# Mitochondrial Function Regulates Nucleotide Metabolism and Affects Genomic Stability: Mechanisms and Biomarker for Cognitive Function

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Mitochondria are the powerhouse of the cell and where cellular energy supplies in the form of ATP are generated. Because of this pivotal role, mitochondrial dysfunction is very damaging for the cell and can lead to numerous pathological conditions in humans. Most notably, mitochondrial dysfunction is associated with cognitive decline, neurological abnormalities and aging.

Balanced levels of dNTP are important for genomic stability. Accordingly, imbalance of the cytosolic dNTP pool has been demonstrated to decrease the genetic stability. We show that depletion of mtDNA of human cell lines results in an imbalance of the cytosolic dNTP pools and a decrease of chromosomal stability. MtDNA primarily encodes peptides essential for the activity of the mitochondrial electron transport chain and, therefore, also ATP produced by oxidative phosphorylation. The ETC is also linked to the de novo synthesis of pyrimidines through the enzyme dihydroorotate dehydrogenase (DHODHase) located in the inner membrane of the mitochondria. Our findings support a model for the initiation of genome instability through a mitochondrial dysfunction and resulting imbalance of the cytosolic dNTP levels. This places fitness of mitochondria as an important determinant of genomic instability.

Cognitive impairment in adults may be an early indicator of later life dementia. Therefore, it is important to search for early biomarkers of cognitive decline. Our data promote investigation into mitochondrial activities, dNTP levels, and DNA damage as potential correlates or predictors of cognitive decline, which may lead to early treatment initiatives in order to delay or prevent later life dementia.