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Review

Bent out of shape: α-Synuclein misfolding and the convergence of pathogenic pathways in Parkinson's disease

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ABSTRACT

Protein inclusions made up primarily of misfolded α-synuclein (α-Syn) are the hallmark of a set of disorders known as synucleinopathies, most notably Parkinson's disease (PD). It is becoming increasingly appreciated that α-Syn misfolding can spread to anatomically connected regions in a prion-like manner. The protein aggregates that ensue are correlated with neurodegeneration in the various yet select neuronal populations that are affected. Recent advances have begun to shed light on the spreading and toxicity mechanisms that may be occurring in PD. Several key emerging themes are arising from this work suggesting that α-Syn mediated neurodegeneration is due to a combination of relative α-Syn expression level, connectivity to affected brain regions, and intrinsic vulnerability to pathology.

1. Introduction

Parkinson's disease (PD) is the most common age-related motor disorder and second most common neurodegenerative disorder after Alzheimer's disease, affecting an estimated 7 million people worldwide [1,2]. As age is a significant risk factor, PD prevalence is expected to rise sharply as the average life expectancy among the general population continues to increase [3]. Despite its immense social and economic impact, our knowledge regarding the etiology of this condition remains incomplete and no effective treatments which modify the course of disease are presently available.

The most prominent feature in the brains of PD patients is the selective loss of dopaminergic (DA) pigmented neurons within the substantia nigra (SN) and to a lesser extent those residing in the ventral tegmental and retrorubral areas. Significant degeneration is also observed in other nuclei and neurotransmitter systems including the dorsal raphe (serotonergic), locus coeruleus (noradrenergic), nucleus basalis of Meynert (cholinergic) and the dorsal motor nucleus of the vagus nerve [4]. Degeneration in these areas likely contributes to both motor and non-motor symptoms observed in PD, especially hallucinations, depression, and sleep disorders.

For over a century, it has been recognized that neurodegenerative diseases are commonly associated with the accumulation of abnormally folded proteins within or in the vicinity of cells of the central nervous system (CNS) [5]. PD is characterized by the presence of eosinophilic inclusions in the soma of neurons termed Lewy bodies (or Lewy neurites when present in the neurites). Lewy bodies (LBs) represent a complex amalgamation of lipids, neuromelanin, and up to several hundred individual proteins with a key component being alpha-synuclein (α-Syn), an 140 amino-acid protein that is enriched in presynaptic vesicles of vertebrates [6–8]. A highly soluble lipid-binding protein normally thought to regulate synaptic vesicle release through stabilization of SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complexes, α-Syn in Lewy pathology occurs as highly ordered amyloid-type fibrils [6,9,10]. In addition to abnormal conformations, α-Syn in PD brains is also commonly post-translationally modified by cleavage, hyperphosphorylation, ubiquitination, nitrosylation, and oxidation [11–16].

Several lines of evidence point to α-Syn playing a key, and possibly causal, role in PD. For example, the genetic studies that led to the discovery of α-Syn as a major component of LBs also eventually revealed several point mutations which result in autosomal dominant PD [17–21]. Duplication or triplication of the wildtype locus that lead to 1.5–2-fold overexpression also give rise to dominantly-inherited PD, while several polymorphisms in the promoter region are reported to elevate the risk of developing disease [22–24].

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The significance of α-Syn is further supported by large-scale genome-wide association studies that indicate a clear link between the *SNCA* locus and PD [25,26]. Intriguingly, several strong genetic risk factors may have strong interactions with α-Syn. For example, mutations in glucocerebrosidase, which causes the lysosomal storage disorder Gaucher's disease, also elevates α-Syn levels and increases the risk of PD by up to 30-fold in some populations [27,28]. Moreover, Lewy pathology has also been reported in multiple forms of familial PD, such as those involving mutations in DJ-1, PINK1, and GBA, although this is less certain for other genetic forms of PD (e.g., LRRK2, Parkin, ATP13A2) [29–34]. Collectively, these data point to α-Syn dysfunction as a key process in PD pathogenesis. Indeed, the observation that cytoplasmic α-Syn inclusions are also characteristic of several other neurodegenerative conditions, most notably multiple system atrophy (MSA) and dementia with LB, suggests that α-Syn accumulation is not merely a benign product of the degenerative process [5,6,35,36].

Despite the overwhelming evidence for a central role of α-Syn in PD and other synucleinopathies and the explosion in our knowledge regarding this protein in both health and disease, two fundamental questions still remain unanswered. Firstly, what instigates the neurodegeneration that typifies PD? Secondly, why do selective cell populations undergo degeneration? This review discusses some of the recent advances that illustrate the complex pathobiological relationships between α-Syn misfolding and PD.

2. Prion-like properties of pathologic α-Syn

The distribution of α-Syn inclusions observed in the CNS of patients with PD and other synucleinopathies is highly non-uniform. On the contrary, Braak and colleagues have previously demonstrated that α-Syn inclusions in PD form in a predictable manner during disease progression, allowing categorization into at least six distinct clinicopathological stages in the majority of PD patients. Lewy pathology typically begins in the olfactory bulb and deep brain stem nuclei (stages I and II). This pattern correlates with several known prodromal symptoms of PD including olfactory impairment, autonomic dysfunction, and REM sleep disturbances [37]. Inclusion pathology is then detectable in more rostral regions, most notably midbrain DA neurons in stages III and IV. It is during these stages that the motor symptoms associated with PD become evident. In the ultimate stages (V and VI) pathology begins to be observed in the neocortex and has been correlated with the onset of dementia [38,39]. While this stereotypic staging system appears to be valid in up to 80% in multiple patient subpopulations, other studies point to a significant portion of patients (up to 50%) that do not follow this classification [40–43]. Heterogeneity in the initial location where α-Syn aggregates are first detected appears to be a source of this discrepancy resulting in modified or alternative staging systems that attempt to encompass populations that do not fit the conventional caudo-rostral pattern of spread, such as in dementia with LB [44]. Nonetheless, human studies clearly point to the gradual yet inevitable spread of α-Syn pathology originating from select regions. In conjunction with this evidence, post-mortem examination of fetal mesencephalic neurons transplanted into PD patients show that they develop Lewy pathology in a time-dependent manner. As fetal neurons initially lack any of the pathological processes and were unlikely to contain α-Syn inclusions at the time of transplantation, the appearance of pathology several years in a neurodegenerative environment argues that the initiation factor of pathology had been conferred and affected healthy neurons [45,46].

In line with this histopathological evidence, more recent work in cell culture and animals models has provided direct indication that α-Syn pathology is transmissible to recipient cells. In particular, it is now clear that brain homogenates enriched in α-Syn pathology can induce Lewy pathology in the CNS of recipient animals. Importantly, the source of this pathology, whether from transgenic mice exhibiting Lewy-like pathology or from MSA or PD patient-derived extracts are capable of initiating pathological formation [47–50]. Indeed, α-Syn itself can propagate pathology as recombinant α-Syn fibrils (or pre-formed fibrils; PFFs) and induce Lewy-like pathology in cultured cells and neurons, as well as in vivo following intracerebral introduction [51–56]. Not only does α-Syn pathology form in these models, but aggregation develops at sites at considerable distances from the injection site in vivo indicating propagation of the misfolding process [53–55].

Interestingly, intramuscular PFF injection also results in CNS pathology in transgenic mice overexpressing α-Syn, suggesting that pathology can transmit via the PNS, although the mechanism responsible remains unclear [57]. Analogous to this, the preponderance of Lewy pathology in deep brain stem nuclei, especially the dorsal motor nucleus of the vagus, seen in early PD is consistent with a spreading process originating from peripheral sites [39]. One location commonly found to harbor α-Syn aggregates in PD patients are gastrointestinal tract neurons, and a recent report suggests that long term risk of PD is significantly reduced following full vagotomy, raising the interesting possibility of this system as potential route of spread [58,59].

The potential mechanisms by which misfolded α-Syn can initiate and propagate intracellular inclusion formation that is reminiscent of human synucleinopathies have been reviewed in detail elsewhere [5,60–62] and appears to be predicated on three major components: the generation of misfolded α-Syn species, internalization into a permissive cellular environment/compartment, and engagement with the endogenously expressed α-Syn pool.

2.1. Internalization of extracellular α-Syn

Among neurons, endocytosis appears to be a chief mechanism mediating misfolded α-Syn entry into neurons, although the precise steps and whether other internalization pathways play a role is an active area of research [52,63]. Blocking endocytosis with a dynamin dominant negative mutant prevents cell to cell transfer of pathology [64]. It is not clear if this is mediated by a selective uptake mechanism, e.g. a specific receptor that binds α-Syn, although α-Syn aggregates appear to have an affinity for heparan sulfate proteoglycans on neuronal cell surface like tau fibrils [65]. In line with these properties, α-Syn internalization has also been described in multiple cell types, and evidence suggests that microglia, astrocytes and oligodendrocytes are capable to internalizing α-Syn [66–70]. Several commonly used cell lines have also been shown to internalize α-Syn [51,71–73]. Although this provides evidence as to how glia cytoplasmic inclusions (GCIs) could form in MSA, it is unusual that these inclusions form because oligodendrocytes express minimal levels of α-Syn [66,68]. Another potential mechanism that could spread pathology are nanotunnels between cells which have been shown to be capable of spreading prion protein, but this has yet to be reported for α-Syn [74].

The manner in which α-Syn is released from cells remains unknown as well. α-Syn is found in vesicles released by exocytosis and in several body fluids, such as CSF and plasma [75,76]. α-Syn secretion continues when ER-Golgi transport is blocked, ruling out conventional exocytosis as the primary mechanism of α-Syn release [75,77]. Other non-conventional forms of exocytosis are being explored as the mediator of α-Syn spread including exosome release and exophagy, an autophagosome mediated exocytosis [78–81].

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