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Review

Genetically engineered mouse models of Parkinson's disease

Donna M. Crabtree, Jianhua Zhang*

Department of Pathology, University of Alabama at Birmingham, Birmingham, AL 35294, USA

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ABSTRACT

Parkinson's disease (PD) is the most common neurodegenerative movement disorder, affecting more than 1% of the population over age 60. The most common feature of PD is a resting tremor, though there are many systemic neurological effects, such as incontinence and sleep disorders. PD is histopathologically identified by the presence of Lewy bodies (LB), proteinaceous inclusions constituted primarily by α-synuclein. To date, there is no effective treatment to slow or stop disease progression. To help understand disease pathogenesis and identify potential therapeutic targets, many genetic mouse models have been developed. By far the most common of these models are the wildtype and mutant α-synuclein transgenic mice, because α-synuclein was the first protein shown to have a direct effect on PD pathogenesis and progression. There are many other gene-disrupted or -mutated models currently available, which are based on genetic anomalies identified in the human disease. In addition, there are also models which examine genes that may contribute to disease onset or progression but currently have no identified causative PD mutations. These genes are part of signaling pathways important for maintaining neuronal function in the nigrostriatal pathway. This review will summarize the most commonly used of the genetic mouse models currently available for PD research. We will examine how these models have expanded our understanding of PD pathogenesis and progression, as well as aided in identification of potential therapeutic targets in this disorder.

Contents

1. Introduction

Parkinson's disease (PD) is a severe neurodegenerative movement disorder affecting more than 1% of the population over the age of 60 (NINDS Parkinson's Disease Information Page). Originally described two centuries ago by James Parkinson as the "shaking palsy", there is still no effective treatments to slow, stop, or reverse the effects of the disease. The hallmark symptom of PD is an involuntary, resting tremor due to neurodegeneration of dopaminergic

Abbreviations: MPTP, 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine; MPP+, 1-methyl-4-phenylpyridinium; 6-OHDA, 6-hydroxydopamine; COMT, catechol-O-methyltransferase; DA, dopamine; DAT, dopamine transporter; L-DOPA, levodopa; LB, Lewy body; LPS, lipopolysaccharide; MAOB, monoamine oxidase B; PD, Parkinson's disease; ROS, reactive oxygen species; SN, substantia nigra; TH, tyrosine hydroxylase.

* Corresponding author at: Department of Pathology, University of Alabama at Birmingham, SC 930, 1720 7th Ave S, Birmingham, AL 35294-0017, USA.
Tel.: +1 205 996 5153; fax: +1 205 934 6700.
E-mail address: zhanja@uab.edu (J. Zhang).

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neurons in the substantia nigra (SN). SN neurons project to the striatum and together these structures constitute the nigrostriatal pathway. Since its identification as a PD therapeutic, the most effective agent to treat involuntary tremor has been levodopa, or L-DOPA [13,42], the molecular precursor of dopamine (DA) which acts to replace endogenous DA that has been lost due to neurodegeneration. After more than 30 years, L-DOPA is still the first line of treatment given to patients to relieve tremor; however, L-DOPA merely masks the effects of the disease as pathology continues to progress until the extent of dopaminergic degeneration is so great that the drug no longer alleviates the symptoms. Aside from the cardinal resting tremor associated with PD, patients suffering from this disease may also experience additional manifestations of the disorder, including, but not limited to, incontinence, sleep disorder, olfactory disturbance, and cognitive impairment in later stages of the disease, which is reviewed elsewhere [135].

PD is part of a spectrum of disorders clinically classified as Parkinsonisms. Histopathologically, most Parkinsonisms involve aberrant accumulation of the protein α-synuclein into inclusions termed Lewy bodies (LB), which also contain a host of other proteins, many of which will be discussed in this review (Fig. 1). Whether these aggregates directly contribute to pathogenesis or disease progression is still debated; however, genetic duplications and triplications of the α-synuclein gene identified in human pedigrees have been shown to cause disease [19,75,155].

Before genetic models of PD were available, chemicals such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, lipopolysaccharide (LPS), and 6-hydroxydopamine (6-OHDA), were used to induce dopaminergic neurodegeneration as models of PD and have been reviewed elsewhere [12,35,38,138]. MPTP causes an irreversible Parkinsonism resulting from selective loss of dopaminergic neurons of the SN, mediated through endogenous monoamine oxidase B (MAOB) which catalyzes the oxidation of MPTP to 1-methyl-4-phenylpyridinium (MPP+). MPP+ then binds and inhibits mitochondrial complex I and generates reactive oxygen species (ROS) [138]. Rotenone is a common ingredient of industrial pesticides and some epidemiological studies have shown a correlation between pesticide exposure and incidence of PD. Like MPP+, rotenone also causes mitochondrial complex I inhibition [35]. The bacterial endotoxin LPS models the inflammatory aspect of PD, causing glial activation (via binding of TLR-4 receptors) which in turn causes release of proinflammatory cytokines and free radicals with subsequent dopaminergic neurodegeneration [38]. DA can be readily oxidized in the normal cellular environment [2] leading to the formation of potentially cytotoxic adducts (reviewed in [163]). 6-OHDA has been used to model PD though a dual mechanisms of increasing ROS and quinines in the catacholaminergic system [12].

In more recent years, the use of knockout and transgenic mice has revolutionized the way we study human disease, enabling gene deletion, over expression, and mutation *in vivo* (reviewed in [15]). α-Synuclein was the first gene implicated in PD pathology. Originally identified as the non-amyloid component (NAC) of Alzheimer's disease plaques [78], α-synuclein was later found to be the predominant protein in LB inclusions in PD [159]. Since then, mutations in many genes, including PARK2 (encoding Parkin, a E3 ubiquitin ligase), DJ-1, and Leucine-rich repeat kinase 2 (LRRK2), have been linked to familial PD (Table 1). α-Synuclein transgenic mice are the most commonly used genetic model of PD (Table 2); however, many additional models using identified, familial PD genes and other genes important in the nigrostriatal pathway have been created (Table 3). Here we summarize some of the genetic models that have contributed to our understanding of PD neuropathology and helped to reveal potential therapeutic targets for the disorder. We will examine genes and gene mutations that have been shown to be directly responsible for PD pathogenesis as well as those mouse models which have been shown to model specific aspects of PD pathology (summarized in Fig. 2). We will conclude with some of the ways that transgenic and knockout mice have aided in our overall understanding of PD pathogenesis and progression as well as some of the potential therapeutic targets that have been identified through the study of genetic mouse models of PD (illustrated in Fig. 3).

2. PD models with α-synuclein gene modifications

Early genetic models of PD focused on α-synuclein (the *snca* gene) [47,96,112,143,144,165], including wildtype and autosomal dominant mutations in the protein which lead to early onset PD with a more aggressive progression and clinical pathology [24,79,121]. Mouse models carrying the human α-synuclein transgene exhibit diverse phenotypes, which is likely due in part to the insertion site of the gene within the host genome as well as the promoter utilized to drive transgene expression. Mouse models using wildtype α-synuclein have significantly improved our understanding of α-synuclein over expression-induced pathology. In addition to α-synuclein gene over expression, two autosomal dominant mutations in α-synuclein, A53T [136] and A30P [91], were found to lead to early onset autosomal dominant PD. To understand how α-synuclein mutations affect disease pathogenesis, models expressing mutant α-synuclein have been examined. We will discuss several α-synuclein mouse models utilizing various promoters to drive gene expression and how these models differ from one another with respect to PD phenotype.

One of the first developed PD mouse models expressed the human wildtype α-synuclein transgene under transcriptional control of the PDGF-β promoter [112]. These mice developed neuropathology by 2 months of age, evidenced by α-synuclein- and ubiquitin-positive inclusions in the neocortex, hippocampus and SN, resulting in motor dysfunction and nerve terminal degeneration in the basal ganglia. In contrast to protein aggregates found in PD, which are located almost exclusively in the cytoplasm, transgenic mice possessed both cytoplasmic and the nuclear inclusions, which were not fibrillar in nature like LBs. Tyrosine hydroxylase (TH) protein levels and enzymatic activity were significantly reduced, corresponding to observed phenomena in PD [112]. These mice have been subsequently used in multiple studies by other investigators as a platform to further characterize PD pathogenesis and progression as well as to identify potential therapeutic targets [37,158,189]. Using these mice, it was shown that calpain-cleaved α-synuclein preferentially forms aggregates, which were also identified in PD brains [37]. This model was also found to have progressive transcriptional dysregulation which preceded other pathological changes [189], which may also be an early pathological alteration in the human disease. Finally, stereotactic injection of beclin 1, a key regulator in the macroautophagy pathway, was shown to reduce neurodegeneration in this model of synucleinopathy [158], highlighting one potential method for therapeutic intervention.

A wildtype α-synuclein mouse utilizing the mouse Thy-1 promoter was shown to have widespread α-synuclein accumulation in the brain, including the SN [144]. Despite the lack of dopaminergic cell loss in these mice, they developed motor and coordination impairments as early as 2 months of age and by 6 months, sensorimotor deficits were detected [44]. Additionally, olfactory deficits, frequently observed in pre-clinical PD, were found in the Thy-1 mice [45]. These subtle and progressive phenotypes in response to α-synuclein accumulation make the Thy-1 mouse an attractive model for studying early pathological changes which may be occurring in PD as a result of increasing α-synuclein burden. Additionally, models displaying pre-clinical signs of PD may aid