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Advances in Pathogenesis and Treatment of Parkinson's Disease Based on Abnormal Accumulation of Alpha-Synuclein

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Abstract. Parkinson's disease (PD) is an age-related neurodegenerative disease in which dopamine neurons in the substantia nigra of the brain gradually die over time. PD mainly manifests as resting tremor, bradykinesia, stiffness, and ultimately the inability to control motor function and cause severe disability. It has now been shown that neuronal Lewy bodies (LBs) and the intra-synaptic aggregation of α-Synuclein (α-Syn) are hallmarks of brain lesions in PD, and Lewy body lesions have been found to be present in the peripheral nervous system in PD. Interfering with LBs formation has become a new hot topic in Parkinson's disease treatment. The formation of LBs has been linked to the transport of α-Syn in brain cells and the blood-brain barrier. Nonetheless, treatment options still produce little effect. According to past investigations, this paper addresses the question of advances in pathogenesis and treatment of Parkinson's disease using literature review as an investigation method. It introduces the pathogenesis and the latest treatment strategies of PD based on the aspect of abnormal accumulation of α-Syn, which can provide a theoretical basis for subsequent treatment of PD.

Keywords: Parkinson's disease, pathogenesis, treatment, Lewy bodies, Alpha-synuclein

1. Introduction

PD, the second most common neurodegenerative disease that occurs in the middle-aged and elderly population. The number of cases continues to increase in countries with an aging society, such as China [1-2]. In 2005, an estimated number of 4.1 million people worldwide were living with PD. By 2030, this number is expected to rise to 8.7 million. Due to its high prevalence, disability, and chronic course, PD is becoming an important scientific and social issue in the field of population, health, and neuroscience. However, there are still a lot of confusion in clinical practice and no effective way to prevent the progression of this neurodegenerative disease. Thus, research involving the pathogenesis, treatment and prevention of PD becomes vitally essential.

In the past investigation, PD has been studied by many scholars, and more information on the pathogenesis and treatment are being introduced with the advancement of technology. Most scholars now believe that PD is caused by the absence of dopaminergic neurons in the substantia nigra, the presence of LBs, and the abnormal accumulation of α-Syn which is closely related to the development of LBs and PD.

To provide more detailed theoretical guidance for the development of the treatment for abnormal accumulation of α-Syn in PD, this paper will address to the concept of abnormal accumulation of α-Syn as a pathogenesis of PD, the specific treatment for abnormal accumulation of α-Syn, future

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research challenges, and major therapeutic research directions. The treatments are different gene therapy, α-Syn targeting and treatment for the selectively loss of dopaminergic neurons caused by the abnormal accumulation of α-Syn.

The following structure of this paper will contain a short review of the previous part, together with the discussion of α-Syn as a pathogenesis in PD and the function of treatment in relation with curing α-Syn pathogenesis. Lastly, a short conclusion will be made, including the discussion of future research challenges and major therapeutic research directions of PD.

2. Cellular mechanisms in alzheimer's disease

2.1. Genetic factor

In 1997, SNCA (PARK1, PARK4) was the first gene that were found to be PD causative gene. Some people also named it as α-synuclein genes since mutations in the α-synuclein genes Ala53Thr and Ala39Pro lead to abnormal deposition of α-synuclein and eventually the formation of LBs. Overexpression of α-synuclein in mice or Drosophila produces the classic symptoms of PD. In addition, it has been shown that SNCA (PARK1, PARK4) promoter polymorphism variants increase the risk of sporadic PD, and that multiplication of SNCA wild-type motifs is also quantitatively associated with PD susceptibility. For example, additional copies of SNCA lead to earlier age of onset and more severe symptoms such as dementia [3-4]. Although mutations in the α-synuclein gene are only found in a small proportion of patients with familial PD, the fact that the protein expressed in this gene is a major component of LBs suggests that it plays an important role in causing the a-Syn pathogenesis of PD.

2.2. The role of tau protein

As it is proved that mutation in α-synuclein gene (PARK1/PARK4) can triggered PD, various studies also suggest that neuronal LBs and α-Syn, a protein that aggregates within neurons, are hallmarks of brain lesions in PD, and Lewy body lesions have been found to be present in the peripheral nervous system in PD.

LBs are one of the most common types of the clumps of misfolded protein within neurons. One of its typical characteristic components is a misfolded protein called α-Syn. It was first observed in 1997 in the Lewy vesicles of brain tissue from PD by "SPILLANTINI et al" [5]. In the same year, "POLYMEROPOU- LOS et al" [6] showed that point mutations in SNCA, the gene encoding α-Syn, and gene duplication were closely associated with the development of PD. In the nervous system, α-Syn is abundantly expressed at presynaptic terminals and has multiple roles in synaptic transmission. "JANECZEK et al" [7] not only observed that α-Syn negatively regulates dopamine uptake via the dopamine transporter and is an important factor in the negative regulation of dopaminergic neurotransmission, but also found that the level of α-Syn expression has a twofold role in the central nervous system. Normal levels of α-Syn protect the CNS from damage. Nevertheless, increased expression of α-Syn monomers in the normal human nervous system can lead to further aggregation of α-Syn in the oligomeric state and the development of insoluble α-Syn fibres, particularly in the presence of mutations and gene duplications in SCNA, the gene encoding α-Syn. Studies[8-9] have found that the rate of α-Syn fibril formation significantly accelerated, eventually forming toxic α-Syn oligomers and longer fibrils that accumulate in the cytoplasm of nerve cells and impair the normal function of the nervous system as they can impairs the normal differentiation of neural progenitor cells and changes the differentiation from neuronal to glial cells, leading to a decrease in the number of normal neuronal cells and affecting normal neurophysiological activity. Meanwhile, many evidences proved that α-Synuclein not only interferes with the exchange of calcium ions between the mitochondria and endoplasmic reticulum, disrupting intracellular calcium ion homeostasis, but also inhibits the degradation of damaged mitochondria. Therefore, the formation of α-Syn oligomers in neuronal cells is likely to lead to a significant production of reactive oxygen species, which is an important signal for mitochondria-related apoptosis, and its increased

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concentration is likely to lead to widespread neuronal apoptosis and impair the normal function of the nervous system.

Vitro experiments have demonstrated that the uptake of α-Syn oligomers can occur by a variety of mechanisms, with one part of α-Syn expressing in mouse brain nigrostriatal cells and the other part entering the cell by fusion with the cell membrane and cytokinesis. Syn can enter the cell through membrane pore proteins or protein complex channels in the cell membrane, or by endocytosis through fusion with the cell membrane, while another part can induce the production and aggregation of endogenous α-Syn by binding to receptor proteins on the cell membrane, leading to the formation of endogenous α-Syn oligomers [10-11]. During cellular uptake of α-Syn, extracellular α-Syn oligomers can induce lysosomal rupture and induce an increase in histone B-dependent reactive oxygen species in target cells, leading to inflammasome activation [12]. Thus, α-Syn oligomers are not only neurotoxic and affect mitochondrial and proteasomal functions but can also be transferred between neuronal cells through a transport mechanism such as endocytosis and exocytosis, damaging peripheral nerve cells [12-13]. In addition, in the presence of neuronal proteasomal and mitochondrial dysfunction, the rate of α-Syn transport is significantly increased, which in part creates a vicious circle of pathology and accelerates the progression of PD.

In addition, microglia were observed to be activated when α-syn crossed the blood-brain barrier [14]. However, it has been found that although microglia can take up exogenous α-syn through GM1-dependent lipid raft-mediated endocytosis, it lacks the ability to effectively degrade α-syn [15]. This is also related to the impairment of the protease system caused by α-syn. Depending on the phenotype, the M1 and M2 phenotypes are activated and can have either toxic or protective effects on the nervous system. M1-type microglia are mainly found at the site of injury at the end of the disease, when the immunoregulatory and repair functions of M2-type are suppressed. α-Syn also acts as a chemoattractant, inducing microglia to damaged cells [16]. Thus, α-Syn chemotactic and activating microglia of the M1 type leads to damage in several parts of the nervous system due to incomplete clearance of α-Syn and inflammatory responses. This accelerates the progression of PD.

3. Treatments for abnormal accumulation of alpha-synuclein in pd

Active and passive immunity are two main tools used to treat the pathogenesis of α-Syn.

Gene therapy to prevent the pathogenic spread of α-Syn. Targeting extracellular α-Syn and reducing the spread of intercellular α-Syn is mainly achieved by classical immunotherapy [17-18]. Extracellular α-Syn is used as an immunotherapeutic substrate to inhibit α-Syn transmission by blocking or downregulating the expression of receptors that promote intercellular transmission. Vector-based immunotherapies that deliver anti-α-Syn antibodies directly to the CNS via viral vectors are being explored to enhance cellular target engagement, and with the advent of mRNA vaccines, immunotherapy-based gene therapy targeting α-Syn may be on the horizon. In addition, direct production of intracellular antibodies in target cells through gene therapy is important to reduce α -Syn-related pathological damage [19-20].

Gene therapy to down-regulate α-Syn expression. α-Syn-targeted gene silencing approaches antisense oligonucleotides (ASO), small interfering RNA (siRNA), short hairpin RNA (shRNA), and zinc finger nucleases (ZFN), etc, using liposomal and viral vectors as delivery routes [21-23]. A cluster of regularly spaced short palindromic repeats (CRISPR) was used to down-regulate α-Syn expression by transcriptionally regulating the Cas9 (dCas9) system of nucleic acid endonuclease inactivation. Although α-Syn-targeted gene silencing has been shown to be effective in preventing the toxic effects of -Syn [24], rodent and non-human primate models have shown that nigrostriatal hypofunction is a direct consequence of α-Syn knockdown. The inconsistent results of these studies may be due to a compensatory increase in α-Syn [25]. Therefore, down-regulation of soluble α-Syn expression should first consider the minimum threshold at which α-Syn can perform its normal physiological function, below which it can have potentially toxic effects.

Gene therapy to stabilize monomeric α-Syn or accelerate the clearance of aggregated α-Syn. Stabilization of monomeric α-Syn or breakdown of neurogenic fibrillary tangles (NFTs) are possible

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strategies to reduce α-Syn aggregation. Although the main substances that stabilize monomeric α-Syn are small molecules, several gene therapy candidates have emerged that may have similar stabilizing functions: for example, nanobodies designed to target the non-amyloid component of α-Syn could both inhibit misfolding and accelerate clearance, thereby reducing the toxic effects in ex vivo models of synaptic nucleopathy [26].

4. Alpha-synuclein targeting

Apart from gene therapy, α-Syn targeting is also an effective α-Syn treatment. Overexpression of α-Syn causes its accumulation and aggregation, leading to PD. There are two main approaches to targeting α-Syn: reducing its synthesis and increasing its degradation. For reducing α-Syn synthesis, not only small interfering RNA (siRNA) and antisense oligonucleotides (ASO) mentioned in the gene therapy section can be used to recognize small molecules binding to α-Syn and prevent them from participating in the template reaction [27] in order to reduce α-Syn synthesis and treat PD, β2-adrenoceptor agonists can also modulate transcription and reduce α-Syn levels, which may be a new target for the treatment of PD.

In terms of increased α-Syn, degraded α-Syn is degraded via the ubiquitin-protease system and the autophagy-lysosome pathway. The small molecule inhibitor of the deubiquitinating enzyme USP14, 1-[1-(4-fluorophenyl-2,5-dimethylpyrrol-3-yl)-2-pyrrolidin-1-ylethanone (1-[1-(4-fluorophenyl)-2,5-dimethylpyrrol-3-yl]-2-pyrrolidin-1-ylethanone, IU1) increases the clearance of α-Syn by enhancing proteasomal activity [28]. The mammalian target of rapamycin (mTOR) pathway has also been implicated in the degradation of α-Syn, and the mTOR inhibitor rapamycin protects neuronal cells in animal models [29].

5. Treatment for the selectively loss of dopaminergic neurons caused by the abnormal accumulation of alpha-synuclein

Currently, dopamine receptor (DR) agonists are the common and mainly used treatment for the selectively loss of dopaminergic neurons triggered by the abnormal accumulation of α-Syn. It has a neuroprotective effect and plays a major role in increasing the activity of dopamine neurons. However, other novel drugs have recently been found to protect dopamine neurons, such as glitazone.

Scientists in the UK have found that diabetic patients taking glitazones (rosiglitazone or pioglitazone) have a 28% lower risk of developing PD than those taking other antidiabetic drugs. As a peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist, pioglitazone protects nigrostriatal dopaminergic neurons from neuronal death and has a potent neuroprotective effect against the various mechanisms involved in the progression of neurodegeneration in PD [30]. However, phase II clinical trials have found that pioglitazone is unlikely to alter early PD progression and is not suitable for further study [31].

Meanwhile, deep brain stimulation (DBS) can be performed by surgically implanting electrodes in specific nuclei in the brain to release high frequency electrical stimulation, thereby suppressing the electrical impulses of these neurons that are over-excited due to a decrease in dopaminergic neurons, reducing their hyper-excitable state and alleviating Parkinson's symptoms. It relieves the three main symptoms of PD — tremor, rigidity, and bradykinesia — and has a very good effect on the midline symptoms, such as difficulty starting, turning over, etc.

6. Conclusion

This paper discusses the pathogenesis and treatment strategy of abnormal accumulation of α-Syn. According to the discussion, we found out that although all the studies indicate that the treatment of PD have improved the patient's symptoms to a certain extent and inspired the development of more effective treatment, they have not achieved precise treatment based on specific pathogenesis. For example, the inhibition of genetic mutation could trigger the abnormal accumulation of α-Syn. Simultaneously, whilst current drug treatment becomes increasingly less effective over time and may eventually be not effective at all, many novel treatments are still on their ways to clinic trail.

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Therefore, the main challenges are to ensure the effectiveness of drug treatment while finding out more pathogenesis of PD. For major therapeutic research directions of PD, techniques and methods that target abnormal accumulation of α-Syn caused by genetic mutation and a means of inhibiting transport by targeting a protein in one of the multiple transport pathways of the α-Syn transport mechanism between nerve cells can all be explored in the future to achieve precise treatment.

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