Metabolic Manifestations of Parkinson's Disease in Cell Models Derived from Induced Pluripotent Stem Cells

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Abstract

Induced pluripotent stem cell (iPSC)-based models represent an innovative approach to studying the pathogenesis of inherited Parkinson's disease (PD) at molecular and cellular levels. The ability to derive neurons, astrocytes, and microglia carrying SNCA gene mutations from iPSCs significantly advances our understanding of key metabolic disturbances in PD. Each specific type of SNCA gene mutation (A53T, A30P, triplications, duplications, etc.) exhibits individual effects on functional and biochemical characteristics of differentiated cells. These differences involve synaptogenesis, extramitochondrial oxygen consumption, and protein metabolism. The diversity of effects makes critical the selection of strictly defined iPSC lines depending on research objectives. The **aim** *of this review is to examine metabolic features of brain cells derived from iPSCs with inherited PD associated with SNCA mutations, as well as the potential of using iPSCs to develop personalized in vitro models for understanding disease mechanisms. This approach will facilitate identification of new therapeutic targets and refinement of existing technologies for diagnosis and targeted therapy.*

Keywords: *Parkinson's disease; SNCA gene; metabolic plasticity; induced pluripotent stem cells; astrocytes; neurons; microglia*

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Метаболические проявления болезни Паркинсона в клеточных моделях, полученных из индуцированных плюрипотентных стволовых клеток

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Аннотация

Модели на основе индуцированных плюрипотентных стволовых клеток (ИПСК) являются частью инновационного подхода к изучению патогенеза наследственных форм болезни Паркинсона на молекулярном и клеточном уровнях. Возможность получения из ИПСК нейронов, астроцитов и микроглии, несущих мутации в гене SNCA, позволяет существенно продвинуть понимание ключевых метаболических нарушений, сопровождающих данную патологию. Каждый отдельный тип мутаций в гене SNCA (A53T, A30P, трипликации, дупликации и др.) по-разному влияет на функциональные и биохимические характеристики дифференцированных клеток. Эти различия затрагивают процессы синаптогенеза, внемитохондриального потребления кислорода и белкового обмена. Разнообразие эффектов делает актуальным выбор строго определённых линий ИПСК в зависимости от задач исследования. ***Целью*** *обзора является изучение метаболических особенностей клеток головного мозга, полученных из ИПСК с генетической формой болезни Паркинсона, ассоциированной с мутациями*

в гене SNCA, а также потенциала использования ИПСК для разработки персонализированных моделей in vitro для понимания механизмов заболевания, что будет способствовать выявлению новых мишеней и усовершенствованию существующих технологий для диагностики и таргетной терапии.

Ключевые слова: *болезнь Паркинсона; ген SNCA; метаболическая пластичность; индуцированные плюрипотентные стволовые клетки; астроциты; нейроны; микроглия*

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Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by the loss of dopaminergic neurons in the substantia nigra, leading to reduced dopamine levels and diverse motor and non-motor symptoms. The disease is defined by the presence of Lewy body aggregates composed of aberrant α-synuclein. Although PD was first described over 200 years ago, our understanding of its biological basis remains fragmented and insufficiently profound. Hypotheses linking PD to oxidative stress, mitochondrial dysfunction, inflammatory processes, protein metabolism system impairments, and other factors have been proposed [1]. However, none of these theories fully explains all aspects of the disease, underscoring the need for a comprehensive research approach.

In recent decades, significant progress has been made in diagnosing and treating this neurodegenerative disorder, yet many key mechanisms underlying its pathogenesis remain unclear. Genetic studies identifying PD-associated genes, including *SNCA, PRKN, PINK1, GBA*, and *LRRK2*, have played a pivotal role in elucidating PD pathogenesis [2]. The extent of environmental factors, lifestyle changes, and aging effects on disease manifestation in mutation carriers continues to be actively investigated [3].

Current research aims to develop models that most accurately reflect the pathophysiological processes occurring in PD: *in silico* modeling, *in vitro* cellular technologies (including human cells), and *in vivo* experimental organisms, with each system having its own advantages and limitations [4]. Shortly after the groundbreaking discovery that adult human somatic cells can be reprogrammed into an embryonic state through the expression of a specific set of pluripotent transcription factors [5], human disease modeling reached a qualitatively new level. This technology enabled the use of various patient-derived cells, including skin fibroblasts, peripheral blood mononuclear cells, and urine-derived epithelial cells, to generate induced pluripotent stem cells (iPSCs). iPSCs represent a virtually unlimited source of human cells that retain the donor's unique genetic profile and possess the capacity for directed chemical and/or transcriptional differentiation into specific cell types. This breakthrough provides unprecedented opportunities to study molecular and cellular mechanisms of pathogenesis under conditions that closely approximate physiological states. Unlike traditional cell line-based models, iPSCs retain endogenous mechanisms, making them more representative for studying complex hereditary and molecular aspects of PD [6]. Additionally, iPSCs and cells differentiated from them serve as key tools for modeling biological processes in cells and tissues that are difficult to obtain from living donors, particularly those of the neurovascular unit (NVU) and blood-brain barrier.

Most PD studies predominantly focus on iPSCs differentiated into dopaminergic neurons, as the loss of these cells underlies the motor symptoms of the disease. Only a few studies have explored other cell types (astrocytes, oligodendrocytes, microglia, etc.).

This review **aims** to examine the metabolic features of brain cells derived from iPSCs with inherited PD associated with *SNCA* gene mutations, as well as the potential of using iPSCs to develop personalized *in vitro* models for understanding disease mechanisms. Such models could facilitate the identification of new therapeutic targets and the refinement of existing approaches for diagnosis and targeted therapy.

Current Cellular and Molecular Hypotheses of Parkinson's Disease Pathogenesis

The current concept of PD pathogenesis views it not as a single disease, but as a combination of pathological processes characterized by an individual interplay of genetic factors, environmental influences, and comorbid disorders [1]. The contribution of each process varies among patients depending on their predisposition to the disease. Several cellular and

molecular hypotheses describe PD pathogenesis, including the role of mutations in PD-associated *SNCA, PRKN, PINK1, GBA*, and *LRRK2* genes as predisposing risk factors. Biallelic mutations in *PRKN* and *PINK1* genes demonstrate complete penetrance. Mutations in *GBA* and *LRRK2* genes may increase individual risk and are not associated with complete penetrance. Regardless of genetic predisposition, the key processes contributing to PD pathogenesis are mitochondrial dysfunction and pathological α-synuclein accumulation [7].

The mitochondrial damage theory is associated with diverse cellular-molecular mechanisms and bioenergetic disturbances. Mitochondrial dysfunction causes neuronal death in the substantia nigra, promotes oxidative stress, membrane/protein/DNA damage, enhances mitophagy, and depletes autophagy resources. Increased production of reactive oxygen species (ROS) disrupts lysosomal and proteasomal systems, stimulating aggregation of aberrant α-synuclein [8]. Damaged mitochondria release mitochondrial DNA, which amplifies proinflammatory cytokine production and activates cytotoxic T-cells, thereby linking neurodegeneration and neuroinflammation. Under pathogenic stimuli (injury, infection, aging, α-synuclein fibrils, mitochondrial dysfunction), glial cells (astrocytes and microglia) transition from physiological to reactive states, secreting proinflammatory cytokines and activating the complement system. Chronic activation leads to blood-brain barrier permeability disruption, peripheral immune cell infiltration, increased local inflammatory mediator production, and exacerbated oxidative stress [9].

The hypothesis about the role of pathological α-synuclein in PD pathogenesis is based on aberrant protein structures forming toxic fibrillar complexes – Lewy bodies, which can spread between neurons and cause neurodegeneration. α-Synuclein aggregation may result from excessive production of endogenous α-synuclein, particularly in cases of *SNCA* mutations, which can suppress efficient protein clearance pathways; these pathways may also be disrupted by *GBA* gene mutations. α-Synuclein aggregates disrupt membrane integrity, increase intracellular calcium levels, and exacerbate cellular stress. The efficiency of proteasomal degradation and lysosomal clearance decreases, leading to the accumulation of oxidized and aggregated proteins, ROS formation, and worsening cellular damage [10–12]. Chaperones such as GroEL promote the amyloid transformation of α-synuclein, linking microbiota to the pathogenesis of neurodegenerative diseases [13].

Thus, the precise mechanism of dopaminergic neuron loss in PD remains a subject of active research and discussion. Existing hypotheses (α-synuclein toxicity, inflammation, mitochondrial dysfunction, genetic predisposition) describe various critical links in the pathogenesis of neuronal cell degradation. However, each of these research areas highlights the complexity and multifactorial nature of the process, where interactions between different pathophysiological mechanisms create an interconnected network that contributes to disease progression.

Metabolic Plasticity of NVU Brain Cells

The metabolic plasticity of NVU brain cells reflects the ability of various cellular components to adapt their metabolic pathways in response to microenvironmental changes and functional demands. The NVU is a complex multicellular brain structure comprising neurons, astrocytes, cerebrovascular endothelial cells, pericytes, and microglia [14]. 25% of the body's energy expenditure is allocated to the brain. Within NVU cells, there is continuous activation of glycolytic processes (predominant in astrocytes, reactive microglia, and mature oligodendrocytes) as well as oxidative phosphorylation (prevailing in mature neurons, resting microglia, cerebral vascular endothelial cells, and oligodendroglial progenitor cells) [15].

The regulation of energy metabolism and metabolic demands occurs through intercellular interactions. Lactate serves as a crucial energy source for neurons, being synthesized in astrocytes from glucose and transported to neurons via monocarboxylate transporters. After entering neurons, lactate undergoes oxidation in mitochondria providing cellular energy requirements [16]. Mature neurons primarily rely on mitochondrial metabolism to support synaptic activity and can transport mitochondria along dendrites to perisynaptic regions [17]. Activated neurons exhibit increased dependence on lactate of both neuronal and astrocytic origin, which becomes a vital energy substrate during complex cognitive tasks [18]. Glutamate metabolism is tightly regulated through the glutamate-glutamine cycle involving astrocytes. Glutamate and oxaloacetate modulate mitochondrial processes by influencing ROS production [19].

Astrocytes synthesize and utilize fatty acids to support neurons and protect their mitochondria from oxidative stress [20]. Astrocytes possess glutaminolytic enzymes, can synthesize glutamine from glutamate, participate in the glutamate-glutamine cycle essential for neuronal activity [21], and exhibit high pentose phosphate pathway activity to generate NADPH and maintain antioxidant defenses [22]. Furthermore, astrocytes play a key role in regulating local blood circulation by rapidly responding to neuronal demands through the release of vasoactive metabolites [23–25].

During stimulation and polarization, microglia switch from mitochondrial oxidative phosphorylation to glycolysis, associated with lactate-induced histone lactylation and epigenetic changes linked to a pro-inflammatory phenotype [26]. Microglia actively metabolize fatty acids through beta-oxidation, which is crucial for brain plasticity and memory [27]. Under glucose deficiency, microglia utilize glutaminolysis to generate tricarboxylic acid cycle metabolites and energy, maintaining metabolic flexibility for migration and surveillance [28]. Pro-inflammatory factors – interleukin-1 and tumor necrosis factor-α, produced by activated microglia, shift astrocytes into an active phenotype, amplifying inflammatory processes. The close interaction of glial cells within the NVU supports immune functions while maintaining CNS homeostasis [29, 30].

NVU cell metabolism is highly dependent on the local microenvironment and activation states of different cell types, leading to metabolic reprogramming and altered contributions of specific pathways to energy production and biomolecule synthesis, playing a key role in regulating brain plasticity [24]. PD-associated mutations cause mitochondrial dysfunc-

tion and impaired energy metabolism, reducing oxidative phosphorylation efficiency and ATP synthesis. Additionally, these mutations disrupt intercellular interactions, metabolite transport, and the expression and function of relevant transporters, potentially accompanied by vascular changes and other pathophysiological processes. A critical focus is the study of metabolic characteristics in NVU cells derived from iPSCs with *SNCA* gene mutations.

Metabolic features of iPSC-derived neurons with *SNCA* mutations

The *SNCA* gene, first identified as associated with familial PD, encodes α-synuclein protein – a key pathological marker of the disease [31, 32]. Pathogenic *SNCA* variants include point mutations (*A53T*, *A30P*, *E64K*, *H50Q*, *G51D* и *A53E*) and structural variations such as gene duplication and triplication [33]. These mutations or *SNCA* replications induce conformational changes in α-synuclein or increase protein expression, contributing to PD pathogenesis. The association of *A53T* substitution with PD was first identified by M.H. Polymeropoulos et al. [32]. Subsequent studies characterized other substitutions (*A30P*, *E46K*, *G51D*, *A53E*) [34–36] and genotypes with 2 [37, 38], 3 [39], or 4 *SNCA*copies [40]. *SNCA* triplication was first detected in 2003 in an American family with hereditary PD [39]. iPSCs with *SNCA* triplication and differentiated midbrain dopaminergic neurons successfully replicated α-synuclein accumulation phenotypes [41]. Some metabolic alterations in *SNCA*-mutated iPSC-derived brain cells directly contribute to neurodegeneration, while others may represent compensatory mechanisms reflecting cellular adaptation to stress and toxic effects of aberrant protein aggregates.

Morphofunctional Cell Features

In cortical neurons derived from iPSCs with the *SNCA A53T* mutation, significant neurite shortening is observed – their length is 30% less compared to controls, indicating impaired capacity for normal growth and development [42]. These morphological changes reflect disruptions in intracellular transport and cytoskeletal organization, as evidenced by altered gene expression patterns [43]. Dopaminergic neurons derived from iPSCs with heterozygous duplication of exons 2–7 of the *SNCA* gene demonstrate cytoplasmic vacuolization represented by autophagolysosomes of varying density localized in the perinuclear area and processes. Mitochondrial fragments are detected within vacuoles, while axonal swellings contain massive autophagic inclusions that disrupt the parallel arrangement of microtubules [44]. In animals with transplanted iPSC-derived microglia subjected to lipopolysaccharide-induced stimulation, an increased number of amoeboid cells was observed compared to healthy controls [45].

Transcriptomic analysis of dopaminergic neurons with the *SNCA A53T* mutation revealed increased expression of genes responsible for histone modification and chromatin organization, specifically the inhibitor of differentiation *(ID)* family (*ID1–ID4*), which are hypothesized to regulate dopaminergic signaling [43]. In *SNCA* triplication, downregulation of key genes was observed: delta-like homolog 1 (*DLK1*), gamma-aminobutyric acid type B receptor subunit 2 (*GABABR2*), nuclear receptor-related 1 protein (*NURR1*), G protein-coupled inwardly rectifying potassium channels (*GIRK-2*), and tyrosine hydroxylase (*TH*), indicating impaired cellular differentiation [46]. Cortical neurons with the *SNCA A53T* mutation exhibited an increased number of cells with activated caspase 3/7, suggesting enhanced apoptosis [42]. Molecular analysis revealed activation of the ERK1/2 and JNK signaling pathways, which play a central role in regulating cell death [42]. Thus, neurite shortening, cytoplasmic vacuolization with microtubule disorganization, increased caspase-3/7 expression, and ERK1/2-JNK signaling represent direct pathological shifts leading to neuronal dysfunction and activation of apoptotic cascades. The proinflammatory response of microglia further exacerbates neuroinflammation and cellular damage. Autophagolysosome formation serves as a compensatory mechanism for clearing defective organelles and proteins.

Synaptogenesis impairment of is one of the key pathological aspects of PD. Neurons with the *SNCA A53T* mutation exhibit significant alterations in the expression of genes responsible for preand postsynaptic processes. Specifically, dysregulated expression of presynaptic proteins is observed: synaptophysin 3 (SYN3), synaptic vesicle protein 2C (SV2C), rabphilin 3A (RPH3A), and the double C2-like domain-containing beta protein (DOC2B). At the postsynaptic level, reduced expression of SLITRK1, SLITRK2, and SLITRK4 proteins, which regulate dendritic spine morphogenesis and synaptic plasticity, is noted, along with decreased levels of DLG-associated protein 2, GRIN2D, and GRIP2, involved in excitatory synaptic transmission [47]. These findings indicate impairments in synaptogenesis and synapse maturation. Reduced transcription of cadherin family genes (*CDH13* and *CDH15*) suggests defects in intercellular adhesion [47]. A marked decrease in the expression of calcium-binding and calcium-associated proteins (RCN3, HPCA, CCBE1, CACNA2D4, CACNA1D), critical for signal transduction and neurotransmitter release regulation, as well as receptors and ion channels directly involved in synaptic transmission, has been demonstrated. Notably, altered expression of *FABP7* and *ABLIM3* points to issues in axonal guidance [47]. Concurrent downregulation of preand postsynaptic proteins, along with CDH13/15 cadherins, disrupts synaptic morphogenesis and maturity, impairs intercellular adhesion, and compromises proper axonal growth orientation. Reduced GRIN2D expression limits calcium-dependent excitotoxicity but appears insufficient to fully compensate for functional deficits.

Alterations in Protein Homeostasis

Under physiological conditions, α-synuclein is predominantly localized in presynaptic terminals where it regulates the synaptic vesicle cycle by maintaining the reserve pool through interactions with SNARE complex proteins (VAMP2, syntaxin, SNAP-25) and facilitating full neurotransmitter exocytosis. Additionally, in dopaminergic neurons, it modulates tyrosine hydroxylase activity, controlling dopamine synthesis, storage, and metabolism. Recent studies confirm α-synuclein involvement in SNARE-dependent release of postsynaptic endocannabinoids, expanding our understanding of its functions [48].

Neurons differentiated with 3-4 copies of the *SNCA* gene and the *A53T* mutation accumulate higher amounts of α-synuclein [49–51]. Concurrently, reduced expression of the *SNCG*

gene encoding γ-synuclein is observed, potentially reflecting a cellular compensatory mechanism against α-synuclein overabundance. The expression of β-synuclein *SNCB* gene remains stable. Wild-type β-synuclein is known to exert a protective effect by suppressing α-synuclein aggregation [41]. Astrocytes with *SNCA* mutations (*A30P*, *A53T*, duplication, triplication) also demonstrate α-synuclein accumulation. The highest levels of α-synuclein aggregates are observed in astrocytes with *A30P* and *A53T* point mutations and *SNCA* triplication, though their concentrations remain lower than in neurons with triplication [52]. These findings correlate with clinical manifestations: earlier disease onset and greater severity are associated with the *A53T* mutation and *SNCA* triplication, which correspond to increased markers of cell death [39].

Excess α-synuclein in neurons with *SNCA* triplication induces significant endoplasmic reticulum (ER) stress, triggering a cellular response – the unfolded protein response (UPR) to counteract the accumulation of unfolded or misfolded proteins [53,54]. Among the three main stress sensors in the UPR system (PERK, ATF6, and IRE1α), the transcription factor IRE1α demonstrates the highest sensitivity to α-synuclein accumulation. Its activation enhances XBP1 mRNA splicing, generating the active XBP1(S) isoform that translocates to the nucleus to upregulate ER homeostasis genes while simultaneously initiating apoptosis via CHOP and BIM factors, accompanied by reduced levels of the anti-apoptotic protein BCL-2 [53]. However, some studies report insufficient UPR activation during misfolded protein accumulation and ER fragmentation in *SNCA*-triplication neurons, indicating protein quality control system dysfunction [55]. Modeling ER stress in *SNCA*-mutant neurons reveals upregulated expression of genes involved in ubiquitin-proteasomal degradation (*UBB, UBC, RNF187, UCHL1, PSMC4, PSMB1*), heat shock response (*DNAJC4, DNAJB9, HSPA5, PARK7*), and ER stress (*PDIA4, DDIT3*). Concurrently, decreased expression is observed in genes regulating synaptic vesicle transport (*PCLO, RAB3B, RAB3C, ITSN1*) and axonal transport (*KIF2A, KIF1B, KIF3A*), reflecting impaired neuronal communication [43]. *SNCA*-triplication neurons exhibit reduced β-glucocerebrosidase (GCase) activity, with immature enzyme forms accumulating in aggregates, leading to glycosphingolipid deposition and promoting neurodegeneration [55].

Thus, *SNCA* gene mutations (*A30P*, *A53T*, triplication) lead to the accumulation of α-synuclein aggregates, which play a critical role in PD pathogenesis. α-Synuclein fibrils impair presynaptic membrane function by blocking SNARE-dependent exocytosis, resulting in deficient neurotransmitter release and compromised transmembrane transport. These aggregates interfere with clathrin-dependent endocytosis, interact with membrane lipids and cholesterol, and destabilize synaptic membrane structure and function. While the aggregation process is well-documented in literature, the mechanisms underlying α-synuclein dysfunction in *SNCA* mutations and their connection to toxicity remain poorly understood. The *A30P* mutation reduces the protein's ability to associate with lipid vesicles compared to wild-type α-synuclein [56], diminishing synaptic vesicle clustering capacity and adversely affecting neurotransmission [57]. The *A53T* mutation directly accelerates protein nucleation rates, promoting aggregation processes [58, 59]. Elevated α-synuclein levels result from stabilization of mutant forms rather than gene overexpression. *SNCA* triplication drives pathological processes through excessive α-synuclein concentration, though whether this mutation alters individual protein functionality remains unresolved. Pathological changes leading to exocytosis blockade and neurodegeneration arise from combined intracellular and extracellular α-synuclein accumulation, functional alterations, and associated metabolic disturbances. Cells adapt to α-synuclein toxicity by activating the IRE1α-XBP1 unfolded protein response (UPR) pathway, but these protective mechanisms gradually fail, ultimately leading to neuronal death.

Autophagy

In dopaminergic neurons with four copies of *SNCA*, accumulation of the autophagosome marker LC3 is observed [46]. α-Synuclein suppresses autophagy by impairing the fusion of autophagosomes with lysosomes, leading to reduced autolysosome formation [60]. Metabolic disturbances associated with *SNCA* mutations are accompanied by dysfunction in calcium homeostasis regulatory mechanisms [51]. The imbalance between autophagic activity and calcium homeostasis promotes the accumulation of pathological α-synuclein aggregates and increases the susceptibility of dopaminergic neurons to apoptotic death. Altered autophagy activity initially acts as a compensatory mechanism aimed at removing α-synuclein aggregates and damaged organelles. However, prolonged accumulation of autophagic substrates causes autophagosomes to lose their efficiency, transforming into non-functional vacuoles, thereby shifting this process from compensatory to pathological.

Energy Metabolism

In dopaminergic neurons with the *SNCA A53T* mutation and *SNCA* gene triplication, significant metabolic profile alterations are observed, characterized by decreased levels of lactate, N-acetylaspartate, pantothenic acid, and cholesterol, along with increased expression of sirtuin 1 (SIRT1). In response to oxidative stress, neurons carrying this mutation exhibit altered expression profiles of genes associated with glycolysis (*LDHA, ENO1, TPI1, ALDOA*), oxidative phosphorylation (*NDUFA1, COX6A1*), and cholesterol biosynthesis (*SQLE, HMGCS1, MSMO1*) [43]. The metabolic reprogramming, accompanied by reduced levels of lactate, N-acetylaspartate, and cholesterol, as well as suppression of oxidative phosphorylation genes, reflects pathological disruptions in glycolytic flux, mitochondrial functions, and neuronal metabolic activity. Concurrently, elevated SIRT1 levels and induction of glycolytic enzymes LDHA and ENO1 suggest a compensatory shift toward anaerobic ATP production, accompanied by activation of mitophagy and antioxidant pathways.

Neurons with the *SNCA A53T* mutation and *SNCA* triplication exhibit significant mitochondrial dysfunction. Characteristic features include reduced basal respiration and decreased ATP production. These functional changes are accompanied by morphological abnormalities in mitochondria (rounded shape), pronounced fragmentation, and reduced membrane potential, indicating impaired organelle function [49]. Similar impairments were observed in neurons with 4 copies of

the *SNCA* gene, where additional functional reorganization of ATP synthase occurs. The enzyme operates in reverse mode to maintain membrane potential through ATP hydrolysis, accompanied by increased ROS generation, reduced levels of reduced glutathione, and enhanced oxidative stress [51]. Furthermore, increased α-synuclein production due to *SNCA* triplication was shown to cause direct interaction of oligomeric protein forms with mitochondrial ATP synthase complexes. This leads to decreased NADH redox index, exacerbates energy imbalance, and intensifies oxidative stress [61]. In differentiated astrocytes with *SNCA* mutations, cytosolic calcium levels are elevated, with calcium being released at a higher rate in *A30P* and *A53T* mutant lines. *A53T* mutant astrocytes additionally exhibit reduced reserve respiratory capacity, indicating impaired mitochondrial ability to adapt to energy demands [52].

Mitochondrial impairments are a well-documented pathological consequence of *SNCA* gene mutations. Decreased oxygen consumption and ATP production demonstrate that aberrant α-synuclein disrupts efficient oxidative phosphorylation, leading to energy supply deficits. Fragmented depolarized mitochondria are prone to releasing ROS and pro-apoptotic molecules, threatening cell survival. To prevent loss of mitochondrial membrane potential, cells resort to ATP hydrolysis and increased cytosolic calcium levels. Activation of mitophagy serves as a crucial compensatory mechanism that prevents accumulation of damaged mitochondria and suppresses ROS production.

Oxidative Stress

Studies have shown that *SNCA* triplication causes increased α-synuclein mRNA levels in differentiated neurons, overexpression of oxidative stress markers, and heightened susceptibility to H_2O_2-induced oxidative damage [62]. These changes indicate reduced cellular capacity to manage excessive ROS production, leading to impaired mitochondrial function and energy metabolism. Additionally, there is a significant increase in the expression of key genes involved in the oxidative stress response, such as *HMOX2* (heme oxygenase 2). Concurrent activation occurs in genes encoding heat shock proteins (*DNAJA1, HSPB1*) and components of the ubiquitin-proteasome protein degradation system (*UCHL1*) [46, 62], suggesting proteostasis disruption due to increased burden on the degradation system for damaged or misfolded proteins. Differentiated microglia with the *A53T* mutation exhibit elevated oxidative stress levels, increased expression of the *SLC11A1* gene (associated with ROS protection in *in vivo* animal transplantation) [45]. ROS overproduction and heightened sensitivity to redox agents indicate pathological vulnerability of brain cells with *SNCA* gene mutations. The increased expression of these genes likely represents a compensatory mechanism to enhance protective responses under oxidative stress conditions.

The **table** summarizes metabolic alterations observed in human brain cells differentiated from iPSCs carrying mutations associated with inherited PD. These data reveal both shared and distinct metabolic features in *SNCA* mutations, providing insights into pathophysiological mechanisms underlying inherited PD.

Conclusion

There is no consensus regarding the precise understanding of the mechanisms underlying PD. Despite existing hypotheses about PD pathogenesis, including genetic factors, accumulation of aberrant α-synuclein, exposure to mitochondrial toxins, and neuroinflammation, the true cause of PD remains unknown. It is hypothesized that PD etiology is multifactorial, influenced by genetic background variability, environmental conditions, lifestyle factors, and individual manifestations, resulting in each patient having a unique disease form.

By analyzing numerous studies, we identified that mutations in the *SNCA* gene induce complex metabolic alterations in brain cells (neurons, astrocytes, microglia, etc.) differentiated from iPSCs. Research has demonstrated increased secretion and aggregation of pathological α-synuclein, activation of ER stress, heat shock protein response and UPR, oxidative stress, mitochondrial and lysosomal enzyme dysfunction, and disruptions in lipid, protein, and carbohydrate metabolism. These metabolic defects are accompanied by impaired differentiation, reduced neurite outgrowth, and activation of apoptotic signaling pathways. The findings underscore the pivotal role of mitochondrial dysfunction linked to altered mitochondrial gene activity, energy homeostasis disruptions, and impaired intercellular transport in the disease pathogenesis. Despite the abundance of molecular patterns associated with PD, our understanding of its etiology remains merely the tip of the iceberg. Further research should focus on developing personalized *in vitro* cellular models, including iPSC-derived organoids, and implementing omics technologies such as exposomics to identify diverse etiological components and potential lifelong epigenetic changes. From the perspective of clinical practice and therapeutic development, refining personalized approaches, discovering targeted molecular pathways, and identifying novel biomarkers for early diagnosis are critical priorities. Additionally, iPSC-based models provide a platform for high-throughput screening and preclinical testing of new pharmacological agents, enhancing predictive value while reducing costs and timelines for drug development. Thus, despite substantial progress, continued fundamental and clinical research is essential to address these challenges and successfully implement iPSC-driven personalized strategies that could significantly improve early diagnosis, treatment efficacy, and patients' quality of life.

Metabolic features of neurons and astrocytes differentiated from iPSCs with *SNCA* mutations

Cell type	Mutation	Features	Manifestations	Sources
Dopaminergic neurons	*SNCA* (A53T)	· short neurites · synaptic defects · ↑ phosphorylated α-synuclein · ↑ sirtuin 1 · ↓ lactate · ↓ N-acetylaspartic acid · ↓ pantothenic acid · ↓ cholesterol	· mitochondrial dysfunction · dysfunction of protein quality control systems (UPR/ autophagy) · increased basal ROS production · oxidative stress · impaired calcium homeostasis · ↑ α-synuclein	[42, 43, 47, 49, 50, 63]
	SNCA (triplication)	· impaired neuronal differentiation and maturation · ↑ autophagy · ↓ β-glucocerebrosidase activity		[41, 46, 49, 50, 53, 55, 62, 63]
Cortical neurons	*SNCA* (A53T)	· impaired protein translation · ↑ nicastrin · ↑ nitrosative stress	· mitochondrial dysfunction; · ↑ α-synuclein	[53, 54, 64, 65]
	SNCA (triplication)	· reductive stress · abnormal NADH levels · ER stress · ↓ membrane potential		[53, 61]
Astrocytes	*SNCA* (A53T)	· ↑ number of pyknotic nuclei · ↓ rate of extracellular oxidation · ↓ extramitochondrial oxygen consumption	· mitochondrial dysfunction; · ↑ α-synuclein · ↑ cytosolic calcium	[52]
	SNCA (A30P)	· ↓ extramitochondrial oxygen consumption		[52]
	SNCA (triplication)	· ↑ number of pyknotic nuclei · ↓ rate of extracellular oxidation		[52]

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