

Is Parkinson's disease a prion disorder?

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In this issue of PNAS, Desplats et al. (1) demonstrate that nerve cells that overexpress tagged α -synuclein can transmit the protein to neural stem cells in both in vitro and in vivo models. This important study could explain the remarkable finding that human embryonic dopamine nerve cells implanted into the striatum of patients with Parkinson's disease (PD) develop PD pathology with loss of dopamine markers and classic Lewy bodies (2, 3). It also provides insight into how α -synuclein pathology might sequentially spread throughout the nervous system in PD.

PD is an age-related, neurodegenerative disease that affects approximately one million persons in the United States. Pathologically, the disease is characterized by a loss of dopamine neurons in the substantia nigra pars compacta coupled with proteinaceous inclusions in nerve cells and terminals, known as Lewy bodies and Lewy neurites, respectively. PD pathology is also known to affect nondopamine neurons in the upper and lower brainstem, olfactory system, cerebral hemisphere, spinal cord, and autonomic nervous system. The cause of cell death in PD is not known, but proteolytic stress with the accumulation of misfolded proteins has been implicated (4).

That the aberrant accumulation of proteins might feature in the pathogenesis of PD is a reasonable posit, given that Lewy bodies, the hallmark of the disease, are composed of a variety of aggregated proteins. Among these, α -synuclein has attracted particular attention. α -Synuclein is a 140-aa synaptic protein that is unstructured in aqueous buffers, but adopts an α -helical-rich conformation when bound to membranes (5), and can acquire a β -sheet-rich structure that readily polymerizes into fibrils when present in high concentration or in a mutant form (6).

Mutations in α -synuclein have been reported in association with familial PD (7). More interestingly, cases of familial PD have also been described with duplication and triplication of the wild-type protein (8, 9). These findings suggest that increased production of mutant or wild-type α -synuclein can by itself lead to the development of PD. Indeed, gene delivery of α -synuclein to the substantia nigra induces degeneration of dopamine neurons with inclusions that stain for

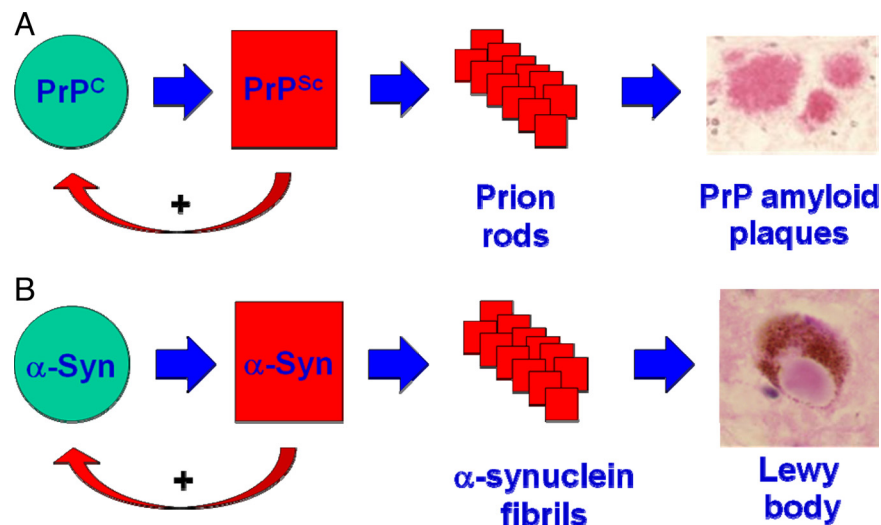


Fig. 1. Schematic illustration demonstrating similarities in the relationships between the PrP^C protein and prion diseases, and the α -synuclein protein and Parkinson's disease. (A) The cellular prion protein (PrP^C) comprises ≈ 210 aa. The function of PrP^C is unknown. PrP^C has a largely α -helical conformation and resides on the surface of cell membranes. When PrP^C misfolds, it acquires a high β -sheet content and assembles into rods that coalesce to form amyloid plaques. PrP^{Sc} is the sole component of the infectious prion and can lead to disease in animals and humans (19). (B) α -Synuclein is a protein of ≈ 140 aa. The function of α -synuclein is unknown. α -Synuclein acquires a largely α -helical conformation when it binds to cell membranes. When α -synuclein misfolds, it acquires a high β -sheet content and polymerizes into fibrils that are associated with the formation of Lewy bodies. Overexpression of α -synuclein alone can induce a PD syndrome in animals and humans.

α -synuclein and mirrors the pathology of PD (10). Most cases of PD, however, do not appear to be inherited, but rather occur sporadically. In these cases as well, α -synuclein has been implicated because it is a major component of Lewy bodies and neurites (11). Increased levels of α -synuclein in these cases might derive from impaired clearance of the protein by the lysosome and proteasome, as alterations in these systems have been observed in patients with sporadic PD (12, 13). Further, inhibition of protein clearance produces dopamine neuronal degeneration with the formation of inclusions that stain for α -synuclein (14).

Increased levels of α -synuclein, regardless of cause, can promote self-aggregation and interfere with proteasomal and lysosomal functions, leading to further accumulation of the protein (15, 16). Thus, increased production or impaired clearance of α -synuclein could initiate a vicious cycle with continued accumulation and misfolding of the protein and the subsequent formation of potentially toxic oligomers and amyloid fibrils.

The role of α -synuclein misfolding in the pathogenesis of cell death in PD and its potential to spread from one nerve cell to another has been highlighted by the recent discovery that embryonic dopamine neurons that had been transplanted into PD patients 11–14 years earlier developed PD pathology with classic Lewy bodies that stained for α -synuclein and thioflavin-S (a marker for β -sheet-rich protein polymers) (2, 3). The likelihood that these embryonic neurons had been adversely affected by the accumulation and misfolding of α -synuclein is supported by evidence of reduced staining for the dopamine transporter and tyrosine hydroxylase (in some nerve cells). Because α -synuclein-positive inclusions have not previously been seen in such young nerve cells, and because the transplants were derived from multiple, genetically unrelated donors, it seems likely that the inclusions

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arose as a consequence of factors inherent to the PD brain. One possible explanation is that misfolded α -synuclein was transmitted from pathologically affected neurons to healthy grafted embryonic dopamine neurons, and there recruited nascently produced α -synuclein to misfold.

Now come the exciting results of Desplats et al. (1) demonstrating that α -synuclein can be directly transferred from nerve cells that overexpress the protein to neighboring healthy embryonic stem cells both in tissue culture and in transgenic animals. This, in turn, was associated with pathological changes in acceptor cells as evidenced by the development of inclusion bodies and neuronal degeneration with markers of apoptosis. This same mechanism might account for the accumulation of misfolded α -synuclein and the development of PD pathology in the implanted dopamine neurons. It could also account for the pathologic findings of Braak et al. (17) in the PD brain, which suggest that α -synuclein spreads in a sequential and predictable manner, beginning in the dorsal motor nucleus in the lower brainstem and extending to involve upper brainstem nuclei (including the substantia nigra) and cerebral hemispheres. Indeed, it is possible that aggregated α -synuclein, frequently detected in autonomic plexi of the gastrointestinal tract of neurologically intact individuals who

are suspected of having preclinical PD (18), might be the initial site of α -synuclein misfolding.

Based on the available evidence, there is much to suggest that α -synuclein behaves like a prion, and that PD might be a prion disorder (Fig. 1). Both α -synuclein and the cellular form of the

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prion protein (PrP^C) adopt an α -helical-rich conformation under physiological conditions, and both are capable of refolding into a β -sheet-rich conformation that readily aggregates into oligomers and amyloid fibrils. Both of these misfolded proteins (especially the oligomers) are thought to be toxic and capable of inducing neurodegeneration. Furthermore, protein aggregates formed from each of these misfolded proteins can promote the misfolding of additional wild-type protein, and in this way, act as prion conformers (5, 19, 20). One can envision that the continued accumulation of misfolded proteins challenges the capacity of the lysosomal and proteasomal systems to clear these unwanted proteins, thus promoting their

further accumulation and the development of a self-propagating cycle that eventually leads to cell death. Now, there is also evidence that, as in the prion diseases, α -synuclein can be directly transmitted from pathologically affected to healthy, unaffected cells, thereby potentially extending the disease process throughout the nervous system.

It is thus possible that PD is a prion disorder resulting from increased production and/or impaired clearance of proteins such as α -synuclein, leading to misfolding and the formation of toxic oligomers, aggregates, and cell death. Further, it is possible that α -synuclein is a prion protein that can self-aggregate and be transmitted to unaffected cells, thus extending the disease process. While genetic causes represent an obvious source of increased levels of aberrantly folded α -synuclein in familial PD cases, a combination of aging, oxidative stress, inflammation, environmental toxins, hereditary factors, and impaired clearance may all feature in varying ways in causing altered metabolism of α -synuclein, resulting in the pathogenesis of sporadic PD. This concept suggests that drugs directed toward reducing the formation and/or facilitating the clearance of misfolded α -synuclein, so as to arrest or reverse the self-propagation process, might represent a novel therapeutic interventions for the treatment of PD.

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