CHAPTER 5

Cell Cycle and Chromosome Segregation Defects in Alzheimer's Disease

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Abstract

Despite a common set of hallmark neuropathological lesions and clinical symptoms, Alzheimer's disease has an apparently complex etiology. The disease can be caused by autosomal dominant mutations in at least three genes (encoding the amyloid precursor protein (APP) and the two presenilins). In addition, it can be influenced by certain allelic variants of at least three "risk factor" genes (apolipoprotein E, antichymotrypsin, and interleukin-1), or may arise "sporadically" with no evident genetic component. In the end, as many as 30-40% of individuals over the age of 85 may have some symptoms of Alzheimer's—underscoring the fact that age itself is the strongest risk factor for the disease.

It has been known for almost twenty years that individuals with trisomy 21 (Down syndrome) exhibit Alzheimer neuropathology by the time they are 30-40 years old. Somewhat later, they also develop dementia, and eventually die of Alzheimer's disease. Because the gene for amyloid precursor protein (APP) resides on chromosome 21, its consequent overexpression in trisomy 21 cells presumably contributes to the development of Alzheimer's disease in Down syndrome individuals.

The connection between Down syndrome and Alzheimer's disease and the application of Occam's Razor led me to hypothesize that many cases of classical Alzheimer's disease—both of the genetic and late-onset, sporadic forms—might similarly be caused by chromosome mis-segregation leading to a small number of trisomy 21 cells developing during the life of the affected individual.

In this chapter, I will consider evidence from several laboratories that defects in mitosis, and particularly in chromosome segregation, may be a part of the Alzheimer disease process. In particular, mutations in the presenilin genes that cause Alzheimer's disease also cause chromosome instability. By generating a mosaic population of trisomy 21 and other aneuploid cells, such a mitotic defect could lead to Alzheimer pathology and dementia by inducing inflammation, apoptosis, and/or altered processing of the APP protein into the neurotoxic amyloid β-protein—all characteristic features of the disease. The possibility that many cases of Alzheimer's disease are mosaic for trisomy 21 suggests novel approaches to diagnosis and therapy.

Introduction

Alzheimer's disease arises when neurons in certain regions of the brain, particularly those involved in memory and cognition, are damaged and ultimately killed. A key step in this
process is the polymerization of the Aβ peptide into neurotoxic protein filaments. Aggregates of these filaments accumulate in the brain as the characteristic neuropathological lesions termed “amyloid” and are thought to be an essential contributor to neuronal cell death in Alzheimer’s disease.\(^1^\)\(^-^\)\(^5\) This hypothesis has been supported by many in vitro and in vivo experiments\(^6^\)\(^-^\)\(^1^2\) and has been recently strengthened greatly by our demonstration that amyloid formation catalyzed by the action of two amyloid-associated proteins, apolipoprotein E (apoE) and antichymotrypsin (ACT), on Aβ is required for neuronal dysfunction and cognitive impairment in a mouse model of Alzheimer’s disease.\(^1^2\) Together with the genetic evidence implicating the amyloid precursor protein (APP), apoE4, and ACT-A in the disease (for review, see reference 5), these results strongly point to either the process or product of amyloid formation as the key to Alzheimer’s disease. The unanswered questions are how does amyloid formation arise in the majority of non-inherited Alzheimer’s disease and what initiates neuronal cell death.

An important clue to the mechanism of Alzheimer’s disease was the discovery that Down syndrome patients who live beyond the age of 30 or 40 develop brain neuropathology indistinguishable from that observed in classical Alzheimer’s disease.\(^1^3^-^1^5\) Down syndrome is caused by the presence of three copies of chromosome 21, instead of the usual two, in every cell of the body from the moment of conception. The implication of this finding is that trisomy for chromosome 21 not only causes Down syndrome, but is also sufficient to cause Alzheimer’s disease later in life.\(^1^6\)

One possible explanation for the link between Down syndrome and Alzheimer’s disease is that, in both disorders, a gene on chromosome 21 is over-expressed—due either to the 50% increased dosage of chromosome 21 genes in Down syndrome, or to potential somatic or inherited mutation or gene duplication in Alzheimer’s disease.\(^1^7^-^1^8\) Indeed, the Aβ peptide, which is the major component of the pathological amyloid deposits found in Alzheimer’s disease brain, is encoded by a gene (amyloid precursor protein; APP) that resides on chromosome 21.\(^1^9^-^2^2\) APP is actually over-expressed in Down syndrome individuals somewhat more than the 50% expected from gene dosage alone.\(^2^3^-^2^5\) However, no known cases of Alzheimer’s disease have resulted from a simple duplication of the APP gene or over expression of APP. It therefore seems to me more likely that trisomy 21 results in multiple abnormalities in gene expression that together result in Alzheimer’s disease decades later.

One weekend, some years ago, I was deep in the New Hampshire woods attending a retreat for the MD-PhD students and faculty of The Harvard Medical School. Taking advantage of a relaxed atmosphere, I tried to concentrate on the curious relationship between Alzheimer’s disease and Down syndrome. It occurred to me that if complete “trisomy 21” could lead to early Alzheimer’s disease in Down syndrome, perhaps the slow development of some trisomy 21 cells over a lifetime could cause the Alzheimer’s disease that affects elderly individuals.\(^2^6\) The more I thought about it the more it became clear that this model explained many, seemingly unrelated facts about Alzheimer’s disease. It could also account for both the inherited and more common, non-familial form of the disorder, depending upon whether the defect in chromosome segregation that led to trisomy 21 mosaicism was the result of a genetic mutation or some environmental insult.

In order to be useful, a scientific model must be able to make testable predictions. The trisomy 21 model for Alzheimer’s disease makes at least two major ones. The first is that Down syndrome and Alzheimer patients should share clinical features besides dementia that might be used as a diagnostic test for Alzheimer’s disease.\(^2^6\) One such potential test is based on the finding that Down syndrome and Alzheimer’s disease individuals have cholinergic deficits that, for instance make them hypersensitive to the pupil dilating effect of cholinergic antagonists.\(^2^6^-^2^7\) We and others are still in the process of testing this prediction. Increasingly promising results suggest that even individuals that are seemingly cognitively normal can dilate abnormally in response to the cholinergic antagonist tropicamide and can show cholinergic pathology and