Mitochondrial dysfunction of induced pluripotent stem cells-based neurodegenerative disease modeling and therapeutic strategy

Hong-Mei Luo¹, Jia Xu¹,², Dan-Xia Huang¹, Yun-Qiang Chen¹, Yi-Zhou Liu¹, Ya-Jie Li¹ and Hong Chen¹,²*
¹Department of Rehabilitation, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, ²Stem Cell Research Center, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Neurodegenerative diseases (NDDs) are disorders in which neurons are lost owing to various factors, resulting in a series of dysfunctions. Their rising prevalence and irreversibility have brought physical pain to patients and economic pressure to both individuals and society. However, the pathogenesis of NDDs has not yet been fully elucidated, hampering the use of precise medication. Induced pluripotent stem cell (iPSC) modeling provides a new method for drug discovery, and exploring the early pathological mechanisms including mitochondrial dysfunction, which is not only an early but a prominent pathological feature of NDDs. In this review, we summarize the iPSC modeling approach of Alzheimer’s disease, Parkinson’s disease, and Amyotrophic lateral sclerosis, as well as outline typical mitochondrial dysfunction and recapitulate corresponding therapeutic strategies.

KEYWORDS
neurodegenerative diseases, mitochondrial dysfunction, therapeutic strategy, iPSCs (induced pluripotent stem cells), mitochondrial dynamic, mitochondrial transport, mitochondrial energy metabolism

1 Introduction

With the aging of the population, neurodegenerative diseases (NDDs) are affecting an increasing number of people. By 2030, seventy-eight million individuals would have been affected by dementia (predominantly Alzheimer’s disease), with up to 55 million cases by 2021 (WHO, 2021). NDDs are characterized by the progressive loss of motor, sensory, and/or cognitive functions as a result of neuronal cell death (Pasterning-Vuhrman et al., 2021). Several common NDDs, including Alzheimer’s disease (AD), Parkinson’s disease (PD), and amyotrophic lateral sclerosis (ALS), have a remarkably complex pathogenesis. Due to its high etiologic heterogeneity, interplayed with diverse genetic backgrounds, and environmental factors, there are few target strategies despite decades of research...
Diving into the pathogenesis of NDDs remains a prioritized step toward their understanding and treatment. Although several models have been developed to aid mechanistic research, much remains elusive (Ke et al., 2021; Okano and Morimoto, 2022). The autopsy sample serves as an ideal model for investigation; however, it is featured as the late stage of NDDs, which is unfit for early pathophysiologic studies. Animal models have been utilized in numerous studies, but the translational clinic applications remain a long way off (Okano and Morimoto, 2022). With such a predicament, it is essential to develop accurate models that reflect the early stages of the pathological processes in NDDs (Israel and Goldstein, 2011; Grekhnev et al., 2022).

Induced pluripotent stem cells (iPSCs) are pluripotent, which indicates their capacity to differentiate into almost all human cell types with identical genetic background of the donor patient (Li and Fraenkel, 2021). This process provides developmental cues to areas of interest. Moreover, patient-specific iPSCs combined with gene editing technology can also be used for the development of therapeutic targets and clinical drug screening (Okano and Yamanaka, 2014; Park et al., 2014). NDDs affect specific types of neurons; therefore, the in vitro modeling of patient-specific iPSCs to thoroughly understand the pathological processes of NDDs has significantly furthered the exploration of their mechanisms.

Mitochondria are organelles that continuously undergo fusion and fission in eukaryotic cells and play a crucial role in bioenergetic and biosynthetic pathways, calcium homeostasis management, and the regulation of programmed cell death (Friedman and Nunnari, 2014). Mitochondrial dysfunction has emerged as one of the major participants in the neuropathology of AD patients due to defective mitophagy (Fang et al., 2019). For instance, mitochondrial transport disturbances were found in ALS SOD1G93AMN (Magrané et al., 2012; Shaltouki et al., 2015; Fang et al., 2019). This evidence indicates that different types of mitochondrial dysfunction occur in NDDs. Although it is still unknown whether mitochondrial dysfunction is the cause or functional outcome of NDDs, reversing mitochondrial dysfunction can be an effective means of treating the disease (Burtcher et al., 2022). iPSC modeling shows great potential in figuring out the occurrence of mitochondrial dysfunction in NDDs. In this review, we summarize several differentiation methods that induce iPSCs into characteristic neurons for modeling NDDs such as AD, PD, and ALS. We also recapitulated the mitochondrial abnormalities in differentiated neurons including mitochondrial dynamics and transport, mitochondrial reactive oxygen species (ROS) and mitophagy, mitochondrial energy metabolism dysfunction, and treatment approaches targeting mitochondrial abnormalities.

2 IPSC differentiation protocols in neurodegenerative diseases

AD, a common neurodegenerative disease, is the major cause of dementia (Ayodele et al., 2021). The neuropathology of AD is characterized by the progressive accumulation of parenchymal amyloid-β (Aβ) and by the hyperphosphorylation and aggregation of tau protein into neurofibrillary tangles (Venkatramani and Panda, 2019; Pardo-Moreno et al., 2022). Thus, researchers have differentiated hPSCs into specific neurons, including neural stem cells, cortical neurons, and astrocytes, to explore the pathological changes in AD (Emdad et al., 2011; Krencik and Zhang, 2011; Roybon et al., 2013; Tew et al., 2017). Dual SMAD signaling was inhibited by SB431542 (SB, an inhibitor of activin-nodal signaling) and LDN193189 (LDN, an inhibitor of BMP signaling) at the first neural induction step (Chambers et al., 2009), following which several small-molecule compounds were used to obtain cortical tissue. For instance, Neurobasal and B27 supplements replaced NPC culture medium at day 10 and were supplemented with 20 ng/ml brain-derived neurotrophic factor (BDNF) to induce final neural maturation at day 30 (Martin-Maestro et al., 2017). For astrocyte differentiation, after the NPCs were obtained, the cells were cultured in suspension with an astrocyte differentiation medium supplemented with basic fibroblast growth factor (bFGF or FGF2) and epidermal growth factor (EGF). The spheres were maintained in suspension for 5–7 months, after which they were associated and plated on Matrigel-coated dishes using ciliary neurotrophic factor (CNTF) and bone morphogenetic protein 4 (BMP4) for maturation (Oksanen et al., 2017). Because the differentiation process of astrocytes can take months, some innovative techniques have been created. Li et al. found that CRISPR-Cas9-mediated expression of the transcription factors nuclear factor I A (NFIA) or NFIA plus SRY-box transcription factor 9 (SOX9) enables the rapid acquisition of astrocytes from hPSCs within 4–7 weeks, which undoubtedly speeds up the iPSC-derived astrocyte modeling of diseases (Li X. et al., 2018).

PD is the second most common neurodegenerative disease. It is predicted that by 2040, there will be 14.2 million persons with PD, up from 6.9 million in 2015 (Dorsey and Bloem, 2018). Patients diagnosed with PD always have movement and physical problems, such as tremors, stiffness, slowness, and imbalance (Armstrong and Okun, 2020). The pathological hallmark of PD is the Lewy body consisting largely of α-synuclein protein aggregations and loss of dopaminergic neurons in the substantia nigra (Armstrong and Okun, 2020). The floor plate (FP) cells are located at the ventral midline of the neural tube and are the source of midbrain dopamine neurons (DA neurons) (Placzek and Briscoe, 2005; Ono et al., 2007). The protocols to obtain DA neurons are also being modified (Cooper et al., 2010; Kricks et al., 2011; Xi et al., 2012; Wang et al., 2015; Kim et al., 2021). Christopher A. Fasano induced hiPSC to FP cells using...
The generation of highly pure motor neurons requires improving the purity of motor neurons, resulting in CHAT expression in 16 days. Because of the shorter time for differentiation, the protocol has been widely applied in the disease modeling research (Ding et al., 2022; Liu et al., 2020). Modiﬁcation of CHIR concentration to a narrow range was reported to play an important role in inducing DA neurons from iPSC (Xi et al., 2012). They used 0.4 µM CHIR and 500 ng/ml SHH to treat iPSC for 12 days, and then added 20 ng/ml SHH with 100 ng/ml FGF8 at day 13–28, resulting in TH+/En1 co-expressing DA neurons.

ALS is a fatal neurodegenerative disease that causes selective degeneration of motor neurons (MNs) in the motor cortex, brainstem, and spinal cord (Vandoorne et al., 2019). ALS patients always suffer from progressive muscle weakness and respiratory failure and ultimately die within 3–5 years (Brown and Al-Chalabi, 2017). Since MNs were used to study the pathology of ALS in recent years, the differentiation protocol of iPSCs to MNs is constantly being reﬁned (Hu and Zhang, 2009; Egawa et al., 2012; Qu et al., 2014; Du et al., 2015; Daﬁnca et al., 2020). In 2006, Hu and Zhang published a protocol that can generate more than 50% of HB9-expressing motor neurons within 5 weeks. They induced iPSCs into neuroepithelial (NE) with a neural differentiation medium including instantly added cAMP, ascorbic acid, BDNF, glial-derived neurotrophic factor (GDNF), and insulin-like growth factor-1 (IGF1). The authors used 100 nM retinoic acid (RA) on day 10 and 1 µM purmorphamine (targeting smoothened of the SHH signaling pathway, pur) at day 15 to pattern NE cells to ventral spinal progenitor fate, which expresses Olig2. After plating spheres on substrates, several neurotrophic factors and cAMP are added to support the survival and process outgrowth of motor neurons expressing HB9 (Hu and Zhang, 2009). Although later reports added dual inhibition of SMAD signaling and smoothed agonist (SAG) or compound C (AMPK inhibitor) on the basis of a previous protocol (Amoroso et al., 2013; Qu et al., 2014), signiﬁcantly shortening the differentiation time, the purity of motor neurons still requires improvement. Surprisingly, Du and his colleagues (Du et al., 2015) used a small-molecule cocktail including SB, DMH1 (SMAD inhibitor), CHIR, RA, and pur to obtain a near-pure population of OLG2− MNPs in 12 days. Then, they added compound E (a NOTCH inhibitor) during MN maturation to improve the purity of motor neurons, resulting in the generation of highly pure (>90%) motor neurons expressing CHAT in 16 days. Because of the shorter time for differentiation into highly pure motor neurons, the protocol has been widely applied in the disease modeling research (Ding et al., 2022; Liu et al., 2022).

AD, PD, and ALS involve corresponding neurons, thereby accurate differentiation of iPSC is significant for research. For instance, mature dopamine neuron subtypes co-expressing TH, NR4A2, and FOXA2 have different gene expression proﬁles and have differential responses to oxidative stress (Fernandes et al., 2020), emphasizing that there remains a need for referring to the protocol established by other laboratories using small chemical molecules to generate more mature and speciﬁc neurons. Table 1 summarizes the mainstream protocols of astrocytes, DA neurons, and MNs differentiation. The most widely applied protocols were featured as less time-consuming and with high purity. The cost of small molecule compounds applied in the protocol also needs to be considered.

3 IPSC modeling in neurodegenerative diseases

AD is divided into familial AD (FAD) and sporadic AD (sAD), and FAD constitutes less than 3% of all AD subtypes. The APP gene and the proteolytic enzymes that produce peptide Aβ, presenilin 1 and 2, are the two primary genes that are mutated in FAD (Garcia-Morales et al., 2021). iPSC modeling demonstrates that there are some common pathological features in FAD and sAD (Belanger et al., 2011; Piers et al., 2020). Jones et al. induced astrocytes derived from AD iPSC have been reported to display cellular atrophy and to have aberrant expression and localization of S100B, EAAT1 and GS, which are cell-autonomous instead of compromised neuronal intermediates, supporting the conjecture that astrocyte dysfunction is an early hallmark of AD (Jones et al., 2017). Moreover, iPSC modeling provides a comprehensive phenotype study of AD. PSEN1 iPSC-derived astrocytes displayed robust accumulation of full-length presenilin-1, increased secretion and compromised uptake of Aβ1–42, disturbed Ca2+ signaling, and altered metabolism (Oksanen et al., 2017). In addition, astrocytes derived from AD iPSC co-cultured with healthy astrocytes provide an opportunity to observe the pathological microenvironment, including the effects of AD astrocytes and autonomic response of healthy astrocytes.

Likewise, SNCA (α-synuclein), PARK2 (parkin), PARK7 (DJ-1), PINK1 and LRRK2 are the mutated genes of parkinsonism, among which mutations in both PARK2 (parkin) and LRRK2 are the most common genetic causes (Healy et al., 2008). However, the cause of PD remains unclear at the molecular level. iPSC modeling of mutant genes, including PARK2 and LRRK2, helps to investigate PD occurrence and development, and can target a pathway to delay disease progression (Cooper et al., 2012; Wasner et al., 2022). In PD iPSC-derived DA neurons, Jian Feng found higher protein level of tyrosine hydroxylase (TH) and high ROS levels. Moreover, there is no significant alterations in DA levels, which might be due to homeostatic regulation (Ren et al.,
However, decreased TH mRNA level and DA release were reported in postmortem brain tissues and cerebrospinal fluid of PD patients respectively (Goldstein et al., 2012; Zhang et al., 2022). The inconsistent phenotype between iPSC modeling and postmortem tissues may precisely account for the transition from early to late stage of diseases. Young-onset PD iPSC-derived DA neurons displayed increased accumulation of soluble α-synuclein protein and phosphorylated protein kinase Ca, as well as dysregulated of lysosomal biogenesis and function, establishing a highly predictive phenotype of young-onset PD (Laperle et al., 2020).

ALS familial ALS (fALS) and sporadic ALS (sALS). In fALS, mutations in the "superoxide dismutase 1" (SOD1) gene are the most popular genetic factor, and the remaining common mutation genes are "fused in sarcoma" (FUS), "TAR DNA binding protein" (TARDBP), or a hexanucleotide repeat expansion in the "chromosome nine open reading frame 72" (C9ORF72) (Taylor et al., 2016). ALS-related iPSC modeling is

### TABLE 1 Protocols of Astrocytes, DA neurons and MNs differentiation.

| Cell type   | EGF   | FGF2  | CNTF   | Days | Purity | reference                  |
|-------------|-------|-------|--------|------|--------|----------------------------|
| Astrocytes  | D21-D90 10 ng/ml | D21-D90 10 ng/ml | D84-D90 10 ng/ml | 90–120 | >90% S100β/GFAP° | Krencik and Zhang, (2011) |
| Day6-12 20 ng/ml | Day6-9 10 ng/ml (FGF) | Day9-35 20 ng/ml | Day9-15 20 ng/ml | 35 | 78% GFAP° | Emdad et al. (2011) |
| Day28–35 | Day28–35; Day90-97 50 ng/ml | Day15-31 | Day15-45 20 ng/ml | 100 | ~100% S100β° | Roybon et al. (2013) |
| — | Day15-45 20 ng/ml | — | — | 45 | 90% S100β° 82% GFAP° | Tcw et al. (2017) |

| CHIR | SHH | FGF8 | Days | purity | References |
|------|-----|------|------|--------|------------|
| DA neurons | - | Day12-42 100 ng/ml | Day12-42 100 ng/ml | 49 | <1% TH/β-tubulin/FOX2° | Cooper et al. (2010) |
| Day3-13 3μM | Day1-7 100 ng/ml | Day 1-7 100 ng/ml | 50 | 70%-80%TH° | Kriks et al. (2011) |
| Day1-11 0.4 μM | Day11-11 500 ng/ml | Day12-28 100 ng/ml | Day12-28 20 ng/ml | 35 | 43.6 ± 6.2% cells TH°, which co-expressed Nurr1 (95.3 ± 2.4%), En1 (96.2 ± 1.1%) | Xi et al. (2012) |
| Day1-6 1 μM | Day7-18 100 ng/ml | Day7-18 100 ng/ml | 32 | 10.5% TH°/GIRK2° | Wang et al. (2015) |
| Day0-4 0.7 μM | Day0-7 500 ng/ml | - | - | - | Kim et al. (2021) |
| Day4-10 7.5 μM | — | — | — | — | — |
| Day10-11 3 μM | — | — | — | — | — |

| CHIR | Compound C | SHH | Days | purity | References |
|------|------------|-----|------|--------|------------|
| MNs | — | Day15-28 100 ng/ml | Day15-28 100 ng/ml | 35 | ~50% HB9 ° | Hu and Zhang, (2009) |
| — | Day0-12 2 μM | Day12-22 100-500 ng/ml | Day12-22 | 35 | — | Egawa et al. (2012) |
| — | Day0-6 1 μM | Day6-20 100 ng/ml (purmorphamine) | Day6-20 100 ng/ml | 24 | 69.5% HB9° | Qu et al. (2014) |
| Day0-6 3 μM | — | Day6-12 0.5 μM | Day6-12 0.5 μM | 28 | 90% HB9° | Du et al. (2015) |
| Day0-6 12 μM | — | Day12-18 0.1 μM | Day12-18 0.1 μM | 95% ISL1° 91% CHAT° | |
| Day0-6 3 μM | Day0-6 1 μM | Day2-19 500 ng/ml | Day2-19 500 ng/ml | 30 | 90% Tuji1° 90% CHAT° | Dafinca et al. (2020) |

FGF, epidermal growth factor; FGF2/8, Fibroblast growth factor2/8; CNTF, ciliary neurotrophic factor; CHIR, GSK3 inhibitor; SHH, sonic hedgehog agonist; Compound C, AMPK, inhibitor.
able to reveal the sequence of its occurrence and development and provide a platform to explore the molecular mechanism of its pathology (Chen et al., 2014; Kiskinis et al., 2014; Lopez-Gonzalez et al., 2016; Dafina et al., 2020; Altman et al., 2021). Chen et al. generated MNs and non-MNs derived from ALS SOD1 iPSC to reveal that neurofilament aggregation is an early event in ALS pathogenesis, resulting from the dysregulation of NF subunit proportion caused by SOD1 mutant binding NF-L mRNA in MNs (Chen et al., 2014). Likewise, iPSC modeling undoubtedly provides a good research tool for studying of sporadic ALS (Burkhardt et al., 2013; Fujimori et al., 2018a; Fujimori et al., 2018b; Coyne et al., 2021). Moreover, it has been found that intranuclear TDP-43 aggregation in iPSC-derived MNs reprogrammed from three sALS patients and firstly validated it in postmortem tissue from one of the previous sALS patients, which highlights the importance of iPSC modeling in sALS (Burkhardt et al., 2013).

4 Advantages and disadvantages of iPSC modeling

IPSC modeling of different phenotypes using mature protocols showcased stability and scalability, which together with its high yield facilitates high-throughput screening of clinical drugs (Pasteuning-Vuhman et al., 2021). In addition, iPSC modeling overcame the problem of clinical drug screening caused by heterogeneity of NDDs patients. Okano et al. used two types of MNs carrying FUS and TDP43 to screen 1,232 drugs. They ultimately selected ropinirole as the candidate, which is ineffective on the phenotypes of SOD1-mutant iPSC-derived MNs (Fujimori et al., 2018a). Thus, iPSC-derived neurons carrying patients' specific genetic background help to identify drug responders, contributing to patient stratification in clinical studies (Haston and Finkbeiner, 2016).

In addition, iPSC-based disease modeling in vitro is different from animal models, including the neuronal physiological morphology and function and the molecular characteristics of pathological states. In AD, human protoplasmic astrocytes are bigger and more complex than their rodent counterparts, and the calcium wave in mouse astrocytes transmitted much more slowly than in human astrocytes (Oberheim et al., 2009). Chen et al. reported that there was no SOD1 aggregation or mitochondrial swelling in human ALS MNs but these appeared in SOD1 transgenic mice (Chen et al., 2014). Most importantly, mouse models fail to mimic sporadic neurodegenerative diseases, which account for most NDDs (Hawrot et al., 2020). However, mouse models are advantageous because they exhibit complex interactions between cells and the microenvironment, as well as provide behavioral assessment and pharmacokinetics features (Ke et al., 2021). Therefore, a promising way with the combination of advantages in both iPSC modeling and mouse models would contribute to a complementary and comprehensive view of NDD researches.

There are still some limitations for iPSC remodeling NDDs, such as the lack of aging-signature. Lorenz Studer and his lab overexpressed progeria with the treatment of modified-RNAs in PD iPSC-derived DA neurons, and found a significant reduction in dendrite length and downregulation of AKT signaling (Miller et al., 2013). Moreover, chemical pretreatment also accelerates the maturation of neurons (Fujimori et al., 2018a). Thus, progerin-induction or chemical pretreatment combing with iPSC-modeling overcomes the problem of iPSCs taking a long time to naturally develop into the degenerative disease stage, which mainly includes the expression of aging signatures. Another modeling method is direct neuronal conversion to induced neurons (iNs), which maintains the aging signature and epigenetic status of neurons (Vierbuchen et al., 2010; Mertens et al., 2015). However, the high cost and low cell output limit its application; future improvements should address these issues.

5 Normal mitochondrial function

IPSC modeling has undoubtedly greatly contributed to the knowledge of degenerative diseases, including mitochondrial dysfunction. Healthy mitochondria can maintain their own homeostasis through mitochondrial dynamics and autophagy even in the face of external stimuli, thereby exerting stable functions (Figure 1).

5.1 Mitochondrial dynamics and transport

Mitochondria continuously undergo fusion and fission, which are known as mitochondrial dynamics, to exchange metabolites (Schreper and Scorrano, 2016). MFN1 (membrane protein mitofusin 1) and MFN2 (membrane protein mitofusin 2) are fusion-related proteins, while DRP1 (dynamin-related protein 1) and Fis1 (mitochondrial fission one protein) are responsible for mitochondrial fission. Mitochondrial transport between Soma and distal axonal was mediated by motor proteins kinesin and dynein, which correspond to anterograde and retrograde transport respectively (Lin and Sheng, 2015). Moreover, miro and Milton serve as motor adaptors involved in mitochondrial transport (Lin and Sheng, 2015). It is reported that defective mitochondrial transport has been associated with NDDs (Cozzolino et al., 2013; Cai and Tammineni, 2017; Prots et al., 2018).

5.2 Mitochondrial ROS and mitophagy

Reactive oxygen species (ROS) include free radicals such as superoxide anion (O2\(^-\)), hydroxyl radical (HO\(^-\)), and non-radical hydrogen peroxide (H\(_2\)O\(_2\)), which are the endogenous sources of a mitochondrial respiratory chain under the high
demand of neurons for oxygen and ATP (Chen et al., 2012). There is a hypothesis that mutant SOD1 has the ability to generate HO$^-$ from H$_2$O$_2$, thus creating an oxidative environment and toxic aggregates in MNs (Julien, 2001).

As for PINK1/parkin-mediated mitophagy, When the mitochondrial membrane potential decreases, PINK1 accumulates in mitochondria and gets autophosphorylation, which subsequently triggers ubiquitin phosphorylation, and recruits parkin to damaged mitochondria. Subsequently, Parkin ubiquitinates mitochondrial outer membrane proteins and Optineurin interacts with these proteins tagged by ubiquitin and targets the isolation membrane to damaged mitochondria, which are eventually sent to lysosomes for degradation (Wei et al., 2015; Rasool et al., 2018; Goiran et al., 2022; Pradeepkiran et al., 2022).

5.3 Mitochondrial energy metabolism

Neurons in the brain need energy expenditure to maintain various functional activities, including synaptic transmission processes (Faria-Pereira and Morais, 2022). The major metabolic precursors for biosynthesis and energy generation come from the TCA cycle and glycolysis (Zheng et al., 2016). The pyruvate molecules produced in cytosolic glycolysis can be imported into the mitochondria and generate acetyl-CoA molecules, which will enter the tricarboxylic acid (TCA) cycle. Finally, OXPHOS complexes located in mitochondrial inter membrane uses NADH and FADH2 to generate ATP.

![Diagram of mitochondrial dynamics, transport, PINK1/parkin-mediated mitophagy and energy metabolism](https://BioRender.com)
Mitochondrial dysfunction and therapeutic strategies in iPSC modeling

It is widely recognized that neurodegenerative diseases are closely related to mitochondrial dysfunction (Wang et al., 2009; Queliconi et al., 2021; Mehta et al., 2022). Just as the same disease may manifest in different ways, so the same disease modeling will also have different representations of mitochondrial dysfunction. Tables 2–4 summarizes the iPSC-based modeling of AD, PD, ALS, and the associated characterization of mitochondrial dysfunction. As for neurons derived from AD or PD iPSC, they mostly exhibit impaired mitophagy and dysregulated mitochondrial dynamics including increased mitochondrial fragments, while aberrant mitochondrial transport and reduced MMP are more common in ALS iPSC derived MNs (Dafinca et al., 2016; Zanon et al., 2017;...
Naumann et al., 2018; Martín-Maestro et al., 2019; Li et al., 2020). Also, PD iPSC modeling has shown abnormal mitochondrial morphology and increased ROS level (Imaizumi et al., 2012; Shaltouki et al., 2015; Chung et al., 2016). Furthermore, neurons from iPSC of NDDs manifest abnormal energy metabolism, showing decreased basal glycolysis and ATP level in AD iPSC modeling (Bélanger et al., 2011; Konttinen et al., 2019), reduced of complex I activity and decreased basal respiration in PD iPSC modeling (Zanon et al., 2017; Zambon et al., 2019), as well as impaired basal respiration and increased glycolysis in ALS iPSC modeling (Hor et al., 2021; Mehta et al., 2021). Sometimes neurons carrying the same mutant gene displayed different even contradictory energy metabolism, which may be attributed to the culture state and sensible to testing environment. Moreover, these pathological mechanisms are interconnected. Many studies have confirmed that the mitochondrial fusion and fission machinery is coupled with mitochondrial transport and mitophagy (Misko et al., 2010; Wu et al., 2016; Gao et al., 2017). Mitophagy regulates the mitochondrial energetic status in neurons (Han et al., 2021), thus damage to any link may lead to the occurrence and development of NDDs. Next, we describe mitochondrial dysfunctions of mitochondrial dynamic, transport, mitophagy, and energy metabolism abnormalities in AD, PD, ALS, and their corresponding treatment strategies.

### 6.1 Alzheimer’s disease

In AD, a study reported that the balance of mitochondrial fusion and fission was disrupted in PSEN1-E120K iPSC-derived cortical neurons, with an increase in DRP1 and a decrease in MFN1 (Li L. et al., 2018). After 2 years, this team found the same phenomenon in PSEN1-S170F iPSC-derived cortical neurons (Li et al., 2020). Aβ and phosphorylated tau interact with DRP1, which activates DRP1 by different pathways, causing impairments in mitochondrial dynamics (Manczak et al., 2011; Kandimalla et al., 2016). Since Aβ is produced by the sequential cleavage of APP via β-site APP cleaving enzyme 1 (BACE1), so γ-secretase, an inhibitor of BACE1 (BSI and 5 μmol/L LY2884721), significantly reduced the levels of Aβ and p-Tau (Li et al., 2020). However, Fang explained that defective mitophagy induces AMPK activation (p-AMPK), which leads to excessive mitochondrial fragmentation. They used two mitophagy detection nematode lines to screen the enhancer for mitophagy, which ameliorated neuronal pathology and mitochondrial fragments in AD iPSC-derived cortical neurons (Fang et al., 2019).

Mitophagy plays an important role in maintaining cell homeostasis, including the removal of damaged mitochondria and resistance to oxidative stress (Scheibye-Knudsen et al., 2015). Martin-Maestro et al. demonstrated dysregulation of mitophagy because of deficient lysosomal function in iPSC-derived cortical neurons from FAD patients harboring PSEN1 A246E mutation (Martin-Maestro et al., 2017). After 2 years, they found the same problem in PSEN1 M146L iPSC-derived NSCs, along with the downregulation of oxidative phosphorylation (OXPHOS)-related proteins, suggesting an impaired mitochondrial respiratory chain (Martin-Maestro et al., 2019). Deficiency in autophagy induction and lysosomal acidification was confirmed as the main reason for mitophagy failure, and that was corrected by using bexarotene, an FDA-approved retinoid X receptor (RXR) agonist, whose therapeutic efficacy stems from increased mitophagy flux (Martin-Maestro et al., 2019). Another study reported that the abnormal accumulation of Aβ and p-Tau decreases the levels of TABLE 4 Mitochondrial dysfunction in iPSC-derived MNs modeling of ALS.

| Type  | Mutated gene | Mitochondrial dysfunction | References                               |
|-------|--------------|---------------------------|-----------------------------------------|
| fALS  | C9orf72      | Increased ROS level       | Lopez-Gonzalez et al. (2016)            |
| fALS  | FUS          | Stalled and short mitochondrion, lost membrane potential on distal axon | Naumann et al. (2018)                   |
| sALS  | C9orf72      | Reduced MMP, abnormal mitochondrial morphology | Dafinca et al. (2016)                   |
| fALS  | FUS          | Reduced number of moving mitochondria | Guo et al. (2017)                       |
| fALS  | A4V          | More vacuolar mitochondria, reduced number of moving mitochondria | Kiskinis et al. (2014)                  |
| fALS  | C9orf72 TARDBP | Impaired mitochondrial Ca2+ buffering | Dafinca et al. (2020)                   |
| fALS  | TARDBP       | Reduced number of moving mitochondria | Fazal et al. (2021)                     |
| fALS  | SOD1         | Reduced MMP, increased mean length of mitochondria, Reduced ATP Levels | Gunther et al. (2022)                   |
| fALS  | TARDBP       | Mitochondrial fragmentation | Choi et al. (2020)                      |
| fALS  | C9orf72      | Impaired basal respiration | Mehta et al. (2021)                     |
| fALS  | SOD1 TARDBP C9orf72 | Reduced basal respiration and ATP production, increased glycolysis and lactate | Hor et al. (2021)                      |
| sALS  | sALS2        | Reduced basal respiration and ATP production, increased glycolysis and lactate | Hor et al. (2021)                      |
| sALS  | sALS3        |                                                                           |                                          |
activated mitophagy proteins in AD iPSC-derived cortical neurons, leading to the accumulation of damaged mitochondria and the elevation of ROS levels (Fang et al., 2019). The authors screened two mitophagy inducers (urothiin A and actininon) to restore mitophagy, further improving mitochondrial function by reducing mitochondrial ROS and ameliorating AD’s pathology. As mentioned above, treatments targeting impaired mitophagy display a significant role in rescuing neuronal apoptosis (Shaltouki et al., 2018; Fang et al., 2019). In addition, Kshirsagar et al. found that several mitophagy enhancers, especially UA were able to rescue mitochondrial dysfunction and increase cell survival in AD HT22 cell models, indicating that mitophagy enhancers could developed as drugs to delay neurodegenerative pathology in clinical patients (Kshirsagar et al., 2021, 2022).

With regard to energy metabolism, Minna Oksanen et al. reported increased basal respiration and decreased basal glycolysis in PSEN1 iPSC-derived astrocytes, as typical astrocytes rely more on glycolysis (Bélanger et al., 2011). Additionally, the authors detected more cellular ROS and less lactate secretion in these astrocytes, suggesting that the energy metabolism activity of the PSEN1 mutation made a switch from glycolysis to OXPHOS (Oksanen et al., 2017). Given that neurons may sustain themselves with lactate generated by glycolysis, this alteration may not be advantageous to astrocytes (Figley, 2011). Similarly, another study conducted by the same laboratory reported impaired fatty acid oxidation (FAO) except for the same changes in basal respiration and basal glycolysis in PSEN1 iPSC-derived astrocytes, and using a PPARβ/δ-agonist is beneficial for impaired FAO and memory deficits in APP/PSEN1 mice (Konttinen et al., 2019). Ryu et al. published a more specific metabolism study of AD astrocytes and NPC. Their results showed increased mitochondrial respiration, energy (ATP) output, and elevated glycolytic activity, which are partly different from the results of previous studies. Considering the reduced ability to absorb glucose, as well as the deficiencies in the generation and transfer of reducing agents throughout the glycolytic process and the mitochondrial respiratory chain, upregulating OXPHOS and glycolysis is the way for AD astrocytes and NPCs to overcompensate. Moreover, the levels of NAD+ and NADH are significantly decreased in AD astrocytes in NPC, despite the general biochemical reducing power in LOAD not being compromised, which reflects aberrant energy metabolic activity in AD astrocytes and NPC (Ryu et al., 2021).

6.2 Parkinson’s disease

Regarding PD, its main mutated genes, PARK2 and PINK1, are involved in mitochondrial functions, and there is no doubt that mitochondrial dysfunction is one of the pathological features of Zanon reported that DA neurons derived from the PARK2 mutation carrier iPSC-B125 showed fragmented mitochondria, which was compensated by SLP-2 overexpression (Zanon et al., 2017). Parkin and SLP-2 are able to interact functionally to maintain mitochondrial function (Zanon et al., 2017). Ke et al. detected upregulation of the fission proteins DRP1 and Fis1 and downregulation of the fusion protein Mfn1 in PLA2G6 mutant DA neurons (Ke et al., 2020). The PLA2G6 mutant induced ER stress, which facilitated the unfolded protein response (UPR), resulting in decreased signaling of CREB and final mitochondrial fragments. Thus, they used azoramide (a small-molecule modulator) to enhance the CERB signaling, and rescue mitochondrial function, thereby preventing the apoptosis of DA neurons (Ke et al., 2020). Given that the PD-associated LRRK2 mutant interacts with DRP1 to recruit and phosphorylate mitochondrial DRP1 (Wang et al., 2012), it is not surprising that Su and Qi found increased mitochondrial fragmentation in LRRK2 G2019S-derived DA neurons, and used P110 to inhibit the hyperactivation of DRP1 to reduce mitochondrial fragments (Su and Qi, 2013).

Mitophagy is closely related to the pathological mechanism of PD. Aberrant elimination of mitochondria treated with carbonyl cyanide m-chlorophenyl hydrazine (CCCP) was reported in PARK2 iPSC-derived neurons (Imaizumi et al., 2012). Mitophagy plays an important role in maintaining cell homeostasis, including the removal of damaged mitochondria and resistance to oxidative stress (Scheibe-Knudsen et al., 2015). Yu-Chin Su and colleagues detected increased mitochondrial fragmentation, which resulted in a defective ETC complex and an elevated level of mitochondrial ROS by DRP1 hyperactivation in LRRK2 G2019S DA neurons (Su and Qi, 2013). Subsequently, increased mitochondrial fragmentation simulates excessive mitophagy, which causes a loss of mitochondrial mass. This mitochondrial dysfunction was solved by P110 treatment which inhibits DRP1 hyperactivation (Su and Qi, 2013). Some studies focusing on PARK2 and PINK1 iPSC-derived DA neurons respectively reported higher mitochondrial ROS levels and defective mitophagy (Chung et al., 2016; Oh et al., 2017), among which the author found the PINK1(C568A) mutant could be able to mimic PINK1 S-nitrosylated caused by endogenous NOS, and this PINK1(C568A) mutant prevented parkin from translocating to mitochondrial membrane, thus resulting in impaired mitophagy and neuronal death (Oh et al., 2017). Treatment of these cells with L-NAME could be able to ameliorate damaged mitophagy and neuronal death by inhibiting the production of NOS (Oh et al., 2017).
mitophagy starts (Glater et al., 2006; Wang et al., 2011). Shaltouki and Hsieh found that accumulation of mir1 delayed the initiation of mitophagy in both LRRK2 G2019S and SCNA A53T iPSC-derived DA neurons, and decreased the level of mir1 protein by RNAi promoted mitophagy, and further rescued neurodegeneration (Hsieh et al., 2016; Shaltouki et al., 2018).

In PD SNCA iPSC-derived DA neurons, Zambon et al. found a decrease in basal respiration, spare capacity, ATP and lactate production, and no significant differences in glycolytic activity, suggesting deficits in mitochondrial energy metabolism (Zambon et al., 2019). This suggests that the association between α Syn and TOM20 leads to mitochondrial metabolic dysfunction (Di Maio et al., 2016; Zambon et al., 2019). PINK1 mutant iPSC-derived DA neurons were found to have reduced levels of ATP production, which was improved by treatment with cerulenin to rescue PINK1 deficiency (Vos et al., 2017). Fernandes5 reported downregulation of OXPHOS-related gene expression and upregulation of glycolysis-related gene expression under oxidative stress conditions in one type of SNCA DA neurons (Fernandes et al., 2020). PARK2 knockout DA neurons were reported to have reduced basal respiration and ATP production under only lactate respiration, along with decreased glycolysis and accumulation of lactate, which was confirmed by proteomic and metabolomic analysis of dysregulated key factors and enzymes in mitochondrial energy metabolism (Bogetofte et al., 2019; Okarmus et al., 2021).

### 6.3 Amyotrophic lateral sclerosis

Impaired mitochondrial dynamics can also be observed in ALS-related MN. It was reported that activation of PP1 dephosphorylates DRP1 S616, resulting in increased mitochondrial fission in cortical neuron carrying PSEN1 mutant, and BACE1 inhibited the abnormal accumulation of Aβ and p-Tau to ameliorate mitochondrial fission. Abnormal accumulation of Aβ and p-Tau decreased the levels of activated mitophagy proteins, leading to the abnormal mitophagy in AD iPSC-derived cortical neurons; actinonin, urolithin A and bexarotene are able to restore abnormal mitophagy through their own mechanism. AD iPSC-derived astrocytes showed abnormal energy metabolism including increased mitochondrial respiration and elevated glycolytic activity.
movement-related protein miro1 preferentially localizes in MAM sites; thus, mitochondrial transport will decrease (Macaskill et al., 2009; Stoica et al., 2014). Interestingly, both different MNs’ mitochondrial transport defects can be solved by HDAC inhibitors, possibly because a rise in the acetylation of α-tubulin increases the number of motor proteins binding to the microtubules, which leads to an increase in mitochondrial transport (Guo et al., 2017).

Surprisingly, mutant forms of proteins (such as optineurin OPTN and TBK1) involved in mediating mitophagy are associated with ALS (Wong and Holzbaur, 2014; Moore and Holzbaur, 2016; Harding et al., 2021); however, there are few articles related to iPSC-based ALS modeling that characterized by defects in mitophagy. Moreover, ALS animals and other cells which transfected the mutated gene of ALS were used to report mitophagy defects (Palomo et al., 2018; Foster et al., 2020). For instance, the mitochondria in N2A cells transfected with SOD1 displayed low levels of mitophagy and high levels of ROS. This can be explained by the fact that mutated SOD1 binds to OPTN and sequesters it in N2A cells, thereby disrupting mitophagy, which in turn leads to increased ROS release (Tak et al., 2020). Overexpression of OPTN reduces the cytotoxicity of mutant SOD1, thus improving mitophagy and decreasing ROS levels (Tak et al., 2020). In addition, there are pathways to control mitochondrial quality except for mitophagy (Lin et al., 2017; Gautam et al., 2019).Mukesh Gautam et al. found a unique self-destructive path for mitochondria, and the morphology of defective mitochondria changed including being elongated and curling themselves, then beginning to disintegrate from the inner membrane and the cristae, and...
finally being eliminated (Gautam et al., 2019). Therefore, whether mitophagy disorder occurs in iPSC-derived MNs carrying mutated ALS-related genes warrants further investigation.

Mitochondrial energy metabolic dysfunction is also a pathologic characteristic of ALS. There are diverse, specialized cell populations in the mammalian brain, and related studies have also suggested that bioenergetic genes and metabolic patterns in different cell types are differentially altered in developing cells or diseases, such as astrocytes and MNs (Qi et al., 2019). Vandoorne et al. reported an interesting finding that when iPSC is differentiated into MNs, its metabolic pattern shifts from glycolytic to oxidative metabolism, along with reduced glycolytic flux and elevated TCA cycle activity (Vandoorne et al., 2019). In addition, the ALS-related FUS mutant does not change the energy metabolism of MNs. Another study focusing on MNs carrying the C9orf72 mutant reported impaired basal and maximal mitochondrial respiration; however, glycolytic function was not affected (Mehta et al., 2021). Moreover, the transcriptomic analysis showed decreased gene expression of the mitochondrial ETC, which was restored by overexpression of PGC1α to stimulate mitochondrial biogenesis and improve mitochondrial function (Mehta et al., 2021). Günther et al. reported that SOD1 mutant iPSC-derived MNs displayed low levels of ATP without other mitochondrial metabolic changes (Günther et al., 2022). Hor and colleagues used three sALS iPSC line-derived MNs and three fALS iPSC line-derived MNs carrying SOD1, TDP43, and C9orf72 mutants to find reductions in basal respiration, ATP production, and spare respiratory capacity, causing increased glycolysis and lactate. These abnormal changes illustrate impaired mitochondrial respiration and a compensatory response by ALS MNs (Hor et al., 2021). Notably, treatment with C12 ameliorated the mitochondrial energetic through the restoration of OXPHOS and glycolysis as well as the correction of mitochondrial dysfunctions have become increasingly important therapeutic targets for delaying the progression of NDDs (Cannane et al., 2020).

7 Discussion

NDDs are one of the most widespread diseases with a low cure rate, bringing enormous physical pain and economic pressure to patients and a heavy burden to society. At present, our exploration of the NDD is not thorough yet. iPSC modeling provides a panoramic view of the pathophysiology of NDDs. Unlike other models, this type of modeling enables the early-phase mechanism to be uncovered. Moreover, in the era of precise medication, it is a promising method for the personalized identification of unique molecular features in NDDs of either the sporadic or the familiar type.

This review showed different mitochondrial dysfunction in AD, PD, and ALS, along with feasible treatments ameliorating these mitochondrial defects or even inhibiting disease progress (Figures 2–4). Mitochondrial dysfunction is one of the early pathological features of NDDs (Lin and Beal, 2006). Moreover, the impairment of mitochondria can directly threaten neural survival and trigger neurodegeneration, and the deteriorating microenvironment of neurodegeneration in turn exacerbates mitochondrial dysfunction, leading to the continued progression of NDDs (Onishi et al., 2021; Jetto et al., 2022). Therapeutic measures are divided into two types those that target pathways and those that target sources—for example, targeting a molecule in the disease signaling pathway or targeting compensation for damaged mitochondria to correct mitochondrial dysfunction. However, extensive animal experiments and preclinical trials are required to confirm the safety and efficacy of drugs before these therapeutic strategies can be translated into clinical drugs.

In conclusion, the use of iPSC-based modeling to characterize mitochondrial dysfunction in NDDs reviewed in this paper can provide a reference for other research studies, and these modeling methods provide an effective platform for mechanistic research and drug screening in NDDs. In the future, developing more effective and affordable treatment strategies may improve the quality of life for the majority of NDD patients.

Author contributions

H-ML designed and wrote the manuscript. D-XH, Y-QC, Y-ZL, Y-JL searched and interpret the relevant literature. JX, HC supervised and revised the paper. All authors have read and agreed to the published version of the manuscript.

Funding

This work was supported by the National Natural Science Foundation of China (82171422); Key Research and Development Project of Hubei Province of China (2022BCA028).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.
regionalization by retinoic acid.

neural cells from patients with familial Parkinson
dopaminergic neurons requires a high activity form of SHH, FGF8a and speci

activity in amyotrophic lateral sclerosis.

et al. (2021). Nuclear accumulation of CHMP7 initiates nuclear pore complex injury

neurons exhibit mitochondrial dysfunction and

E. V., et al. (2016). Parkin and PINK1 patient iPSC-derived midbrain dopamine

References

Dorsey, E. R., and Bloem, B. R. (2018). The Parkinson pandemic-A call to action.

References

Luo et al. 10.3389/fcell.2022.1030390

Frontiers in Cell and Developmental Biology frontiersin.org 13

Frontiers in Cell and Developmental Biology
Okarmus, J., Havelund, J. F., Ryding, M., Schmidt, S. I., Bogetofte, H., Heon, Robert, R., et al. (2021). Identification of bioactive metabolites in human iPSC-derived dopaminergic neurons with PARK2 mutation: Altered mitochondrial and energy metabolism. Stem Cell Rep. 16 (6), 1510–1526. doi:10.1016/j.stemcr.2021.04.022

Oksanen, M., Petersen, A. J., Naumenko, N., Puttonen, K., Lehkonen, S., Gabert, Olive, M., et al. (2017). PSEN1 mutant iPSC-derived model reveals severe astrocyte pathology in Alzheimer’s disease. Stem Cell Rep. 9 (6), 1885–1897. doi:10.1016/j.stemcr.2017.10.016

Onishi, M., Yamano, K., Sato, M., Matsuda, N., and Okamoto, K. (2021). Molecular mechanisms and physiological functions of mitophagy. EMBO J. 40 (3), e104705. doi:10.15252/embj.2020104705

Ono, Y., Nakatani, T., Sakamoto, Y., Minahara, E., Minaki, Y., Kuma, M., et al. (2007). Differences in neurogenic potential in floor plate cells along an anteroposterior location. Midbrain dopaminergic neurons originate from mesencephalic floor plate cells. Development 134 (17), 3213–3225. doi:10.1242/dev.02879

Palomo, G. M., Granatiero, V., Kawamura, H., Konrad, C., Kim, M., Arregui, A. J., et al. (2018). Parkin is a disease modifier in the mutant SOD1 mouse model of ALS. EMBO Mol. Med. 10 (10), e8888. doi:10.15252/emmm.201808888

Pardo-Moreno, T., González-Acedo, A., Rivás-Dominguez, A., García-Morales, V., García-Gozar, F. J., et al. (2022). Therapeutic approach to Alzheimer’s disease: Current treatments and new perspectives. Pharmaconas 14 (6). doi:10.3930/pharcomet.1406117

Park, C. Y., Kim, J., Kweon, J., Son Jeong, S., Lee Jae, S., Yoo, J.-E., et al. (2014). Targeted inversion and reversion of the blood coagulation factor 8 gene in human iPSC cells using TALENS. Proc. Natl. Acad. Sci. U. S. A. 111 (25), 9253–9258. doi:10.1073/pnas.1323941111

Pastue, U., Fhausen, S., de Jongh, R., Timmers, A., and Pasterkamp, R. J. (2021). Towards advanced iPSC-based drug development for neurodegenerative disease. Trends Mol. Med. 27 (3), 263–279. doi:10.1016/j.molmed.2020.09.013

Piers, T. M., Coaker, K., Mallach, A., Johnson, G. T., Guerreiro, R., Hardy, J., et al. (2020). A locked immunometabolic switch underlies TREM2 R47H loss of function in human iPSC-derived microglia. Faseb J. 34 (2), 2436–2456. doi:10.1096/fj.2019024775

Placzek, M., and Briscoe, J. (2005). The floor plate: Multiple cells, multiple signals. Nat. Rev. Neurosci. 6 (3), 230–240. doi:10.1038/nrn1628

Pradeepkiran, J. A., Ahn, H., Kohsiras, R., and Reddy, P. H. (2022). Are mitochondria the therapeutic target for Alzheimer’s disease? Biomed. Pharmacother. 149, 112918. doi:10.1016/j.biopha.2022.112918

Prots, I., Girosh, J., Brazez, R. M., Simmacher, K., Veber, V., Hartveck, S., et al. (2018). s-Yunuclein oligomers induce early axonal dysfunction in human iPSC-models of synucleinopathies. Proc. Natl. Acad. Sci. U. S. A. 115 (30), 7813–7818. doi:10.1073/pnas.1713129115

Qi, G., Mi, Y., and Yin, F. (2019). Cellular specificity and inter-cellular coordination in the brain bioenergetic system: Implications for aging and neurodegeneration. Front. Physiol. 10, 1531. doi:10.3389/fphys.2019.01534

Qu, Q., Li, D., Louis, K. R., Li, X., Yang, H., Sun, Q., et al. (2014). High-efficiency motor neuron differentiation from human pluripotent stem cells and the function of Islet-1. Nat. Commun. 5 (1), 3449. doi:10.1038/ncomms4449

Quellicioni, B. B., Kojima, W., Kimura, M., Imai, K., Udagawa, C., Motono, C., et al. (2021). Unfolding is the driving force for mitochondrial import and degradation of the Parkinson’s disease-related protein DJ-1. J. Cell Sci. 134 (22), 258653. doi:10.1242/jcs.258653

Rasool, S., Soya, N., Tranog, L., Croteau, N., Lukacs, G. L., and Trempe, J. F. (2018). PKIN1 autophosphorylation is required for ubiquitin recognition. EMBO Rep. 19 (4), e44981. doi:10.15252/embr.201744981

Ren, Y., Jiang, H., Pu, J., Li, L., Wu, J., Yan, Y., et al. (2022). Molecular features of Parkinson’s disease in patient-derived midbrain dopaminergic neurons. Mov. Disord. 37 (1), 70–79. doi:10.1002/mds.28786

Rybovn, L., Lasma, N. J., Garcia-Diaz, A., Yang, E. J., Sattler, R., Jackson-Lewis, V., et al. (2013). Human stem cell-derived spinal cord astrocytes with defined mature or reactive phenotypes. Cell Rep. 4 (5), 1035–1048. doi:10.1016/j.celrep.2013.06.021

Ryu, W. I., Bormann, M. K., Shen, M., Kim, D., Forester, B., Park, Y., et al. (2021). Brain cells derived from Alzheimer’s disease patients have multiple specific innate abnormalities in energy metabolism. Mol. Psychiatry 26 (10), 5702–5714. doi:10.1038/s41380-021-01686-3

Scheibye-Knudsen, M., Fang, F. F., Croteau, D. L., Wilson, D. M., 3rd, and Bohr, V. A. (2015). Protecting the mitochondrial powerhouse. Trends Cell Biol. 25 (3), 158–170. doi:10.1016/j.tcb.2014.11.002
delays mitophagy and targeting Miro rescues neuron loss in Parkinson’s models. Acta Neuropathol. 136 (4), 607–620. doi:10.1007/s00401-018-1873-4

Shaltouki, A., Svapatham, R., Pei, Y., Gerencer, A. A., Momčilović, O., Rao, M. S., et al. (2015). Mitochondrial alterations by PARKIN in dopaminergic neurons using PARK2 patient-specific and PARK2 knockout inogenic iPSC lines. Stem Cell Rep. 4 (5), 847–859. doi:10.1016/j.stemcr.2015.02.019

Stoca, R., De Vos, K. J., Paullussen, S., Mueller, S., Sancho, R. M., Lau, K. F., et al. (2014). ER-mitochondria associations are regulated by the VAPB-PTPIP51 interaction and are disrupted by ALS/FTD-associated TDP-43. Nat. Commun. 5, 3996. doi:10.1038/ncomms4996

Su, Y.-C., and Qi, X. (2013). Inhibition of excessive mitochondrial fission reduced aberrant autophagy and neuronal damage caused by LRRK2 G2019S mutation. Hum. Mol. Genet. 22 (22), 4455–4461. doi:10.1093/hmg/ddt301

Tak, Y. J., Park, J. H., Rhim, H., and Kang, S. (2020). ALS-related mutant SOD1 aggregates interfere with mitophagy by sequestering the autophagy receptor optineurin. Int. J. Mol. Sci. 21 (20), E7525. doi:10.3390/ijms21207525

Taylor, J. P., Brown, R. H., Jr., and Cleveland, D. W. (2016). Decoding ALS: From genes to mechanism. Nature 539 (7628), 197–206. doi:10.1038/nature20413

Tow, J., Wang, M., Pimenova, A. A., Bowles, K. R., Hartley, B. J., Lacin, E., et al. (2017). An efficient platform for astrocyte differentiation from human induced pluripotent stem cells. Stem Cell Rep. 9 (2), 600–614. doi:10.1016/j.stemcr.2017.06.018

Vandoorne, T., Veys, K., Guo, W., Sicart, A., Vints, K., Swijnen, A., et al. (2019). Differentiation but not ALS mutations in FUS reverses motor neuron metabolism. Nat. Commun. 10 (1), 4147. doi:10.1038/s41467-019-12099-4

Venkatramani, A., and Panda, D. (2019). Regulation of neuronal microtubule dynamics by tau: Implications for tauopathies. J. Biol. Macromol. 133, 473–483. doi:10.1016/j.jbmac.2019.04.120

Vierbuchen, T., Ostermeier, A., Pang, Z. P., Kokubu, Y., Südhof, T. C., and Wernig, M. (2010). Direct conversion of fibroblasts to functional neurons by defined factors. Nature 463 (7284), 1035–1041. doi:10.1038/nature08797

Vos, M., Geens, A., Böhm, C., Deaulderiere, L., Swerts, J., Rossi, M., et al. (2017). Cardiolipin promotes electron transport between ubiquinone and complex I to rescue PINK1 deficiency. J. Cell Biol. 216 (3), 695–708. doi:10.1083/jcb.201511044

Wang, S., Zou, C., Fu, L., Wang, B., An, J., Song, G., et al. (2015). Autologous iPSC-derived dopamine neuron transplantation in a nonhuman primate Parkinson’s disease model. Cell Discov. 1, 15012. doi:10.1038/celldisc.2015.12

Wang, W., Li, L., Liu, W., Dickson, D. W., Petrucelli, L., Zhang, T., et al. (2013). The ALS disease-associated mutant TDP-43 impairs mitochondrial dynamics and function in motor neurons. Hum. Mol. Genet. 22 (23), 4706–4719. doi:10.1093/hmg/ddt319

Wang, X., Su, B., Zheng, L., Perry, G., Smith, M. A., and Zhu, X. (2009). The role of abnormal mitochondrial dynamics in the pathogenesis of Alzheimer’s disease. J. Neurochem. 109 (1), 153–159. doi:10.1111/j.1471-4159.2009.05867.x

Wang, X., Winter, D., Ashrafi, G., Schild, J., Wong, Y. L., Sellke, D., et al. (2011). PINK1 and Parkin target Miro for phosphorylation and degradation to arrest mitochondrial motility. Cell 147 (4), 893–906. doi:10.1016/j.cell.2011.10.018

Wang, X., Yan, M. H., Fujisaka, H., Liu, J., Wilson-Delhis, A., Chen, S. G., et al. (2012). LRRK2 regulates mitochondrial dynamics and function through direct interaction with DLP1. Hum. Mol. Genet. 21 (9), 1931–1944. doi:10.1093/hmg/ddd03

Wasner, K., Smajic, S., Ghelfi, J., Delcambre, S., Prada-Medina, C. A., Knappe, E., et al. (2022). Parkin deficiency impairs mitochondrial DNA dynamics and propagates inflammation. Mov. Disord. 37 (7), 1405–1415. doi:10.1002/mds.29025

Wei, H., Liu, L., and Chen, Q. (2015). Selective removal of mitochondria via mitophagy: Distinct pathways for different mitochondrial stresses. Biochem. Biophys. Acta 1853 (10), 2784–2790. doi:10.1016/j.bbamar.2015.03.013

WHO (2021). World Health organization dementia factsheet [online]. Available at: https://www.who.int/en/news-room/fact-sheets/detail/dementia (Accessed 8 28, 2022).

Wong, Y. C., and Holzbaur, E. L. (2014). Optineurin is an autophagy receptor for damaged mitochondria in parkin-mediated mitophagy that is disrupted by an ALS-linked mutation. Proc. Natl. Acad. Sci. U. S. A. 111 (42), E4439–E4448. doi:10.1073/pnas.140572111

Wu, H., Wei, H., Sehgal, S. A., Liu, L., and Chen, Q. (2016). Mitophagy receptors sense stress signals and couple mitochondrial dynamic machinery for mitochondrial quality control. Free Radiol. Biol. Med. 100, 199–209. doi:10.1016/j.freeradbiomed.2016.03.030

Xi, J., Liu, Y., Liu, H., Chen, H., Emborg, M. E., and Zhang, S. C. (2012). Specification of midbrain dopamine neurons from primate pluripotent stem cells. Stem Cells 30 (8), 1655–1663. doi:10.1002/stem.1152

Zambon, F., Cherubini, M., Fernandes, H. J. R., Yang, C., Ryan, B. J., Volpato, V., et al. (2019). Cellular α-synuclein pathology is associated with bioenergetic dysfunction in Parkinson’s iPSC-derived dopamine neurons. Hum. Mol. Genet. 28 (12), 2801–2013. doi:10.1093/hmg/ddz038

Zannon, A., Kalvakuri, S., Rakovic, A., Foco, L., Guida, M., Schwienbacher, C., et al. (2017). SLF-2 interacts with Parkin in mitochondria and prevents mitochondrial dysfunction in Parkinson-deficient human iPSC-derived neurons and Drosophila. Hum. Mol. Genet. 26 (12), 2412–2425. doi:10.1093/hmg/ddz038

Zhang, Z. W., Tu, H., Jiang, M., Vanan, S., Chia, S. Y., Jang, S. E., et al. (2022). The APP intracellular domain promotes LRRK2 expression to enable feed-forward neurodegenerative mechanisms in Parkinson’s disease. Sci. Signal. 15 (748), eabk3411. doi:10.1126/scisignal.abk3411

Zhang, X., Boyer, L., Jin, M., Mertens, J., Kim, Y., Ma, L., et al. (2016). Metabolic reprogramming during neuronal differentiation from aerobic glycolysis to neuronal oxidative phosphorylation. Elife 5, e13374. doi:10.7554/elife.13374