α-Synuclein Aggregation and Propagation in the Pathomechanisms of Parkinson’s Disease

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Parkinson’s disease is a neurodegenerative disorder that manifests with motor dysfunction, such as bradykinesia, tremor, and rigidity. Furthermore, patients experience many non-motor problems, including dementia, psychosis, pain, sleep disturbances, and autonomic dysfunction, which impact their quality of life. Thus, disease-modifying therapies for Parkinson’s disease are needed. The pathological hallmark of this disease is dopaminergic neuronal loss with intraneuronal aggregations, known as Lewy bodies, which contain proteins and lipids. Recently, it was revealed that several membranous organelles, such as mitochondria, lysosomes, autophagosomes, and synaptic vesicles, are involved in Lewy bodies. Moreover, the main protein component of Lewy body, α-synuclein, binds to lipid membranes via two α-helices at the N-terminus. Interestingly, disrupted associations between lipid membranes and α-synuclein might trigger the formation of Lewy body. Accordingly, α-synuclein aggregation and lipid–synuclein interactions are important for the pathomechanisms of Parkinson’s disease. In this review, I will focus on (1) the role of lipid metabolism in Parkinson’s disease, and (2) α-synuclein aggregation and propagation in Parkinson’s disease.

Key words: parkinson’s disease, α-synuclein, prosaposin, PLA2G6, Lewy body

Introduction

Parkinson’s disease is the second most prevalent neurodegenerative disorder after Alzheimer’s disease. Neurodegeneration within the substantia nigra pars compacta is a specific finding of Parkinson’s disease; accordingly, affected patients show hypokinetic abnormal movements such as bradykinesia, tremor, and rigidity. Although motor dysfunctions are ameliorated by administration of levodopa, marked degeneration of dopaminergic neurons will reduce its effectiveness, resulting in motor fluctuations that directly impair the quality-of-life of patients. Furthermore, as Parkinson’s disease progresses, the expansion of neurodegeneration from the peripheral to central nervous system induces various non-motor symptoms, such as autonomic dysfunction, dementia, anxiety, and sleep disturbances. Almost none of the non-motor symptoms of Parkinson’s disease are alleviated by symptomatic treatment, therefore, patients with Parkinson’s disease usually have many unmet medical needs. In this context, disease-modifying therapy is needed for Parkinson’s disease. To develop such therapies, the pathomechanisms of this disease must be elucidated. The Lewy body is a key structure underlying the neuropathology of Parkinson’s disease. Although Lewy body contain many lipids and proteins, the most abundant component is α-synuclein. Furthermore, reported pathogenic α-synuclein mutations, such as p.A30P, p.E46K, p.H50Q, p.G51D, and p.A53T, have been associated with autosomal dominant familial Parkinson’s disease. Thus, aggregation of α-synuclein might be the dominant pathomechanism of Parkinson’s disease. In addition, recent pathological inves-
tigations revealed that neuronal degeneration occurring with the aggregation of α-synuclein might propagate along neuronal circuits. Specifically, conformational changes that transform the normal structure of α-synuclein can exacerbate self-aggregation. Moreover, abnormally structured α-synuclein, called a seed, can propagate from neuronal cell to cell, like a prion protein. In this review, I focus on the propagation and aggregation of α-synuclein in pathomechanisms of Parkinson’s disease.

Lewy body and α-synuclein

Lewy body is a classical pathological hallmark of Parkinson’s disease. Dystrophic neurites, a known precursor of this aggregation, include ubiquitin and α-synuclein. Ubiquitin plays essential roles in the ubiquitin–proteasome system, which performs protein degradation. Abnormally structured proteins are usually conjugated with ubiquitin by E3 ligase, resulting in their ATP-dependent degradation by proteasomes. Ubiquitin is typically localized within the core of Lewy body, whereas α-synuclein localizes to the outermost layer. Furthermore, the structure of Lewy body in the brainstem is slightly different from that of Lewy body in the cortex. Brainstem-type Lewy bodies present as intracytoplasmic, single or multiple, spherical or elongated, eosinophilic masses with a dense core and peripheral halo in hematoxylin and eosin staining; whereas, cortical-type Lewy bodies exhibit eosinophilic irregular structures without a conspicuous halo or core. Previous electron microscopic analyses revealed that Lewy body has outer filamentous structures with dense cores. Further immunopathological studies identified the main component of the filamentous structure as α-synuclein. Notably, it is difficult to precisely observe Lewy bodies using transmission electron microscopy because of issues discriminating these structures from background and other abnormal features. However, the recently developed correlative light and electron microscopy method can merge electron microscopic analysis with immunohistochemistry. This method revealed the involvement of Lewy bodies with many types of organelles, such as mitochondria, lysosomes, autophagosomes, membranes, and synaptic vesicles. Furthermore, Lewy body formation might be triggered by the disruption of interactions between α-synuclein and lipid membranes. Thus, mechanisms underlying α-synuclein aggregation may be the most important pathogenic pathway in Parkinson’s disease. α-synuclein, an amphipathic protein with a molecular weight of 14 kDa, contains two α-helices at its N-terminus that are important for binding to lipid membranes. In cytosol, α-synuclein moves dynamically and does not have a specific structure. However, conformational alterations of the structure of α-synuclein, which includes β-sheet structures, are associated with self-aggregation. Furthermore, α-synuclein exhibiting an abnormal β-sheet structure can induce other normal α-synuclein to adopt the abnormal β-sheet structure, which exacerbates aggregation (also known as fibrillation). Previous investigations revealed that the disruption of interactions between α-synuclein and lipid membranes can induce conformational changes of α-synuclein. Thus, elucidating the association between lipid metabolism and α-synuclein aggregation might be helpful for understanding the pathomechanisms of Parkinson’s disease. Clinical reports indicate that genetic dysfunction of several lipid enzymes is associated with familial Parkinson’s disease. Pathogenic mutations of PLA2G6, a phospholipase, cause autosomal recessive familial Parkinson’s disease. Whereas biallelic pathogenic mutations of glucocerebrosidase (GBA) cause Gaucher disease, heterozygous GBA mutation is a known risk factor for Parkinson’s disease. Moreover, enzymes and functional proteins in glycolipid metabolic pathways, such as arylsulfatase A, SMPD-1, and prosaposin, have been associated with Parkinson’s disease. Thus, dysregulation of phospholipid and/or glycolipid metabolic pathways might be an important mechanism underlying the aggregation of α-synuclein.

PLA2G6 and α-synuclein aggregation

PLA2G6 is a phospholipid enzyme that hydrolyzes the sn-2 ester bonds of phospholipids, generating free fatty acids and lysophospholipids. PLA2G6 was identified as the causative gene of infantile neuroaxonal dystrophy, and as well as neurodegeneration with brain iron accumulation. PARK14 are associated with early-onset autosomal-recessive familial Parkinson’s disease, which can also arise from mutations of PLA2G6.
Collectively, the neuronal death associated with these three neurodegenerative disorders caused by PLA2G6 mutations is referred to as PLA2G6-associated neurodegeneration. The clinical phenotype of PARK14-linked Parkinson’s disease is levodopa-responsive dystonia parkinsonism with cognitive decline and frontotemporal lobar atrophy. Moreover, postmortem examinations have revealed a marked Lewy body pathology in PARK14-linked Parkinson’s disease. However, the detailed function of PLA2G6 in Lewy body pathology remains unclear. To elucidate roles of PLA2G6 in Parkinson’s disease, I and my colleagues generated a PLA2G6-knockout drosophila model. PLA2G6-knockout drosophila developed motor and sleep dysfunction with dopaminergic neurodegeneration similar to patients with Parkinson’s disease. These phenotypes and neuronal degeneration were rescued by overexpression of human wild-type PLA2G6, but not PLA2G6 harboring the pathogenic p.A80T mutation. A digenic PLA2G6-knockout and α-synuclein-overexpression drosophila model exhibited aggregation of both α-synuclein and ubiquitin. In addition, alterations of lipid composition were observed in the brains of PLA2G6-knockout drosophila. In this model, the ratio of acyl chain 18:0/18:0 (X = 0, 1, and 2) to acyl chains 14:0/14:0 and 14:0/16:1 was significantly increased compared with wild-type drosophila brain. Because of alterations of lipid composition, the synaptic vesicles of PLA2G6-knockout model drosophila were smaller than those of wild-type drosophila, resulting in synaptic dysfunction. These alterations were improved by overexpression of human wild-type PLA2G6, but not PLA2G6 harboring the p.A80T mutation. Interestingly, administration of linoleic acid could normalize the abnormal lipid composition of PLA2G6-knockout drosophila to ameliorate phenotypes including motor and sleep dysfunction, dopaminergic neuronal degeneration, synaptic vesicle structure, and α-synuclein aggregation. These findings suggest that a lipid diet might prevent neuronal degeneration and α-synuclein aggregation. Therefore, a balanced lipid diet might lead to disease-modifying effects on Parkinson’s disease.

**Prosaposin and Parkinson’s disease**

Glycolipids are mainly metabolized in lysosomes, a membranous organelle containing approximately 40 types of hydrolases. All enzymes in lysosomes are acid hydrolases, and H+-ATPases present on the lysosomal membrane use the energy of ATP hydrolysis to take in and maintain protons at an acidic pH. Complete dysfunction of lysosomal enzymes causes lysosomal storage disorders, known as lipidoses. However, recent investigations revealed that partial dysfunction of lysosomal enzymes may be associated with Parkinson’s disease and related disorders. Complete dysfunction of GBA (associated with Gaucher disease) impairs the storage of glucosylceramides, a substrate of glucocerebrosidase. Although enzyme replacement therapy can rescue the systemic dysfunction of patients with Gaucher disease, it cannot ameliorate neurodegeneration because it does not cross the blood–brain barrier. During long-term enzyme replacement treatment of patients with non-neuropathic Gaucher disease, several patients developed Parkinson’s disease. Furthermore, a genetic association study revealed that heterozygous mutation of GBA is a risk factor for Parkinson’s disease, but not Alzheimer’s disease. Sidranskey and colleagues performed a 16-centers analysis of GBA mutations in Parkinson’s disease, which concluded that the odds ratio for any GBA mutation in Parkinson’s disease versus controls was 5.43 across centers.

As mentioned above, previous studies revealed that not only GBA, but also other glycolipid enzymes such as arylsulfatase A, acid sphingomyelinase, and hexosaminidase can cause Parkinson’s disease and/or α-synuclein aggregation. Thus, disturbances of glycolipid metabolic pathways play important role in the pathomechanisms of Parkinson’s disease. In lysosomes, four types of sphingolipid activator proteins (saposins A, B, C, and D) are needed for glycolipid enzymes to be fully active. Saposins are generated from prosaposin following cleavage by cathepsin D in the lysosome. Each saposin interacts with a specific enzyme: saposins A, B, and C interact with galactosylceramidase, arylsulfatase A, and glucocerebrosidase, respectively; however, the function of saposin D function (which may activate acid ceramidase) remains unknown. The clinical phenotype of complete saposin deficiency closely resembles that of diseases associated with the dysfunction of interacting enzymes. For example, saposin C deficiency...
can cause phenotypes similar to that of patients with Gaucher disease\textsuperscript{40}. However, an association between saposin D and human disease had not been revealed. Recently, I and my colleagues identified patients with three independent autosomal familial Parkinson’s disease associated with pathogenic mutations of saposin D (PARK24)\textsuperscript{25}. The proband had p.Q453P mutation, while the second and third patients had a p.C451_L447 deletion and p.C412Y mutation, respectively. The clinical phenotypes of patients with pathogenic saposin D mutations mimicked that of idiopathic Parkinson’s disease, but the age of onset was relatively earlier than the usual idiopathic type. \textsuperscript{123}I–MIBG cardiac scintigraphy revealed the degeneration of cardiac sympathetic nerves and a DAT scan depicted the degeneration of striatonigral neurons, similar to idiopathic Parkinson’s disease. Saposin has three disulfide bonds that are important for its function. The p.Q453P mutation disrupts the formation of an α-helix structure in the saposin D domain. The p.C451_L447del mutation ablates two cysteine residues, resulting in the breaking of two disulfide bonds, which disrupts the α-helix structure in the saposin D domain. The p.C412Y mutation also potentially ablates a disulfide bond in the saposin D domain. Thus, mutations in saposin D are likely to have a major impact on prosaposin function.

Prosaposin, a precursor protein of saposins, is trafficked to the lysosome via the endoplasmic reticulum (ER)–Golgi–endosome network, also known as the membrane trafficking system. The association of sphingomyelin is important for proper membrane trafficking of prosaposin\textsuperscript{40}. A previous report suggested that the interaction site with sphingomyelin is within the saposin D domain. Saposin D with a disrupted structure might not bind to the membrane, resulting in mislocalization of prosaposin. Indeed, in dopaminergic neurons derived from induced pluripotent stem cells of patients with PARK24-linked Parkinson’s disease, the pathogenic mutant prosaposin localized to the ER; in contrast, wild-type prosaposin localized to lysosomes in control neurons. Furthermore, fibroblast cells obtained from patients with PARK24–linked Parkinson’s disease had abnormally enlarged autolysosomes and significantly increased expression of LAMP2, a lysosomal membrane protein, compared with control cells. Moreover, dopaminergic neurons derived from induced pluripotent stem cells of patients with PARK24–linked Parkinson’s disease exhibited significantly increased expression of an aggregating form of α-synuclein compared with normal dopaminergic neurons. These results suggest that pathogenic heterozygous mutations in saposin D will impair its function in lysosomes or endow a toxic function that results in dopaminergic neuronal degeneration with aggregation of α-synuclein due to lysosomal dysfunction\textsuperscript{25}.

**Propagation of α-synuclein**

Conformational changes of α-synuclein tend to result in fibrillation. Early intermediates in the fibril formation pathway of α-synuclein are known as protofibrils, which can propagate from cell to cell like prion proteins\textsuperscript{43}. Accordingly, the propagation of α-synuclein might be one of the most important mechanisms underlying Parkinson’s disease progression. Postmortem histological analyses performed by Braak and colleagues concluded that α-synuclein aggregation might start from two neuronal circuits: the olfactory and vagus systems\textsuperscript{44}. Indeed, hyposmia and constipation are some of the earliest symptoms of Parkinson’s disease\textsuperscript{39}. Furthermore, studies of two large cohorts found that truncal vagotomy might prevent the prevalence of Parkinson’s disease\textsuperscript{39}. In addition, following direct inoculation of α-synuclein fibrils and Lewy bodies into animal brains, the spread of α-synuclein aggregations in areas along the neuronal circuit was observed several months after injection\textsuperscript{47}. To reveal the speed of propagation of α-synuclein in the mouse striatum, I and my colleagues performed a callosotomy before or after the inoculation of α-synuclein fibrils\textsuperscript{40}. Interestingly, callosotomy 24 hours before the injection was able to prevent the propagation of α-synuclein to the contralateral striatum; however, in the mice with callosotomy 24 hours after injection, α-synuclein was extensively aggregated. These findings indicate the speed by which α-synuclein fibrils spread is very fast, allowing them to propagate from neuron to neuron within 24 hours. In addition, to reveal the manner of propagation in vivo, the contralateral striatum was treated with botulinum toxin 3 days before and 1 day after α-synuclein inoculation in the striatum. Pre-treatment with botulinum toxin, which inhibits synaptic vesicle exocytosis by cleaving
SNARE protein, prevented the propagation of α-synuclein. Thus, synaptic exocytosis might be one mechanism by which transmission of α-synuclein fibrils occurs.

**Conclusion**

This review focused on the aggregation and propagation of α-synuclein in the pathomechanism of Parkinson’s disease. However, previous reports have indicated the importance of other pathogenic systems in Parkinson’s disease, such as protein degradation, mitochondrial dysfunction, neuroinflammation, and ER stress. Considering that many membranous organelles, such as mitochondria, autophagosomes, lysosomes, and synaptic vesicles, are involved with Lewy bodies, multiple dysfunctions in neurons and/or glial cells may contribute to the neurodegeneration in Parkinson’s disease (Figure 1). Thus, to reveal the key event in the pathogenesis of Parkinson’s disease, further investigation should be needed.

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**Figure 1** α-Synuclein, an amphipathic protein, contains two N-terminal α-helices that are important for binding to the membrane. In the cytosol, α-synuclein moves dynamically and does not have specific structure. The conformational alteration of α-synuclein, which includes β-sheet structures, is associated with self-aggregation. Disruptions of interaction between α-synuclein and lipid membranes due to pathogenic α-synuclein mutations and/or dysregulated phospholipid and glycolipid metabolism may induce conformational changes of α-synuclein. Correlative light and electron microscopy revealed that Lewy bodies involve many types of organelles, such as mitochondria, lysosomes, autophagosomes, membranes, and synaptic vesicles. Thus, aggregation of α-synuclein will induce many abnormalities of cellular function. Furthermore, α-synuclein seeds will propagate along the neuronal circuit, resulting in the systemic α-synuclein aggregations observed in Parkinson’s disease.
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Conflict of interest statement

The author declares that there are no conflicts of interest.

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