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α-synuclein aggregation and its modulation

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ABSTRACT

Parkinson's disease (PD) is a neurological disorder marked by the presence of cytoplasmic inclusions, Lewy bodies (LBs) and Lewy neurites (LNs) as well as the degeneration of dopamine producing neurons in the *substantia nigra* region of the brain. The LBs and LNs in PD are mainly composed of aggregated form of a presynaptic protein, α-synuclein (α-Syn). However, the mechanisms of α-Syn aggregation and actual aggregated species responsible for the degeneration of dopaminergic neurons have not yet been resolved. Despite the fact that α-Syn aggregation in LBs and LNs is crucial and mutations of α-Syn are associated with early onset PD, it is really a challenging task to establish a correlation between α-Syn aggregation rate and PD pathogenesis. Regardless of strong genetic contribution, PD is mostly sporadic and familial forms of the disease represent only a minor part (<10%) of all cases. The complexity in PD further increases due to the involvement of several cellular factors in the pathogenesis of the disease as well as the environmental factors associated with the risk of developing PD. Therefore, effect of these factors on α-Syn aggregation pathway and how these factors modulate the properties of wild type (WT) as well as mutated α-Syn should be collectively taken into account. The present review specifically provides an overview of recent research on α-Syn aggregation pathways and its modulation by several cellular factors potentially relevant to PD pathogenesis. We also briefly discuss about effect of environmental risk factors on α-Syn aggregation.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease in the elderly affecting millions of people worldwide [1]. PD is characterized by the progressive degeneration of dopamine producing neurons (dopaminergic neurons) in the *substantia nigra* region of the brain, which results in impaired motor functions, displayed as compromised postural reflexes, muscular rigidity and bradykinesia in PD patients [2–5]. Despite several years of intense and inter disciplinary research, the exact mechanism of selective degeneration of dopaminergic neurons is not well known probably due to the multi factorial nature of the disease. Complexity in PD arises from the involvement of several environmental and genetic risk factors, which worsen neurodegeneration and PD pathology. Interestingly, despite strong genetic contribution, PD is mostly sporadic and familial forms of the disease represent only a minor part (<10%) of all cases [6]. However, irrespective of the origin of disease (sporadic/familial), the main pathological hallmark in most PD cases is the presence of Lewy bodies (LBs) and Lewy neurites (LNs) in the PD patients' brains [7]. These LBs and LNs are mainly composed of the aggregated form (amyloid fibrils) of α-synuclein (α-Syn), a highly conserved presynaptic 140 amino acid protein [7,8]. This finding suggests that aggregation of α-Syn into amyloid fibrils and its subsequent accumulation in LBs and LNs (Fig. 1) is a central event in the pathogenesis of both sporadic and familial PD. In connection with this idea, several pioneer studies suggest that duplication, triplication and several mutations in the *SNCA* gene on chromosome 4q21-23, which encodes for the α-Syn protein, are associated with early onset familial form of PD [5,9–17].

The hypothesis that accelerated fibrillation of α-Syn may worsen PD pathology and disease progression was inspired from the seminal discovery of two α-Syn mutants (A53T and E46K) with increased fibrillation propensity *in vitro*, which are associated with familial PD [18–20]. Furthermore, a recently discovered mutation of α-Syn (H50Q) linked to familial form of PD is also shown to accelerate the fibrillation rate of α-Syn [16,17,21]. On the contrary, several other mutations (A30P, G51D, and A53E) associated with familial forms of PD have been shown to decrease the fibrillation rate of α-Syn [15,22–25]. This suggests that the fibrillation rate of α-Syn is not directly correlated to disease pathogenesis. This complexity may be resolved to some extent by monitoring the effect of familial α-Syn mutations on oligomerization rate rather than the fibrilla-

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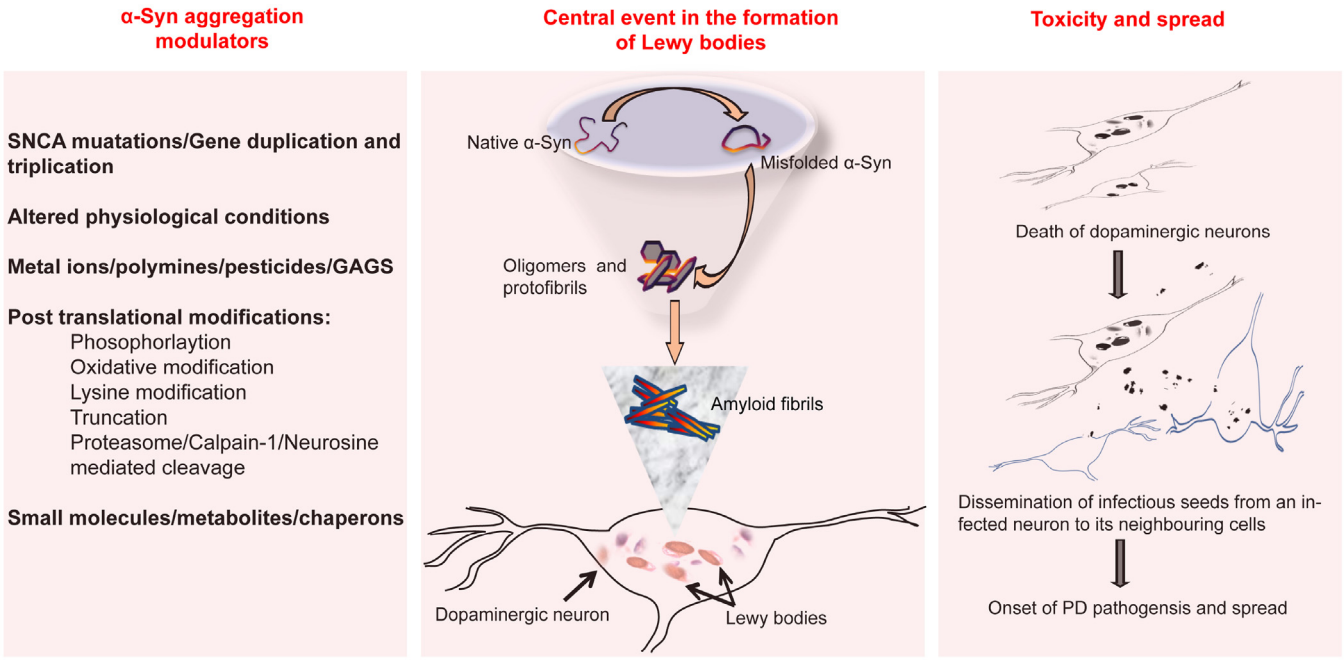

Fig. 1. Schematic representation of modulation of α-Syn aggregation, accumulation in dopaminergic neurons and spread of toxicity. Different factors that modulate α-Syn aggregation and amyloid formation are shown (Left panel). Once native α-Syn is misfolded, it oligomerizes and form amyloid fibrils, which get accumulated in LBs and LNs in dopaminergic neurons of PD patient's brain. This subsequently results in toxic cascade of events leading to neuronal death (middle and right panel).

tion rate. Evaluating oligomerization kinetics may be a promising approach since several studies have claimed that pre fibrillar α-Syn oligomers are probably the most potent toxic entities responsible for neuronal death in PD [26]. Consistent with this observation, it is well established that despite their differential effects on fibril formation rate, both mutations (A53T and A30P) accelerate oligomer formation, which ultimately leads to early onset PD pathology [27]. Moreover, one could explain the association of the H50Q mutation with late-onset PD because it is a faster fibril-forming mutant, thus, accumulation of toxic prefibrillar oligomers is less likely due to their rapid conversion into fibrils. However, this rationale does not hold true for E46K mutant, which also has faster fibril formation rate resulting in lesser accumulation of toxic pre-fibrillar oligomers but is still associated with early onset familial PD. Therefore, establishing a correlation between α-Syn aggregation rate and PD progression is really a puzzling task. Furthermore, favored oligomers formation and its subsequent slow fibril conversion rate are only well established for the A30P mutant and are either not clearly seen or not studied well yet for other slow fibril forming mutants (G51D and A53E).

Some of these contradictions may be partially sorted out by considering the fact that PD is a multifactorial disease, where several environmental factors such as exposure to metal ions and pesticides as well as dietary factors and altered cellular micro environment may also affect α-Syn aggregation *in vivo* and in turn affect PD pathology [28]. For example, the properties and functions of α-Syn would depend on the extent of its interaction with membrane, post-translational modifications, local folding in cellular crowded milieu, which will eventually affect the extent of aggregation and production toxic species of α-Syn. Additionally, the interaction/co-aggregation of α-Syn with other proteins and biomolecules such as polyamines could also be equally important for α-Syn mediated PD pathogenesis [28].

Along with these factors, various physical and chemical parameters such as aggregation surface, pH, ionic strength, metal ions, and temperature are also shown to affect the α-Syn aggregation *in vitro* [28–31]. Thus, correlating α-Syn aggregation in test tubes with disease progression *in vivo* becomes a daunting task. As research on the factors associated with PD and/or modulating α-Syn aggregation is subject of active investigation by huge number of laboratories, reviewing all these factors is beyond the scope of this review. However, we tried to provide some overview of research on α-Syn aggregation pathways and its modulation by cellular factors and selected environmental factors that may modulate PD pathogenesis.

2. α-Syn: a brief history and its biophysical properties

α-Syn is a protein, which belongs to the synuclein protein family found in vertebrates [8]. Synuclein was first identified in the year 1988 as a protein localized in the synaptic vesicles and nucleus of the cholinergic neurons in Pacific electric ray (*Torpedo californica)* [32]. Based upon its synaptic and nuclear localization, the protein was named as synuclein [8,32]. The synucleins were present as three major forms (molecular mass ~17.5, ~18.5 and ~20 kDa) in the torpedo central nervous tissue.

Human α-Syn is a protein with molecular mass ~14 kDa (containing 140 amino acid residues) (Fig. 2A), which is expressed abundantly in the brain and at reduced levels in other organs as well as hematopoietic tissue [33–35]. Other three synuclein family members are identified as β-Syn, γ-Syn and synoretin [8,36]. β-Syn is a human homologue of bovine phosphoneuroprotein (PNP) 14 and contains 134 amino acid residues [37]. γ-Syn is found in the peripheral nervous system having homology with α- and β-Synucleins, containg 127 amino acid residues [8,38]. The three synuclein protein family members, α-, β- and γ -synucleins contain an imperfect repeat sequence, KTKEGV, which is highly conserved in the N-terminus (Fig. 2A). β-Syn shares ~90% and ~33% homology in the N-terminus and C-terminus, respectively with α-Syn (Fig. 2B). On the other hand, both γ-Syn and synoretin share ~78% and ~6% homology in the N-terminus and C-terminus, respectively with α-Syn. Among the synuclein family proteins, α-Syn has the maximum tendency to form amyloid deposits [39]. The main difference for aggregation propensity between α-Syn and β-