions and memory. Additional neuropathological hallmarks of AD brains include large numbers of amyloid plaques (APs) containing fibers of Aβ peptides and neurofibrillary tangles (NFTs) consisting of overphosphorylated tau protein. Sporadic AD (SAD) is the most common form of dementia and accounts for more than 90 % of all cases. The etiology of SAD is complex and may be driven by both environmental and genetic factors. Presence of ApoE4 allele is the most important genetic risk factor for SAD although in the last 5 years additional genes were identified with smaller effects on the disorder. Several theories have been developed to explain the molecular basis of AD but none of these seems to offer a satisfactory explanation for the neurodegenerative phenotype of the disorder.

Familial AD (FAD) represents about 5 % of all AD cases. In contrast to sporadic AD, FAD is caused by specific mutations in several genes including those of the amyloid precursor protein (APP), presenilin1 (PS1) and presenilin2 (PS2). Currently over 200 FAD mutations have been mapped to PSs and about 20 to APP. PS proteins are important components of the γ-secretase system that processes cell surface proteins and receptors including APP. Importantly, γ-secretase processing of APP is involved in the production of Aβ peptides that aggregate to form the amyloid fibers used to define the disorder. In addition, γ-secretase stimulates production of peptides that function in cell signaling and gene expression, key events in neuronal survival. Thus, by inhibiting the activity of γ-secretase and production of signaling peptides FAD mutations may interfere with the flow of cellular information. In this keynote talk we will discuss mechanisms by which genetic mutations lead to neurodegeneration and dementia and will examine genetic and environmental factors involved in SAD. In addition, we will illuminate recent efforts for the development of second-generation diagnostics and therapeutics.

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