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Parkinson's Disease, a Noxious Concerto by Two Villains: α -Synuclein and Leucine-Rich Repeat Kinase 2

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease in the world. The pathological marker of PD is the loss of dopaminergic neurons in the substantia nigra pars compacta. Although the signaling pathway involving molecules responsible for neurodegeneration of dopaminergic neurons is partially veiled, the accumulation of α-synuclein (αSyn) in dopaminergic neurons is regarded as a pivotal mechanism in PD pathogenesis. The accumulation of αSyn accelerates the aggregation of αSyn in dopaminergic neurons, and αSyn aggregates are associated with neuronal degeneration. The upregulation of leucine-rich repeat kinase 2 (LRRK2) activity is closely associated with the pathogenesis of PD. Notably, LRRK2 is associated with neuroinflammation, a crucial factor for PD progression. Neuroinflammation in the brain is primarily mediated by microglia and astrocytes. LRRK2 regulates inflammatory responses, and its kinase activity plays a key role in neuroinflammation. Evidence suggests that crosstalk occurs between microglial LRRK2—a regulator of neuroinflammation—and neuron-released αSyn—a promoter of microglial activation and neuroinflammatory responses—in neuroinflammation-mediated PD progression.

Keywords: Parkinson's disease α-synuclein; Leucine-rich repeat kinase 2

Abbreviations: PD: Parkinson's disease; αSyn: α-synuclein; LRRK2: Leucine-rich repeat kinase 2

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, and the loss of motor skills is the primary symptom of PD, and the death of dopamine neurons is the primary pathological cause of PD [1]. Although, the mechanism underlying the pathway in dopaminergic neuronal degeneration is not completely understood, dopamine neuronal death is caused not only by physiological degeneration within the neuron, but also by effects on surrounding brain cells [2]. Alpha-synuclein (αSyn) is a primary pathological factor of PD. Oligomeric αSyn is formed by the accumulation via an aberrant protein quality control and promotes oxidative stress, mitochondrial dysfunction, and neuroinflammation in the substantia nigra [3]. The propagation of αSyn is a critical factor in the progression of PD, particularly in the context of aging [4].

Leucine-rich repeat kinase 2 (LRRK2) is important in the pathogenesis of PD, and increased kinase activity of LRRK2 is involved in several pathological mechanisms, including mitochondrial dysfunction, impaired endoplasmic reticulum

trafficking, cellular senescence, abnormal autophagy-lysosomal pathways, and neuroinflammation [5]. Therefore, in this study, we aim to describe the progression of PD induced by αSyn oligomers and LRRK2 kinase activity and how they crosstalk.

Culprits of PD pathogenesis

α-Synuclein

αSyn is a major component of Lewy bodies (LB), which are known to be a pathogenic marker of PD [6]. The accumulation of αSyn is caused by dysfunction of the protein degradation machinery, including the ubiquitin-proteasome system [7], chaperone-mediated autophagy [8], and lysosomal activity [9]. Misfolded or chemically modified αSyn would be resistant to degradation and is responsible for the generation of oligomeric αSyn in the cytosol or vesicles such as late endosome, autophagosome or lysosome [10]. The degradation of αSyn is a potential therapeutic target, as a cleaner of accumulated αSyn [11]. The accumulated αSyn oligomers is shown to demolish the membrane potential of mitochondria within dopaminergic neurons, resulting in degeneration of dopaminergic neurons [12]. And αSyn oligomers disrupt the homeostasis of intracellular calcium ion regulation and stimulate various cell death signaling [13]. Recently, αSyn oligomers have been known to accelerate the progression of PD by the transmission of neuron-to-neuron [14], and αSyn oligomers released from neurons have been found to stimulate microglia or astrocytes, thereby promoting neuroinflammation [15,16].

LRRK2

LRRK2 contains GTPase and kinase domain and their respective enzymatic activities are altered in pathogenic mutations. The G2019S LRRK2 mutation is the most common and studied mutation and its kinase activity is increased. LRRK2 interacts with and phosphorylates several substrates that regulate biological signaling and cell survival [17]. The tumor suppressor p53 is an important transcription factor, and phosphorylation of p53 is a very important process that regulates its activation state [18]. Activated p53 is known to induce the transcription of genes involved in apoptosis and cell cycle arrest [19]. Several studies have shown that p53 activation is associated with neurodegenerative diseases [20]. PD, which is caused by LRRK2, is known to be a late-onset disease, and PD is also an age-related disease [21]. In particular, the p53-p21 intracellular signaling pathway is the most common pathway for cellular senescence. Our findings are that cellular senescence is the result of p53 phosphorylation by LRRK2 [22]. In addition, p53 promotes the expression of cytokines in inflammatory responses, and it was also shown that LRRK2 involvement induces phosphorylation of p53, resulting in neuroinflammation [23,24].

The crosstalk between αSyn and LRRK2 in PD

Recent studies have reported that αSyn oligomers released from neurons act as ligands for toll-like receptors in microglia [25], where the neuroinflammatory response in microglia is activated by LRRK2 kinase, leading to the release of inflammatory cytokines [26], which ultimately results in the death of surrounding dopaminergic neurons [27]. Interestingly, it has been reported that LRRK2-induced cellular senescence is associated with increased accumulation of αSyn due to a disruption of autophagy-lysosomal degradation or an inability to degrade already formed oligomeric αSyn, which further exacerbate αSyn aggregates [28,29]. Recently, we found that neurotrophic factors are reduced in astrocytes expressing G2019S mutations that increase the LRRK2 kinase, thereby reducing the expression of factors involved in dopamine production in dopaminergic neurons [30]. Presumably, when alpha-synuclein reactivates astrocytes, the phosphorylation of LRRK2 increases, which may result in a decrease in dopamine production due to a decrease in neurotrophic factors.

Conclusion

The interaction of LRRK2 and alpha-synuclein with neurons, microglia, and astrocytes facilitates the progression of PD via various signaling pathways. LRRK2-mediated cellular senescence exacerbates the aggregation of alpha-synuclein, resulting in increased release of alpha-synuclein oligomers from neurons. This, in turn, stimulates microglia and astrocytes to increase LRRK2-mediated neuroinflammation. In Parkinson's disease, which is particularly age-related, this vicious cycle accumulates over time, making dopaminergic neurons increasingly vulnerable.

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Conflicts of Interest

The authors declare no competing financial interests.

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