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Review

Insulin-like growth factor 1 (IGF-1) therapy: Mitochondrial dysfunction and diseases

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ABSTRACT

This review resumes the association between mitochondrial function and diseases, especially neurodegenerative diseases. Additionally, it summarizes the major role of IGF-1 as a mitochondrial protector, as studied in several experimental models (cirrhosis, aging …). The contribution of mitochondrial dysfunction to impairments in insulin metabolic signaling is also suggested by gene array analysis showing that reductions in gene expression, that regulates mitochondrial ATP production, are associated with insulin resistance and type 2 diabetes mellitus. Moreover, reductions in oxidative capacity of mitochondrial electron transport chain are manifested in obese, insulin-resistant and diabetic patients. Genetic and environmental factors, oxidative stress, and alterations in mitochondrial biogenesis can adversely affect mitochondrial function, leading to insulin resistance and several pathological conditions, such as type 2 diabetes. Finally, it remains essential to know the exact mechanisms involved in mitochondrial generation and metabolism, mitophagy, apoptosis, and oxidative stress to establish new targets in order to develop potentially effective therapies. One of the newest targets to recover mitochondrial dysfunction could be the administration of IGF-1 at low doses. In the last years, it has been observed that IGF-1 therapy has several beneficial effects: restores physiological IGF-1 levels; improves insulin resistance and lipid metabolism; exerts mitochondrial protection; and has hepatoprotective, neuroprotective, antioxidant and antifibrogenic effects. In consequence, treatment of mitochondrial dysfunctions with low doses of IGF-1 could be a powerful and useful effective therapy to restore normal mitochondrial functions.

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1. Introduction

Mitochondria are ovoid organelles with a variable transverse diameter (0.1–0.5 μm) and length (1–2 μm) [1]. The number of mitochondria per cell is uneven (500–2000/cell, from none in erythrocytes to 10,000 in striated muscle cells) [2], depending on the energetic and oxygen cell's requirement. These organelles represent approximately one-fifth of the cell volume [2], and they can interact reciprocally and establish a mitochondrial network [3,4]. Even more, mitochondria are extraordinarily plastic organelles, frequently varying their form, fusing each other or splitting into two independent structures [3]. In most cells, mitochondria are located close to microtubules to facilitate their movement through the cytoplasm. Nevertheless, in other cells, such as myocardiocytes or around the flagellum in the spermatozoon, mitochondria stay motionless to supply ATP directly to these cells with high energetic demands [2,3].

Mitochondria are limited by a double lipid bilayer: the outer membrane and the inner membrane with invaginations or cristae [3]. Both membranes show different compositions, structures and functions; and they enclose an area called the intermembrane space. This double membrane-bound organelle take part in several metabolic functions, such as thermogenesis, calcium homeostasis, reactive oxygen species (ROS) formation, innate immune responses

Abbreviations: ΔΨm, membrane potential; *AD*, Alzheimer's disease; *AMPK*, adenosine-monophosphate-activated kinase; *ATG proteins*, autophagy-related proteins; *ATP*, adenosine triphosphate; *CaMKs*, calcium-calmodulin-activated kinases; *CDKs*, cyclin-dependent kinases; *CNS*, central nervous system; *CREB*, cAMP response-element binding protein; *DJ-1*, protein deglycase-1; *eNOS*, endothelial nitric oxide synthase; *$FADH_2$*, flavin adenine nucleotide; *FMN*, flavin mononucleotide; *GH*, growth hormone; *GHR*, growth hormone receptor; *GLT-1*, glutamate transporter-1; *HUVECs*, human umbilical vein endothelial cells; *IGF-1*, insulin-like growth factor-1; *IGF-2*, insulin-like growth factor-2; *KO*, knock-out; *LRRK2*, leucine-rich repeat kinase 2; *MF2*, myocyte enhancer factor-2; *MNGIE*, mitochondrial neurogastrointestinal encephalomyopathy; *MS*, multiple sclerosis; *mtDNA*, mitochondrial DNA; *NADH*, nicotine adenine dinucleotide; *NRF-1α*, nuclear respiratory factor 1α; *OXPHOS*, oxidative phosphorylation; *PARKIN*, E3 ubiquitin protein ligase; *PD*, Parkinson's disease; *PGC-1α*, peroxisome proliferator-activated receptor γ coactivator 1α; *PI3K*, phosphoinositide 3-kinase; *PINK*, PTEN-induced putative kinase 1; *PPAR*, peroxisome proliferator activated receptor; *RC*, respiratory chain; *ROS*, reactive oxygen species; *SNCA*, Alpha synuclein (non A4 component of amyloid precursor); *SOD*, superoxide dismutase; *TFAM*, mitochondrial transcription factor A; *TIM*, translocase of the inner membrane; *TOM*, translocase of the outer membrane; *UCPs*, uncoupling proteins; *UQH*, ubisemiquinone; *VDAC*, voltage-dependent anion-selective channel.

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and apoptosis. However, the main mitochondrial function is to generate chemical energy to supply the cell's requirements. Such energy is produced as ATP through oxidative phosphorylation (OXPHOS) of metabolites. [4–6].

2. Mitochondrial structure and metabolism

As described above, mitochondria are limited by two membranes. The permeability of both lipid bilayers substantially differs from each other, according to the metabolic functions that occur in mitochondrial compartments (Table 1). The outer membrane is only permeable to small neutral molecules (<10 kDa), such as H_2O and gases (O_2, CO_2, N_2). Also, this outer membrane is non-specifically permeable to the metabolites involved in oxidative phosphorylation. Ions and proteins smaller than 5 kDa diffuse throughout the membrane across porins, a family of integral membrane proteins [7]. In eukaryotes, the major porin is the voltage-dependent anion-selective channel (VDAC), which has three different isoforms in vertebrates (VDAC1, VDAC2 and VDAC3) [8]. VDAC allows the movement of small hydrophilic molecules at low or zero membrane potential. Nonetheless, this channel changes to a closed conformation at potentials above 30–40 mV [8]. The intermembrane space is essential for the development of proton gradient [1] and contains crucial enzymes and molecules, such as adenylate kinase, creatine phosphokinase and cytochrome *c*.

The internal membrane is composed of several proteins and lipids (~70%), mainly cardiolipin, phosphatidylethanolamine and phosphatidylcholine. It is impermeable to even the smallest of ions, the hydrogen ion. Such strict control of inner mitochondrial membrane permeability is vital for efficient ATP synthesis. Therefore, anions and cations move into the mitochondrial matrix through channels (Table 1). Such channels are essential to control the osmotic balance between cytosol and mitochondria [8]. For example, potassium efflux is a main factor in homeostasis, and the imbalance of this flux induces water exchange through the lipid bilayer. Of interest, it has been reported that K^+ channels (mito-K_{ATP} and mito-K^{2+}_{Ca}) are involved in cardioprotection against ischemic injury, and the permeability transition pore is related with cell necrosis and apoptosis [6,10]. Mitochondrial Ca^{2+} uniporter channels control Ca^{2+} influx into mitochondria depending on energetic demands [11, 12]. For instance, in conditions of augmented cardiac work, adrenaline promotes the activation of dehydrogenase and 2-oxoglutarate dehydrogenase complexes by increasing the intramitochondrial concentration of Ca^{2+} [12]. Additionally to the aforementioned channels, aquaporins have been observed in the inner mitochondrial membrane. These channels facilitate water movement [9]. Furthermore, molecules used by the mitochondria to obtain energy, such as aspartate, glutamate, phosphate, pyruvate, fatty acids, ornithine, carnitine or glutamine, require specific carriers to cross this inner membrane [1,12].

On the other hand, mitochondrial proteins synthesized in the cytosol are imported into the appropriate mitochondrial compartment by specific proteins transporter complexes present in both outer (TOMs) and inner (TIMs) membranes (Fig. 1). TOM complex comprises several subunits that recognize the N-terminal targeting sequence characteristic of most immature mitochondrial proteins. TIM complex, in turn, integrates two different complexes with different functions: Tim22 and Tim23 [13–15]. Tim 23 includes Tim9p, Tim10p and Tim12p subunits, bound to the outer side of the inner membrane [14–16]. It is involved in the translocation of all matrix and some intermembrane space proteins, in an ATP dependent process. Moreover, Tim 22 mediates the insertion of transmembrane proteins through a mechanism regulated by the mitochondrial membrane potential [16,17]. During all these processes, proteins are cleaved, folded and placed in the right localization to work properly [13,15].

The respiratory chain (RC), located in the inner membrane, includes four protein complexes (complexes I to IV), coenzyme Q10 and the ATP synthase (complex V) (Table 2 and Fig. 2). According to Mitchell's chemiosmotic theory [19], movement of electrons through the respiratory chain generates an energy release that is used to pump protons into the intermembrane space against its electrochemical gradient. This process increases proton gradient between intermembrane space and mitochondrial matrix [19]. In fact, it was demonstrated that four H^+ are pumped per two electrons across complexes I, III and IV (in total, $10H^+$ when $NADH^+$ is used as substrate or $6H^+$ when $FADH_2$ is employed). Then, four electrons and four H^+ react with one molecule of O_2 to form two H_2O molecules in a reaction catalyzed by complex IV. Finally, this proton gradient is dissipated by their influx to the matrix through the F_0-ATP synthase component. ATP synthase generates free energy and uses it to synthetize ATP [20]. In total, three protons are needed for the synthesis of one molecule of ATP and another one for transporting this molecule to the cytoplasm [21]. In summary, each NADH produced in the conversion of pyruvate to acetyl CoA by Krebs cycle is worth 3 ATP and every $FADH_2$ is worth 2 ATP.

One characteristic of the respiratory chain is related to its efficiency. Theoretically, one O_2 is consumed per 3 ATP produced (P/O ratio) for NADH-linked substrates (via complex I), and 2 ATP produced for succinate (via complex II). However, this process is not as efficient. IP/O ratios of 2.5 for NADH-linked substrates and 1.5 for succinate have been reported [21]. A possible explanation for this variance in P/O ratios may involve cations and metabolite transport, nicotinamide-nucleotide transhydrogenase reaction, proton pumps and proton leak. Proton pumps and proton leak are regulated by uncoupling proteins (UCPs) [22,23]. UCPs are mitochondrial membrane proteins specialized in inducible proton conductance. They belong to the superfamily of anion-carrier proteins. Mammals express five types of UCPs (UCP1 to 5), with several functions, regulation and tissue expression (Table 3) [22, 24]. The main functions of UCPs is to control the cellular energetic balance, to regulate the membrane potential and to reduce the oxidative stress [25]. All of them improve mitochondrial efficiency [26,27].

Furthermore, mitochondrial matrix contains several enzymes implicated in crucial biochemical reactions, such as fatty acid oxidation, Krebs cycle and amino acid degradation. As a result of all these biochemical reactions, electrons and protons are produced in form of NADH and $FADH_2$. Both molecules are used in the OXPHOS process. Some other biochemical reactions have been also reported to be carried out within the mitochondrion, as heme group biosynthesis [28], steroid metabolism and uric acid cycle [12], thus underlining the crucial role of this organelle in cell (and body) homeostasis.

Table 1
Mitochondrial membrane permeability.

Outer mitochondrial membrane		Inner mitochondrial membrane	
Type of transport	Molecules	Type of transport	Molecules
Simple diffusion	H_2O, CO_2, O_2, N_2	Simple diffusion	O_2
		Aquaporins	H_2O
Porins	Ions and proteins <5 kDa	ANT	ADP
		Phosphate transporter	P_i for OH^-
		Carboxylate transporter, carnitine transporter	Respiratory metabolites
VDAC	Ca^{2+}	Ca^{2+} uniporter (Na^+-dependent or independent)	Ca^{2+}
		mitoK_{ATP}, mito-K_{Ca2+}, mito$K_{v.13}$, TASK-3	K^+

3. Mitochondrial biogenesis

Mitochondrial biogenesis is regulated by peroxisome proliferator-activated receptor-γ coactivator (PGC-1α), a member from a family of transcription coactivators that interacts with a broad range of transcription factors, such as nuclear respiratory factor NRF-1α and peroxisome proliferator-activated receptors (PPAR-γ and PPAR-α). PGC-1α activates NRF-1α, promoting synthesis of mitochondrial transcription factor A (TFAM), which subsequently increases mitochondrial biogenesis,

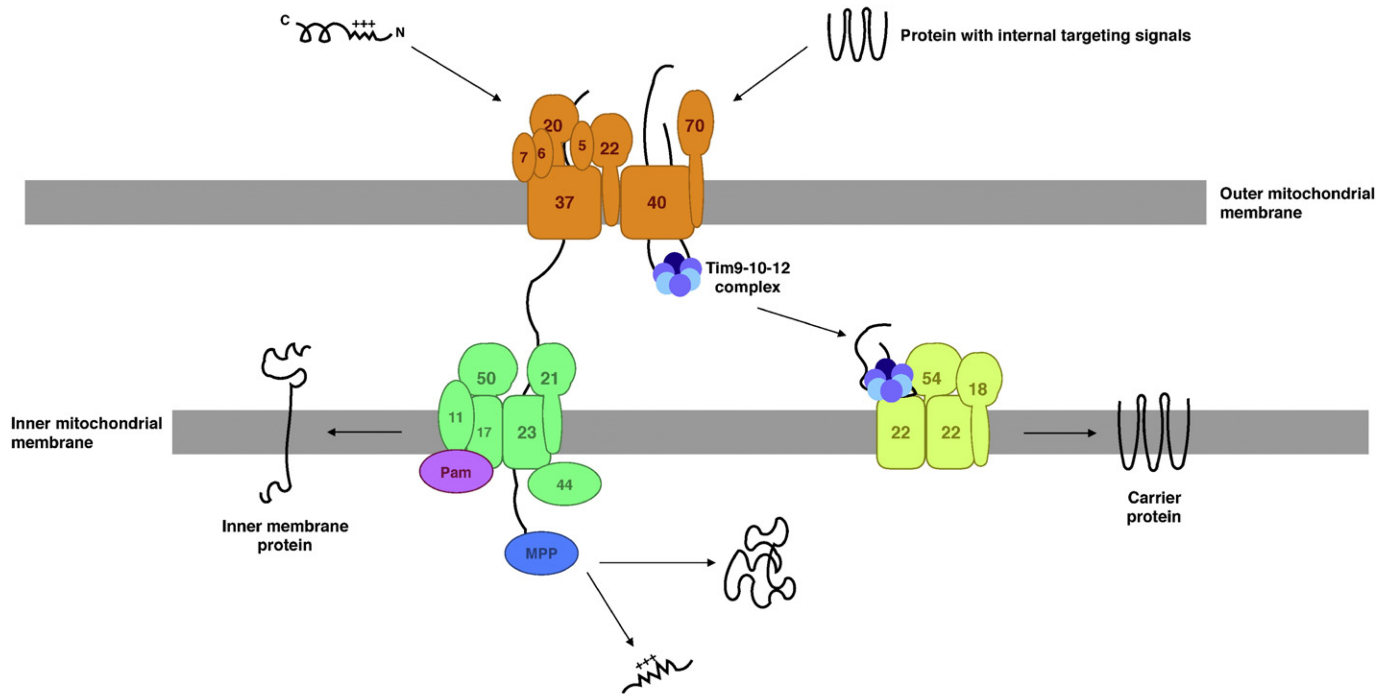

Fig. 1. Protein transporter complexes present in both outer (TOM) and inner (TIM) mitochondrial membranes. MPP: mitochondrial processing peptidase.

replication and transcription of mitochondrial DNA, including genes encoding proteins involved in OXPHOS [29–31]. PGC-1α plays a main role in the regulation of several metabolic processes, such as glucose and fatty acid metabolism, fiber type switching in skeletal muscle, and heart development [32]. PGC-1α concentration is increased upon cellular ATP demands, and its expression or activation can be regulated by thyroid hormone, adenosine-monophosphate-activated kinase (AMPK), cyclin-dependent kinases (CDKs), calcium-calmodulin-activated kinases (CaMKs) and β-adrenergic stimulation (β/cAMP) [30,33,34]. For instance, during exercise or ischemia, an augment in AMP concentrations induces AMPK activation. This activation promotes PGC-1α activation by phosphorylation. Once activated, the coactivator PGC-1α forms protein complexes with CREB or MEF2 (both transcription factors) and it induces protein synthesis related with glucose uptake, glycolysis and ATP production [35].

Interestingly, the expression of PGC-1α and NRF-1 are decreased in several conditions of mitochondrial dysfunction, such as aging, insulin-resistance and diabetes [36–38].

4. Mitochondrial diseases

Mitochondrial morphology and number is essential for normal cell function and homeostasis [39]. In fact, variations of both parameters have been observed in heart, skeletal muscle and liver from insulin resistant, overweight, cardiac, diabetic and Alzheimer's patients [36–38,40,41]. In this regard, mitochondrial oxidative capacity depends on the number and size of mitochondria [39]. The decrease of mitochondrial oxidative capacity correlates with the reduced expression of mitochondrial proteins encoded by both mitochondrial genome (cytochrome *c* oxidase 1) and nucleus (succinate dehydrogenase and pyruvate dehydrogenase). In addition, reduced expression of PGC-1α, NRF-1α and TFAM have been reported in Alzheimer's disease [41].

Mitochondrial number and function are checked by a process called mitophagy or degradation of mitochondria by autophagy [39]. In this process, cooperation of Beclin1/PI3K complex with ATG proteins induces autophagosome formation, a double membranous vesicle that degrades several cytoplasmic materials (proteins, ribosomes,

Table 2
Electronic transport and oxidative phosphorilation complexes.

Complex	Name	Subunits	mtDNA	Proteins encoded
I	NADH dehydrogenase	41	7	NADH dehydrogenase 1 NADH dehydrogenase 2 Mitochondrially encoded NADH dehydrogenase 3 Mitochondrially encoded NADH dehydrogenase 4 Mitochondrially encoded NADH dehydrogenase 5 Mitochondrially encoded NADH dehydrogenase 6 Mitochondrially encoded NADH 4 L
II	Succinate dehydrogenase	4	0	
III	Ubiquinone cytochrome *c* oxidoreductase	11	1	Mitochondrially encoded cytochrome *b*
IV	Cytochrome c oxidase	13	3	Mitochondrial encoded Cytochrome c oxidase subunit 1 Mitochondrial encoded Cytochrome c oxidase subunit 2 Mitochondrial encoded Cytochrome c oxidase subunit 3
V	ATP synthase	14	2	Mitochondrially encoded ATP synthase 6 Mitochondrially encoded ATP synthase 8

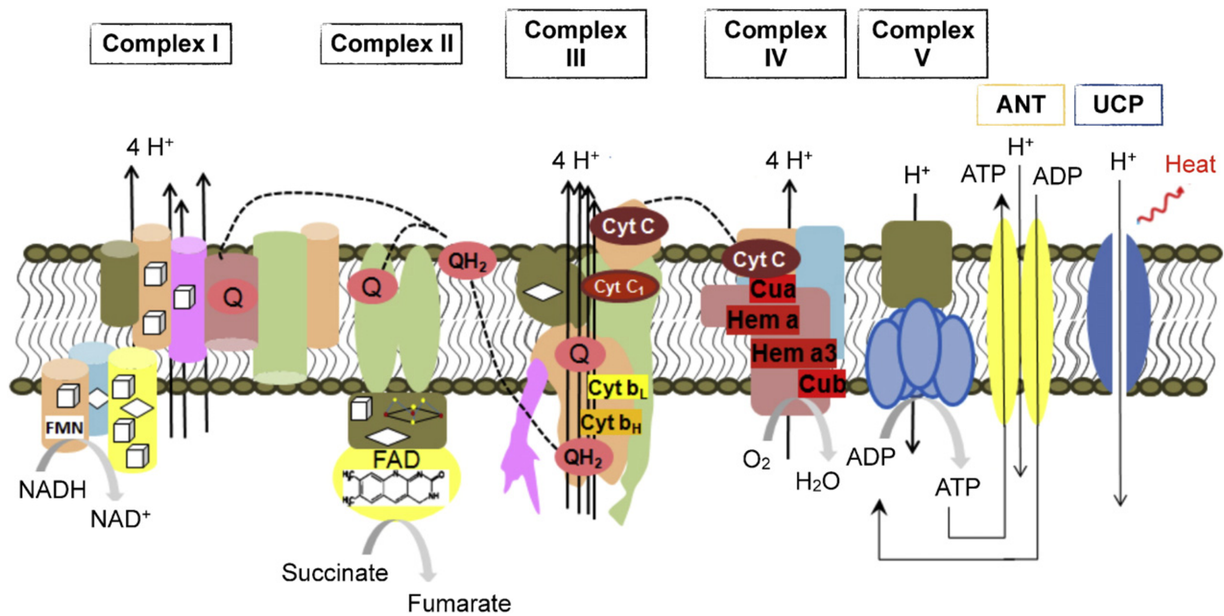

Fig. 2. Mitochondrial membrane complex. Electrons move through to FeS and citochrome groups and H^+ are pumped to the intermembrane space. ◇: 2Fe2S clusters. : 4Fe4S clusters. : 3Fe4S groups. ANT: Adenine nucleotide translocator. UCP: Uncoupling proteins. FMN: flavin adenine mononucleotide. FAD: flavin adenine dinucleotide. Cyt C: cytochrome C. Cu: Cupper.

endoplasmic reticulum and mitochondria). Such degrading process plays an important role in controlling mitochondrial number and quality. Of interest, mitochondria can regulate mitophagy themselves in several ways [42]. Comparatively, damaged mitochondria may be recognized through the voltage-sensitive kinase PINK1. Mutations in PINK1 induce loss of mitophagy, and lead to the accumulation of ineffective mitochondria that could contribute to the physiopathology of Parkinson's disease [42]. In spite of, alterations in autophagy are related with a number of human diseases, including cancer [43] and neurodegenerative disorders [44].

On the other hand, mitochondrial metabolism and activity of several oxidases (NADPH oxidase, xanthine oxidase cyclooxygenases, and lypooxygenase) are the major source of ROS, the main source that induce oxidative stress. Nonetheless, DNA mutations (both nuclear and mitochondrial), environmental factors (radiation), a poor diet, tissue damage or inflammation can also contribute to the formation of these highly reactive species. This relation between mutations and/or oxidative stress and diseases will be broadly described below.

4.1. DNA mitochondrial mutations and diseases

The human mitochondrial genome is a long circular double-stranded DNA chromosome (16.569 base pairs) [45]. The nucleotide sequence and gene reorganization were described by Anderson et al. in 1981 [45].

Table 3
UCPs: Functions and tissue expression.

Name	Predominant tissue expression	Function
UCP1	Brown adipocytes	- Dissipate the proton electrochemical gradient. - Increase the production of heat in infants.
UCP2	Whole body	- Control of cellular energetic balance.
UCP3	Skeletal muscle	- Prevention of oxidative stress induced by ROS formation.
UCP4	Brain	- Regulate the temperature and metabolism. - Regulate membrane potential and ATP levels. - Reduce oxidative stress.
UCP5	Brain, testes	- Works synergistically with UCP4. - Improve mitochondrial efficiency.

They show an unbalanced nucleotide composition, that allowed the separation of mtDNA into heavy (H) and light (L) strands, by a density gradient centrifugation. Importantly, in opposition to nuclear DNA, mitochondrial genome does not contain non-coding sequence (introns).

Mitochondrial genes encode 13 protein subunits up to 85 polypeptides that constitute the OXPHOS complexes, 22 transfer RNAs (tRNA), 12S and 16S ribosomal RNAs (rRNA) genes and other 13 polypeptide-encoding genes (mRNAs) [45]. Complementary, nuclear DNA encodes >98% of mitochondrial proteins. For example, it encodes the majority (70) of proteins from complexes I to V [45].

Up to date, about 200 different mutations in genes encoding mitochondrial proteins have been characterized in both, nuclear and mitochondrial DNAs [46]. However, mitochondrial DNA presents a higher mutation ratio as compared to nuclear DNA due to its close location to ROS, produced by the respiratory chain. Deletions or rearrangements have also been described [46]. The incidence of these alterations is about 1 in 400 in general population [47], most of them are asymptomatic, and clinical manifestations affect about 9 individuals per 100.000 habitants [48]. Such mutations affect mitochondrial tRNAs and rRNAs, enzymes, structural and signaling proteins, carriers, channels and heat shock proteins, although most frequent mutations have a direct or indirect impact on the OXPHOS system [49]. These alterations cause a decrease in mitochondrial energetic function, leading cells to apoptosis or necrosis processes when ATP needs are higher than produced, thus inducing subsequent tissue damage. Due to this damage, several symptoms arise: neurological deficits, cardiac disease, liver disease, muscle weakness, pain, gastro-intestinal disorders, poor growth, anemia, diabetes, respiratory complications, seizures, lactic acidosis, developmental delays and susceptibility to infection (Table 4). Mutations can affect mainly an organ (such as brain, heart, liver, skeletal muscle, kidney), endocrine or respiratory systems (Tables 5A and 5B). For instance, a naturally occurring thymidine to cytidine mutation in mitochondrial tRNA gene is associated with metabolic disorders, hypertension and hypercholesterolemia-related cardiovascular diseases [43, 46,47,50]. Moreover, mutations can cause alterations in various organs. As an example, patients with a mutation in *tymp* gene develop mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). A detailed classification of mitochondrial mutations and associated diseases is available at: http//www.mitomap.org/. Nevertheless, mutations can also be due to

Table 4
Clinical manifestations of mitochondrial diseases.

Neuromuscular	Systemic	Sensory	Endocrine
Muscle weakness	Vomiting	Droopy eyelids	Diabetes Mellitus
Myoclonus	Hepatopathy	Nystagmus	Hypoparathyroidism
Limited mobility of the eyes	Blood coagulation disorders	Diplopia	Exocrine pancreatic dysfunction
Exercise intolerance	Metabolic	Blindness	Adrenal insufficiency
Cardiac conduction defects	Acidosis nephropathy	Retinitis pigmentosa	Adrenocortical hyperfunction
Neuropathy	Swallowing disorders	Cataract	
Ataxia	Pigmentation disorders	Deafness	
Speech disorders	Infertility		
Seizures	Dysphagia		
Dementia	Anemia		
Heart Failure			
Heart arrhythmia			
Stroke-like episodes			

other causes, such as infections, inflammation, drugs, toxins and environmental factors, among others [51–53].

Furthermore, when mutations are located in nuclear DNA, they are transmitted in a classical Mendelian genetic. However, if the alteration is placed in mtDNA, it will involve a maternal inheritance. It is well known that cells contain hundreds of mitochondria and that each mitochondria encloses from 2 to 10 copies of mtDNAs. Hence, when a mitochondrial mutation occurs, the cell will be managing two types of mitochondria: one with normal mtDNA or another one with mutant mtDNA. Following mitosis, these organelles will be randomly spread into two cells, those can contain normal mtDNA, mutant mtDNA, or both. Eventually, after some splitting cycles, cells will include only normal or mutant mtDNA.

4.2. Mitochondrial damage and oxidative stress

OXPHOS system is the main source of intracellular free radicals [54]. In particular, mitochondrial complexes I and III are the major sites that contribute to the production of superoxide anion (O_2^-), although complex II and complex IV may also participate [54,55]. Two main reactions are involved in O_2^- generation: 1) oxidation of flavin mononucleotide (FMN), a coenzyme of the NADH dehydrogenase, and 2) autooxidation of intermediate semiquinones UQH•. In fact, ubiquinone is the primary source of O_2• and this process might be regulated by membrane potential [55].

O_2^- production is determined by the number and size of mitochondria, and the number of subunits of the respiratory chain expressed by every mitochondria. Ratios of 0.9 ± 0.1 nmol of O_2^-/min per mg of protein at pH 7.4 and at 30 °C in mammals have been observed.

In normal conditions, about 0.15% of the total oxygen consumed during OXPHOX produces superoxide anion, which is detoxified into hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD), either in the cytosol (SOD1) or mitochondria (SOD2) [54]. Korshunov et al. observed that H_2O_2 flow from mitochondria to cytoplasm depending on the membrane potential [55]. Familial amyotrophic lateral sclerosis patients present mutations in SOD in approximately 20% of cases [56]. This antioxidant enzyme is also related to other neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases [57].

In the cytoplasm, H_2O_2 is transformed in water by catalase enzyme. Superoxide is also converted in mitochondrial matrix to another ROS, peroxynitrite ($ONOO^-$). In normal conditions, $ONOO^-$ concentrations of 2–5 nM have been observed, and levels higher than 20–30 nM are harmful. Peroxynitrite reacts with nucleic acids, lipids, and tyrosine

Table 5A
Mitochondrial nuclear DNA mutations associated with complexes impairments and diseases.

Disease	*Gen*	Protein	Complex
Childhood encephalopathy	*NDUFS1*	NADH dehydrogenase (ubiquinone) Fe—S protein 1	I
Encephalomyopathy	*NDUFAF2*	NADH dehydrogenase (ubiquinone) complex I, assembly factor 2	I
Encephalomyopathy	*COX6B1*	Cytochrome c oxidase subunit VIb polypeptide 1	IV
Encephalomyopathy	*TUFM*	Tu translation elongation factor, mitochondrial	I
Cardiomyopathy, encephalopathy	*NDUFS2*	NADH dehydrogenase (ubiquinone) Fe—S protein 2	I
Cardiomyopathy, encephalopathy	*NDUFV2*	NADH dehydrogenase (ubiquinone) flavoprotein 2	I
Multisystem complex I deficiency	*NDUFS4*	NADH dehydrogenase (ubiquinone) Fe—S protein 4	I
Leigh syndrome	*NDUFS1*	NADH dehydrogenase (ubiquinone) Fe—S protein 1	I
Leigh syndrome	*NDUFS3*	NADH dehydrogenase (ubiquinone) Fe—S protein 3	I
Leigh syndrome	*NDUFS4*	NADH dehydrogenase (ubiquinone) Fe—S protein 4	I
Leigh syndrome	*NDUFS7*	NADH dehydrogenase (ubiquinone) Fe—S protein 7	I
Leigh syndrome	*NDUFS8*	NADH dehydrogenase (ubiquinone) Fe—S protein 8	I
Leigh syndrome	*NDUFV1*	NADH dehydrogenase (ubiquinone) flavoprotein 1	I
Leigh syndrome	*SDHA*	Succinate dehydrogenase complex, subunit A	II
Leukodystrophy, myoclonic epilepsy	*NDUFV1*	NADH dehydrogenase (ubiquinone) flavoprotein 1	II
Encephalomyopathy, Leukodystrophy	*SDHA*	Succinate dehydrogenase complex, subunit A	II
Encephalomyopathy, Leukodystrophy	*SDHAF1*	Succinate dehydrogenase complex assembly factor 1	II
Hereditary paranglioma	*SDHB*	Succinate dehydrogenase complex, subunit B	II
Hereditary paranglioma	*SDHD*	Succinate dehydrogenase complex, subunit D	II
BVHNT	*SDHC*	Succinate dehydrogenase complex, subunit C	II
Gracile syndrome	*BCS1L*	BC1 (ubiquinol-cytochrome *c* reductase) synthesis-like	III
Hepatopathy, ketoacidotic come	*SCO1*	SCO1 cytochrome *c* oxidase assembly protein	IV
Infantile cardioencephalomyopathy	*SCO2*	SCO2 cytochrome *c* oxidase assembly protein	IV
Charcot-Marie-Tooth type 1 A	*COX10*	Cytochrome c oxidase assembly homolog 10	IV
Defect haem biosynthesis	*COX15*	Cytochrome c oxidase assembly homolog 15	IV
MELAS	*MT-CO1*	Mitochondrial encoded Cytochrome c oxidase 1	IV
MELAS	*MT-CO2*	Mitochondrial encoded Cytochrome c oxidase 2	IV
MELAS	*MT-CO3*	Mitochondrial encoded Cytochrome c oxidase 3	IV
MELAS	*MT-ND1*	Mitochondrially encoded NADH dehydrogenase 1	I
MELAS	*MT-ND3*	Mitochondrially encoded NADH dehydrogenase 3	I
MELAS	*MT-ND6*	Mitochondrially encoded NADH dehydrogenase 6	I

BVHNT: Benign vascularized head and neck tumours.
MELAS: Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes.

Table 5B
Mitochondrial nuclear DNA mutations associated with diseases.

Disease	Gene	Protein
Encephalomyopathy	*ATPAF2*	ATP synthase mitochondrial F1 complex assembly 2
Encephalomyopathy	*TSFM*	Ts translation elongation factor, mitochondrial
Leigh syndrome	*LRPPRC*	Leucine-rich pentatricopeptide repeat containing
Leigh syndrome, leukodystrophy	*SURF1*	Surfeit 1
Barth syndrome	*TAZ*	Taffazin
Hereditary spastic paraplegia	*SPG7*	Paraplegin
Familial cerebellar ataxia	*CABC1*	aarF domain containing kinase 3
X-linked Leigh syndrome	*PDHA1*	Pyruvate dehydrogenase
Developmental delay, encephalopathy	*PC*	Pyruvate carboxylase
ARSP 13	*HSPD1*	HSP60
Mohr-Tranebjaerg syndrome	*DDP1*	Translocase of inner mitochondrial membrane 8 homolog A
ADPEO, Familial hypertrophic cardiomyopathy	*ANT1*	Solute carrier family 25 (ANT), member 4
Mycrocephaly	*SCL25A19*	Mitochondrial thiamine pyrophosphate transporter
MNGIE	*TYMP*	Thymidine phosphorylase
Myopathic (mitochondrial DNA depletion)	*TK2*	Thymidine kinase 2, mitochondrial
CPEO	*C10orf2*	Twinkle
Friedreich ataxia	*FXN*	Frataxin
CMP myopathy, hepatomegaly, retinopathy	*HADHA-B*	Hydroxyacyl-CoA dehydrogenase/3-ketoacyl-CoA thiolase/enoyl-CoA hydratase, alpha subunit
HHH syndrome	*SLC25A15*	Solute carrier family 25 (ornithine transporter) 15
Neuropathy, dysarthria, CPEO	*POLG1*	Polymerase (DNA directed), gamma
Optic atrophy	*OPA1*	Optic atrophy 1
Optic atrophy	*OPA2*	Optic atrophy 2
Seizures, encephalopaty	*HMGCS2*	3-hydroxy-3-methylglutaryl-CoA synthase 2
Hepatopathy, hypotonia, failure to thrive	*DGUOK*	Deoxyguanosine kinase
Encephalopathy, hepatomegaly	*HMGCL*	3-hydroxymethyl-3-methylglutaryl-CoA lyase
Menkes disease, occipital horn syndrome	*MNK*	ATPase, Cu^{++} transporting, alpha polypeptide
E3-deficient maple syrup urine disease	*DLD*	Dyhidrolipoamide dehydrogenase
Alpers-Huttenlocher syndrome, MNGIE, SANDOP, PEO with mtDNA deletions 1	*POLG1*	Polymerase (DNA directed), gamma
Encephalopathies (coenzyme Q deficiency)	*ADSS1*	Adenylosuccinate synthase
Mitochondrial encephalomyopathy, nephropathy	*COQ2*	Coenzyme Q2 homolog, prenyltransferase
ARNOP coenzyme Q10 deficiency	*COQ9*	Coenzyme Q9 homolog (*Saccharomyces cerevisiae*)
Coenzyme Q10 deficiency	*ADSS*	Adenylosuccinate synthase
ARNOP coenzyme Q10 deficiency	*PDSS1*	Prenyl (decaprenyl) diphosphate synthase, subunit 1
Coenzyme Q10 deficiency	*PDSS2*	Prenyl (decaprenyl) diphosphate synthase, subunit 2
HDFHE	*ACADM*	Acyl-CoA dehydrogenase, C-4 to C-12 straight chain
Leigh syndrome	*MT-ATP6*	Mitochondrially encoded ATP synthase 6
Leigh syndrome	*MT-TL1*	Mitochondrially encoded tRNA leucine 1 (UUA/G)
Leigh syndrome	*MT-TK*	Mitochondrially encoded tRNA lysine
Leigh syndrome	*MT-TW*	Mitochondrially encoded tRNA tryptophan
Leigh syndrome	*MT-TV*	Mitochondrially encoded tRNA valine
Leigh syndrome	*MT-ND1*	Mitochondrially encoded NADH dehydrogenase 1
Leigh syndrome	*MT-ND2*	Mitochondrially encoded NADH dehydrogenase 2
Leigh syndrome	*MT-ND3*	Mitochondrially encoded NADH dehydrogenase 3
Leigh syndrome	*MT-ND4*	Mitochondrially encoded NADH dehydrogenase 4
Leigh syndrome	*MT-ND5*	Mitochondrially encoded NADH dehydrogenase 5
Leigh syndrome	*MT-ND6*	Mitochondrially encoded NADH dehydrogenase 6
Leigh syndrome	*MT-CO3*	Mitochondrially encoded cytochrome *c* oxidase III
Neurogenic muscle weakness, ataxia, and retinitis pigmentosa	*MT-ATP6*	Mitochondrially encoded ATP synthase 6
LHON	*MT-ND1*	Mitochondrially encoded NADH dehydrogenase 1
LHON	*MT-ND2*	Mitochondrially encoded NADH dehydrogenase 2
LHON	*MT-ND4*	Mitochondrially encoded NADH dehydrogenase 4
LHON	*MT-ND4L*	Mitochondrially encoded NADH 4 L
LHON	*MT-ND5*	Mitochondrially encoded NADH dehydrogenase 5
LHON	*MT-ND6*	Mitochondrially encoded NADH dehydrogenase 6
MERF	*MT-TK*	Mitochondrially encoded tRNA lysine
MERF	*MT-TF*	Mitochondrially encoded tRNA phenylalanine
MERF	*MT-TP*	Mitochondrially encoded tRNA proline
MELAS	*MT-TL1*	Mitochondrially encoded tRNA leucine 1 (UUA/G)
MELAS	*MT-ND5*	Mitochondrially encoded NADH dehydrogenase 5
MELAS	*MT-TC*	Mitochondrially encoded tRNA cysteine
MELAS	*MT-TK*	Mitochondrially encoded tRNA lys
MELAS	*MT-TV*	Mitochondrially encoded tRNA valine
MELAS	*MT-TF*	Mitochondrially encoded tRNA phenylalanine
MELAS	*MT-TQ*	Mitochondrially encoded tRNA glutamine
MELAS	*MT-TS1*	Mitochondrially encoded tRNA serine 1 (UCN)
MELAS	*MT-TS2*	Mitochondrially encoded tRNA serine 2 (AGU/C)
MELAS	*MT-TW*	Mitochondrially encoded tRNA tryptophan
MELAS	*MT-CYB*	Mitochondrially encoded cytochrome *b*
Maternal inherited Diabetes, deafness	*MT-TL1*	Mitochondrially encoded tRNA leucine 1 (UUA/G)
Maternal inherited Diabetes, deafness	*MT-TK*	Mitochondrially encoded tRNA lysine
Maternal inherited Diabetes, deafness	*MT-TE*	Mitochondrially encoded tRNA glutamic acid

ADPEO: Autosomal dominant progressive external opthalmoplegia. ANT: Adenine Nucleotide Translocator. ARNOP: Autosomal recessive neonatal onset primary. ARSP 13: Autosomal recessive spastic paraplegia 13. CPEO: Chronic Progressive external ophthalmoplegia. HDFHE: Hepatic dysfunction, fasting hypoglycemia, and encephalopathy. HHH: Hyperornithinemia–hyperammonemia–homocitrullinemia syndrome. LHON: Leber Hereditary Optic Neuropathy. MELAS: Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes. MERF: Myoclonic Epilepsy Associated with Ragged Red Fibers. MNGIE: Mitochondrial neurogastrointestinal encephalomyopathy. PEO: Progressive external ophthalmoplegia. SANDOP: Sensory ataxic neuropathy dysarthria and ophthalmoparesis.

residues in several proteins, and forms 3-nitrotyrosine. The quantification of 3-nitrotyrosine is an indirect index of peroxynitrite concentration and oxidative stress in tissues. There are some molecules that protect against $ONOO^-$ oxidation, such as $NADH_2$, ubiquinone, glutathione and CO_2. High concentrations of these molecules are present in mitochondria.

Furthermore, endothelial nitric oxide synthase (eNOS) transforms O_2^- in nitric oxide, a secondary messenger with several biological functions (vasodilatation, neurotransmission, smooth muscle contraction and growth, platelet aggregation, and leukocyte adhesion). eNOS competes with SOD, thereby reducing the elimination of superoxide and inducing

superoxide accumulation. The adaptor protein p66shc is also implicated in the regulation of oxidative stress response. After serine 36 phosphorylation, p66shc translocates into the mitochondrial intermembrane space and catalyzes the production of hydrogen peroxide (H_2O_2) [58]. H_2O_2 increases the permeability of both mitochondrial membranes, leading to apoptosis or cell death. The expression of p66shc is higher in diabetic patients, which is associated with glycemic control and changes in oxidation/reduction balance [59].

Intracellular concentration of ROS depends on the relation between ions and the antioxidant mechanisms described above. Low levels of ions are useful in normal physiology, as they play a role in signal transduction involved in cellular proliferation and differentiation. Expression of PGC-1α is regulated by the endothelial NO synthase, and exogenous NO or cGMP increases mitochondrial biogenesis. Also, ions are involved in developmental processes, such as spermatogenesis, oogenesis, early development, morphogenesis, angiogenesis and cell migration.

However, unrestrained raise of free radicals, due to increased production or insufficient elimination, results in oxidative stress, which favors growth arrest and apoptosis [6]. There are some causes of oxidation–reduction imbalance. Genetic mutations are the main cause for mitochondrial dysfunction. Such mutations can induce detrimental metabolic processes and they can increase oxidative stress, which is associated to mitochondrial dysfunction either. Also, situations of high energetic demand or mitochondrial damage due to environmental factors cause the loss of membrane potential ($\Delta\Psi$m), which increases ROS production. In addition, oxidative stress is a major pathophysiological pathway to collapse $\Delta\Psi$m. If a threshold is exceeded, free radicals induce the production of more reactive species and a harmful cycle of oxidative stress and mitochondrial dysfunction arises. This physiopathological process is called ROS-induced ROS release [60].

Moreover, lipid peroxidation can be particularly injurious to mitochondria. This peroxidation can alter the phospholipid bilayer with loss of the normal membrane fluidity and permeability. Such peroxidation can lead to mitochondrial swelling and uncoupling between electron transport and proton gradient. Lipid hydroperoxides and their breakdown products, such as aldehydes, are involved in damage to specific mitochondrial proteins and transport systems either by direct inhibition of enzymes or by forming covalent bindings with thiols and sulfhydryl groups of proteins. Furthermore, the oxidation of sulfhydryl groups likely contributes to the deactivation and degradation of mitochondrial enzymes and transport proteins [6].

In conclusion, ROS, especially NO and $ONOO^-$, can induce oxidative stress and mitochondrial dysfunction, one of the primary mechanisms of tissue damage in inflammatory diseases, neurodegeneration and aging (Table 6) [6].

Table 6
Oxidative stress associated diseases.

Cancer	Inflammatory diseases	Neurologic diseases	Cardiovascular diseases
Bladder	Pulmonary fibrosis	Parkinson's Disease	Atherosclerosis
Brain tumor	Acute respiratory distress syndrome	Alzheimer's Disease	Acute myocardial infarction
Breast	Obesity	ALS	Heart failure
Ovarian	Diabetes	Multiple sclerosis	Hypertension
Cervical	Crohn's disease	Guillain-Barré syndrome	
Multiple Myeloma	Celiac disease		
Leukemia	Systemic lupus erythematosus		
Lymphoma	Rheumatoid arthritis		
Lung	Inflammatory joint disease		
Liver	Ischemia–reperfusion syndrome		
Oral			
Gastric			
Pancreatic			
Prostate			
Melanoma			
Sarcoma			

ALS: Amyotrophic lateral sclerosis.

4.3. Oxidative stress and neurodegenerative diseases

The central nervous system (CNS) is an organ with the higher metabolic rate and oxygen consumption. For this reason, mitochondria in the brain are more exposed to oxidative stress than others located in diverse tissues. Neurons are mainly dependent on mitochondria for energy production since they have restricted glycolytic capacity. Moreover, the high concentrations of polyunsaturated fatty acids and transition metals, and lower antioxidant defenses make the CNS particularly vulnerable to ROS. Also in aging, this phenomenon is increased since the antioxidant systems are less efficient. This process could be explained because there are some disorders such as, Alzheimer's disease, Huntington's disease, Wilson disease, Multiple Sclerosis, Parkinson's disease and Amyotrophic Lateral Sclerosis where mutations linked with the disease have not been found, but a mitochondrial dysfunction has been observed [46].

4.3.1. Multiple sclerosis

Demyelination and neurodegeneration are the principal features of multiple sclerosis (MS), a chronic inflammatory disease of the central nervous system. The mechanisms involved in tissue damage are poorly understood. However, recent data suggest that mitochondrial injury [61–63] and oxidative stress [62,63] play an important role in the physiopathology of the disease. Mitochondrial dysfunction can induce tissue damage through apoptosis induction, production of reactive oxygen species and energy failure. Oligodendrocyte apoptosis is a hallmark in some kind of lesions. These data correlate with those from Barnett et al. [64], who observed oligodendrocyte apoptosis and microglia activation in newly formed lesions. These alterations could be due to impaired NADH dehydrogenase activity in association with oxidative damage to mtDNA, detected in chronic active plaques in early stages of multiple sclerosis lesions [62]. In addition, immunohistochemistry confirms the increase of oxidative damage in nuclear DNA in chronic active plaques [65]. These findings are correlated with upregulated expression of genes related with mitochondrial protein synthesis and adenine nucleotide translocation. This upregulated gene expression is induced by oxidative stress and is involved in the defense against oxidation, observed by microarray techniques [62]. Anatomopathological analysis has also demonstrated the presence of lipid peroxidation-derived-molecules in the cytoplasm of oligodendrocytes, and oxidized phosphatydilcholine in axonal spheroids with disturbed axonal transport in active white matter and cortical lesions [66]. Overexpression of NADH oxidase enzyme by macrophages and microglia, that co-localized with oxidized DNA and lipids in active MS lesions, could be a main mechanism [62]. As demyelinated axons loose the saltatory conduction of action potential, they also show a reorganization of voltage-gated Na^+ channels along the axon to recover the impulse conduction. Possibly, this phenomenon needs increased ATP production. However, it was observed alterations in Complex IV, I and III, a mechanism whereby reduced ATP production is produced in demyelinated segments of upper motor neuron axons [62,64–66]. The imbalance between ATP consumption and production, due to defective oxidative phosphorylation or nitric oxide production, induces a chronic state of virtual hypoxia in chronically demyelinated axons. Energy failure explains the predominant destruction of small caliber axons, which are more sensible to the increase of Ca^{2+} in axoplasm as a result of the low mitochondria number present in these axons.

4.3.2. Alzheimer's disease

Alzheimer's disease (AD) is an age-related neurodegenerative disorder characterized by the progressive loss of memory and cognitive

functions [67,68]. The main pathological hallmarks of the disease are the amyloid protein deposits and neurofibrillary mess constituted by an abnormal and hyperphosphorylated tau protein, neuronal death and diminution of synaptic connections. The pathogenesis is not yet elucidated. The most accepted hypotheses include the amyloid-β peptide, excitoxicity, inflammation and oxidative stress. In fact, injured neurons show high levels of oxidative stress associated with lower mitochondrial mass, increased cytoplasmic mtDNA and autophagy [69,70]. The cause of mitochondrial damage is still unknown, but in vitro studies have demonstrated that the culture of neurons with amyloid-β protein induce O_2^- production, diminution of ATP concentration and mitochondrial calcium uptake which induce apoptosis. The impairment in mitochondrial complex IV gene expression [71,72] and the consequent diminution of its activity could explain a decrease in energy production observed in these patients [72].

Dysfunction of mitochondrial OXPHOS could be the source of free radicals, which could participate in tissue damage characteristic of the disease. High levels of protein carbonyls and nitration of tyrosine residues have been observed in AD patients [67,68]. Both protein modifications could affect cellular function by several pathways. Oxidized proteins are spliced by 20S proteasome in an ATP- and ubiquitin-independent pathway [73]. However, AD oxidized proteins are highly resistant to proteolytic degradation [73]. In addition, oxidized glutamate transporter (GLT-1) promotes the release of glutamate to external medium and results in neuronal death. Moreover, free radicals can induce energy dysfunction since modified enzymes such as, creatine kinase, triosephosphate isomerase, phosphoglycerate mutase-1, ATP synthase and α-enolase observed in these patients, showed a decreased activity [74,75]. These enzymes are involved in energy metabolism and ATP production, and diminution of the metabolic rate is one of the major alterations observed in Alzheimer's CNS. Additionally, increased lipid peroxidation, determined by measurement of malondialdehyde, 4-hydroxy-2-*trans*-nonenal, isoprostanes and a different lipid composition [76], observed in the brain of AD patients, affect membrane permeability and cellular function. Finally, elevated levels of 8-hydroxy-2-deoxyguanosine, 8-hydroxyguanosine, and indexes of DNA and RNA oxidation have been observed in patients with the disease [77,78].

4.3.3. Parkinson's disease

Parkinson's disease (PD) is a movement disorder that represents the second most common neurodegenerative syndrome. The clinical manifestations conform to the tetrad of motor neuron injury: tremor, rigidity, bradykinesia, and poor balance [79]. The main finding observed in the brain of PD patients is the presence of Lewy bodies in the *substantia nigra* and other specific brain regions [80]. Such Lewy bodies are constituted by insoluble aggregates of ubiquitin and α-synuclein [80]. Molecular analyses showed mutations in genes encoding proteins implicated in mitochondrial function, such as PARKIN [81], DJ-1, LRRK2 [82], SNCA [83] and PINK1 [84], but the association between mitochondrial damage and Parkinson's disease is not completely understood. The levels of respiratory chain subunits are significantly higher in neurons containing α-synuclein, although mitochondrial density is the same in nigral neurons with and without deposits. The most reliable evidence for mitochondrial dysfunction is that the activity of RC complex I is decreased in the *substantia nigra* and cortex [85]. Moreover, deletions in mtDNA have a deleterious effect on cytochrome *c* oxidase activity (Complex IV) in the neurons of these patients [86]. Alterations in RC assembly due to a reduced expression of the OXPHOS complexes subunits and a reduced electron transfer rates through complex I subunits were observed in the brain of these patients [87].

In accordance to these observations, increased lactate measurement and Pi/ATP ratio have been observed in PD patients [88]. All these results demonstrate alterations in PD. For example, dysfunction of mitochondrial metabolism shifts to anaerobic metabolism, which could promote the oxidation/reduction imbalance observed in these patients. Oxidative damage could be initiated by glutathione depletion, one of the earliest oxidative events observed in the evolution of the disease [89]. Additionally, microglial cells and, in particular NADPH oxidase, play a main role in the physiology of the disease [90]. Furthermore, nitrite, and inducible nitric oxide synthase are increased in the central nervous system of PD patients. Oxidative stress induce lipid, protein and DNA oxidation observed in necropsies samples from the brain of PD patients and may contribute to dopamine neuronal death [90,91].

5. Future treatments

Due to the involvement of mitochondria in different diseases, great efforts have been done to develop potential therapeutic agents. Therapeutic agents used to date attempt to prevent oxidative stress, improve metabolic function, modulate calcium homeostasis and regulate biogenesis and turnover of mitochondria (Table 7). Unfortunately, they are not completely successful yet. All of them are only palliative [92]. The reason is that many of these agents are not as effective in vivo because they cannot overpass the double mitochondrial membrane. To resolve this issue, lipophilic molecules have been developed to improve the passage of these bioactive agents through the lipid bilayer [93].

A further problem to set new therapeutic targets is that the mechanisms involved in metabolism, generation and turnover of mitochondria are not completely understood. In this regard, we have observed that IGF-1 (insulin-like growth factor-1), a hormone-like polypeptide with several metabolic and anabolic properties, is related with mitochondrial function and oxidative stress regulation [94–97].

5.1. IGF-1 as a novel therapeutic strategy

IGF-1 is a single chain polypeptide with a molecular weight about 7.649 Da. Its structure shows high similarity to proinsulin (about 50%), positions 1 to 29 are homologous to insulin B chain and positions 42 to 62 to insulin A chain.

Table 7
Potential therapies for mitochondrial associated diseases.

Treatment	Mitochondrial effect	Disease
Polydatin	Prevent mPTP	Cardiovascular diseases
Cyclosporin A	Inhibit mPTP	Alzheimer's disease
Sanglifehrin A	CypD In vivo	Myocardial disease
Bongkrekic acid	ANT	HD, MELAS
Szeto–Schiller (SS) peptides	Antioxidant, anti mPTP, anti swelling	Cardiovascular diseases
Ro 68–3400	ANT	Cardiac diseases
S15176	Unknown	Liver disease
Sildenafil	Unknown	Cardiovascular diseases
Debio-025	CypD binding with ANT	Muscular diseases
TRO19622	VDAC	Neurodegenerative
Antamanide	CypD	Multiple sclerosis
UQ(0): CoQ10, MitoQ, Idebenone, Decyclubiquinone	ANT, ERC, Antioxidant	Neurodegenerative
Dimebon	Indicate its ability to block mPTP	Alzheimer's disease
XJB-5-131	Oxidative DNA damage	Huntington's disease
Nortriptyline	Inhibits mtPTP	ALS, HD
Sirtuin	Increase Biogenesis	Age associated diseases
Bezafibrate	Increase Biogenesis	Mitochondrial myopathy
IGF-1	Antioxidant, MMP improvement	Liver diseases

ANT: Adenine nucleotide translocator. CypD: Peptidyl-prolyl *cis*-trans isomerase F. mPTP: ERC: electron respiratory chain. Mitochondrial. VDAC: Voltage dependent anion channel. Dimebon:(2,3,4,5-tetrahydro-2.8-dimethyl-5[2-(6-methyl-3-pyridinyl)ethyl]-1H-pyrido[4.3-*b*]indole). Polydatin: 3, 4′, 5-trihydroxystibene-3-monoglucoside. DIDS: disodium 4.4′-diisothiocyanatostilbene-2.2′-disulfonate ALS: amyotrophic lateral sclerosis. HD: Huntington's disease. MMP: mitochondrial membrane potential.

IGF-1 is probably the most important regulator of intrauterine growth [98]. This hypothesis is supported by the remark that deleterious mutations of IGF-1 or IGF-receptor are related with reduced intrauterine growth and development [96]. Also, this hormone is responsible for normal cell and bone growth [99]. Growth hormone (GH) regulates IGF-1 production in hepatic and non-hepatic tissues. In turn, IGF-1 inhibits GH production in a negative feedback process. The liver is the main source of IGF-1 ($\approx$70%) [100], but it is also produced in multiple tissues including brain, liver, testes, skeletal muscle, bone and cartilage (Fig. 3).

Additionally, IGF-1 interacts with insulin to modulate its control on carbohydrate metabolism. The secretion of both IGF-1 and insulin is stimulated by food intake and inhibited by fasting [99]. Likewise, GH and IGF-1 play a role in controlling insulin sensitivity. This is not surprising, since the IGF-1 type I receptor, that mediates the biological effects of IGF-1, has 60% amino acid sequence homology with the insulin receptor, and the intracellular signaling pathways induced by insulin are shared by IGF-1 [101].

Furthermore, it has been reported that IGF-1 is useful in rescuing neurons, hematopoietic cells and fibroblasts from apoptosis, and plays an important role in regulation of several neuroendocrine functions [102].

5.2. Low doses of IGF-1 and mitochondrial dysfunction

Our group has reported that the exogenous administration of IGF-1 in aging rats (which showed decreased serum levels of this hormone) restores IGF-1 circulating levels, similar to those found in young controls. IGF-1 therapy also improved glucose and lipid metabolism, increased testosterone levels and antioxidant capability, and reduced oxidative damage in brain and liver. It was also associated with a normalization of antioxidant enzyme activities [94,95]. Additionally, we demonstrated that untreated aging rats showed a significant mitochondrial dysfunction, characterized by: depletion of membrane potential, increased proton leak rates and intramitochondrial free radical production, and a reduction of ATPase and complex IV activities [94,95]. In addition, these mitochondria from untreated aging rats showed an increased oxidative damage. Accordingly, untreated aging rats showed a significant overexpression of the active fragment of caspases 3 and 9. IGF-1 therapy in these aging rats corrected all these parameters of mitochondrial dysfunction and reduced caspase activation. In conclusion, these results show that the cytoprotective effect of IGF-1 is closely related to a mitochondrial protection, leading to a reduction of free radical production, oxidative damage, and apoptosis, and to an increasing of ATP production [95].

On the other hand, similar findings were obtained in experimental cirrhosis, with untreated and treated rats with low doses of IGF-1. In this study, IGF-1 replacement therapy was able to restore all parameters of mitochondrial dysfunction observed in untreated cirrhotic rats [103, 104]. As a consequence, a clinical trial of cirrhotic patient was carried out, resulting that IGF-1 therapy induced a significant increase of albumin serum levels and an increment in resting energy expenditure [105]. This last finding could be understood as a greater ATP availability.

More recently, our group used an experimental model of mice with partial IGF-1 deficiency (Hz, $igf^{+/-}$). In this model, a significant oxidative liver damage was observed in Hz group, as compared to both WT (control, $igf^{+/+}$) and IGF-1 treated (Hz + IGF-1) groups [105]. Untreated animals did not receive any exogenous insult and showed, additionally, mitochondrial dysfunction. In addition, the protective effect of IGF-1

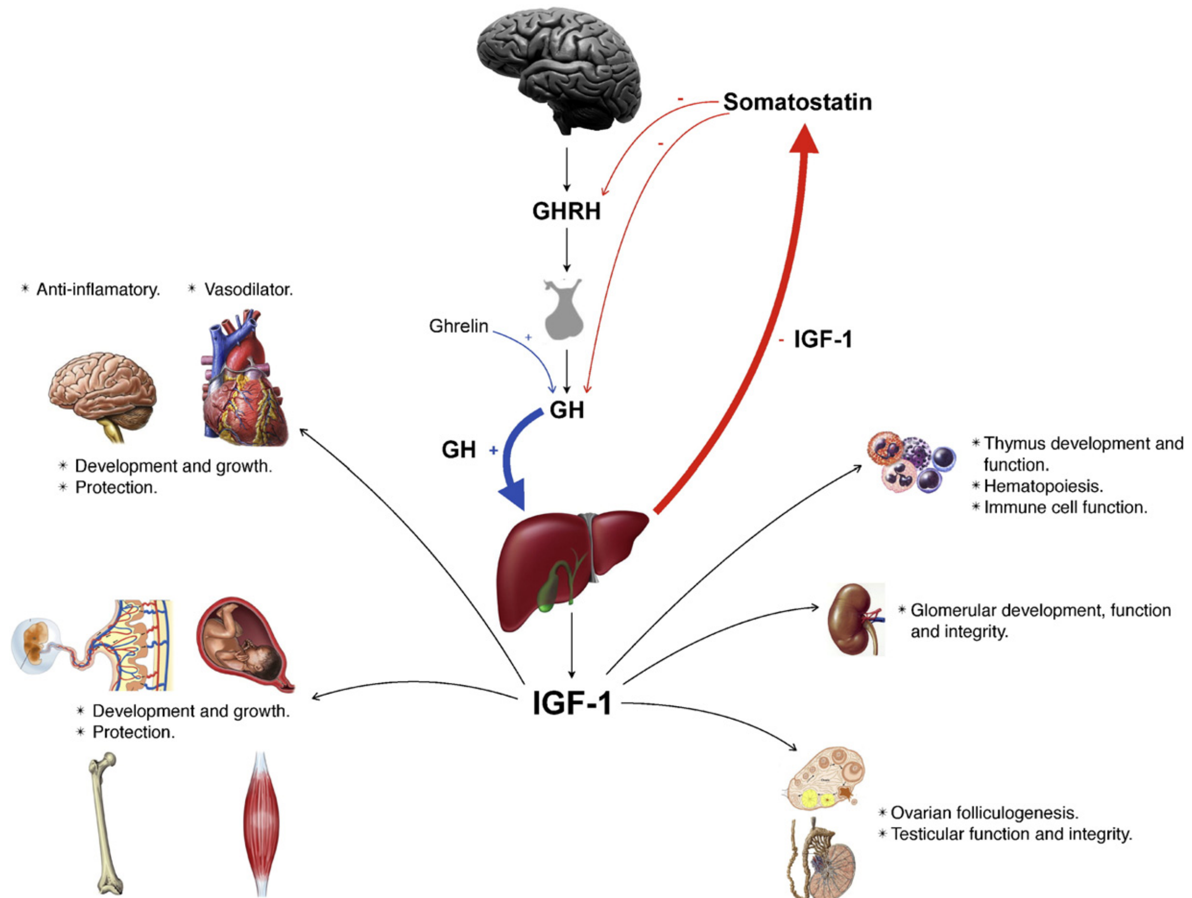

Fig. 3. GH/IGF-1 axis (modified from Martín-Estal et al. 2015). Hypothalamus-pituitary-liver axis regulates the production of IGF-1. IGF-1 promotes the growth of various tissues like bone, muscle, and regulates glucose homeostasis. IGF-1 regulates GHRH and GH release in a negative feedback process.

is mediated by heat shock proteins (HSPs) as shown in the brain, liver and testes. These proteins act as sensors of cellular redox changes and may intervene in the reparation and clearance of damaged proteins. They also play a role in regulating apoptosis and inflammation [106].

All these data agree with those published by Hao et al. [97], who observed that IGF-1 showed beneficial effects on apoptosis mediated by oxidative stress in human umbilical vein endothelial cells (HUVECs). Hydrogen peroxide addition to HUVECs induced typical apoptotic changes (DNA fragmentation, altered mitochondrial membrane potential and caspase-3 activity) in these cells. However, IGF-1 addition improved oxidative stress damage. This effect seems to be related with the improvements in mitochondrial function, since HUVECs treated with IGF-1 showed a conserved mitochondrial membrane potential, decreased mitochondrial cytochrome *c* release, and a reduced caspase-3 activity. These findings could explain the physiopathological mechanism involved in cardiovascular diseases, which is one of the main causes of mortality. In fact, low serum IGF-1 and IGF-Binding protein-1 levels are related with higher prevalence of cardiovascular disease in older adults.

6. Conclusions

Mitochondrial dysfunction has been shown to compromise insulin signaling through serine phosphorylation of insulin receptor substrate. The contribution of mitochondrial dysfunction to impairments in insulin metabolic signaling is also suggested by gene array analysis. Such gene array analysis showed reductions in gene expression, that regulate mitochondrial ATP production. The alteration in these gene expressions is associated with insulin resistance and type 2 diabetes mellitus. Moreover, a diminution in oxidative capacity of mitochondrial electron transport chain is manifested in obese, insulin-resistant and diabetic patients. Genetic and environmental factors, oxidative stress, and alterations in mitochondrial biogenesis can adversely affect mitochondrial function, leading to insulin resistance and several pathological conditions, such as type 2 diabetes.

Finally, it remains essential to know the exact mechanisms involved in mitochondrial generation and metabolism, mitophagy, apoptosis, and oxidative stress to establish new targets in order to develop potentially effective therapies.

One of the newest targets to recover mitochondrial dysfunction could be the administration of low doses of IGF-1. In the last years, it has been observed that IGF-1 therapy has several beneficial effects: restores physiological IGF-1 levels; improves insulin resistance and lipid metabolism; exerts mitochondrial protection; and has hepatoprotective, neuroprotective, antioxidant and antifibrogenic effects. In consequence, treatment of mitochondrial dysfunctions with low doses of IGF-1 could be a powerful and useful effective therapy to restore normal mitochondrial functions.

Transparency document

The Transparency document associated with this article can be found, in online version.

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