Mitochondrial respiratory chain dysfunction: implications in neurodegeneration

María Morán[1,2,*], David Moreno-Lastres[1,2], Lorena Marín-Buera[1,2], Joaquín Arenas [1], Miguel A. Martín [1,2], and Cristina Ugalde[1,2]

[1]Laboratorio de enfermedades raras: mitocondriales y neuromusculares, Instituto de Investigación Hospital Universitario 12 de Octubre (i+12), Madrid, Spain; [2]Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), U723, Spain.

*Corresponding author: Dr. María Morán, Laboratorio de enfermedades raras: mitocondriales y neuromusculares. Instituto de Investigación Hospital Universitario 12 de Octubre (i+12). Centro de Actividades Ambulatorias, 6ª planta. Avenida de Córdoba s/n, 28041 Madrid. Phone: +34 91 779 2784, FAX: +34 91 390 8544, e-mail: mmoran@h12o.es

Abstract

For decades mitochondria have been considered static round shaped organelles in charge of energy production. On the contrary, they are highly dynamic cellular components that undergo continuous cycles of fusion and fission influenced, for instance, by oxidative stress, cellular energy requirements, or the cell cycle state. New important functions beyond energy production have been attributed to mitochondria, such as the regulation of cell survival due to their role in the modulation of apoptosis, autophagy and aging. Primary mitochondrial diseases due to mutations in genes involved in these new mitochondrial functions, and the implication of mitochondrial dysfunction in multifactorial human pathologies like cancer, Alzheimer's and Parkinson's diseases, or diabetes has been demonstrated. Therefore, mitochondria are set at a central point of the equilibrium between health and disease, and a better understanding of mitochondrial functions will open new fields to explore the role of these mitochondrial pathways in human pathologies. The present review will dissect the relationships between the activity and assembly defects of the mitochondrial respiratory chain, oxidative damage, and alterations in mitochondrial dynamics, with special focus at their implications in neurodegeneration.

Keywords: mitochondria, respiratory chain dysfunction, assembly, reactive oxygen species, mitochondrial dynamics, neurodegeneration.

1. Introduction

A number of essential cellular functions take place in the mitochondria. These include regulatory pathways of the intermediate metabolism, steroid metabolism, amino acid biosynthesis, fatty acid oxidation, and apoptosis. However, the mitochondrial major function is the production of adenosine 5'-triphosphate (ATP), the key energy source of the cell (Reid et al., 1966). The final biochemical step of this process takes place in the oxidative phosphorylation (OXPHOS) system. The mammalian OXPHOS system comprises five multiprotein complexes (complexes I to V) and two mobile electron carriers (ubiquinone and cytochrome c) embedded in the lipid bilayer of the mitochondrial inner membrane. The first four redox complexes (complexes I to IV) constitute the respiratory chain (RC), which transfers electrons from NADH and $FADH_2$ to molecular oxygen, the terminal electron acceptor. The energy released by the oxidation of these substrates is used to generate a proton gradient across the mitochondrial inner membrane that will be used by complex V for the synthesis of ATP (Reid et al., 1966; Mitchell and Moyle, 1967). Each of the OXPHOS complexes consists of multiple polypeptide subunits encoded either by nuclear or mitochondrial DNA (mtDNA), except for complex II that is exclusively encoded by the nuclear genome (nDNA). The correct biosynthesis of the OXPHOS complexes is thus a highly intricate and regulated process that requires the concerted action of the two cellular genomes (Ryan and Hoogenraad, 2007). The nuclear-encoded subunits are synthesized on free ribosomes in the cytosol and post-translationally imported into mitochondria (Devaux et al. 2010), where they assemble together with the mitochondrial-encoded subunits and prosthetic groups to build up the OXPHOS complexes. The assembly process depends on its final steps on the regulatory action of chaperones or assembly factors that are specific for each complex (Fontanesi et al., 2008; Fernandez-Vizarra et

al., 2009; Leary and Sasarman, 2009; Ludlam et al., 2009; Zara et al., 2009; McKenzie and Ryan, 2010; Rutter et al., 2010; Smith et al., 2012; Stiburek and Zeman, 2010). Any disturbance in the delicate balance between nuclear and mitochondrial gene products during the biosynthesis of the OXPHOS complexes represents an adverse situation in which the aggregation of unassembled subcomplexes and hydrophobic mitochondrial translation products may occur in the mitochondrial inner membrane. These assembly defects and structural changes of the OXPHOS complexes would subsequently lead to a decreased ATP production, and more dangerously to electron -leakage, accumulation of toxic reactive oxygen species, and release of apoptotic-inducing factors that would ultimately lead to cell death and the degeneration of the affected tissues (DiMauro and Hirano, 2009). This review will update the relationships between mitochondrial respiratory chain assembly defects leading to the dysfunction of the OXPHOS system, the production of reactive oxygen species (ROS) and mitochondrial dynamics, and their implications in mitochondrial and the most frequent neurodegenerative disorders.

2. Respiratory chain dysfunction: a coupling of defective assembly and malfunctioning enzyme activities.

At the molecular level, the most obvious consequence of genetic defects in OXPHOS components is the hampered assembly of the RC complexes either due to the malfunctioning of essential chaperones, or due to conformational changes or a complete lack of the affected subunits (Fernandez-Vizarra et al., 2009; Leary and Sasarman, 2009; Ugalde et al., 2009). This is highly relevant because RC complexes associate in higher order assemblies called supercomplexes or respirasomes (Schagger and Pfeiffer, 2000; Schagger and Pfeiffer 2001; Schagger, 2002; Bianchi et al., 2004; Schagger et al., 2004; Dudkina et al., 2005, Boekema and Braun, 2007; Acin-Perez et al., 2008;

Dudkina et al., 2011), which have been suggested to offer structural and functional advantages to the system, such as the prevention of the destabilization and degradation of RC complexes, the enhancement of electron transport efficiency and substrate channeling, or the reduction of electron or proton leakages (Wittig and Schagger, 2009; Koopman et al., 2010; Lenaz and Genova, 2010). As a consequence of their organization in the respirasomes, structural interdependences amongst the individual RC complexes exist (Acin-Perez et al., 2004; Schagger et al., 2004; D'Aurelio et al., 2006; Diaz et al., 2006; Li et al., 2007; Saddar et al., 2008; Soto et al., 2009; Vempati et al., 2009). This has major biological as well as biomedical implications, since structural alterations primarily affecting one given complex often induce pleiotropic deleterious effects of the other enzymes. As a result, combined RC enzyme deficiencies can be attributed to the genetic defect of a single complex. Mitochondrial complex I is functionally associated to the supercomplexes, and complexes III and IV are known play an essential role in the stabilization of complex I within these structures (Acin-Perez et al., 2004; Schagger et al., 2004; Diaz et al., 2006; Li et al., 2007). For this reason structural alterations that severely impair the biosynthesis of complexes III and IV may induce pleiotropic deleterious effects on the assembly and enzyme activity of complex I that will be probably translated into combined respiratory deficiencies of two or more RC complexes. Accordingly, pathogenic mutations in the cytochrome *b* (*CYTB*) or *BCS1L* genes that severely affect complex III assembly, may lead to pleiotropic activity defects of other RC complexes in patients´ tissues (Lamantea et al., 2002; Fernandez-Vizarra et al., 2007; Moran et al., 2010a). Similarly, mutations in the *COX1* gene that hamper complex IV assembly may cause combined enzyme deficiencies of complexes I and IV (D'Aurelio et al., 2006); and conversely, mutations affecting complex I subunits or assembly factors have been described in patients´ tissues with

combined deficiencies of RC complexes I and III (Budde et al., 2000; Ugalde et al., 2004), or I and IV (Saada et al., 2011).

Till recently, the biosynthetic mechanisms and functional significance of the mitochondrial respirasomes, formed at least by the association of RC complexes I, III and IV, remained unsolved. Pulse-chase experiments that analyzed the time-course incorporation of the thirteen mitochondrial-encoded proteins into RC complexes and supercomplexes suggested that supercomplexes originated by the direct association of single fully-assembled complexes (Acin-Perez et al., 2008). However, the observation that, in the absence of monomeric complex IV, newly-imported nuclear subunits from this complex were preferentially integrated into supercomplexes, suggested that the respirasomes formation could also be achieved through the association of partially-assembled complexes and free subunits (Lazarou et al., 2009). In a recent study, our group addressed the biosynthetic pathway of mitochondrial RC supercomplexes by partially depleting control cell lines of OXPHOS complexes with doxycycline, a reversible inhibitor of mitochondrial translation. The synthesis of mitochondrial-encoded subunits resumed after the drug removal, and the time-course incorporation of nuclear and mitochondrial RC subunits into supercomplex assembly intermediates was investigated. Based on the alignment and analysis of these intermediates we proposed a multistep assembly model of mitochondrial supercomplexes (Moreno-Lastres et al., 2012) [Figure 1]. The conceptual novelty of this model is that the respirasome biogenesis involves a complex I assembly intermediate acting as a scaffold for the combined incorporation of free subunits and subcomplexes from complexes III and IV. The process ends with the association of the complex I NADH dehydrogenase catalytic module, which leads to complex I and the respirasome activation. Our studies revealed that while complexes III and IV can assemble either as individual holoenzymes or by

incorporation of free subunits into supercomplexes, the respirasomes constitute the structural units where complex I is assembled and activated, thus explaining the essentiality of the respirasomes for complex I function (Schagger et al., 2004).

Importantly, this model aids explaining the structural interdependences among OXPHOS complexes, and why certain genetic defects affecting a single complex may lead to combined RC enzyme defects in patients. For instance, mutations in COX1 may lead to pleiotropic complex I defects (D'Aurelio et al., 2006; Hornig-Do et al., 2012) because the insertion of this complex IV subunit into supercomplexes occurs prior or in parallel with the incorporation of subunits from the complex I N catalytic module (NDUFV1 and NDUFS4). Consequently, severe structural abnormalities or the lack of COX1 affect the assembly or stability of NDUFS4 and NDUFV1 within supercomplexes. This in turn leads to the accumulation of a defective supercomplex $I+III_2$ intermediate that partially lacks the complex I N catalytic module, thus explaining the severe reduction in complex I activity detected in the complex IV mutant cells. A similar assembly phenotype has been recently described in a *NDUFS4* knock-out mice (Calvaruso et al., 2011). The same argument would serve to explain why failures in the insertion of the complex III subunits cytochrome b or RISP may lead to combined complex I and complex III deficiencies in human tissues (Lamantea et al., 2002; Acín-Perez et al., 2004; Fernandez-Vizarra et al., 2007; Moran et al., 2010a). However exceptions exist and, contrary to what is commonly accepted, there is no such a clear correlation between the severity of the assembly impairments of RC complexes III and IV, and the supposed pleiotropic complex I assembly and activity defects. Exceptions can be applied for instance to complex III-deficient patients harbouring mutations in the assembly factors *BCS1L* and *TTC19*, who showed normal complex I activity levels despite of a dramatic loss of fully-assembled complex III in different tissues

(Fernandez-Vizarra et al., 2007; Ghezzi et al., 2011). Similarly, mutations in complex IV subunits or assembly factors often lead to isolated complex IV defects without complex I being affected (Tiranti et al., 1998; Zhu et al., 1998; Papadopoulou et al., 1999; Rahman et al., 1999; Valnot et al., 2000a; Valnot et al., 2000b; Antonicka et al., 2003; Massa et al., 2008). Such differences might be attributed to the nature of the mutation or the functional role of the OXPHOS mutated gene, and suggest that not all complexes III and IV structural genes are equally necessary to maintain complex I stability. The fact that complex III and complex IV can get assembled either as individual holoenzymes or by direct binding of free subunits to supercomplex assembly intermediates supports the existence of several independently-regulated assembly pathways for the biosynthesis of these two complexes, and explains why decreased complex I levels usually lead to isolated complex I deficiency in mammalian tissues (Acin-Perez et al., 2004; Schagger et al., 2004). However, once more exceptions have been reported (Budde et al., 2000; Ugalde et al., 2004; Saada et al., 2011), making necessary to gain more insight in the mechanisms that regulate the structural and functional interdependences between OXPHOS complexes.

3. Cellular pathophysiological consequences of RC dysfunction in mitochondrial disorders and neurodegeneration

3.1. Oxidative stress

Mitochondria consume ~85-95% of the oxygen inspired during respiration, most of which is reduced to water in the final step of the RC activity (Shigenaga et al., 1994). Nevertheless, a small amount (0.1-4 %) of the electrons that flow through the RC leaks and causes one-electron reduction of oxygen, producing a relatively stable free radical, the superoxide anion ($O_2^{\cdot -}$) (Lenaz et al., 2002; Fridovich, 2004; Bayne et al., 2005).

Complexes I and III are considered the primary sites of the RC that produce $O_2^{\cdot-}$. Some reports indicate that damaged or mutated complex II is able to produce $O_2^{\cdot-}$; however, it is considered that all $O_2^{\cdot-}$ due to complex II activity occurs at complex I due to reverse electron flow (Zhang et al., 1998; Guzy et al., 2008; Murphy, 2009). Although complex IV does not produce $O_2^{\cdot-}$ itself, changes in its phosphorylation/dephosphorylation state can favour $O_2^{\cdot}$ production at the other RC points (Kadenbach et al., 2009).

Once superoxide is generated, it can be eliminated by the enzyme superoxide dismutase (SOD), which dismutates superoxide into hydrogen peroxide (H_2O_2) rendering very low superoxide levels (Murphy, 2009). In some circumstances, such as RC dysfunction due to mutations that affect the electron transfer properties of the RC complexes, an increased superoxide production can favor the accumulation of H_2O_2 and the appearance of other molecular oxygen-derived free radicals and precursors, known collectively as reactive oxygen species (ROS) (Turrens, 2003). Some of them are reactive molecules able to oxidize macromolecules such as lipids, DNA and proteins. Therefore, if ROS are not efficiently eliminated by the cellular antioxidants the cellular components become damaged by oxidation, which in turn leads to further oxidative stress, cellular dysfunction and even cell death (for a review in cellular antioxidants, repair of oxidative damage and their implication in neurodegeneration see Gros et al., 2002; Ahsan et al., 2009; Fernandez-Checa et al., 2010).

The mitochondrial free radical theory of aging proposed, decades ago, that the molecular damage induced by the free radicals produced by the RC is the main cause of aging (Harman, 1956). Nowadays this theory is matter of debate, since recent mounting evidence revealed that ROS are not simply subproducts of mitochondrial metabolism, but they perform important signaling roles in the healthy cell. In addition, several studies on long-lived vertebrate species, mutants and transgenic animals challenged the

old theory (for a review see Lapointe and Hekimi, 2010). Although this new view of the ROS is gathering strength, many studies clearly demonstrate that excessive ROS production is involved in several human pathologies that include mitochondrial diseases and neurodegenerative disorders such as Alzheimer´s and Parkinson´s diseases.

3.1.1. In mitochondrial disorders

In primary mitochondrial diseases, as a consequence of the RC dysfunction, disturbances in the electron transport and proton pumping across the system occur, leading to decreased mitochondrial membrane potential and OXPHOS-derived ATP (Iuso et al., 2006; Distelmaier et al., 2009; Moran et al., 2010b). Besides the energetic defect, the altered electron transport can induce increased rates of superoxide production; probably due to a high reduction state of the components of the RC upstream the mutated point.

Studies in skin fibroblasts from complex I-deficient patients described an inverse correlation between the severity of the complex I assembly and enzyme defects and increased superoxide production (Verkaart et al., 2007a; Verkaart et al., 2007b). Another group reported increased superoxide and hydrogen peroxide levels in cells from a patient harboring the c.C1564A mutation in the *NDUFS1* complex I subunit gene, which prevented complex I complete assembly and led to a marked complex I enzyme activity decrease (Iuso et al., 2006); however, the relatively more deleterious c.G44A nonsense mutation in the *NDUFS4* structural gene displayed normal ROS levels (Iuso et al., 2006). Likewise, our group analyzed the hydrogen peroxide levels in complex I-deficient fibroblasts with mutations in the *NDUFA1* and *NDUFV1* structural genes, without finding differences in the H_2O_2 levels between the mutant and control cells (Moran et al., 2010b). These discrepancies could be attributed to the functional nature of the mutated subunits and the particular effect of each mutation on the

accumulation of fully- and partially- assembled complexes, on the supercomplexes assembly and activation processes, on the NADH binding and oxidation, and on the electron transfer and shielding of the redox centers. Contradictory results have even been described in cells from patients harbouring the same mutations in the NDUFV1 subunit, which holds the NADH binding site and the FMN (Verkaart et al., 2007a, Verkaart et al., 2007b; Morán et al., 2010b). These results suggest that the genetic background may also influence ROS production and the final antioxidant capacity of each cell line, which will determine the pathophysiological effect of a specific mutation in the context of the whole respiratory chain.

Regarding complex III enzyme deficiency, two studies analyzed the impact on ROS production of mutations in the BCS1L assembly factor, involved in the insertion of the catalytic Rieske Iron Sulphur Protein (RISP) into complex III (Cruciat et al., 1999; Hinson et al., 2007; Moran et al., 2010a). One of these studies revealed defective complex III enzyme activities and respirasome assembly defects that correlated with increased superoxide levels in isolated mitochondria of lymphocytes from patients with either complex III deficiency or Björnstad syndrome (Hinson et al., 2007). The second study was performed with skin fibroblasts from six complex III-deficient patients with *BCS1L* mutations, which showed a marked correlation between the severity of the enzyme deficiencies and assembly defects of the RC complexes I, III and IV and raised H_2O_2 levels, together with an unbalanced expression of the cellular antioxidant defenses (Moran et al., 2010a). Accordingly, complexes I, III, IV and supercomplexes were decreased in RISP-deficient mouse cells that displayed high superoxide levels (Diaz et al., 2011). However, the stable silencing of the RISP protein in 143B cells and mice showed low superoxide induction and normal hydrogen peroxide levels despite a severe complex III deficiency and decreased expression of the OXPHOS genes, which could

indicate a shift towards the anaerobic energy metabolism to improve cellular survival (Hughes and Hekimi, 2011; Levanets et al., 2011).

The discrepancies shown make unclear whether, in mitochondrial diseases due to mutations in RC subunits or assembly factors, the altered assembly of the RC is a direct cause of increased ROS production. Depending on which subunit is mutated, the electron flow in the RC will be either altered, favoring superoxide induction, or could be simply blocked, leading only to a catalytic defect without increased ROS production.

3.1.2. In neurodegenerative disorders

3.1.2.1. In Alzheimer´s disease

The hallmarks of Alzheimer´s disease (AD), the most common form of dementia among older people, are the extracellular accumulation of amyloid β (Aβ) plaques and the intracellular deposition of neurofibrillary tangles of hyperphosphorylated tau protein. Familial AD has been associated with mutations in the amyloid precursor protein (APP), which is cleaved sequentially by β- and γ-secretases to yield Aβ, and also has been associated with mutations in the presenilins 1 and 2, which are components of the c-secretase complex. Several studies suggested that Aβ-induced neurotoxicity in AD could be mediated by oxidative stress (Mecocci et al., 1994; Hirai et al., 2001; Castellani et al., 2002; Wang et al., 2005). This AD-related oxidative damage has been associated with an altered function of the RC through a decreased complex IV enzyme activity, a common finding in different human and rodent AD cellular models (reviewed in Morais and De Strooper, 2010; Patten et al., 2010). In this regard, APP and Aβ have been shown to induce RC activity defects and oxidative stress by mechanisms that are now beginning to be elucidated. For instance, Hong et al described that the levels of mRNAs expressing mitochondrial complex IV subunits were down-regulated after exposure to Aβ in human neuroblastoma cells (Hong et al., 2007).

Other authors showed that in human brain, the amyloid precursor protein (APP) could interact with and accumulate in the mitochondria import channels TOM40 and TIM23 (Devi et al., 2006; Hansson Petersen et al., 2008). This would inhibit the entry of nuclear-encoded complex IV subunits IV and Vb into mitochondria, leading to decreased mitochondrial complex IV activity, ATP synthesis and membrane potential (Anandatheerthavarada et al., 2003; Devi et al., 2006). Accordingly, alterations in the assembly and enzyme activities of the RC complexes I and IV were demonstrated in rat choroid plexus epithelial cells treated with Aβ, and also in human choroid plexus cells from patients suffering AD (Vargas et al., 2010). The import blockage of complex IV constituents towards mitochondria could lead to an abnormal assembly of complex IV and the respirasome, which in turn would be responsible for the partial loss of complex I activity (Schagger et al., 2004; Li et al., 2007; Moreno-Lastres et al., 2012). APP can not only alter mitochondrial function by blocking the mitochondrial protein import system, but can also exert its deleterious effects inside the organelle. In cultured SH-SY5Y cells, APP was shown to be a substrate of the mitochondrial γ-secretase, where APP processing would lead to local Aβ production inside mitochondria, thus contributing to the organelle dysfunction (Pavlov et al., 2011). Direct import of Aβ into the inner mitochondrial membrane has also been reported in Aβ-treated rat mitochondria (Hansson Petersen et al., 2008). Once inside mitochondria, Aβ, either produced by APP processing or by direct import, could induce the RC inhibition. Canevari et al., and Casley et al., showed that nonsynaptic brain mitochondria from rats treated with a truncated form of Aβ displayed a specifically complex IV inhibition, whereas other RC complexes remained unaltered (Canevari et al., 1999; Casley et al., 2002). Moreover, Parks et al., reported Aβ-induced complex IV inhibition in rat liver isolated mitochondria (Parks et al., 2001). This complex IV inhibition could lead to

further instability or alterations in the assembly of this complex or the respirasome, subsequent alterations in the electron flux, and even increased ROS production due to the backup of reduced complexes upstream in the RC, as mentioned in previous sections.

In agreement with the hypothesis of a direct effect of Aβ inside mitochondria, Lustbader et al., demonstrated that Aβ binds to the mitochondrial β-amyloid-binding alcohol dehydrogenase (ABAD) (Lustbader et al., 2004), an up-regulated enzyme in patients' brain, which resulted in free radical production and oxidative stress, and increased expression of the cytosolic antioxidant enzyme peroxiredoxin II as a cellular defense response (Yao et al., 2007; Ahsan et al., 2009). In fact, the inhibition of the Aβ-ABAD interaction has been shown to reduce Aβ accumulation and to improve mitochondrial function in transgenic mice and neuroblastoma cells (Lim et al., 2011; Yao et al., 2011). ABAD converts estrone to estradiol, a key antioxidant compound for neurone survival whose intracellular levels are decreased due to the interaction between Aβ and ABAD, a phenomenon that may contribute to Aβ-induced toxicity (Yang et al 2007; Lim et al., 2011). In addition, ABAD is a component of the mitochondrial RNAse P involved in the processing of immature mitochondrial tRNAs (Holzmann et al., 2008). The Aβ-induced inhibition of ABAD could result in an altered translation of the mitochondrial-encoded RC subunits, disturbing the assembly of the RC complexes and supercomplexes and leading to further oxidative stress.

In addition, Aβ can also bind cyclophilin D, a component of the permeability transition pore, leading to increased ROS production, mitochondrial membrane potential dissipation, decreased respiration, and release of pro-apoptotic factors to induce cell death (reviewed in Du and Yan, 2010). Further Aβ-induced alteration of mitochondrial permeability could be due to its ability to penetrate lipid bilayers perturbing its

properties and creating channels (Seelert et al., 2009). Finally, Aβ has been proved to bind to heme groups, reducing their bioavailability inside cells and generating a peroxidase enzyme able to oxidize biomolecules (Atamna, 2006; Atamna and Boyle, 2006). This reduction in heme groups would enhance complex IV deficiency since heme-α is essential and rate-limiting for the assembly of this complex (Atamna and Frey, 2004; Atamna and Boyle, 2006). Therefore, increasing evidences point towards a toxic effect of Aβ on mitochondrial function, with a number of mechanisms disturbing complex IV assembly and activity and therefore, RC supercomplexes stability and ROS production. These alterations may be enhanced by Aβ deleterious effects on other mitochondrial components such as ABAD or cyclophilin D, inducing a loop of further increased ROS production and mitochondrial dysfunction that finally could boost Aβ deposition (Figure 2). Despite of these evidences, it remains unclear whether the mitochondrial dysfunction responsible of increased ROS production in AD could be a previous step to the Aβ plaques accumulation. In this regard, some studies describe ROS production as an early event before the plaques appearance that could induce the Aβ accumulation (Caspersen et al., 2005; Manczak et al., 2006; Yao et al., 2007; Karuppagounder et al., 2009).

To further complicate the view of mitochondrial dysfunction in AD, the microtubule associated protein tau, which in its phosphorylated state forms the neurofibrillary tangles detected in AD brains, can in turn induce mitochondrial alterations such as decreased expression of complex I and complex V subunits, subsequent decreases in these complexes activities, lower mitochondrial membrane potential, altered calcium buffering, increased ROS production and up-regulation of cellular antioxidants (David et al., 2005; Quintanilla et al., 2009; Rhein et al 2009; Quintanilla et al., 2012). Moreover, tau and Aβ can interact synergistically to impair

mitochondrial function. For instance, over-expression of truncated tau plus Aβ treatment increased ROS production in cultured neurons (Quintanilla et al., 2012). In triple transgenic AD mice expressing tau and APP, the decreased respiratory rates and mitochondrial membrane potential in aged mice were enhanced in comparison with either APP or tau transgenic animals (Rhein et al., 2009). Nevertheless, a hierarchical relationship between both proteins has also been proposed, where tau would mediate Aβ toxicity (for a review see Ittner and Gotz, 2011). In any case, to date, the precise relationships between tau, Aβ-induced mitochondrial dysfunction and ROS production are still matter of investigation.

3.1.2.2. In Parkinson´s disease

In Parkinson´s disease (PD), which is the second most common neurodegenerative disorder after AD, the most prominent neuropathological hallmarks of the disorder are insoluble aggregates of ubiquitin and α-synuclein found in many regions of the brain and central nervous system (CNS) (Spillantini et al., 1998a; Spillantini et al., 1998b; Gomez-Tortosa et al., 1999). The degeneration of dopaminergic neurons of the *substantia nigra* is the classical sign of the disease, and the cause of the beginning of clinical symptoms. Mitochondrial dysfunction and oxidative stress have been consistently described in brains from PD patients (Jenner, 1993; Devi et al., 2008; Henchcliffe and Beal, 2008; Zhou et al., 2008; Arthur et al., 2009) and different cellular models of this disease (Piccoli et al., 2008; Esteves et al., 2009; Banerjee et al., 2010; Wang et al., 2010). However, the link between mitochondrial dysfunction and PD is not yet clearly elucidated (Xie et al., 2010). In the last years, mutations in genes encoding proteins related directly or indirectly to mitochondrial function, *PINK1*, *PARKIN*, *DJ-1*, *LRRK2* and *SNCA*, have been reported and implicated

in the appearance of PD (Albrecht, 2005; Andres-Mateos et al., 2007; Dodson and Guo, 2007; Devi et al., 2008; Ramsey and Giasson, 2008; Dagda et al., 2009).

The most common mitochondrial alteration associated with PD is RC complex I deficiency, which can be detected not only in the CNS but also in skeletal muscle, platelets and fibroblasts. Less consistent changes in the expression levels and function of the reminder OXPHOS complexes have also been reported (reviewed in Xie et al., 2010; Zhu and Chu, 2010). However, in *substantia nigra* from patients with PD and aged individuals, high levels of deleted mtDNA were described to affect other RC enzyme activities, like cytochrome c oxidase (Bender et al., 2006; Kraytsberg et al., 2006). In agreement, a generalized defect in the respirasome assembly due to reduced steady-state expression levels of subunits from mitochondrial OXPHOS complexes I-V was later reported in brain mitochondria from PD patients (Arthur et al., 2009) . These results could suggest that alterations in the assembly of the RC might be the cause of the increased oxidative stress detected in the tissues from PD patients. Nevertheless, if mitochondrial dysfunction is the cause or effect of protein aggregation in PD is still controversial. Some studies showed that complex I inhibition with drugs like rotenone promoted a number of PD symptoms, such as degeneration of *substantia nigra* neurons, increased ROS and α-synuclein aggregates (reviewed in Fukui and Moraes, 2008 and Chinta and Andersen, 2011). In addition, the increased α-synuclein oligomerization in PD cybrids through a complex I-mediated mechanism that involves the cystoskeleton disorganization, supported the hypothesis of a mitochondrial dysfunction-induced PD (Esteves et al., 2009). More recent evidences showed that, in a mouse model of nigrostriatal degeneration, complex I inhibition was due to NO-mediated S-nitrosylation and nitration of some complex I subunits, NDUFS1, NDUFS2 and NDUFB7, as a consequence of an oxidative insult caused by glutathione depletion (Chinta et al., 2007;

Danielson et al., 2011). Glutathione depletion is one of the earliest oxidative signs detected in the course of PD and indicates that oxidative damage can occur even before complex I deficiency (Jenner, 1993). Some of these altered amino acids in oxidized complex I are cysteine residues within iron-sulfur clusters that could be further affecting the electron transport in the RC (Danielson et al., 2011).

Other evidences point to a role of α-synuclein in the induction of mitochondrial dysfunction and ROS production in PD. Some studies suggested that α-synuclein can be localized at mitochondria where it inhibits complex I (Devi et al., 2008; Liu et al., 2009; Loeb et al., 2010; Chinta et al., 2010), leading to increased ROS production (Devi et al., 2008; Parihar et al., 2008). Other studies demonstrated increased ROS levels and alterations in the expression levels of complex I subunits due to α-synuclein treatment or over-expression (Pennington et al., 2010; Wang et al., 2010). However, other controversial studies showed that α-synuclein would exert an inhibitory effect on complex I activity rather than affecting mitochondrial protein levels or complex I assembly (Loeb et al., 2010). Therefore, further studies are necessary to elucidate the origin of the mitochondrial dysfunction found in this pathology.

3.1.3. Role of the mtDNA genetic background on the RC dysfunction and ROS production

Studies analyzing the impact of mutations in mtDNA-encoded genes on ROS production in different mitochondrial disease models (fibroblasts, transmitochondrial cybrids and neuronal NT2 cells) have frequently revealed increased ROS levels (Pitkanen and Robinson, 1996; Rana et al., 2000; Geromel et al., 2001; Wong et al., 2002; Beretta et al., 2004; Floreani et al., 2005; Gonzalo et al., 2005; Vives-Bauza et al., 2006). The deleterious effect of each mutation could be influenced by the genetic background of a specific patient, as the biosynthesis of the OXPHOS complexes implies

the interaction between many different subunits and regulatory factors. It is a matter of debate whether the presence of polymorphisms in the mtDNA or in nuclear genes encoding RC components could modify the effects of a particular mutation on the biosynthesis and electron transfer properties of the RC complexes. In this regard, a genetic modifying role for the mtDNA haplogroup background has often been proposed in the clinical expression of LHON, a maternally-inherited blinding disease that constitutes the most common mitochondrial disorder (Brown et al., 1997; Carelli et al., 1997; Hofmann et al., 1997; Torroni et al., 1997; Brown et al., 2002; Carelli et al., 2006; Yen et al., 2006; Hudson et al., 2007; Carelli et al., 2009). An increased complex I-dependent ROS production and decreased antioxidant defenses have been reportedly proposed as the main contributors to the pathogenesis of LHON (Wong et al., 2002; Floreani et al., 2005; Beretta et al., 2006; Sala et al., 2008). Our group analyzed the effect of the most common LHON mutations that lead to complex I deficiency on the assembly of the native mitochondrial RC complexes, and also checked whether distinct mitochondrial genetic backgrounds differentially affected this process (Pello et al., 2008). This work demonstrated that the same mutation could produce different alterations not only in the assembly kinetics of complex I, but also in complexes III and IV in the mutant cells, which depended on the analyzed mitochondrial haplogroup. These results provided evidence that the severity of the RC assembly defect, and its consequent oxidative damage, could depend on the association of the primary LHON mutations with specific mtDNA backgrounds. Similar results were recently reported in a cybrid model of complex III deficiency that harbored a novel mutation in the mitochondrial cytochrome *b* gene (Gil Borlado et al., 2010), suggesting that specific mtDNA polymorphisms may modify the pathogenic potential of mtDNA mutations by affecting the overall biogenesis and function of the OXPHOS complexes. In agreement,

the role of certain mtDNA haplotypes on mitochondrial transcription and replication has been demonstrated (Suissa et al., 2009). Likewise, the mtDNA genetic background has been shown to play an important role in modulating the bioenergetics and biochemical defects in cybrid cells hosting the NARP/MILS mutation (D'Aurelio et al., 2010).

As oxidative stress is also involved in neurodegenerative diseases and mtDNA variations can lead to differences in OXPHOS performance and ROS production, the influence of mitochondrial haplogroups on neurodegenerative diseases has also been investigated. For instance, research was conducted to analyze the role of mtDNA haplogroups in AD with controversial results (for a review see Ienco et al., 2011). As an example, Mancuso et al., analyzed the frequency of the most common European mtDNA haplogroups in AD patients and controls of Italian origin, excluding any association between mtDNA haplogroups, age of onset and mean survival (Mancuso et al., 2007). Another group evaluated the involvement of haplogroups or haplogroup clusters and some mtDNA polymorphism in the pathogenesis of AD in the Polish population. These authors observed that the HV cluster was significantly associated with the risk of AD (Maruszak et al., 2009). More recent investigations in this field supported the Polish work, due to the finding that sub-haplogroup H5 is a risk factor for late-onset AD appereance in the Italian population (Santoro et al., 2010). Other studies tried to link the existence of mutations or polymorphisms in mtDNA-encoded complex I subunits as cause of PD, but these results were inconsistent (reviewed in Fukui and Moraes, 2008), showing no clear correlations between the mitochondrial haplogroups and the risk of suffering PD (Latsoudis et al., 2008; Arthur et al., 2009; Mehta et al., 2009; Simon et al., 2010).

3.2. Alterations in mitochondrial dynamics

Technical improvements in the microscopy field allowed the researchers to realize that the "old static" mitochondria were able to move continuously, fuse with each other creating mitochondrial networks, and also, to become solitary units after fission events. The overall mitochondrial morphology in each cell line is determined by the equilibrium between these fusion and fission events, rendering mitochondrial networks that may range from mainly tubular to highly fragmented. However, the cellular functions of mitochondrial dynamics have only begun to be elucidated. On one hand, mitochondrial fusion would either allow the complementation between different mitochondria that mix their matrix contents or the electric coupling of different mitochondria. On the other hand, fission would either generate small mitochondria that can be delivered to distant regions of the cell where energy is required, as the synaptic boutons in neuronal axons, or would allow the segregation of pre-existing mitochondria between daughter cells during mitosis (Nakada et al., 2001; Skulachev, 2001; Detmer and Chan, 2007; Twig et al., 2008a). Pioneering works from several laboratories have described some of the proteins involved in the fusion and fission events, amongst which the best characterized are: mitofusin1 and mitofusin 2 (Mfn1, Mfn2), that are involved in the fusion of the outer mitochondrial membrane; OPA1, that mediates mitochondrial inner membrane fusion; and Drp1, known to be essential for mitochondrial fission (reviewed in Chen and Chan, 2009; Sauvanet et al., 2010). Mutations in genes encoding proteins involved in mitochondrial dynamics have been reported and linked to neurodegeneration (Weber and Reichert, 2010). For example, Charcot-Marie Tooth type 2a is caused by mutations in the *MFN2* gene (Zuchner et al., 2004), and autosomal dominant optic atrophy (DOA) is due to alterations in the *OPA1* gene (Alexander et al., 2000; Delettre et al., 2000). Mutations in other genes encoding proteins still poorly

characterized but related to mitochondrial morphology may also cause neurodegenerative disorders (reviewed in Weber and Reichert, 2010), such as the GDAP1 involvement in Charcot-Marie Tooth type 4a (Baxter et al., 2002; Cuesta et al., 2002), or deletions of the *LETM1*gene, which have been associated with Wolf-Hirschhorn Syndrome (Endele et al., 1999). It is worth noting that most studies regarding mitochondrial dynamics have been performed in cultured cells and data about human tissues are scarce. Therefore, the dysfunctions due to alterations in mitochondrial dynamics that occur in tissues from human patients remain unexplored.

3.2.1. The feedback loop between ROS production and mitochondrial dynamics.

Several studies support a role for ROS in the modulation of mitochondrial dynamics. It was described that in cultured cells the oxidative stress due to treatment with inhibitors of respiratory chain complexes I and III induced mitochondrial fission, a phenomenon that was also induced by H_2O_2 and prevented with antioxidants (Pletjushkina et al., 2006). Likewise, mitochondrial fragmentation and neuronal cell death due to complex II inhibition by 3-nitropropionic acid, used to induce Huntington's disease symptoms in primate and rodent models, was caused by a ROS-dependent pathway (Liot et al., 2009). More recently, it has been shown that ionizing radiation-induced ROS accelerates mitochondrial fission involving a delayed further increase in the production of mitochondrial reactive oxygen species (Kobashigawa et al., 2011). Different cultured cells, including neurons, under oxidative stress due to NO or H_2O_2 treatment showed extensive mitochondrial network fragmentation and increased cell death (Barsoum et al., 2006; Yoon et al., 2006; Jahani-Asl et al., 2007; Jendrach et al., 2008). Although the precise mechanisms by which oxidative stress modulates mitochondrial dynamics are not well understood, some authors suggested that ROS could modulate the expression levels and post-traslational modifications of the proteins

involved in mitochondrial dynamics. In this regard, decreased fission and fusion events due to an altered expression of the *FIS1*, *DRP1* and *MFN1* mRNAs after H_2O_2 exposure were described (Jendrach et al., 2008). Accordingly, over-expression of proteins involved in mitochondrial fusion prevented mitochondrial fragmentation and cell death in cerebellar granule neurons treated with H_2O_2 (Jahani-Asl et al., 2007; Jahani-Asl et al., 2011). The mitonetwork response to oxidative stress seemed to be dose-dependent, as higher concentrations or higher exposure times to H_2O_2 increased the mitochondrial fragmentation extent and cell death rates (Yoon et al., 2006; Jahani-Asl et al., 2007; Jendrach et al., 2008). In agreement, lower H_2O_2 doses induced mitochondrial hyperfusion associated to decreased Fis1 expression levels and augmented Mfn1 and Mfn2 (Yoon et al., 2006). Probably hyperfusion represents a cellular defensive response, because elongated mitochondria display higher efficiency in ATP production that may aid the recovery from the oxidative insult (Mitra et al., 2009; Tondera et al., 2009). In addition, the onset of the mitochondrial permeability transition, process frequently followed by mitochondrial network fragmentation and apoptosis, was subject to redox regulation by oxidation of some components of the mitochondrial permeability transition pore (MPTP), such as critical thiols in the adenine nucleotide translocase and nitration of tyrosines of the voltage-dependent anion channel (for a review see Daiber, 2010). The mitochondrial membrane potential collapse induced by the MPTP opening led to the proteolytic cleavage of OPA1 by activation of specific proteases sensitive to mitochondrial membrane potential, with the subsequent impairment of mitochondrial fusion (Suen et al., 2008). Interestingly, in a cellular model of H_2O_2-induced cell death, Drp1 loss of activity impaired mitochondrial fragmentation, causing resistance to apoptosis (Tanaka et al., 2006). This probably occurs because, during apoptosis induction, Drp1 is recruited to the mitochondria and stabilizated at the organelle by

SUMOylation (Harder et al., 2004), favoring mitochondrial fission that is necessary for apoptosis to occur. Therefore, although oxidative stress seems to induce alterations in the expression of proteins involved in mitochondrial dynamics at both the translational and post-traslational levels, leading either to enhanced fission or fusion, more studies are needed to better understand the regulation of mitochondrial dynamics by ROS.

Opposingly, mitochondrial dynamics can also affect ROS production. Changes in mitochondrial number, density and the spatial distribution of these organelles can modulate the process called ROS-induced-ROS release (RIRR) (Zorov et al., 2000; Aon et al., 2003). For instance, spontaneous ROS production in a small population of damaged or dysfunctional mitochondria at a given subcellular location can induce ROS generation in the surrounding mitochondria by RIRR, thus contributing to increase whole cellular ROS levels and affecting cell viability. This is supported by a recent mathematical model predicting that the cellular ROS signaling pattern, that is, ROS propagation speed, oxidative stress vulnerability and the acting key messenger ROS molecule, is affected by mitochondrial network dynamics (Park et al., 2011). Experimental data also support an influence of mitochondrial dynamics on ROS generation. Cells cultured in high glucose medium displayed increased ROS levels and apoptosis, phenomenon preceded by fragmentation of the mitochondrial network, which were prevented by inhibition of mitochondrial fission (Yu et al., 2006; Yu et al., 2008). In liver and cardiovascular cells, this high glucose–induced fission and rise in ROS production was mediated by increased intracellular calcium levels and ERK1/2-dependent Drp1 phosphorylation (Yu et al., 2011), whereas in muscle cells under chronic hyperglycemia the mitochondrial fragmented state was associated to a decrease in Mfn2 (Bach et al., 2003; Bach et al., 2005). Decreased mitochondrial fission due to FIS1 down-regulation also induced sublethal stress associated to mitochondrial

elongation, loss of mitochondrial potential and increased ROS levels (Lee et al., 2004). All in all, these evidences indicate that a tightly coordinated feed-back loop exists between ROS production and mitochondrial dynamics, where an initial ROS signaling cascade will be modulated by mitochondrial dynamics, probably leading to its scaling and to oxidative stress, which will further alter mitochondrial dynamics and have an impact on cellular viability

3.2.2. In mitochondrial disorders

Alterations in mitochondrial morphology have been frequently reported in cultured cells from patients with OXPHOS disorders. Mitochondrial network fragmentation has been mainly described in complex I and complex III-deficient cells (Pham et al., 2004; Benard et al., 2007; Koopman et al., 2007; Moran et al., 2010a). However, this is not a general observation. A number of studies revealed no significant mitochondrial fragmentation in RC-deficient cells, which included fibroblast harboring mutations in complex I subunits, even in stressful metabolic conditions (Hanson et al., 2002; Guillery et al., 2008; Moran et al. 2010b), and only in some cell lines a decreased rate of mitochondrial tubules formation after treatment with protonophores was detected (Guillery et al., 2008; Moran et al., 2010b). Some authors have suggested that the lowest complex I residual activity in fibroblasts could be associated with the highest ROS levels, and thus to more pronounced mitochondrial morphology alterations (Koopman et al., 2007). However, in many cases a straightforward relationship between decreased RC activities, increased ROS levels, and mitochondrial fragmentation cannot be established. For instance, neither significant ROS production nor mitochondrial fragmentation was observed by our group in fibroblasts from patients harboring mutations in complex I subunits that led to a severe complex I deficiency (Fernandez-Moreira et al., 2007; Moran et al., 2010b). Complex III-deficient patients' fibroblasts

can show normal RC enzyme activities and ROS levels but mitochondrial derangements (Moran et al., 2010a), and severe complex II and complex IV deficient-cells without alterations in mitochondrial shape or mitochondrial number have been described (Willems et al., 2009). Therefore, the linkage between RC dysfunction, ROS production and alterations in mitochondrial dynamics remains unclear.

3.2.3. In neurodegenerative disorders

3.2.3.1. In Alzheimer´s Disease

Alterations of mitochondrial dynamics and morphology have also been reported in AD brains, where decreased levels of proteins involved in mitochondrial fusion and Drp1 were found, besides an increase in FIS1 expression levels, and an altered mitochondrial distribution showing reduced mitochondria in the cell periphery (Wang et al., 2009). Despite the overall decrease in Drp1 levels found in AD brains, the Drp1 fraction associated to mitochondria was not altered, suggesting that enough Drp1 is traslocated to mitochondria to induce fission (Wang et al., 2009). In addition, higher levels of phosphorylated and nitrosylated Drp1 were found in AD brains compared with control brains (Wang et al., 2009; Cho et al., 2009), together with post-translational modifications associated to enhanced mitochondrial fission activity that, interestingly, can be induced by Aβ (Taguchi et al., 2007; Cho et al., 2009). Finally, Drp1 was reported to interact and colocalize with Aβ monomers and oligomers in human and mice AD brains, interactions that increase with disease progression (Manczak et al., 2011), thus supporting a direct role of Aβ on Drp1 pathological modifications. Also, in several models of AD, such as fibroblasts from AD patients, Aβ and APP-treated cells, and transgenic mice, altered mitochondrial distribution and fragmentation of the mitochondrial network were reported to occur due to alterations in Drp1 levels and other proteins involved in mitochondrial dynamics (Wang et al., 2008; Liu et al 2010;

Calkins et al., 2011). Another potential mechanism that can cause mitochondrial network alterations in AD is an altered mitochondrial movement. For instance, Aβ induced tau-dependent alterations in mitochondrial axonal transport (Vossel et al., 2010), and over-expression of truncated tau and Aβ treatment decreased the number of moving mitochondria and their velocity, and increased oxidative stress in cultured neurons (Quintanilla et al., 2012). In a mouse model of AD, increased fission and decreased fusion and anterograde movement of mitochondria were also reported (Calkins et al., 2011). In this latter study the mitochondrial motility alterations were associated to increased oxidative stress and could be partially reverted by treatment with mitochondrial targeted antioxidants (Calkins et al., 2011). The mechanisms of Aβ-induced altered mitochondrial movement are not well understood, but it has been recently described that Aβ peptides decreased acetylated tubulin levels and tau hyperphosphorilation, causing disturbances in microtubule dynamics and alterations in macroautophagy, whereas taxol treatment restored microtubule network and reduced Aβ oligomers accumulation (Silva et al., 2011). These findings support the notion that in AD, Aβ can alter mitochondrial dynamics by inducing post-translational modifications of the proteins involved in fission and fusion, leading to an enhancement of fission and also disturbing the tracks along which mitochondria move in the cell, which would in turn alter the delivery of functional mitochondria to neuronal axons and dendrites. In addition, Aβ would impair the elimination of dysfunctional mitochondria and Aβ oligomers by autophagy, processes which together may contribute to neuronal synapse loss and cell death in AD.

3.2.3.2. Linking oxidative stress and mitochondrial dynamics in PD, a new field to explore in neurodegeneration

In the last years mitochondrial dynamics has been widely analyzed in cellular models of PD, where alterations in the mitochondrial networks have been described (Exner et al., 2007; Mortiboys et al., 2008). The reason for this emerging research field was the discovery of mutations in PD-related genes such as *Park2*, which encodes the E3ubiquitin ligase Parkin; *PINK1 (Park6)*, encoding the PTEN-induced kinase 1, and *DJ-1* (also called *Park7*), which causes familial PD (Andres-Mateos et al., 2007; Dodson and Guo, 2007; Devi et al., 2008; Ramsey and Giasson, 2008; Dagda et al., 2009). The proteins encoded by these genes have been implicated in the maintenance of a healthy mitochondria population through a combined system of mitochondrial dynamics and autophagy that involves the specific elimination of some mitochondria, a process that was termed mitophagy (Lemasters, 2005; Kim et al., 2007; Twig et al., 2008a; Twig et al., 2008b). This recent theory postulates that cells get rid off dysfunctional mitochondria by their specific elimination after molecular labeling and isolation of the mitochondrial network by fission, being finally degraded by the lysosomal autophagy pathway (Kim et al., 2007; Twig et al., 2008a; Twig et al., 2008b).

A pioneering work by Narendra and coworkers revealed that Parkin is translocated from the cytosol to depolarized mitochondria in mammalian cells, labeling them for further autophagosome engulfment and autophagy (Narendra et al., 2008). Later studies have supported Narendra's findings showing that PINK1 acts upstream from Parkin, and that both proteins are recruited to depolarized mitochondria (Kim et al., 2008; Kawajiri et al., 2010; Matsuda et al., 2010; Vives-Bauza et al., 2010). The DJ-1 protein, already known by its antioxidant, chaperone-like and transcriptional modulator functions, has been recently proposed to act in parallel with PINK1 and

Parkin to control mitochondrial function, morphology and mitophagy (Irrcher et al., 2010; Krebiehl et al., 2010; Thomas et al., 2011). The mitochondrial recruitment of Parkin induces the ubiquitination of several mitochondrial proteins such as VDAC, Mfn1 and Mfn2 (Gegg et al., 2010; Geisler et al., 2010). This phenomenon is followed by the recruitment of ubiquitin-binding autophagic components that leads to mitochondrial clearance, and could also aid the mitochondrial fission necessary for mitophagy to occur. Recent works have studied in depth in the role of PINK1 in cellular physiology, showing that PINK1 is not only involved in Parkin recruitment to mitochondria, but also regulates mitochondrial movement. For instance, Wang and coworkers showed that PINK1 phosphorylates Miro, a protein involved in mitochondrial motility, inducing mitochondrial detachment from microtubules, thus preventing mitochondrial movement and activating proteasomal degradation in a Parkin-dependent manner (Wang et al., 2011). Furthermore, proteolitic processing of PINK1 and phosphorylation by MARK2, a protein also involved in AD, regulate mitochondrial transport in neurons, either inducing anterograde transport in healthy mitochondria with normal membrane potential, or mediating retrograde transport and mitophagy of depolarized organelles (Matenia et al., 2012). Therefore, mutations in PINK1, Parkin or DJ-1 are expected to induce accumulation of dysfunctional mitochondria that could in turn lead to an increase in cellular ROS levels and to the bioenergetic defects that are frequently observed in PD. These events would create a vicious cycle of mitochondrial-induced damage that could contribute to the disease. Very recently, it has been reported that the complex I deficiency and altered mitochondrial morphology shown by *PINK1* mutant flies can be rescued by the over-expression of a yeast complex I NADH dehydrogenase, but not by modulating mitochondrial fusion and fission, which indicates that complex I deficiency is not

secondary to the morphological defect and suggests that PINK1 could regulate complex I function (Vilain et al 2012).

Other evidences link mitochondrial dynamics alterations in PD with the α-synuclein pathway. Kamp and coworkers demonstrated tha α-synuclein inhibited mitochondrial fusion by stabilizing the lipid packaging in membranes, and that overexpression of PINK1, Parkin and DJ-1 blocked this effect (Kamp et al., 2010). These authors speculated with the idea that, in healthy cells, α-synuclein could be involved in the inhibition of espontaneous membrane fusion, and that PINK1, Parkin and DJ-1 could protect mitochondria against the deleterous effects of α-synuclein over-expression, perhaps by its interaction with the mitochondrial dynamics machinery. Another protective role of Parkin against α-synuclein toxicity in PD would be the reduction in the Parkin-induced phosphorylation state of α-synuclein, which would reduce α-synuclein aggregation (Khandelwal et al., 2010). Mutations in LRRK2 (*Park8*), a protein that seems to be involved in neurite growth, have also been implicated in the genesis of PD (Cookson, 2010). Mitochondrial elongation and interconnectivities were increased in cells from PD patients with mutations in LRRK2, as well as a decrease in mitochondrial-ATP production and membrane potential (Mortiboys et al., 2010). Finally, the high-temperature requirement A2 protein (HTRA2) is the last player in the field of PD. Mutations in this gene may increase the risk of PD, and increased ROS levels and altered mitochondrial morphology have been described in several cellular models of HTRA2 dysfunction (for a review see Lim et al., 2011). In addition, it seems to be an inductor of autophagy (Li et al., 2010), but the precise role of this protein in PD, mitochondrial dynamics and autophagy is still unclear.

These new findings link different causes of PD to mitophagy and mitochondrial dynamics, and open more new questions to answer. In this context, controversial results have arisen from the observation of absence of degenerative changes in *substantia nigra* of a triple knock-out transgenic mouse for PINK1, Parkin,and DJ-1 (Kitada et al., 2009). Many studies analyzing the role of PINK1/Parkin pathway in mitophagy and PD have been performed in inmortalized cell lines (MEFs, HeLa, neuroblastoma cells, etc), and studied under stressful experimental conditions that may not resemble what actually happens in brain tissues from PD patients (Narendra et al 2008; Kawajiri et al 2010; Narendra et al., 2010; Vives-Bauza et al., 2010). Contradictory studies have been published regarding the behavior of PINK1/Parkin and mitophagy induction. For instance, Van Laar et al., demonstrated that in primary cortical neurons massive mitochondrial depolarization neither induces Parkin traslocation to mitochondria nor mitophagy (Van Laar et al., 2011). These authors suggested that the different bioenergetic profiles between neurons and other cells less dependent on OXPHOS-derived ATP would explain their different response to depolarization. On the contrary, other authors have found Parkin accumulation in depolarized mitochondria of primary neurons (reviewed in Lim et al., 2011). To further complicate this scenario, previous work by Kuroda et al., indicated that Parkin induced mitochondrial biogenesis after mitophagy in proliferating cells (Kuroda et al., 2006). Although neurons are postmitotic cells, a role of Parkin in mitochondrial renewal in brain could also be supported by a recent work, which describes a protein called PARIS that is able to repress PGC1-α, the master regulator of mitochondrial biogenesis, and that is downregulated by Parkin (Shin et al., 2011). Strikingly, PGC1-α is downregulated in PD brains, suggesting that impaired mitochondrial biogenesis could contribute to the disease (Shin et al., 2011). Therefore, more studies are required to unravel the physiological role of all these

proteins and pathways in cell function, to validate these atractive theories and to shed ligh in the role of the alterations of mitophagy in PD.

3.3. Alteration of the equilibrium between cell survival and cell death response

As a final remark, it is worth to mention that mitochondrial ROS production acts as a redox signal to regulate autophagy and apoptosis (Yen and Klionsky, 2008). Low levels of ROS damage may induce the mitochondrial depolarization, and provide a signal leading to the induction of autophagy and clearance of the potentially dangerous ROS-producing mitochondria (Rodríguez-Enríquez et al., 2004; Narendra et al 2008). But if alterations of the mitophagy pathway occur due, for instance, to mutations in PINK1 or Parkin, this protective elimination route may be impaired. In this case, the ROS-producing organelles would accumulate, generating more oxidative stress and damage that in turn could activate apoptosis or even necrosis (Yen and Klionsky, 2008). Therefore, the alteration of the mitophagy pathway that may occur in PD can impair the equilibrium between protective autophagy and a deleterious apoptosis/necrosis cellular response. Moreover, as aging process induces a decline in the cellular autophagic capacity due to a reduced expression of proteins involved in autophagy (Rubinzstein et al., 2011), aging itself becomes a risk factor for the accumulation of dysfunctional mitochondria and protein aggregates that would finally lead to pathological consecuences. This would also be applied to neurodegenerative disorders such as AD, where aging is the non-genetic major risk factor for sporadic forms of disease.

4. Concluding Remarks

Mitochondrial alterations, including RC dysfunction due to enzyme and assembly defects, increased ROS production, morphological alterations of the mitochondrial

network, and cell death are frequent features of neurodegenerative diseases of different genetic origins. In mitochondrial respiratory chain disorders and other pathologies that involve mitochondrial dysfunction, such as PD and AD, a clear relationship between the alterations in the biosynthesis of the mitochondrial RC complexes, and their specific pathophysiological consequences, has not been fully-elucidated yet. Significant effort must still be done to better understand how a malfunctioning RC may affect the different cellular mechanisms, in the search of new therapeutic approaches. The discovery of new cellular processes like mitochondrial dynamics and autophagy is helping to identify the origin of some diseases, and opens new fields to explore and understand the implication of mitochondria in human health. New potential drugs able to modulate autophagy and mitochondrial dynamics, such as rapamycin or imdivi-1, have been proposed as potential therapeutic drugs that could help mitigating some neurodegenarative diseases (Du and Yan, 2010; Lackner and Nunnari, 2010; Schon et al., 2010), but further studies are needed to confirm their potential therapeutic use.

Conflict of interests

There are no actual or potential conflicts of interest with other people or organizations**.**

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FIGURE LEGENDS

Figure 1. Mitochondrial respirasome assembly pathway in human control cells. In stage 1, the biosynthesis and activation of fully-assembled complexes III and IV occur until reaching a threshold that probably triggers the accumulation of free subunits and assembly intermediates from these two complexes (stage 2). At this stage, complex I assembly also takes place to building up an ~830 kDa subassembly that constitutes the first supercomplex assembly intermediate (SC1). This subcomplex remains in a stable competent state for the subsequent incorporation (stage 3) of structural subunits from complex III (CORE2) and complex IV (COX4 and COX5A), to form a second supercomplex assembly intermediate (SC2). The incorporation of the structural complex I subunit NDUFS4 and the catalytic complex IV subunit COX2, plus maybe other free RC subunits or subassemblies, take place in a third step (SC3). The insertions into supercomplexes of the catalytic complex III RISP and complex IV COX1 subunits and the structural complex IV subunit COX6C occur in a fourth step (SC4). The final supercomplex assembly step involves the association of the catalytic subunits that form the complex I NADH dehydrogenase module prior to the respirasome activation (SC5).

Figure 2. **Mitochondrial derangement in Alzheimer's disease**. APP initially synthesised in the endoplasmic reticulum, binds TOM and TIM proteins in the mitochondrial membranes blocking the translocation of nuclear encoded complex IV subunits inside the mitochondria, leading to complex IV deficiency, altered respirasome assembly and abnormal ROS production. Intramitochondrial Aβ binding to heme groups further decreases complex IV biosynthesis and respirasome function. Aβ, either produced inside the mitochondria by APP processing or incorporated by direct translocation of cytosolic Aβ, can increase ROS production due to direct inhibition of

respiratory chain activities, and by ABAD binding. The inhibition of ABAD would also alter mitochondrial tRNA processing and mitochondrial mRNA translation, further disturbing the respirasome assembly due to lack of mitochondrial encoded subunits, and exacerbates increased ROS production. Aβ interaction with cyclophilin D contributes to the decreased mitochondrial membrane potential, also lowered by respirasome misassembly, and favours the release of apoptotic factors. Aβ-induced alterations in mitochondrial dynamics machinery due to interaction and modification of proteins such as Drp1, leads to increased mitochondrial fragmentation. Finally, Aβ may also alter microtubules disturbing autophagy and mitochondrial motility. All these processes create a loop of mitochondrial damage and dysfunction that may contribute to neurite loss and cell death.