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The Role of Mitochondria in Neurodegenerative Diseases: the Lesson from Alzheimer's Disease and Parkinson's Disease

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Abstract

Although the pathogenesis of neurodegenerative diseases is still widely unclear, various mechanisms have been proposed and several pieces of evidence are supportive for an important role of mitochondrial dysfunction. The present review provides a comprehensive and up-to-date overview about the role of mitochondria in the two most common neurodegenerative disorders: Alzheimer's disease (AD) and Parkinson's disease (PD). Mitochondrial involvement in AD is supported by clinical features like reduced glucose and oxygen brain metabolism and by numerous microscopic and molecular findings, including altered mitochondrial morphology, impaired respiratory chain function, and altered mitochondrial DNA. Furthermore, amyloid pathology and mitochondrial dysfunction seem to be bi-directionally correlated. Mitochondria have an even more remarkable role in PD. Several hints show that respiratory chain activity, in particular complex I, is impaired in the disease. Mitochondrial DNA alterations, involving deletions, point mutations, depletion, and altered maintenance, have been described. Mutations in genes directly implicated in mitochondrial functioning (like Parkin and PINK1) are responsible for rare genetic forms of the disease. A close connection between alpha-synuclein accumulation and mitochondrial dysfunction has been observed. Finally, mitochondria are involved also in atypical parkinsonisms, in particular multiple system atrophy. The available knowledge is still not sufficient to clearly state whether mitochondrial dysfunction plays a primary role in the very initial stages of these diseases or is secondary to other phenomena. However, the presented data strongly support the hypothesis that whatever the initial cause of neurodegeneration is, mitochondrial impairment has a critical role in maintaining and fostering the neurodegenerative process.

Keywords Neurodegeneration · Mitochondria · Alzheimer's disease · Parkinson's disease · Pathogenesis

Background

Neurodegenerative diseases represent one of the most important challenges which have to be faced by modern societies, with millions of patients affected worldwide [1].

Despite the devastating effects that neurodegenerative diseases cause to patients and despite the substantial rebound on families and on the entire community, the pathogenic mechanisms of these diseases remain widely unclear and only few therapeutic options are available.

Several molecular mechanisms have been proposed to be involved in the pathogenesis of these diseases, and mitochondria have often been considered as potential candidates implicated in the degenerative process.

Mitochondria are intracellular organelles which contribute to several metabolic pathways. They are complex structures composed of two membranes, an intermembrane space and a matrix. They contain their own DNA which encodes part of

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the proteins which are necessary for their functioning. In addition to many other important tasks, mitochondria play a crucial role in energy production, since they are responsible for some of the most important energetic pathways in the cell, including oxidative phosphorylation. [2]

Several diseases are characterized by a direct and primary involvement of mitochondria and are usually denoted as mitochondrial diseases [3–5]. However, considering the importance of these organelles, it is not surprising that they have often been implicated in apparently unrelated disorders, including neurodegenerative diseases.

The purpose of the present review is to highlight the importance of mitochondria in neurodegeneration by providing an up-to-date overview of their role in the two most common neurodegenerative diseases: Alzheimer's disease (AD) and Parkinson's disease (PD). The review examines most of the features related to this topic. However, a particular emphasis has been used to discuss the hints which suggest a primary or secondary role of mitochondria in neurodegeneration and the relationship between mitochondrial dysfunction and anomalous protein accumulation.

Alzheimer's Disease

AD is the most common neurodegenerative disorder, with a prevalence of 10–30% and an incidence of 1–3% in the population over 65 years of age [6].

Dementia, intended as the combination of memory impairment and executive dysfunction which interfere with daily life, is the main clinical feature. However, atypical presentations characterized by the impairment of other domains, including language, visual, or executive functions, are also possible. [7]

Extracellular β-amyloid plaques and intracellular hyperphosphorylated tau protein neurofibrillary tangles are the main neuropathological hallmarks of the disease [8].

Although several progresses have been made in recent years, AD pathogenic mechanisms are still not completely clear. The most widely accepted hypothesis explaining the pathogenesis of the disease is represented by the amyloid hypothesis, which is supported by several important pieces of evidence. However, multiple mechanisms, including mitochondrial dysfunction, may be implicated and some investigators have even proposed a mitochondrial cascade hypothesis.

According to the amyloid hypothesis, the initial trigger of the disease is represented by the anomalous deposition of amyloid plaques in the extracellular environment of specific brain areas. In this perspective, the involvement of specific cellular compartments, including mitochondria, would represent a secondary phenomenon. The amyloid hypothesis is strongly supported by the fact that mutations in the genes encoding amyloid precursor protein (APP) and presenilins (involved in APP cleavage) are responsible for rare genetic forms of the disease [8, 9].

On the other hand, according to the mitochondrial cascade hypothesis, mitochondrial dysfunction would represent the initial trigger of most AD cases and the other pathological features should be considered as a secondary effect [10, 11].

In both cases, mitochondria play a role, either as primary or secondary effectors (Fig. 1).

Signs of Mitochondrial Involvement

The first, although indirect, evidence supporting the role of mitochondria in AD is represented by the finding of reduced glucose and oxygen metabolism in patients' brains.

The evaluation of glucose utilization rate in a small cohort of patients and controls through 18-FDG positron emission tomography (PET) has demonstrated a reduction of metabolic activity in patients, which correlated with the degree of cognitive impairment [12]. A wider study, based on the same technique, has proposed that glucose metabolism alterations of specific brain regions correlate with the most prominent clinical features of each subject [13]. It has also been observed that the reduced 18-FDG uptake of AD brains is particularly striking in the temporoparietal cortex [14], although other groups have shown that the metabolic defect is common to several brain areas [15]. This topic has been investigated by various subsequent studies, and 18-FDG PET now represents one of the available diagnostic tools in the management of the disease [16].

In addition to reduced glucose metabolism, various studies have pointed out impaired oxygen consumption in patient brains, thus providing further evidence about bioenergetic dysfunction and mitochondrial impairment in the disease. Studies are consistent in detecting reduced oxygen metabolism in various brain regions in AD, while the finding of a reduced oxygen extraction fraction has not always been confirmed [17–20].

In addition to clinical features, mitochondrial involvement has been demonstrated by several descriptive studies detecting structural and functional abnormalities in these organelles.

Electron microscopy analyses have pointed out altered mitochondrial morphology in brains of AD patients, including decreased size, altered and broken cristae, osmophilic material accumulation, lipofuscin vacuoles, and elongated interconnected organelles [21–23].

Defective activity of mitochondrial enzymes, including pyruvate dehydrogenase and ketoglutarate dehydrogenase complexes [24–26], has been detected in patients. However, the most remarkably affected mitochondrial enzyme is cytochrome oxidase (respiratory chain complex IV), which has been widely studied in AD. An initial study, performed on a small number of subjects, has identified a reduction of

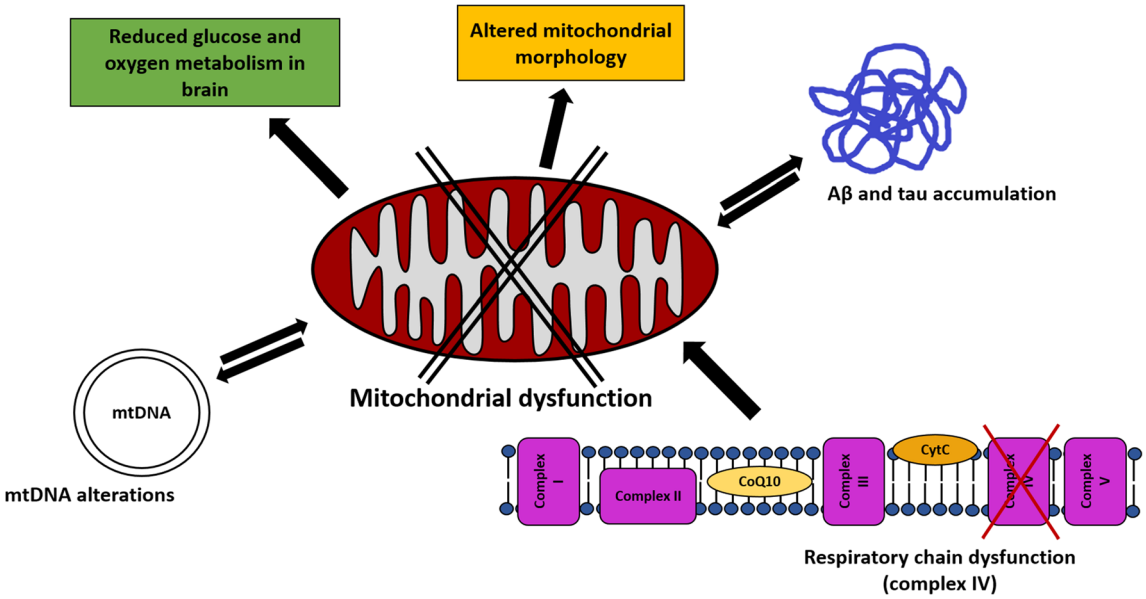

Fig. 1 Mitochondrial dysfunction in Alzheimer's disease. The figure summarizes the main mitochondria-related mechanisms which have been proposed to be involved in the pathogenesis of AD. A defective mitochondrial functioning is supported by various findings, including altered mitochondrial morphology and reduced glucose and oxygen consumption in patients' brains. An impairment of respiratory chain activity, in particular complex IV, has been detected in the disease. Extracellular Aβ and intracellular tau protein accumulation, prominent neuropathological findings in AD, have been proposed to be bi-directionally linked to mitochondrial dysfunction. Mitochondrial DNA alterations have also been detected in the disease

cytochrome oxidase activity (but not of other electron transport chain enzymes) in platelets of patients [27] and the same finding has been confirmed in an independent study detecting reduced ATP levels, increased reactive oxygen species, and decreased cytochrome oxidase activity (but normal cytochrome oxidase subunits amount) in platelets of AD patients [28]. Cytochrome oxidase activity has been found to be reduced also in brain tissue: a first study, performed on 9 patients and 8 controls, has detected a generalized reduction of electron transport chain activity in AD, particularly striking for cytochrome oxidase, and the amount of cytochromes b, c1, and aa3 has not shown significant differences between groups [29]. A wider subsequent study, performed on brains of 19 patients and 30 controls, has detected a significant reduction of cytochrome oxidase activity in frontal and temporal cortices, but not in other brain areas [30].

Although only few studies have been performed in this field, also mitophagy has been proposed to be involved in AD. Indeed, an impairment of the mitophagic machinery has been detected in both human AD samples and experimental models and mitophagy stimulation has been found to improve neuropathological and clinical features in these models [31–34].

The role of mitochondrial DNA (mtDNA) alterations has been widely investigated in AD [35]. Several reports have pointed out a reduction of mtDNA content in brain tissue and cerebrospinal fluid of AD subjects [36–40], although a few groups have detected contrasting results [22]. Mitochondrial haplogroup U has been associated with increased (males) or decreased (females) risk of developing AD [41], and sub-haplogroup H5 has been proposed to be a risk factor for the disease [42], as well as mitochondrial clusters UK [43] and HV [44]; however, independent studies have not found an association between mitochondrial haplogroups and AD or early-onset AD [45–47]. AD has been associated with a mitochondrial haplotype characterized by modifications at positions 5633, 7476, and 15,812 [48], while a decreased risk of developing the disease has been associated with haplotypes H6A1A and H6A1B [49]. The tRNA(Gln) gene variant at nucleotide pair 4336 has been found to be more frequent in patients [50], and this finding has been confirmed by independent groups [51, 52], with some exceptions [53, 54]. The mtDNA 4977 deletion has been shown to be more common in brain cortex of young AD patients compared to age-matched controls [55] and subsequent analyses have detected a similar finding also in temporal cortex of elderly patients [56]; however, the same result has not been replicated in independent studies [57, 58]. An increased point mutation frequency has been detected in brains of AD subjects [57] and an analogous result has been found comparing elderly subjects and AD patients to young individuals [59]; however, this latter study does not explain whether the increased mutational burden is due to aging or to the disease. A wide study, focused on alterations of mtDNA control region (CR), has pointed out that the T414G mutation is detectable in 65% of AD brains, but not in controls [36]. Furthermore, a 63% increase of heteroplasmic CR mutations, including the T414C, T477C, T146C, T195C, and A189G mutations, has been

found in patients [36]. Recent studies, performed on a remarkable number of samples, indicate that inherited polymorphisms and mtDNA heteroplasmy are not likely to play a significant role in AD pathogenesis [40, 60]. To conclude, several efforts have been dedicated to the comprehension of the role of mtDNA in AD, but, although several interesting hints have emerged, the elevated heterogeneity of the results does not allow drawing a definite hypothesis.

The findings listed above merely describe some mitochondrial abnormalities which can be detected in patients, but do not explain whether mitochondria play a primary or secondary role in the pathogenesis of the disease. However, various pieces of evidence have been provided to support both the hypotheses.

Evidence for Mitochondrial Primary Involvement

Since mtDNA inheritance is exclusively maternal, the finding of an increased risk to develop AD in case of maternal disease family history [61] is supportive for a mitochondrial primary role. Furthermore, subjects with maternal family history of AD display a decreased glucose metabolism in the brain [62], an extensive brain volume reduction at voxel-based morphometry [63], and an increase of Pittsburgh compound B (binding amyloid) at PET [64] when compared with subjects with no family history or paternal family history.

Moreover, various studies have suggested that amyloid and tau deposition may be the consequence of mitochondrial dysfunction. Treating rats with complex IV inhibitor sodium azide leads to nerve cell loss in the frontal cortical area, corkscrew-like dendrites, dendritic and axonal thickening, pyknotic nerve cells, and tau-positively-staining granules in the frontal cortical area [65]. Rats treated with complex I inhibitor rotenone show abnormally high levels of tau protein in the cytoplasm of neurons, oligodendrocytes and astrocytes, filamentous material staining positive for phosphorylated tau and cell bodies staining positive for thioflavin S, nitrotyrosine, and ubiquitin [66]. The administration of another complex I inhibitor, annonacin, to cultures of rat striatal neurons, is followed by redistribution of tau from axons to cell bodies, cell death, ATP level reduction, and mitochondria retrograde transport [67]. Inhibiting cytochrome oxidase in cells through sodium azide enhances the transformation of APP into amyloidogenic derivatives [68, 69]. APP/Ld mice display an increased burden of Aβ42 and amyloid plaques when crossed with the PolgA D257A mice (defective for mitochondrial DNA polymerase γ) [70]. The fusion of mitochondrially depleted cells with platelet-derived mitochondria of AD subjects (the AD "cybrids" model) leads to reduced complex IV activity and increased ROS production [71, 72], increased Aβ40 and Aβ42 secretion, increased intracellular Aβ40 level, and Congo red-positive Aβ deposits [73]. Mitochondrial impairment in AD cybrids, involving oxygen and glucose fluxes, bioenergetics regulatory mechanisms, and mitochondrial fission/fusion, has been recently confirmed in an independent study [74], although various concerns have been raised about the suitability of cybrids to model AD [75]. Finally, it has been suggested that oxidative stress, closely related to mitochondrial function, may play an important role in amyloid processing. [76]

Evidence for Mitochondrial Secondary Involvement

Aβ administration to cultured cells has been demonstrated to affect mitochondrial function in several ways: inhibiting respiratory chain (complexes I, III and, most of all, IV), depolarizing the mitochondrial membrane and decreasing oxygen consumption [77]. The administration of β-amyloid fragment 25–35 to rat-isolated mitochondria has been associated with a reduction of the activity of respiratory chain complex IV, but not complexes I, II–III or citrate synthase [78]. Furthermore, treating mitochondria with the Aβ42 peptide leads to a reduction of cytochrome c oxidase activity in a dose-dependent manner in the presence of Cu^{2+} [79]. The finding that Aβ-mediated damage cannot be observed in mitochondria-depleted (rho-0) cells has led to hypothesize that toxicity is mediated by electron transport chain [80]. A similar conclusion has been drawn by the authors of a study showing that transgenic mice knockout for *COX10* and mutated in *APP* and *PS1* display reduced Aβ42 protein level and reduced Aβ plaque accumulation [81].

According to another line of investigation, Aβ influences mitochondrial function by altering the balance between fusion and fission. Reduced levels of Fis1 and increased levels of Drp1, Opa1, Mfn1, and Mfn2 have been detected in hippocampal tissue of AD patients [82] and Drp1 reduction has been confirmed also in fibroblasts of sporadic AD [83]. Overexpressing APP in cells has been shown to lead to Drp1 and Opa1 downregulation and Fis1 upregulation [84]. A more recent study has shown that both mRNA and protein levels of Drp1 and Fis1 are upregulated in AD brains while Mfn1, Mfn2, and Opa1 are downregulated. Moreover, an interaction between Drp1 and Aβ has been observed in both AD brains and primary neurons of AβPP transgenic mice [85].

Another topic which has recently gained interest is represented by the effect of β-amyloid on mitochondrial proteostasis. In this perspective, it has been shown that the expression of mitochondrial unfolded protein response (UPR^{mt}) genes is upregulated in brains of sporadic and familial AD cases [86] and that both UPR^{mt} and mitophagy-related transcripts are increased in brains of patients with mild cognitive impairment, as well as with mild and moderate AD, while oxidative phosphorylation related genes have been found to be downregulated in these subjects [87]. This latter study [87] has also investigated mitochondrial proteostasis in the GMC101 worm model of Aβ proteotoxicity. Various

mitochondria-related findings have been detected in these worms, including an upregulation of mitochondrial stress response ortholog genes, reduced respiratory capacity, increased expression of oxidative phosphorylation genes, and reduced mitochondrial mass. The overexpression of atfs-1, a transcription factor involved in mitochondrial function, has been shown to be associated with UPR^{mt} induction and with an improvement of the phenotype in these worms. The authors have also observed an upregulation of genes involved in UPR^{mt} and mitophagy, as well as an improvement in health and lifespan, when treating worms with doxycycline, when silencing the mitochondrial ribosomal protein mrps-5, and when administering NAD^+-boosting compounds [87].

Furthermore, APP and Aβ have been described to localize also in mitochondria [88–90] and a mitochondrial targeting motif has been detected on AβPP [91, 92]. Various hypotheses have been proposed to explain the relationship between mitochondrial Aβ localization and mitochondrial dysfunction. For example, Aβ-binding alcohol dehydrogenase (ABAD) has been involved, since oxidative stress is ameliorated by blocking the interaction between ABAD and Aβ [93]. Cyclophilin D, located in the mitochondrial transition pore, is another protein putatively involved in this process. Indeed, knocking out cyclophilin D leads to reduced Aβ-induced apoptosis and improved cognitive performance in transgenic mice. [94] Finally, Aβ-mediated mitochondrial dysfunction may also involve calcium homeostasis alteration [95].

It is also important to highlight the role that tau pathology plays in this context. As already mentioned, tau neurofibrillary tangles represent one of AD neuropathological features and several studies have pointed out the role of tau in the pathogenesis of the disease [96]. Among other lines of investigation, it has been proposed that tau accumulation may contribute to the observed mitochondrial dysfunction, as supported by several findings in experimental models [97], and various hypotheses have been proposed [98, 99]. In this perspective, it has been suggested that tau accumulation may impair the transport and distribution of mitochondria along neurons [100, 101] and that tau may also interfere with the mitochondrial fission/fusion mechanisms [102, 103].

Some studies have hypothesized that Aβ and tau may synergistically concur to determine mitochondrial dysfunction in the disease. For example, the investigation of a triple mutant mouse model (obtained by cross-breeding $APP^{sw}/PS2^{N141I}$ mice and P301L-tau mice) has shown signs of mitochondrial dysfunction, including altered mitochondrial membrane potential, increased reactive oxygen species production, and impaired respiratory chain activity [104]. Many of these findings were more pronounced in triple transgenic mice than in $APP^{sw}/PS2^{N141I}$ or P301L-tau mice [104]. The authors of the same study have also suggested that Aβ mainly causes a complex IV defect, while tau mainly affects complex I [104]. Signs of mitochondrial dysfunction involving reduced enzymatic activity and increased oxidative stress have also been observed in another AD triple transgenic mouse model [105].

To conclude, several studies have pointed out that mitochondria play an important role in AD pathogenesis. It is still a matter of debate whether mitochondrial dysfunction only represents a consequence of amyloid deposition or also plays a direct role in the very initial steps of the disease. Amyloid pathology and mitochondrial dysfunction may also play a synergic role in the pathogenic pathway, as suggested by the results of various studies [70]. However, considering the relevance of the matter, further investigation is needed.

Parkinson's Disease

PD is the second most common neurodegenerative disorder.

It is clinically characterized by variable combinations of bradykinesia, rigidity, rest tremor, and postural instability, accompanied by other motor and non-motor symptoms.

Although the neuropathological presentation of the disease is complex, the main feature is represented by the progressive degeneration of dopaminergic neurons in midbrain substantia nigra (SN). Microscopically, PD is characterized by intracellular protein aggregates, mainly composed of alpha-synuclein (α-syn) and often denoted as Lewy bodies [106].

Although mitochondria have been found to be involved in many neurodegenerative diseases, their role is particularly striking in PD (Fig. 2), as supported by numerous biochemical and genetic findings [107–109].

The Involvement of Respiratory Chain

Several studies have investigated the presence of defects in the activity of mitochondrial respiratory chain. Interestingly, although a certain variability can be observed among individuals [107], various reports are consistent in describing a selective deficiency of respiratory chain complex I and this finding is particularly evident when the enzymatic activity is measured in patients' SN [110–114]. The evaluation of complex I activity in other tissues has provided contrasting results. For example, some laboratories have reported a reduced complex I activity in skeletal muscle of PD patients [115–117], while others have not [112, 118]. Similarly, various studies have provided evidence for a reduced complex I activity in patients' platelets [119–121], but, also in this case, with exceptions [122]. Contrasting results have been detected in patients' leukocytes [122–124]. A deficiency of other respiratory chain complexes (namely complexes II + III or complex IV) has only sporadically been described [115–117, 119, 124]. Although the reason for the selective involvement of complex I has not been elucidated yet, two neuropathological studies, performed on patients' SN and striatum and aimed at

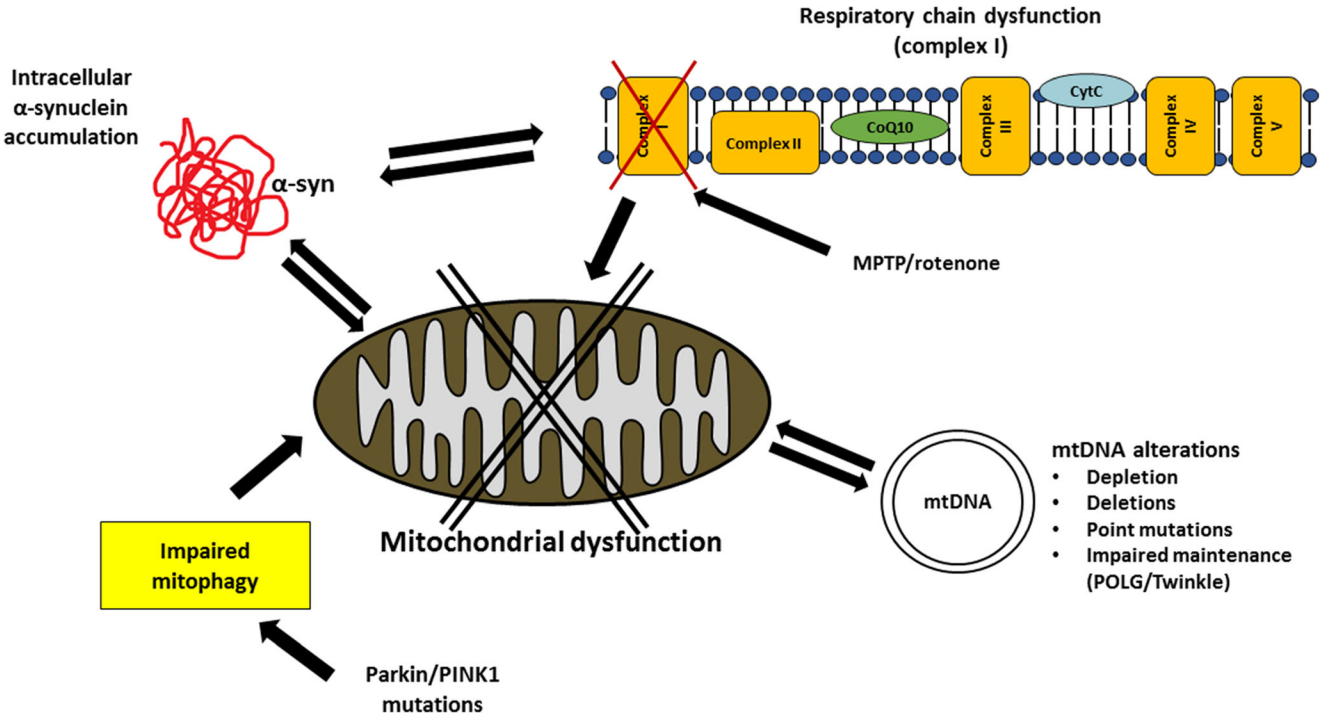

Fig. 2 Mitochondrial dysfunction in Parkinson's disease. The figure summarizes the main mitochondria-related mechanisms which have been proposed to be involved in the pathogenesis of PD. Respiratory chain activity (in particular complex I) is dysfunctional in the disease and mitochondrial inhibitors (MPTP and rotenone) cause clinical and neuropathological parkinsonian features. Intracellular alpha-synuclein accumulation is bi-directionally linked to mitochondrial dysfunction. Alterations of mitochondrial DNA, including depletion, deletions, point mutations and impaired maintenance, have been described. Mitophagy is also involved in the disease, as supported by rare familial PD cases due to mutations in *Parkin* and *PINK1*

assessing the amount of respiratory chain complexes in these tissues, have described a reduction of complex I subunits in patients [125, 126]. Another piece of evidence supporting complex I dysfunction in PD is represented by "cybrids," obtained by repopulating mtDNA-depleted human cells with mitochondria derived from platelets of patients or controls. PD cybrids are characterized by various pathological features, including reduced complex I activity, increased oxidative stress, and increased susceptibility to toxin-mediated apoptosis [127, 128].

The possible role of complex I in the pathogenesis of PD is further supported by the finding that the administration of complex I inhibitors to humans and animal models is accompanied by the onset of parkinsonism and striatonigral degeneration. In 1979, a 23-year-old man has been reported to have developed chronic parkinsonism after the intravenous injection of a meperidine analogue (4-propyloxy-4-phenyl-*N*-methylpiperidine). This subject has shown motor features persisting for more than 18 months and responding to dopamine receptors stimulation; moreover, neuropathological evaluation has pointed out a damage of SN aminergic neurons [129]. In 1983, another report [130] has described four subjects who have developed a severe form of parkinsonism after the intravenous injection of a drug which resulted positive for 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) and, to a lesser extent, 1-methyl-4-phenyl-propionoxy-piperidine (MPPP). Furthermore, it has been shown that the administration of MPTP to animal models is accompanied by a rapid onset of parkinsonism. For example, the intravenous injection of this compound to rhesus monkeys induces parkinsonian clinical features like akinesia, tremor, and rigidity which are reversed by L-DOPA administration, as well as neuropathological alterations, including neuronal depletion in SN pars compacta, although classical Lewy bodies pathology has not been reported [131]. The parenteral administration of MPTP to mice is followed by analogous findings, including nerve cell loss in SN pars compacta [132]. Since these first descriptions, MPTP-based animal models have often been used to investigate the disease [133–135]. It is interesting to point out that MPTP exerts its toxicity by inhibiting mitochondrial respiratory chain complex I [136], and its mechanism of action, mainly mediated by the metabolite MPP+, has been widely investigated. It has been proposed that MPTP is oxidized to MPDP+ by monoamine oxidase B in glia and serotonergic neurons and is then converted to MPP+. The high affinity of MPP+ for dopamine transporters may contribute to explain the selectivity of MPTP toxicity for specific neuronal populations and the ability of this compound to determine a parkinsonian phenotype [137–139]. Several complex I inhibitors have been described [140], and MPTP is not the only

one which has been associated with PD. Some of these compounds have been used as pesticides and, among them, a particular attention has been attributed to rotenone [141]. The administration of rotenone to rats has been associated with the onset of parkinsonian clinical features, including hypokinesia, unsteady movements, hunched posture, rigidity, and shaking. Moreover, degeneration of dopaminergic neurons and cytoplasmic aggregates containing α-syn and ubiquitin has been detected in these animals [142]. In addition, treating neuroblastoma cells with rotenone induces α-syn and ubiquitin accumulation, oxidative damage, and apoptosis upregulation [143]. However, not all the studies are consistent with the hypothesis of a selective involvement of SN dopaminergic neurons as a consequence of rotenone administration, since a more generalized neuronal loss also involving cholinergic, noradrenergic, and serotonergic neurons has been found in treated rats [144]. Moreover, some authors have questioned whether the detrimental effect of these toxins is actually mediated by complex I inhibition [145]. Annonacin is another complex I inhibitor whose administration to rats induces neurodegeneration: a significant loss of SN dopaminergic neurons and of striatal GABAergic and cholinergic neurons has been observed in these animals [146].

The Role of Mitochondrial DNA

Several pieces of evidence support the hypothesis that also mtDNA plays a role in the pathogenesis of PD [108]. The load of mtDNA deletions has been one of the first aspects to be analyzed, and conflicting results have emerged. Two old studies have proposed that the occurrence of mtDNA deletions, although physiologically detectable in elderly subjects, is accelerated in the striatum of PD patients [147, 148]. However, other reports of the same period have not detected an increased amount of mtDNA deletions in the SN, putamen, and frontal cortex [149–151]. A subsequent investigation [152], based on long-extension polymerase chain reaction, has confirmed the initial hypothesis, detecting an increased level of mtDNA deletions/rearrangements in the SN and other brain areas of PD patients in comparison to healthy controls and subjects with other neurodegenerative disorders. A high mtDNA deletion burden has been observed in PD SN also by another group [153], and a significant increase of mtDNA deletions has been associated with the disease by evaluating DNA from SN individual neurons of patients and controls [154]. Therefore, although data remain conflicting, independent studies suggest that mtDNA deletions may be increased in the disease. In this perspective, since mtDNA deletions are also numerous in the SN of aged individuals [155], it would be crucial to distinguish between the load of deletions due to the disease and that due to aging.

Another major field of investigation is represented by the finding of mtDNA point mutations. Old studies [50, 156–159] have reported a high mutational load in PD. Furthermore, relatively more recent investigations have observed homoplasmic mutations in *MT-ND1* and *MT-ND2* genes, potentially contributing to neuronal vulnerability, in patients' SN and platelets [160] as well as heteroplasmic mutations of *MT-ND5* in PD SN [161]. However, the role of mtDNA mutations in PD has not always been confirmed and the issue remains controversial. For example, the analysis of the sequence of mitochondrial tRNA and complex I genes in five couples of monozygotic twins discordant for the disease has detected a certain amount of mtDNA mutations, but no differences have been observed between affected and unaffected siblings [162]. The analysis of the entire mtDNA sequence in the SN of 8 PD subjects and 9 healthy controls has not provided significant results: despite a remarkable mutational burden, no major differences have been observed between patients and controls [163]. A similar observation has emerged from another study aimed at sequencing several mtDNA-encoded genes in affected and unaffected individuals [164]. Recent reports, based on large cohorts of subjects, have not been useful to definitely elucidate the issue. The evaluation of brain samples from 180 PD patients and 40 controls has pointed out an increased mutational load in patients' frontal cortex and SN [165], and another report has proposed that mtDNA mutations are particularly frequent in the SN of early PD patients [166]. On the other hand, a wide study [40] investigating mtDNA in brain samples of subjects affected by various neurodegenerative diseases (including 89 DLB-PD) and 351 controls has not observed an increased mutational burden in PD. Furthermore, mtDNA point mutational load has not been described to be increased also in an already mentioned study which has evaluated mtDNA in individual neurons of patients and controls [154].

It is also interesting to highlight that specific mitochondrial haplogroups have been associated with an increased or decreased risk of developing PD. A wide study [167] investigating 609 PD patients and 340 healthy controls has shown that subjects with haplogroups J or K are less susceptible to develop the disease than those carrying haplogroup H. The authors have also pointed out that this protective effect may be related to the single-nucleotide polymorphism 10398G. These findings have been confirmed by a subsequent investigation [168] which has analyzed 455 PD patients and 447 healthy controls and has observed an association between the UKJT haplogroup cluster and a reduced risk of developing the disease. Furthermore, the same report suggests that this protective effect is specific for PD, since analyses on AD patients have not provided similar results. Two independent studies have confirmed a reduced risk of developing the disease in patients harboring mitochondrial haplogroups K [169] and UK [170], respectively. The findings of these studies partially disagree with the description of an association between the mitochondrial polymorphism 4216C [171], strictly associated

with haplogroups J and T, and an increased risk of developing PD. However, this latter finding has not been replicated by the same group when analyzing a cohort of young healthy controls. In a more recent two-stage association study, it has been confirmed that PD risk is decreased in subjects carrying haplogroups J, K, and T, while it is increased in subjects carrying the super-haplogroup HV [172].

It has been reported that also mtDNA amount may be altered in PD. The investigation of cell-free circulating mtDNA in cerebrospinal fluid of patients and age-matched controls has shown a reduction in patients [173]. Various studies have observed a reduced mtDNA content also in PD SN [154, 174, 175], but not in other brain areas [40, 175]. The report of the same finding also in blood samples [175] suggests a possible peripheral response to mitochondrial dysfunction.

Finally, another independent, although indirect, piece of evidence which suggests a correlation between mtDNA alterations and parkinsonism is represented by patients carrying mutations in genes involved in mtDNA maintenance. Polymerase γ is the polymerase involved in mtDNA replication and is encoded by *POLG* gene. *POLG* mutations have been described to be responsible for some cases of progressive external ophthalmoplegia (PEO) with mtDNA deletions [176]. A wide study [177] has assessed the incidence of parkinsonian features in PEO patients from seven families. Clinical evaluation has pointed out a co-segregation between *POLG* mutations and parkinsonism, and imaging studies have shown dopaminergic neuronal loss. The post-mortem evaluation of two of these subjects has confirmed a loss of pigmented neurons in the SN, although Lewy bodies have not been detected. Various other subsequent studies have described the presence of parkinsonian features in *POLG*-mutated subjects [178–185]; moreover, additional neuropathological studies have confirmed the finding of neuronal loss in the SN, although sometimes accompanied by AD-like pathological features [186, 187]. The recent evaluation of 11 *POLG*-mutated subjects has highlighted an involvement of the nigrostriatal pathway even if parkinsonian clinical features were not present: DAT-scan and PET analyses have shown nigral neuronal loss and nigrostriatal depletion, while the post-mortem assessment of SN has demonstrated a severe depletion of dopaminergic neurons, reduced complex I amount, and reduced mtDNA content [188]. The involvement of *POLG* mutations in idiopathic PD is debated [189–193]; furthermore, the investigation of the role of a trinucleotide CAG repeat located in *POLG* gene has provided conflicting results, since some groups have reported an association between the repeat length and PD [189, 194–196], while others have not [190, 197, 198]. Finally, it is interesting to highlight that *POLG* is not the only mtDNA maintenance-related gene to be associated with parkinsonism. Indeed, parkinsonian features have been detected in patients carrying mutations in Twinkle [199–201], a mitochondrial DNA helicase which has been associated with PEO [202].

To conclude, a remarkable amount of work has been done to understand the role of mtDNA in PD and several interesting results have emerged. However, as already mentioned when discussing the same topic in AD, the elevated heterogeneity of the results across different studies, often contradictory with one another, makes it difficult to draw clear and definite conclusions about this issue. Further investigation is therefore needed, and the availability of larger datasets will probably help in this direction.

Insights from Genetics: Parkin and PINK1

Another important hint which suggests a role of mitochondria in the pathogenesis of PD is provided by genetics. Indeed, some of the genes which have been found to cause familial cases of PD are directly involved in mitochondrial biology. The most prominent examples are represented by *Parkin* and *PINK1*, whose pathogenic mutations are responsible for autosomal recessive forms of early-onset PD [203, 204]. Both PINK1 and Parkin are involved in the mitophagic machinery, thus contributing to coordinate the directing of damaged mitochondria to degradation. PINK1 monitors mitochondrial status, detects damages, and recruits and activates Parkin. Parkin, once recruited, conjugates ubiquitin onto proteins of the outer mitochondrial membrane, thus fostering the pathway which leads to the engulfment of mitochondria into the autophagosome. This latter structure subsequently fuses with a lysosome and initiates the pathway which leads to mitochondrial degradation [205]. The synergic action of PINK1 and Parkin in directing mitochondria to degradation, with PINK1 acting upstream of Parkin, has been confirmed by investigating Drosophila mutants [206, 207].

It is interesting to point out that Parkin and PINK1 have also been demonstrated to be involved in mitochondrial fission and fusion [208]. Studies performed on Drosophila models have shown an involvement of this pathway in *Parkin* or *PINK1* mutants and have observed that the inhibition of mitochondrial fusion or the enhancement of mitochondrial fission is able to rescue the pathological phenotype in these flies [209, 210]. Interestingly, analogous findings have also been observed in models not directly related to Parkin or PINK1, since flies expressing human α-syn are characterized by enlarged mitochondria and decreased Drp1 mitochondrial localization and show a behavioral and pathological improvement after Drp1 overexpression [211]. However, contrasting results have been obtained by analyzing human cells. In this case, *PINK1/Parkin* silencing has been shown to be accompanied by mitochondrial fragmentation. Moreover, a rescue of the pathological phenotype has been observed by enhancing the fusion-related proteins Mfn2 and Opa1 or by negatively modulating the fission-related protein Drp1 [212]. Another

study has also proposed to target the fission/fusion pathway as a possible therapeutic approach for PD and has shown that the inhibition of Drp1 ameliorates the phenotype of *PINK1*-mutated mice and of the MPTP toxin-mediated murine model [213].

Finally, it must be acknowledged that a pathological phenotype, often involving mitochondria-related aspects, has been detected in various PINK1 or Parkin models: Drosophila models [214], mouse models [215], iPSC-based models [216–222], and other cellular models [223].

Mitochondria and Alpha-Synuclein

Another field of investigation which is providing important insights about the role of mitochondria in PD is represented by the correlation between α-syn accumulation and mitochondrial dysfunction. As already reported, PD is neuropathologically considered as a synucleinopathy, that is, a disease characterized by the anomalous intracellular deposition of α-syn. α-Syn is a 14 KDa protein which is physiologically expressed in the human brain. Although it has been proposed to be involved in synaptic vesicle trafficking and neurotransmitter release, its physiological function is not completely clear [224–226]. However, the role of α-syn in the pathogenesis of PD is supported not only by the finding of its accumulation in neurons, but also by the fact that multiplications and point mutations of *SNCA* gene are responsible for rare genetic forms of the disease [227–230].

In this perspective, various studies have investigated the effect of α-syn accumulation on mitochondrial functioning. Only to provide some examples, signs of mitochondrial dysfunction have been observed in brain of mice overexpressing α-syn under the neuronal Thy-1 promoter [231], in primary neurons of *SNCA* A53T-mutated mice [232], in mouse-isolated mitochondria treated with soluble prefibrillar α-syn [233], in rat brain mitochondria incubated with recombinant α-syn [234, 235], and in rat dopaminergic neurons treated with preformed α-syn fibrils [236]. Some laboratories have specifically described a correlation between α-syn and complex I deficiency: a dysfunctional activity of this complex has been observed after overexpressing α-syn (both wild-type and mutated) in animals [237, 238] and cellular models [239, 240]. It has also been reported that the α-syn-mediated inhibitory effect on complex I is dose dependent in rat brain [241]. Furthermore, it has been proposed that the effect of specific parkinsonism-inducing toxins may be mediated, or at least facilitated, by α-syn. For example, the detrimental effect of MPTP has been found to be enhanced in mice which overexpress human α-syn [242, 243] and in *SNCA* A30P-mutated transgenic animals [244]. Moreover, α-syn-null mice display increased resistance to the MPTP-mediated degeneration of dopaminergic neurons [245, 246] and an analogous resistance has been observed in α-syn knocked-down neuroblastoma cells [247]. Similar results have been obtained also with rotenone, since animals or cellular models overexpressing α-syn or carrying pathogenic mutations in *SNCA* gene have been shown to be more sensitive to the detrimental effects of this compound [248, 249]; instead, contrasting opinions exist about the protective effect of *SNCA* downregulation on rotenone toxicity [247, 250]. Although the issue remains widely unclear, a few groups have also tried to investigate the effect of mitochondrial inhibition on α-syn accumulation. Two already mentioned studies have reported that treating rats [249] or neuroblastoma cells [250] with rotenone induces α-syn accumulation; moreover, the continuous administration of MPTP to mice is accompanied by the formation of nigral inclusions positive for α-syn, while the same effect is not observed after the sporadic administration of the same compound [251]. Although most of these studies suggest an association between α-syn and complex I dysfunction, an interaction between this protein and other respiratory chain complexes, in particular ATP synthase, has also sporadically been described [252].

The exact mechanism which explains the relationship between α-syn accumulation and mitochondrial dysfunction is not completely clear. However, various hypotheses have been suggested. Among these, it is interesting to point out that a mitochondrial targeting motif has been detected in the N-terminal domain of human α-syn [239]. It has also been proposed that α-syn interacts with the mitochondrial protein import machinery. In particular, specific forms of α-syn have been shown to bind to the translocase of the outer membrane 20 (TOM20), thus inhibiting the interaction between TOM20 and TOM22. This finding, observed in both experimental models and in human post-mortem tissues, has been supposed to affect the efficiency of the mitochondrial protein import mechanisms and, consequently, the overall mitochondrial functioning [253]. Another group has reported that TOM40, another component of the mitochondrial import machinery, but not TOM20, is reduced in brains of PD patients. Furthermore, overexpressing wild-type or A53T-mutated, but not A30P-mutated α-syn in rat neuroblastoma cells, results in TOM40 reduction. Overexpressing TOM40 in PDGF-α-syn-transgenic mice leads to reduced oxidative stress, increased ATP levels, and reduced and redistributed α-syn in these animals [254]. According to other studies, based on various experimental models, α-syn is responsible for an increased mitochondrial fragmentation [255, 256]; one of these reports suggests that α-syn also inhibits mitochondrial fusion and that the α-syn-induced mitochondrial fragmentation is rescued by the co-expression of wild-type PINK1, Parkin, and DJ-1 [255]. An alternative recent hypothesis suggests that a portion of α-syn is not localized in mitochondria, but in mitochondria-associated endoplasmic reticulum membranes (MAM). Furthermore, according to the same study, *SNCA* point mutations reduce the amount of MAM-

associated α-syn, impair MAM function, and trigger mitochondrial fragmentation through a Drp1-independent mechanism [257, 258].

Mitochondria in Atypical Parkinsonisms: the Example of Multiple System Atrophy

It is interesting to observe that mitochondrial dysfunction has not been detected only in classical PD, but several hints suggest an involvement of these organelles also in atypical parkinsonisms, in particular multiple system atrophy (MSA). MSA is a severe neurodegenerative disease which is clinically characterized by variable combinations of parkinsonism, cerebellar ataxia, dysautonomia, and other motor and non-motor symptoms. Two clinical subtypes, MSA-P and MSA-C, have been described on the basis of the predominant symptomatology, parkinsonian or cerebellar respectively. Similarly to PD and dementia with Lewy bodies, MSA is neuropathologically characterized by the intracellular accumulation of α-syn. However, the peculiarity of MSA is that α-syn accumulates not only in neurons but also in oligodendrocytes. The causes of this aberrant protein localization have been extensively investigated, although a definite mechanism has not been demonstrated yet [259, 260]. The role of mitochondria in MSA has been poorly considered for several years, and only a few studies [152, 261, 262] have been published until 2013, when a causative role of *COQ2* gene mutations has been proposed in familial and sporadic cases of MSA [263]. COQ2 is one of the enzymes involved in the biosynthesis of Coenzyme Q10 (CoQ10), a molecule which plays several roles in cell biology and, prominently, in mitochondrial respiratory chain, being responsible for transferring electrons from complexes I and II to complex III. Mutations in genes encoding CoQ10 biosynthesis enzymes, including *COQ2*, had already been found to cause rare multi-organ syndromes, often characterized by a severe neurological symptomatology, when inherited in an autosomal recessive fashion [264, 265], but the association with MSA had not been reported before. Therefore, several groups have tried to recapitulate the same genetic finding in independent cohorts of MSA patients and conflicting results have emerged [266–271]. Although the finding of *COQ2* mutations in MSA remains controversial, further investigation has tried to address whether CoQ10 may be anyway involved in the disease. Interestingly, a reduced CoQ10 amount has been observed, independently from *COQ2* mutational status, in MSA cerebellum [272, 273], cerebrospinal fluid [274], plasma [275], serum [276], and fibroblasts [277]. Also, CoQ10 biosynthesis enzymes have been found to be altered in the disease, with reduced PDSS1 and COQ5 in patients' brain [272], increased COQ5 and COQ7 in fibroblasts [277], and increased PDSS1, PDSS2, COQ4, and ADCK3 in iPSC-derived dopaminergic neurons [278]. Furthermore, it has recently been shown that iPSC-derived neurons from a *COQ2*-mutated MSA patient are characterized by mitochondrial dysfunction, reduced CoQ10 level, and increased oxidative stress [279]. The role of mitochondria in MSA has been investigated in two recent extensive studies based on cellular models, already mentioned when discussing the CoQ10-related pathology [277, 278]. In these reports, an impaired activity of respiratory chain complexes, in particular complex II, has been observed in MSA primary fibroblasts and iPSC-derived neurons. Fibroblasts' analyses have also suggested an impaired mitophagic flow, while neurons' evaluation has highlighted an alteration of the amount of respiratory chain complexes and an increased mitochondrial mass.

The comprehension of the specific role of mitochondria in MSA still needs further investigation. Also in this case, it will be important to understand whether these organelles play a primary role in the very initial stages of the disease, as suggested by the still controversial "COQ2 hypothesis," or their dysfunction is just secondary to other phenomena, in particular protein accumulation. Differently from PD, no studies have so far been performed to understand the relationship between α-syn accumulation and mitochondrial dysfunction in MSA. However, the administration of the mitochondrial inhibitor 3-nitroproprionic acid to transgenic MSA mouse models overexpressing human α-syn in oligodendrocytes causes a worsening of both clinical and neuropathological features of these animals, which suggests that mitochondrial dysfunction and α-syn accumulation may play a synergic effect in the pathogenesis of the disease [280, 281].

The Role of Aging

Another topic which has to be highlighted is the link which connects neurodegeneration, mitochondrial dysfunction, and aging. Indeed, the onset of neurodegenerative diseases most often occurs at an advanced age and aging has been demonstrated to be an independent risk factor itself [282]. Therefore, although this is not the main topic of the present review, a few hints are here provided.

Aging is a complex process which involves several pathways, including proteostasis, telomere loss, and DNA damage [283]. In this intricate scenario, mitochondria play an important role as well [109, 284–286]. A progressive accumulation of mitochondrial defects has been described to occur during lifespan. For example, an increased load of mtDNA mutations and deletions [287–289] and a reduced respiratory chain activity [290, 291] have been observed in tissues of elderly individuals and experimental models. However, not only signs of mitochondrial dysfunction can be observed in aged subjects, but the impairment of mitochondrial functions seems to be directly implicated in the aging process. In this perspective, various mechanisms have been proposed. For example, mitochondrial defects have been suggested to contribute to the

age-related inflammatory status by releasing specific molecules, including mtDNA, which activate the inflammatory cascade [284]. Another possibility is that mitochondrial dysfunction interferes with stem cell biology [285]. It has also been proposed that the mitophagic machinery becomes defective at advanced age [292], thus not allowing to properly eliminate old and malfunctioning mitochondria and contributing to the dysfunction of these organelles. The hypothesis which suggests a mitochondria-mediated oxidative stress which contributes to the aging process has been widely investigated [293] and remains suggestive, although some possible criticisms have emerged [284]. The link between aging and mitochondria is also supported by experimental models. For example, a mouse model with defective mitochondrial DNA polymerase, which accumulates a high amount of mtDNA mutations, is characterized by signs of precocious aging, including reduced lifespan, hair loss, and kyphosis [294, 295]. Further investigation is needed, but, considering the direct role of mitochondrial dysfunction in both aging and neurodegenerative diseases, it is intriguing to hypothesize a possible link. In this perspective, age-related mitochondrial dysfunction may contribute to trigger the neurodegenerative process and, on the other hand, mitochondrial damages spontaneously occurring during life or triggered by specific agents (e.g., toxins) may contribute to the aging of specific tissues and concur to neurodegeneration.

Conclusions

Considering the remarkable amount of data which have been described so far, it is rational to conclude that mitochondria play an important role in the pathogenesis of Alzheimer's disease and Parkinson's disease. These results are also suggestive for a more general role of these organelles in neurodegeneration.

A critical question which arises is whether mitochondrial dysfunction directly contributes to the initial steps of neurodegeneration, therefore being primarily responsible for triggering the pathogenic process, or it only represents a secondary phenomenon caused by other mechanisms, in particular anomalous protein accumulation, or a general response to cell suffering. The issue is controversial and several pieces of evidence have been provided in favor of both the hypotheses. As far as AD is concerned, the finding that mutations in APP and presenilins' genes are responsible for genetically inherited forms of the disease is the most direct hint which supports the primary role of Aβ deposition in the pathogenic cascade. The finding that Aβ administration is followed by mitochondrial dysfunction in experimental models further supports this hypothesis. On the other hand, it must be acknowledged that the administration of specific mitochondrial toxins contributes to amyloid pathology in animals and cells and that other hints, including the increased risk of developing the disease in the presence of maternal family history, are also supportive for a primary contribution of mitochondria. When considering PD, the issue is even more intricate. The fact that multiplications and point mutations in *SNCA* gene cause familial cases of PD is suggestive for a primary role of α-syn accumulation; the finding of mitochondrial dysfunction in several experimental models treated with α-syn is also supportive in this direction. However, the pieces of evidence which support the role of mitochondria in the very initial stages of PD are even stronger than in AD. Not only the administration of mitochondrial toxins, in particular MPTP and rotenone, are able to induce a clinical and neuropathological parkinsonian phenotype in humans and animal models (despite the already mentioned limitations), but mutations in genes directly related to mitochondria have also been found to be associated with the disease. Indeed, mutations in *Parkin* and *PINK1*, involved in the mitophagic machinery, are responsible for rare young-onset familial PD cases and an association between parkinsonism and mutations in *POLG* gene, which encodes the mitochondrial polymerase, has been described (Table 1). Another aspect which should be considered when discussing this topic and which applies to both AD and PD is that classical mitochondrial diseases, reliable examples of primary mitochondrial dysfunction because directly caused by mutations affecting the mitochondrial machinery, are often characterized by the involvement of multiple organs and systems, including the nervous system, the muscle, the eye, the kidney, and the gastrointestinal system [3, 296], while only specific neuronal populations are affected in AD and PD. However, it must also be acknowledged that the clinical presentation of mitochondrial diseases is highly variable and that different mutations cause remarkably different clinical phenotypes, thus suggesting that each cellular population may be selectively vulnerable to specific mitochondrial defects. Moreover, it has been proposed that specific neuronal subtypes, in particular dopaminergic neurons, are particularly sensitive to energetic dysfunction [297]. Furthermore, hypothesizing a primary mitochondrial role in neurodegeneration does not necessarily rule out the involvement of other co-occurring factors, also acting as primary effectors, which may be more specific for the affected neuronal types. On the basis of all these considerations, it is not possible to provide a definite answer about the primary hit which triggers the neurodegenerative process. However, it is interesting to observe that both Aβ and α-syn have been found to trigger mitochondrial dysfunction and that, on the other hand, mitochondrial inhibition has been found to trigger the accumulation of pathological proteins. Therefore, it is suggestive to hypothesize that, once the neurodegenerative process has started, whatever the initial cause is, mitochondrial dysfunction contributes to the progression of the disease by fostering a self-propagating loop which involves protein accumulation and mitochondrial dysfunction and which

Table 1 Hints suggesting a primary or secondary role of mitochondria in the pathogenesis of AD and PD

Primary role	AD	Mitochondrial toxins contribute to amyloid pathology in animals and cells
		Maternal family history increases the risk of developing the disease
	PD	Mitochondrial toxins (MPTP and rotenone) induce clinical and neuropathological parkinsonian features in humans and animal models
		Mutations in Parkin and PINK1 genes (directly involved in mitophagy) cause rare young-onset familial cases of the disease
		Mutations in POLG gene, encoding the mitochondrial polymerase, are associated with parkinsonian features
Secondary role	AD	Aβ administration is followed by mitochondrial dysfunction in experimental models
		Mutations in APP and presenilins' genes are responsible for genetically inherited forms of the disease
	PD	Mitochondrial dysfunction is enhanced by α-syn administration in experimental models
		SNCA gene multiplications and point mutations are responsible for genetically inherited forms of the disease

contributes to neuronal suffering and, ultimately, neurodegeneration (Fig. 3).

Another interesting aspect which emerges from this review is that, although mitochondrial dysfunction appears to be a common motif in neurodegeneration, it differently manifests in different diseases. In this perspective, it is particularly informative to analyze the topic of respiratory chain dysfunction. Respiratory chain is composed of five complexes and is responsible for oxidative phosphorylation. Although a generic dysfunction has been observed in several neurodegenerative disorders, each disease is characterized by a more pronounced involvement of certain complexes. For example, complex IV has been shown to be particularly affected in AD, while plenty of studies have been performed to elucidate the involvement of complex I in PD. The same can be said about other neurodegenerative diseases which have not been described in this review: for example, Huntington's disease is prominently characterized by the involvement of complex II [298]. Another hint which suggests a disease-specificity is provided by the genetic factors which point toward mitochondrial dysfunction in neurodegenerative diseases. Indeed, some of these factors, such as mtDNA alterations (depletion, deletions, point mutations), although very controversial, have been described in both AD and PD, while other, like *Parkin* and *PINK1* mutations in PD, are specific for a single disease. These specificities are interesting because they may help to understand why, despite the common finding of mitochondrial dysfunction, clinical and neuropathological features are so different in distinct diseases. However, the available knowledge is not sufficient to provide a solid and comprehensive hypothesis and further investigation is needed.

Finally, it must be acknowledged that the finding of a so prominent involvement of mitochondria in neurodegenerative diseases lays the foundations to investigate novel pharmacological approaches. Various studies have already been performed or are in progress and have targeted, at a preclinical or clinical level, multiple mitochondria-related aspects, including oxidative stress, mitochondrial dynamics, mitochondrial biogenesis, and mitochondrial proteostasis [87, 213, 216, 299–302], not always with positive results [303]. However, as shown in the present review, the mitochondrial targets which may be worth taking into consideration are numerous. The paucity of effective available therapeutic tools for neurodegenerative diseases urges a far more intense effort and the

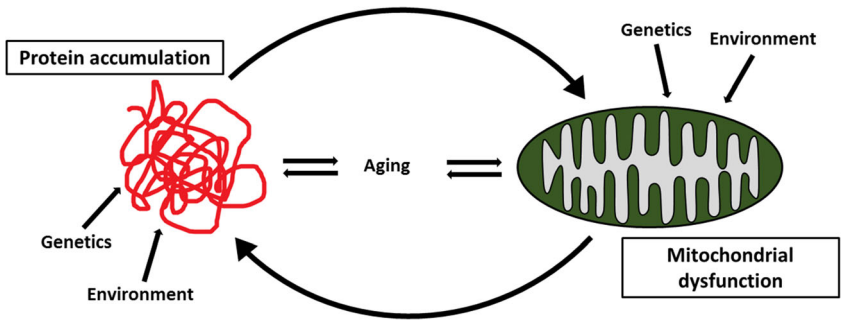

Fig. 3 Anomalous protein accumulation and mitochondrial dysfunction are involved in the pathogenesis of neurodegenerative diseases. Both genetic and environmental factors are implicated and aging plays a role as well. Although the identification of the initial causative mechanism is still a matter of debate, it is interesting to observe that mitochondrial dysfunction triggers anomalous protein accumulation and, vice versa, anomalous protein accumulation contributes to mitochondrial dysfunction. Therefore, it is suggestive to hypothesize that whatever the initial causative mechanism is, once the neurodegenerative process has started, mitochondrial dysfunction and anomalous protein accumulation form a self-propagating loop which contributes to the maintenance and progression of the disease

investigation of new mitochondria-targeting compounds, in addition to therapies acting on different pathways, is compelling.

To conclude, the present review summarizes the remarkable amount of data which have been collected during the last decades about the role of mitochondria in AD and PD and, in general, in neurodegenerative diseases. The emerging evidence suggests an important role of these organelles during the neurodegenerative process, and the understanding of these diseases has been strongly improved by the results of these studies. However, as described in detail in the review, various topics are still controversial and several questions are still waiting for an answer. Therefore, further investigation will be crucial in this field. Among other issues, it will be relevant to better elucidate the relationship between mitochondrial dysfunction and anomalous protein accumulation, to investigate the correlation between mitochondrial dysfunction and neuronal suffering, to understand the specificity of each neurodegenerative disease and, in the meantime, to understand whether common pathways can be detected across different disorders. Finally, as already mentioned, it will be important to understand whether this considerable amount of basic science data can be translated into clinical practice by investigating novel therapeutic approaches targeting these pathways.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

Abbreviations AD, Alzheimer's disease; PD, Parkinson's disease; APP, amyloid precursor protein; PET, positron emission tomography; mtDNA, mitochondrial DNA; CR, control region; ABAD, Aβ-binding alcohol dehydrogenase; UPR^{mt}, mitochondrial unfolded protein response; SN, substantia nigra; α-syn, alpha-synuclein; MPTP, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine; PEO, progressive external ophthalmoplegia; TOM20, translocase of the outer membrane 20; MAM, mitochondria-associated endoplasmic reticulum membranes; MSA, multiple system atrophy; CoQ10, coenzyme Q10

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