RESEARCH AND PERSPECTIVES IN ALZHEIMER’S DISEASE

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Presenilins
and Alzheimer’s Disease

With 17 Figures and 4 Tables
Molecular and biochemical studies of Alzheimer's disease have recently undergone a major revolution with the discovery of the presenilin genes. Since 1995 when these genes were first identified to carry defects responsible for up to half of early onset familial Alzheimer’s disease cases (Sherrington et al. 1995; Levy-Lahad et al. 1995), over 50 Alzheimer-associated mutations have been found in the presenilin genes, PS1 and PS2 (reviewed in Tanzi et al. 1996). Over 200 papers have been published regarding the characterization of the presenilins. Not since the amyloid β protein Precursor (APP) was isolated in 1987 (Kang et al. 1987; Goldgaber et al. 1987; Robakis et al. 1987; Tanzi et al. 1987) has the discovery of novel genes had such an impact on the field of Alzheimer’s disease research. To whit, five separate sessions at the 1997 Society for Neuroscience Meeting are devoted solely to studies of the presenilins. The presenilins genes have clearly taken the field of Alzheimer's disease research by storm and appropriately so since defects in these genes can cause Alzheimer's disease as early as in one’s late twenties.

One of the greatest revelations to arise from molecular studies of the presenilins is the finding that, like the familial Alzheimer’s disease mutations in APP, the mutations in the presenilin genes lead to increased production and secretion of the longer form of the Aβ peptide, Aβ42 (Scheuner et al. 1995), which seeds β-amyloid formation in the brain. The presenilins have also been implicated in the process of programmed cell death (apoptosis; Kim et al. 1997; Wolozin et al. 1997). At the more basic biological level, these proteins have been linked to the developmental pathway involving the Notch genes (Levitan and Greenwald, 1995). These and other findings have provided great clues to the roles of the presenilin in both health and disease. It is thus appropriate that the Fondation IPSEN organized a meeting in July of 1997 to bring together a group of leaders in the area of presenilin biology to discuss ideas regarding the biological function of the presenilins and how defects in these genes cause the earliest onset form of Alzheimer’s disease. An understanding of the mechanisms by which mutations in the presenilin genes cause neurodegeneration and dementia should greatly facilitate the development of novel strategies for treating Alzheimer's disease and related disorders.

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