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Oxidative Stress Induced Mitochondrial DNA Overproliferation and Deletion in the Context of Cancer and Alzheimer Disease

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Oxidative stress initiates mitochondrial DNA overproliferation and/or deletion of the organ and/or tissues, especially the mitochondrial energy demands, have been implicated in the pathogenesis of several diseases, including Alzheimer disease (AD), tumor growth, and metastasis. The present study has determined if an intimate, i.e. causal, relationship between oxidative stress and mitochondrial damage and/or vascular lesions occurs before the development of human AD, in animal models that mimic human neurodegenerative diseases and human colorectal carcinoid cancer or primary malignant brain cancer. In situ hybridization and ultrastructural analysis of the mitochondria (mitochondria with electron dense matrix, mitochondrial-derived lysosomes) showed that mitochondria with the abnormal structures and lipofuscin appear to be features of hippocampal damaged neurons in human AD, aged Tg (+) mice, 2 and 3 vessel occlusion model of the brain hypoperfusion, and malignant primary and metastatic cancer. The abnormal mitochondria appeared to be a permanent feature in all cellular compartments; in situ hybridization analysis with mouse and human mtDNA probes found a large amount of deleted mtDNA in human AD and in all models that mimic human AD (mice, rats etc.) hippocampus and cancer tissues compared to aged controls. The majority of these mtDNA deletions were found in mitochondrial-derived lysosomes in regions closely associated with lipofuscin and/or tumor growth regions. In situ hybridization with a chimeric cDNA probe for the 5kb common deletion indicated that the 5kb mtDNA is increased at least 3 and 4 fold respectively in AD and malignant tumor cases as compared to controls. Only hippocampal and cortical vulnerable neurons as well as malignant cancer tissues showed immunopositive staining for RNA oxidation markers visualized by using 8-OHG-staining, NOSs, and all oxidative stress markers. The mitochondrial DNA overproliferation and deletion detected by using cytological techniques suggests that successful dysregulation of the cell cycle is also the hallmark of neoplasm; early mitochondrial dependent cell-cycle pathophysiology in AD may recruit oncogenic signal transduction mechanisms and hence, can be viewed as an abortive neoplastic transformation. The common features on the mitochondrial abnormality were seen on the brain during tumorigenesis and AD indicating that mitochondrial DNA overproliferation and/or deletion are the key initiating factors for development, maturation, and progression of neurodegeneration as well as tumor growth and/or metastases.

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Brain Fog and Inflammation in Autism and Alzheimer'sDisease-Benefit of Luteolin

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Brain fogis defined by reduced cognition, concentration and short-term memory found in patients with autism spectrum disorders (ASDs), chronic fatigue syndrome, fibromyalgia, mastocytosis and "minimal cognitive impairment," an early presentation of Alzheimer's disease. Brain fog may be due to inflammatory cytokines and histamine released from mast cells, which then activate microglia, leading to focal brain inflammation. The flavone luteolin has anti-oxidant, anti-inflammatory, neuroprotective and memory enhancing properties. A luteolin formulation in olive fruit extract improved attention in children with ASDs and brain fog in mastocytosis patients. We showed that some methylated luteolin analogues are more potent and also possess brain-derived neurotrophic factor (BDNF) activity. Liposomal preparations of these flavones could be formulated for intranasal administration that would permit targeted delivery to microglia through the cribriform plexus for the treatment of brain fog in neuropsychiatric disorders (US Patents No. 7,906,153; 8,268,365; 13/009.282).

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