Molecular Mechanisms of Dementia

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Preface

The past decade has witnessed a revolution in the attempts of scientists to understand the molecular basis of dementia. Although dementia, as defined by global cognitive decline involving gradual loss of memory, reasoning, judgment, and orientation, presents most commonly in the form of Alzheimer's disease (AD), an assortment of other less common disorders, such as prion and Pick's disease, can also lead to symptoms that are similar to those observed in patients with AD. The primary goal of *Molecular Mechanisms of Dementia* is to address the various mechanisms and multifaceted approaches currently being employed to more clearly delineate the etiological and pathogenic events responsible for the onset of dementia.

Perhaps the greatest boon to obtaining a clearer understanding of the causes of AD has come from genetic and molecular biological studies carried out over the past decade. At the genetic level, it has become increasingly clear that AD is a heterogeneous disorder that can be broadly classified into two categories. "Late onset" (>60 yr) cases, which account for the vast majority of AD, genetically involve "susceptibility" genes representing risk factors for the disease (e.g., inheritance of the ε4 allele of the Apolipoprotein E gene). In many cases, the susceptibility gene can act as a "modifier" that modulates the pathogenic cascade occurring subsequent to a separate etiological event "initiating" or "causing" the disorder. "Early-onset" (<60 yr) cases account for 15–20% of AD and appear to involve "causative" or "deterministic" gene defects sufficient to cause the disorder (e.g., mutations in the amyloid β protein precursor gene and the presenilin genes). Following the identification of gene defects associated with dementia, a logical next step involves attempts to establish cell culture-based models and transgenic animals as experimental models for dementia. This strategy has already proven successful for prion disease, and a great deal of progress has recently been made in developing a viable animal model for AD.

Though genetic studies aimed at identifying gene defects leading to dementia do not require a biological hypothesis to arrive at the end result, a large volume of literature exists in which molecular biological strategies have been implemented to test a wide variety of models for the etiological and pathogenic mechanisms of dementia. Topics addressed in *Molecular Mechanisms of Dementia* include apoptosis, energy metabolism, excitotoxicity and calcium-mediated cell death, free radicals, electrophysiological abnormalities, inflammatory and complement activation pathways, environmental toxins, degeneration of neural networks, and modifications of the cytoskeleton. Additionally, a common phenocopy for AD and related disorders is onset of dementia owing to the occurrence of multiple infarctions; thus, mechanisms by which ischemia and hypoxia result in dementia are also covered here.

The powerful combination of genetic studies leading to the identification of gene defects associated with dementia and molecular biological, biochemical, and immunohistochemical strategies for testing possible mechanisms underlying neuronal cell death has already provided a much more lucid understanding of the molecular basis of dementia. The goal of *Molecular Mechanisms of Dementia* is to review the tremendous progress that has been made in developing testable models of the molecular mechanisms of dementia, as well as to provide direction for future investigations of dementia.

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