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Mitochondrial control of cell bioenergetics in Parkinson's disease

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Abstract

Parkinson disease (PD) is a neurodegenerative disorder characterized by a selective loss of dopaminergic neurons in the *substantia nigra*. The earliest biochemical signs of the disease involve failure in mitochondrial-endoplasmic reticulum cross talk and lysosomal function, mitochondrial electron chain impairment, mitochondrial dynamics alterations, and calcium and iron homeostasis abnormalities. These changes are associated with increased mitochondrial reactive oxygen species (mROS) and energy deficiency. Recently, it has been reported that, as an attempt to compensate for the mitochondrial dysfunction, neurons invoke glycolysis as a low-efficient mode of energy production in models of PD. Here, we review how mitochondria orchestrate the maintenance of cellular energetic status in PD, with special focus on the switch from oxidative phosphorylation to glycolysis, as well as the implication of endoplasmic reticulum and lysosomes in the control of bioenergetics.

Keywords

Parkinson's Disease; mitochondria; lysosome; autophagy; glycolysis; pentose-phosphate pathway; neurodegeneration; redox

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder clinically characterized by motor deficits such as tremor, bradykinesia, rigidity and postural instability, eventually accompanied by non-motor complications such as dementia [1]. These symptoms are mainly associated with loss of dopaminergic neurons (DA) of the *substantia nigra* (SN). The mechanisms underlying DA death have been investigated in many cellular and animal models [2–7]. Mitochondrial dysfunction plays a key role in the development of PD [8, 9].

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Damage of mitochondrial electron transport chain (ETC) affecting complex I, mutation of genes involved in mitochondrial function and defects in the regulation of mitochondrial dynamics has been widely reported in PD pathogenesis [10–13]. Being the main energy-producing organelles of the cell, mitochondria oxidize carbons obtained from carbohydrates and fat, producing ATP through the oxidative phosphorylation (OXPHOS) [14, 15]. Accordingly, any process impairing mitochondria may lead to metabolic switching aimed to compensate for their diminished ability to produce ATP. For instance, switching from OXPHOS to glycolysis is a well-known phenomenon in cancer –the Warburg effect [16]. Here, we address the notion that, similarly to cancer, PD is a metabolic-like disease. Actually, many PD-related genes are also altered in cancer, suggesting common mechanisms in both pathologies [17]. Thus, several epidemiological studies have reported an association between PD and cancer, although this link is yet controversial. Thus, whilst initially it was described an inverse correlation between PD and cancer vulnerability, a recent study reports a positive relationship, at least for certain cancer types, including skin, breast and brain cancer [18]. This odd association provides a new perspective to a well-known opposing cell fate of degeneration and death of post-mitotic neurons, and the uncontrolled division and enhanced resistance to death of cancer cells. An example of this is the loss of function of parkin (one of the genes altered in both PD and cancer). Thereby, parkin mutations results in the deficiency of E3 ligase activity leading to unfolded protein system (UPS) dysfunction and cyclin E build up. CDK2/cyclin E phosphorylates the tumour suppressor retinoblastoma releasing the transcription factor E2F-1 from inhibition. In mitotic cells E2F-1 up-regulates proteins that facilitate cell cycle progression, but in post-mitotic neurons E2F-1 triggers apoptosis through p53 and Bax [19, 20].

Mitochondrial dysfunction leading to metabolic shift and, eventually, neuronal death, may also be a consequence of decreased ability to clear the damaged mitochondria. This can lead to a positive loop of mitochondrial damage, as complex I inhibition, observed in PD and some PD experimental models, increases mROS formation that in turn can oxidize mitochondrial DNA (mtDNA) and other components of the ETC that contribute to oxidative stress [21]. Thus, defects in regulation of mitochondrial dynamics leading to mitochondrial dysfunction may also be involved in PD and, although the specific role of mitochondrial dynamics in PD pathogenesis remains unknown, both toxin and genetic models of PD show signs that interrelate them. Thus, toxins such as MPTP cause Drp1-dependent mitochondrial fragmentation and increased mitophagy in SH-SY5Y cells and dopaminergic neurons [22]. Rotenone, at high concentrations, induce mitochondrial fission and cell death in primary neurons, being this ameliorated by increased fusion or inhibited fission after overexpression of Mnf1 or inhibition of Drp1 [23]. In the case of genetic models, α-synuclein overexpression inhibits mitochondrial fusion by interaction with mitochondrial membranes leading to fragmented mitochondria [24, 25]. Loss of Parkin and Pink1 triggers increased vulnerability to mitochondrial damage in cells [10, 27, 28]. Under normal conditions, parkin protein is recruited in impaired mitochondria *via* a Pink1-dependent mechanism to induce mitophagy [29]. This process involves ubiquitylation of mitochondrial aberrant proteins for proteasomal degradation. Accordingly, the lack of function of Pink1 or Parkin leads to the accumulation of misfolded proteins, such as α-synuclein, which is accumulated in the PD brain. Furthermore, under normal conditions, PINK1 and Parkin promote fission and inhibit

fusion processes, hence the loss of either protein alters mitochondrial morphologies, producing Drp1-dependent mitochondrial fragmentation and decreasing the mitochondrial membrane potential and ATP production [30, 31]. Loss of DJ-1 in cortical neurons reduces fission and increase mitophagy, which is reverted by PINK1 and Parkin [26]. DJ-1is also involved in the degradation of misfolded proteins, thus protecting from mitochondrial fragmentation after damage; it has been observed that Parkin, Pink1 and DJ-1 form a complex having E3 ligase activity [32]. However, many reports have shown that DJ-1 acts in parallel to, or up-stream of, the Pink1/Parkin pathway [33, 34]. DJ-1, *via* its Cys^{106}, may also act as a redox sensor protein exerting protection against oxidative stress [35]. Finally, LRRK2 also affects mitochondrial function and dynamics. Thus, aged transgenic mutant LRRK2 mice exhibit increased damaged mitochondria and mitophagy in cerebral cortex and cultured neurons. This may be mediated by Drp1 because LRRK2 interact with Drp1 enhancing its recruitment into mitochondria. However, this is yet controversial as it depends on the cell type, thus further studies still need to be done [36].

The endoplasmic reticulum (ER)-mitochondria crosstalk is critically important to preserve mitochondrial and cellular integrity. ER-mitochondria contact sites transfer Ca^{2+} from ER to mitochondria to sustain cell metabolism and bioenergetics [28, 37, 38]. Recent studies suggest PD to be linked to other metabolic diseases, such as diabetes or metabolic syndrome [39]. For instance, epidemiological evidence links type 2 diabetes mellitus (T2DM) with the pathogenesis of PD, since mitochondrial dysfunction and ER-stress leads to insulin resistance [40]. Interestingly, DJ-1 activity is reduced in both PD patients and patients with T2DM [41]. ER-stress alters protein folding leading to accumulation of α-synuclein to form the PD typical Lewy bodies cytoplasmic inclusions [42], as well as reduces insulin secretion in diabetes [43]. Inflammation, another key factor risk in PD [44, 45] is also observed in T2DM [46]. Insulin receptors are present in the *substantia nigra* [47] and impaired insulin signalling affects glucose uptake in this brain area and causes neuronal dysfunction by inactivating K_{ATP} channels [48]. High fat diets lead to insulin resistance and accelerate PD progression in a rodent model [49]. Lipids and ceramides, generated from saturated fatty acids, are antagonists of insulin activity, thus likely connecting insulin resistance with neurodegeneration [50]. Cytochrome P450, a typical liver enzyme that is regulated by the brain dopaminergic system in rodents, has been found damaged in PD patients [51, 52]. Finally, there are similarities in DJ-1 signalling pathways found in brain and pancreas [41].

In summary, there is a large body of evidence suggesting the occurrence of important links between glucose homeostasis and PD, being mitochondria a critical nexus. Here, we review this novel aspect of neurodegeneration with the aim to contribute shedding light on the search for future novel therapeutic strategies.

1.1 Dopaminergic neurons are particularly sensitive to metabolic imbalance

The dopaminergic neurons of the *substantia nigra pars compacta* (SNpc DA neurons) are highly energy demanding, a feature that is likely due to the metabolic sustaining of their unusually large axonal arborisation [6, 53]. Interestingly, by reducing the arborisation of the SNpc DA neurons using semaphorin-7A, OXPHOS activity and survival are decreased when exposed to the parkinsonian-like compounds MPP^+ and rotenone [53]. mROS production in

the SNpc DA neurons is higher than in other neurons due to the dopamine oxidative metabolism, and takes place in the axon terminals, where the mitochondrial density is higher than in the ventral dopaminergic neurons [53, 54]. Iron content has been reported to be high in the SNpc DA neurons, which may be consequence of its enhanced release from ferritin caused by $O_2^{\bullet -}$, from haemoglobin and cytochrome c by peroxides, and/or from iron-sulfur proteins by peroxynitrite ($ONOO^-$). Thus, increased of metal ions such as Fe^{2+} enhance H_2O_2 conversion to $^{\bullet}OH$ *via* the Fenton reaction, which amplifies oxidative stress [55]. Interestingly, iron-mediated oxidative stress can promote α-synuclein aggregation by catalysing α-helix conversion into β-sheet, which forms the partially-folded intermediates that are susceptible to aggregation [55]. Antioxidants, such as reduced glutathione and peroxiredoxin 5, are weakly synthesized in the SNpc DA neurons [55–57]. SNpc DA neurons pacemaking is dependent on a particular L-type voltage-dependent Ca^{2+} channels that leads to large Ca^{2+} influx and subsequent ATP-dependent extrusion, thus increasing ATP requirements and oxidative stress [58–61]; in fact, antagonists of this L-type channel are neuroprotective [59, 62]. Finally, 1-acetyl-6, 7- dihydroxyl-1, 2, 3, 4-tetrahydroisoquinoline (ADTIQ), a neurotoxin found in the brain of PD patients, is synthesized from a dopamine-derived tetrahydroisoquinoline (TIQ) and methylglyoxal, a major side product of glucose metabolism. Thus, glycolytic up-regulation after mitochondrial dysfunction, along with increased TIQ synthesis in DA neurons, could enhance the synthesis of ADTIQ, thus contributing to DA neuron degeneration [63]. Altogether, these observations suggest that the particular metabolism and morphology of SNpc DA neurons render them more vulnerable to perturbations of mitochondrial functions in response to multiple factors, such as gene mutations, environmental toxins, and aging.

2. Mitochondrial dysfunction, mROS and energetic metabolism in PD

ROS are continuously produced in all tissues, and their production and detoxification are tightly balanced. Shifting this balance enables ROS to activate intracellular signalling and/or generate oxidative stress, eventually inducing cell death. Oxidative stress is one of the hallmarks of PD, being the major sources of ROS the DA neurons [64–66]. Dopamine is an unstable molecule able to produce reactive quinones and free radicals by tyrosinase and monoamine oxidase (MAO)-catalysed auto-oxidation [67, 68]. Intra-mitochondrial iron overloading causes oxidative stress, since ferric and ferrous ions (Fe^{3+}, Fe^{2+}) can react with superoxide anion ($O_2^{\bullet -}$) and hydrogen peroxide (H_2O_2) to generate hydroxyl radicals through the Fenton reaction; these ROS synergize with dopamine oxidation to trigger neurotoxicity [69, 70]. Hydroxyl radicals generation and decreased glutathione contributes to ROS toxicity and neurodegeneration associated with PD [71]. Maintaining Ca^{2+} homeostasis requires ATP-dependent pumps [72], which increase the energy demand and OXPHOS activity, consequently leading to higher ROS generation. As above-mentioned, SNpc DA neurons express L-type Ca^{2+} channels for Ca^{2+} influx, which causes basal mitochondrial oxidative stress likely responsible for cell death acceleration [72].

PD is associated with chronic neuroinflammation, a phenomenon controlled by the brain microglial cells. Microglial activation has thus been observed in both sporadic and familial PD patients [73]. Microglial activation in turn leads to increased cytokine formation, ROS production and decreased secretion of trophic factors, inducing neuronal death [66, 74, 75].

Toxins, such as MPTP and rotenone, as well as mutations of PD-associated proteins like α-synuclein, Parkin, Pink1, DJ-1 and LRRK2, have been reported to activate glial cells and release ROS, inducing astrocyte activation thus amplifying the pro-inflammatory response and increasing microglial phagocytosis [76–79]. As already indicated, mitochondrial dysfunction triggers ROS formation [80]. Complex I and, to a smaller extent, complex III of the ETC are considered to be the main sites of mROS production [21]. Complex I inhibition results in enhanced ROS production, and excess ROS inhibit complex I. Inhibition of complex I activity is well known to occur in the SNpc of PD patients [81–83]. Environmental factors, such as MPTP or rotenone, as well as the loss-of-function of PD-related proteins such as Parkin, Pink1 or DJ-1, are known factors that inhibit complex I directly or indirectly, thus disrupting ATP synthesis and increasing ROS [84–88]. Interestingly, the alternative electron carrier methylene blue (MB), which accepts electrons from NADH and transfers them to cytochrome *c* thus bypassing complexes I–III, is able to increase cellular oxygen consumption and to reduce glycolysis in cultured cells, attenuating the toxicity of complex I inhibition by rotenone [89].

When mROS is produced in excess and OXPHOS is impaired, it is often observed a compensative enhanced glycolytic activity, thus suggesting that mROS and glycolysis interact during cell energy homeostasis [90]. For instance, in skeletal muscle and cultured cells, H_2O_2 stimulates glucose uptake [91–94]. Interestingly, in L6 myoblast, glucose uptake inhibition leads to increased ROS [95] and suggests a possible antioxidant-like role for glucose. Out of the 14 glucose transporter (GLUT) isoforms described so far [96], GLUT1 is up-regulated by ROS [97]. In fact, GLUT1 transcriptional expression is governed by transcription factors including hypoxia-inducible factor-1 (HIF-1) [98]. HIF-1 is composed by two subunits, α and β, being its activity mainly regulated through the stabilization of its α-subunit. Under normoxic conditions, the α-subunit is degraded by the proteasome, which requires hydroxylation on the Pro residues present in the O_2-dependent degradation domain. During hypoxia, hydroxylation is inhibited hence HIF-1α is stabilized, enabling the formation of a complex with HIF1β that is translocated into the nucleus to promote the expression of several genes, including those encoding GLUT1 and enzymes of the glycolytic pathway [87, 99]. Interestingly, mROS also stabilize HIF1α [87]. In muscle, GLUT1 activity is increased by 5′-AMP-activated protein kinase (AMPK) [100], a protein kinase that is activated by LKB1-mediated phosphorylation during elevated AMP/ATP ratio or mROS [101–103]. Both HIF1 and AMPK activation leading to increased glucose uptake has been observed in PD models [87, 104]. GLUT1 activity can also be increased by translocation to the plasma membrane, which takes place through a ROS-mediated oxidation of key sulfhydryls in the Ataxia Telangiectasia Mutated (ATM) protein forming an active dimer [105, 106]. ATM is localized close to the mitochondria, suggesting that its dimerization is mediated by mROS [107].

Glucose metabolism can play a role in regulating the ROS production and scavenging balance. For instance, glucose oxidation through the pentose phosphate pathway (PPP) produces reducing equivalents in the form of NADPH, which is necessary to recycle antioxidant glutathione from its oxidised status [108]. This is especially important in neurons because they are more vulnerable to oxidative stress than other cell types. In neurons, the limiting glycolytic enzyme 6-phosphofructo-2-kinase/fructose-2,6-

bisphosphatase-3 (PFKFB3) is continuously degraded by the proteasome, and this is why they preferentially metabolize glucose via the PPP instead glycolysis, in contrast to what happens with other cells with more robust antioxidant system [109]. Thus, inhibiting glucose flux through the PPP increased levels of oxidative stress and neuronal death [109]. In addition, certain stimuli are able to stabilize PFKFB3, switching from PPP to glycolysis [110]. This leads to increased oxidative stress and apoptotic neuronal death that counteract with overexpression of glucose-6-phosphate dehydrogenase, the rate-limiting enzyme of the PPP. Both increased glycolysis and decreased PPP were shown to be abolished by siPFKFB3 indicating that both metabolic pathways are fully controlled by this protein [110]. Thus, proteasome dysfunction during the loss of Parkin or other PD-related proteins would likely stabilize PFKFB3 leading to a switch from PPP to glycolysis and oxidative stress. Interestingly, a down-regulation of PPP rate-limiting enzymes has been documented in post-mortem brain samples of PD patients [111], strongly supporting the hypothesis that PPP disruption may be an important factor in the pathogenesis of PD [111, 112] and aging [112].

3. Implications of mitochondrial quality control for metabolism in PD

Failure in the mitochondrial quality control mechanisms impairs the mitochondrial ability to generate energy by OXPHOS, which can invoke glycolysis as an attempt to maintain cellular ATP (Fig. 1). Mitochondrial quality control mechanisms require communication between mitochondria and other organelles, including the ER and lysosomes, as disruption of this process has been observed in PD and other neurodegenerative disorders such as Gaucher disease (GD) [113].

3.1 Mitochondria-lysosome crosstalk

Mitochondrial dysfunction in neurodegenerative diseases involves alterations in the mitochondrial quality control mechanisms [114–116]. Mitochondrial turnover mainly occurs by autophagy, a process requiring functional lysosomes. Lysosomes are critical for protein and organelles degradation [117], calcium signalling [118, 119], endocytic processes [120], and nutrient sensing [121]. During autophagy, lysosomes fuse with autophagosomes to promote degradation of engulfed organelles and proteins. The membrane origin of autophagosome remains unclear; some studies suggest that they are generated “de novo”, whereas other studies suggest that they arise from other organelles such as ER or mitochondria [122]. The process is initiated by activation of Vps34 and its interaction with Beclin-1. This is produced only if the anti-apoptotic protein Bcl2 is phosphorylated and dissociated from Beclin-1, indicating a link between autophagy and apoptosis [122]. After maturation, autophagosome fuses with the lysosome to form the autophagolysosome, in which organelles and/or misfolded proteins are degraded and recycled. Thus, failure in these processes may lead to the accumulation of aberrant mitochondria and misfolded proteins, which are hallmarks of PD. In addition, mutations in genes encoding lysosomal proteins cause lysosomal storage diseases (LSDs), which are accompanied by the accumulation of damaged mitochondria. Actually, failure in lysosomal function seems to be an event occurring earlier than mitochondrial damage [123]. Amongst other substrates, α-synuclein is aggregated [124]. Mutant α-synuclein tightly binds to the lysosomal membrane to inhibit the autophagy-lysosome pathway, resulting in degradation of wild type α-synuclein [116].

Besides PD, α-synuclein aggregates are also observed in GD, the most common of the LSDs caused by recessive mutations in glucocerebrosidase (GBA). Thus, GD and PD have similar hallmarks including loss of DA neurons of SNpc, α-synuclein accumulation, tremor, bradykinesia and rigidity. In addition, mitochondrial membrane potential ($\Delta\psi_m$) collapse and mitochondrial complex I-derived ROS-mediated ETC damage also occur [113, 122].

3.2 ER-mitochondria tethering

Mitochondria and ER are tightly interconnected, both physically and functionally. ER-mitochondria contact sites, known as mitochondria-associated membranes (MAMs) [125], facilitate Ca^{2+} and lipid transfer between these organelles, acting as platforms for signals regulating cell death and survival mechanisms [126–129]. Mitochondrial Ca^{2+} levels regulate ATP synthesis by activating tricarboxylic acid (TCA) dehydrogenases [130] and ATP synthase [131, 132]. However, mitochondrial Ca^{2+} also triggers apoptotic cell death [133, 134] through mechanisms that take place at the ER-mitochondria interface. Disruption of normal ER function leads to misfolded and unfolded protein accumulation in the ER, a process known as the unfolded protein response (UPR) that is an adaptive cellular response to ER stress aimed to restore ER homeostasis [135]. Interestingly, UPR includes changes in metabolism focused to provide metabolic support for the cellular adaptation. Thus, the increase in ER-mitochondrial contact sites leads to an increase in mitochondrial Ca^{2+} uptake, mitochondrial metabolism and ATP production [136]. On the contrary, disruption of ER-mitochondrial contacts, or blockage of Ca^{2+} transfer, increases cell death in response to ER stress [135, 136]. Thus, although ER-mitochondria contacts are beneficial in early stages of ER stress, these contacts lead to cell death if stress is maintained for long periods of time by Ca^{2+} overloading.

ER-mitochondrial contact sites are important for cell signalling. Thus, MAM are involved in insulin signalling [137], as several components of the insulin cascade, such as Akt and mTORC2, have been found at the MAM [137–139]. Inhibition of mitochondrial Ca^{2+} uptake, in skeletal muscle cells and cardiomyocytes, reduces insulin-dependent Akt phosphorylation, GLUT4 membrane translocation, and glucose uptake [140, 141]. Obesity in mice is accompanied by an increase in MAM and Ca^{2+} overloading, suggesting a pathophysiological role of MAM in insulin resistance and T2DM [142]. MAM disruption may also be involved in neurodegeneration, particularly in PD, since Parkin, Pink1, DJ-1 and α-synuclein are present in the ER-mitochondrial contact sites to support Ca^{2+} transfer. For instance, α-synuclein mutations decrease the number of ER-mitochondria contact sites, causing ER stress and mitochondrial fragmentation [37]. Thus, ER-mitochondria tethering is disrupted in both T2DM and PD, further suggesting a link between these disorders.

4. Metabolic disturbances in sporadic models of PD

As above mentioned, mitochondrial complex I damage has been shown in post-mortem brains, skeletal muscle, platelets and lymphocytes of PD patients [81, 143–147]. Inhibitors of complex I activity, such as methyl-4-phenylpyridinium (MPP^+) and rotenone induce mitochondrial dysfunction in dopaminergic cells [148]. Likewise, 6-hydroxydopamine (6-OHDA) is used as a dopamine analogue to induce ROS-associated degeneration of SNpc DA

neurons [149]. Since MPP^+, rotenone and 6-OHDA are widely used to model the dopaminergic neuronal death of PD, both in cultured cells and in experimental animals, we revisit the metabolic disturbances found in several chemical models of PD.

4.1 MPP^+

MPP^+, the bioactive metabolite of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), causes a clinical picture similar to PD syndrome in humans and non-human primates, being widely used to investigate therapeutic strategies [150, 151]. Thus, MPTP is metabolized in the brain in astrocytes, by monoamine oxidase-B, to MPP^+, which is released to the extracellular space and taken up by dopaminergic neurons through the dopamine transporter (DAT) [152]. MPP^+ is accumulated in mitochondria where it inhibits complex I [151, 153, 154]. Consequently, OXPHOS is blocked and neurons become dependent on glycolysis for ATP production. Thus, by increasing the rate of glycolysis, neurons could compensate for the mitochondrial deficiency in ATP synthesis and hence to meet the cell energy demands [155, 156]. In fact, it has been found that maintaining cell ATP concentrations *via* glycolysis attenuates MPP^+-induced toxicity [157]. On the contrary, a glucose-deficient environment exacerbates MPP^+-induced toxicity [158]. Studies in neuroblastoma cells and in rat brain indicate that glucose prevent MPP^+ toxicity by attenuating ATP depletion without recovering mitochondrial respiration, hence indicating increased glycolysis [159, 160]. Interestingly, at MPP^+ concentrations below 1 mM, its toxicity depends of glucose depletion; however, at MPP^+ concentrations between 1 and 10 mM, cells undergo a metabolic collapse with a switch from OXPHOS to glycolysis that leads to cell death [159]. Thus, the mechanism of MPP^+ toxicity is biphasic, namely (i) the DAT-mediated mechanism selective for dopaminergic neurons (at low concentrations) and (ii) the oxidative mechanism that occur a higher concentrations [160]. In SH-SY5Y and differentiated human neural progenitor ReNcell VM cells, microRNA-7 increases the neuronal expression of GLUT3 through targeted repression of RelA, which promotes glycolysis as evidenced by increased glucose consumption and lactate release, increased ATP and prevention against low dose MPP^+-induced cell death [161].

4.2 Rotenone

Rotenone, initially used as an insecticide and fish poison, increased PD incidence in farming communities exposed to this compound [162]. Rotenone crosses the blood brain barrier and plasma membranes due to its hydrophobicity. DA neurons are particularly susceptible to rotenone-induced degeneration [163]. *In vitro* and *in vivo* exposure to rotenone induces both soluble and insoluble α-synuclein aggregates, increased caspase activation and apoptosis [164–166]. Inhibition of complex I and cellular respiration by rotenone results in the compensatory induction of glycolysis, loss of bioenergetics reserve capacity, activation of apoptotic pathways, and cell death [167]. Rotenone decreases maximal respiration and reserve capacity at doses that MPP^+ increases this reserve capacity, indicating that both compounds act a different level of the ETC; while rotenone inhibits complex I, MPP^+ inhibits both complex I and ATP synthase or related [167]. However, rotenone shows a mechanism of action other than solely ETC disruption leading to ROS production [168], since it induces glyceraldehyde-3-phosphate dehydrogenase (GAPDH) expression and nuclear and mitochondrial translocation. Accumulated GAPDH promotes intermolecular

disulphide bonding resulting in the formation of intracytoplasmic aggregates of GAPDH, which may contribute to the formation of inclusion bodies, such as Lewy bodies, and neuronal apoptotic death [169].

4.3 6-Hydroxydopamine (6-OHDA)

6-OHDA, the hydroxylated analogue of dopamine, has been found in human brain and urine from PD patients treated with L-dopa [170, 171]. 6-OHDA reversibly inhibits the activities of complexes I and IV in rat brain mitochondria [172], although it also induces degeneration of SNpc neurons by oxidative damage *via* auto-oxidation, which forms reactive quinones that generate hydrogen peroxide and superoxide [173]. 6-OHDA reacts with Fe^{3+} causing its release and subsequent cellular damage [174]. This is particularly relevant for PD pathogenesis since SNpc DA neurons contain higher iron levels associated to neuromelanin [175, 176]. Differentiated SH-SY5Y treated with 6-OHDA do not show, however, OXPHOS inhibition, thus 6-OHDA likely impacts on mitochondrial redox signalling rather than on bioenergetics [167]. However, the oxidative stress produced by 6-OHDA indirectly causes mitochondrial dysfunction, which leads to glycolysis up-regulation [177].

4.4 Paraquat

The herbicide paraquat (1,1′-dimethyl-4,4′-bipyridinium dichloride) is structurally similar to MPTP, and it has been associated with PD [162, 178]. Paraquat causes selective and-dose dependent loss of SNpc DA neurons [179, 180]. It is unlikely that paraquat inhibits complex I, but it produce ROS [181] both *in vitro* and *in vivo* by multiple mechanisms, including redox cycling [182, 183] and nitric oxide synthase activity [184]. Thus, the mechanism whereby paraquat exerts neurotoxicity is different from those used by MPP^+, rotenone or 6-OHDA [177]. Using a combined metabolomics approach by nuclear magnetic resonance (NMR) and direct-infusion electrospray ionization mass spectrometry (DI-ESI-MS), it has been revealed that human dopaminergic neuroblastoma cells exposed to paraquat presented deeper alteration in PPP metabolome. Thus, metabolites of PPP such as glucose-6-phosphate, fructose-6-phosphate, glucono-1,5-lactone, and erythrose-4-phosphate have been found increased after paraquat treatment, an effect that was accompanied by inhibition of glycolysis and TCA cycle activity. In addition, increased expression of glucose-6-phosphate dehydrogenase (G6PD), which supplies NADPH, was observed with paraquat. These findings have led to the proposal that increased PPP, by enhancing NADPH levels, would be necessary for paraquat redox cycling causing oxidative stress [177].

5. Metabolic disturbances in genetic models of PD

During the last two decades, several genetic mutations have been found to be associated with familial forms of PD with similar clinical and pathological features of those in idiopathic PD [185–187]. The study of the proteins encoded by these genes has revealed the close link with mitochondrial function and metabolism, thus providing important insight about the molecular pathways and mechanism that may underlie neurodegeneration in PD.

5.1 α-synuclein

Mutations such as A530T, A30P and E46K, as well as duplication or triplication of the α-synuclein gene (PARK1, SNCA) have been associated with autosomal dominant PD [188–191]. α-synuclein is a hydrophobic protein prone form the typical fibrillar aggregations observed in Lewy bodies, which links this protein with both sporadic and familial forms of PD [42]. α-synuclein aggregation inhibits mitochondrial complex I activity, elevates ROS production [192] and increases protein-carbonyl levels [193]. *In vitro*, the interaction of α-synuclein with mitochondria leads to cytochrome *c* release, enhances mitochondrial Ca^{2+}, and triggers oxidative modifications of mitochondrial components [194]. These findings suggest an interrelation between protein aggregation and mitochondrial dysfunction, granting to α-synuclein a role as a modulator of oxidative stress. α-synuclein increases with ageing along with a loss of tyrosine hydroxylase-positive neurons [195, 196]. The accumulation of unfolded/misfolded α-synuclein leads to ER stress, which activates UPR [197] and correlates with markers of the UPR pathways protein kinase RNA-like ER kinase (PERK) and activating transcription factor-6 (ATF6), as well as its downstream pro-apoptotic CCAAT/-enhancer-binding protein homologous protein (CHOP) [197]. Overexpression of the ER chaperone, glucose regulated protein 78 (GRP78/BiP), decreases α-synuclein toxicity by down-regulating ER stress mediators [197]. Such an ER stress response reprograming prevents DA neurons death, reinforcing the key role of ER in PD neurodegeneration. In addition, α-synuclein is also present in MAM [37], hence connecting ER and mitochondria to regulate Ca^{2+} homeostasis and cholesterol metabolism [125, 127, 198]. Mutated α-synuclein reduces its association with MAM concomitantly with a decrease in ER-mitochondria juxtaposition and increased mitochondrial fragmentation. Overexpression of the mitochondrial fusion protein MFN2 or inhibition of the mitochondrial fission protein Drp1 do not revert such phenotype, indicating that α-synuclein acts downstream of the mitochondrial fusion/fission machinery [37].

Besides the above-mentioned functions linked to mitochondrial dysfunction, α-synuclein directly alters carbohydrate and lipid metabolism. Using a mouse model of PD that express the mutant form of human α-synuclein A53T, it has been observed that a high caloric diet induces a metabolic phenotype similar to that of the PD patients; this consists of a reduction of total and visceral body fat, hypoleptinemia, and increased energy expenditure without insulin resistance [199]. α-synuclein, which is present in pancreatic β-cells, down-regulates insulin secretion by interacting with K_{ATP} channels; however, if over-expressed, or expression of the mutant α-synuclein, results in excessive inhibition of insulin secretion contributing to diabetes, generating cellular stress and apoptosis resembling PD [200]. In contrast, α-synuclein ablation exacerbates insulin resistance in mouse adipose tissue and skeletal muscle, as well as in patients with low α-synuclein blood levels and increased insulin resistance [201]. In the adipose tissue and skeletal muscle of α-synuclein knockout mice, it has also been observed an increase in GLUT4-driven glucose uptake through an insulin-independent mechanism [202].

5.2 Parkin

Mutations in Parkin (PARK2) gene produce autosomal-recessive juvenile PD [203, 204]. As an E3 ubiquitin ligase involved in the proteasomal degradation of several substrates, loss of

Parkin causes accumulation of potentially toxic protein aggregates eventually involved in PD pathogenesis [205]. Parkin is confined to mitochondria, where it binds transcription factors such as the mitochondrial transcription factor TFAM [206]. Parkin prevents cytochrome *c* release [207] and α-synuclein aggregation, thus protecting mitochondria and attenuating DA neuronal loss [208]. In contrast, loss of Parkin impairs complex I and IV activities both in humans and mice, leading to mitochondrial respiration impairment and oxidative stress [86, 209]. Parkin loss also increases toxins sensitivity [210, 211] and disturbs mitochondrial dynamics and autophagy [29, 212]. Thus, Parkin participates in mitochondrial fission and fusion processes, mitochondrial transport, and removal of damaged mitochondria through mitophagy *via* a mechanism dependent on Drp1 [29, 213–215]. The triggering mechanism of Parkin-dependent mitophagy is the loss of mitochondrial membrane potential ($\Delta\psi_m$), which activates its recruitment to the mitochondria through PINK1 (see section below).

Parkin mRNA and protein levels increase during ER stress *via* the UPR pathway transcription factor ATF4, which binds the CREB/ATF elements in the Parkin promoter to increase its expression, thus preventing ER stress-induced mitochondrial damage and cell death [216]. In HeLa and neuroblastoma cells, Parkin favours ER-mitochondria contacts and the transfer of Ca^{2+} from ER to mitochondria, thus activating ATP synthesis [217]. Parkin has also a role in fat uptake [218]. Parkin knockout mice display lower weight gain preceding the mitochondrial and neurological abnormalities, which is more evident under a high-fat diet [86, 218]. Thus, a high fat diet to wild type mice induces Parkin levels in several tissues favouring fat uptake *via* mono-ubiquitylation, leading to stabilization, of the CD36 fatty acid translocase [218]. These results suggest that diet would be an interesting factor to consider for delaying the onset, or reduce the risk, of PD.

Parkin is a target of p53 and a potential tumour suppressor [219]. Thus, p53 induces *Parkin* gene transcription, in humans and mice, to mediate the p53 effects on glucose metabolism and antioxidant defence. Accordingly, loss of Parkin increases glucose uptake, glycolysis and lactate production, and reduces mitochondrial respiration. In addition, Parkin loss down-regulates the expression of several mitochondrial proteins, such as pyruvate dehydrogenase (PDHA1), which catalyses pyruvate conversion to acetyl-CoA in the mitochondria. This triggers a Warburg effect that can be restored by over-expressing Parkin [219]. Such a Warburg effect has also been linked with other functions of Parkin, such as mitophagy [220], mitochondrial dynamics [221] and genome integrity [222]. It should be mentioned that the regulation between Parkin and p53 differs depending on the cell line or tissue [219]. Nevertheless, it seems well established that loss of Parkin induces a Warburg effect contributing to the development of tumours by facilitating cell proliferation [223–225].

5.3 PINK1

PINK1 (PTEN-induced putative kinase; PARK6) mutations are, after Parkin, the second most common cause of early onset autosome recessive PD [226]. PINK1 is a serine/threonine kinase that is stabilized upon $\Delta\psi_m$ collapse into the mitochondria [227], where it recruits Parkin from the cytosol [10, 29]. PINK1 knockdown in human dopaminergic neurons and mouse primary neurons causes morphological changes in mitochondria, decreased $\Delta\psi_m$, high ROS production and apoptosis [228, 229]. Whilst loss of PINK1 in

mice decreases complex I and IV activities and impairs mitochondrial respiration, it can also exacerbate mitochondrial respiration when exposed to H_2O_2 or mild heat shock [230]. PINK1 prevents cytochrome *c* release from mitochondria and apoptotic neuronal death [231, 232], and protects against MPTP-mediated oxidative stress [233].

PINK1 controls mitochondrial dynamics, hence being essential in energy metabolism maintenance, mitochondrial quality control, and cell viability [234, 235]. PINK1 promotes mitochondrial fission by inducing Drp1, and inhibits mitochondrial fusion by down-regulating mitofusins (MFN1 and MFN2) [214, 221, 236]. Parkin recruitment by PINK1 participates in the mitochondrial quality control process by triggering mitophagy [29, 212, 220]. A subpopulation of mitochondrial-derived vesicles (MDVs) requires Parkin and PINK1 to be formed. MDVs mediate the transport of mitochondria to lysosomes for the degradation of oxidized cargo proteins, thus regulate mitochondrial quality control under mild stress; however, failure of this protective system causes irreversible mitochondrial damage leading to mitophagy [237].

As most PD-related proteins, Parkin and PINK1 are present in MAM. PINK1 is involved in the regulation of ER-mitochondria Ca^{2+} transfer by increasing ER-mitochondrial contact sites [238]. As above-mentioned, Ca^{2+} transfer is essential for mitochondrial respiration and normal cell bioenergetics. In PINK1 deficient cells, Ca^{2+} homeostasis is a controversial matter. In neurons, PINK1 regulates Ca^{2+} efflux from mitochondria through Na^+/Ca^{2+} exchanger, and PINK1 loss results in Ca^{2+} overload, inhibition of glucose transporter, and respiration impairment [239]. However, other studies report impaired respiration and increased glycolytic activity in myocytes and neurons from PINK1 knockout mice [239]. Glucose uptake is impaired in PINK1-deficient pancreatic β-cells, which produce an increase in intracellular Ca^{2+} and insulin secretion under low glucose conditions resulting in glucose tolerance *in vivo* [240]. Myocytes, which have higher ATP producing capacity and $\Delta\psi_m$, can buffer cytosolic Ca^{2+} rendering these cells resistant to Ca^{2+} stress [241]. Knockout and knockdown mouse neuroblastoma and embryonic fibroblasts (MEFs) for PINK1 showed reduced mitochondrial Ca^{2+} uptake and impaired mitochondrial ATP synthesis, leading to Ca^{2+} efflux [28]. In other studies performed in MEFs and primary cultured neurons from PINK1 knockout mice, mitochondrial deficiency leads to increased glycolysis with lactate release, along with increased glucose uptake leading to a Warburg-like effect through HIF1α stabilization [87, 242].

PINK1 was identified originally because of its tumour suppressor action [243]. However, whether loss of PINK1 represses or enhances cell proliferation is yet controversial. Thus, PINK1 is induced by the tumour suppressors PTEN and FOXO3a, and it is associated with Beclin-1, which is a tumour suppressor [243–245]. In addition, PINK1 acts upstream of Parkin, which is a tumour suppressor through interaction with p53 [219]. Furthermore, *PINK1* gene is located in a region of chromosome 1p36 that contains tumour-suppressive activity [246]. In contrast, PINK1 is necessary for optimal activation of the oncogenic pathway IGF1/Akt, which indicates pro-oncogenic functions [247]. As indicated above, PINK1 is essential for mitochondrial dynamics, Ca^{2+} homeostasis and mitophagy, which are processes related to the cell cycle regulation [248–252]. MEFs isolated from PINK1 knockout mice show altered cell cycle, with cells multinucleated arrested in G2/M phase and

a decreased number of cells in G0/G1 [253]. This leads to a reduction in cell proliferation and an increase in mitochondrial fission according to the high levels of Drp1 observed [253]. However, in another study using identical PINK1 knockout cells, the opposite result was found, i.e., the proportion of cells in G2/M phase increased and the proportion of cells in the G0/G1 phase decreased, leading to enhanced cell proliferation rate concomitant with a higher glycolytic rate [87]. In this study, the rate of glycolysis was found to be essential for cell proliferation, since the inhibitor 2-deoxyglucose abrogated it. Moreover, the increase in the glycolytic rate was mediated by HIF1α, as silencing of this transcription factor reverted both the increase in glycolysis and in cell proliferation [87]. Interestingly, in this study PINK1 knockout mice primary neurons were also used, in which it was observed a shift from PPP to glycolysis that led to apoptosis [87]. Thus, PINK1 loss of function may have dual consequences, cell proliferation or apoptosis, depending on the cell type and the environmental factors. Thus, whilst the cell cycle effects of PINK1 deficiency may be responsible for cancer, it may also be involved in neurodegeneration, since the abortive cell cycle re-entry is mechanistically linked to the death of post-mitotic neurons [254–257].

5.4 DJ-1

Mutations in *DJ-1* (*PARK7*) gene causes autosomal recessive early onset parkinsonism [258]. DJ-1 is a multifunctional protein that under basal conditions is mainly localized in the cytosol. However, upon oxidative stress, DJ-1 translocates to the mitochondria and later to the nucleus to exert its neuroprotective function [259–261]. Nuclear translocation of DJ-1 occurs by oxidation of the Cys^{106} that acts as a redox sensor [259, 262]. Neurons and MEF defective in DJ-1 show decreased complex I activity and mitochondrial respiration [88, 263], along with increased oxidative stress accompanied by enhanced glycolysis [33]. MEF knockout for DJ1 show decreased $\Delta\psi_m$ and increased mitochondrial permeability transition pore [264]. In neurons, DJ-1 knockdown causes ER stress, inhibition of the proteasome, and increased cell death [265, 266]. Cell models from human and mouse knockouts for DJ-1 show altered mitochondrial morphology and accumulation of defective mitochondria [267]. In addition, DJ-1-deficient mice show SNpc DA neuronal loss, elevated DA levels and enhanced DA re-uptake [268]. In these cells, DJ-1 loss sensitizes them against toxins such as MPTP and paraquat, while its overexpression protects them [269, 270]. All these effects can be reversed either by over-expressing DJ-1 or by antioxidant treatment, suggesting a key role for DJ-1 in antioxidant signalling. On the other hand, DJ-1 fosters the communication between RE and mitochondria [238], hence reducing DJ-1 levels causes mitochondrial fragmentation and decreased mitochondrial Ca^{2+} uptake. In HeLa cells, overexpression of p53 impairs the transfer of Ca^{2+} from ER to mitochondria increasing mitochondrial fragmentation; this was reversed by DJ-1 overexpression rescuing the ER-mitochondria contact sites, but not by Drp1 inhibition, indicating that mitochondrial fragmentation was independent of Drp1 activation [38]. Thus, besides its antioxidant role, DJ-1 participates in the maintenance of mitochondria integrity by improving ER-mitochondria communication.

DJ-1 is involved in glucose homeostasis. Thus, DJ-1 expression can be regulated under hyperglycemic conditions *in vitro* and *in vivo* [271, 272]. DJ-1 expression is increased under non-diabetic conditions in human and mouse islets during aging to prevent oxidative stress and to maintain the mitochondrial integrity that is necessary for glucose-stimulated insulin

secretion. Interestingly, decreased DJ-1 expression is observed in PD patients and in patients suffering from T2DM, indicating the interrelation between these diseases [41]. In addition, DJ-1 has been shown to transcriptionally co-activate PINK1 expression by binding to FOXOa3; accordingly, DJ-1 loss causes decreased complex I activity and increased glycolysis *via* regulating PINK1 [33]. Similar effects on glucose metabolism take place in DJ-1 knockout mouse skeletal muscle, where a higher energy expenditure, AMPK activation, and uncoupled mitochondrial respiration has been observed leading to a Warburg-like metabolic reprogramming [273]. In good agreement with the view that the Warburg effect may favour cell proliferation, loss of DJ-1 increases cell proliferation *via* regulating PINK1 [33].

5.5 LRRK2

Mutations in the leucine-rich repeat kinase 2 gene (LRRK2) are the most common genetic cause of PD and cause both autosomal dominant and sporadic PD [274, 275]. Several LRRK2 mutations showing gain-of-function cause apoptotic neuronal death that can be attenuated by inhibition of mitochondrial-dependent caspases, suggesting mitochondrial dysfunction in LRRK2-mediated pathogenesis [276]. In cortical neurons, LRRK2 mutations increase ROS and impair mitochondrial morphology and dynamics [277]. LRRK2 interacts with Dynamin like protein 1 (DLP1) in neurons, and expression of LRRK2 leads to translocation of DLP1 from the cytosol to the mitochondria, suggesting a functional role of LRRK2 in mitochondrial dynamics [277]. Mitochondrial elongation and interconnectivity are also altered in patients with LRRK2 G2019S mutation, indicating that LRRK2 is related to mitochondrial morphology maintenance. Skin biopsies obtained from this LRRK2 mutant PD patients also showed $\Delta\psi_m$ collapse and ATP depletion [278]. These findings, together with the fact that LRRK2 is located in mitochondria [279, 280], suggest that mutant LRRK2 toxicity is linked to mitochondrial damage. Interestingly, the G2019S LRRK2 knock-in mouse shows transcriptional down-regulation of OXPHOS genes and up-regulation of glycolytic genes; furthermore, this mutant mouse down-regulates ubiquitylation and trafficking of proteins, suggesting that the accumulation of aberrant proteins and ER failure may underlie the OXPHOS-glycolysis shift [281].

5.6 Other relevant genetic mutations

Genome-wide association (GWAs) studies have revealed the occurrence of novel PD relevant loci [282]. For instance, ATP13A2 encodes a lysosomal transmembrane protein that belongs to the 5P-type ATPase subfamily [283], the mutations of which are associated with PD. ATP32A2 inhibition impairs the lysosomal ability to degrade certain proteins, including α-synuclein, by the autophagosome [284, 285]. Furthermore, mutant ATP13A2 causes $\Delta\psi_m$ collapse, ATP depletion, reduced mitophagy, and increased ROS, which can contribute to neurodegeneration [286–288]. Similar biochemical signs have been found with the mutant PLAG6, another PD-related protein with calcium-independent phospholipase A_2 activity [289]. Finally, GIGYF2 loss of function causes neurodegeneration linked to insulin signalling impairment [290].

6. Conclusions and perspectives

PD is a complex pathology with both genetic and environmental components. Regardless its specific cause, mitochondrial redox and energetic failure are essential pathogenic mechanisms in which an intact mitochondrial communication with ER and lysosomes are important. Failure in this communication increases misfolded proteins and impairs Ca^{2+} transfer, which accelerates dopaminergic cell death by defective mitochondria accumulation. Increased ROS, a key hallmark of this disorder, is linked to a metabolic OXPHOS-glycolysis shift aimed to maintain ATP, minimize mROS production and prevent apoptotic death. Mutant genes, such as α-synuclein, Parkin, PINK1 or DJ-1, cause excess mROS that are relevant for the SNpc DA neurons, which show a particularly high oxidative metabolism. Importantly, prolonged oxidative stress can trigger irreversible damage to mitochondria leading to a bioenergetics failure that cannot be compensated by increased glycolysis (Fig. 1). Since under normal conditions glucose utilization *via* the PPP is an essential antioxidant mechanism for neurons, an increased glycolysis aggravates neuronal oxidative stress in PD. In addition, the OXPHOS-glycolytic shift facilitates cell proliferation, which may explain the link between PD and some tumour development, but also neurodegeneration due to a possible aberrant cell cycle re-entry of post-mitotic neurons. Finally, besides the nervous system, other tissues affected in PD, such as the liver and pancreas, show important metabolic alterations including those related with insulin secretion and impaired glucose uptake, which may link diet habits with T2DM in PD. Thus, loss of the mitochondrial control of bioenergetics appears to be behind the causes of this metabolic syndrome-like picture in PD. This may provide clues when designing novel future therapeutic strategies against PD.

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Abbreviations

6-OHDA	6-hydroxydopamine
ADTIQ	1-acetyl-6, 7- dihydroxyl-1, 2, 3, 4-tetrahydroisoquinoline
AMPK	5′-AMP-activated protein kinase
ATF	activating transcription factor 6
ATM	ataxia telangiectasia mutated
CHOP	CCAAT/-enhancer-binding protein homologous protein
DA	dopamine
DAT	dopamine transporter
DI-ESI-MS	direct-infusion electrospray ionization mass spectrometry

PFKFB3	6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3
G6PD	glucose-6-phosphate dehydrogenase
GAPDH	glyceraldehyde-3-phosphate dehydrogenase
GBA	glucocerebrosidase
GD	Gaucher disease
GLUT	glucose transporter
GRP78/BiP	glucose regulated protein 78
HIF-1	hypoxia inducible factor 1
LSDs	lysosomal storage diseases
MAMs	mitochondrial-associated membranes
MB	methylene blue
MDVs	mitochondrial-derived vesicles
MPP^+	methyl-4-phenylpyridinium
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
Paraquat	1,1′-dimethyl-4,4′-bipyridinium dichloride
PD	Parkinson’s disease
PDHA	pyruvate dehydrogenase
PERK	protein kinase RNA-like ER kinase
PINK1	PTEN-induced putative kinase 1
PPP	pentose phosphate pathway
SN	substantia nigra
SNCA	α-synuclein gene
T2DM	type 2 diabetes mellitus
TIQ	tetrahydroisoquinoline
UPR	unfolded protein response

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Highlights

- Neuronal management of energetic status in Parkinson's Disease (PD) is reviewed
- Mitochondria, endoplasmic reticulum and lysosomes involvement in PD are discussed
- Mitochondrial dysfunction leads to neuronal metabolic re-programming in PD
- Increased neuronal glycolysis shifts down pentose-phosphate pathway (PPP) in PD
- Down-regulation of PPP in neurons may account for PD-associated oxidative stress

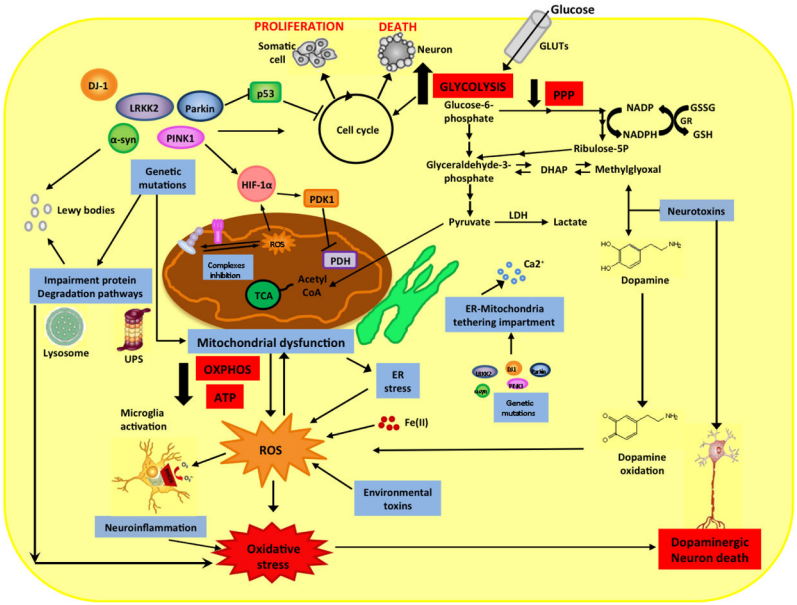

Figure 1. Cellular pathways associated with bioenergetics in PD

Genetic mutations in PD-related genes and/or exposure to environmental toxins lead to an increased oxidative stress and mitochondrial failure that affect several metabolic pathways. Dysfunctional mitochondria induce the aggregation of proteins, such as α-synuclein, due to impairment in the ubiquitin/proteasome and autophagy/lysosome pathways. This also leads to alterations in the cross-talk between mitochondria and ER, contributing to increased mROS. Additional factors, such as dopamine metabolism or glial activation may also contribute to increased ROS. Excessive ROS interfere with ATP synthesis and contribute to the stabilization of proteins, such as HIF-1, which mediates glycolytic up-regulation in order to compensate for the mitochondrial energy impairment. However, increased glycolysis may have adverse effects in neurons. Thus, glycolysis facilitates a failed attempt of post-mitotic cells to re-enter the cell cycle, a feature that may be important in genetic PD-related mutations affecting p53. Also, certain glycolytic intermediates may interact with dopamine derivatives generating neurotoxins. Finally, increased glycolysis impairs antioxidant PPP. Thus, the compensative increase in glycolysis contributes to the cascade of events leading to selective degeneration of dopaminergic neurons.

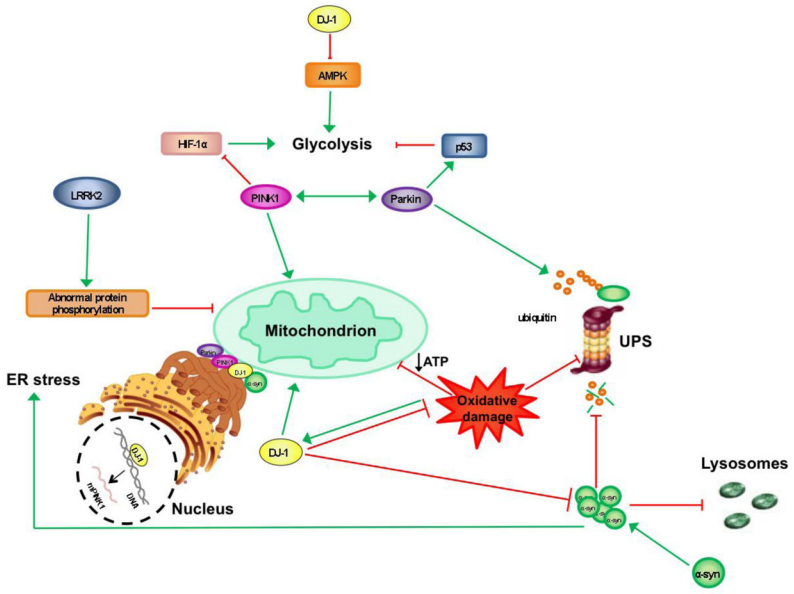

Figure 2. Metabolic shift in familial parkinsonism

Mutations in familial PD-linked genes encoding α-synuclein, parkin, DJ-1, PINK1 and LRRK2 are associated with PD pathogenesis. These mutations contribute to PD causing mitochondrial dysfunction, oxidative damage and abnormal protein aggregation and phosphorylation, compromising neuronal function and survival. α-Synuclein undergoes aggregation as a consequence of its mutation or indirectly by mutation of other PD-related genes, endangering protein degradation pathways and inducing ER stress and mitochondrial dysfunction. Mitochondrial dysfunction and oxidative damage lead to deficits in ATP, which activates glycolysis. This glycolytic increase can also be consequence of genetic mutations in Parkin, PINK1 and DJ-1, which act on specific glycolytic regulatory proteins. In addition, Parkin, being an E3 ubiquitin ligase, promotes proteasomal degradation, participates in mitochondrial fusion and fission processes, and reverses PINK1-induced mitochondrial dysfunction. DJ-1 protects mitochondria against oxidative stress, it functions as a transcriptional co-activator of PINK1, amongst others, and blocks α-synuclein aggregation. PINK1 protects against mitochondrial dysfunction, preventing mitochondrial ROS production and recruiting Parkin into mitochondria, thus controlling mitochondrial dynamics. LRRK2 seems to play a role in synaptic vesicles formation. LRRK2 causes abnormal protein phosphorylation, which induces mitochondrial-dependent cell death. Furthermore, familial PD-linked genes such as Parkin, PINK1, DJ-1 and α-synuclein favour ER-mitochondria crosstalk through maintenance of contact sites, thus promoting cell survivalGreen arrows indicate activating effects, and red lines with blunt ends inhibitory effects).