DOI: 10.1590/0004-282X20150167

Challenges to understand the mitochondrial respiratory diseases caused by mitochondrial DNA mutations

Os desafios na compreensão das doenças respiratórias mitocondriais causadas por mutações do DNA mitocondrial

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Conflict of interest:
There is no conflict of interest to declare.

Received 08 September 2015
Accepted 15 September 2015

Mitonchondria is a special organelle with its own genoma that when mutated causes diseases related to mitochondrial respiratory chain deficiency. More than 200 point mutations on mictochondrial DNA (mtDNA)[1] have been described associated to such diseases since the first description of mtDNA mutation in 1988[2,3]. An estimated frequency is of 1:5,000 individuals with mitochondrial respiratory chain disease has been reported in Western populations[4], and among these point mutations, the most common m. 3243 A>G transition in the tRNALeu(UUR)[5] may reach a prevalence of 1:424 in Australia[6].

In spite of being a single nucleotide change from A to G in the ***transferRNA-Leucine*** gene of mtDNA, this change causes a heterogeneous disease phenotype ranging from maternally inherited diabetes and deafness (MIDD)[7], cardiomyopathy to mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)[8,9]. A systematic description of the clinical, neuroimaging, laboratorial, biochemical and histological features of MELAS was reported by Lorenzoni et al.[10], in this issue, to facilitate the establishment of this diagnosis.

A thorough characterization of MELAS cases is helpful to unveil the still unknown mechanisms and in the search for therapeutic strategies for this disease. To this end, the understanding of mechanism of mtDNA segregation may be a hot subject. The heteroplasmy, cells carrying both normal and mutant mtDNA, is a typical feature of pathogenic mtDNA mutations, that contributes to the clinical variability. The threshold amount of mutant mtDNA and its consequences varies among tissues, as confirmed by the diversity of respiratory chain complexes deficiencies detected in different autopsy tissues of the same patient harboring m.3243A>G mutation[11]. If the cell was able to select only the mitochondria with non-mutant mtDNA, i.e. to direct the mtDNA bottleneck towards homoplasmy of wild-type mtDNA, then it would be possible to revert the pathogenic phenotype.

The attempts to introduce exogenous DNA into mitochondria to create a mitochondrial disease model have been unsuccessful, but Suomalainen´s group in Finland, in 2013, succeeded in establishing ***in vitro*** model for MELAS mutation[12,13], refining an innovative approach previously reported by Prigione et al. in 2011[14]. The Finland group generated induced pluripotent stem cells (iPSC) from fibroblasts with m3243A>G mutation. And, during reprogramming they obtained a bimodal segregation of mtDNA: mutant and wild-type homoplasmy. iPSC derived neurons and other mesoderm, ectoderm and endoderm tissues derived from teratoma manifested cell-type specific respiratory chain deficiency patterns, indicating that respiratory chain complex activities depend on tissue-specific factors. These findings may allow to address ***in vitro*** the variability of the disease manifestations. Moreover, an active respiratory chain complex I degradation was demonstrated upon neuronal differentiation, recapitulating the major complex I deficiency described in MELAS patient brains.

And, more recently,the Japanese group has also established MELAS-iPSC-derived fibroblast with high heteroplasmic levels showing deficiency of complex I activity[15].

This iPSC model using cells harboring m3243A>G mutation mimicked previous observations reported in MELAS patients, and this approach has proved to be an useful tool to comprehend the pathological mechanisms of this disease. A selection of drugable targets from the analysis of disturbed signaling pathways in this MELAS-model is expected, and mostly translated into clinical trial, in the near future.

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