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MITOCHONDRIAL DNA VARIABILITY INFLUENCE GLOBAL DNA METHYLATION LEVELS

GIORDANO M., D'AQUILA P., CROCCO P., PISANI F., ROSE G., PASSARINO G., BELLIZZI D.

Department of Cell Biology, University of Calabria, 87036 Rende (Italy)

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Epigenetic changes to DNA during human lifetime are modulated by environmental and genetic factors. Among these factors, mitochondrial functions are emerging to have a key role, probably to their central position between energy uptake and energy production.

Mitochondrial DNA inherited variants (mtDNA), determining mtDNA haplotypes and groups of haplotypes (haplogroups), are thought to contribute to the inter-individual variability in mitochondrial function. These variants affect the quality of aging and age-related pathologies, such as Alzheimer's and Parkinson's diseases, diabetes and cancer. The molecular mechanisms by which mtDNA variability influences these traits are likely to involve a complex interaction between mtDNA and the nuclear genome, possibly through the modulation of oxidative phosphorylation (OXPHOS). The importance of this interaction has also emerged either from studies on epigenetic changes and, more specifically, on the DNA methylation of cytosines, either from *in vitro* studies carried out in cybrids, engineered cells that share the same nuclear genome but harbor different mitochondrial genomes.

On the basis of these observations, population and *in vitro* studies were carried out to investigate the relationship between age-related epigenetic modifications and mtDNA variability. To this purpose, using methyl-sensitive restriction endonucleases (*CpG*lobal method), we measured global DNA methylation levels both in peripheral blood DNAs collected from 354 (153 males and 191 females) unrelated adult subjects, previously analyzed for their mtDNA variability, and in cybrid cells harbouring mtDNA molecules of H, J, U, X, and T haplogroup. In these cells we also analyzed the expression profiles of different genes involved in methylation processes and the ATP and ROS levels, important regulators of the above processes and key elements of the mitochondria-to-nucleus cross-talk.

From our population association study and *in vitro* analyses, it has emerged that the subjects and cybrid cells harboring mtDNA molecules belonging to the J haplogroup have higher global DNA methylation levels than non-J carriers. Moreover, in this cell line we measured an over-expression of the methyltransferase *MAT1A* gene and low ATP and ROS levels.

Data we obtained indicate that mtDNA variability could influence DNA methylation by regulating the expression of MAT1A gene that plays a crucial role in these processes. We hypothesize that this influence is likely exerted through the activation of mediators of the cross-talk between mitochondria and nucleus such as ATP and ROS. In fact low ATP and ROS levels occurring in the J cybrids might induce the activation of transcriptional activators of the *MAT1A* gene, leading to its over-expression and thus to DNA hypermethylation.

On the whole our data provide the first evidence that mtDNA variability modulates global DNA methylation levels, possibly via the regulation of OXPHOS efficiency and indicate that

mtDNA-specific interactions between mitochondria and nucleus could regulate epigenetic changes in a mtDNA haplogroup dependent-manner.