

ABSTRACT

(Yan Yang, Case Western University)

Mild cognitive impairment (MCI) is a clinical diagnosis that characterizes elderly individuals with memory impairment that is insufficient to meet criteria for dementia, but with cognitive decline more severe than that associated healthy aging. Despite its modest presentation, MCI patients are at high risk for developing Alzheimer's disease (AD) within five years, implying that the pathology of AD, including neuronal loss, contributes to the cognitive dysfunctions of MCI. At the end-stage of AD, neurons in vulnerable populations re-express a number of cell cycle-related proteins (e.g., Cyclins B & D, PCNA, Cdk4) suggestive of entrance into an abortive cell cycle. Using fluorescent in situ hybridization, our lab has provided direct evidence that chromosomal DNA has been replicated. Together, these data support the concept that at the end of the disease a lethal cell division process underlies much if not all neuronal cell death seen in AD. We wished to determine whether cell cycle induced cell death was merely a consequence of deteriorating brain function or whether it was equally involved in the early stages of AD as well. To achieve this we evaluated the expression of cell cycle markers using immunohistochemistry in samples from the hippocampus and basal nucleus of people who had died with a diagnosis of MCI. These studies revealed that cell cycle proteins are re-expressed in the MCI and AD cases, but not in non-demented controls. Significantly, the percentage of cells that are positive for these markers in our MCI cases was similar to that found at end-stage AD. The results suggest that cell cycle re-entrance is a critical factor in nerve cell degeneration at all stages of the disease process. This suggests that an intervention based on inhibiting cell cycle entrance will be as effective in the early stages of the disease as at the end. ***Supported by AG08012, NS20591, AG14449, AG09466, AG10161, Blanchette Hooker Rockefeller Foundation***