Mitochondrial dependent oxidative stress induced cellular hypoperfusion in context of neurodegeneration and cancer offers new and successful strategy for the drug development

Neurodegeneration [Stroke and Alzheimer disease (AD)] and cancer are fast becoming one of the leading causes of age-associated disability, dementia, and death. In addition, the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics recently reported that AD has surpassed diabetes as a leading cause of death and is now considered the sixth-leading cause of death in the United States.

Oxidative stress induced 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 AD, tumor growth, and metastasis. Decline in mitochondrial function during the development and maturation of the neurodegeneration, tumor growth, and metastases characterizing the tissue oxygen deficiency may lead to cellular energy defects, which will compensate vital cellular components and regulators. The overexpression of the enzymes such as NOS induce the production of unwanted large amounts of free radicals that cause the oxidative stress, cellular change, and particularly the concomitant mitochondrial lesions and decline in normal organ function. 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 neurodegeneration and human colorectal carcinoid cancer or 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 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, and suggests that proliferation, deletion, and duplication of mtDNA occurs in mitochondria, many of which have been fused with lysosomes in human AD, Tg(+) mice, and malignant tumors. Moreover, the biopsy and perfused brain samples from AD and the animals’ models that mimics human AD as well as cancer patients were dominated by abnormal mitochondria as compared to a control group. 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. In quantitative analysis of the mtDNA deletion and 8OHG in the same cases, we found a strong significant positive correlation (r=0.934). 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. This observation indicates that the oxidative stress markers seen in the AD brain and malignant cancer selectively affects the population of vulnerable neurons, vascular EC, and perivascular cells, suggesting that oxidative stress induced mitochondrial DNA overproliferation and/or deletion plays a key role in the pathogenesis of AD and cancer. 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.