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General review

Alpha-synuclein-based models of Parkinson's disease

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ABSTRACT

Parkinson's disease is a progressive neurodegenerative disorder mainly characterized by the loss of dopaminergic neurons from the substantia nigra pars compacta and the presence, in the affected brain regions, of protein inclusions called 'Lewy bodies'. Most cases are sporadic, but mutations in several genes, including SNCA, which encodes α-synuclein, are associated with disease development. A myriad of α-synuclein-based models for studying Parkinson's disease have been generated over the last two decades through different methodologies. Collectively, these models offer new opportunities to elucidate the mechanisms underlying the relentless progression of protein aggregation and neurodegeneration in Parkinson's. The present, non-exhaustive review focuses on mammalian models and the main strategies that are currently available, including transgenesis, viral vector gene delivery and the recently developed 'prion-like' models.

1. Introduction

Parkinson's disease (PD) is the most prevalent neurodegenerative movement disorder, affecting 1–2% of people over 60 years of age. Besides the cardinal motor symptoms (akinesia, rigidity, tremor and postural instability), numerous non-motor symptoms such as anosmia, constipation, orthostatic hypotension, fatigue, pain, depression and anhedonia complete the clinical spectrum and may even occur before the motor signs [1]. In addition to the progressive loss of dopaminergic neurons in the substantia nigra (SN), noradrenergic, serotonergic and adrenergic systems are also affected to various extents by the degenerative process [2–4]. A century after the discovery by Friedrich Heinrich Lewy that intracytoplasmic neuronal inclusions are a cytopathological hallmark of PD, and nearly 20 years after the identification of the presence of α-synuclein (α-syn) in the so-called Lewy bodies (LB) [5], α-syn is now recognized as a key element of the disease process, and currently considered one of the most viable and promising therapeutic targets.

This 140-amino-acid, highly conserved protein (> 95% homology between human and rodent sequences) is widely expressed in the brain [6,7] and abundantly present at the periphery, particularly in blood plasma [8]. Initially shown to be enriched at presynaptic terminals or associated with the

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nuclear membrane [9], α-syn can also be found in the cell soma and within mitochondria-associated membranes (for a review, see Guardia-Laguarta et al. [10]). Under physiological conditions, α-syn may be seen in several forms, including either an unfolded monomer [11] or helically folded tetramer [12]. Post-translational modifications initially considered to be associated with PD neuropathology (for example, phosphorylation and truncation) are also present under physiological conditions [13]. In addition, α-syn is degraded by both chaperone-mediated autophagy and the ubiquitin–proteasome system [14]. Upon initial misfolding, which results in enrichment of β-pleated sheets, the misfolded monomers assemble themselves into oligomeric species that subsequently form protofibrils, and then amyloid fibrils [15].

It is of interest that the first link between α-syn and neurodegenerative disorders was not made in PD, but in Alzheimer's disease, when Ueda and colleagues [16] identified α-syn as a precursor of the non-amyloid component of amyloid plaques. Since then, six unique point mutations in the *SNCA* gene have been identified in familial forms of PD [15]. More importantly, families with either duplication or triplication of a locus encompassing the wild-type α-syn gene [17–19] have demonstrated that an increased expression of α-syn is sufficient to trigger the disease process. Such a pathogenetic property of α-syn is further supported by studies demonstrating a gene dosage effect, with earlier age at onset, faster progression, and more pronounced cognitive decline and dysautonomia in triplication vs duplication cases [20]. These observations settled the disease mechanism, and paved the way to tackling α-syn expression and degradation as potential therapeutic strategies. Besides PD, the family of synucleinopathies also comprises multiple system atrophy and dementia with Lewy bodies, where α-syn accumulates preferentially in oligodendrocytes and cortical neurons, respectively. Why a single neuronal protein aggregates within different cell types and triggers distinct disorders is currently unknown, and simply highlights how much is still not understood of the multifaceted roles of α-syn.

Because of its direct relevance to the disease process, numerous models have been developed to elucidate how aggregation of pathologically conformed α-syn can trigger synaptic dysfunction and the ensuing neurodegeneration. The present review focuses on mammalian models and the main strategies that are currently available, including transgenesis, viral vector gene delivery and the recently developed 'prion-like' models.

2. Transgenic models of α-synuclein

Following the initial development of a mouse expressing human wild-type α-syn under the control of a platelet-derived growth factor subunit B (PDGF-β) promoter that demonstrated inclusion formation, loss of striatal tyrosine hydroxylase and motor deficits [21], numerous transgenic mouse models expressing either point mutations full length or truncated wild-type α-syn have been generated. As these models have been extensively reviewed [22,23], only a brief overview of the behavioral and pathological outcomes of α-syn overexpression in mice is provided here, with emphasis on the models that led to dopaminergic neurodegeneration. Indeed, if motor behavioral impairment occurs in most α-syn transgenic mice [22], as well as altered dopamine homeostasis in some lines (tissue content, release, reuptake) [24,25], then degeneration of dopaminergic neurons has not been consistently achieved. Only a few transgenic lines display neuronal loss in the SN, including mice overexpressing truncated α-syn (50% loss) [26] and α-syn with A30P + A53T mutations (50% loss) [27], and bacterial artificial chromosome (BAC) transgenic mice overexpressing wild-type α-syn (30% loss; Table 1) [28]. Whenever investigated, other neurotransmitters such as serotonin were not affected [26,27]. In addition to the constitutive expression of α-syn, several lines of mice with conditional overexpression of human wild-type or mutated α-syn have also been generated, resulting in motor impairment and 40% nigral degeneration by 12 months of age [29].

Interestingly, BAC transgenic models provide mouse or rat models that can recapitulate striatal dopaminergic dysfunction, motor impairment and degeneration of nigral dopaminergic neurons. Indeed, in BAC transgenic mice overexpressing wild-type α-syn, gastrointestinal dysfunction, reduction of evoked striatal dopamine release and altered clustering of presynaptic vesicles precede late-onset motor dysfunction and nigral degeneration [28]. Another recent development using BAC transgenesis in rats yielded a progressive model recapitulating several features of PD [30]. In these BAC α-syn rats, expression of the full human wild-type α-syn sequence, together with 30 kb of upstream and 45 kb of downstream regions, resulted in aggregation of insoluble α-syn and early olfactory deficits, followed by motor dysfunction and 40% dopaminergic neurodegeneration [30]. Compared with classical transgenic models, BAC transgenesis offers the opportunity to insert not only the gene of interest, but also its adjacent upstream and downstream regulatory DNA elements, thereby better reproducing the endogenous pattern of expression and its transcriptional regulations.

Considered altogether, these models indicate that overexpression of α-syn in rodents can induce α-syn accumulation (although not with the specific structure of LB) and synaptic dysfunction, leading to behavioral impairment. Dopaminergic neuronal loss is not systematically observed and may be linked to α-syn expression levels, pathogenetic properties of different forms of α-syn (truncated or mutated *vs* wild-type) and compensatory mechanisms following constitutive overexpression of α-syn, as well as patterns of expression in the brain and transcriptional regulatory mechanisms specific to the *SNCA* gene. Despite a lack of robust dopaminergic neurodegeneration in most transgenic models, thus making them unsuitable for testing neuroprotective strategies, these models nevertheless recapitulate a wide clinical spectrum that is not limited to motor impairment and, therefore, offers the opportunity to study the underlying mechanisms of non-motor symptoms of PD, and to develop therapeutic strategies against prevalent and disabling non-motor features of PD. Furthermore, in addition to replicating dopaminergic neurodegeneration and motor and non-motor deficits, BAC transgenesis using the *SNCA* promoter enables study of the role of transcriptional dysregulation of α-syn in the pathogenesis of PD and, thus, appears to be the best transgenic models available.

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