Pathophysiological mechanisms underlying Parkinson's disease

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Abstract. Parkinson's disease is a neuronal synucleinopathy disease triggered by the abnormal aggregation of the presynaptic α-synuclein protein. Those abnormal α-synuclein protein undergo a series of post-translational modifications such as phosphorylation and ubiquitination and become pathological aggregates, which then flourish and spread within a wide range of neurons. The spread of the α-synuclein aggregates, also known as the Lewy Body, eventually leads to the succumb of almost the entire brain, contributing to serious clinical symptoms and death of the PD patients. On the other hand, many attributes of the α-synuclein protein and the Lewy body still remain unclear. For instance, the physiological functions of the α-synuclein protein and how it exactly develops into pathological bodies remain vague. In this perspective, we review the basic physiology of the α-synuclein protein. Also, we review the basic pathology and the post-translational modifications of the Lewy Body. Eventually, we review the formation and the spreading of the Lewy body on both cellular and clinical levels in human and animal models.

Keywords: Parkinson's disease; α-synuclein protein; Lewy body; physiology and pathology; post-translational modifications.

1. Introduction

Parkinson's disease is a human nervous system disease triggered by two specific inclusion bodies: Lewy neurites and Lewy bodies [2, 5]. It is typically characterized by three major hallmarks: formation of inclusions, extensive loss of dopamine neurons, and clinical non-motor symptoms [2].

The PD-related inclusion bodies, namely the Lewy bodies (LBs) and Lewy neurites (LNs), are identified as the first and the most important pathology that initiates the Parkinson's disease [5]. Through multiple cell-to-cell pathways, the inclusions are able to freely transmit throughout the PD patient's brain, causing massive neuronal death [3]. LBs and LNs are majorly made up of lipids, cytoskeletal proteins, organelle and membrane fragments [3]. The most notable component of the PD-related inclusion bodies is the α-synuclein protein aggregate, which can be found in presynaptic terminals of the neuronal cells [4]. As a major member of the synuclein family, α-synuclein is able to lead to multiple pathologies due to its aggregate-prone property and several post-translational modifications, such as ubiquitination and phosphorylation etc [2]. Unfortunately, besides some most basic facts about α-synuclein's expression, function and localization, the scientists are still unable to figure out α-synuclein's more complicated functions due partly to the compensation made by the other two synuclein proteins in the absence of α-synuclein— Beta and Gamma synuclein [3].

On the other hand, the loss of dopamine acceptor neurons, also known as the DA neurons, can also be clearly observed in the affected parts of the brain, especially those that suffer the most severely from the invasion of the inclusion bodies, such as midbrain, substantia nigra pars compacta (SNpc), and striatum [2, 5]. As these PD pathologies gradually spread and flourish, clinical symptoms become clearer [5]. The affected patients would develop tremor, postural instability, and multiple motor deficits during the mid- and late stages of the development of PD-related pathologies [5].

Lastly, the motor-related clinical symptoms such as, tremor, motor deficits, and additional cognition impairment occur at the late stages of Parkinson's disease [5]. The most crucial pathology hallmark that accounts for these clinical symptoms is the spread of inclusions in human brain, namely the PD-related brain pathology [5]. At first, the LBs and LNs start to develop and flourish in the lower brainstem and are highly confined to the medulla oblongata [5]. Then, they gradually spread

themselves into upper brainstem, the surrounding regions such as the SNc [5]. Eventually, during the last stages of the spread of the inclusions in the brain, the inclusions pass through the brainstem and massively invade mesocortex and neocortex [5].

In this review of Parkinson's disease, we are going to explore the basic α-synuclein-related pathology underlying the Parkinson's disease, the physiological functions and biochemical makeups of a normal α-synuclein protein, the α-synuclein aggregation, the cell-to-cell spreading of the inclusions, and the spreading of inclusions in human brain.

2. Physiology of α-synuclein

α-synuclein is known to be the most important component of the PD-related inclusions [1]. Both LBs and LNs are majorly made up of the abnormal α-synuclein aggregates under pathological conditions, and these aggregates are highly mysterious, as current technology and experiments still fail to fully explain how α-synuclein turns from a healthy, normal protein into an abnormal aggregate [1]. Although scientists have already come up with several theoretical models (which will be discussed later), there are still so many mysteries waiting to be uncovered regarding the α-synuclein aggregation [1]. As a result, many scientists decide to first turn to the physiological function and the biochemical makeup of the normal α-synuclein protein, seeking to discover its properties as a normal protein which might lead to its aggregation.

2.1 Sequence and Structure

α-synuclein is a small, soluble protein that is made up of a repeated 11 amino acid residue sequence: XKTKEGVXXXX [1]. This 11-residue sequence is repeated 7 times in order to produce an α-synuclein protein [1]. α-synuclein has two common structures: a soluble, unstructured form and a membrane-bound, structured status [1]. α-synuclein protein is intrinsically unstructured [1]. However, most α-synuclein exert their functions when binding to membrane phospholipids [1]. Under the membrane-bound status, the α-synuclein forms an α-helix structure, requiring acidic lipid head groups for attachment with the membrane [1]. More importantly, α-synuclein is reported to develop two different forms when adopting α-helix structure: a single, elongated α-helix and a broken α-helix [1]. Such difference in the structure depends on the size and the curvature of the membrane that bound the α-synuclein [1]. If the membrane is large and consequentially less curved, the α-synuclein usually develops elongated α-helix structure [1]. In contrast, if the membrane is small and highly curved, the α-synuclein usually develops broken α-helix structure [1]. Often, the α-synuclein prefers a broken structure, thus actively transforming large vesicle membrane into a smaller and more curved shape, increasing the membrane's curvature and reducing its own length [1].

2.2 Expression and Localization

α-synuclein is expressed predominantly in the brain neurons [1]. Although α-synuclein is highly enriched in particular parts of the brain such as neocortex, hypothalamus, hippocampus, and striatum, it can also be observed in other body parts and tissues, such as muscle, heart, lung, livers, blood plasma, and red blood cell etc [1].

α-synuclein is known for its binding with the neuronal cells' presynaptic terminals [1]. During the development of the neuron, the α-synuclein first roots in the cell body of the immature neuron, and then gradually spread towards the synapse as the neuron develops [1]. In the end, the α-synuclein flourishes in the presynaptic terminals [1]. The scientists have also discovered the α-synuclein's preference to attach to the synaptic vesicle membrane and the vesicular SNARE protein synaptobrevin-2 [1]. The α-synuclein in the presynaptic terminals usually appear in the vesicles or bind to the SNARE protein in order to function properly [1]. In fact, the examination of α-synuclein's binding with either vesicle membrane or the SNARE protein has become the most important method to target α-synuclein to the synapse [1].

2.3 Function

Two of the most certain functions of α-synuclein that have already been proved are its interaction with the membranes and its chaperone activity of assisting SNARE complex formation [1].

α-synuclein's binding to the phospholipids of the membranes grants it two abilities: modulation of vesicle curvature and sensation of lipid-packing defects [1]. As previously described, when binding to the presynaptic vesicles, α-synuclein prefers a broken status, and thus tends to transform the vesicle membrane into smaller and more curved status, allowing itself to remain in a broken, small structure [1]. Moreover, α-synuclein can also sense lipid-packing defects and affect the lipid packing [1]. In other words, α-synuclein plays a crucial role in remodeling the membranes made of phospholipids [1].

α-synuclein can also function as a protein chaperone capable of binding to other proteins and assisting their missions [1]. Having similar structure with the 14-3-3 family of chaperone proteins, α-synuclein can protect neurons from degeneration by protecting the cochaperone CSPa and assisting the assembly of synaptic SNARE complex [1]. This function is highly crucial for the survival and the long-term development of neurons, and scientists have found out that the knockout of all the synucleins indeed reduce SNARE complex formation, thus proving a causal-effect relationship between the α-synuclein chaperon activity and the SNARE complex assembly [1].

3. Overview of synucleinopathy

The formation of pathogenic α-synuclein protein aggregates in the brain is a crucial hallmark of Parkinson's disease. Therefore, the underlying causes behind the formation of abnormal α-synuclein aggregates are highly important for the scientists to continue future researches. So far, there are two major ways through which α-synuclein assemble abnormally and lead to synucleinopathy lesions [2]. First, special familial-hereditary mutations may occur in the α-synuclein gene, which leads to familial synucleinpathies [2]. However, this pathology only represents a very limited population, and in contrast, the post-translational modification of α-synuclein is much more important since this accounts for the majority of the synucleinopathy lesions [2]. Scientists have already targeted some specific post-translational α-synuclein modifications, and one of the most important elements that directly contribute to the final fibrillation of the α-synuclein is the phosphorylation of the amino acid residue Serine 129, which takes place in the urea-soluble fraction of the aggregated α-synuclein [2].

The phosphorylated Serine 129 is first discovered in an experiment that seeks for the difference between normal and aggregated α-synuclein [2]. In the experiment, the researches extract cerebral cortices with Lewy bodies and other relevant inclusion bodies in four solutions: Tris-HCL, 1% Triton-X100, 1% Sarkosyl, and 8M urea [2]. In the end, compared with the control group, there is a special fraction in the affected cerebral cortices that is urea-soluble, which is a property not shown in the normal, asymptomatic samples [2]. As a result, the scientists conclude that the substance which leads to the aggregation of α-synuclein lies within the urea-soluble fraction of the α-synuclein protein [2]. Next, by processing and investigating the urea-soluble fraction of the affected cerebral cortices, the scientists generate a MALDI-TOF MS analysis, which compares the urea-soluble fraction's corresponding amino acid residues with the normal fraction's residues [2]. The scientists target three candidate phosphate acceptors which may explain the difference between the mass to charge ratio of urea-soluble and normal fractions [2]. In the end, through the nano ES-MS/MS test, the phosphorylated Serine 129 is eventually recognized as the amino acid residue that causes the difference between the normal and aggregated α-synuclein [2].

Researches regarding the pathology of α-synuclein aggregates go far beyond the theoretical level that is previously mentioned [2]. Phosphorylated Serine 129 is not only the most important difference between the chemical analysis of the urea-soluble and normal α-synuclein fractions, it is also discovered in the inclusion bodies of the synucleinopathy lesion sites, which perfectly support the previous chemical analysis [2]. By treating the affected cerebral cortices with anti-PSer129 antibody, an antibody that specifically reacts with the amino acid residues 124-134 plus a phosphorylated Serine

129 residue, the scientists find out that the phosphorylated Serine 129 can be clearly observed in inclusion bodies and those affected brain areas [2].

In conclusion, the urea-soluble fraction of α-synuclein is specifically phosphorylated at Serine 129 amino acid residue, which accounts for the difference between the normal and pathogenic α-synuclein [2]. It's also discovered that over 90% of the Serine 129 residues are phosphorylated in the urea-soluble fraction of the pathogenic α-synuclein aggregates, which ensures a direct relationship between phosphorylated Serine 129 and the abnormal α-synuclein aggregates [2]. Finally, Serine 129 is positively stained and detected by the anti-PSer129 antibody in human and mouse brain samples with inclusion bodies, and those asymptomatic samples are never immunostained by the antibody [2]. This observation indicates that the α-synuclein aggregates in the synucleinopathy lesion sites in the different parts of the brain are definitely phosphorylated at Serine 129 residue, and it strongly supports the relationship between the phosphorylation and the α-synuclein aggregate [2].

4. Formation and spreading mechanisms of Lewy bodies

Many researchers have supposed some theoretical models for the formation and the spreading of Lewy bodies [3]. These models assume that the α-synuclein first undergoes changes from physiological to pathological state, and then gradually mature, form aggregates and make up inclusions in the neuronal cell [3]. In the end, the newly-generated inclusion seeds are spread to the surrounding neuronal cells, where they experience a new cycle of formation, maturation, and spreading [3].

4.1 LB formation (stage 1-9):

Stage 1: physiological state
During stage 1, everything remains under control. The α-synuclein in the neurons still exhibit its normal structures [3]. The α-synuclein observed during this first stage either is unstructured or forms an α-helix structure when bounded in membrane [3].

Stage 2: aging, toxic insult or genetic predisposition
During stage 2, the normal physiological conditions start to transform into pathological conditions, and as a result, α-synuclein level increases and begins to form accumulations [3]. The commonest pathologies observed during stage 2 are aging, insult of neurotoxins, and genetic predisposition [3]. As a result of these pathological changes, the protein degradation mechanism can be impaired, and there will start to accumulate a certain amount of misfolded α-synuclein that cannot be properly degraded [3]. In addition, the neuronal cells will experience mitochondrial dysfunction and increasing oxidative stress, which are both common attributes that prompt the development of α-synuclein [3].

Stage 3&4: initiation of aggregation
During stage 3 and 4, abnormal α-synuclein accumulations are transformed into disorganized fibril and granular accumulations that will severely damage the cytosol and the entire neuron in the later stages [3]. During stage 3, two pathways are utilized for the α-synuclein aggregation [3]. Nucleation-dependent polymerization pathway is the most classic pathway that transforms α-synuclein in a highly ordered sequence [3]. The α-synuclein is first transformed into partially folded intermediate [3]. Then it forms nucleation-competent oligomers, which then become protofilaments [3]. At last, the protofilaments are transformed into α-synuclein fibrils, which become the disorganized fibrillar accumulations ready for further development [3]. On the other hand, the condensation pathway is also utilized to convert α-synuclein to the amyloid state [3]. During this conversion, the α-synuclein undergoes liquid-liquid separation and form droplets [3]. After that, the highly concentrated and saturated environment prompts the formation of α-synuclein aggregates which mature into amyloid-rich hydrogels [3]. Regardless of the specific process, both pathways produce the disorganized α-synuclein fibrils and granules by the end of stage 4 that will then be transferred into cytosol [3].

Stage 5&6:

During stage 5 and 6, the α-synuclein will be taken up by the lysosomes, and those that fail to degrade the α-synuclein actually prompts its further accumulation, thus forming the secondary lysosomes full of α-synuclein aggregates [3]. By the beginning of stage 5, the neuronal cell attempts to degrade the misfolded α-synuclein through several pathways, and one of the most notable ones is the lysosomal-mediated pathway [3]. Through the lysosomal-mediated pathway, the α-synuclein is first taken into the the lysosomes, where the lysosomes try to degrade these misfolded proteins [3]. However, special circumstances occur when such pathway is blocked or stalled, causing disastrous consequences [3]. For instance, the lysosomes with low pH for contain reactive oxygen metabolites (ROS) can promote the misfolding of α-synuclein [3]. Moreover, the lysosomes can also develop lipofuscin granules, a substance highly attractive and helpful for the development of α-synuclein, exacerbating α-synuclein aggregation [3]. By the end of stage 6, such deterioration ends with a completely affected lysosome, known as the secondary lysosome, containing huge amounts of abnormal α-synuclein aggregates [3].

Stage 7: lysosomal breakdown

At some point, the affected secondary lysosome breaks down, and the huge amounts of α-synuclein are expelled into the cytoplasm, which then undergo a series of a post-translational modifications and form the final inclusions during the next stages [3].

Stage 8: recruitment of organelles, membranes, and increasing PTMs

During stage 8, the α-synuclein aggregates released into the cytoplasm recruit multiple additional elements, such as free floating α-synuclein monomers, organelle membrane, and then combine into the final inclusions [3]. Also, multiple post-translational modifications occur during this stage, including phosphorylation at S129, ubiquitination, and other modifications that facilitate the final assemble of the α-synuclein aggregates [3].

Stage 9: maturation

During stage 9, all soluble proteins are expelled out of the affected neuronal cell, and the α-synuclein accumulations, along with other components in the cell, form a well-organized spherical structure, known as the Lewy body [3].

4.2 LB spreading

Release:

After becoming mature, Lewy bodies have to send seeds from the damaged neurons in order to spread the pathology [3]. As a result, there are multiple pathways through which the LB seeds can successfully escape out of the neurons and become ready for transmission:

Direct passive release

The LB seeds are able to escape the neuron in the most straightforward way, namely the direct passive release from their dying neurons [3]. The fibrillar α-synuclein can escape through the plasma membranes of the affected neurons and enter the recipient neuron through its plasma membrane during later stages [3].

Release through nanotube

Similar to the direct passive release, the nanotube pathway is also a highly straightforward pathway, through which the fibrillar α-synuclein seeds that escape out of the neurons are transferred into a nanotube that connects the releasing and recipient neurons [3]. Through the nanotube, the LB seeds are able to quickly transfer to surrounding neurons [3].

Exosomal vesicles

The LB seeds can also be released through the exosomal vesicles [3]. The LB seeds first coalesce into large multivesicular bodies and then be packaged into the large exosomal vesicles, where they will be released from the releasing neuron [3]. A very important reminder is that the exosomal pathway is the only membrane-bound pathway out of the 4 releasing pathways [3]. In other words, the LB seeds only remains membrane-bounded when they are released in exosomal vesicles [3]. Otherwise, these LB seeds are in a naked form [3].

Reception:

Once the LB seeds are released from the releasing neuron, they are received by the recipient neuron through multiple pathways [3]. The final destination of these seeds is the cytosol of the recipient cell, where they can interact with local α-synuclein protein and prompt further misfolding of these newly affected neurons [3]. There are usually 2 pathways taken by the LB seeds:

Membrane disruption

The LB seeds that arrive in naked form and have certain membrane-disruptive capability are able to bind the plan membrane and aggregate into large structures by incorporating the free floating α-synuclein protein [3]. As a result, the LB seeds can have access to the cytosol and contribute to a new round of LB formation and spreading [3].

Ensosomal fusion with the autophagosomes

For both the naked and the membrane-bound LB seeds, they are able to reach the cytosol through ensosomal fusion with the autophagosomes [3]. After being released from the releasing neuron, the LB seeds can bind to the ensosomes of the recipient neuron and be transmitted inside the recipient cell [3]. The ensosomes can then bind with the autophagosomes [3]. Such binding with the autophagosomes grant the LB seeds within the ensosomes access to the cytosol [3]. If the LB seeds arrive in the membrane-bound form, it can also directly bind to the autophagosomes and access the cytosol similarly [3].

5.   Spreading of Lewy pathology in human brain

In addition to all of the experiments that are carried on animal or cellular models, some researchers have successfully figured out the spreading pattern and some basic information of the Lewy pathology in PD patients' human brain [5]. These real-life situations that undergo real clinical symptoms perfectly make up the last part of this review, which will discuss the spreading of Lewy pathology in human brain [5].

The development of Lewy neurites and Lewy bodies in human brain can not only lead to destructive damage of the substantia nigra par compacta (SNC), but can also severely harm many other parts of the brain, such as the dorsal IX/X motor nucleus and the brain cortex [5]. Both inclusion bodies mostly target the lipofuscin and neuromelanin-laden projection neurons in different parts of the brain, thus often creating a pale body after completely destroying the lipofuscin and neuromelanin granules of an affected area [5]. More importantly, different parts of the brain and different neural cells have different susceptibility towards the PD inclusion bodies, meaning that there is a predetermined sequence of the topographical progression of the PD-related brain pathology [5]. Such staging of PD-related brain pathology is usually classified into 6 major stages [5].

Stage 1: During stage 1, the PD-related pathology is highly restricted to the medulla oblongata, and inclusion bodies only invade a small area of the lower brain stem, extending from the ala cinerea to the ventrolateral surface of the lower brain stem [5]. The brains only develop Lewy neurites and Lewy bodies in the projection neurons of the dorsal IX/X motor nucleus, anterior olfactory nucleus, and the reticular zone [5]. During stage 1, Lewy neurites greatly outnumber Lewy bodies, and many nerve cell bodies refrain from being affected [5]. More importantly, the PD-related inclusion bodies mostly target the lipofuscin granules in the medulla oblongata instead of the neuromelanin-laden nerve cells in stage 1 [5]. Most of the other parts of the brain such as the SNC, solitary tract, area postrema, and cortex remain intact during stage 1 [5].

Stage 2: During stage 2, the PD-related pathology of those parts of the brain that gets affected during stage 1 deteriorates, and more Lewy bodies begin to develop in the dorsal IX/X motor nucleus and the reticular zone [5]. However, in general, Lewy neurites still outnumber Lewy bodies during stage 2 [5]. In addition, Lewy neurites and Lewy bodies also continue to spread to more parts of the brain [5]. During stage 2, PD-related inclusion bodies invade the lipofuscin-laden projection neurons of the caudal raphe nuclei and the reticular formation [5]. Furthermore, they appear in the first neromelanin-laden nerve cells of the coeruleus-subcoeruleus complex [5]. Yet, the development of the inclusion bodies in stage 2 is still highly confined [5]. Most of the other nerve cells besides the

neuromelanin- and lipofuscin-laden neurons remain uninvolved during stage 2, and other parts of the brain such as the SNC and the cortex are free from the inclusion bodies [5].

Stage 3: During stage 3, the severity of the previous lesions increases. The neuromelanin-laden nerve cells of the dorsal IX/X motor nucleus and the intermediate reticular zone begin to develop Lewy bodies [5]. Yet, a more important hallmark that defines stage 3 is the involvement of the neuromelanin-laden nerve cells of the SNC and the lipofuscin-laden neurons of the basal forebrain [5]. Moreover, some other mesencephalic prediction sites such as the pedunculopontine segmental nucleus and the Ammon's horn also begin to develop inclusion bodies [5]. However, during stage 3, the inclusion bodies have just begun to invade these areas, and as a result, only a few very limited parts of the affected regions develop inclusion bodies, such as the posterolateral and posteromedial sub nuclei of the SNC and the second sector of Ammon's horn [5]. Most of the non-melanized nerve cells and the mesocortex and neocortex remain exempt from the affection, and the severity of the lesions of those newly-affected regions is still relatively mild [5].

Stage 4: By stage 4, many of the previous lesions have already become very severe [5]. Regions such as the SNC, the dorsal raphe nucleus, and the pedunculopontine segmental nucleus have suffered severe damage and loss of melanized- and lipofuscin-rich neurons [5]. The anterior olfactory nucleus, the Ammon's horn, the magnocellular nuclei of basal forebrain, and hypothalamic tuberomamillary nucleus also develop more inclusion bodies and are seriously destructed [5]. The inclusion bodies also spread to more parts of the brain [5]. The oral raphe nuclei, stria terminalis of amygdala, additional mesencephalic nuclear grays such as paranigral nucleus and parabrachial nucleus start to develop networks of Lewy neurites and Lewy bodies [5]. However, the most important hallmark of stage 4 is the involvement of anteromedial temporal mesocortex [5]. During stage 4, the outer cellular layers of the antermedial temporal mesocortex develop a network of Lewy neurites, while the inner cellular layers develop globular Lewy bodies in small and medium-sized neurons [5]. The involvement of the anteromedial temporal mesocortex is highly crucial, as this not only symbolizes the transfer of PD-related brain pathology from brain stem to the cortex, but also offers a pathway for the inclusion bodies to further invade neocortex in the next stages [5].

Stage 5: During stage 5, the inclusion bodies have completely destroyed most of the melanin- and lipofuscin-laden neurons in the previous lesion sites [5]. SNC, dorsal IX/X motor nucleus, reticular zone, and coeruleus-subcoeruleus complex are almost denuded of melanin-laden and lipofuscin-rich neurons, leading the appearance of many pale bodies under microscope inspection [5]. Other regions are also severely affected. The olfactory system is seriously damaged, and the long Lewy neurites in the second Ammon's horn sector gradually spread to its first and third sector, conquering the entire Ammon's horn [5]. More importantly, the inclusion bodies make a pathway through the anteromedial temporal mesocortex and enter the neocortex during stage 5 [5]. Large numbers of Lewy bodies are carried within pyramidal cells and appear in the sensory association area, the anterior cingulate cortex, the agranular and granular insular fields, and the prefrontal areas of the neocortex [5]. At this stage, however, some farther parts of the neocortex such as the first order sensor association and premotor areas remain free of the inclusion bodies [5].

Stage 6: During stage 6, the entire neocortex is involved [5]. Yet, some parts that are farther away from the anteromedial temporal mesocortex such as the first order sensory association and primary sensory areas, the premotor areas, primary motor field suffer relatively mild changes [5].

6. Discussion

Indeed, more and more information regarding PD-related pathology and the properties of α-synuclein as both normal protein and abnormal aggregates have been continuously disclosed by many researches these years. As a result, our knowledge of the Parkinson's disease is also constantly improving, including more and more experimental and clinical information. However, we have to acknowledge that there still remains a large number of gaps of information that are still unknown to us. For example, although we manage to propose theoretical models for the spreading and formation

of LBs, how practical these models are and the how the early stages advance still remain mysterious [3]. Similarly, most of the physiological function related with the localization of the α-synuclein still remains unknown [3]. As a result, researchers are continuing to improve the technology required for more precise observation and work on those unknown mysteries, so that one day the Parkinson's disease and the α-synuclein protein can be more familiar with the human beings, and that the clinical symptoms of Parkinson's disease can be improved and relieved.

References

[1] Jaqueline Burré, Manu Sharma, Thomas C. Südhof. Cell Biology and Pathophysiology of α-Synuclein. Cold Spring Harbor Laboratory Press, January 20, 2017.

[2] Hideo Fujiwara, Masato Hasegawa, Naoshi Dohmae, et al. α-Synuclein is phosphorylated in synucleinopathy lesions. Nature Cell Biology. Vol.4 (2002), p.160-164.

[3] Mohamed Bilal Fares, Somanath Jagannath, Hilal A. Lashuel. Reverse engineering Lewy bodies: how far have we come and how far can we go? Nature Reviews. Vol.22 (2021), p.111-131.

[4] Kelvin C. Luk, Victoria Kehm, Jenna Carroll, et al. Pathological α-Synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. Science. Vol.338 (2012), p.949-953.

[5] Heiko Braak, Kelly Del Tredici, Udo Rüb, et al. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiology of aging. Vol.24 (2003), p.197-211.