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Historical Perspective on Mitochondrial Medicine

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Abstract

In this review, we trace the origins and follow the development of mitochondrial medicine from the pre-molecular era (1962-1988) based on clinical clues, muscle morphology, and biochemistry into the molecular era that started in 1988 and is still advancing at a brisk pace. We have tried to stress conceptual advances, such as endosymbiosis, uniparental inheritance, intergenomic signaling and its defects, and mitochondrial dynamics. We hope that this historical review also provides an update on mitochondrial medicine, although we fully realize that the speed of progress in this area makes any such endeavor akin to writing on water.

Keywords

mitochondria; mitochondrial DNA; maternal inheritance; intergenomic signaling

Call Outs

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“the relative clinical specificity of individual mutations remains a mystery: why the m.3243A>G mutation in tRNA^{Leu} (UUR) causes MELAS and the m.8344A>G mutation in tRNA^{Lys} causes MERRF still escapes us.”

“[Primary CoQ10 deficiencies] are important to consider in the differential diagnosis of infantile encephalomyopathies with nephrosis and in ataxic syndromes because they respond, sometimes dramatically, to oral supplementation of CoQ₁₀.”

“While for most forms of mtDNA depletion there is no effective therapy, remarkable success was obtained in one patient with MNGIE using allogeneic bone marrow transplantation, the first example of stem cell therapy in mitochondrial diseases”

“Mitochondria, faithful to their bacterial origin, are extremely dynamic organelles, often conjoined into tubular aggregates that are constantly reshuffled through the processes of fission and fusion. Mitochondria are capable of moving long distances, for example from the soma of an anterior horn motor neuron to the neuromuscular junction, along microtubular “rails” and propelled by motor proteins (dynamins and kinesins).”

“A woman carrying a mtDNA tRNA mutation ... could have the pronucleus of her fertilized oocyte removed as cleanly as possible ... and transferred to an enucleated host oocyte..., which would then be implanted in her uterus.”

1. The pre-molecular era

It is fair to say that few areas of medicine have seen as many conceptual innovations as mitochondrial medicine. First and foremost was the concept of endosymbiosis, which was proposed at the beginning of last century but was popularized in 1967 by Lynn Sagan Margulis (Sagan, 1967). Endosymbiosis occurred about two billion years ago, when the earth's atmosphere, until then composed of hydrogen, ammonia, and methane, became increasingly rich in oxygen and hydrogen, toxic compounds to most organisms. Early eukaryotic cells, threatened by this poisonous environment, were invaded – and rescued - by bacteria, which had adapted to the oxygen-rich atmosphere. They had also developed means by which oxygen had become the terminal electron acceptor of a pathway (the respiratory chain, RC) that “detoxified” oxygen to produce water and generated much more energy than anaerobic glycolysis. This biological event is oddly reminiscent of Prometheus' mythical gift of fire to humans.

A corollary of endosymbiosis is that all eukaryotic cells, including ours, still contain, in addition to their original nuclear DNA (nDNA), a genetic “relic” (but not a fossil, as we will see) of the protobacterial invaders, namely mitochondrial DNA (mtDNA). As two genomes in one cell cannot function any better than two governments in one country, it is hardly surprising that, in the course of evolution, mtDNA has given up much of its autonomy (in fact, most of its genes have actually been transferred to the nuclear genome) and it has become the slave of nDNA. Curiously, clinical scientists have ignored mtDNA – whose presence was documented in the early 1960s (Nass and Nass, 1963a; Nass and Nass, 1963b; Schatz et al., 1964) – until 1988, when the first mutations in mtDNA were associated with human disease (Holt et al., 1988; Wallace et al., 1988). This was the beginning of the “molecular era” of mitochondrial medicine, but we are running ahead of ourselves, as the history of mitochondrial medicine started more than two decades earlier.

In 1962, a group of investigators at the Karolinska University in Stockholm, including the endocrinologist Rolf Luft, the biochemist Lars Ernster, and the morphologist Björn Afzelius, described a young Swedish woman with severe hypermetabolism unrelated to thyroid dysfunction (Luft et al., 1962). This exemplary piece of translational investigation was based on three sets of data: morphological evidence of abnormal mitochondria in muscle; biochemical documentation of “loose coupling” of oxidation and phosphorylation in isolated muscle mitochondria; and logical correlation between biochemical abnormalities (loose coupling) and clinical features (hypermetabolism). To let Rolf Luft himself, who died in 2007, tell the story: “*I was in the position to undertake the first studies of a cell organelle in 1959-62. They were performed following observations made at the bedside of a patient with striking symptoms never encountered before. These clinical observations, first, led to an idea about the origin of the symptoms, and, second, to studies of this particular organelle, the mitochondrion.*” (Luft, 1994)

It is noteworthy that this paper introduced not only the concept of mitochondrial medicine but also that of “organellar medicine,” because the paper by Henry-Géry Hers on inborn lysosomal diseases was not published until three years later (Hers, 1965). In another twist of history, it turns out that “Luft disease” must be the rarest of all mitochondrial disorders, having been confirmed only in one other patient, about 10 years after Luft's report (DiMauro et al., 1976; Haydar et al., 1971). Another interesting feature of Luft disease is that its molecular basis remains unknown.

In the decade that followed Luft's report, the attention of clinical scientists was largely directed to muscle disorders and to muscle morphology. At the University of Pennsylvania, G. Milton Shy and Nicholas Gonatas conducted systematic ultrastructural investigations of muscle biopsies (Shy and Gonatas, 1964; Shy and Gonatas, 1966) and gave fanciful Greek names to myopathies with too many normal-looking mitochondria (“pleoconial myopathy”) or with greatly enlarged mitochondria (“megaconial myopathy”). In fact, Shy and Gonatas may have foretold the importance of mtDNA in 1965, when they stated, “If mitochondria are self-replicating organelles as recent chemical and morphological evidence has suggested, these two myopathies [pleoconial and megaconial] may be due to a defective gene,” which seems to imply mitochondrial genetics (Gonatas and Shy, 1965).

In 1963, W. King Engel, then at the NIH, introduced a simple histochemical assay - a modification of the Gomori trichrome stain (Engel and Cunningham, 1963) - that revealed abnormal mitochondrial proliferation in muscle as irregular purplish patches in fibers that were famously called “ragged-red” (RRF).

Biochemical studies were not conducted systematically until the 1970s, when the application of specific biochemical assays led to the description of increasing numbers of metabolic defects, including deficiencies of pyruvate dehydrogenase complex (PDHC) (Blass et al., 1970), palmitoylcarnitine transferase (CPT) (DiMauro and DiMauro-Melis, 1973), and carnitine (Engel and Angelini, 1973; Karpati et al., 1975), as well as defects of individual complexes of the RC, including complex III (Spiro et al., 1970) and complex IV (Willems et al., 1977).

In 1985, we proposed a general biochemical classification of the mitochondrial diseases, based on the five main steps of mitochondrial metabolism: defects of substrate transport (e.g. CPT deficiency); defects of substrate utilization (e.g. PDHC deficiency); defects of the Krebs cycle (e.g. fumarase deficiency); defects of the electron-transport chain (e.g. cytochrome *c* oxidase [COX] deficiency); and defects of oxidation/phosphorylation coupling (e.g. Luft disease) (DiMauro et al., 1985). While this classification is still valid and new specific entities have been added to each category, it has also become generally accepted that the term “mitochondrial encephalomyopathies,” introduced in 1977 by Yehuda Shapira to acknowledge the often multisystemic nature of these disorders (Shapira et al., 1977), be reserved to diseases due to defects in the RC. This conventional wisdom is supported by the biochemical complexity of the mitochondrial RC, by its unique dual genetic control, and by the extraordinary clinical and genetic heterogeneity of the diseases related to its dysfunction.

The multisystemic nature of most mitochondrial diseases resulted in a controversy between “splitters,” who found it useful to identify distinct syndromes (Rowland, 1994), and “lumpers,” who considered individual clinical pictures simply as variations of a continuum (Petty et al., 1986). To the credit of the splitters, there are several well-defined and easily recognizable syndromes identified by often unpronounceable acronyms, such as MELAS (Pavlakakis et al., 1984), MERRF (Fukuhara et al., 1980), and MNGIE (Bardosi et al., 1987). To the credit of the lumpers, there are many examples of overlap syndromes, although these seem to be more the exception than the rule.

It is not our intention to minimize the enormous contributions that increasingly sophisticated diagnostic techniques, most notably neuroradiology and mass spectrometry, have made to our recognition of mitochondrial diseases. However, it is also fair to say that major advances in our understanding and ability to classify these disorders have come from molecular genetic studies and on these we will focus the rest of this review.

2. The molecular era

2.1. Mutations in mtDNA

As mentioned above, the molecular era of mitochondrial medicine started in 1988 and the last decade of the first millennium was dominated by breakneck discoveries of pathogenic mutations in the small circle of mtDNA, which somewhat unexpectedly turned out to be a veritable Pandora's box. After Anita Harding and coworkers described single, large-scale mtDNA deletions in patients with mitochondrial myopathies (Holt et al., 1988), our group at Columbia University associated them with Kearns-Sayre syndrome (KSS) (Zeviani et al., 1988) and, more generally, with sporadic progressive external ophthalmoplegia (PEO) (Moraes et al., 1989). After Doug Wallace and coworkers described the first [homoplasmic] point mutation in the ND4 gene of complex I in patients with Leber hereditary optic neuropathy (LHON) (Wallace et al., 1988), the most common point mutations causing MELAS and MERRF were identified (Goto et al., 1990; Shoffner et al., 1990) and, at the dawn of the new millennium, 115 mutations were listed in the catalogue of *Neuromuscular Disorders* (Servidei, 2001).

More importantly, our rapidly increasing clinical experience largely validated the conceptual rules of mitochondrial genetics: maternal inheritance, multisystemic but heterogeneous clinical involvement depending on heteroplasmy and threshold effect, variable course due to mitotic segregation (DiMauro and Davidzon, 2005).

However, we also found exceptions to the mitochondrial genetic rules and we realized that we had come to some erroneous conclusions. One glaring exception was the patient with myopathy, who had inherited his muscle mtDNA (but not the pathogenic mutation) from his father (Schwartz and Vissing, 2002). We should keep in mind that the common heteroplasmic nature of pathogenic mutations does not imply that homoplasmic mutations are never pathogenic (Carelli et al., 2006; Horvath et al., 2009; McFarland et al., 2002; Taylor et al., 2003; Wallace et al., 1988). Although tissue-specificity is not expected in mtDNA-related disorders, it does occur, due to extremely skewed heteroplasmy in one tissue or, probably more often, to *de novo* somatic mutations, especially in skeletal muscle (Andreu et al., 1999). While it is true that most mtDNA mutations behave as functionally “recessive” (to borrow a Mendelian term) in the sense of having pathogenic thresholds that are both high and steep, there are notable exceptions (Sacconi et al., 2008). Finally, the expression of mtDNA mutations, and especially homoplasmic ones, depends on multiple potential factors, including mtDNA haplogroup and – an important area of current research – modifier nuclear genes (Horvath et al., 2009; Hudson et al., 2007; Shankar et al., 2008).

Our understanding of the pathogenic mechanism of mtDNA mutations was greatly aided by Giuseppe Attardi's application to mitochondrial diseases of cytoplasmic hybrid (cybrid) cells (King and Attardi, 1989), that is, established human cell lines first depleted of their own mtDNA, then repopulated with various proportions of mutated genomes (Chomyn et al., 2000; King et al., 1992; Masucci et al., 1995). However, there is still a disconnect between our knowledge of the molecular basis of mtDNA-related disorders and their pathogenesis. While much can be explained by the rules of mitochondrial genetics and by studies of cybrid cell lines, the relative clinical specificity of individual mutations remains a mystery: why the

m.3243A>G mutation in tRNA^{Leu} (UUR) causes MELAS and the m.8344A>G mutation in tRNA^{Lys} causes MERRF still escapes us.

Although mtDNA-related disorders were considered rare, several epidemiological studies conducted at the beginning of the new millennium came to the conclusion that the overall prevalence of mtDNA diseases was about 1 in 5,000, higher than we had thought (Darin et al., 2001; Schaefer et al., 2007; Schaefer et al., 2004; Skladal et al., 2003). Then, in 2008, Chinnery and coworkers screened mtDNA for 10 pathogenic point mutations in over 3,000 cord bloods of normal newborns and concluded that at least 1 in 200 individuals harbor pathogenic mtDNA mutations (Elliott et al., 2008). When one considers only the typical “MELAS mutation,” m.3243A>G, the prevalence was 1 in 750, similar to that (1 in 423) encountered in Australia (Manwaring et al., 2007). As the frequency of typical MELAS is obviously much lower, the mutation is either present in subthreshold amounts in many asymptomatic individuals or it surpasses the pathologic threshold in individual tissues in patients with diseases other than MELAS, such as diabetes mellitus (Kadowaki et al., 1994).

In 2000, one of the authors (SDM) entitled a review on mtDNA-related disorders “Are we scraping the bottom of the barrel?” (DiMauro and Andreu, 2000). Ten years later, it is obvious that we are still far from it.

2.2. Mutations in nDNA

2.2.1. Defects of the respiratory chain—Although we are still far from scraping the bottom of the mtDNA barrel, inevitably the “low fruit” of mtDNA mutations became less attainable in the mid 1990s and we started directing our attention to the nuclear genome, which, after all, encodes about 99% of mitochondrial proteins and about 86% of RC subunits.

Not too surprisingly, the first “direct hit”, *i.e.* the first mutations in a gene encoding a respiratory chain subunit, affected complex II, which is small and entirely encoded by nDNA. The year was 1995, the authors Arnold Munnich and coworkers, and the patients two sisters with Leigh syndrome who were homozygous for a mutation in the flavoprotein subunit (Bourgeron et al., 1995).

Next, the group of Nijmegen bravely confronted the Goliath of the respiratory chain, complex I, and, in a stream of elegant papers, reported numerous mutations in at least 10 highly conserved structural proteins in patients with isolated complex I deficiency and, most commonly, Leigh or Leigh-like syndromes (for review, see (Janssen et al., 2006; Smeitink and van den Heuvel, 1999; Smeitink et al., 2001). The latest direct hit reported by the Nijmegen group concerns NDUFS1, one of the seven “core subunits” associated with the mtDNA-encoded ND proteins (Hoefs et al., 2010). Interestingly, two patients harboring mutations in the NDUFA1 gene, had the first X-linked recessive RC disease (Fernandez-Moreira et al., 2007).

There is only one reported mutation of a complex III nuclear subunit, QP-C or subunit VII, in a girl with a rather benign hepatopathy with hepatomegaly and hypoglycemia (Haut et al., 2003).

Our group sequenced most of the nuclear genes encoding cytochrome *c* oxidase (COX) subunits and we looked assiduously for direct hit mutations in patients with COX-deficient Leigh syndrome (LS), to no avail. That these mutations must be very rare is suggested by the fact that the first such mutation was reported just two years ago (Massa et al., 2008).

Only for complex V (ATP synthetase), have we not yet identified mutations that directly affect any one of its 12 nDNA-encoded subunits.

A peculiar kind of direct hit can be considered mutations in genes involved in the biosynthesis of CoQ₁₀ (Lagier-Tourenne et al., 2008; Lopez et al., 2006; Mollet et al., 2008; Quinzii et al., 2006), as they cause primary CoQ₁₀ deficiency, which often results in a severe block of the respiratory chain (Quinzii et al., 2008). These newly recognized disorders [Primary CoQ₁₀ deficiencies] are important to consider in the differential diagnosis of infantile encephalomyopathies with nephrosis and in ataxic syndromes because they respond, sometimes dramatically, to oral supplementation of CoQ₁₀.

With the term “indirect hits” we refer to mutations in nuclear genes that do not affect respiratory chain subunits directly, but alter proteins needed for the assembly and maintenance of respiratory chain complexes. Because of the difficulties in finding direct hits for complex IV in patients with COX deficiency, it stands to reason that this was the first complex for which mutations in an assembly protein were identified. The year was 1998, the protein SURF-1, and two groups, that of Shoubridge in Montreal and that of Zeviani in Milan, reported mutations in patients with LS and COX deficiency (Tiranti et al., 1998; Zhu et al., 1998), which are probably the most common molecular causes of COX deficiency in humans. That discovery opened the gates to a flood of mutant assembly genes, including *SCO2* (Papadopoulou et al., 1999), *SCO1* (Valnot et al., 2000a), *COX10* (Antonicka et al., 2003a; Valnot et al., 2000b), and *COX15* (Antonicka et al., 2003b). The introduction of “integrative genomics,” based on bioinformatics-generated intersection of DNA, mRNA, and protein data sets, facilitated the discovery of two more COX assembly genes: the *LRPPRC* gene (encoding the leucine-rich pentatricopeptide repeat cassette protein) in patients with Leigh syndrome, French Canadian type (LSFC) (Mootha et al., 2003); and the *ETHE1* gene, responsible for ethylmalonic encephalomyopathy (EE), a devastating early-onset encephalopathy with microangiopathy, chronic diarrhea, and massively increased levels of ethylmalonic acid and short-chain acylcarnitines in body fluids (Tiranti et al., 2004).

The first mutations in an assembly protein for complex I were described by Shoubridge's group (Ogilvie et al., 2005) and several more reports soon followed (Dunning et al., 2007; Saada et al., 2008; Saada et al., 2009; Sugiana et al., 2008).

One complex III assembly protein has been associated with human disease and is encoded by the *BCSIL* gene. Mutations in *BCSIL* can cause a fatal infantile syndrome dubbed GRACILE (growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis and early death) (Fellman, 2002), less severe infantile encephalomyopathies (Blazquez et al., 2009; Fernandez-Vizarra et al., 2007), or a relative mild adult condition (Björnstad syndrome) characterized by sensorineural hearing loss and pili torti (Hinson et al., 2007).

Four years elapsed between the first report of mutations in an assembly gene for complex V, *ATP12* (De Meirleir et al., 2004) and the identification of a commonly affected gene (*TMEM70*), especially among the Roma (Gypsy) population (Cizkova et al., 2009).

2.2.2. Defects of intergenomic communication—From a chronological point of view, the first description of garbled dialogue between the nuclear and the mitochondrial genomes preceded the discovery of mutations directly or indirectly affecting the respiratory chain. In fact, as early as 1989 Massimo Zeviani described Italian families with autosomal dominantly inherited PEO and RRF that harbored *multiple* mtDNA deletions in muscle (Zeviani et al., 1989).

This observation started a chase for nuclear genes associated with Mendelian PEO and multiple mtDNA deletions in muscle. The first such gene to be identified was *TYMP* (formerly known as *ECGFI*), which encodes thymidine phosphorylase and, when mutated, causes MNGIE (mitochondrial neurogastrointestinal encephalomyopathy) (Nishino et al., 1999). In the same year, Kaukonen and coworkers identified mutations in *ANTI*, which encodes the adenine nucleotide translocator 1, in patients with autosomal dominant PEO (Kaukonen et al., 2000). The following year, Spelbrink and coworkers associated autosomal dominant PEO with mutations in *PEO1* (formerly known as *Twinkle*) (Spelbrink et al., 2001), and Van Goethem and coworkers identified the first mutations in *POLG*, encoding the mitochondrial polymerase (pol γ), in patients whose PEO could be inherited either as a dominant or as a recessive trait (Van Goethem et al., 2001). It took five more years before mutations in *POLG2*, the gene encoding the accessory subunit of pol γ , were found in a single case of dominant PEO (Longley et al., 2006).

Somewhat surprisingly, mutations in the gene (*OPA1*) encoding a dynamin-related protein of crucial importance for mitochondrial fusion and for the integrity of the inner membrane, besides causing dominant optic atrophy (DOA) (Alexander et al., 2000; Delettre et al., 2000), are also a major cause of dominant PEO, ataxia, deafness, and multiple mtDNA deletions (Hudson et al., 2008; Yu-Wai-Man et al., 2010).

To consider the second major category of faulty intergenomic signaling, affecting mtDNA abundance rather than mtDNA integrity, we have to back-pedal to 1991, when Carlos Moraes, then at Columbia University, described the first patients with severe and tissue-specific mtDNA depletion (Moraes et al., 1991). Two major syndromes were associated with mtDNA depletion: myopathy, which could manifest in infants and be rapidly fatal or present later in childhood, sometimes mimicking muscular dystrophy or spinal muscular atrophy (SMA); or hepatocerebral involvement, exemplified by Alpers-Huttenlocher syndrome (AHS). The first genetic defects were discovered simultaneously in Israel and were rather neatly associated one (mutations in the *TK2* gene, encoding thymidine kinase) with the myopathic presentation (Saada et al., 2001) and the other (mutations in the *DGUOK* gene, encoding deoxyguanosine kinase) with the hepatocerebral syndrome (Mandel et al., 2001). A third clinical syndrome should be added, MNGIE, because in muscle from these patients Hirano and coworkers have documented the coexistence of mtDNA multiple deletions and site-specific mtDNA point mutations (Nishigaki et al., 2003). Yet another gene known to cause PEO and mtDNA multiple deletions, *PEO1* (see above), can also cause hepatocerebral syndrome with mtDNA depletion (Hakonen et al., 2007; Sarzi et al., 2007).

Nine nuclear genes have now been associated with mtDNA depletion syndromes, *TK2*, *DGUOK*, *POLG*, *SUCLA2*, *SUCLG*, *RRM2B*, *PEO1*, *TYMP*, and *MPV17* (Poulton et al., 2009; Rotig and Poulton, 2009; Smits et al., 2010; Spinazzola et al., 2009). Except for *MPV17*, an inner mitochondrial membrane protein whose precise function is unclear, all of the proteins encoded by these genes are involved in the homeostasis of the mitochondrial nucleoside/nucleotide pool, the “building blocks” of mtDNA. While for most forms of mtDNA depletion there is no effective therapy, remarkable success was obtained in one patient with MNGIE using allogeneic bone marrow transplantation, the first example of stem cell therapy in mitochondrial diseases (Hirano et al., 2006).

Defects of mtDNA translation: Are the third example of faulty intergenomic communication, as multiple nuclear factors control the translational machinery of mtDNA. These disorders usually present in infancy, are accompanied by lactic acidosis, and cause multiple respiratory chain enzyme deficiencies (Smits et al., 2010) (Jacobs and Turnbull, 2005). Mutations have been identified in genes encoding translation elongation factors

(Coenen et al., 2004; Miller et al., 2004), pseudourydilation (Bykhovskaya et al., 2004), and tRNA synthetases (Edvardson et al., 2007; Scheper et al., 2007).

3. Other mitochondrial diseases

Thus far, we have dealt with disorders directly impairing respiratory chain function. Other types of mitochondrial dysfunction affect the respiratory function indirectly. The resulting disorders can be clinically very similar, as we have described above. Conversely, we are discovering that some forms of well known neurodegenerative diseases, such as Charcot-Marie-Tooth (CMT) neuropathy, and hereditary spastic paraplegia (HSP), are due to mutations in mitochondrial proteins, which, while controlling general functions, such as phospholipid biosynthesis, organellar dynamics, or protein importation, may well affect the respiratory chain and the production of reactive oxygen species (ROS).

3.1. Defects of the inner mitochondrial membrane milieu

The gene responsible for an X-linked mitochondrial myopathy and cardiomyopathy described in 1983 by the Dutch pediatrician Peter Barth (Barth syndrome) (Barth et al., 1983) was identified in 1996 by the Italian geneticists Silvia Bione and Daniela Toniolo (Bione et al., 1996). The gene (*TAZ*) encodes a protein dubbed tafazzin, which turns out to be an acetyltransferase (Xu et al., 2006). After Ronald Wanders established a relationship between tafazzin mutations and cardiolipin, the most abundant phospholipid in the mitochondrial inner membrane (Vreken et al., 2000), Michael Schlame documented severe cardiolipin deficiency in multiple tissues from Barth syndrome patients (Schlame and Ren, 2006).

Cardiolipin is much more than a mere scaffold for the respiratory chain, serving as a critical determinant of respiratory chain structure and function (Claypool, 2009; Gohil et al., 2004; Sedlak et al., 2006; Zhang et al., 2005). Thus, it stands to reason that respiratory chain dysfunction may play an important role in the pathogenesis of Barth syndrome. It is also reasonable to assume that other genetic alterations of phospholipid metabolism may affect mitochondrial membranes and cause disease.

3.2. Defects of mitochondrial protein import

Although the number of proteins to be imported from the cytoplasm is huge and the import machinery correspondingly complicated (Bolender et al., 2008), very few human diseases have been ascribed to defective protein transport. A few mutations in the gene sequences of mitochondrial target signals explain specific enzyme defects, including a form of methylmalonic acidemia (Ledley et al., 1990) and one form of PDH deficiency (Takakubo et al., 1995). The few disorders due to mutations affecting the general import machinery include: the X-linked Mohr-Tranebjaerg (deafness-dystonia) syndrome due to mutations in the *TIMM8A* gene (Roesch et al., 2002); an autosomal dominant form of hereditary spastic paraplegia (HSP type 13 or SPG13) due to mutations in *HSPD1*, which encodes the import chaperonin HSP60 (Hansen et al., 2002); an early-onset autosomal recessive neurodegenerative disorder with brain hypomyelination and leukodystrophy also due to mutations in *HSPD1* (Magen et al., 2008); and an autosomal recessive dilated cardiomyopathy with ataxia (DCMA) clinically similar to Barth syndrome but due to mutations in *DNAJC19*, which encodes an inner mitochondrial membrane protein similar to a yeast co-chaperonin (Davey et al., 2006).

3.3. Defects of mitochondrial dynamics

Mitochondria, faithful to their bacterial origin, are extremely dynamic organelles, often conjoined into tubular aggregates that are constantly reshuffled through the processes of

fission and fusion. Mitochondria are capable of moving long distances, for example from the soma of an anterior horn motor neuron to the neuromuscular junction, along microtubular “rails” and propelled by motor proteins (dynamins and kinesins). One important result of mitochondrial dynamics is an equitable (to use a teleological term) distribution of energy in the various domains of the cell.

Not surprisingly, tampering with mitochondrial dynamics leads to disease, often affecting long neural pathways. Thus, the first disorder to be described affected the optic nerve (dominant optic atrophy, DOA) and was due to mutations in *OPA1*, a gene that controls a “fusion” protein and has also been associated with dominant PEO and multiple mtDNA deletions (see above) (Alexander et al., 2000; Delettre et al., 2002). The most important peripheral nerve disorder due to altered mitochondrial dynamics is Charcot-Marie-Tooth (CMT), various forms of which (2A, 4A, 6) have been attributed to mutations in *MFN2*, encoding mitofusin 2 (Zuchner et al., 2004) or in *GDAP1*, which encodes ganglioside-induced differentiation protein 1 (Pedrola et al., 2005). Another neurological phenotype associated with mutations in genes controlling mitochondrial dynamics is hereditary spastic paraplegia, including SPG10, due to mutations in the kinesin gene *KIF5A* (Fichera et al., 2004). More generally, there are clear relationships between the mitochondrial genes that cause major neurodegenerative disorders, such as Parkinson disease, amyotrophic lateral sclerosis (ALS), and Alzheimer disease (AD) and abnormal mitochondrial dynamics (for review, see (DiMauro and Schon, 2008)

4. Conclusion

Ultimately, the goal of translational research is to come up with rational therapeutic strategies, a goal largely unfulfilled for the mitochondrial diseases, with few exceptions, as for the primary CoQ₁₀ deficiencies and MNGIE. However, there is a fervor of research in laboratories around the world, exemplified by recent achievements in pronuclear transfer to prevent transmission of mtDNA diseases.

Indeed, one plight of unaffected women carrying mtDNA mutations – at least carrying tRNA mutations - is the lack of prenatal diagnosis. A theoretical solution exists, one that had been partially implemented to increase the success of in vitro fertilization (IVF) (Barritt et al., 2001). A woman carrying a mtDNA tRNA mutation (say, the common MELAS mutation) could have the pronucleus of her fertilized oocyte removed as cleanly as possible (i.e. with minimal amount of accompanying cytoplasm) and transferred to an enucleated host oocyte (obviously not from a maternally related donor), which would then be implanted in her uterus. If successful, this approach would guarantee mitochondrially normal children carrying the nuclear traits of both parents. Actually, this basic principle has been successfully applied in monkeys all the way to the birth of normal twins devoid of their mother's mtDNA (Tachibana et al., 2009) and it worked in human oocytes to the blastocyte stage in vitro (Craven et al, 2010). On this hopeful note it seems appropriate to conclude this bird's eye view of mitochondrial medicine. Stay tuned.

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