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Some Immune Mechanisms of Parkinson's Disease

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Abstract

Neurodegenerative diseases, which predominantly occur in advanced age, are characterized by progressive neuronal loss, disruption of cellular homeostasis, and activation of several immune-related mechanisms. Among these, Parkinson's disease (PD) is the second most common neurodegenerative disorder worldwide. Despite extensive research, its pathophysiology remains incompletely understood, and no curative therapy is currently available. Multiple cellular and molecular mechanisms are implicated in the development of PD. Abnormal protein aggregation, particularly of α-synuclein, mitochondrial dysfunction with impaired energy metabolism, and oxidative stress leading to DNA, lipid, and protein damage represent central pathogenic processes. Endoplasmic reticulum (ER) stress, disturbances in protein folding, and dysfunction of the ubiquitin-proteasome system further promote neuronal injury. Moreover, microglial activation and chronic neuroinflammation, together with excitotoxicity and apoptotic pathways, accelerate the degeneration of dopaminergic neurons. Heat shock proteins, although primarily protective, are also critically involved in the regulation of protein homeostasis and apoptotic signaling. These mechanisms, when considered collectively, not only explain the complexity of neuronal loss in PD but also highlight their potential as therapeutic targets. In vitro models and cell culture studies provide valuable insights into these pathways, supporting the development of novel neuroprotective and disease-modifying strategies. As the global prevalence of PD is projected to reach nearly 13 million by 2040, understanding the interplay of immune-mediated mechanisms is essential for identifying preventive approaches and improving patient outcomes. Current pharmacological therapies such as L-DOPA remain effective for symptom control, yet future advances depend on translating mechanistic knowledge into clinically applicable interventions.

Keywords: Parkinson's disease, oxidative stress, neuroapoptosis, ER stress, immune mechanisms

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Introduction

Neurodegenerative diseases, which predominantly affect the elderly population, are characterized by progressive neuronal loss, structural deterioration, and activation of cellular stress and immune pathways. Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease and is defined clinically by both motor and non-motor symptoms. Tremor at rest, bradykinesia, rigidity, postural instability, and dementia represent its major features, while its prevalence has nearly doubled in the last 25 years, highlighting its growing health and socioeconomic burden (1, 2).

At the anatomical and physiological level, PD is primarily linked to dysfunction within the basal ganglia circuitry. Normally, the direct pathway facilitates cortical activation through dopaminergic stimulation of D1 receptors, whereas the indirect pathway inhibits cortical activity through D2 receptor signaling. Dopamine maintains a delicate balance between these two pathways, but loss of dopaminergic neurons in the substantia nigra pars compacta disrupts this equilibrium in favor of the indirect pathway, resulting in reduced thalamocortical output and the hallmark motor symptoms of PD. The latest prevalence data shared by the WHO on PD is from 2019, showing that the prevalence of PD has doubled in the last 25 years. There are approximately 8.5 million patients with PD, and it has resulted in approximately 350,000 deaths since 2020 (3).

It is important to know the structural and functional properties of dopamine, a neurotransmitter that has a very important role in understanding the pathogenesis and clinical symptoms of PD, its cellular connections, and its relationships with immune system mechanisms, and these relationships should be evaluated as a premise in scientific studies. In this context, if we examine the mechanism of the disease in its simplest form, there are two pathways between the cerebral cortex and basal ganglia. Direct pathway increases the activity of the cortex while indirect pathway decreases the activity of the cortex. In the direct pathway, basal ganglia afferent signals from the frontal and parietal cortex enter the putamen, heading towards to Globus pallidus internal (Gpi) and Substansia nigra pars reticulata (SNr) and return to the cortex via thalamus. In the indirect pathway, signals from the cortex to the putamen travel to the globus pallidus external segment (Gpe) and subthalamic nucleus (STN), then heading towards to the Gpi and SNr and return to the cortex via the thalamus (Figure 1). The direct pathway is gabaergic and its neurons express D1 type receptors. On the other hand, the indirect pathway is also gabaergic but its neurons express D2 type receptors. Dopamine has an excitatory effect when it binds to D1 type receptors and an inhibitory effect when it binds to D2 type receptors. Dopamine activates the cortex by stimulating the direct pathway and suppressing the indirect pathway, increasing thalamocortical output signals in both pathways. Under normal conditions, these two pathways are in balance with each other. However, with the decrease in dopamine in PD, this balance is disrupted to favor the indirect pathway. The effect of the indirect pathway on the thalamus increases and cortical activation decreases, resulting in PD symptoms (4).

Progressive loss of neurons in the SNc is the main pathological change seen in Parkinson's disease. These neurons are involved in DA transmission to the striatum. This loss of neurons leads to dysfunction in circuits involving motor cortical areas and basal ganglia. As a result, these changes lead to movement abnormalities that negatively affect the individual's life and are the main symptoms of PD. Another characteristic feature of Parkinson's is Lewy bodies (LBs) (6). LBs and enlarged neurites are composed of normal, misfolded and truncated proteins and

ubiquitin clusters stored in the cytoplasm as intact by-products of the degenerative process. The main component of these are Alpha-Synucleins (ASNs), which are abnormally phosphorylated, nitrated and oxidized. ASNs are now known to be a major component of LBs in both sporadic and hereditary PD (6, 7). There are a number of immune mechanisms and intercellular connections that occur in PD. Although the causes of neurodegeneration in PD are unknown, there are many different conditions that have been proposed in the pathologic evaluation of the disease. These include abnormal protein accumulation in dopaminergic neurons (Ubiquitin-Proteasome System (UPS)), Endoplasmic Reticulum (ER) stress, mitochondrial dysfunction, oxidative stress, microglial activation and inflammation, excitotoxicity, apoptosis, Heat Shock Proteins (Hsp), environmental and genetic factors (8-12).

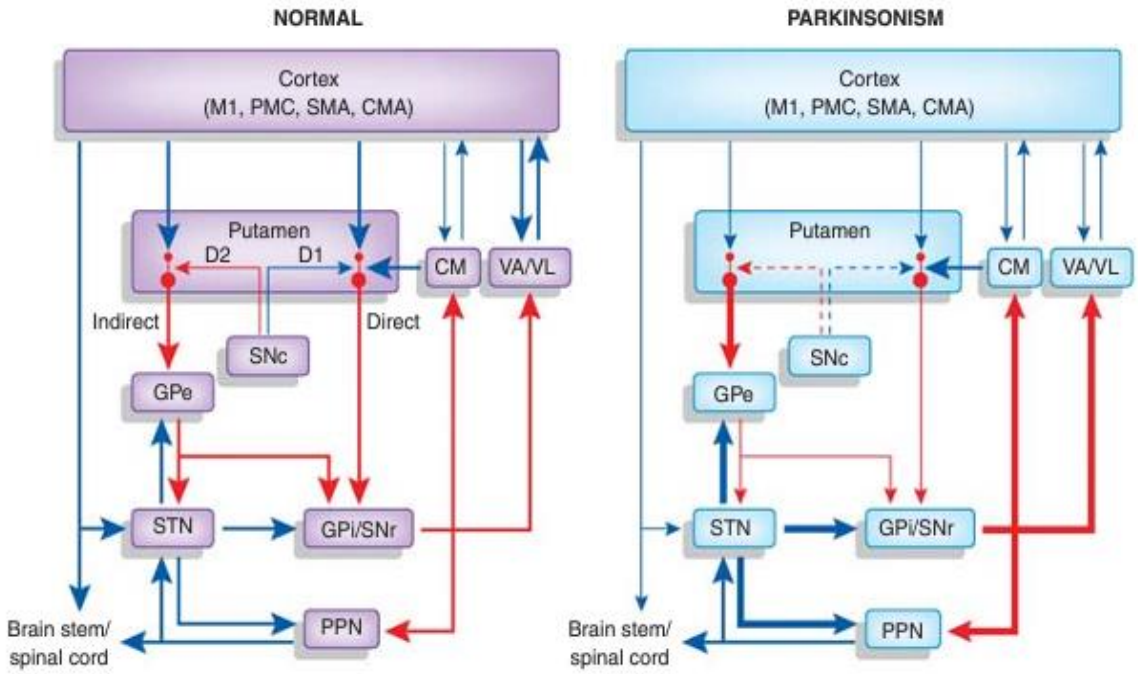

Figure 1. Mechanisms of basal ganglia functioning in normal and PD states (5). CM, Centromedian nucleus; Gpe, Globus pallidus external segment; Gpi, Globus pallidus internal segment; PPN, Pedunculopontine nucleus; SNc, Substantia nigra pars compacta; STN, Subthalamic nucleus; VA/VL, Ventral anteriyor, ventral lateral nucleus; SNr, Substantia nigra pars reticulata

The Immune mechanisms of PD and Evaluation of it: Here is some basic information about some immune mechanisms and their relationship with PD;

(I) Mitochondria is the intracellular powerhouse that performs important cellular reactions. It has many functions, including energy production, regulation of cell death, calcium metabolism and production (13). Recent scientific studies indicate that mitochondrial dysfunction plays an important role in PD (14, 15). Direct evidence of mitochondrial dysfunction in PD has been found by examining the patients' brain samples and it has been reported that mitochondrial complex-I activity is highly reduced in SNc of patients with PD. Characteristics of mitochondrial dysfunction include high production of reactive oxygen species (ROS), reduced ATP, mtDNA deletion and caspase release. ROS production causes mitochondrial dysfunction by inducing damage to complexes I and III and oxidation

of proteins. Impaired mitochondrial dysfunction leads to oxidative stress and affects several intracellular events leading to cell damage and cell death. Oxidative stress is one of the most important pathogenic mechanisms of nigral dopaminergic cell death in PD (16, 17). It is well-known that Complex-1, ROS and RNS are among the most important parameters about this mechanism.

(II) Oxidative stress is a pathological condition resulting from a disturbed balance between the formation and excretion of free radicals that can lead to neurodegeneration. Increased oxidative stress in the substantia nigra causes damage to cellular DNA and lipids, resulting in cells losing their properties. Different pathways resulting from genetic modifications in PD-related genes and their dysfunctions lead to increased oxidative stress. Mutations or altered expression of these proteins result in mitochondrial disruption, oxidative stress and protein misfolding. Furthermore, dopamine metabolism can be oxidized to reactive dopamine quinones that contribute to increased levels of reactive oxygen species. Alpha-synuclein is modified and accelerates its aggregation. Increased oxidative stress enhances the impaired function of the UPS. Environmental toxins impair mitochondrial function, increase the formation of free radicals and lead to the accumulation of proteins including alpha-synuclein. Mitochondrial dysfunction occurs through the effects of complex-I inhibition, adding an increase in oxidative stress and a decrease in ATP production, leading to damage of intracellular components and cell death. Furthermore, neuroinflammatory mechanisms may contribute to the enhanced consequences leading to cell death. In summary, all of these several cellular mechanisms attributed to oxidative stress are involved in the selective degeneration of dopaminergic neurons (18-20). The most important parameters about this immune mechanism are superoxide dysmutase (SOD), glutathione (GSH) and malondealdehyde (MDA).

(III) One of the most prominent causes of PD is neuroinflammation. This inflammation is caused by cells called microglia, which are cells of the central nervous system and originate from myeloids. Microglia engage in a phagocytic function to remove damaged neurons and foreign substances and participate in immunological surveillance by releasing proinflammatory factors such as prostaglandins, TNF-alpha, IL-1-beta, IL-6 and free radicals such as superoxide and nitric oxide. Although these toxic factors are essential for normal biological function, the microglial response needs to be tightly regulated to prevent overactivation and severe neurotoxic outcome. There is strong evidence in the literature that when microglia are activated and proliferate following brain injury or stimulation by various pro-inflammatory factors, this activation plays an important role in the initiation and development of several neurodegenerative disorders such as AD, PD and MS (21, 22). TNF-alpha, IL-1-beta, IL-6, IFN-gamma and glutamine are among the most important parameters that are actively involved in the aforementioned neuroinflammation process.

(IV) The ER is a very important dynamic organelle of the cell and is also called the “Ca+2 pool”. If Ca+2 release is disrupted, cytoplasmic Ca+2 concentration increases. This leads to activation of Ca^{+2}/calmodulin-dependent protein kinase II and signal transducer and activator of transcription-1, which triggers multiple proapoptotic pathways through the death receptor “Fas”, followed by an increase in reactive oxygen compounds and nicotinamide adenine dinucleotide phosphate. Severe Ca^{+2} imbalance can also cause cell death such as necrosis and necroptosis (23, 24). Translation of membrane and extracellular proteins is carried out by ribosomes on the cytosolic surface of the ER. Newly synthesized proteins leave the ribosome as

unfolded polypeptide chains, enter the ER and undergo different modifications before they can be folded. The process of protein synthesis takes place with the help of specialized folding enzymes and chaperone proteins. Protein misfolding can occur due to problems during transcription or translation, resulting in protein aggregation. Oxidative stress, extreme temperature and pH changes can also lead to protein aggregation. Advancing age is also one of the reasons that increase protein aggregation. In addition, changes in Ca^{+2} concentration in the ER and viral infections are also known to cause protein aggregation in the ER (25, 26). In addition to this general information, it has been suggested that ER stress may be involved in the pathology of PD, along with neuronal death, oxidative stress and mitochondrial dysfunction (27). Although the etiology of the reduction in dopaminergic neurons in PD remains unclear, evidence from studies in the brains of individuals with PD suggests that ER stress is a common feature in this disease and contributes to neurodegeneration, and that protein kinase RNA (PKR)-like ER kinase (PERK) is involved in this process, activating transcription factor (ATF-6), ATF-4, inositol-requiring kinase 1 (IRE1), C/EBP homologous protein (CHOP) genes are actively involved (28). These signaling molecules, which increase the expression of chaperones that help protein folding, attenuate translation and restore ER homeostasis by degrading mRNA to reduce protein load in the ER, are activated by the accumulation of misfolded and unfolded proteins in the ER lumen. Under continuous and high levels of stress, these molecules drive the cell to apoptosis (via the CHOP and JNK pathway) (Figure 3). IRE-1, ATF-4, ATF-6, and CHOP are among the most important parameters about this mechanism.

(V) Apoptosis literally means programmed cell death and is divided into caspase-dependent (Type 1) and caspase-independent (Type 2 and Type 3). Both mechanisms intersect at the mitochondrial organelle. In type 1 apoptosis, external signaling molecules bind to the receptor (FasL) on the cell membrane and trimerization of the inner part of the receptor occurs. The FADD molecule inside the receptor activates the enzyme caspase 8. In type 2 apoptosis, mitochondria are located at the center of the system. In this mechanism, ROS products begin to accumulate in the mitochondria as a result of the failure of ETZ enzymes in the inner membrane of the mitochondria to fulfill their functions. Accumulated ROS products cause oxidative stress in mitochondria. The oxidative stress disrupts the balance of antiapoptotic Bcl-2 and proapoptotic Bax molecules on the outer membrane of mitochondria. As a result of the disturbed balance, a pore forms on the outer membrane of mitochondria. Cytochrome C molecules pass through the pore into the cytosol and exits. As cytochrome C molecule exits into the cytosol, AIF and other apoptotic factors in the cytosol combine to form the apoptosome complex. The apoptosome complex activates caspase enzymes and causes the apoptotic process to start (29, 30). PD has a mechanism based on the killing of neurons due to neuroapoptosis. The apoptosis pathway involved here is also associated with ER stress. There are 4 different pathways in ER stress-related apoptosis. Activation of pathways caused by CHOP, B-cell lymphoma-2 (Bcl-2), JNK pathway and/or caspases can initiate apoptosis. IRE-1 binds to TNF-related factor 2 and activates the JNK pathway and apoptosis signal-regulating kinase (ASK). The JNK pathway leads to apoptosis through different mechanisms such as activation of caspase 12 and inhibition of the anti-apoptotic function of Bcl-2. Another pathway is the initiation of mitochondrial activation of apoptosis by binding to Bcl-2-related X protein and Bcl-2 homologous antagonist lethal protein, resulting in cell death (31). CHOP, which is not synthesized or under-synthesized under normal conditions, is strongly stimulated by various cellular stresses, resulting in growth arrest and apoptosis. All

UPR pathways (including PERK and eIF2α phosphorylation) have the ability to activate CHOP (23). Bax, Bcl, Caspase 3, Caspase 9, TH and Cytochrome C are among the most important parameters that play an active role in the aforementioned apoptosis process.

(VI) Another important mechanism involved in the pathogenesis of PD is excitotoxicity, which plays a pathologic role in the exacerbation of nigrostriatal degeneration (32). The altered neurotransmission observed in the basal ganglia in PD affects the glutamatergic system, suggesting that glutamate-mediated excitotoxicity plays a critical role in pathogenesis. The excessive presence of glutamate and its binding to its receptors generates a sustained and high amount of stimulation in the neuron. This event is called excitotoxicity because it triggers apoptosis mechanisms in the cell. Two mechanisms are proposed to cause excitotoxicity in PD. The first of these mechanisms is that the pars compacta of the substantia nigra is rich in glutamate receptors. Therefore, the discharge of neurons in terms of glutamate increases with the decreasing amount of dopamine during the disease. This results in excitotoxicity. The second mechanism is the loss of activity of Complex 1 enzyme in the ETZ chain in mitochondria. As a result, intracellular ATP levels decrease. With decreased ATP levels, magnesium blockade on N-methyl-D-aspartic acid (NMDA), a glutamate receptor, is released. Excitation within the neuron increases and excitotoxicity occurs. Another molecule thought to cause excitotoxicity is nitric oxide (NO). NO levels increase with glutamate-induced increase in intracellular calcium. NO reacts with peroxynitrite and OH- radicals, which are among the strong ROS in the cell. These radicals cause damage to the DNA structure (Figure 2) (33, 34).

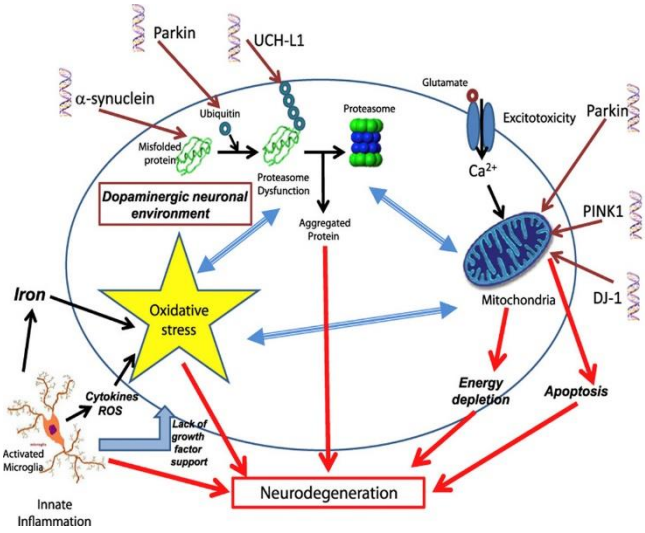

Figure 2. Intracellular Mechanism of Excitotoxicity (35).

NO, dynamin-like protein-1 (Dlp-1), glutamate transporter-1 (GLT-1) and NMDA receptor subunits GluN1, GluN2A, GluN2B, GluN2C, GluN2D and finally PINK1, which is one of the genes responsible for mitophagy and mitochondrial homeostasis, are the most important parameters that are actively involved in the aforementioned excitotoxicity process.

(VII) Numerous studies show that at least two components of cellular proteins are associated with PD. One of the most important of these is Heat Shock Proteins (Hsp), which we will examine in detail in our planned future study. As is known, in PD, where dopaminergic neurons are damaged, the cellular stress response becomes important. Hsps are important components of this stress response. They normally allow for proper folding, recognition and modification of proteins by ubiquitination systems or hydrolysis by the proteasome. Mammalian Hsps are classified according to their molecular weight as Hsp27, Hsp40, Hsp60, Hsp70, Hsp90 and Hsp100. Although different Hsps have different functions, they have 3 main functions; (a) bind to nascent, unfolded, unfolded, partially folded or denatured proteins to promote their proper folding, (b) promote degradation of misfolded and aggregated proteins by clearing them, and (c)

decompose structured aggregates into folded functional monomers (36). Studies have reported that Hsp90, Hsp70 and Hsp27 are particularly active in PD and bind to alpha-synuclein fibrils and prevent their aggregation. In addition to alpha-synuclein, Parkin protein, which was previously known to be a neuroprotective gene but was later shown to induce cell proliferation and apoptosis and is regulated by N-myc, ATF4, Max, and p53 genes, is also associated with Hsps. On the other hand, Hsps play an active role in reducing apoptosis by blocking cytochrome c and inducing caspase activation (especially Hsp27), and to activate this mechanism, they use the serine/threonine kinase Akt/protein kinase B (PKB) signaling pathway, which regulates growth factors and ensures cell survival (37).

All these mechanisms have important roles in exacerbating the pathogenesis of PD by causing neuronal loss. As can be seen in Figure 3, many parameters contribute to the processes that result in neuroinflammation and neuroapoptosis and lead to neuronal loss. Since many types of neurodegenerative diseases, including PD, are currently incurable, understanding the cellular and molecular basis of neurodegeneration is of utmost importance for developing new therapeutic strategies. In this context, cellular models provide fundamental, sustainable, cost-effective and as optimized as possible outputs of systemic disorders under in vitro conditions.

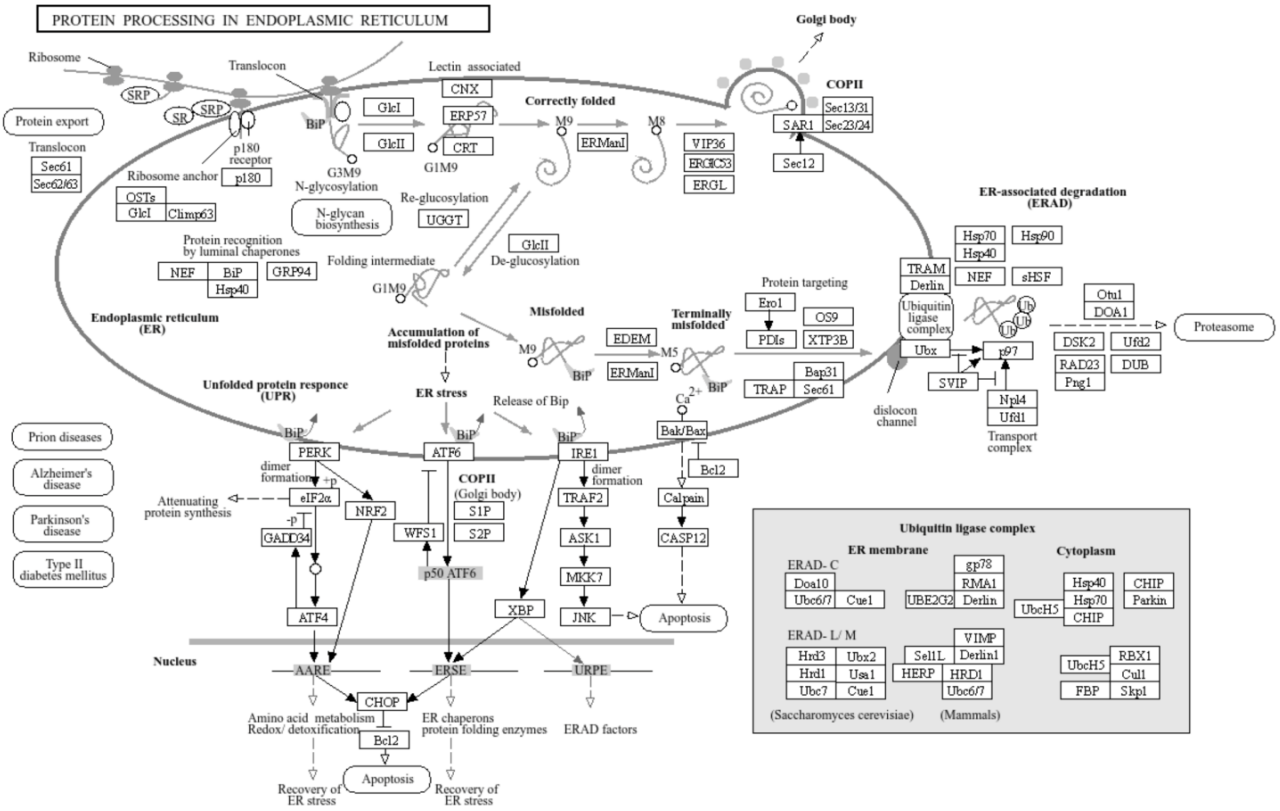

Figure 3. General view of UPS, Hsp, mitochondrial dysfunction, apoptosis, and ER stress processes (38).

Moreover, in vitro model approaches are used for many pathologies such as cardiovascular and respiratory disorders, various cancers, ischemia, viral and bacterial diseases, and neurological disorders, and provide indispensable solutions for the molecular level of cellular abnormalities. Therefore, new approaches to model neurodegenerative diseases in vitro are constantly being explored. Cell culture research not only contributes to future animal and human phase studies but also provides new data in its own right.

After reviewing the pathogenesis of PD and the pathways/proteins/genes that play an active role in this process in great detail above, we think it is necessary to focus on preventive and therapeutic actions for PD. The prevalence of PD is expected to increase rapidly as the global population ages, affecting approximately 13 million people by 2040 (39). With this increase, the economic and social burden will increase unless the disease is treated or prevented more effectively. Current treatments significantly improve the quality of life of patients, but there is currently no definitive cure. So far, giving patients 3,4-dihydroxyphenylalanine (L-DOPA) is one of the most effective treatment options. Therefore, in addition to medication, alternative treatment options are being sought to improve the quality of life.

Conclusion

In summary, several interrelated immune mechanisms play a central role in the pathogenesis of Parkinson's disease:

• Oxidative stress and mitochondrial dysfunction: Excessive production of reactive oxygen species and impaired mitochondrial activity accelerate the degeneration of dopaminergic neurons.

• ER stress and protein misfolding: Disturbances in protein folding promote α-synuclein aggregation and trigger apoptotic pathways.

• Neuroinflammation and microglial activation: Dysregulated microglial responses release pro-inflammatory mediators that exacerbate neuronal damage.

• Apoptosis and excitotoxicity: Programmed cell death and glutamate-mediated excitotoxicity further amplify neuronal loss.

• Heat shock proteins: These molecular chaperones regulate protein folding and apoptosis, exerting potential neuroprotective effects.

Collectively, these mechanisms not only provide insights into the complex molecular basis of PD but also underscore their clinical relevance as potential therapeutic targets. A deeper understanding of these processes may guide the development of disease-modifying strategies and help bridge the gap between in vitro findings and clinical application.

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