Progress in Pathogenesis of Parkinson's Disease

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Abstract. Parkinson's disease (PD) is a neurodegenerative disease that affects the elderly. The global prevalence of PD is increasing year by year, causing serious harm to patients and families. PD is a complex mechanism resulting from the combined effects of multiple factors. This article reviews the pathogenesis of PD.

Keywords: Parkinson disease, oxidative stress, α-synuclein, neuroinflammation, genetic factors, intestinal flora imbalance

1 Introduction

Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder predominantly affecting the elderly population, characterized by the selective degeneration of dopaminergic neurons in the substantia nigra pars compacta and the abnormal aggregation of α-synuclein (α-syn). These pathological changes lead to a deficiency of dopamine in the basal ganglia, manifesting clinically as cardinal motor symptoms including bradykinesia, resting tremor, rigidity, and postural instability [1]. Beyond motor impairments, PD frequently induces non-motor symptoms such as cognitive decline, psychiatric disturbances, and autonomic dysfunction, severely compromising patients' quality of life and social engagement, thereby imposing substantial burdens on families and society. Epidemiological studies indicate that over 4 million individuals worldwide are affected by PD, with incidence escalating sharply with age [2]. The prevalence reaches 0.7‰ in individuals over 50 years and 3%–5% in those over 60 years. Notably, most cases are sporadic, while hereditary forms account for only 5–10% of total cases. Current therapeutic strategies primarily include pharmacological interventions (e.g., levodopa, anticholinergics), neuroprotective approaches, and surgical procedures such as deep brain stimulation [3]. This review synthesizes recent advances in understanding PD pathogenesis, with a focus on oxidative stress, protein misfolding, neuroinflammation, genetic factors, and gut microbiota dysregulation, aiming to provide insights for early diagnosis, precision therapy, and drug development.

2 Oxidative Stress

Oxidative stress arises from an imbalance between the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and the body's antioxidant defense

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capacity, resulting in excessive accumulation of these reactive molecules [4]. This imbalance triggers oxidative damage to cellular macromolecules, including lipids, proteins, and DNA, thereby disrupting normal cellular functions. A critical consequence of oxidative stress is mitochondrial dysfunction: as the primary site of cellular energy production, impaired mitochondria exhibit reduced ATP synthesis, enhanced ROS leakage, and perturbed calcium homeostasis, ultimately leading to cellular dysfunction or apoptosis. Dopaminergic neurons in the substantia nigra are particularly vulnerable to oxidative stress due to several inherent features: (1) the auto-oxidation of dopamine generates quinones and ROS; (2) high iron content in the substantia nigra catalyzes Fenton reactions, amplifying ROS production; and (3) relatively low expression of antioxidant enzymes such as glutathione peroxidase. Cumulative evidence suggests that mitochondrial dysfunction, exacerbated by oxidative stress, represents a key driver of dopaminergic neuron degeneration in PD [5]. For instance, post-mortem studies of PD brains reveal decreased complex I activity in nigral mitochondria, accompanied by elevated lipid peroxidation and protein carbonylation markers.

3 Protein Misfolding and Aggregation

Protein misfolding and aggregation are closely linked to perturbations in cellular protein homeostasis, which maintains a dynamic balance between protein synthesis, folding, trafficking, and degradation [6]. Disruption of this balance—caused by genetic mutations, oxidative damage, or impaired degradation systems—leads to the accumulation of misfolded proteins, which aggregate into toxic species and induce neuronal damage. A hallmark pathological feature of PD is the abnormal accumulation of α-syn in neurons, forming intracellular inclusions known as Lewy bodies and Lewy neurites. Under physiological conditions, α-syn is a soluble, natively unfolded protein primarily localized at presynaptic terminals, where it regulates synaptic vesicle trafficking. However, in PD, α-syn undergoes conformational changes, adopting β-sheet-rich structures that assemble into oligomers and insoluble fibrils [7]. These aggregates exhibit prion-like properties, propagating between neurons and spreading pathology throughout the brain. Impaired clearance mechanisms further exacerbate α-syn accumulation. The ubiquitin-proteasome system (UPS) and autophagy-lysosome pathway (ALP) are responsible for α-syn degradation, but their dysfunction—due to genetic mutations or oxidative stress—reduces clearance efficiency. For example, mutations in PARK2 (encoding parkin, an E3 ubiquitin ligase) impair UPS-mediated degradation, while lysosomal dysfunction hinders autophagic clearance of α-syn aggregates.

4 Neuroinflammation

Microglia are important non-specific immune cells, accounting for 10% of the total number of glial cells in healthy people's brain, and are the most abundant cell types involved in the immune response of the central nervous system [8]. As shown in Figure 1, microglia-induced neuroinflammation acts as a "double-edged sword": microglia provide neuroprotection in the early stages of PD by eliminating foreign pathogens and

toxins, but in the middle and late stages, overproduced or misfolded alpha-syn secreted by neurons in multiple brain regions over-activates microglia, leading to a proinflammatory response with elevated cytokine levels (e.g., IL-1β, IL-6, TGF-α), increased free radical production, and consequent neuronal toxicity and loss, which drives PD progression. Hyperactivation of microglia leads to a decrease in its ability to clear α-syn, and α-syn that cannot be metabolized is transformed from a dissolved monomer into an insoluble polymer, which becomes an autoantigen that can activate adaptive immune response. Microglia phagocytizing α-syn express Major Histocompatibility Complex Class II molecule (MHC II), and function as antigen presenting cells, presenting α-syn to T cells infiltrating central nervous system by direct contact, inducing T cells to activate to produce TGF-α and other cytokines, further inducing M1 activation of microglia, forming malignant activation cycle and accelerating PD progression. Astrocytes are the most numerous glial cells in the central nervous system and are involved in regulating extracellular concentrations of ions and neurotransmitters, synaptic formation and transmission, blood flow and water transport, and maintaining the structural and functional integrity of the blood-brain barrier [9]. α-syn stimulates astrocytes to release pro-inflammatory cytokines, further damaging neuronal health. Furthermore, upregulation of MHC II expression in astrocytes with α-syn inclusion bodies can act as antigen presenting cells to recruit and activate T cells around blood vessels and infiltrating into brain parenchyma, further promoting neuroinflammation and PD disease progression. Existing studies have shown that innate immune responses triggered by microglia and astrocytes, as well as adaptive immune responses induced by NK cells, B cells, and T cells, play a key role in DA-neuron damage and PD disease progression [10]. These responses are activated and infiltrate into the brain of PD patients.

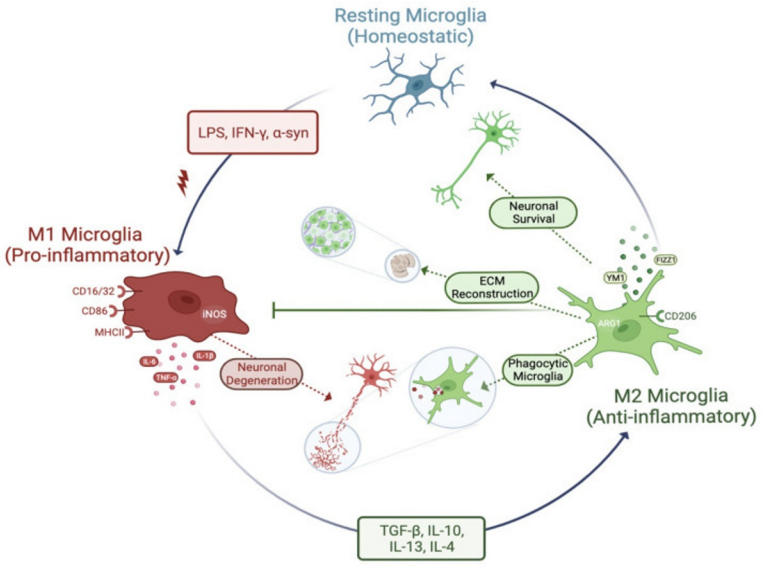

Fig. 1. The function of microglia [11].

5 Genetic Factor

5.1 SNCA Gene

SNCA gene encodes α-syn protein. Mutations in the SNCA gene have been found to be closely associated with familial PD [12]. These mutations cause structural changes in the α-syn protein, making it more prone to misfolding and aggregation to form Lewy bodies that damage dopaminergic neurons. In addition, SNCA gene copy number variation (such as gene duplication or amplification) is also an important cause of PD. Gene duplication or amplification can lead to overexpression of α-syn protein, increasing the risk of protein aggregation and thus promoting PD.

5.2 PARK2 Gene

PARK2 gene encodes parkin protein, an E3 ubiquitin ligase involved in protein degradation in cells [13]. Mutations in the parkin gene cause parkin protein to lose function, making it impossible for cells to properly degrade misfolded proteins, causing these proteins to accumulate in cells, forming aggregates and damaging neurons.

5.3 DJ-1 Gene

DJ-1 protein encoded by DJ-1 gene is a hydroperoxide-responsive protein, which participates in oxidative stress response [14]. Mutations in the DJ-1 gene cause a loss of function of the DJ-1 protein, making cells less resistant to oxidative stress and increasing the risk of oxidative stress damage, which in turn damages neurons.

5.4 LRRK2 Gene

LRRK2 protein encoded by LRRK2 gene is a kinase involved in a variety of intracellular signal transduction processes. Mutations in the LRRK2 gene result in increased kinase activity of the LRRK2 protein, affecting intracellular signal transduction and protein homeostasis, and thus damaging neurons [15].

5.5 Other Genes

In addition to the above genes, there are many genes related to the pathogenesis of PD, such as UCH-L1 gene, ATP13A2 gene, PLA2G6 gene, FBX07 gene, etc [16]. Mutations of these genes may lead to mitochondrial dysfunction, protein homeostasis imbalance, lysosomal dysfunction and other problems, thus promoting the occurrence and development of PD.

6 Alteration of Intestinal Flora

There are 1,000 - 1,150 species of bacteria in the human gut, and the total weight is about 1.5 kg. The metagenomics of the human gut microbiome contains about 100 times as many genes as the human body itself. Adult intestinal flora composition can be maintained stable for a long time, but there are certain differences among different individuals affected by factors such as dietary habits, drug intervention and living environment. Bifidobacterium and Lactobacillus are two of the most important probiotics in human intestinal tract [17]. Their quantity and composition play a key role in maintaining healthy intestinal environment and improving immune function. Intestinal flora plays an important role in promoting the absorption of human nutrients, synthesizing vitamins, promoting immunity, system development, and maintaining the normal function of the immune system. Intestinal flora can resist the invasion of foreign pathogenic microorganisms by constructing mucosal barriers, including physical barriers and chemical barriers, and by shielding and affecting the immune system of the body, so as to maintain the stability and microecological balance of the intestinal environment. There is increasing evidence that PD may originate in the gut and is closely related to changes in intestinal flora [18]. Disorder of intestinal microbiota is common in PD patients. As shown in Figure 2, it is now clear that intestinal microbiota and their metabolites can lead to inflammation, intestinal barrier damage, and activation of glial cells.

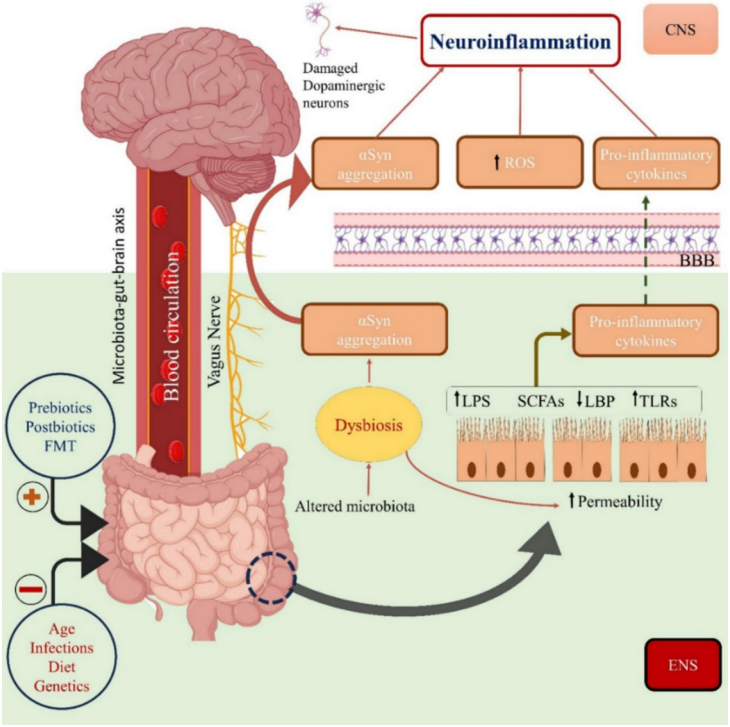

Fig. 2. The gut-brain axis in PD [19].

7 Conclusion

Parkinson's disease, the second most common neurodegenerative disorder after Alzheimer's disease, poses a significant threat to elderly health and societal well-being. Its pathogenesis involves intricate interactions between genetic susceptibility, oxidative stress, protein misfolding, neuroinflammation, and gut microbiota dysregulation. For example, genetic mutations (e.g., SNCA, LRRK2) enhance α-syn aggregation and oxidative stress vulnerability, while gut dysbiosis amplifies neuroinflammation via the gut-brain axis. Despite progress, the precise mechanisms underlying PD remain incompletely understood. Future research focusing on cross-talk between these pathways may identify novel therapeutic targets, enabling early intervention and improved management of this devastating disease.

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