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Mitochondrial Aging and Metabolism: The Importance of a Good Relationship in the Central Nervous System

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Additional information is available at the end of the chapter

Abstract

The mitochondrial theory of aging suggests that mitochondria have a decrease in production capacity of adenosine triphosphate (ATP). The question may seem trivial, but it becomes more complex when considering that dysfunctional mitochondria can be eliminated by lysosomal digestion and that cell with dysfunctional mitochondria can undergo the process of apoptosis. In organs with regenerative capacity, like the liver, cell proliferation can almost completely hide mitochondrial dysfunction. However, evidence indicates selective damage in mitochondria during aging, and so the mitochondrial aging theory is gaining recognition and respect. There is solid evidence that accumulated DNA damage in mitochondria is a cause directly related to metabolic disorders such as diabetes and degenerative disorders such as Alzheimer's disease. The central nervous system is particularly susceptible to oxidative damage due to several factors, among which are its high oxygen consumption, its dependence on aerobic carbohydrate metabolism, and its complex composition of membrane lipids. Free radicals are generated at many cell sites, and the mitochondrial respiratory chain is one of the main sources. While many studies have been conducted in experimental animal models, the results are relevant because at least some of their interventions suggest a directing aim at reducing the effects of aging.

Keywords: mitochondria, aging, nervous system, regulation, oxidative stress

1. Mitochondria and DNA

Mitochondria are double-membrane organelles that are found in the cytoplasm of most eukaryotic cells, and they are essential for the functioning of tissues that are highly dependent on aerobic metabolism, like the brain and heart, since they produce more than 90% of the energy needed for cellular functions [1]. The human mitochondrial genome (mtDNA) is a double circular molecule of 16,571 pairs of nucleotides (16.5 Kb) which contains 37 genes that code for 22 transfer RNAs, 2 ribosomal RNAs, and 13 subunits that encode mitochondrial DNA. These 13 subunits are key in the respiratory chain and in the oxidative phosphorylation system which contains 7 subunits of complex I, 1 subunit of complex III, 3 subunits of complex IV or cytochrome oxidase, and 2 subunits of complex V or ATP synthase (ATPase6 and ATPase8) (**Figure 1**) [1–3].

1.1. Specific characteristics of mitochondrial genetics

The type of inheritance of the mitochondrial genetic system, its location in a cytoplasmic organelle, and the continuous arrangement of genes with almost no intermediate nucleotides or introns and polyplasmy (high number of copies in each cell) provide genetic characteristics that clearly differentiate them from those of nuclear DNA. Each cell contains between 1000 and 10,000 copies of mtDNA depending on the tissue, surpassing a few hundred in the sperm and up to 100,000 in the oocyte [4]. Each mitochondrion contains between 2 and 10 molecules. The mtDNA is primarily maternally inherited by a vertical non-Mendelian pattern. Very small amounts of parental mtDNA have been detected; for example, a case of a 28-year-old male with mitochondrial myopathy was reported due to a new 2 bp deletion in the mtDNA of the ND2 gene (also known as MTND2), which encodes a subunit of the complex I enzyme of the mitochondrial respiratory chain. In this study, it was determined that
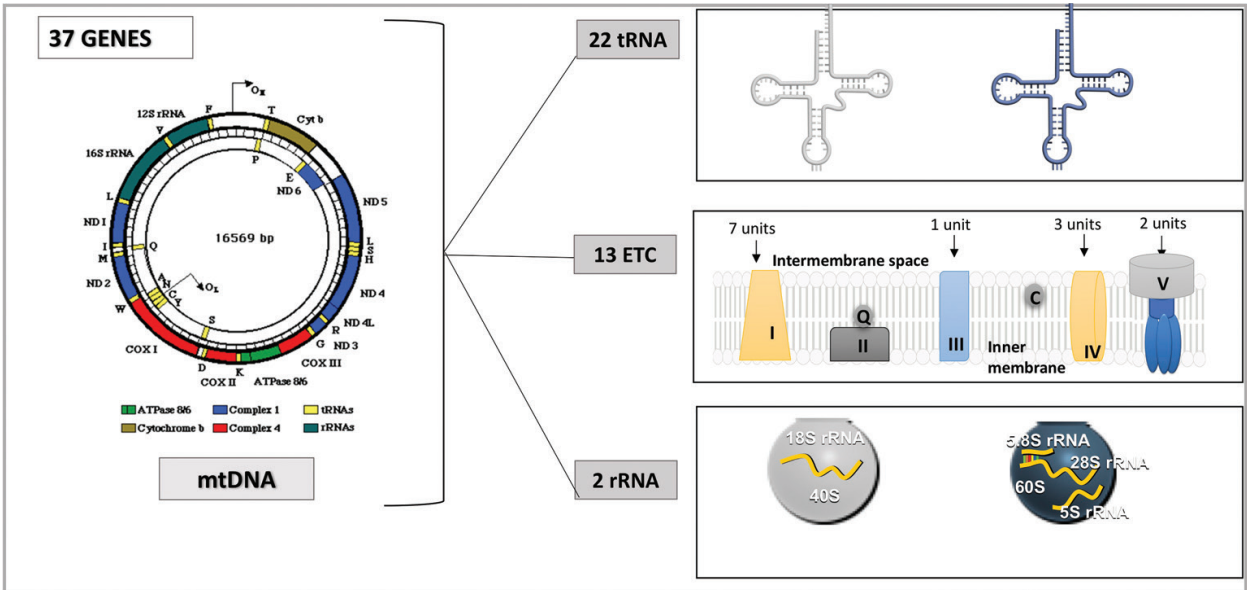

Figure 1. The mitochondrial genome. Mitochondrial DNA (mtDNA) contains essential genes for normal mitochondrial function, including protein production and electron transport chain (ETC) assembly. This image is a modification of QIAGEN's original [Sánchez-Lopez AL].
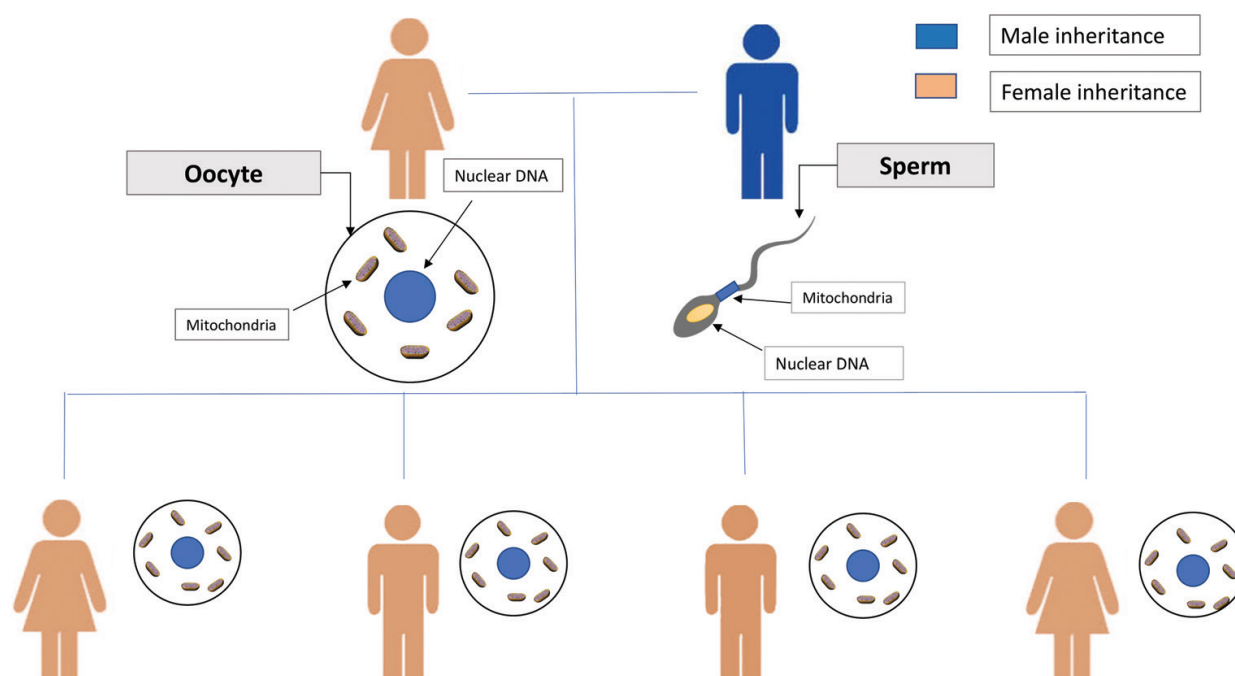
Figure 2. Inheritance pattern of mitochondrial DNA. mtDNA is transferred along material lineage; sperm-derived paternal mitochondria enter the oocyte cytoplasm after fertilization but are eliminated from the cytoplasm of gametes. Mitochondrial disease is always related in the maternal line.

the mtDNA harboring the mutation was of paternal origin and was calculated to be present in 90% of the mtDNA of the patient's muscle [5].

The general pattern is that mothers transmit their mitochondrial genome to all of their off-spring, but only daughters will pass it on to all of the members of the next generation. This is due to the high number of mtDNA molecules that exist in the ovules (between 100,000 and 200,000 copies) compared to a few hundred in the sperm. In addition, paternal mitochondria that enter the fertilized ovum are eliminated by an active process (**Figure 2**) [6, 7].

1.2. Mitotic segregation

The phenotype of a cell line can vary during cell division because the mitochondria are randomly distributed among daughter cells; so, if in a cell two populations of mtDNA coexist, one normal and one mutated (heteroplasmy), throughout divisions three different genotypes may originate: homoplasmic for normal mitochondrial DNA, homoplasmic for mutated mitochondrial DNA, and heteroplasmic DNA. Therefore, the phenotype of a cell with heteroplasmy will depend on the per-centage of mutated DNA it contains. If the number of damaged mtDNA molecules is relatively low, complementation with normal DNA molecules occurs, and the genetic defect will not manifest [8]. When the mutated DNA exceeds a certain threshold, a pathogenic phenotype will develop accord-ing to a threshold effect: if ATP production is below the minimum necessary for the functioning of the tissues, due to defective proteins encoded in the mtDNA, illness might develop [7, 9, 10]. The number of DNA molecules is different in each organ and tissue depending on the required energy amounts for functioning. Therefore, the most affected organs and systems are vision, the central nervous system, skeletal muscle, heart, pancreatic islets, kidney, and liver (**Figure 3**) [6, 11, 12].
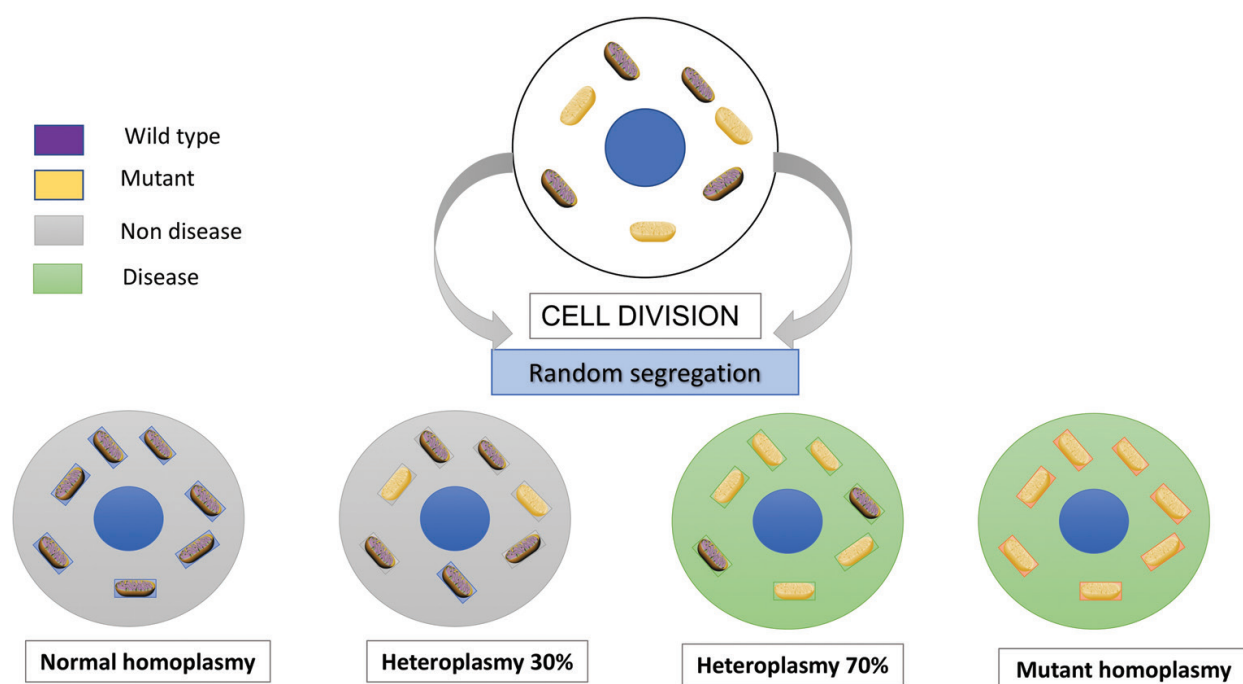
Figure 3. Mitochondrial homoplasmy and heteroplasmy. The expression of mitochondrial diseases is variable; a single cell may receive a uniform collection of mtDNA (homoplasmy) or a mixture of mutant and wild-type mtDNA (heteroplasmy). The proportion of mutant mtDNA molecules determines the penetrance and severity of expression.

1.3. High mutation speed

The mtDNA has a spontaneous mutation rate 10 times higher than that of nuclear DNA. Continuous mitochondrial production of oxygen radicals by the final oxidation of carbon compounds probably damages the unprotected mtDNA (e.g., mtDNA reminds bacterial genomes as it lacks histones). Therefore, the within-species individual sequence variation is large, up to about 70 nucleotides. Within single individuals, low heterogeneity levels in the mtDNA will be generated throughout life. It has been proposed that the decrease in respiratory capacity of the tissues, which takes place during aging, may be due to an accumulation of such mitochondrial damages. This theory was first evidenced in a study by the Attardi Group, who documented that the mitochondria deteriorate with age as a result of the accumulation of mutations [13]. Mitochondrial dysfunction is characterized by a deficient production of energy, a failure in calcium homeostasis, an activation of proteases and phospholipases, activation of nitric oxide synthase, and an abundant generation of free radicals [14–16]. Mitochondria, besides being the main source of free radicals, are also very susceptible to oxidative stress, which is made evident by a massive induction of lipid peroxidation, protein oxidation, and mutations in mtDNA. Oxidative stress also induces apoptotic death, and the mitochondria play a central role in this phenomenon since there is cytochrome c release to the cytoplasm and opening of the permeability transition pore [16].

1.4. Metabolic regulation and the central nervous system: the central role of mitochondria

Mitochondria provide the energy required for neuron function because they transform the potential chemical energy stored in covalent bonds of glucose or fatty acids into chemical

energy stored in the covalent bonds between ATP phosphates. This last form of potential chemical energy is easily usable by the cell and has been selected throughout evolution as the mechanism by means of which all cellular processes that require the use of energy readily dispose of it [10, 17]. The body must maintain a balance between the needs of cells and the availability of fuel, which is called metabolic homeostasis. The constant availability of fuel in the blood is called caloric homeostasis, whereby the blood level of fuel (in ATP equivalents) does not decrease below certain limits regardless of whether the individual is in a state of good nutrition or fasting. The maintenance of metabolic homeostasis is achieved through the integration of three main factors: (1) the concentration of nutrients in the blood, which affects the speed with which these are used and stored in different tissues, (2) hormone levels in blood (first messengers) that transmit information to specific tissues on the state of the organism and the contribution or demand of nutrients, and (3) the central nervous system (CNS) that by way of neural signals controls the metabolism directly or through the release of hormones [9, 18]. Despite its essential role in the energy metabolism of the brain and other tissues, the amount of circulating glucose is limited. To ensure its continued provision, the body stores metabolic fuels to provide glucose or energy in case of need. Within the homeostatic mechanisms that allow regulation of the availability of combustible molecules, hormonal control is one of the most important. Insulin and glucagon are the main hormones that regulate the storage and use of fuels. Insulin is an anabolic hormone that promotes the storage, while glucagon is the hormone that stimulates the mobilization of the combustible molecules [17, 18]. Other hormones, such as adrenaline, are released as a CNS response to hypoglycemia, exercise, and other types of physiological stress. Along with other stress hormones (glucocorticoids), adrenaline increases the availability of fuels. One of the requirements to maintain and perpetuate life is the preservation of homeostasis, that is, the constancy of the internal environment (blood levels of ions, lipids, and carbohydrates) within narrow limits. These conditions must be maintained even in varied situations such as rest, exercise, satiety, or fasting. How is our body harmonized to survive in different metabolic situations? In mammals, the coordination of metabolism is achieved through the neuroendocrine system. The main hormones involved in the regulation of intermediate metabolism are insulin, glucagon, catecholamines, and cortisol [19–21].

The brain must generate large amounts of ATP to maintain the membrane potential, which is essential for the transmission of nerve impulses. Under normal conditions the brain only uses glucose as fuel, oxidizing it through aerobic glycolysis. It does not use fatty acids. In fact, 60% of the total glucose consumed by the body is used by the brain. The metabolism of the brain is totally aerobic, consuming 20% of the total oxygen consumed by the body. It does not have appreciable reserves of glycogen or other fuels so it requires the constant supply of oxygen and glucose that cross the blood–brain barrier with ease [19, 22].

Practically, until adulthood, we are well protected against damage to mitochondria since the body is able to produce antioxidant systems that defend us from it [23]. But as we get older, changes occur inside our cells that determine the progressive destruction of mitochondria and, therefore, bring about aging and disease [24].

The sequence variations existing between different individuals have been very useful for anthropological, ethnological, and forensic studies and are the basis for the hypothesis that all existing humans descend from a woman who lived in Africa about 250,000 years ago (**Figure 4**) [25–27].
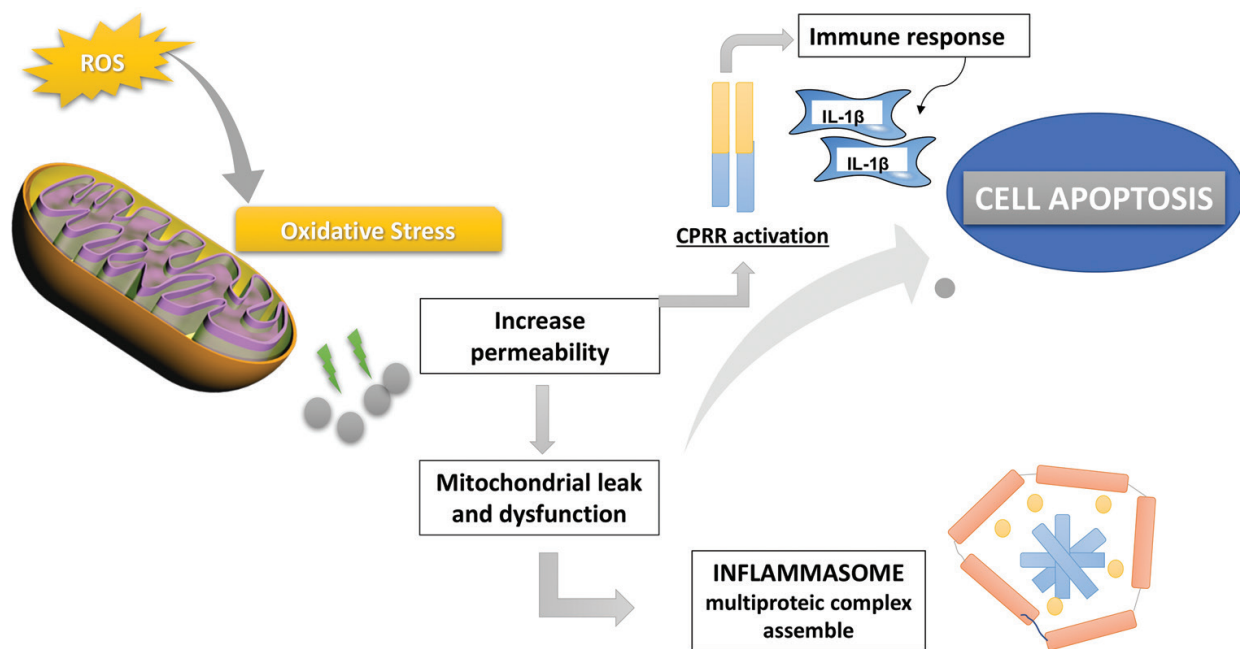
Figure 4. Mitochondrial aging theory. The production of intracellular free radicals, and its effects on cellular components, is a determinant of lifespan. Mitochondria is the prime target for oxidative damage; accumulation of reactive oxygen species (ROS) leads to changes of the inner membrane permeability causing release of intramitochondrial content and activating a cytoplasmic immune response leading to apoptotic cell death.

Mitochondria in the elderly are, for the most part, dysfunctional, unlike young individuals in whom little mitochondrial damage is observed: with the passage of time, devastating changes occur inside our cells that lead to the destruction of mitochondria and consequently trigger aging and disease [15, 28]. Production rates of superoxide anions and hydrogen peroxide (free radicals) increase significantly, specifically deteriorating the mitochondria. At the same time, the levels of endogenous antioxidants (which would contribute to diminishing the harmful effects of free radicals) decrease. There is also a significant reduction of molecules capable of capturing free radicals before they can attack other molecules. Both factors decrease mitochondrial defenses which then become more vulnerable [29, 30]. Oxidative damage accumulated in mitochondrial DNA and other components of the mitochondria (as well as in the cell as a whole) leads to the deterioration of mitochondria, and as a consequence of that deterioration, more free radicals are produced [24].

According to the mitochondrial theory of aging, this growing spiral of deterioration is a process of aging in itself; the number and functional state of the mitochondria determine, in a very specific way, the biologically determined lifespan of individuals. The recent research identifies this mitochondrial aberration associated with age as one of the main mechanisms in chronic inflammation [Ref]. Specifically, mitochondrial dysfunction acts as a mechanism of inflammation in the following manner [31, 32]:

a. The accumulation of free radicals induces a greater permeability in the membrane of the mitochondria.

b. The molecular components normally contained within the mitochondria pass into the cell cytoplasm.

c. The cytoplasmic pattern recognition receptors (CPRRs), which detect and initiate the immune response against intracellular pathogens, recognize the molecules of the mitochondrial discharge as potential threats.

d. After detecting potential threat, the CPRRs form a complex called inflammasome that captures the inflammatory cytokine interleukin-1β, which then recruits components of the immune system to destroy the altered cell.

These four steps represent a simplified diagram of mitochondrial dysfunction that leads to cell destruction; however, free radicals are not the only inducers of cell death by inflammation [33, 34].

Circulating carbohydrates, mainly glucose and fructose, also participate in aging processes. When these blood sugars come into contact with proteins and lipids, a harmful reaction occurs that forms compounds called advanced glycation end products (AGEs). The AGEs bind to a receptor on the surface of the cells called the PFG receptor (receptor for advanced glycation end products (RAGE)). After activation, the RAGEs induce the movement of the nuclear mediator factor kappa-B (NF-kB) to the nucleus where numerous inflammatory genes are activated. AGEs are formed mainly in vivo, and glycation is exacerbated by elevated blood glucose levels. Dietary AGE also contributes to inflammation [17, 18, 35].

Hence, molecules that protect and revitalize mitochondria could recreate a "juvenile" state of protection against free radicals (**Figure 5**) [36].

Mitochondria in the elderly are, for the most part, are dysfunctional, unlike young individuals in whom no mitochondrial damage is observed. So much so is the mitochondrial dysfunction caused by oxidative damage due to free radicals that are already a marker of aging and pathologies associated with age [37].

The mitochondrial theory, which proposes that mitochondrial defects associated with age are controlled by the accumulation of mutations in mitochondrial DNA. There is, however, a growing body of contradictory evidence that has raised questions about the validity of this theory. It has been suggested that the mitochondrial defects associated with age are not controlled by the accumulation of mutations in mitochondrial DNA but by another form of genetic regulation. Contrary to the mitochondrial theory of aging, the epigenetic regulation of respiration controls defects associated with age [37].

Damage to mitochondrial DNA causes changes or mutations in the DNA sequence. The accumulation of these changes is associated with a reduced life expectancy and the early onset of characteristics related to aging such as weight and hair loss, the curvature of the spine, and osteoporosis [38]. There is, however, a growing body of contradictory evidence that has raised questions about the validity of this theory. Tsukuba's team, in particular, has made a compelling research that has led them to propose that the mitochondrial defects associated with age are not controlled by the accumulation of mitochondrial DNA mutations but by another form of genetic regulation [2, 39, 40]. The researchers compared mitochondrial respiration and the amount of DNA damage in the mitochondria, expecting that respiration would decrease and DNA damage would increase in the cells of the elderly group. The elderly group had lower respiration as the accepted theory indicates; however, there was no difference in amounts of
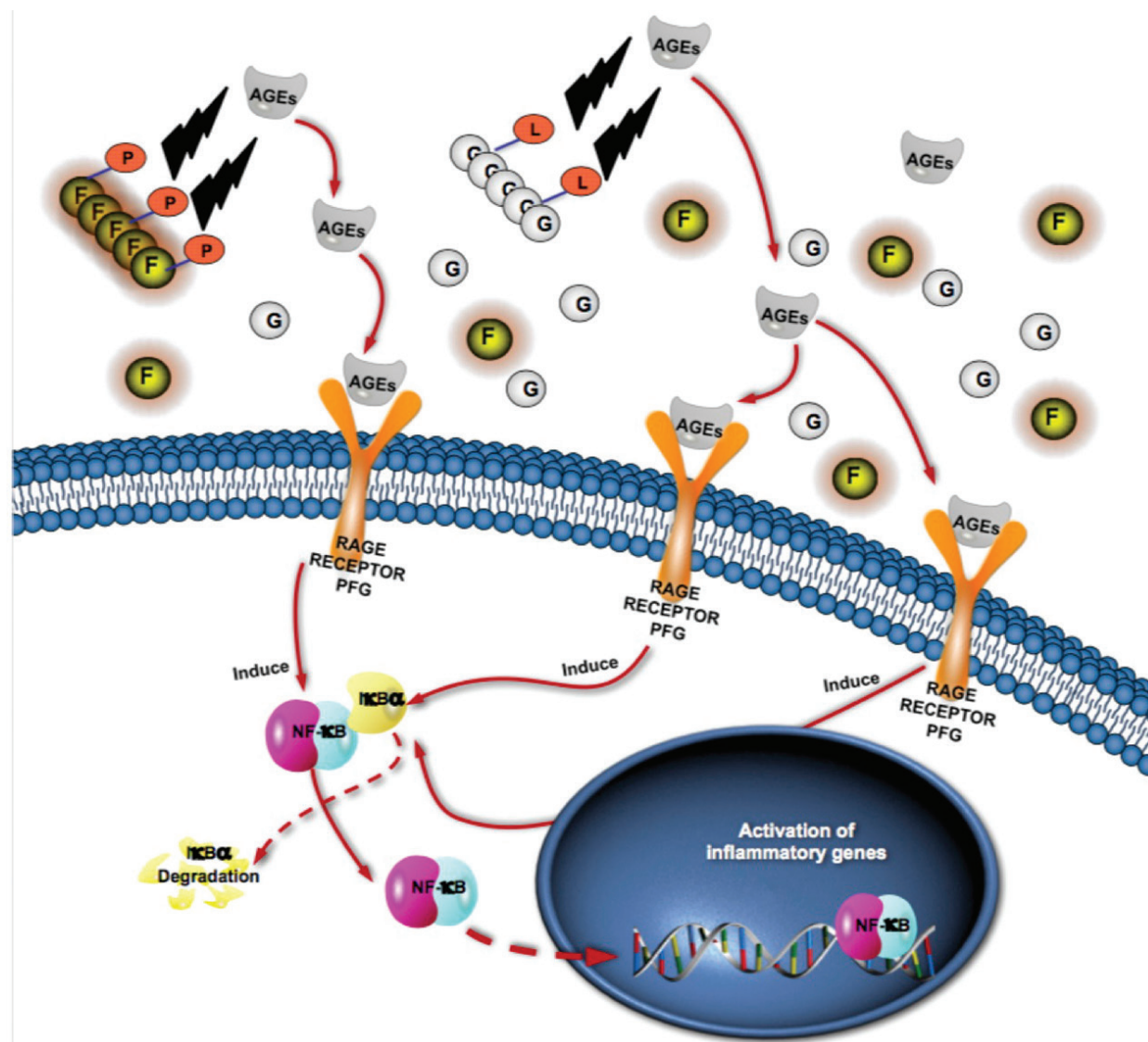
Figure 5. AGEs. The activation of inflammatory genes is triggered by the formation of AGEs. AGEs activate NF-kB through a cascade of reactions. This image is a modification of QIAGEN's original [Torres-Sánchez ED].

DNA damage. This epigenetic regulation may be responsible for the effects associated with age that is seen in mitochondria [7, 41, 42].

To test this theory, a research reprogrammed human fibroblast cell lines derived from the young and from the old to a state similar to that of embryonic stem cells. Then, they returned these cells back to their fibroblast form, and their mitochondrial respiratory function was examined; the researchers looked for genes that could be controlled epigenetically causing these mitochondrial defects associated with age and found two that regulate the production of glycine in the mitochondria, CGAT, and SHMT2 and showed that by changing the regulation of these genes, they can produce defects or restore mitochondrial function in fibroblast cell lines. The addition of glycine for 10 days in the culture medium of the fibroblast cell line of the 97-year-old people restored its respiratory function. This suggests that glycine treatment can reverse the breathing defects associated with aging in elderly human fibroblasts.

Incredibly, the defects associated with age had reversed: all fibroblasts had respiration rates comparable to those of the fetal fibroblast cell line, regardless of whether they were derived from the young or the elderly. This indicates that the aging process in the mitochondria is controlled by epigenetic regulation, not by mutations [37].

2. Oxidative stress and aging

Mitochondria are the easiest target for damage by free radicals due to two reasons:

1. They are exactly where free radicals are produced.

2. They lack the antioxidant defenses that are present in other parts of the cell [43, 44].

There is strong evidence that the accumulated DNA damage of mitochondria is directly related to aging metabolic disorders and diseases [45]. The difference between mitochondria and other intracellular compartments is that the mitochondria have their own DNA. The production of free radicals (including superoxide anions and hydrogen peroxide) in mitochondria is a corollary to energy production (**Figure 6**). The accumulation of these by-products inside mitochondria damages their structure and their DNA. This damage is similar to that produced by ionizing radiation, and today there is an important scientific consensus that considers it as one of the main factors of aging [46]; so much so, that mitochondrial dysfunction caused by oxidative damage due to free radicals is already a marker of aging and the pathologies associated with aging, like in Alzheimer's disease, Parkinson's disease, and cancer [47–49].

The energy metabolism intrinsic to the maintenance of the organism and environmental factors (pollution, smoking) determine the continuous generation of oxygen radicals. These radicals produce oxidative damage to lipids, proteins, and DNA, and damaged molecules accumulate during aging [44, 46]. The deterioration secondary to aging is observed more clearly in postmitotic cells, which, when damaged, cannot be replaced by new cells, as is the case of the neuron. Although it has not been possible to demonstrate with certainty what is the role of this damage in senescence, oxidative stress would be one of the mechanisms possibly involved in neurodegenerative diseases [50].

Oxidative stress can increase with aging, both due to increased generation of oxygen radicals and by the decrease in the ability to eliminate these radicals (antioxidant mechanisms) [51]. There is still discussion regarding the apparent decrease in antioxidant mechanisms during aging [51, 52]. However, the available evidence, with respect to the maximum lifespan of individuals, suggests that the mechanisms of defense against oxidation would not be very relevant [52, 53]. The levels of antioxidant enzymes and the low molecular weight antioxidants show an inverse correlation with the maximum longevity of the animals, which indicates that pro-oxidative activity as such is the most relevant one [54]. Nor has it been found that supplementation with antioxidants (or the opposite effect, the elimination of antioxidant mechanisms) significantly modifies the maximum lifespan of an animal. In contrast, studies
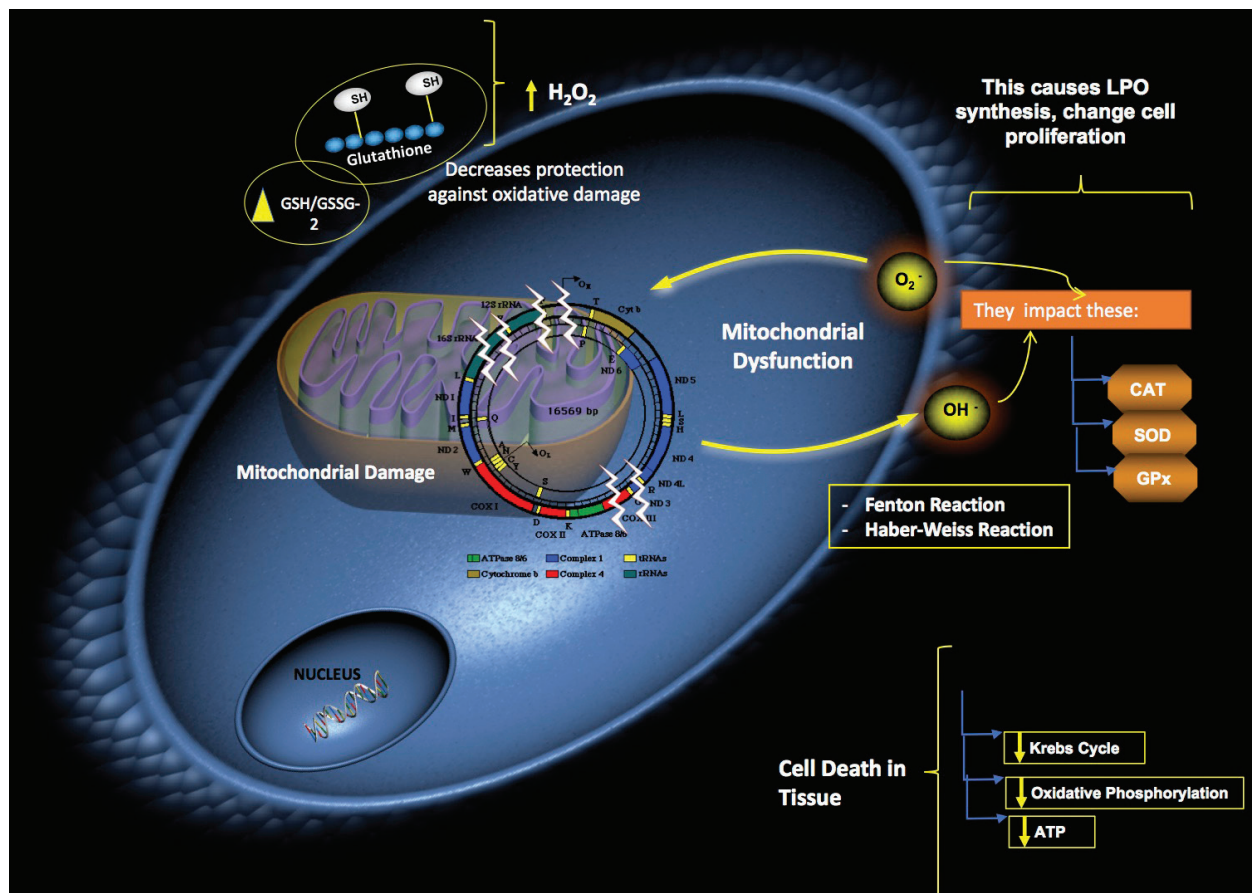
Figure 6. Mitochondrial dysfunction. The mitochondria are the main endogenous generator of free radicals. This production acts in a vicious circle that damages the mitochondria and therefore the mitochondrial primordial functions as shown in the figure. This image is a modification of QIAGEN's original [Torres-Sánchez ED].

of average survival suggest that in animals treated with antioxidant therapy these can effectively, nonspecifically protect against various causes of early mortality [55, 56]. These protective effects can have great importance for the human population given that due to their living conditions humans live in an adverse environment and are subjected, for example, to radiation and toxic compounds, so they are exposed to damage by oxidative stress of exogenous origin [57–59].

The animals would have regulatory mechanisms active during development that would monitor mitochondrial activity and, in response, establish the rates of respiration, behavior, and aging that persist during adult life [15, 60]. Although many of these studies have been carried out in experimental models, the results are relevant since they suggest that at least some of the interventions aimed at reducing the effects of aging should be considered in the early stages and not during the adult life of the individual [61]. Also, mitochondria that have suffered oxidative damage also contribute to the aging process [62–64]. Based on the studies that associate the increase of oxidative stress with aging, a line of research has been strengthened which proposes that the decrease in caloric intake is associated with an increase in the resistance of the central nervous system to suffer the neurodegenerative disorders of aging (**Figure 7**) [65]. The neuroprotective effect would depend on the decrease in the generation of oxygen radicals and an increase in the production of neurotrophic factors and protein chaperones [66, 67].
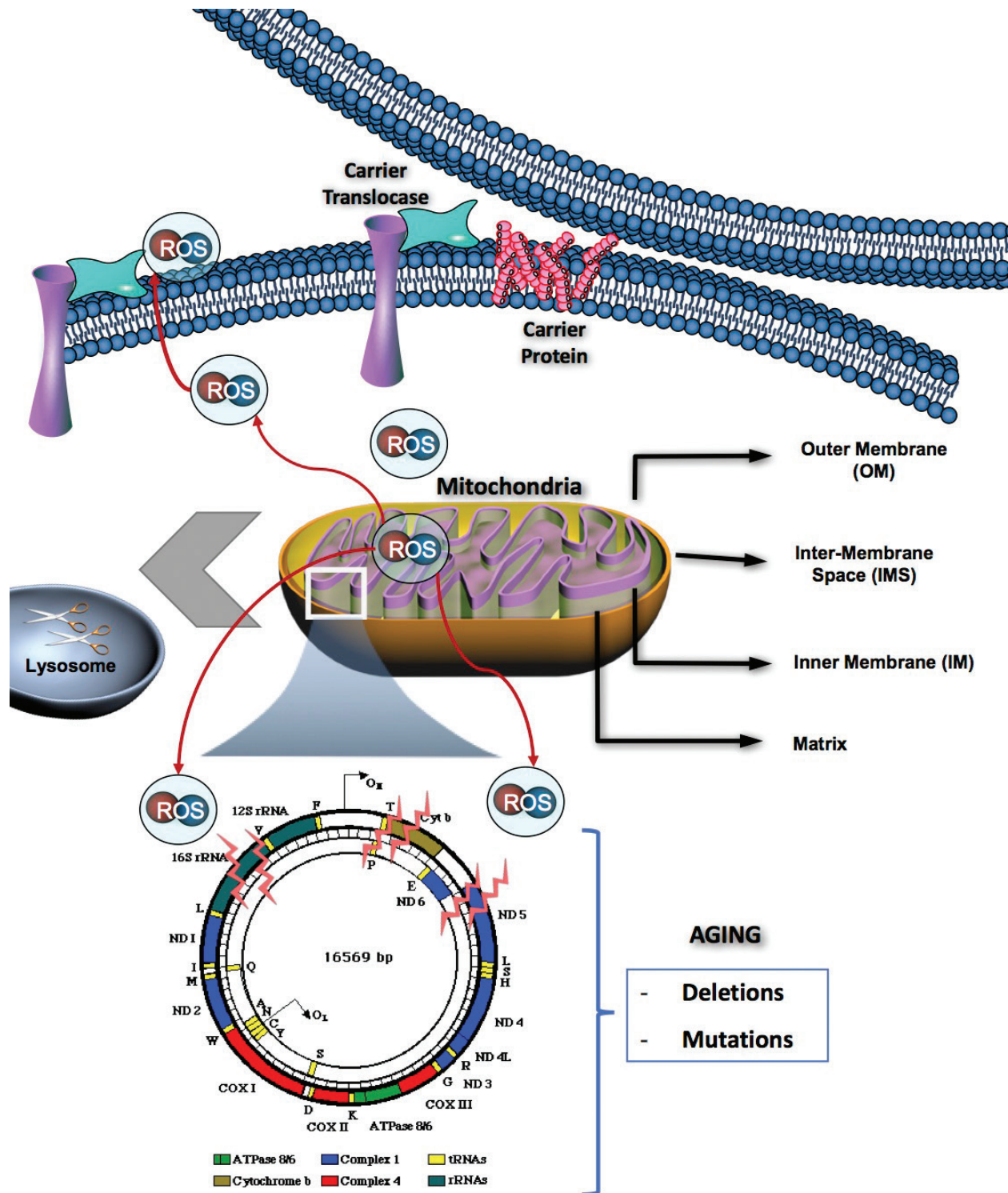
Figure 7. Aging and mitochondrial DNA. DNA damage is important for aging; reactive oxygen species (ROS) generated damage mtDNA and therefor mutations and other alterations. This image is a modification of QIAGEN's original [Torres-Sánchez ED].

3. DNA mitochondria and disease

Mitochondrial diseases are a group of disorders whose common feature is a defect in the production of ATP. However, this term is frequently applied to disorders caused by damage to the

oxidative phosphorylation (OXPHOS) system because for many years only mutations in mtDNA related to these diseases had been detected. But, identification of nuclear genes encoding proteins of the OXPHOS system complexes, or responsible for their assembly, has been described [68].

Mitochondrial disease can associate with any symptom, in any organ, at any age, but some symptoms and signs are actually more suggestive of a mitochondrial disorder than others. These "warning signs" warrant the onset of a diagnostic assessment of mitochondrial diseases. In contrast, numerous nonspecific symptoms occur frequently in infants and children with mitochondrial disease, but they have a broad differential diagnosis and lead more often to other diagnoses [68]. For example, pigmentary retinopathy in a preadolescent child may be a trait of mitochondrial disease but should suggest the possibility of juvenile neuronal ceroid lipofuscinosis or another genetic syndrome. Thus, nonspecific symptoms, especially isolated ones, do not indicate per se a mitochondrial problem. However, when combined, the likelihood of mitochondrial disorder increases, especially if the nonspecific aspects affect different organ systems, which leads to the initiation of appropriate initial diagnostic investigations [53, 69].

The defects of the respiratory chain of Mendelian inheritance are included in four groups:

1. Mutations in genes that code for subunits of the respiratory chain

2. Mutations in genes that code for anchor proteins

3. Defects in intergenomic communication

4. Defects that affect the constituent lipids of the inner mitochondrial membrane where CR is embedded

4. Diseases caused by mutations in genes that encode subunits of the respiratory chain

The most frequent of these diseases are those that code for subunits of complexes I and II and cause Leigh's syndrome, which is a fatal neurodegenerative disease that begins in the first years of life due to a profound defect in the production of ATP in the developing brain. It is defined by the presence of bilateral necrotic lesions in ganglia of the base and brain stem, characterized histologically by cavitated areas, vascular proliferation, neuronal loss, and demyelination. Individuals with Leigh's syndrome can also present variable symptoms that do not fit into any defined syndrome (hypotonia, cardiomyopathy, ataxia, developmental delay, etc.) [70]. The most important genes that code for complex I subunits are NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS8, NDUFV1, and NDUFV2 [71–73].

4.1. Diseases caused by mutations in genes that code for anchor proteins

This group of diseases includes mutations in genes that code for proteins that, while not part of the mitochondrial respiratory chain, are necessary for the correct assembly of proteins encoded by the nuclear and the mitochondrial genomes. Examples are mutations in the nuclear SURF1, LRPPRC, and NDUFA12L genes, which code for proteins necessary for the assembly of cyclooxygenase (COX) [73, 74].

Primary deficits of coenzyme Q10 (CoQ10) include various disorders caused by defects of their biosynthesis at different levels. The CoQ10 transports electrons from complexes I and II to complex III and receives electrons from the beta-oxidation pathway via electron-transferring-flavoprotein dehydrogenase (ETFDH) [75]. There are at least nine enzymes necessary for the synthesis of CoQ10, and mutations in the genes that encode them are responsible for different cases of encephalomyopathies. There are also disorders due to CoQ10 secondary deficits, including autosomal recessive cases of cerebellar ataxia of unknown cause in children, apraxia syndrome with oculomotor ataxia 2 (AOA2) caused by mutations in the aprataxin gene (APTX), and myopathic form of glutaric aciduria type II (GAII) caused by mutations in the gene that encodes the ETFDH [76, 77]. The importance of knowledge of these disorders is that supplements with CoQ10 improve the symptoms in these patients. Defects have also been described in proteins involved in the assembly of complex III (BCS1L) and complex V (ATPAF2) [3, 74].

4.2. Diseases secondary to defects in intergenomic communication

These diseases are due to defects in nuclear factors involved in the replication, maintenance, and translation of mtDNA. The resulting disorders are characterized by quantitative alterations (depletion syndromes) or qualitative alterations (multiple deletions) of mtDNA or by defects in the translation of respiratory chain components encoded in the mtDNA. Thus, many of these disorders are due to alterations in the pool of nucleotides necessary for the synthesis of mtDNA or in the enzymes necessary for the replication of mtDNA itself [78, 79].
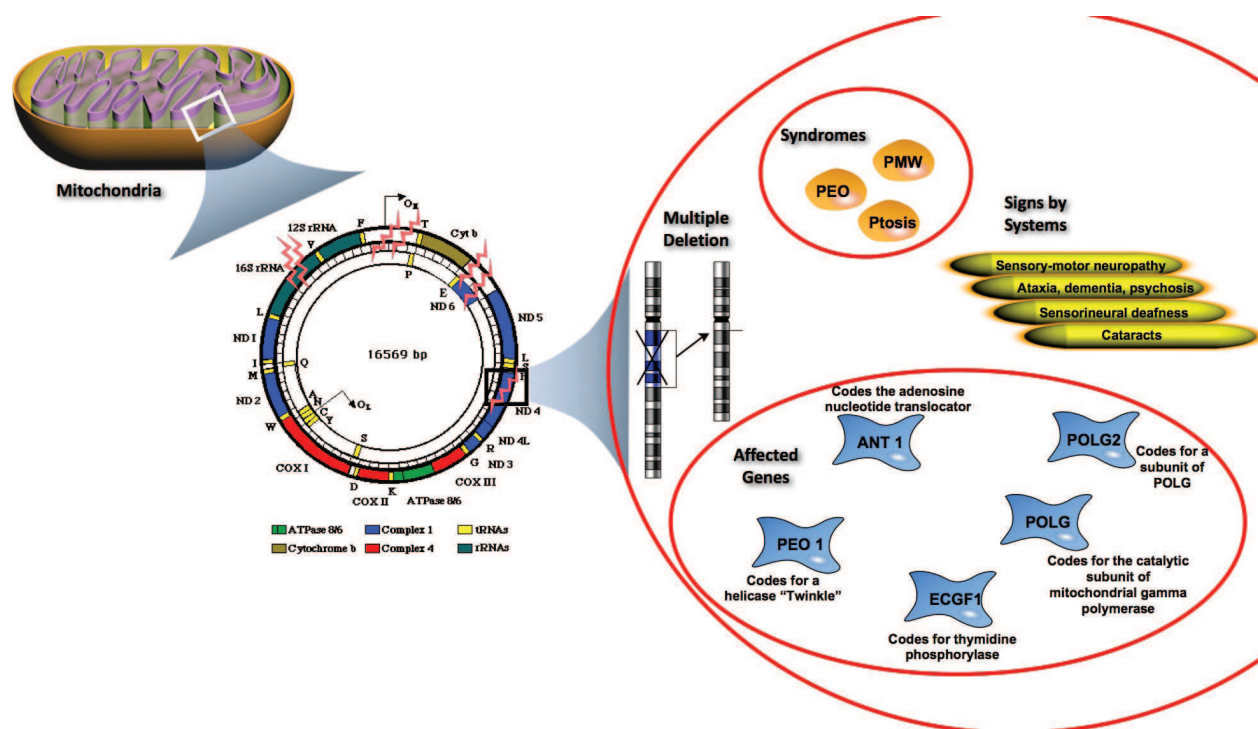

Figure 8. Multiple deletions of mtDNA. Mitochondrial damage is regulated by multiple deletions in the PEO, ANT1, ECGF I, POLG, and OLG2 genes. The deletions will trigger the syndromes and signs that are illustrated in the image. This image is a modification of QIAGEN's original [Torres-Sánchez ED].

4.3. Multiple deletions of mtDNA

From the clinical point of view, the multiple deletion syndromes of mtDNA are character-ized by progressive external ophthalmoparesis (PEO), ptosis, and proximal muscle weak-ness associated with signs of involvement of other systems that include the peripheral nerves (sensory-motor neuropathy), the brain (ataxia, dementia, psychosis), the ear (sensorineu-ral deafness), and the eye (cataracts). Genes involved in the homeostasis of the mitochon-drial pool of nucleotides are associated with the presence of PEO and multiple deletions in mtDNA. They include ANT1 (encodes the adenosine nucleotide translocator), PEO1 (codes for a helicase known as Twinkle), ECGF1 (which codes for thymidine phosphorylase or TP), POLG (encodes for the catalytic subunit of mitochondrial gamma polymerase), and POLG2 (which codes for a subunit of POLG) (**Figure 8**) [14, 80, 81].

Mitochondrial neurogastrointestinal encephalomyopathy or MNGIE is a multisystemic disease of autosomal recessive inheritance, of presentation in young adults secondary to mutations in TP (thymidine phosphorylase). It is characterized by PEO, neuropathy, leukoencephalopathy, and severe gastrointestinal dysmotility, leading to profound cachexia and early death. The decrease in thymidine phosphorylase activity leads to a defect in the synthesis of mtDNA, causing not only multiple deletions in the mtDNA but also depletion of same and point mutations that are reflected in the muscle, even though it expresses little TP. The damage, therefore, seems to be mediated by toxins. Thus, thymidine and deoxyuri-dine are toxic intermediaries that accumulate in the blood of these patients, and their elimi-nation leads to clinical improvement. Different approaches have been carried out to favor the elimination of these toxic intermediaries from the blood, by means of hemodialysis, platelet transfusion, and, finally, allogeneic bone marrow transplantation [35, 80].

Mutations in mitochondrial gamma polymerase (POLG) may occur in the form of PEO at the onset of adulthood and multiple deletions in mtDNA and be accompanied by ataxia, peripheral neuropathy, Parkinsonism, psychiatric symptoms, myoclonic epilepsy, and gas-trointestinal symptoms. These disorders can have both dominant and recessive inheritances. An example of a clinical syndrome secondary to mutations in this gene is SANDO (sensory ataxic neuropathy, dysarthria, ophthalmoparesis). Mutations in POLG are also responsi-ble for the Alpers syndrome in children, a recessively inherited disorder characterized by encephalopathy and severe hepatopathy and associated with mtDNA depletion [80].

4.4. Depletion of mtDNA

Some mutations in POLG are responsible for a fatal hepatocerebral syndrome in children (Alpers syndrome) characterized by a profound depletion of mtDNA. Mutations in proteins that affect the control of the pool of nucleotides in mitochondria also produce depletion of mtDNA, highlighting two syndromes:

• Hepatocerebral syndrome caused by mutations in POLG or in DGUOK (encodes the en-zyme deoxyguanosine kinase (dGK))

• Myopathic syndrome caused by mutations in TK2 (which codes for the mitochondrial form of thymidine kinase), in SUCLA2 (beta subunit of succinyl-CoA synthetase), or in RRM2B (p-53 inducible ribonucleotide reductase) [80, 82]

4.5. Defects in mtDNA translation

In the translation of the 13 subunits of the respiratory chain encoded in the mtDNA, the participation of many nuclear coding factors such as polymerases, ribosomal proteins, RNA-modifying enzymes and initiation, elongation, and termination factors, among others, is necessary. These defects result in deep combined deficits of all the respiratory chain complexes. Clinically, they manifest as necrotizing leukoencephalopathies, cardiomyopathies, and hepatocerebral syndromes among others. Genes involved include GFM1 (encodes a ribosomal elongation factor), MRPS16 (encodes the 16 subunit of the mitochondrial ribosomal protein), TSFM (encodes the mitochondrial elongation factor EFTs), and TUFM (encodes the elongation factor Tu) [80, 82, 83].

4.6. Mitochondrial secondary disease

Even when a sophisticated biochemical analysis confirms mitochondrial dysfunction, it can be challenging to distinguish whether the cause of this dysfunction is a gene that directly affects the electron transport or is secondary to an unrelated genetic or environmental cause. Thus, the definitive diagnosis of mitochondrial disease cannot be based solely on biochemical findings, since the in vitro activity of the electron transport chain enzyme in a sample of patient tissue may be diminished as a consequence of other metabolic diseases or issues related to the handling of samples. Mitochondrial dysfunction that may or may not be clinically relevant is observed when the main defect lies in another metabolic pathway related to energy, such as the oxidation of fatty acids or the metabolism of amino acids. In addition, alteration of OXPHOS has been observed with decreased in vitro activity of the electron transport chain enzyme in up to 50% in tissue samples from patients with other metabolic diseases [84]. Of course, other diagnoses that have finally been confirmed in individuals with suspected mitochondrial disease and biochemical samples of mitochondrial dysfunction in vitro include disorders of copper metabolism (Menkes disease and Wilson's disease), lysosomal disorders (neuronal ceroid lipofuscinosis and Fabry disease), peroxisomal disorders, neurodegeneration associated with pantothenate kinase, holocarboxylase synthetase deficiency, molybdenum cofactor deficiency, and neonatal hemochromatosis [85]. It is increasingly accepted that the alteration of OXPHOS may contribute to the pathology in some genetic alterations that are not typically classified as mitochondrial or metabolic disorders, such as Rett syndrome, Aicardi-Goutières syndrome, various neuromuscular disorders, and Duchenne muscular dystrophy. In addition, the activities of the electron transport complexes in skeletal muscle can decrease in malnourished children, correcting to normal values after improvement of nutrition [41, 74, 86].

Medications and toxins can also significantly alter mitochondrial function. Sodium valproate can alter mitochondrial function by inducing carnitine deficiency, depression of intramitochondrial oxidation of fatty acids, and/or inhibition of OXPHOS, which should suggest the use of an alternative anticonvulsant in mitochondrial disease, especially in patients with POLG1 mutations. Other important examples of drugs that can induce mitochondrial dysfunction are retroviral nucleoside analogs in HIV infection, as well as salicylates that can alter the hepatic mitochondria in Reye syndrome. Since there are so many nonspecific clinical features that can raise the suspicion of mitochondrial diseases, the differential diagnosis can be very broad. The clinical presentation of mitochondrial disease in children can mimic other multisystem disorders, such as congenital disorders of glycosylation or Marinesco-Sjögren syndrome, or even be confused with a syndrome of vascular or immunological stroke. Although the clinical
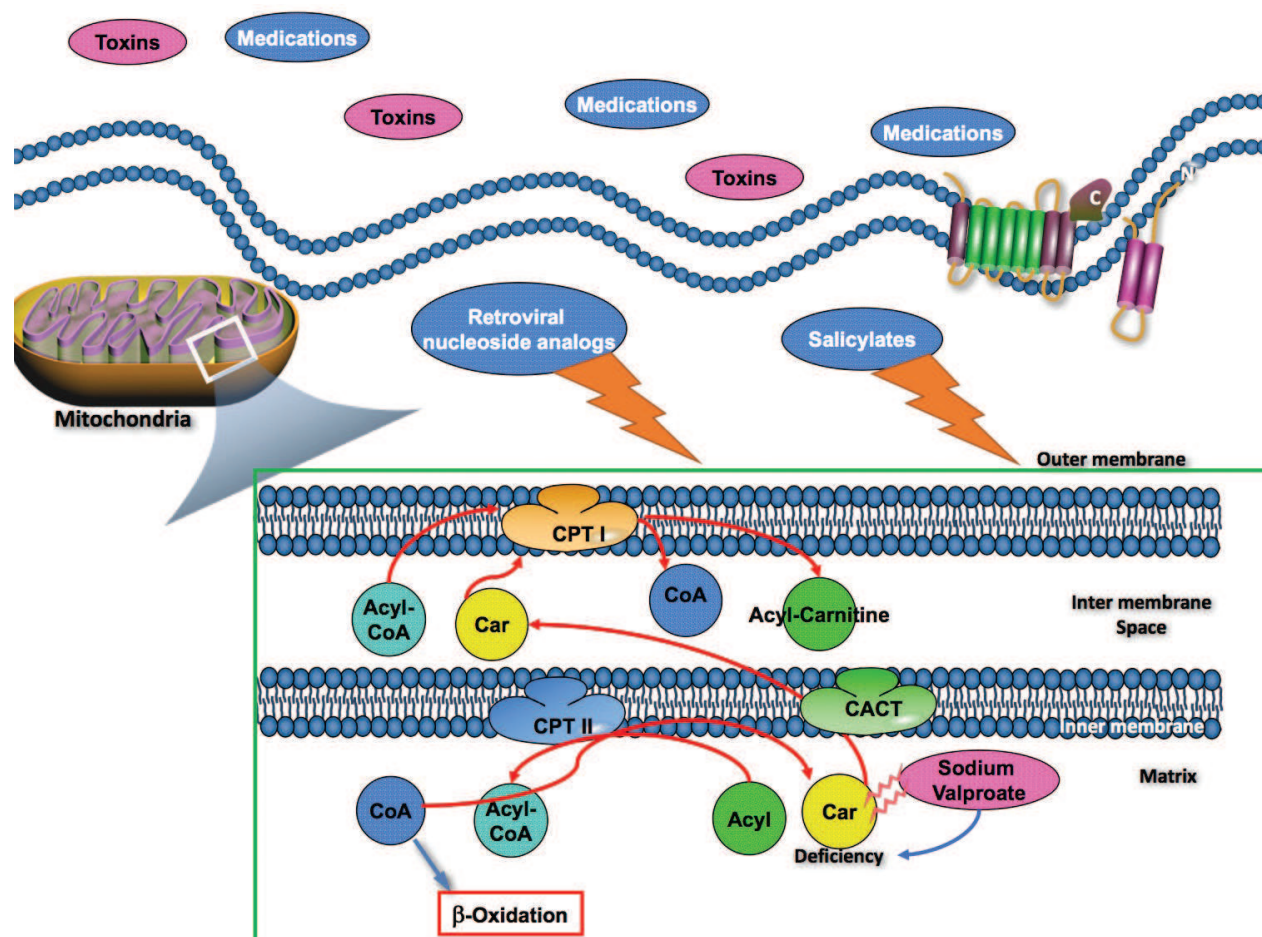
Figure 9. Medications and toxin in mitochondria: Alteration of mitochondrial function by exogenous metabolites; the main damage affects cell respiration, but also damage in the oxidation of fatty acids is observed. This image is a modification of QIAGEN's original [Torres-Sánchez ED].

and neuroimaging features of Leigh's syndrome often clearly suggest a mitochondrial disorder, other alterations may give rise to striatal necrosis, which should be taken into account. Similarly, clinical and neuroimaging findings may sometimes suggest other leukoencephalopathies or degenerative disorders (**Figure 9**) [85, 86].

5. Assessment and diagnostic process

The main challenge to correctly establish mitochondrial dysfunction as the cause of the presentation of a specific patient is the absence of a definitive biomarker that characterizes mitochondrial disease in all patients. Thus, the diagnostic assessment is necessarily broad and of many levels, with a focus on integrated training from many sources: complete medical and family history, clinical findings that may suggest a mitochondrial disease, abnormalities of the biochemical laboratory such as lactic acidosis (which, as we

analyzed earlier, is not sensitive or specific as an isolated biomarker in many mitochondrial disorders), tissue biopsy tests of the abnormal activity of the electron transport chain enzyme or an alteration of the respiratory capacity, and, if possible, the identification of a pathogenic mutation of mtDNA or nDNA. This process usually involves sophisticated tests that request invasive procedures, such as muscle or liver biopsy to obtain the tissue for assessment in specialized laboratories. These investigations may offer intermediate or ambiguous results, and the decrease in the activities of the enzymes of the electron transport chain may be secondary to non-respiratory chain disorders. To assist in the interpretation, two diagnostic schemes have been proposed for infants and children to classify the probability of a specific patient's mitochondrial disease as clear, probable, possible, or improbable. Recently, guidelines were proposed for the diagnosis and treatment of mitochondrial disorders in infants and children; however, these complex and sophisticated diagnostic algorithms are aimed for the metabolic specialist and have a limited clinical utility for the family physician who contemplates the start of the diagnostic evaluation of a specific patient [20, 21, 87].

The diagnostic evaluation typically begins with the general clinical assessment and goes through the systematic, imaging, and metabolic screening tests up to the most specific biochemical and genetic determinations. This starts with the less invasive evaluations and moves on to the biopsy-based, more invasive analyses, as needed. Obviously, the complete diagnostic process can be complicated and including the early intervention of a local specialist in metabolism can be very useful. Recommendation to a metabolic specialist should occur whenever the symptoms and signs clearly suggest a mitochondrial disease, patients are potentially unstable with the classic features of metabolic disease, there is lactic acidosis in the blood or the cerebrospinal fluid (CSF), a pattern of maternal inheritance is observed, or anomalies are identified in the initial diagnostic assessment. Referral by a primary care physician is also prudent when a more elaborate study is necessary, such as a provocation test or a muscle biopsy with the study of the enzymes of the electron transport chain [79, 88]. If a biochemical diagnosis has been established but its molecular basis remains unknown, further study and genetic counseling should be coordinated by a specialist. Mitochondrial disease is clearly not a single entity but rather a heterogeneous disorder of energy dysfunction caused by hundreds of different mutations, deletions, duplications, and other defects of nuclear and mitochondrial genes. Thus, at present, there is no accepted and gene-based diagnostic algorithm that is useful for all patients or used by all metabolic specialists. The study of nDNA mutations can be performed on any tissue, including blood. However, most of the diagnostic study of nDNA genes should not be done a priori but guided by the clinical picture, the specific headlines, and the biochemical findings in a given patient. On the contrary, the most informative study of mtDNA mutations is performed in a muscle biopsy sample, although urinary sediment and buccal cells may also be useful.

It is important to recognize that dietary advice should always be offered in a specialized setting. In addition, although there are only a few viable therapeutic options for mitochondrial disease, it is best to be offered by clinicians with experience in these disorders [89].

What was once considered a few rare diseases to be described in clinical sessions or in the form of clinical cases in journals are today disorders that are commonly known and observed in a wide range of consultations.

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