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REVIEW

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Parkinson's disease: a rethink of rodent models

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Abstract Parkinson's disease (PD) is a multifactorial disease with a complex etiology that results from genetic risk factors, environmental exposures and most likely a combination of both. Rodent models of parkinsonism aim to reproduce key pathogenic features of the syndrome including movement disorder induced by the progressive loss of dopaminergic neurons in the *substantia nigra*, accompanied by the formation of α-synuclein containing Lewy body inclusions. Despite the creation of many excellent models, both chemically induced and genetically engineered, there is none that accurately demonstrates these features. Recent pathological staging studies in man have also emphasized the significant non-CNS component of PD that has yet to be tackled. Herein, we summarize rodent models of PD and what they offer to the field, and suggest future challenges and opportunities.

Keywords Parkinson's disease · Mouse · Toxin · Genetic

Introduction

Parkinson's disease (PD) affects 5% of the general population by the age of 85, whereas early-onset disease < 50 years is infrequent (Twelves et al. 2003). Clinically the condition is characterized by parkinsonism, the triad of motor features including resting tremor, bradykinesia and rigidity that present asymmetrically and progressively worsen. Pathologically, neuronal loss is observed for the pigmented, dopamine producing neurons of the *substantia nigra* whilst Lewy bodies containing aggregated α-synuclein are found in surviving cells of the brainstem. Initially, patients respond well to dopaminergic replacement therapy but treatment is effective for only a limited period and fails to halt disease progression. Neuroprotective interventions and the ability to measure their efficacy are required.

The etiology of PD is unknown; however, it has long been suggested that environmental factors may contribute. The first acute models were created using 6-hydroxydopamine (6-OH-DOPA) and provided fundamental insights into basal ganglia physiology, whereas mitochondrial complex I poisons such as 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) or rotenone, chronically administered at low dose, have provided more progressive models of disease. Proteosome inhibitors, such as epoxomicin, have been shown to recapitulate many of the central features of PD including motor impairment and neuropathology, but these effects have been difficult to reproduce (McNaught et al. 2004). Genetic mutations identified in familial parkinsonism have recently provided new tools to implicate and understand the molecular pathways affected. In the past decade, recessively inherited loss-of-function mutations in *Parkin (PRKN)*, *DJ-1* and *PTEN-induced putative kinase-1 (PINK1)* were found to cause early-onset (< 50 years at onset), l-DOPA-responsive parkinsonism. The slowly progressive and predominant motor phenotype in these patients suggests a disorder largely restricted to dopaminergic neuronal loss. PINK1 and DJ-1 cases have not yet to come to autopsy, but the majority of patients with Parkin-linked disease demonstrate neuronal loss restricted to the *substantia nigra*. In contrast, dominantly inherited, gain-of-function mutations in α-synuclein *(SNCA)* and leucine-rich repeat kinase (*LRRK2*) result in more typical, late-onset, Lewy body parkinsonism with multi-system involvement (reviewed by Ross and Farrer 2005).

The future of drug therapies for PD depends on developing animal models that recapitulate the disease and in which new compounds may show efficacy. Focusing primarily on rodent models we review progress to date and opportunities for future research.

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Toxins and the environment

6-OH-DOPA

6-OH-DOPA administration causes nigrostriatal depletion when stereotaxically injected into the *substantia nigra*, median forebrain bundle or striatum. 6-OH-DOPA destroys catecholaminergic structures through a combination of reactive oxygen species and increased toxic quinones (reviewed by Bove et al. 2005). After injection in rats dopaminergic neurons die within 24 h, show apoptotic morphology (Jeon et al. 1995) and decreased α-synuclein mRNA (Kholodilov et al. 1999; Zeng et al. 2002) but Lewy body formation has not been demonstrated. Nevertheless, unilateral lesions result in an asymmetric circling behavior that has been used extensively to evaluate anti-parkinsonian therapeutics.

MPTP

MPTP was inadvertently used as a 'street drug' in the eighties and results in parkinsonism (Langston et al. 1983). MPTP is a potent and irreversible mitochondrial complex I inhibitor whose toxic metabolite MPP+ is selectively transported by the dopamine transporter DAT (Kopin and Markey 1988; Speciale 2002; Schober 2004; Watanabe et al. 2005). Although dopaminergic neurons in rats are relatively resistant to MPTP-induced toxicity (Bove et al. 2005), in mice susceptibility of the nigrostriatal pathway to neurodegeneration is strain-dependent with C57BL6 being more sensitive and Balb/c more resistant to MPTP-induced neurotoxicity (Sedelis et al. 2001). In humans acute intoxication with MPTP does not result in Lewy bodies (Langston et al. 1983), but in both rodents and primates α-synuclein expression is chronically upregulated after an acute dose (Vila et al. 2000; Purisai et al. 2005). Transgenic mice overexpressing wild type and mutant human α-synuclein have increased sensitivity to MPTP (Song et al. 2004; Nieto et al. 2005), whereas α-synuclein knock-out mice have reduced sensitivity, suggesting genetic and environmental causes may converge (Dauer et al. 2002; Schluter et al. 2003; Drolet et al. 2004; Robertson et al. 2004; Klivenyi et al. 2005).

Paraquat

The herbicide paraquat is structurally similar to MPP+ and is also a mitochondrial complex I inhibitor; however, it differs in its mechanism of action from MPP+ in that it is not a substrate or an inhibitor of the dopamine transporter, DAT (Richardson et al. 2005). When administered to mice paraquat also leads to upregulation and aggregation of α-synuclein (Manning-Bog et al. 2002). In addition, combined exposure to herbicide paraquat and the fungicide maneb leads to selective loss of dopamine and dopaminergic neurons in the *substantia nigra* of mice, an effect which is more pronounced postnatally than compared with administration in adults (Cory-Slechta et al. 2005).

Rotenone

Chronic administration of rotenone in rodents can produce a progressive model of parkinsonism associated with α-synuclein upregulation and accumulation in Lewy-like pathology (Betarbet et al. 2000; Sherer et al. 2002, 2003). In contrast to MPTP and paraquat, which accumulate selectively in dopaminergic neurons, chronic exposure to rotenone can produce mild but systemic complex I inhibition. When a degenerative lesion results it is selective to the nigrostriatal system, indicative of the vulnerability of this neuronal population to oxidative stress.

Epoxomicin

Systemic administration of the proteasomal inhibitor epoxomicin to adult rats has been shown to reproduce many key features of PD. In the original study, animals develop progressive parkinsonism with bradykinesia, rigidity, tremor, and an abnormal posture which improves with apomorphine treatment (McNaught et al. 2004). Using positron emission tomography, degeneration of the nigrostriatal pathway was indicated by reduction in carbon-11-labeled 2-beta-carbomethoxy-3-beta-(4-fluorophenyl) tropane binding to dopaminergic nerve terminals in the striatum. Postmortem analyses showed striatal dopamine depletion and dopaminergic cell death with apoptosis and inflammation in the *substantia nigra*. Additionally, intracytoplasmic, eosinophilic, α-synuclein/ubiquitin-containing inclusions resembling Lewy bodies were present in some of the remaining neurons (McNaught et al. 2004). This model promised to be one of the most successful in recapitulating the progressive movement disorder and pathology associated with PD but has since proven very difficult to reproduce.

Recessive genes implicated in parkinsonism

Parkin models

Homozygous and compound heterozygous Parkin mutations were originally identified in Japanese families with autosomal recessive, juvenile parkinsonism (Kitada et al. 1998). Point mutations, exonic rearrangements, deletions and duplications are common (reviewed by Mata et al. 2004). Through imaging studies carriers of heterozygous Parkin mutations have been associated with clinically asymptomatic deficits of dopaminergic function (Khan et al. 2002; 2005; Pramstaller et al. 2005). However, whether these individuals have increased susceptibility to late-onset PD remains unclear (West et al. 2002; Lincoln et al. 2003). Mutations in Parkin are thought to impair its E3 ubiquitin protein ligase activity and result in

improper targeting of substrates for proteasomal degradation, and may lead to subsequent neurotoxic accumulation. A number of substrates have been reported including Parkin-associated endothelin-like receptor, a rare glygosylated form of α-synuclein and the p38 subunit of the aminoacyl-tRNA synthetase complex (reviewed by Moore et al. 2005).

Several groups have also described spontaneous and targeted knockout of the Parkin gene in mice (Goldberg et al. 2003; Itier et al. 2003; Lorenzetti et al. 2004; Von Coelln et al. 2004; Perez and Palmiter 2005). Homozygous *Quaking* mice lack both Parkin and Parkin co-regulated gene (*PACRG*), although their demyelination phenotype has long been attributed to the neighboring locus and dysregulation of quaking mRNA expression (Lockhart et al. 2004; Lorenzetti et al. 2004). Surprisingly, these mice have no evidence for dopaminergic cell loss (Lorenzetti et al. 2004). Targeted knock-out mice deficient in Parkin via deletion of exon 3 or 7 also have normal brain morphology and have normal numbers of dopaminergic neurons. However, subtle nigrostriatal deficits are apparent, including increased levels of extracellular dopamine (Goldberg et al. 2003; Itier et al. 2003; Von Coelln et al. 2004), reduction in synaptic excitability in the striatum (Goldberg et al. 2003) and altered energy metabolism, protein handling and synaptic function (Periquet et al. 2005). In contrast, homozygous mice lacking exon 2 of Parkin are indistinguishable from their wild-type littermates (Perez and Palmiter 2005). Administration of 6-OH-DOPA or metampthetamine did not reveal any increased sensitivity in this model (Perez et al. 2005). However, overexpression of Parkin mediated by adenoviral delivery does ameliorate α-synuclein-induced dopaminergic neuron loss and consequent motor dysfunction (Yamada et al. 2005).

DJ-1 models

Mutations in DJ-1, originally described in a Dutch kindred (Bonifati et al. 2003), are rare accounting for less than 1% of early-onset parkinsonism. DJ-1 is a member of the ThiJ/PfpI family of molecular chaperones which are induced during oxidative stress; the protein exists primarily as a dimer localized to mitochondria (Tao and Tong 2003; Zhang et al. 2005). Loss-of-function mutations are thought to cause PD via impaired oxidative stress protection. DJ-1 null mice with either exons 1–5 deleted or only exon 2 deleted display subtle behavioral deficits, increased striatal dopaminergic re-uptake rates and elevated dopamine levels (Chen et al. 2005; Goldberg et al. 2005). In mice with homozygous exon 2 deletion, long-term depression was found to be absent and was reversible by D2 but not D1 agonist treatment suggesting an essential role for D2-receptor mediated function. No changes in dopaminergic neuronal number were observed in either model. DJ-1 null mice treated with MPTP showed increased striatal denervation and dopaminergic neuron loss compared to wild-type mice, whereas DJ-1 adenoviral vector delivery mitigates this phenotype. Indeed, wild-type mice that receive adenoviral delivery of DJ-1 effectively resist MPTP induced striatal damage (Kim et al. 2005). Thus, in vivo data suggest loss of DJ-1 may lead to parkinsonism by conferring hypersensitivity to dopaminergic insults, whereas DJ-1 overexpression appears to protect against neuronal oxidative stress.

Dominant genes implicated in parkinsonism

α-synuclein models

SNCA encoding α-synuclein was the first gene to be linked to familial parkinsonism for which three missense and several multiplication (duplication and triplication) mutations have now been described (reviewed by Hope and Farrer 2004). Neither homolog β- nor γ-synuclein has been convincingly implicated in PD.

Knock-out mice

Several knock-out mice (KO) models have been created, all are viable and show subtle phenotypic effects (if any). Initial efforts to ablate *SNCA* exons 1 and 2 resulted in a modest decrease of striatal dopamine levels and attenuated locomotor activity in response to amphetamine (Abeliovich et al. 2000). In contrast, mice with disruption of *SNCA* exons 4 and 5 did not display changes in locomotor activity following amphetamine treatment. A reduction in the reserve pool of synaptic vesicles in the hippocampus was observed but striatal dopamine levels were not significantly decreased (Cabin et al. 2002). In another model disruption of *SNCA* exon 2 did not result in altered dopamine levels or dopamine uptake, although modest upregulation of β-synuclein was noted in the striatum (Schluter et al. 2003). In a subpopulation of C57BL/6J mice the *SNCA* locus was also discovered to be spontaneously deleted. Consistent with findings in targeted knockout models, the mice were phenotypically normal and there was no evidence of compensatory upregulation of β- or γ-synuclein proteins (Specht and Schoepfer 2001). Of note, double α- and β-synuclein knockouts have normal survival and brain function, showing only small compensatory increases in γ-synuclein, a subset of 14-3-3 proteins (involved in signaling and phospho-protein dimerization), and in complexin, which like synuclein is a small soluble pre-synaptic protein (Chandra et al. 2004). Overall, these findings suggest ablation of α- and β-synuclein family members has little impact on the development of the murine brain.

Mutant and wild-type over-expression α-synuclein models

Despite its seemingly superfluous role in mice, mutant and wild-type α-synuclein is clearly associated with PD in humans (reviewed by Hope and Farrer 2004). A variety of α-synuclein transgenic mouse models have now

been described, most utilizing a cDNA construct with a heterologous promoter. Wild-type overexpression recapitulates many of the features of PD including mislocalization of α-synuclein from its normal axonal/synaptic location into neuronal cell bodies (Kahle et al. 2000; Masliah et al. 2001; Matsuoka et al. 2001; Richfield et al. 2002; Rockenstein et al. 2002), non-fibrillar and detergent insoluble accumulation of α-synuclein (van der Putten et al. 2000; Kahle et al. 2001; Masliah et al. 2001), reduced dopaminergic (tyrosine hydroxylase positive) nerve terminals in the striatum and motor abnormalities (Masliah et al. 2000; van der Putten et al. 2000; Masliah et al. 2001; Fleming et al. 2004).

Human A30P mutant α-synuclein mice also display mislocalization of α-synuclein (Kahle et al. 2000; Matsuoka et al. 2001; Lee et al. 2002; Gomez-Isla et al. 2003) but lack fibrillar inclusions, although detergent insoluble accumulation has been observed in one model (Kahle et al. 2001). In addition gliosis (Gomez-Isla et al. 2003), progressive motor abnormalities (Gomez-Isla et al. 2003), altered short-term hippocampal synaptic plasticity (Steidl et al. 2003), increased tau phosphorylation at Ser 396/404 and Ser 202 (Frasier et al. 2005) and motor dysfunction (Gomez-Isla et al. 2003) have all been described. Kahle and colleagues also showed that A30P α-synuclein was normally transported to synapses in contrast to in vitro data (Jensen et al. 1998; Kahle et al. 2001).

The human A53T α-synuclein mutation appears to have the most toxic effects when expressed in mice (Kahle et al. 2000; Matsuoka et al. 2001; Lee et al. 2002; Gomez-Isla et al. 2003). As well as mislocalization of α-synuclein (van der Putten et al. 2000; Giasson et al. 2002; Lee et al. 2002; Gispert et al. 2003) and severe progressive motor abnormalities (van der Putten et al. 2000; Giasson et al. 2002; Lee et al. 2002), A53T expression leads to pathological non-fibrillar (van der Putten et al. 2000; Lee et al. 2002; Gispert et al. 2003) and fibrillar (Giasson et al. 2002) accumulations of α-synuclein and ubiquitin (van der Putten et al. 2000; Giasson et al. 2002; Lee et al. 2002). Mitochondrial DNA damage and degeneration, including reduced complex IV activity, has also been observed in A53T α-synuclein mice (Martin et al. 2006).

Of note, mice expressing both mutations A53T and A30P do not show exacerbated pathological or motor phenotypes in comparison to the single mutant models described above (Richfield et al. 2002). In contrast, β-synuclein overexpression may ameliorate motor deficits, neurodegenerative alterations and the neuronal α-synuclein accumulation observed in human α-synuclein transgenic mice (Hashimoto et al. 2001). Endogenous mouse α-synuclein was also shown to be protective in a prion-promoted (mPrP) human A53T α-synuclein model when compared to the same mouse on an α-synuclein null background (Cabin et al. 2005).

Only somatic gene transfer in adults has provided models with neuronal cell loss. Adeno- or lenti-viral delivery of human wild type and mutant (A30P, A53T) α-synuclein to the *substantia nigra* of rats and primates leads to loss of dopaminergic neurons, α-synuclein inclusions and neuritic pathology (Kirik et al. 2002, 2003 Klein et al. 2002; Lo Bianco et al. 2002; Lauwers et al. 2003; Yamada et al. 2004) as well as ubiquitin-positive inclusions (Lauwers et al. 2003). Mild motor impairment assessed by drug-induced rotational behavior was also noted in two rat models (Kirik et al. 2002; Lauwers et al. 2003). Lentiviral delivery of wild type and A53T α-synuclein into the striatum and the amygdala induced similar changes to those seen after *nigral* delivery, indicating that the Lewy-like pathology and neurodegeneration are not restricted to dopaminergic cells (Lauwers et al. 2003).

A new player in PD; LRRK2

As one of the most important genetic causes of autosomal dominant late onset-PD, the discovery of mutations in leucine-rich repeat kinase 2 (*LRRK2*; Lrrk2) has undoubtedly opened a whole new gateway for PD animal models (Zimprich 2004). Postmortem analysis of patients from Family A harboring a Lrrk2 Y1699C mutation, and Family D with Lrrk2 R1441C, reveals pleomorphic pathology including neuronal loss with α-synuclein, tau and ubiquitin lesions (Zimprich 2004). However, the vast majority of brains with Lrrk2 G2019S, the most common mutation identified to date have transitional/brainstem restricted Lewy body pathology found in typical, late-onset idiopathic PD (Mata et al. 2005; Ross et al. 2006). Lrrk2 G2019S displays variable, age-associated penetrance (Kachergus et al. 2005; Kay et al. 2005). *In silico* modeling and recent in vitro data have shown Lrrk2 mutants G2019S and I2020T have increased kinase activity (Gloeckner et al. 2005; West et al. 2005). Aberrant Lrrk2 activity may impact both Ras and MAPK signaling and serves to highlight the potential importance of these pathways in idiopathic PD. We and others have recently shown that *LRRK2* mRNA expression in mice is most abundant in dopamine-innervated areas, rather than the dopamine synthesizing neurons (Melrose et al. 2006; Simon-Sanchez et al. 2006) and highest in the striatum and the olfactory tubercle. The first Lrrk2 BAC model with physiologically and temporally relevant patterns of expression shows tau-positive neurodegenerative changes, reminiscent of that observed in some human patients with Lrrk2-associated disease (Dr. H.L. Melrose, personal communication at the World Congress of Parkinson's disease, Feb 22–26, 2006). We postulate Lrrk2 is essential for dopaminergic neuronal survival whereas mutant Lrrk2 may diminish trophic support in the nigrostriatal pathway via disruption of proteins involved in synaptic release, trafficking or axonal retrograde transport.

Animal models of mutant or wild type *LRRK2* will enable the biological function of Lrrk2 and its relevance to PD to be assessed. The synergistic effects of α-synuclein and tau may be studied on this background, given neuronal cell death, Lewy bodies and tauopathy are the major pathologies associated with *LRRK2* mutations in

man. The susceptibility of these models to epidemiologic and toxin exposures may be explored, as well as the efficacy of MAPK inhibition to prevent Lrrk2-induced neurodegenerative disease.

Time for a rethink

While many models of PD have been created to date no single model, either based on toxins or genetic, has been able to recreate all the key features of disease. Neurotoxins, herbicides, pesticides, fungicides and proteasomal inhibitors have been shown in varying capacity to induce some features of PD in rodents. These symptomatic models have provided considerable therapeutic insight into basal ganglia physiology and response to drug therapy. However, paraquat, rotenone and epoxomicin are systemic poisons and produce considerable morbidity and mortality and it remains unclear why the animals that survive have selective nigrostriatal deficits. In contrast, 6-OH-DOPA and MPTP are preferentially metabolized by dopaminergic neurons in which their effects are limited. Presently, it is also unknown whether genetic causes identified in rare, Mendelian forms of parkinsonism highlight pathways affected in idiopathic PD. Nevertheless, knock-out, overexpression and mutations in single genes provide a powerful new set of molecular tools to study etiology. Parkinson's syndrome most likely results from an intricate combination of gene and gene–environment interactions. This is a complicated scenario that poses an exigent challenge for the animal modeler. An understanding of the limitations of current models in PD and what can be done to improve them is needed.

Firstly, we must better define what we are attempting to model. Although neurologists have primarily characterized PD as a movement disorder, this is a biased view. The reality is that multiple systems are affected. The earliest signs of PD typically occur in the gut with constipation in mid-life, with seborrhea in the skin, with sympathetic denervation of the heart and with anosmia of the olfactory bulbs (Fahn 2003). REM sleep behavior disorder and depression are also early features, possibly reflecting dysfunction in the dorsal raphe (Fahn 2003). Although seldom considered predictive, these clinical observations are not new; James Parkinson stated constipation and sleep disorder in his original 1817 diagnosis. The recent staging proposed by Braak highlights the burden of α-synuclein pathology in these anatomical sites (Braak et al. 2004).

Other than a progressive movement disorder, traditional models of PD require selective cell loss in the *substantia nigra* accompanied by end-stage Lewy body pathology. However, in patients Lewy bodies neither correlates with the movement disorder nor cognitive decline observed (Parkkinen et al. 2005). Even in *SNCA* mutant and multiplication families, the central issue may be temporal, regional and quantitative dysregulation of α-synuclein expression; normal expression of the protein plays an important role in response to toxic insults and environmental stress. As α-synuclein-positive Lewy bodies are only found in surviving neurons they may be protective rather than causal. Although an unorthodox and perhaps heretical view, recent work in *Drosophila* suggests α-synuclein phosphorylation is required for neurotoxicity, whereas non-phosphorylated protein has a propensity to form inclusion bodies (Chen and Feany 2005). In this light, a central focus on α-synuclein aggregates, fibrils, protofibrils, oligomeric or monomeric species and which are pathogenic may be misguided. While Lewy neurites are likely to be detrimental to neuronal connectivity, preventing α-synuclein expression or fibril formation, or disaggregation of existing inclusion bodies, may exacerbate the disease process.

Both toxic and transgenic models will help address this fundamental question and elucidate the dynamics of α-synuclein expression and aggregation in vivo. However, existing models suggest Lewy-like pathology is problematic to create. In mice, high wild type or mutant α-synuclein expression specifically targeted to the dopaminergic neurons of the *substantia nigra* via a tyrosine hydroxylase promoter does not result in pathology (Matsuoka et al. 2001), and in other models the *nigra* appears to be relatively spared even when pathogenic α-synuclein aggregates are present (Fernagut and Chesselet 2004). Although background strain may account for some of the differences between transgenic lines, this is difficult to assess given the variety of heterologous promoters employed. Differences in transgene integration site may influence α-synuclein expression pattern/levels. In addition, endogenous α-, β- and/or γ-synuclein expression, both across and within congenic strains, may developmentally compensate for human α-synuclein overexpression. The phenotype of progressive toxin models, including rotenone and epoxomicin, is also technically challenging to achieve and results are variable, as when animals survive they may not develop a lesion. These apparent differences in susceptibility/resistance may again be due to intra-strain variability.

Transgenic models with the most pronounced phenotypes have used promoters that direct inappropriately high α-synuclein expression in the brainstem and the spinal cord, but have little or no expression in the striatum although this structure is an integral component of the basal ganglia and displays considerable endogenous α-synuclein expression. No transgenic model yet reproduces the physiological expression pattern of α-synuclein, which in humans and mice is low in sub-cortical regions and higher in the cortex and limbic system (Rockenstein et al. 2002). BAC/PAC genetic models that rely on human gene promoters, coupled with recent advances in BAC/PAC mutagenesis, might now overcome this limitation (Sopher and La Spada 2006). The generation of 'humanized mice' via null crosses can also help achieve tissue-specific expression and appropriate post-translational protein modifications. For example, genomic PAC mice developed to model human tauopathy did not

develop tau neurofibrillary pathology (Duff et al. 2000) until they were crossed onto a tau-null background (Andorfer et al. 2003).

If *SNCA* multiplication patients reflect the underlying molecular events in idiopathic PD, models created using a *SNCA* BAC transgenic approach may provide fundamental insight into the staging of α-synuclein pathology. Furthermore as transgene expression is not restricted to the brain, studies of peripheral tissues may have predictive value in human patients. In PD, non-motor symptoms clearly precede the onset of parkinsonism by many decades and if neuroprotection trials are to meet with success, early and accessible biomarkers of disease progression are essential. Models of α-synuclein biology may be especially insightful combined with toxin exposures, as they may help explain the reduced age-associated penetrance of familial PD. Lrrk2 models are being created, and while the function of this protein is yet unknown, insights gained from the development of α-synuclein and tau models and crosses with these lines should prove invaluable in exploring the pleomorphic pathology observed. Loss-of-function mutations in Parkin, DJ-1 and PINK1 clearly implicate impaired protein handling, oxidative stress and mitochondrial dysfunction as important players in dopamineric neurons and the pathogenesis of PD. However, genetic knockout of Parkin and DJ-1 in mouse models have subtle phenotypes. This may reflect the predominant movement phenotype in these patients that typically requires only low doses of l-DOPA to remedy; in contrast to idiopathic PD, non-motor and probably non-dopaminergic features are not as problematic. Chemically induced rodent models have long shown that mitochondrial complex I dysfunction has a selective effect on the nigrostrial system. Curiously, overexpression of Parkin or DJ-1 in combination with toxin exposure appears to provide some protective benefit. DJ-1 viral delivery into MPTP treated mice ameliorates striatal deficit and dopaminergic loss, whereas Parkin viral delivery rescues α-synucleinopathy in a rat model (Lo Bianco et al. 2004; Kim et al. 2005).

Thus, although parkinsonism may have many causes a finite number of overlapping pathways appear to be affected. Animal models allow those pathways to be explored and novel treatment strategies developed. The recent discovery of single gene defects that lead to the phenotype, including *SNCA* and *LRRK2* provides the simplest and most powerful approach. Manipulating these endogenous genes, using knock-in and knock-out strategies and BAC methods may be most physiologically relevant, whereas inducible/regulatable transgene expression will address specific questions in limited tissues. In combination, and with toxin models, most of the features of PD can now be modeled, and with these tools both neuroprotective and symptomatic therapies can be developed.

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