

REVIEW

Does a prion-like mechanism play a major role in the apparent spread of α -synuclein pathology?

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Abstract

Parkinson's disease, the most common movement disorder, results in an insidious reduction for patients in quality of life and ability to function. A hallmark of Parkinson's disease is the brain accumulation of neuronal cytoplasmic inclusions comprised of the protein α -synuclein. The presence of α -synuclein brain aggregates is observed in several neurodegenerative diseases, including dementia with Lewy bodies and Lewy body variant of Alzheimer's disease. These disorders, as a group, are termed synucleinopathies. Mounting evidence indicates that α -synuclein amyloid pathology may spread during disease progression by a prion-like (self-templating alteration in protein conformation) mechanism. Clear *in vitro* and cell culture data demonstrate that amyloidogenic α -synuclein can readily induce the conversion of other α -synuclein molecules into this conformation. Some data from experimental mouse studies and autopsied brain analyses also are consistent with the notion that a self-promoting process of α -synuclein amyloid inclusion formation may lead to a progressive spread of disease *in vivo*. However, as pointed out in this review, there are alternative explanations and interpretations for these findings. Therefore, from a therapeutic perspective, it is critical to determine the relative importance and contribution of α -synuclein prion-like spread in disease before embarking on elaborate efforts to target this putative pathogenic mechanism.

Parkinson's disease and related disorders

Parkinson's disease (PD) is the second most common neurodegenerative disease in the developing world, affecting 1% of the population over 65 years of age and

4% to 5% over 85 years of age. It is characterized clinically by resting tremor, bradykinesia, postural instability, and muscle rigidity [1,2]. These motor impairments have been attributed largely to a progressive and extensive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) [3-5]. PD is associated with a range of other progressive clinical manifestations such as dementia, autonomic dysfunction, depression, seborrhea, sleep disturbance, and sensory symptoms, which most likely are associated with the demise of additional specific neuronal populations [2,6-9]. Although some therapeutic (for example, Levodopa) and surgical (for example, deep brain stimulation) interventions can alleviate some of the motor symptoms of PD, there is still no treatment to prevent disease progression. In addition to displaying neuronal loss and neuro-inflammation, most PD brains display the presence of intracytoplasmic inclusions known as Lewy bodies (LBs) and Lewy neurites (LNs) in some of the remaining dopaminergic neurons of the SNpc, but many other neuronal populations are also affected [9-12]. LBs and LNs are formed as a result of the aberrant amyloid-type aggregation of the neuronal pre-synaptic protein α -synuclein [12-14]. α -Synuclein neuronal inclusions can present in a spectrum of neurodegenerative disorders, termed synucleinopathies, as exemplified by the more widespread presentation of LBs and LNs in the brains of patients with the disorder dementia with LBs (DLB) [12,13]. DLB often presents concurrently with Alzheimer's disease pathological markers (that is, neurofibrillary tangles and $A\beta$ amyloid plaques), a disease entity sometimes referred to as the LB variant of Alzheimer's disease. There is also evidence that $A\beta$ and neurofibrillary tangle pathologies can spread in a similar prion-type mechanism as α -synuclein and that α -synuclein may cross-seed both of these pathologies [15], but in this review we will focus only on the findings directly involving α -synuclein.

Etiology of Parkinson's disease

Although PD used to be viewed predominantly as an idiopathic disease and most cases are still sporadic, many gene defects that can cause PD have been identified (reviewed in [16-18]). Indeed, missense mutations in the

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α -synuclein (*SNCA*) gene were the first genetic causes of PD identified and this finding led to a disease paradigm shift toward the importance of the aberrant aggregation of this protein in the etiology of PD. To date, three missense mutations (A53T, A30P, and E46K) have been identified and linked to PD or DLB [19-21]. In addition, short chromosomal duplications or trisomies containing the *SNCA* gene, plus relatively short flanking regions on chromosome 4, were discovered in patients with PD or DLB [22,23], indicating that a 50% increase in the expression of α -synuclein is sufficient to cause disease. Although the precise mechanism of toxicity of α -synuclein is still debated, most evidence indicates that some form of protein aggregation is involved [13,24].

Evidence for a prion/spreading mechanism of α -synuclein pathology

The cause of disease progression in PD and DLB has long been elusive, but recent findings suggest that α -synuclein aggregation may proceed via a 'prion-like' mechanism that leads to a spreading of α -synuclein pathology. The term 'prion-like' is used because there is no evidence that α -synuclein aggregates are transmitted between individuals (that is, there is no evidence for infectability), but as reviewed below, α -synuclein aggregation can clearly seed and self-template *in vitro* and in cultured cells under conditions that favor the entry of preformed amyloid into cells. Furthermore, it may be able to propagate between cells.

Although α -synuclein was viewed typically as a cytoplasmic protein, investigators have shown that both soluble and aggregated α -synuclein can be released from cells [25,26] and that α -synuclein is present in brain interstitial fluid, cerebrospinal fluid, and blood plasma [26-30]. Furthermore, recent studies have demonstrated the ability of α -synuclein to be imported or exported across cell membranes [31-34] and to be transferred between host and grafted neurons in mouse brains [33,35,36].

It is well established that *in vitro* α -synuclein aggregation into amyloid is a nucleation-dependent process and can be greatly induced by the addition of a 'seed' or 'nucleus' of pre-aggregated α -synuclein [37,38]. Cellular studies have shown that the entry of a small amount of preformed α -synuclein fibrils using reagents that promote the entry of these seeds across the plasma membrane can very efficiently induce the formation of large intracellular amyloid inclusions [39-41]. More recently, it was shown that the simple addition of extracellular α -synuclein fibrils to primary neurons can also induce the formation of intracellular α -synuclein inclusions [42]. Collectively, these studies suggest that α -synuclein amyloid formation may have the ability to spread between cells, although in a robust cellular model

of seeded intracellular α -synuclein inclusion formation, it was not possible to observe transmission or propagation of α -synuclein amyloid between cells [40].

A prion-like spreading of α -synuclein pathology is consistent with the Braak staging of disease that appears to follow neuroanatomical pathways [43]. This staging is based on the semi-quantitative immunocytochemical analysis of brain α -synuclein pathology distribution in patients with PD and age-matched controls and indicates a temporal sequence or stages of ascending severity. Other studies also suggest that α -synuclein can spread in human brains and that it may even start in the peripheral nervous system, more specifically the enteric nervous system [44-46]. This has led to the speculation that a pathogen, perhaps a virus or agent that could alter α -synuclein conformation, may initiate disease at the periphery and propagate back to the brain. The *in vivo* propagation of α -synuclein is also suggested by the presence of LB formation in fetal dopaminergic neurons that were transplanted in the striatum of PD patients as attempted therapeutic interventions [47-49].

More recently, it was reported that intracerebral injection of extracts from sick A53T human α -synuclein transgenic mice (line M83) into younger healthy M83 transgenic mice could induce disease [50,51]. The M83 transgenic mice normally develop a late-onset (8 to 15 months of age) severe motor phenotype that leads to death and that results from the widespread formation of neuronal α -synuclein amyloidogenic inclusions [52]. The intracerebral injection of extracts from affected M83 mice resulted in an earlier presentation of both pathology and phenotype, and this induction was not observed in the younger mice injected with extracts generated from healthy mice [50,51]. Furthermore, brain injection of preformed recombinant α -synuclein fibrils can induce α -synuclein pathology that appears to spread from the injection site [50], suggesting that these α -synuclein species can initiate and perhaps lead to transmission of α -synuclein pathology. Nevertheless, it is also possible that the observed induced pathology from both types of injections could be the result of a focal brain insult that initiates alternatively proposed pathological cascades such as oxidative stress, excitotoxicity, and neuro-inflammation [53] that could result in similar observations.

Is the apparent spread of α -synuclein due solely to intra- and intercellular templating of α -synuclein aggregation?

Although many lines of evidence support the notion that α -synuclein may propagate *in vivo* via a prion-like mechanism, several findings are not completely consistent with this model. For example, pathological assessment of A53T (line M83) and E46K (line M47) human α -synuclein

transgenic mice demonstrated that α -synuclein inclusion formation in these mice is late-onset, relatively rapid, and likely synchronized, but there is a paucity of neuronal inclusion clustering that is inconsistent with a spreading mechanism [54].

Although Lewy pathology was observed in some transplanted cells of several PD patients who received fetal mesencephalic grafts [47-49], this phenomenon was observed in only a minority of these patients, even though some patients without Lewy pathology in grafted cells survived for a similar period of time following the transplant surgery [47,53,55]. It is possible that transmission is a very slow or inefficient process or, as noted above, that other alternative mechanisms may also lead to the observed induction of Lewy pathology in the transplanted cells [53]. Furthermore, extensive reviews of large cohorts of autopsied patients with PD/DLB have revealed that, for a significant percentage of patients, the distribution of α -synuclein pathology is not consistent with the Braak scheme of α -synuclein neuronal pathology spread [56-58].

Moreover, the progression of pathology via a prion-like mechanism is not consistent with what is observed in multiple system atrophy (MSA). MSA is an adult-onset neurodegenerative disease that is characterized by varying degrees of parkinsonian features, cerebellar ataxia, and autonomic dysfunction [59-61] but that is defined pathologically by the presence of glial cytoplasmic inclusions (GCIs) [62]. GCIs usually appear as flame or sickle inclusions in oligodendrocytes found throughout the white matter, but the greatest abundance of these inclusions occurs in the basal ganglia, the substantia nigra, the pontine nucleus, medulla, and cerebellum [63-65]. Like Lewy pathology, GCIs are comprised predominantly of polymerized amyloidogenic α -synuclein [63,66,67]. Whereas most pathological inclusions in MSA are in oligodendrocytes, some α -synuclein protein aggregates can also be observed in the form of neuronal cytoplasmic inclusions, most of which are indistinguishable from LBs, and in neuritic processes, especially in the pontine nuclei and striatum [65,68,69]. α -Synuclein is expressed predominantly in neurons where it is localized to presynaptic terminals [70-72] and is expressed only at very low levels or levels below detectability in oligodendrocytes [73,74], and its expression is not increased in MSA [63,66,73]. Therefore, it is unclear why oligodendrocytes are affected predominantly in MSA. More importantly, if a prion-like mechanism is the primary mechanism for the spread of α -synuclein pathology, why is it confined predominantly to cells that express low levels of α -synuclein in MSA? Why does it not efficiently transmit to neurons? One possible mechanism that has been suggested to contribute to the spread of α -synuclein pathology is the release of amyloidogenic α -synuclein

from dying cells. In MSA brains, 'ghost' GCIs where the cells have died are a common observation, suggesting that amyloidogenic α -synuclein from these cells should be readily available for the seeding in other neighboring cells.

Conclusions

Despite mounting evidence that a prion-like mechanism may contribute to the spread/progression of α -synuclein pathology in PD and DLB, several inconsistencies or alternative explanations [53,75] for the observed experimental findings indicate that the pathogenic landscape is complex. Further experimental studies are needed to determine the relative importance and involvement of various pathogenic mechanisms, including self-templating resulting in altered protein conformation, neuroinflammation, oxidative stress, and excitotoxicity, in the apparent spread of α -synuclein pathology. This is especially important since extracellular α -synuclein aggregates that would likely be involved in a prion-like spread of disease could lead to the design of novel therapeutic interventions such as conformation-specific monoclonal antibody therapy and regulation of specific extracellular proteases. The validity of pursuing this target will require a clearer understanding of both the pathological findings and experimental paradigms that point in this direction. Nevertheless, the possibility of preventing PD/DLB disease progression by blocking brain prion-like amyloid spread is an attractive hypothesis.

Abbreviations

DLB, dementia with Lewy bodies; GCI, glial cytoplasmic inclusion; LB, Lewy body; LN, Lewy neurite; MSA, multiple system atrophy; PD, Parkinson's disease; SNpc, substantia nigra pars compacta.

Competing interests

The authors declare that they have no competing interests.

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