The role of α-synuclein in Parkinson disease

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Abstract. Parkinson disease (PD) was a common insidious neurodegenerative disorder that occurs in middle-aged and elderly people, where the dopaminergic neurons in the midbrain substantia nigra (Dopamine, DA) die over time and the main clinical manifestations are resting tremor, motor bradykinesia, rigidity and eventual inability to control motor functions [1] The specific pathogenesis of PD was complex and not yet clear, but misfolding and aggregation of α-synuclein (α-Syn) is considered to be the hallmark of PD. Since early diagnosis of the disease is difficult, this review summarizes how α-Syn is involved in several aspects into neuronal function and recent advances in targeting α-Syn for PD, providing a theoretical basis for subsequent treatment of PD.

Keywords: Parkinson disease, Pathophysiology, Review.

1. Introduction

PD is the second most common neurodegenerative disease after Alzheimer's disease. It affects a large population base, is prevalent in middle-aged and elderly groups, and has a significant impact on daily life and can be severe and life-threatening. It is a chronic, progressive, age-related and fatal neurological disease. The main clinical features are resting tremor, bradykinesia, muscle rigidity, postural gait disturbances, and non-motor symptoms, which can eventually lead to severe disability due to the inability to control motor functions [2]. The pathological mechanism is mainly due to the degeneration and death of DAergic neurons in the dense part of the midbrain substantia nigra, where α-synuclein (α-Syn) is a central target in the pathogenesis of the disease, and it plays a key role in the existence of bidirectional links with several mechanisms. At the same time, as a humoral biomarker, α-Syn has many advantages over clinical diagnostics in terms of confirming the diagnosis as an objective indicator that is not affected by the rate of misdiagnosis due to clinical features [3]. α-Syn is a major component of Lewy bodies (Lbs) [4], which are misfolded, insoluble, and form β-rich folded amyloid aggregates, which accumulate and constitute intracellular inclusion bodies [5]. As early diagnosis of the disease is difficult, this review summarizes how α-Syn is involved in multiple aspects of neuronal function and recent advances in targeting α-Syn for PD, providing a theoretical basis for subsequent treatment of PD [6]-[7].

2. Biological properties of α-Syn

In the human body α-Syn is mainly expressed by neurons and erythrocytes [8]-[9], and consists of three distinct regions [10]. The N-terminal structural domain of the protein (amino acids 1-60) binds to lipids and contains all known disease-associated mutations. The central structural domain is known as the non-amyloid component (NAC) (amino acids 61-95), which is relatively hydrophobic and aggregates easily. The acidic and glutamate-rich C-terminal sequence (amino acids 96-140), which contains most of the phosphorylation sites, especially serine 129, is the main reason for the interaction with other proteins and small molecules [11]-[12]. α-Syn aggregation and delivery, especially the association with mitochondria and lysosomes [13], is closely linked to PD pathogenesis. α-Syn has the ability to nucleate during the nucleation dependent process of aggregation in amyloid structures [14], a process that acquires neurotoxic properties during pathogenesis, in which soluble monomers form oligomers, then small protofibrils, and eventually large insoluble α-Syn protofibrils (i.e., Lbs) [15]-[16]. It is in equilibrium between the soluble and membrane-bound states, and its secondary structure depends on the state of α-Syn [13]. To date, the exact physiological function of α-Syn is

unknown, but its misfolding and aggregation are currently considered to be the main cause of synaptic dysfunction, while toxic oligomers activate microglia back and induce neuroinflammation leading to PD development. α-Syn plays a role in the regulation of neurotransmitter release, synaptic function and plasticity [17]-[18].

3. Neuronal functions in which α-Syn is involved

The clinical diagnosis of PD is generally based on typical motor symptoms, but the clinical overlap of PD symptoms poses difficulties in differential diagnosis, especially in the early stages of the disease [19]-[20], and delayed diagnosis can have a significant impact on treatment; therefore, there is an urgent clinical need to discover a reliable and accurate PD-related biomarker. α-Syn accumulation can lead to a variety of pathogenic factors, mitochondrial dysfunction, autophagy dysfunction, oxidative stress, and inflammation [21], while at the same time, these same pathological features contribute to the exacerbation of abnormal α-Syn expression and aggregation.

For example, during oxidative stress, Reactive Oxygen Species (ROS) target mitochondria, causing them to dysfunction and produce less energy, while nigrostriatal DAergic neurons have high energy consumption due to their extra-long unmyelinated nerve fibers [22]. In PD patients, the ROS generated when the cells are under oxidative stress make the energy demand of DAergic neurons far exceed the supply, which eventually leads to the impaired death of DAergic neurons. The surviving DAergic neurons, on the other hand, will have an accelerated rate of DA synthesis, metabolism and renewal due to compensatory effects, thus generating more ROS and further aggravating oxidative stress [23]. During this process, DJ-1 protein acts as a molecular chaperone and reactive oxygen species burster, exerting its neurocytoprotective effects on different oxidative stress responses through multiple modal mechanisms. It has been shown that the expression levels of α-Syn and DJ-1 are closely related and that α-Syn is negatively correlated with the expression level of DJ-1[24], and its accumulation leads to an exacerbation of oxidative stress. Likewise, in neuroinflammation, impaired Ca^{2+} homeostasis, and mitochondrial dysfunction, α-Syn interacts with these pathological factors to form a vicious cycle, which amplifies the damage and eventually causes cell death.

Recent studies suggest that α-Syn is transmitted in a prion-like manner, and once he forms aggregates in neurons, he can be transported from intra-axonal to other regions of the brain and released extracellularly to be taken up by adjacent neurons [25]. While oxidation, nitration, ubiquitin-proteasome, and lysosomal autophagy systems are all associated with the degradation of α-Syn [26], especially the ubiquitin-proteasome system and the lysosomal autophagy system. The ubiquitin-proteasome system plays a role mainly in the degradation of short-lived soluble proteins and is associated with the Parkin gene encoding [27]. In contrast, the lysosomal autophagy system mainly degrades long-lived macromolecular proteins, and his role in PD is associated with the related proteins LRRK2, GBA, VPS35, and DNAJC13 genes encoding [28], which are closely linked to α-Syn.

4. Therapeutic approaches targeting alpha-Syn

Currently, the clinical diagnostic accuracy of PD remains poor, and PD is neither curable nor preventable, and given that α-Syn aggregation is a hallmark of PD pathology, it is considered a promising diagnostic and therapeutic target [7]. A growing number of studies have shown that α-Syn treatment by gene targeting and the use of immunotherapy can help improve PD symptoms by reducing α-Syn production, inhibiting α-Syn aggregation, and promoting the degradation of intracellular α-Syn aggregates.

Small interfering RNAs (siRNAs) and antisense oligonucleotides (ASOs) recognize small molecules that bind to α-Syn and prevent their participation in the template reaction [29], thus reducing α-Syn mRNA to reduce α-Syn approach. In addition, $\beta 2$ adrenergic receptor agonists can modulate transcriptional reduction of α-Syn levels, which is expected to be a new target for the

treatment of Parkinson's disease [30]. To prevent α-Syn from forming aggregates, a number of small molecules that can cross the Blood Brain Barrier (BBB) have been identified, including NPT200-11, NPT100-18A, NPT088, Anle138b, ENT-01[31]-[35].

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 (IU1), increases α-Syn clearance by enhancing proteasome activity [36] The mammalian target of rapamycin (mTOR) pathway has also been implicated in the degradation of α-Syn. The mTOR inhibitor rapamycin reduces α-Syn accumulation in SNCA transgenic mice [37], and alleviates motor function in A53T α-Syn transgenic mice [38], protecting neuronal cells [39]. It was found that mutations encoding the enzyme glucocerebrosidase (GBA) reduced the activity of glucocerebrosidase (GCase) in PD brain, and it was GCase that disrupted α-Syn degradation [40]. The glucocerebrosidase inhibitor Venglustat was able to delay the accumulation of α-Syn in $Gba^{D409V/D409V}$ mice and improve their cognitive function after 8 months of treatment [41]. The use of the GBA agonist LTI-291 (NCGC-6078) was able to restore lysosomal function to clear α-Syn from brain neurons in PD patients [42]. In an open-label clinical trial in 17 PD patients, amiloride was shown to cross the BBB and bind to β-glucocerebrosidase. It was able to increase protein levels of β-glucocerebrosidase as well as CSF α-Syn levels without substantial effects in patients with GBA gene mutations [43]. Leucine-rich repeat kinase 2 (LRRK2) inhibition is another therapeutic target, and one study reported that DNL-201, which inhibits LRRK2, is well tolerated and can inhibit more than 90% of LRRK2 kinase activity at peak concentrations in the brain[44].

Immunotherapy is also a very promising intervention. Active and passive immunotherapies are being used to test the neutralizing effect of α-Syn based on the immunogenic epitopes within the C- and N-termini of α-Syn [45] [46]. PD01A AFFITOPE (AFFiRiS) is an active immune vaccine that has been reported to produce serum antibodies against α-Syn in 55% of patients [47]. Passive immune antibodies are also under development.

Similar to the treatment strategy for Alzheimer's disease, timely guidance of multi-targeted therapies for all aspects of PD pathogenesis would be an effective approach to slow the progression of PD patients [48].

5. Summary

PD, as the second most common neurodegenerative disease after Alzheimer's disease, has been a research hotspot due to the large number of people affected and the difficulty of clinical treatment. And as the prevalence of PD is increasing year by year with the trend of lowering age, coupled with its complex pathogenesis, early diagnosis is difficult and treatment is ineffective. Based on this, this paper reviews the biological functions of α-Syn, a humoral biomarker involved in several aspects of neuronal function, and how it is involved in different neuronal functions and plays an influential role, and summarizes the latest progress of targeting PD by α-Syn accordingly. The future selection of PD biomarkers will enable early diagnosis, simple manipulation and disease prediction, and as the accuracy of diagnostic techniques improves, the treatment of PD will move toward eliminating the cause, while therapeutic studies targeting α-Syn will promote the discovery of more effective drugs in the direction of PD treatment.

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