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Mitochondrial dysfunction in neurodegenerative diseases: A focus on iPSC-derived neuronal models

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ABSTRACT

Progressive neuronal loss is a hallmark of many neurodegenerative diseases, including Alzheimer's and Parkinson's disease. These pathologies exhibit clear signs of inflammation, mitochondrial dysfunction, calcium deregulation, and accumulation of aggregated or misfolded proteins. Over the last decades, a tremendous research effort has contributed to define some of the pathological mechanisms underlying neurodegenerative processes in these complex brain neurodegenerative disorders. To better understand molecular mechanisms responsible for neurodegenerative processes and find potential interventions and pharmacological treatments, it is important to have robust in vitro and pre-clinical animal models that can recapitulate both the early biological events undermining the maintenance of the nervous system and early pathological events. In this regard, it would be informative to determine how different inherited pathogenic mutations can compromise mitochondrial function, calcium signaling, and neuronal survival. Since post-mortem analyses cannot provide relevant information about the disease progression, it is crucial to develop model systems that enable the investigation of early molecular changes, which may be relevant as targets for novel therapeutic options. Thus, the use of human induced pluripotent stem cells (iPSCs) represents an exceptional complementary tool for the investigation of degenerative processes. In this review, we will focus on two neurodegenerative diseases, Alzheimer's and Parkinson's disease. We will provide examples of iPSC-derived neuronal models and how they have been used to study calcium and mitochondrial alterations during neurodegeneration.

1. Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder associated with aging. It is estimated that 10 % of the population aged 65 and older has AD-related dementia [1]. The second age-associated neurodegenerative disorder is Parkinson's disease (PD), considered the most prevalent movement disorder [2]. PD occurs in 2–3 % of the population aged 65 and older. Although extensive

Abbreviations: AA, Ascorbic Acid; AD, Alzheimer's disease; ADDLs, Oligomeric amyloid-β-derived diffusible ligands; AKT, Protein kinase B; AMBRA1, BECN1-regulated autophagy protein 1; APOE, Apolipoprotein E; APP, Amyloid protein precursor; Aβ, Amyloid β; BDNF, Brain-derived neurotrophic factor; CACNA1A, calcium voltage-gated channel subunit alpha1 A; CaMKIV, Ca^{2+}/calmodulin-dependent protein kinase IV; Drp1, Dynamin-1-like protein; ER, Endoplasmic reticulum; FGF2, Fibroblast growth factor; FUNDC1, FUN14 domain-containing protein 1; GBA, β-Glucocerebrosidase; GDNF, glial cell-derived neurotrophic factor; GSK3β, Glycogen synthase kinase 3β; hNs, Human neurons; hTFAM, Human mitochondrial transcriptional factor A; InsP3R, Inositol 1,4,5-Trisphosphate receptor; iPSC, induced pluripotent stem cells; KGDHC, Alpha-ketoglutarate dehydrogenase complex; KIF5C, Kinesin Family Member 5C; LAMP1, Lysosomal Associated Membrane Protein 1; LC3, Microtubule Associated Protein 1 Light Chain 3 Alpha; LRRK2, Leucine-rich repeat kinase 2; MCU, Mitochondrial Ca^{2+} uniporter; MEF2, myocyte enhancer factor 2; MIRO1, Ras Homolog Family Member T1; Mnf1, Mitofusin 1; Mnf2, Mitofusin 2; mPTP, Mitochondrial permeability transition pore; mROS, mitochondrial reactive oxygen species; mtDNA, mitochondrial DNA; MUL1, Mitochondrial ubiquitin ligase activator of NFKB-1; NAD, Nicotinamide adenine dinucleotide; NFTs, Neurofibrillary tangles; Ngn2, Doxycycline-inducible Neurogenin2; NHEJ, Non-homologous end joining; NMDAR, N-Methyl-D-aspartate receptor; OM, Outer mitochondrial; Opa1, Optic atrophy 1; PD, Parkinson's disease; PI3K, Phosphoinositide 3-kinase; PINK1, PTEN Induced Kinase 1; PSEN1, Presenilin-1; PSEN2, Presenilin-2; SATB2, SATB Homeobox 2; SN, Substantia nigra; TBR1, T-Box Brain Transcription Factor 1; TFEB, Transcription Factor EB; Tomm40, Translocase of outer mitochondrial membrane 40; VDAC1, Voltage-dependent anion channel 1; VPA, Valproic acid.

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investigations aiming to stop or prevent these neurodegenerative diseases have been performed in the last three decades, there is no disease-modifying treatment for AD, while a handful of medications (e.g., levadopa) can ameliorate some of the PD symptoms.

The access to post-mortem human brain samples is limited. Moreover, the quality of the material is influenced by the donor's condition pre-mortem, postmortem interval, collection time, and maintenance strategy [3], enabling limited manipulation. A viable alternative that seeks to better recapitulate the human pathophysiology is the use of human induced pluripotent stem cells (iPSCs) [4]. Since their development, iPSCs are a versatile tool to model human neurons and/or the ability of human neurons to generate functional neuronal networks [5,6]. Over the last decade, patient-derived iPSCs models were generated and validated, especially for their ability to progressively express those pathological markers, such as aggregation of Amyloid β (Aβ), tau hyperphosphorylation and alpha-synuclein (α-synuclein) spreading/phosphorylation/misfolding, that are commonly observed in tissues from AD and/or PD patients [4,7].

Neurodegenerative diseases are characterized by progressive cell death in specific brain areas involved in learning and memory processes (AD) or movement regulation (PD). Cell death mechanisms involve a plethora of cell signaling processes, including altered neuronal activity, protein aggregation, calcium signaling, mitochondrial dysfunction, and impaired protein synthesis. Mitochondria are intracellular organelles which participate in several metabolic pathways, such as oxidation of carbohydrates and fatty acids, Krebs cycle and oxidative phosphorylation, being a key organelle for energy conversion in form of ATP molecules [8]. Mitochondria constantly modify their shape and size, forming a dynamic network throughout the cell, in order to maintain their integrity, quantity, and cellular homeostasis [9]. Mitochondria are one of the major intracellular membrane-enclosed organelles in eukaryotic cells with an important role in bioenergetic and biosynthetic pathways, regulation of calcium homeostasis and control of programmed cell death [8]. Interestingly, Aβ and α-synuclein have been found in the mitochondrial membranes of transgenic animal models of AD and PD and cell lines overexpressing α-synuclein, respectively [10–12]. Moreover, α-synuclein was described to mediate electron chain transport complex I deficiency, impairing mitochondrial function, and resulting in dopaminergic cell death [11,13].

Here, we discuss the contribution of human iPSC-derived neuronal models for the study of mitochondrial alterations aiming to delineate the role of this organelle in AD and PD onset and progression.

2. iPSC-derived neurons as experimental models for neurodegenerative diseases

The development of iPSCs from adult human mitotic cells was a milestone for neuroscience, allowing the direct study of human patient-derived neurons for different neurological conditions [6,14]. In the presence of neurogenic stimuli, iPSCs can be differentiated into neuronal progenitor cells (NPCs), which can be further differentiated into specific neuronal lineages and neuronal subtypes, such as cholinergic, glutamatergic, and dopaminergic neurons, cortical or forebrain interneurons [4,15–18]. iPSC-derived neurodegenerative models focus on the production and characterization of the iPSC-derived cells/neurons, including the expression of distinct neuronal markers, the ability to respond to specific neurotransmitters or second messengers, and the acquisition of electrophysiological features typical of fully differentiated neurons. Generation of iPSC-derived neurons can be obtained using either passive or directed differentiation protocols, although both approaches tend to stimulate the development of glutamatergic neurons. Passive approaches are based on PSC culture in serum-free medium followed by isolation of spontaneously developing neural rosettes and generation of a heterogeneous subpopulation of neuronal cells [19]. Directed differentiation protocols make use of growth factors and morphogens to induce the differentiation of specific neuronal sub lineages, although the purity and efficiency of these protocols vary considerably [20,21]. Currently, the available protocols make use of 3 main approaches to mimic the physiological differentiation clues: an early embryoid body (EB) step, co-culture with neural-inducing feeders, or direct neuronal induction [22].

To date, there are many strategies to ensure the full differentiation and maturation of specific neuronal sublineages (Fig. 1A–C). Neuroprogenitor cells can be obtained through protocols in which PAX6 positive cells are obtained by EB formation combined with SMAD inhibition or the transient expression of transcription factors such as Lmx1a, Nurr1, and Pitx3 [23]. Maturation to cholinergic neurons is obtained in adherent cultures in the presence of BDNF, GDNF, and laminin (as exemplified in Fig. 1A) [7,24]. Similarly, dopaminergic neurons can be generated through the exposure of neuroprogenitor cells to BDNF, GDNF, and TGFβ3 (Fig. 1B) [25].

Astrocytes modulate synaptic transmission and their presence was reported to improve neuron maturation and the generation of electrophysiologic active neuronal networks [26]. Therefore, the utilization of protocols as the one described by Gunhanlar and collaborators, which concomitantly generates neurons and astrocytes in a 60:40 ratio with electrophysiologically active networks [27] is a powerful tool for the study of disease phenotype (Fig. 1C-E).

The plethora of available differentiation protocols represents an important source of otherwise rare cells with patient-specific genetic backgrounds, providing results, and phenotypes that are closer to the human organism. However, the young neuronal phenotypes obtained in protocols that recapitulate embryonic development and the lack of diversity in cellular interactions are still a challenge to overcome [28]. Another major limitation of iPSCs work is to generate and employ the correct controls. In the case of patient-derived cells, one option is to obtain iPSCs from cells of age-matched healthy subjects. However, the considerable differences in terms of genetic backgrounds have sparked a serious debate in the field, that has been partially solved by using isogenic iPSCs lines. Through CRISPR/Cas9 gene editing, scientists can either introduce specific disease-associated mutations in iPSCs lines derived from healthy individuals or correct pathogenic mutations in patient-derived iPSCs lines [29]. Although CRISPR/Cas9 technology can generate off-target mutations, with careful design, it holds the promise of pushing the boundaries of the current knowledge on the initiation and progression of neurodegenerative diseases and indeed, the current findings using iPSC-derived models of brain diseases are already providing new molecular signaling insights into these pathologies.

2.1. Alzheimer's disease

Dementia is caused by progressive cell degeneration in brain regions that are responsible for learning and memory processes. This condition manifests with various cognitive/neurologic symptoms, including memory loss, and communication dysfunction. Dementia affects 47 million people globally, with its prevalence estimated to reach 3.9 % in the over 60 years old population [30–32]. AD is the most common neurodegenerative disease, accounting for 75 % of the cases [1]. It is estimated that by 2050 more than 100 million people will be affected by AD [33].

AD pathophysiology has been associated with two main features: the presence of Aβ plaques and hyperphosphorylated tau aggregates [32]. Amyloid protein precursor (APP) can be processed by β- and γ-secretases, generating $A\beta_{40}$ and $A\beta_{42}$ monomers. These Aβ monomers possess a high propensity to aggregate resulting in various forms of Aβ-derived diffusible ligands, soluble oligomers, and fibrils, or insoluble amyloid plaques [34]. While soluble Aβ-derived ligands associate with receptors impairing synaptic signaling, amyloid plaques increase the inflammatory status [35] and, when present in vicinities of capillary vessels, are considered an indication of impaired clearance [36]. The spatial-temporal Aβ deposits in the brain allow the identification of 5 consecutive stages of the disease: phase I, in which Aβ deposits are

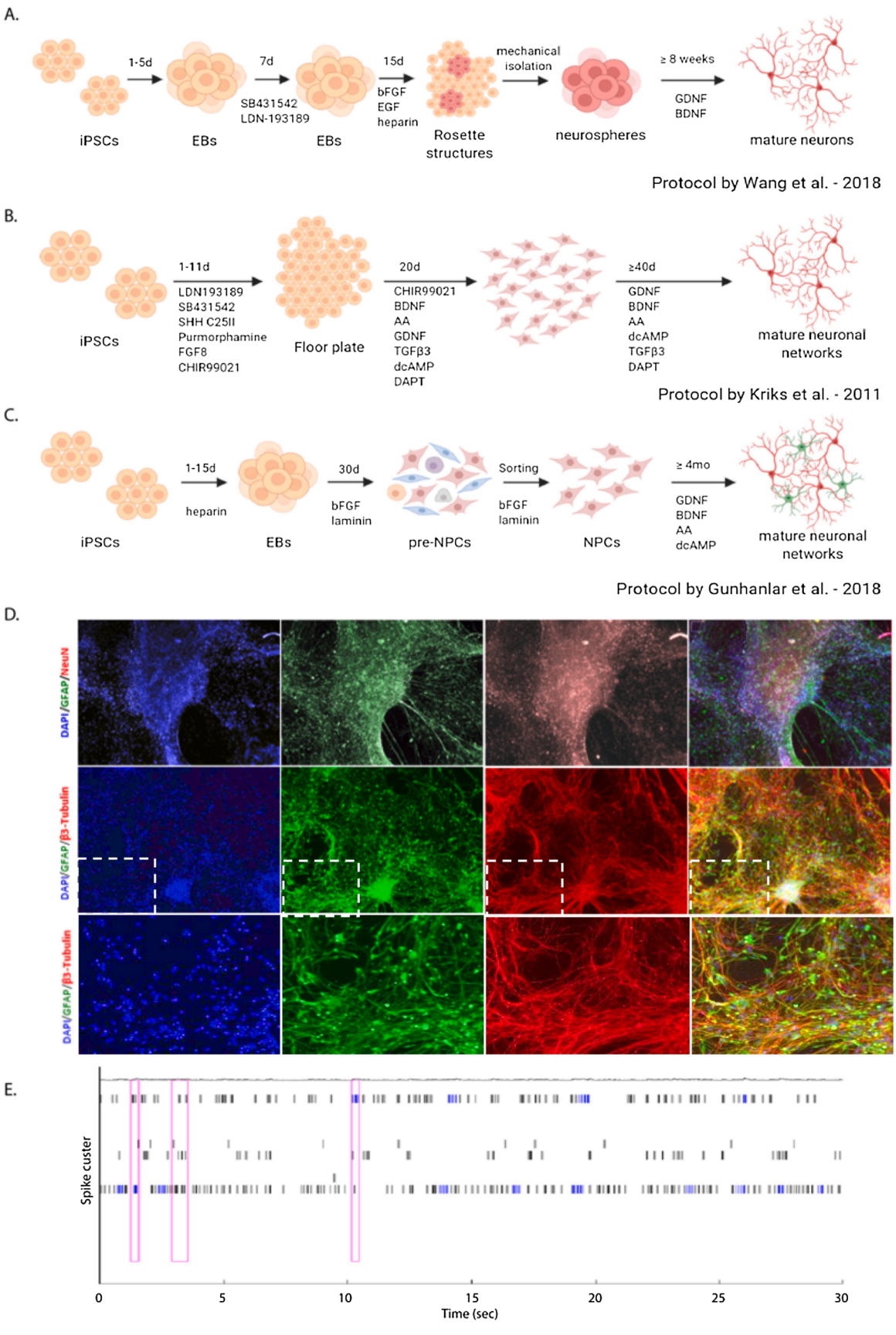

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Fig. 1. Different strategies for neuronal differentiation. A. Protocol published by Wang and collaborators for iPSCs differentiation into cholinergic neurons that makes use of mechanical isolation of rosette structures to select neuronal precursors. B. Protocol published by Kriks and collaborators for iPSCs differentiation into dopaminergic neurons; their protocol makes use of a cocktail of factors that inhibits TGFβ and BMP and induces Wnt and SSH pathways to direct differentiation through the induction of a neuronal floor plate C. Protocol published by Gunhanlar and collaborators for iPSCs differentiation into functional neuronal networks, which makes use of EBs formation to generate neuroprogenitor cells. Important factors used in the protocols are mentioned bellow the arrows and the timeline of the different steps is placed above the arrows, "d" stand for days, and "mo" for months. The interaction between neurons and astrocytes is crucial for the functionality of neuronal networks.
To illustrate this point, we generated iPSC-derived neuronal networks following Gunhanlar's protocol for 68 days and further characterized their phenotype by immunofluorescence and electrophysiological activity by the multielectrode array. D. Immunofluorescence with DAPI in blue, the glial marker GFAP in green, and the neuronal markers β3-tubulin and NeuN in red. E. Representative raster plot indicating instances of spontaneous action potentials. Pink boxes indicate network burst. (Panels A–C created in BioRender).

confined to the neocortex; phase 2, in which allocortical regions are also affected; phase 3, in which abnormalities can be found in the diencephalic nuclei, the striatum, and the cholinergic nuclei of the basal forebrain; phase 4, in which brainstem nuclei are affected; and phase 5, in which the cerebellum is compromised [37].

Tau, a microtubule associated-protein usually found in axons of the central nervous system neurons, aggregates when hyperphosphorylated, forming the neurofibrillary tangles (NFTs) and neuropil threads, straight and paired helical filaments, which disrupts axonal traffic and neuronal communication [38,39]. Although sporadic AD clinical onset usually occurs in patients over 65 years old, abnormal tau phosphorylation and tau-associated lesions can be found as early as in pre-puberty and young adult brains. Tau aggregates can firstly be detected in the transentorhinal cortex, followed by the paralimbic and neocortical regions [40,41]. In fact, the localization of NFT and neuropil threads enable the identification of 6 stages of the disease: Braak I-II, which exhibit mild to severe abnormalities in the transentorhinal cortex and patients are clinically asymptomatic; Braak III-IV, in which the entorhinal cortex is also compromised and there is a mild dysfunction of the first Ammon's horn sector, corresponding to the incipient phase of the disease; and Braak V-VI, in which there is an overall deterioration of the isocortical association areas – at this stage the disease is fully symptomatic [37,40,42].

Mutations in the amyloid protein precursor (APP), or in the catalytic subunits of γ-secretase presenilin-1 (PSEN1) and presenilin-2 (PSEN2) are associated with familial cases of AD with an early onset of the disease – which accounts for approximately 5% of AD cases. Sporadic or late onset AD, which comprises the majority of the cases, has an unknown etiology [43]. Nonetheless, important risk factors were identified, as age, diabetes type 2, lower education, and smoking [44]. Among the risk gene factors, a specific isoform of the Apolipoprotein E (APOE) has been highly associated with AD pathology [45,46]. APOE has three isoforms as a result of two coding single nucleotide polymorphisms, ε2, ε3 and ε4. APOEε4 has been described to increase the AD risk in European descendent populations, while the APOEε2 has been associated with lower AD risk [35,47].

The standard care for AD aims to reduce its symptoms. It makes use of cholinesterase inhibitors like galantamine, rivastigmine, and donepezil, which block acetylcholine processing, and memantine, an N-methyl D-aspartate (NMDA) antagonist, which prevents prolonged abnormal excitability [48]. Many clinical trials are currently targeting the etiology of the disease, including β- and γ-secretase inhibitors, tau aggregation inhibitors, and both passive and active immunotherapy for Aβ and tau aggregates (extensively reviewed [49,50]. However, since memantine approval by the European Medicines Agency (EMA) in the early 2000s, despite more than 200 clinical trials for potential disease-modifying drugs, there was no new approval [51,52]. This lack of translation was attributed to either ineffectiveness, severe side effects, or significant differences between the human organism and animal AD models. Classical pre-clinical models, such as rodents, drosophila, and worms, do not naturally develop AD-like pathology [53].

Transgenic animal models make use of familial AD mutations and genetic variants that increase the risk of developing the disease, being able to mimic important clinical features. One example is the 3xTg mouse model - harboring PS1, APP, and tau transgenes – recapitulating the development of both Aβ plaques and NFTs in aged animals and memory loss [54]. However, the high expression of the transgenes is very artificial and the neurodegenerative phenotype is mild [55]. Nonetheless, there is no animal model that fully covers the complexity of the disease (extensively reviewed in [55–57]).

A regional reduction in glucose metabolism is already observed in early stages [58] and correlates to the severity of the disease during its progression [59–61]. The presence of mitochondria at the synaptic sites is essential for proper synaptic function, and therefore, so is their rapid transport to the site. Aβ oligomers disrupt mitochondrial trafficking in a mechanism dependent on glycogen synthase kinase 3β (GSK3β) [62], and they cause diminished mitochondrial density in neuronal processes [63]. Moreover, Aβ leads to the increased expression of the mitochondrial fission genes dynamin-related protein 1 (Drp1) and fission 1 (Fis1), and a simultaneous decrease in the fusion genes Mfn1 (mitofusin 1), Mfn2 (mitofusin 2), Opa1 (optic atrophy 1), and Tomm40 (translocase of outer mitochondrial membrane 40), resulting in mitochondrial fragmentation [63,64]. APP, Aβ monomers and oligomers were described to accumulate in the inner mitochondrial membrane, being associated with mitochondrial proteins such as Drp1 and causing decreased cytochrome c oxidase activity and increased reactive oxygen species (ROS) production [63–66].

In a similar fashion, tau overexpression is implicated in axonal mitochondrial trafficking impairment [67] and promotes mitochondria perinuclear clustering [68]. Tau is found associated with the mitochondrial outer membrane and also located in the mitochondrial intermembrane space, affecting ER-mitochondria communication [69]. Nonetheless, abnormal tau alters mitochondrial function by decreasing complex I activity and ATP production [70]. In opposition to Aβ effect in mitochondria, tau increases the expression of fusion proteins Opa1 and Mfn1, leading to abnormal mitochondria accumulation [70]. In addition, cytoplasmatic tau interacts with Parkin, preventing its recruitment to the mitochondria and impairing mitophagy [71].

2.1.1. *Calcium signaling in Alzheimer's disease*

The second messenger Ca^{2+} is intrinsically involved in neuronal function, affecting processes such as exocytosis, plasticity, and viability [72]. Therefore, it is not surprising that a imbalanced calcium signaling is observed in AD. Soluble $A\beta_{42}$ was reported to inhibit Ca^{2+} clearance from presynaptic terminals, increasing its basal concentration. As a result, this increase in Ca^{2+} induces the activation of several proteins, including phosphorylation of Ca^{2+}/calmodulin-dependent protein kinase IV (CaMKIV) and its substrate synapsin, impairing synaptic vesicles trafficking and synapse formation by long-term potentiation-induced synaptogenesis [73].

Exposure to Aβ oligomers leads to an increase in mitochondrial Ca^{2+} uniporter (MCU) expression and ER-mitochondria contact points in different neuronal models, which translates into an increased Ca^{2+} transfer to the mitochondria in young neurons. However, in aged neurons treated with Aβ oligomers Ca^{2+} transfer from ER to mitochondria is impaired, decreasing mitochondrial membrane potential, increasing ROS production and promoting apoptosis [74]. Moreover, intracellular Aβ oligomers induce Ca^{2+} release from endoplasmic reticulum (ER)

storage increasing cytosolic Ca^{2+} in a calcium channel Inositol 1,4,5-Trisphosphate receptor (InsP3R)-dependent manner [75,76] and affects plasma membrane Ca^{2+}-ATPases (PMCAs) activity [77], contributing to increased cytosolic Ca^{2+}.

The *APP* gene encodes a transmembrane protein that contains several cleavage sites (alpha, (α); beta (β) and gamma (γ)), generating amyloidogenic and non-amyloidogenic peptides. The harmful amyloidogenic Aβ peptides are formed by the cleaving enzyme activity of β- and γ-secretases. Several studies described APP mutations being associated with familial AD cases [78]. But despite the fact that Aβ clearly leads to Ca^{2+} homeostasis disruption, the role of APP mutations in such alterations is debatable in animal and non-iPSCs human models. The overexpression of different familial AD-associate mutations in human lymphoblasts and rat PC12 cells did not lead to a significant disturbance in Ca^{2+} homeostasis [79,80]. On the other hand, an increase in cytosolic basal Ca^{2+} was reported in primary neurons of APP^{SWE} mice, a mutation that favors APP processing by β-secretase [81], and upon APP silencing in mice embryonic fibroblasts [82]. More detailed studies on human iPSCs models are needed further to explore APP mutation contribution to AD-related Ca^{2+} signaling alterations.

PSEN proteins belong to the γ-secretase complex localized at the ER membrane and are responsible for cleavage of APP and the production of several Aβ forms ranging from 36 to 43 amino acids in length. These Aβ peptides have various aggregation potential, with $Aβ_{42}$ being one of the most aggregation-prone fragments. PSEN1 and PSEN2 (T122 P, N141I, M239I, and M239 V) mutations in neurons lead to increased production of Aβ toxic forms and can aggravate the Aβ plaque burden in the brain [83]. PSEN1 (P117 L, M146 L, L286 V, and A246E) and PSEN2 (M239I, T122R, and N141I) mutations can also induce an altered calcium signaling, and many FAD PSEN mutations are able to lower the Ca^{2+} content of intracellular stores [84]. Tu and collaborators described that wild-type human PSEN1 and PSEN2 are able to form low-conductance divalent-cation-permeable ion channels in lipid bilayers, leading to Ca^{2+} passive leaking from the ER. This property is independent of their γ-secretase activity and is lost in the familial AD mutations PSEN1 (M146 V, M139 V, K239E, V261 F, and A431E) and $PSEN2^{N141I}$ [80,85]. Likewise, Ca^{2+} release from intracellular stores was significantly reduced in fibroblasts from $PSEN2^{M239I}$ FAD patients [61]. On the other hand, astrocytes derived from $PSEN1^{\Delta 9}$ iPSCs displayed increased Ca^{2+} release from the ER [86]. Additionally, PSEN1 deficiency leads to the impairment in lysosomal Ca^{2+} storage/release, therefore affecting autophagosome formation [87]. These results suggest that PSEN role in Ca^{2+} signaling is not limited to their action as γ-secretase.

$PSEN1^{E208A}$ mutation accounts for the largest cohort of early onset autosomal dominant familial AD cases [88]. The analysis of cerebellar samples from this cohort reveled abnormal mitochondrial morphology accompanied by deficient ER-mitochondria contact points. $PSEN1^{E208A}$ tissue presented a lower expression of the Ca^{2+} channels InsP3R, calcium voltage-gated channel subunit alpha1 A (CACNA1A), the mitochondrial transport Ca^{2+}-dependent proteins Ras Homolog Family Member T1 (also known as MIRO1) and Kinesin Family Member 5C (KIF5C) [88,89]. Also, $PSEN1^{M146V}$ neurons have higher cytosolic Ca^{2+} levels while displaying lower mitochondrial Ca^{2+} levels [90]. Thus, highlighting PSEN1 as a key protein in the abnormal ER-mitochondria Ca^{2+} dynamic observed in familial AD.

Mutations in PSEN2 genes mediate dysfunction of Ca^{2+} handling of ER by partially blocking the activity of the Sarco/Endoplasmic Reticulum Ca^{2+}-ATPase (SERCA) in human fibroblasts. Furthermore, the cytosolic calcium measurements showed that both PSEN1 and PSEN2 mutations decrease the expression of Stromal Interaction Molecule 1 (STIM1), resulting in a reduced Ca^{2+} influx in response to store depletion of Store-Operated Ca^{2+} Entry (SOCE) [91]. PSEN regulates potassium/calcium flux, and therefore, could alter neuronal firing properties. Indeed, PSEN mutations in both forms PSEN1 and PSEN2 were shown to decrease neuronal firing rate and excitability and also mediate neuronal cell death [92]. Studies on iPSC-derived basal forebrain cholinergic neurons (BFCNs) from FAD with mutant $PSEN2^{N141I}$ showed reduced neuronal excitability, increased the $Aβ_{42/40}$ ratio, and decrease Ca^{2+} currents. Interestingly, both correction of the mutation by CRISPR/Cas9 or chronic administration of insulin attenuated these $PSEN2^{N141I}$-dependent effects, suggesting a role of insulin to modulate and prevent brain amyloidosis [93,94].

2.1.2. Mitochondrial dysfunction in Alzheimer's disease

Mitochondrial dysfunction is one of the hallmarks of AD, which displays abnormal mitochondrial morphology, distribution, and ER-mitochondria contact points; lower oxidative phosphorylation rates, ATP production; and increased ROS levels [95]. Herein, we discuss the recent findings on the mechanisms of AD mitochondrial alterations in human iPSC-derived neuronal models (summarized in Table 1), a unique model that recapitulates important particularities of the human neuronal networks.

Sporadic AD or non-AD-derived neurons treated with Aβ have as a common trait, mitochondrial DNA (mtDNA) damage, mitochondrial dysfunction, and increased ROS production [96,97]. Aβ was detected in exosomes from AD astrocytes and the dysfunctional mitochondrial accumulation observed in AD can be partially recapitulated when exposing healthy neurons to these exosomes. In fact, AD-exosomes mediate Aβ binding to VDAC1 and triggers neuronal death by caspase activation [98]. These data indicate one of the mechanisms by which Aβ can induce AD-mitochondrial dysfunction.

Although mutated-APP's influence in the Ca^{2+} signaling alterations observed in AD is not clear, it directly affects mitochondrial function. Neurons harboring the APP^{V717L} mutation, which favors $Aβ_{42}$ generation [99], show increased mitochondrial fragmentation associated with an increased phosphorylation of Drp-1, while displaying a decrease in the phosphorylation of mitophagy proteins TBK1 and ULK1 and overall autophagy levels [100]. Both APP^{E693D} and APP^{V717L}-derived neurons showed a higher expression in oxidative stress-related genes, such as peroxiredoxins, oxidoreductase and peroxidase activities, and increases in the ER marker binding immunoglobin protein and ROS production [101].

PSEN1 mutations account for the majority of familial AD cases. Oka and collaborators described that mitochondrial dysfunction linked to mtDNA damage and ROS production observed in neurons derived from $PSEN1^{P117L}$ iPSCs could be partially reversed by the treatment with the mitochondrial transcription factor TFAM, which partially protects mtDNA from oxidative stress and display lower Aβ production [102].

Martín-Maestro and collaborators reported that $PSEN1^{A246E}$-derived neurons displayed accumulated dysfunctional mitochondria due to an impairment in mitophagy. The authors describe that a flawed autophagic process is caused by a diminished autophagy degradation phase as a result of lysosomal anomalies [103]. A similar phenotype is observed in $PSEN1^{M146L}$-derived cells, which already induced significant metabolic changes in a neural stem cell stage of differentiation. $PSEN1^{M146L}$ progenitor cells displayed accumulated dysfunctional mitochondria, which presented a decreased expression of the components of the oxidative-phosphorylation electron-chain reaction NADH: CoQ reductase (complex I), succinate dehydrogenase (complex II), cytochrome c reductase (complex III), cytochrome c oxidase (complex IV), and of ATP synthase (complex V). This mitochondrial accumulation was associated with the reduced expression of the fusion proteins Mfn2 and OPA1, and autophagy related proteins LC3, LAMP1 and TFEB. Indicating early metabolic changes and impairment in mitophagy, which might have relevant consequences to the pathophysiology of the disease [104]. Interestingly, the opposite pattern is observed in apolipoprotein E (APOE) 3/4-derived neurons, the most common risk factor for sporadic AD, which display an increase in the expression of oxidative-phosphorylation chain components complex I–V. Although these cells present increased ROS production, mitochondrial fission and fusion genes are unaltered [105], emphasizing the different mechanisms taking place in the onset of sporadic and familial AD.

Table 1
Alterations in mitochondria in iPSC-derived neurons from AD patients.

Genetic background/ model	Cell type	Main finding	Refs.
Healthy	Neurons	Astrocyte-derived exosomes from AD-patients are ceramide rich and are associated with Aβ. Neurons treated with AD-exosomes displayed mitochondrial clustering, increase in fission protein Drp-1, binding of Aβ to VDAC1 triggering caspase activation.	[98]
Healthy	Neurons positive for MAP2, neurofilament, and synaptophysin	The mitochondrial complex KGDHC is diminished in brains of AD patients. KGDHC downregulation in neurons lead to a decrease in ER calcium stores.	[108]
Healthy	Neural stem cells	Exposure to $A\beta_{42}$ oligomers increases ROS levels, damaged mtDNA and inhibits DNA non-homologous end joining (NHEJ) and favors astrocytic upon neuron differentiation. Treatment with Phytic Acid, stimulating NHEJ reduces $A\beta_{42}$ oligomers-associated mtDNA damage and restores the neural/astrocytic differentiation balance	[109]
APP-V717L mutation, APOE4 and healthy age-matched control	Cortical neurons positive for MAP2, Tuj1 and BRN2	AD-derived neurons displayed impaired mitochondrial homeostasis, increased mitochondrial fragmentation and low ATP levels, reduced OCR, decreased levels of the mitophagy-related proteins phospho-TBK1, AMBRA1, Bcl2L13, FUNDC1, and MUL1 Mitophagy induction by urolithin A treatment restored the OCR of APOE4/E4 neurons to normal levels.	[100]
APOE3/3 and 3/4	Neurons overexpressing Ngn2 and positive for MAP2	AD-derived neurons displayed increase in ROS levels and in the expression of respiratory chain complex subunits.	[105]
APP-E693D mutation, APP-V717L mutation and controls	Cortical neurons positive for SATB2 and TBR1	Neurons with APP mutations have increased ROS production and stress-response genes peroxiredoxin, oxidoreductase and peroxidase expression.	[101]
Non-specified AD and control	Neurons overexpressing Ngn2	PI3K/AKT pathway inhibition lead to increased ROS production and mitochondrial membrane depolarization in AD-derived neurons.	[97]
PSEN1 A246E mutation and control	Cortical neurons positive for MAP2, Tau, NeuN, Calbindin and vGlut1	AD-derived neurons displayed defective mitophagy, with consequent accumulated dysfunctional mitochondria, caused by a diminished autophagy degradation phase presenting lysosomal anomalies.	[103]
PSEN1 M146L mutation and controls	Neural stem cells positive for Nestin, SOX1 and SOX2	AD-derived NPCs displayed: lower expression of the respiratory chain complexes, abnormal mitochondrial abundance and network, reduced expression of autophagy related proteins LC3, LAMP1 and TFEB, elevated expression of PINK1 and Parkin correlating with the accumulation of damaged mitochondria. Autophagy induction by bexarotene treatment lead to the rescue of mitochondria morphology.	[104]
PSEN1 P117L mutation and controls	Cholinergic neurons positive for MAP2	AD-derived neurons showed mitochondrial dysfunction, 8-oxoguanine accumulation, mtDNA single-strand breaks, impaired neuritogenesis, and reduced expression of transthyretin. Recombinant hTFAM treatment increased transthyretin expression and reduced intracellular Aβ.	[102]
Sporadic AD and controls	Neurons positive for PAX6, Nestin and -β-Tubulin III	AD-derived neurons displayed upregulated expression of oxidative stress response genes and downregulation in alanine, aspartate and glutamate metabolism-related genes.	[96]

AD human iPSC-derived models demonstrate the critical role of mitochondrial dysfunction and impaired mitophagy for the pathogenesis of the disease. Hirano and collaborators conducted a careful screening of clinically approved drugs that could enhance autophagy [106]. Memantine, an NMDA antagonist used for AD treatment [107], was identified as an autophagy enhancer by inducing LC3 expression and upregulated the autophagic flux.

2.2. Parkinson's disease

PD is the most common movement disorder, and it is characterized by motor symptoms such as tremors, rigidity, and bradykinesia [110]. Loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) decreases the facilitation of voluntary movements resulting in the motor symptoms in PD [42]. PD involves the formation, propagation, and accumulation of intracellular protein α-synuclein aggregates in Lewy bodies and Lewy neurites in the cell cytoplasm [111,112].

Formation of Lewy bodies can cause abnormal protein and organelle clearance due to defects in autophagy and lysosomal degradation. Besides SNpc, Lewy bodies can also be present in other parts of the brain, including the cerebral cortex that has been associated with dementia symptoms in PD cases [113,114]. However, nonmotor symptoms such as nerve pain, depression, anxiety, apathy, psychosis, disturbances in sleep modes, and constipation result from dopaminergic cell loss, α-synuclein aggregation and dysfunction of the peripheral nervous system [115].

The reason for the damage or the death of the dopaminergic neurons in the substantia nigra is unknown, but several factors are essential for PD development. It has been described that environmental aspects contribute to the pathology of the disease together with other factors, such as age, gender, heredity, area of residence, and exposure to toxic agents [116]. Although the majority of cases of PD are sporadic, there are around 10–15 % of patients with familial PD with mutations in several genes, such as α-synuclein (SNCA), leucine-rich repeat kinase 2 (LRRK2), PTEN-induced kinase 1 (PINK1), Parkin, DJ1, and ATP13A2 [117].

2.2.1. Calcium signaling in Parkinson disease

Calcium signaling plays a crucial role in the pathogenesis of numerous neurodegenerative diseases, including PD. The evaluation of intracellular calcium levels and the expression of calcium channels following challenges with different PD stimuli help to evaluate the function of neural cells in disease compared with normal conditions [118]. Voltage-gated calcium channels (VGCCs) are widely distributed within the CNS, mediating calcium influx in response to membrane depolarization and adjust intracellular processes such as neurotransmission and gene expression [119,120]. VDCCs are composed of several subunits (α1, α2/δ, and β) where α1 is the main subunit and determines the characteristics of each VDCC subtype [121].

Dopaminergic neurons of the SNpc are autonomous pacemakers [122]. This activity is necessary for the sustained release of dopamine in the striatum and proper neuronal activity. Pacemaking in SNpc is accompanied by Ca^{2+} influx through Cav1 Ca^{2+} channels (L-type calcium channels, LTCC), in particular via Cav1.3, contributing to increased intracellular Ca^{2+} levels. Guzman et al. reported that the LTCC channels helped to support pacemaking when challenged with cationic channel inhibitors, as demonstrated by optical and electrophysiological approaches [122]. LTCC channels with a pore-forming Cav1.2 and Cav1.3 subunits contribute to Ca^{2+} oscillation in SNpc DA neurons. Interestingly, Cav1.3 channels open at relatively hyperpolarized membrane potentials and never close fully during the pacemaking cycle, facilitating Ca^{2+} entry and in this way increase the vulnerability of SNpc neurons [123–125]. In PD, dopaminergic neuron susceptibility to cell death has been associated with a distinct pacemaker phenotype that involves an increase of Ca^{2+} entry via LTCC, that result in mitochondrial oxidative phosphorylation [125]. As a consequence, this promotes mitochondrial oxidative stress and boosts mitophagy and proteostasis malfunction. Besides, high levels of mRNA expression of $Cav1.3_{42}$, an alternatively spliced short variant of Cav1.3, was observed in damaged neurons in the ventral midbrain in a sub-chronic MPTP mouse model of PD, indicating that this channel contributes to the degeneration of dopaminergic neurons [126]. The robustness of pacemaking regularity is conferred by the activity of LTCC together with other ion channels, such as small conductance calcium-activated potassium (SK) channels [127–129]. SK channels were shown to be present in human differentiated dopaminergic neurons [130] and in SNpc, where they work in concert with Cav channels to assist neuronal firing [130]. SK channel modulation has been shown to ameliorate PD pathology [131–134].

Hurley and collaborators detected high expression of Cav1.2 channels in the cingulate and primary motor cortex in post-mortem tissue of PD patients using in situ hybridization with Cav1 subtype-specific [35 S]-labeled oligonucleotide probes. Besides, they described Cav1.3 mRNA increase in the cingulate cortex of late PD patients but more surprisingly in the motor cortex in the early stages of PD compared with control subjects [135]. On the other hand, Wang et al. reported that the Cav1.2 channel in microglia inhibits M1 activation and promotes M2 activation under normal conditions [121]. The previous studies (*in vitro* and *in vivo*) underline the importance of VGCCS in neurodegenerative diseases, particularly PD. However, there are few studies that described the importance of these calcium channels in neurons differentiated from iPSCs.

A recent study performed by Benker and collaborators described a potential role of Cav2.3 channels in PD pathology. They showed by pharmacological and genetic methods how oscillations of Ca^{2+} could lead to increased vulnerability to PD stressors, suggesting a potential link between these Ca^{2+} oscillations and the susceptibility of the dopaminergic neurons to neurodegeneration [136].

Generation of dopaminergic neurons from PARK2 (Parkin) patient-specific, isogenic PARK2 null, and PINK1 patient-specific showed higher vulnerability to rotenone-induced mitochondrial stress and cell death. Neurons harboring PARK6 mutations exhibited alterations in calcium homeostasis and higher vulnerability to rotenone-induced toxicity. Interestingly, antagonists or the T-type calcium channel knockdown ameliorated the rotenone-mediated damage [137]. In the same way, Gautier and colleagues demonstrated that loss of PARK2 altered the proximity between the ER and mitochondria and increased Ca^{2+} transients. Aberrant ER-to-mitochondria Ca^{2+} transfers were corrected in fibroblasts from patients with PARK2 mutations by reducing Mfn2, an effect attributed to Mfn2 potential function to modulate ER-mitochondrial coupling [138].

One of the most important genes associated with PD is the leucine-rich repeat kinase 2 (*LRRK2*) gene. There are several pathogenic mutations in the *LRRK2* gene, which are located in different functional domains. Of all the mutations, the G2019S mutation is the most prevalent one [139]. In the G2019S mutation, a glycine is replaced by a serine, which leads to an increased kinase activity of LRRK2 [140]. It has been described that G2019S mutation interferes with Ca^{2+} dynamics in iPSC-derived neurons [141]. Alterations in Ca^{2+} levels in ER and the increase of Ca^{2+} influx generates higher intracellular Ca^{2+} levels, and in this way, LRRK2 are considered main actors in PD pathogenesis [142]. Conversely, Korecka et al. showed deregulation of the ER Ca^{2+} homeostasis in patient-derived iPSCs neurons with $LRRK2^{G2019S}$ mutation [143]. Besides, calcium signaling was impaired, and as a consequence, p62 and LC3-II protein levels were upregulated, reflecting potential alterations in the autophagy system in iPSC-derived neurons compared to control and SNCA [144]. Although some data seem contradictory, it is clear that mutation in $LRRK2^{G2019S}$ modifies the intracellular level of Ca^{2+} and its signaling.

HeLa cells with mutations in A53 T α-synuclein exhibited an elevation of Ca^{2+} transients exclusively in mitochondria, leaving cytosolic and ER Ca^{2+} levels unaffected [145]. However, in SH-SY5Y cells with overexpression of A53 T α-synuclein, it was observed an enhanced Ca^{2+} entry through L-type Ca^{2+} channels [146]. Similarly, A53 T PD-related α-synuclein mutation showed an increase in calcium levels measured by the calcium sensor GCaMP3, and decreased axonal arborization and dopamine release in transgenic mice [147]. On the other hand, PINK1 adjusts calcium efflux in the mitochondria via the exchanger Na^{+}/Ca^{2+}. Likewise, a lack of PINK1 can induce mitochondrial accumulation of calcium, causing calcium overload in the mitochondria. Simultaneously, an increase in ROS production caused changes in mitochondrial respiration, mainly associated with complex I- and II-linked respiration. Both phenomena contribute to open of the mitochondrial permeability transition pore (mPTP) in PINK1-deficient cells, and this opening releases proapoptotic factors such as cytochrome c from the mitochondria that can lead to apoptosis [148,149].

2.2.2. Alterations in mitochondria from neurons in PD

Mitochondrial dysfunction is an inherent player in the development of PD. Loss of mitochondrial function in terms of ATP generation [12], calcium buffering capacity, mitophagy, and mitochondria interaction

with other organelles and proteins was documented at different stages of PD [143,150]. In this section we will discuss recent findings presenting data on how specific PD mutations affect mitochondrial function in patient-derived iPSCs differentiated neurons. Effects of these PD mutations on cellular signaling are listed in Table 2.

Structural changes of neuronal mitochondria have been described in association with LRRK2 mutation. Mitochondrial impairment in PD linked to LRRK2 mutation has been extensively evaluated in various cellular models [151], including iPSCs [152,153]. Treatment with inhibitors of LRRK2: LRRK2 IN-1, GSK2578215A, and CZC25146 showed an improvement in the calcium responses in iPSC-derived neurons, suggesting the importance of this gene in the pathophysiology of PD [144]. Schwab et al. reported that LRRK2^{G2019S} iPSC-derived dopaminergic neurons display increased retrograde mitochondrial velocity and reduced mitochondrial content in the distal neurite, indicating mitochondrial trafficking defects in these neurons [154]. These mitochondrial deficits were accompanied by increased expression of sirtuins, albeit the activity of sirtuin deacetylase was decreased as well as the nicotinamide adenine dinucleotide levels [154]. Hsieh et al., 2019 described how Miro1, the mitochondrial outer membrane protein that mediates mitochondrial motility, is usually removed from depolarized mitochondria, thus allowing mitochondrial clearance by mitophagy. Lack of Miro1 removal from the mitochondrial membranes was associated with LRRK2 mutations in fibroblasts and iPSC-derived neurons. iPSC-derived LRRK2 mutant dopaminergic neurons exhibited the following events: lack of Miro1 removal from mitochondria, reduced mitochondrial degradation, and decreased mitophagy [155].

An increased α-synuclein expression or α-synuclein mutations have been associated with mitochondrial dysfunction in PD. Ryan et al., identified the myocyte enhancer factor 2C (MEF2C)-peroxisome proliferator-activated receptor-γ coactivator-1α (PGC1α) transcriptional pathway in A53 T α-synuclein mutant dopaminergic iPSC-derived neurons as responsible for neuronal damage. Seahorse extracellular flux experiments demonstrated a compromised maximal rate of mitochondrial respiration and a decrease in the spare respiratory capacity in A53 T α-synuclein compared with the isogenic neuronal lines. A53 T α-synuclein induced S-nitrosylation of MEF2C, which decreased expression levels of PGC1α, induced mitochondrial dysfunction, and increased the susceptibility to mitochondrial toxins, such as paraquat and the fungicide maneb [156]. Ludtmann et al., described increased α-synuclein aggregation that can interact with ATP synthase, mediates PTP opening, mitochondrial swelling, and cell death in iPSCs harboring *SNCA* triplication [157]. Interestingly, oligomeric α-synuclein are able to interact with mitochondrial proteins and impair complex I-dependent respiration [142]. Likewise, transcriptomic analysis of dopaminergic neurons derived from iPSCs of PD patients harboring either the A53 T SNCA mutation or the *SNCA* triplication showed alterations in gene expression related to mitochondrial function, decrease in mitochondrial respiration, damage in mitochondrial membrane potential, aberrant mitochondrial morphology, and reduction of levels of pDRP1^{Ser616} and a shift towards mitochondrial fission [158]. These data showed a correlation between α-synuclein cellular pathology and deficits in cellular bioenergetics in PD [158].

It has been reported that mitochondria from Parkin, PINK1, and Glucocerebrosidase (GBA) iPSC-derived dopaminergic neurons are swollen and disorganized [159,160]. Valadas et al., reported an increment in the ER-mitochondria contacts of Parkin and PINK1 neuropeptidergic iPSCs neurons. They did not find substantial changes in mitochondrial volume or mitochondrial morphology between mutant cells and control cells. However, they reported an increase of neuropeptide accumulation in ER and the disbalance of lipid phosphatidylserine causing a defect in secretory vesicles, that are important in the control of circadian rhythms in PD [160]. Similarly, dopaminergic neurons with PINK1 mutations showed increased vulnerability to various toxic stimuli, including MPP^+, valinomycin, and hydrogen peroxide. These neurons also showed increased mitochondrial ROS

Table 2
Alterations in mitochondria in iPSC-derived neurons from PD patients.

Genetic background/ Mutation	Cell type	Findings	Refs.
Parkin PINK1	Neuropeptidergic neurons	Increase in the ER-mitochondria contacts points associated with neuropeptide accumulation in ER and disbalance in phosphatidylserine causing a defect in secretory vesicles, that are important in the control of circadian rhythms in PD.	[160]
PINK 1	Dopaminergic neurons	AKT pathway regulates PINK1 accumulation on depolarized mitochondria, interfering with mitophagy. Endogenous PINK1 is associated with mitochondrial-toxin induced mitophagy, S-Nitrosylated PINK1 reduce Parkin translocation to mitochondrial membranes acting as a negative regulator of mitophagy	[163] [164]
PARK2/Parkin (V324A)		Mitochondrial abnormalities: Enlarged mitochondria, higher mitochondrial-derived oxidants. In consequence, these lines are more susceptible to cell death and α-synuclein aggregation	
PINK1 (Q456X)	Midbrain dopaminergic neurons		[165]
PRKN^{del} Parkin mutant	Dopaminergic neurons	PINK1 and parkin function impair contacts between ER and mitochondria during mitophagy, likely through parkin-mediated OMM protein ubiquitination and turnover, as this process can be blocked by inhibiting proteasomal degradation.	[166]
PARK2	Dopaminergic neurons	Elongated mitochondria, impairment of glycolysis and lactate-pyruvate metabolism; reduction of cell viability	[167]
DJ-1	Dopaminergic neurons	Mitochondrial oxidant stress allowed oxidized dopamine accumulation producing a decrease in glucocerebrosidase activity, lysosomal malfunction and α-synuclein aggregation	[168]
GBA β-Glucocerebrosidase	Dopaminergic neurons	GBA-PD neurons showed mitochondrial demise and alteration	[159]

(*continued on next page*)

Table 2 (*continued*)

Genetic background/ Mutation	Cell type	Findings	Refs.
		in NAD^+ metabolism. NAD^+ precursor nicotinamide riboside (NR) increases NAD^+ and partially protects against mitochondrial damage.	
A53 T α-synuclein	A9 Dopaminergic neurons	A53 T α-synuclein mutant showed nitrosative/oxidative stress alterations and S-nitrosylation of transcription factor MEF2-PGC, increasing the susceptibility to mitochondrial toxins.	[156]
A9			
A53 T SNCA mutation	Dopaminergic neurons	Decrease in OCR, mitochondrial membrane depolarization, perturbations in genes linked to mitochondrial function, abnormal mitochondrial morphology and decreased $pDRP1^{Ser616}$ showing a shift towards mitochondrial fission.	[158]
SNCA	Dopaminergic neurons	PD-derived neurons showed impaired mitochondrial membrane potential and abnormal mitochondrial morphology with reduction of total area and length of mitochondria (fragmentation) compared to control neurons.	[169]
SNCA	Dopaminergic neurons	ER–mitochondria contact points and VAPB–PTPIP51 interaction are reduced.	[170]
Progerin genes	Midbrain dopaminergic neurons	Progerin induces the expression of aging-related markers such as neuromelanin accumulation, dendrite degeneration and mitochondrial swelling.	[162]
PINK1	Midbrain dopaminergic neurons	PINK1 mutation lead to higher susceptibility to mROS	[161]
LRRK2		PD-neurons displayed altered OCR, proton leakage, and intraneuronal mitochondria transport.	
OPA1	Dopaminergic neurons	OPA1 mutated neurons display increased oxidative stress, mitochondrial fragmentation, impairment OCR, and ATP deficiency.	[171]
GTPase optic atrophy type 1			
LRRK2 G2019S	Dopaminergic neurons	Miro accumulates on damaged depolarized mitochondria, prolonging active transport, blocking mitochondrial degradation and decreasing mitophagy	[155, 172]
		Increased mitochondrial motility.	[154]
LRRK2	Dopaminergic neurons	Increased sensitivity to oxidative stress.	[173]
G2019S	Dopaminergic neurons	Elevated vulnerability to rotenone, which was decrease with LRRK2 inhibitor.	[174]
		Higher oxidative stress.	[175]
α-synuclein mutants (E46 K or E57 K)	Dopaminergic neurons	High levels of α-synuclein oligomers reduce anterograde axonal transport of mitochondria due to Tau pathology and redistribution of kinesin adaptor proteins.	[176]
		α -Syn oligomerization lead to synaptic degeneration in human neurons.	
CHCHD2 T61I mutation	Dopaminergic neurons	CHCHD2 mutation induces α-synuclein aggregation in dopaminergic neurons and showed mitochondrial dysfunction.	[177]
Parkin mutated (exon 6,7 deletion), PINK1 mutated (p.C388R/ p. C388R) and control	Midbrain dopaminergic neurons	Parkin and PINK1 mutations lead to an accumulation of damaged mitochondria, which could be reversed by the treatment with AD treatment drug memantine.	[106]

(mROS) in response to low valinomycin concentrations, while the control cells had no alterations in mROS levels. $PINK1^{Q456X}$ mutations in neurons affected cellular bioenergetics, increasing basal respiration, the ATP-linked mitochondrial respiration, and proton leakage, while LRRK2 mutations led to attenuation of the mitochondrial respiration parameters [161]. Moreover, Parkin and PINK1 deficient neurons, which display an accumulation of dysfunctional mitochondria by impaired mitophagy, showed mitochondrial clearance upon memantine treatment [106], thus, reinforcing that mitophagy modulation is a clinically relevant mechanism to be explored in neurodegenerative diseases.

Schondorf et al., described significant changes in neuronal mitochondria mediated by mutations in the lysosomal *GBA* gene, one of the most common genetic risk for PD. GBA-PD dopaminergic neurons showed: ultrastructural abnormalities in the mitochondria compared with isogenic controls, reduction in basal and maximal respiration, oxygen consumption and spare respiratory capacity, increased mROS and impairment of mitophagy. Alteration and damage in NAD^+ metabolism were evident in GBA-PD neurons; likewise, the authors reported the increase in NAD^+ via NAD^+ precursor nicotinamide riboside (NR) that significantly decreased the mitochondrial damage, indicating a potential neuroprotective role of NR in PD and other diseases related to aging, considering that GBA activity is reduced in healthy people at older age [159].

Similarly, mitochondrial dysfunction has been described in

dopaminergic neurons derived from iPSCs with a mutation in progerin, a truncated form of lamin A, that is related to premature aging. Progerin expression caused neuromelanin accumulation, dendrite degeneration, progressive loss of tyrosine hydroxylase expression, mitochondrial swelling and an increase of mitochondrial superoxides, suggesting a harmful increase in oxidative stress in cells with progerin overexpression [162].

3. Conclusion

As the population over 60 years old increases, so does the incidence of age-related diseases. Research on the field aims to increase patient average productive years and quality of life but there is a significant lack of translation from pre-clinical models to the human condition. Animal models have the inherent complexity of the central nervous system but display resistance to most age-related neurodegenerative conditions, as illustrated by the absence of spontaneous Aβ accumulation and NFT in rodents [4]. iPSCs represent a cornerstone for the development of human *in vitro* and organotypic models of neurodegenerative diseases, allowing the analysis of specific genetic backgrounds [54,174,178]. Mitochondrial dysfunction is a hallmark of aging and consists of mtDNA instability, alteration of the electron transport chain complexes, changes in mitochondrial dynamics, defective mitophagy, and increased ROS [179]. The genetic background associated with neurodegenerative diseases, in particular AD and PD, commonly exacerbates one or more of these traits and favors the development of the disease [78,90,117]. Familial AD and PD associated mutations lead to altered Ca^{2+} signaling, with increased cytosolic Ca^{2+} and altered ER-mitochondrial contact points and mitochondrial dysfunction [104,170]. Progerin mutated iPSC-derived neurons display multiple aging-related markers such as dendrite degeneration and mitochondrial swelling [162]. Likewise Parkin/PINK1mutations which impairs mitophagy recapitulates mitochondrial accumulation, altered metabolism, and traffic defects observed in AD and PD [160–162]. Addressing these common traits might not only aid in the treatment of neurodegenerative diseases but also could contribute to healthy aging, and increase overall quality of life.

Credit author statement

MTL, ASG and AMD were involved with the Conceptualization of the review, and Writing (original draft, review & editing). AMD supervised the writing process and was responsible for the concept of the figures. MTL and ASG prepared the tables and the figures.

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Declaration of Competing Interest

The authors report no declarations of interest.

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