Neurons die in Alzheimer's because of faulty cell cycle control before plaques and tangles appear

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The two infamous proteins, amyloid-beta (A?) and tau, that characterize advanced Alzheimer's disease (AD), start healthy neurons on the road to cell death long before the appearance of the deadly plaques and tangles by working together to reactivate the supposedly blocked cell cycle in brain cells, according to research presented on Dec. 17 at the American Society for Cell Biology's Annual Meeting in San Francisco.

Working in a mouse model of AD, George Bloom, PhD, of the University of Virginia (UVA) reports that neurons in AD start dying because they break the first law of human neuronal safety—stay out of the cell cycle.

Most normal adult neurons are permanently postmitotic; that is, they have finished dividing and are locked out of the cell cycle. In contrast, AD neurons frequently re-enter the cell cycle but fail to complete mitosis, and ultimately die. By considering this novel perspective on AD as a problem of the cell cycle, Dr. Bloom and colleagues at UVA and at the University of Alabama, Birmingham, have discovered what they call an "ironic pathway" to neuronal cell death. The process requires the coordinated action of both A? and tau, which are the building blocks of plaques and tangles, respectively. Dr. Bloom's results show just how toxic the two proteins can be even when free in solution and not aggregated into plaques and tangles.

Using mouse neurons grown in culture, the UVA researchers found that A? oligomers, which are small aggregates of just a few A? molecules each, induce the neurons to re-enter the cell cycle. Interestingly, the neurons must make and accumulate tau in order for this cell cycle re-entry to occur. The mechanism for this misplaced re-entry into the cell cycle requires that A? oligomers activate multiple protein kinase enzymes, each of which must then attach a phosphate to a specific site on the tau protein.

Following up on the cell culture results, Dr. Bloom and colleagues confirmed that A?-induced, tau-dependent cell cycle re-entry occurs in the brains of mice that were genetically engineered to mimic brains with human AD. The mouse brains were found to accumulate massive numbers of neurons that had transitioned from a permanent cell cycle stop, known as G0 (G zero), to G1, the first stage of the cell cycle, by the time they were 6 months old. Remarkably, otherwise identical mice that lacked functional tau genes showed no sign of cell cycle re-entry, confirming the cell culture results.

Neuronal cell cycle re-entry, a key step in the development of AD, can therefore be caused by signaling from A? through tau. Thus, A? and tau co-conspire to trigger seminal events in AD pathogenesis independently of their incorporation into plaques and tangles. Most important, Dr. Bloom believes that the activated protein kinases and phosphorylated forms of tau identified in this study represent potential targets for early diagnosis and treatment of AD.

More information: "Amyloid-? signals through tau to drive ectopic neuronal cell cycle re-entry in Alzheimer's disease," Monday, Dec. 17, 2012, 5:55:15 pm, Minisymposium 10: Cell Biology of Neurodegeneration, room 102

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