OXIDATIVE STRESS AND THE PROGRESSION OF ALZHEIMER DISEASE: THE TRIANGLE OF DEATH FOR NEURONS ASSOCIATED WITH ALTERED GLUCOSE METABOLISM, mTOR SIGNALING, AND PROTEIN PHOSPHORYLATION

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Research Abstract
About 10 years after our laboratory discovered the free radical oxidative stress associated with neurotoxic amyloid β-peptide (Aβ) that accumulates in brain of subjects with Alzheimer disease (AD), and subsequently demonstrated that oligomeric Aβ leads to protein oxidation and lipid peroxidation in AD brain and in brain of arguably the earliest forms of AD, amnestic mild cognitive impairment (MCI) and preclinical AD (PCAD) [1], we pioneered the methods of redox proteomics and began to identify specifically oxidatively modified (and therefore dysfunctional) brain proteins in AD, MCI, and PCAD [2, 3]. Among the biochemical pathways severely oxidatively modified in AD and MCI brain were those associated with glucose metabolism, the latter shown by others using PET scanning to be markedly reduced with progression of the disease. This seminar will highlight our ongoing proteomics studies identifying oxidatively modified brain proteins in AD, MCI, and PCAD subjects consistent with altered glucose metabolism. In addition, Aβ oligomers have been proposed to overactivate the PI3K/Akt/mTOR axis, which plays a central role in proteostasis and in insulin signaling, both known to be altered in AD. This seminar will highlight our recent studies of overactivation of this axis in AD, MCI, and PCAD brain [4]. This latter work arose from our recent studies showing altered mTOR signaling and the proteostasis network in brain of subjects with Down syndrome (DS) as a consequence of oxidative stress prior to development of AD neuropathology and dementia, suggesting an early involvement of these processes in neuronal death in DS [5]. Finally, this seminar will highlight our recent phosphoproteomics studies of AD, MCI, and PCAD brain that identified altered phosphoproteins consistent with dysfunction of glucose metabolism and other pathways [6]. New insights into underlying mechanisms for the preservation of memory in the presence of expansive AD pathology in subjects with PCAD have been gained.

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