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The cell cycle as a therapeutic target for Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease worldwide. It is a progressive, incurable disease whose predominant clinical manifestation is memory loss, and which always ends in death. The classic neuropathological diagnostic markers for AD are amyloid plaques and neurofibrillary tangles, but our understanding of the role that these features of AD play in the etiology and progression of the disease remains incomplete. Research over the last decade has revealed that cell cycle abnormalities also represent a major neuropathological feature of AD. These abnormalities appear very early in the disease process, prior to the appearance of plaques and tangles. Growing evidence suggests that neuronal cell cycle regulatory failure, leading to apoptosis, may be a significant component of the pathogenesis of AD. A number of signaling pathways with the potential to activate aberrant cell cycle re-entry in AD have been described. The relationships among these signaling cascades, which involve the amyloid precursor protein (APP), cyclin-dependent kinases (cdks), and the cell cycle protein Pin1, have not yet been fully elucidated, but details of the individual pathways are beginning to emerge. This review summarizes the current state of knowledge with respect to specific neuronal signaling events that are thought to underlie cell cycle regulatory failure in AD brain. The elements of these pathways that represent potential new therapeutic targets for AD are described. Drugs and peptides that can inhibit molecular steps leading to AD neurodegeneration by intervening in the activation of cell cycle re-entry in neurons represent an entirely new approach to the development of treatments for AD.

Keywords: Alzheimer's disease; Amyloid precursor protein; Cell cycle; Apoptosis; Cyclin-dependent kinase; Therapeutic

Abbreviations: AD, Alzheimer's disease; APP, amyloid precursor protein; APP-BP1, APP binding protein 1; cdk, cyclin-dependent kinase; CSN, Cop9 signalosome; FAD, familial AD; JNK3, c-Jun N-terminal kinase 3; NSAID, nonsteroidal anti-inflammatory drug; PAK3, p21-activated kinase 3; PPARγ, peroxisome proliferator-activated receptor γ.

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1. Introduction

Alzheimer's disease (AD) is the leading cause of dementia among older people and is the most prevalent neurodegenerative disease worldwide. This disease has become an alarming health problem in the United States: ~15% of Americans over the age of 65 and 50% of those over age 85 (Evans et al., 1989) have AD. More than 4 million Americans now suffer from the disease, and the number is projected to balloon to 14 million by the year 2050. AD is currently the third most expensive disease to treat in the United States, costing close to US$100 billion annually (Smith, 1998).

AD is a progressive, incurable disease that always ends in death. Its predominant clinical manifestation is memory loss, but a number of other changes in brain function, including disoriented behavior and impairments in language, comprehension, and visual–spatial skills, also characterize this disorder. Neuropathologically, the earliest signs of AD are observed in the entorhinal cortex, hippocampus, and basal forebrain. The 2 major diagnostic markers for the disease are amyloid plaques and neurofibrillary tangles; neuronal loss and dysfunction also characterize the disease. However, our understanding of the role that these features of AD play in the etiology of the disease remains incomplete.

There are currently no medications or other treatments that are known to cure or prevent AD. The drugs that are available treat only the cognitive and behavioral symptoms of AD. Four of the 5 FDA-approved drugs for the treatment of AD are acetylcholinesterase inhibitors; the fifth (Memantine) is an NMDA receptor antagonist. To move beyond the use of palliative treatments for the disease, to those that forestall the progression of the disease, we need to understand its pathogenesis.

As noted above, the hallmarks of AD, namely, neuronal attrition, amyloid deposits, and neurofibrillary tangles, have not as yet explained the etiology and pathogenesis of the disease. However, additional markers of AD have been described that may give some clues to the mechanism by which neurons die in AD brain. Notably, aberrant expression of cell cycle proteins and DNA tetraploidy in neurons in pathologically affected regions of AD brain have been described. It has been shown also that those neurons that have entered the cell cycle subsequently undergo a form of programmed cell death called apoptosis. By now, the evidence that neuronal death in AD may be at least partly due to cell cycle entry followed by apoptosis is considerable. This has clear therapeutic implications; understanding the molecular pathways underlying this cell cycle-mediated neurodegeneration will reveal new therapeutic targets and lead to novel strategies for slowing or even blocking the onset and progression of AD. In this review, we describe the phenomenology of cell cycle reactivation in AD brain and discuss specific cellular signaling events that are thought to be involved. Based on these data, we discuss the prospects for drug therapies that will inhibit molecular steps leading to AD neurodegeneration.

2. Cell cycle abnormalities in Alzheimer's disease

Traditionally, neurons have been considered to be "locked" into the G0 phase of the cell cycle. Normally, the release of a cell from the resting G0 phase results in its entry into the first gap phase (G1), during which the cell prepares for DNA replication in the S phase. This is followed by the second gap phase (G2) and mitosis (M phase). In contrast, in mammalian neurons, the re-expression of cell cycle markers has been linked with the occurrence of certain types of neuronal cell death (reviewed by Copani et al., 2001; Herrup et al., 2004). It has been proposed (Lee et al., 1992) that a neuron is committed to the permanent cessation of cell division, hence that if for any reason it is forced to re-enter the cell cycle after this commitment, it dies. Such a notion appears to be inconsistent with the large number of reports that describe the expression of cell cycle proteins in normal rodent or human brains, suggesting that these cell cycle proteins may be of physiological rather than pathophysiological relevance. However, the apparent contradiction may be resolved if one assumes that the activation of cell cycle proteins in neurons to cause such physiological processes as synaptic reorganization in plastic regions of the adult brain is normally a tightly regulated process, and that if this regulation fails, unscheduled re-entry into the cell cycle may occur. Such a model has been proposed by Ueberham and Arendt (2005). Certain stimuli, such as neuronal injury, hypoxia, seizure activity, loss of trophic support, or even aging, have the potential to cause cell cycle regulatory failure in neurons. It has been hypothesized that the reported evidence of cell cycle activation in AD brain represents such a loss of regulation of the normal neuronal functions of cell cycle proteins.

Nearly 10 years ago, Vincent and Davies showed definitively that activation of cell cycle components occurred in AD brain (Vincent et al., 1996). Soon thereafter, ectopic expression of such cell cycle molecules as cdc2, cdk4, p16, Ki-67, cyclin B1, and cyclin D was reported in pathologically affected or vulnerable neurons in AD brain (Arendt et al., 1996; McShea et al., 1997; Nagy et al., 1997; Vincent et al., 1997; Busser et al., 1998). Busser et al. (1998) found abnormal appearance of cell cycle markers in regions of AD brain where cell death is extensive, and Chow et al. (1998) found increases in expression of genes encoding cell cycle proteins in single neurons in late-stage relative to early stage AD brain. A number of the cell cycle regulators have been detected in vulnerable neurons prior to lesion formation (Kondratick & Vandre, 1996; Busser et al., 1998; Vincent et al., 1998). Patrick et al. (1999) have shown that p25, a truncated form of p35, the regulatory subunit of cdk5, is increased in AD brain.

What are the consequences of the activation of cell cycle proteins for the neuropathology of AD? One of these consequences appears to be that vulnerable neurons in AD brain re-enter the cell cycle. Yang et al. (2001) have demonstrated that a significant number of hippocampal pyramidal (4% vs. 0% in control hippocampus) and basal forebrain neurons in AD brain have undergone full or partial DNA replication, showing that they have completed the S phase. This is not seen in unaffected