Editorial

Vulnerability of retinal ganglion cells to mitochondrial defects

La vulnerabilidad de las células ganglionares de la retina a los defectos mitocondriales

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The high energy consumption of some tissues, including the optic nerve, which is mainly borne by an anaerobic metabolism with the ensuing production of ATP through the mitochondrial breathing chain, is extremely damaging for cells when this energy supply mechanism fails. Despite this paradigm, the biochemical and molecular mechanisms of ocular diseases (mainly retinopathies and ophthamalogies) associated to mitochondrial dysfunctions are far from being fully understood and interpreted. In general terms we could classify ocular mitochondrial disorders on the basis of their origin and age of expression and in this way distinguish hereditary diseases in which genetic defects related to mitochondrial function are known, and on the other hand mitochondrial dysfunction could be assigned a leading role in retina and optic nerve degeneration processes due to aging or altered physical conditions (hypertension, diabetes mellitus, etc.).

Hereditary mitochondrial defects can be traced back to either mitochondrial DNA alterations (DNAm, exclusively maternal origin), or to mutations of nuclear genes that encode mitochondrial location proteins. Whereas the 13 proteins encoded by DNAm are a constituent part of the breathing chain and account for only 0.1% of the overall mitochondrial proteome,1 nuclear encoded mitochondrial proteins associated to ocular defects are not an active part of this chain and their function is only now beginning to be discovered.

Pigment retinitis expressions are well known in response to DNAm defects due to specific mutations (as in the case of Neupathy, Ataxia and Pigment Retinitis [NARP] syndrome) as well as in progressive external ophthamalogy due to sporadic genome deletions (as in the case of the Kearns–Sayre syndrome) and which can also appear as a repercussion of mutations in nuclear genes such as POLG y OPA1.1 On this occasion, let us focus on the degeneration of the optic nerve.

Retinal Ganglion Cells (RGC) are high energy consumers because the initial portion of their axons, i.e., from the optic nerve head up to the lamina cribosa, is demyelinated and therefore is particularly “rich” in mitochondria providing the necessary amounts of ATP for transmitting visual signals. As from the lamina cribosa, the myelin-covered axons have lower energy demand due to the Ranvier nodes which facilitate the transmission of signals (depolarization) and accordingly require less mitochondria in these regions.

Mitochondrial disorders exhibiting RGC degeneration evidence comprise Leber's Hereditary Optic Neuropathy (LHON), Autosomic Dominant Optic Atrophy (ADOA) and the Mohr–Tranebjærg Syndrome (MTS). Said etiologies originate respectively in mitochondrial DNA mutations, OPA family gene defects (mainly OPA1 and OPA3) and mutations of the DDP1/Tim8 gene. The LHON case is a landmark because this disease was the first in which pathogenic mutations were described in the mitochondrial genome.3 The identified

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mutations produce aminoacid changes in complex I subunits of the breathing chain. Various studies have established unequivocally diminished NADH-dehydrogenase activity of about 40% while observing reduced ATP2 production. In LHON it seems reasonable that both the degeneration of reactive oxygen species (ROS) due to poor specific performance of the complex I do to decoupling, together with slower ATP production, are the cornerstones of RGC apoptosis under certain stress conditions.

Leber’s optic neuropathy expresses suddenly with acute, progressive and bilateral loss of eyesight in the second or third decade of life, with central or ceco-central scotomae which mainly affects males. Mothers and carriers of the DNAmt mutation do not necessarily develop the disease, although if studied could exhibit subclinic symptoms such as increased retina nervous fiber layer (RNFL) thickness, determined by optic coherence tomography (OCT). In the acute phase of the disease, RNFL thickening is followed by thinning in the chronic phase, most likely caused by axonal degeneration in the papil-lomacular strand, which causes temporal atrophy of the optic nerve in LHON.

In the case of dominant optic atrophy caused by OPA gene defects, currently available information is mainly derived from studies of OPA1 mutating proteins (there are dozens of mutations described in this locus). The expression of OPA1 is ubiquitous. It is known that it co-localizes in the internal mitochondrial membrade and even though it strongly expresses in RGCs it is not more abundant in these cells than in other retina cells. Phosphorus magnetic resonance spectroscopy has evidenced a defect in oxidative phosphorylation together with diminished ATP production in muscle cells of ADOA patients. Oxygen consumption measurement in fibroblasts has also evidenced a decoupling of the OxPhos system associated to membrane potential reductions. However, the decoupling mechanism is different to that described in LHON: in these cells there is a discrete deficit of complex IV of about 25% and there is an intense controversy on the energy deficit involving ATPase activity according to various studies.2

It is very important to emphasize the observed and ratified fact of incomplete penetration and the huge heterogeneity in the presentation of the disease even among members of the same family. Therefore, the influence of other genetic factors in addition to environmental factors in the expression and development of this mitochondrial disorder is beyond doubt, and this hypothesis is common to any mitochondrial disease (in which phenotypic variability is a constant and not an exception).3 Let us hope that the massive sequencing technology (both for genome and exome) will reveal key points in the overall origin of these pathologies.

Autosomal dominant optic atrophy debut early, in the first 2 decades of life, and express bilaterally and progressively (although considerably slower than LHON), with centrocecal, cecal or paracentral scotomae, with bi-temporal paracentral defects being quite common. Dyschromatopsia is associated. In many cases, the term “ADOA plus” is used because, in addition to blindness, extraocular symptoms can appear, ranging from deafness, cortical dystrophy and ataxia, to peripheral neuropathy among others.3 In contrast with these mitochondrial diseases caused by OPA mutations, loss of vision is the last link in the chain of symptoms which constitute the Mohr–Tranebjaerg syndrome (MTS, also known as Deafness and Dystonia syndrome linked to chromosome X), a virtually unknown disease even in the rare disease category, with hardly one dozen reported families.4 Patients exhibit precocious deafness, sometimes defined as congenital, and only at the end of adolescence or in the third decade of life the males carrying the mutation in the DDPI/Tim8 gene begin to experience dystonia and visual deficit, which may become total blindness. Even though the number of these cases is significantly lower when compared to LHON or ADOA, the anatomic-pathological study in MTS has discovered optic nerve degeneration and suggested a disappearance of RGC in analogy to the death of cochlea ganglion spiral cells, the demonstrated course of deafness in MTS.5

The cause of dystonia, i.e., frontal cortex degeneration, and visual cortex degeneration is proven in the Mohr–Tranebjaerg syndrome and therefore there are reasonable doubts concerning the spatial and temporal synchronicity of vision loss in this disease, even though electroretinogram results of some patients exhibit deficit in the retina function which, in any case, would add up to the existing cortical atrophy. The molecular origin of tissue dysfunctions in MTS is even less clear: in contrast with LHON and ADOA, where the alteration of the breathing chain can be invoked (with or without reduced ATP production) or ROS generation, no deviation of these parameters has been found in patient cells when compared against controls. The Tim8 protein is a chaperon that carries the mitochondrial inter-membrane space which forms part of a small group of similar chaperones and, even though a certain degree of in vitro involvement is recognized in the amount of some substrates when Tim8 is affected, the selective involvement of the central nervous system (which is also applicable to LHON and ADOA)6 has yet to be explained. Probably the reply is linked to the overall mitochondrial function, bearing in mind that mitochondria are grouped in networks and, on the basis of the energy and functional demand of tissue, respond to these changes in the environment with unique plasticity by means of fusion and fission processes of the external and internal membranes. The most recent study characterizing Tim8 describes the tendency towards “rigidity” (elevation of the tubular mesh of the network) as well as changes in individual mitochondrial morphology in fibroblasts of patients and when silencing the gene in HeLa cells.7 In the opposite manner, when the protein is overexpressed the mitochondrial mesh is induced to break, up to the point of observing mitochondria in the form of spherical corpuscles (an anomalous state). These data confirm the initial observation of a role for Tim8 as intermediary in the fragmentation of networks and its involvement in apoptosis.8 Along the line of these results, it is known that the most “aggressive” mutations of ADOA prevent the formation of tubular mitochondrial meshes and induce their fragmentation.9 Finally, we cannot omit the fact that in a subgroup of patients with Charcot-Marie-Tooth neuropathy (type VI) optic atrophies also appear together with the predominant peripheral neuropathy, associated to the myotubin 2 (MFN2) protein defect.9 As its name implies, this external membrane GTPase protein regulates fusion events between organelles and its alterations exhibit a range of phenotypes.

In order to clarify the importance of Tim8 in the formation of mitochondrial networks in specific areas of the SNC
it would be necessary to delve deeper in its tissue differential expression profile and, for example, characterize its presence in the various retinal cell layers. This will also allow us to discern if any damage occurs in photoreceptors due to alterations in Tim8 or whether apoptosis is selective towards RGCs. In contrast with the complex I proteins affected by LHON, OPA1 and MFN2, which express ubiquitously and for which the results of in vitro studies are difficult to interpret because modifications are introduced in their integrity, the more subtle aspects of Tim8 biology could be utilized as tools to reach a better understanding of the mitochondrial physiology in specific nervous cells and their response to apoptotic stimuli.

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