Molecular mechanisms for maintaining mitochondrial DNA stability in Alzheimer's disease

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In animal cells mitochondria are the only organelle that contain their own genome, a circular DNA which encodes for subunits of the oxidative phosphorylation complexes. In mammals, the mitochondrial DNA (myDNA) is quite small (between 16-20 Kb) and encodes only 13 polypeptides, 22 tRNAs and 2 rRNAs. But despite its size, its integrity is essential for cellular homeostasis, as mtDNA mutations, deletions and copy number variation cause several human syndromes and are causally linked to aging and age-associated diseases. As the mtDNA lies close to the reactive oxygen species-generating electron transport chain, it accumulates more oxidative damage than the nuclear DNA. Oxidized bases and single strand breaks are mainly repaired by the base excision repair pathway (BER), which is very active in mammalian mitochondria. we have investigated whether changes in BER are associated with age-associated neurodegeneration using Alzheimer's disease as a model. Our results show that BER activities are decreased in mitochondrial and nuclear extracts from cerebellum and temporal cortex of AD subjects, when compared to age-matched controls and assymptomatic AD. Nonetheless, mtDNA from AD subjects does not accumulates more mutations or deletions than controls, nor displays an altered mutational spectrum, indicating that, in this model, BER deficiency is not associated with elevated mutagenesis. On the other hand, we detected a significant decrease in mtDNA copy number in AD subjects, when compared to the other two experimental groups. Altogether, our results suggest that DNA repair protects mtDNA from damage accumulate that may signal to degradation, possibly via mitophagy upregulation.