J Neurol Neurophysiol 2015, 6:3
http://dx.doi.org/10.4172/2155-9562.S1.026

OMICS International
conferenceseries.com

4th International Conference and Exhibition on
Neurology & Therapeutics
July 27-29, 2015 Rome, Italy

Oxidative stress induced mitochondrial dependent cellular hypoperfusion, erythrocytes metabolism in context of neurodegeneration and cancer offers new and successful strategy for the drug development and treatment

Aliev Gjumrakch
University of Atlanta, USA

Neurodegeneration [Stroke and Alzheimer disease (AD)] and cancer are fast becoming one of the leading causes of age-associated disability, dementia, and death. 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.

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. One of big challenge for the diagnosis of the dementia and/or neurodegeneration appeared to be absence of the peripheral markers. Our extended study showed that age-related defects in erythrocyte 2,3-diphosphoglycerate metabolism and antioxidant status and energy state of erythrocytes in Alzheimer dementia can be used as a successful peripheral markers not only for the diagnosis but also probing for markers regarding the effectiveness' of the treatment. We have found that Erythrocytes (red blood cells: RBC) are considered as passive "reporter cells" for the oxidative status of the whole organism, not active participants in mechanisms of AD pathogenesis and are not well studied in AD. The aim of this work is to assess whether the antioxidant status and energy state of RBC from elderly people change in AD. We measured levels of key products and enzymes of oxidative metabolism in RBC from AD (n = 12) and non-Alzheimer dementia (NA, n = 13) patients, as well as in cells from age-matched controls (AC, n = 14) and younger adult controls (YC, n = 14). Parameters of the adenylate system served to evaluate the energy state of RBC. In both aging and dementia, oxidative stress in RBC increased and exhibited elevated concentrations of H_2O_2 and organic hydroperoxides, decreased the GSH/GSSG ratio and glutathione-S-transferase activity. Reductions in the ATP levels, adenine nucleotide pool size (AN) and adenylate energy charge accompanied these oxidative disturbances. The patterns of changes in these indices between groups strongly correlated with each other, Spearman rank correlation coefficients being r(s) = 1.0 or -1.0 ($p < 0.01$). Alterations of the RBC parameters of oxidative stress and adenylate metabolism were nonspecific and interpreted as age-related abnormalities.

Our study, for the first time, demonstrated the pattern of oxidative stress induced mitochondrial DNA overproliferation and/or deletion as well as mitochondrial enzyme activities during the development of human AD, and animals that mimic human AD, colorectal cancer in liver metastasis, and malignant brain cancers. In addition, the decreased glutathione peroxidase activity in RBC may be considered as a new peripheral marker for AD.

GAliev@uofa.edu