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## LETTER TO THE EDITOR

### Mitochondriogenesis and brain aging

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Since the early 20th century, many countries have been experiencing an epidemiological transition, characterized by an increase not only in the population life expectancy, but also in the prevalence of chronic and degenerative diseases.<sup>1</sup> In this context, the study of pathophysiological mechanisms behind the aging process has become a relevant field of research as it may provide scientific basis to the development of new resources of diagnosis and treatment. One of the main theories proposed to explain the aging phenomenon is the Mitochondrial Free Radical Theory of Aging. According to this theory, reactive oxygen species (ROS) generated in oxidative phosphorylation damage mitochondrial macromolecules, leading to mitochondrial dysfunction and signaling for cellular senescence.<sup>2</sup> ROS are also known to stimulate the mitochondriogenesis (generation of new mitochondria) through a molecular pathway that involves the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 $\alpha$ ) and the mitochondrial transcription factors A, B1 and B2 (TFAM, TFB1M and TFB2M).<sup>3</sup> Given that ROS take part in both aging and mitochondriogenesis, the Laboratory of Molecular and Cellular Biology of the University of Sao Paulo Faculty of Medicine investigated the relationship between age, mitochondria amount and the expressions of *PGC-1 $\alpha$* , *TFAM*, *TFB1M* and *TFB2M* in brain tissue.

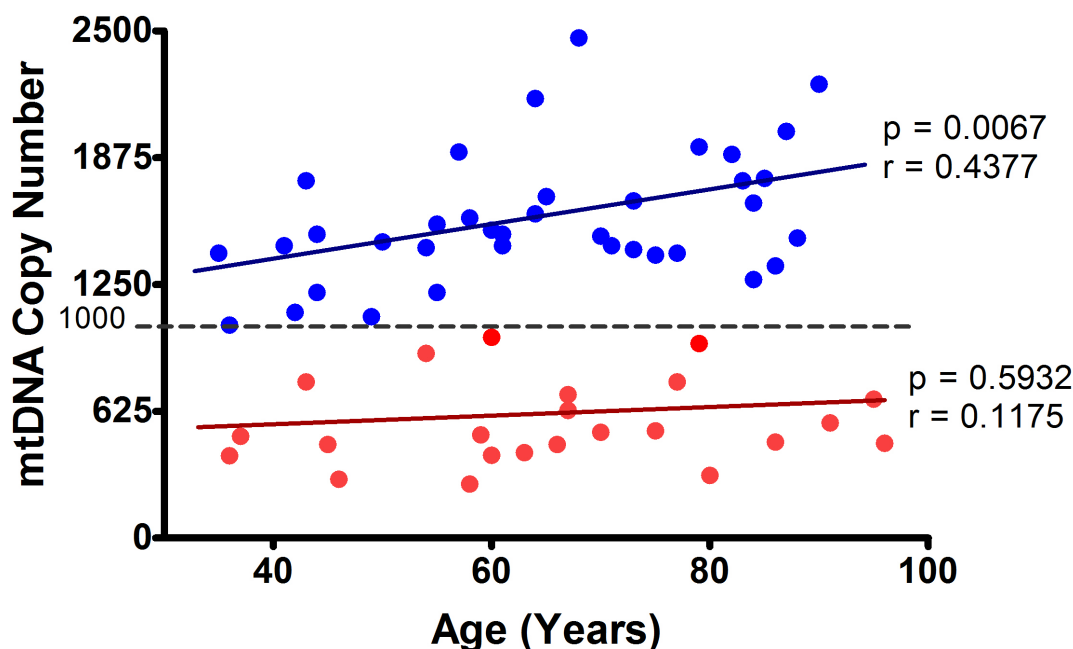
For this investigation, 60 human brain samples were collected during autopsy procedures in the Death Verification Service of the Capital (SVOC), as well as the clinical history of each donor. The samples were transported to the Laboratory and their DNA and RNA were extracted. The mitochondria amount of the samples was accessed by the measurement of the ratio between the quantity of a mitochondrial encoded gene and a nuclear encoded gene, using quantitative polymerase chain reaction (qPCR). The expressions of *PGC-1 $\alpha$* , *TFAM*, *TFB1M* and *TFB2M* were also determined through qPCR and the raw data was submitted to statistical analysis.

It was found that specimens with more than 1000 copies of mtDNA had a direct correlation between mtDNA content and age, while those with less than 1000 copies, did not present any correlation (Figure 1). These results suggest that mtDNA content does not vary in the same way during aging among individuals, but follows at least two different patterns. In one of them, mtDNA amount remains low throughout all age groups, while in the other it is already higher among young individuals and grows even more during aging. These patterns of variation of mtDNA with aging were named Mitochondriogenesis Pattern A (MP-A) and B (MP-B) respectively.

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**Figure 1.** Correlation of mtDNA copy number and age calculated with Pearson test for specimens with more (blue) and less (red) than 1000 copies. Only the group with more than 1000 copies presented a significant correlation between mtDNA amount and age ( $p < 0,05$ )

In order to reach possible explanations for the different evolutions of mtDNA content with aging, the past medical history of the donors was evaluated. It was found that MP-B individuals had higher body mass index (BMI) than MP-A ones by Mann-Whitney test ( $p = 0.0280$ ). Similar result was described in a study with omental adipose tissue, in which mtDNA amount was higher in obeses, that in non-obeses.<sup>4</sup> It was also found that MP-B individuals diagnosed with diabetes mellitus had higher expression of *PGC-1 $\alpha$* , *TFAM*, *TFB1M* and *TFB2M* than non-diabetics by Mann-Whitney test ( $p = 0.0003$ ;  $0.0008$ ;  $0.0005$  and  $0.0044$  respectively). In MP-A group, no difference was observed between diabetics and non-diabetics. Of note, a previous study with peripheral blood cells found that diabetics have higher amount of mtDNA and mutations in the D-loop than non-diabetics<sup>5</sup>. D-loop is the region of the mtDNA where the promoters recognized by TFB1M and TFB2M are located,<sup>6</sup> therefore mutations in D-loop may lead to a decreased affinity for the transcription factors,

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possibly resulting in an overexpression of those factors to compensate the lack of affinity.

The results achieved in the study support the idea that the mitochondriogenesis is upregulated in individuals with metabolic comorbidities, suggesting that the MP-B is probably linked to an unhealthy brain aging. Given that metabolic syndrome has an important role as a risk factor for Alzheimer's Disease (AD)<sup>7</sup> and that oxidative stress and mitochondrial dysfunction are part of AD pathogenesis<sup>8</sup>, the mtDNA increase in brain tissue could be studied not only as a biomarker of mitochondrial dysfunction, as Malik and Czajka (2013) proposed<sup>3</sup>, but also as a risk factor for Alzheimer's Disease. Further investigation is needed to establish a more consistent relationship between the increased amount of mtDNA in brain tissue and AD so that, in the future, the experimental finding of the present study can be translated in a diagnostic tool.

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