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Basic Neuroscience
Review

α-Synuclein and nonhuman primate models of Parkinson's disease

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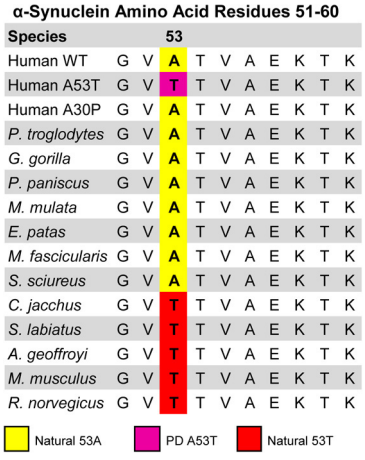
HIGHLIGHTS

- α-Synuclein (α-Syn) accumulation has a significant role in Parkinson's disease (PD).
- α-Syn protein sequence is well conserved across species.
- Nigral α-syn distribution in monkeys changes with age or toxin exposure.
- Viral vector gene transfer of wild type or mutated α-syn induces neurodegeneration.
- Novel PD monkey models are being generated using inoculations of α-syn and transgenesis.

GRAPHICAL ABSTRACT



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ABSTRACT

Accumulation of α-synuclein (α-syn) leading to the formation of insoluble intracellular aggregates named Lewy bodies is proposed to have a significant role in Parkinson's disease (PD) pathology. Nonhuman primate (NHP) models of PD have proven essential for understanding the neurobiological basis of the disease and for the preclinical evaluation of first-in-class and invasive therapies. In addition to neurotoxin, aging and intracerebral gene transfer models, a new generation of models using inoculations of α-syn formulations, as well as transgenic methods is emerging. Understanding of their advantages and limitations will be essential when choosing a platform to evaluate α-syn-related pathology and interpreting the test results of new treatments targeting α-syn aggregation. In this

Abbreviations: α-syn, α-synuclein; 6-OHDA, 6-hydroxydopamine; AAV2, adeno-associated viral vector serotype 2/2; ALP, autophagy-lysosomal pathway; BBB, blood–brain–barrier; c-hGH, cadaver-derived human growth hormone; CK, casein kinases; DA, dopamine; DAT, dopamine acetyltransferase; DLB, disease with Lewy bodies; ECFP, enhance cyan fluorescent protein; EPM1, progressive myoclonus epilepsy type 1; GFP, green fluorescent protein; GRKs, G-protein-coupled receptor kinases; IVF, in vitro fertilization; LB, Lewy body; LN, Lewy neurite; LV, lentivirus; MAO-B, monoamine oxidase-B; MAP, microtubule-associated protein; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NAC, non-Aβ component; NHP, nonhuman primate; PD, Parkinson's disease; PFF, preformed fibril; PK, proteinase K; PLKs, polo-like kinases; ROS, reactive oxygen species; sgRNA, single guide RNA; SN, substantia nigra; SNpc, substantia nigra pars compacta; TH, tyrosine hydroxylase; UCH-L1, ubiquitin carboxy-terminal hydrolase L1; UPS, ubiquitin-proteasome system; WT, wild type.

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Nonhuman primates
Lewy body
Lewy neurite
Animal models

review we aim to provide insight on this issue by critically analyzing the differences in endogenous α-syn, as well as α-syn pathology in PD and PD NHP models.

Contents

1. Introduction

α-Synuclein (α-syn) is a relatively small, 140 amino acid, and 14-kDa presynaptic protein. Current evidence suggests that α-syn is important for normal neuronal function and plays a role in neurotransmitter vesicle release (Bendor et al., 2013). In the presynaptic terminal α-syn ensures successful synaptic transmission by shuttling SNARE proteins and interacting with synaptobrevin-2 (Chandra et al., 2005). Interestingly, α-syn was originally described in neuropathological conditions. It was first identified as the non-Aβ component (NAC) of amyloid plaques in Alzheimer's disease (Ueda et al., 1993). A few years later, a single point mutation of alanine to threonine in the 53rd (A53T) amino acid residue of the α-syn protein sequence was linked to early onset Parkinson's disease (PD) in an Italian and Greek family with an 85% penetrance (Polymeropoulos et al., 1997). Since then, other α-syn mutations have been identified in familial PD cases (Kruger et al., 1998; Lesage et al., 2013). Yet the most striking consequence of α-syn identification was the discovery that wild type α-syn is the main component of Lewy bodies (LBs), which are intracytoplasmic eosinophilic aggregates, and Lewy neurites (LNs), which are abnormal filament-containing neurites. Both, LBs and LNs are characteristic pathologies of PD (Spillantini et al., 1998; Spillantini et al., 1997) (Fig. 1).

PD is the most prevalent movement disorder and the second most common neurodegenerative disease, after Alzheimer's disease (NINDS). PD affects 1% of the population over 60 years old; earlier onset has been described mainly in familial cases. The cause of PD is still unknown, although old age, environmental toxins and genetics are known risk factors. With respect to the latter, several mutations including LRRK2, PINK1, DJ-1 in addition of SNCA, have been linked to PD (Puschmann, 2013).

First described in 1817 by James Parkinson, PD is typically diagnosed by motor signs such as bradykinesia, resting tremor, postural instability, and a characteristic hunched-over posture. Today PD is considered a multisystem disorder as it also presents numerous secondary motor as well as non-motor symptoms including a diminished sense of smell, dysphagia, REM sleep behavior disorder, autonomic dysfunction, and depression (Chaudhuri and Odin, 2010; Chaudhuri et al., 2011; Langston, 2006). These symptoms may precede primary motor signs and are proposed as prodromal symptoms of PD (Postuma et al., 2012). The pathological hallmark of PD is the loss of mesencephalic melanin-pigmented dopaminergic neurons in the substantia nigra pars compacta (SNpc) and the presence of LBs and LNs (described above); primary motor symptoms are related to nigral pathology. By the time the disease has manifested to the point of clinical detection and diagnoses, around 50% of dopaminergic (DA) neurons are lost from the SNpc. Secondary motor as well as non-motor symptoms are associated with neurodegeneration and α-syn positive LBs in several areas of the CNS and PNS, including the locus coeruleus, and autonomic nervous system (Braak et al., 1995; Braak et al., 2004; Seidel et al., 2015).

Current PD treatments are mainly symptomatic; none have yet been proven to be neuroprotective (Stocchi and Olanow, 2013). New ideas regarding PD etiology and possible treatments are emerging based on advances in our understanding of the role of α-syn in PD (Chu and Kordower, 2015; Kalia and Lang, 2015; Shannon et al., 2012; Xilouri et al., 2013). Nonhuman primate (NHP) models of PD have proven essential for understanding the neurobiological basis of the disease and for the preclinical evaluation of