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Parkinson's disease: experimental models and reality

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Abstract

Parkinson's disease (PD) is a chronic, progressive movement disorder of adults and the second most common neurodegenerative disease after Alzheimer's disease. Neuropathologic diagnosis of PD requires moderate-to-marked neuronal loss in the ventrolateral substantia nigra pars compacta and α -synuclein (α S) Lewy body pathology. Nigrostriatal dopaminergic neurodegeneration correlates with the Parkinsonian motor features, but involvement of other peripheral and central nervous system regions leads to a wide range of non-motor features. Nigrostriatal dopaminergic neurodegeneration is shared with other parkinsonian disorders, including some genetic forms of parkinsonism, but many of these disorders do not have Lewy bodies. An ideal animal model for PD, therefore, should exhibit age-dependent and progressive dopaminergic neurodegeneration, motor dysfunction and abnormal α S pathology. Rodent models of PD using genetic or toxin based strategies have been widely used in the past several decades to investigate the pathogenesis and therapeutics of PD, but few recapitulate all the major clinical and pathologic features of PD. It is likely that new strategies or better understanding of fundamental disease processes may facilitate development of better animal models. In this review, we highlight progress in generating rodent models of PD based on impairments of four major cellular functions: mitochondrial oxidative phosphorylation, autophagy-lysosomal metabolism, ubiquitin-proteasome protein degradation, and endoplasmic reticulum (ER) stress/unfolded protein response (UPR). We attempt to evaluate how impairment of these major cellular systems contribute to PD and how they can be exploited in rodent models. In addition, we review recent cell biological studies suggesting a link between α S aggregation and impairment of nuclear membrane integrity, as observed during cellular models of apoptosis. We also briefly discuss the role of incompetent phagocytic clearance and how this may be a factor to consider in developing new rodent models of PD.

Introduction

Parkinson's disease (PD) is a chronic, progressive movement disorder and the second most common neurodegenerative disease after Alzheimer's disease [143]. Pathologically, PD is characterized by selective and progressive loss of dopaminergic neurons projecting from the substantia nigra (SN) *pars compacta* to the corpus striatum, leading to an extrapyramidal motor disorder with bradykinesia, resting tremor, rigidity, and postural instability. Involvement of other regions of the central and peripheral nervous system contributes to a range of non-motor symptoms such as autonomic dysfunction, depression and cognitive

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deficits [103,155]. The characteristic pathological hallmarks of PD are cytoplasmic and neuritic aggregates of the presynaptic protein α -synuclein (α -Syn) in Lewy bodies and Lewy neurites, collectively referred to as Lewy-related pathology [45]. In addition to α -Syn, these structures also contain other proteins, whose specificity and precise role in the disease process are less certain [157]. The distribution of Lewy-related pathology in PD follows a fairly predictable pattern depending upon selective vulnerability or connectivity, which has led Braak and coworkers to propose a staging scheme for PD [23]. Other systems for classification of Lewy-related pathology have also been proposed [9,3,196], but the Braak scheme has been groundbreaking in drawing attention to the multisystem pathology in PD and anatomical “predictability” of disease progression as it relates to evolving signs and symptoms of PD [21]. In the Braak staging scheme there is early involvement of olfactory bulb and central parasympathetic nuclei in the medulla, suggesting that the pathology may actually originate outside of the central nervous system [22]. Indeed, there is evidence for α -Syn pathology in peripheral tissues, albeit little evidence that it precedes brain pathology [85,11,10].

Although it has been two centuries since the description of shaking palsy by James Parkinson [144], the etiology of this disease remains enigmatic. A clue to possible role of environmental factors was the report of a PD-like syndrome in humans exposed to meperidine analogues such as MPTP [104]; however, Lewy-related pathology was not observed at autopsy [59]. Other neurotoxins implicated in PD include pesticides, organic solvents and air pollutants [68]. The discovery of mutations in the gene for α -synuclein (*SNCA*) in familial PD [158] and subsequent demonstration that Lewy-related pathology contained α -Syn [187] solidified the etiologic importance of α S to PD. Genetic studies of kindreds with PD in multiple affected family members led to identification of several other genetic loci implicated in autosomal dominant or recessive forms of PD [98]. Genetic factors implicated in sporadic PD can be ascertained from genome wide association studies (GWAS). A meta-analysis of currently available GWAS by Nalls et al. [140] implicated 28 loci, and an additional locus was identified in an autopsy-confirmed cohort of PD [13]. A curated on-line database of genetic loci implicated in PD is PDGene [109]. The top genetic loci are associated with genes that implicate distinct cellular processes affecting select cellular compartments, notably cytoplasm, cytoskeletal components, mitochondria, endosomes, and lysosomes (Table 1). Perturbations in proteostasis and mitochondrial quality control, and other basic cellular processes, converge in producing PD [40]. It is increasingly recognized that impairment of several major cellular functions associated with energy metabolism, protein degradation and stress response play important roles in α S deposition and programmed cell death in dopaminergic neurons of PD [138,202,117,44,110]. In this review, we highlight recent progress in generating rodent models of PD based on impairments of four major cellular functions: mitochondrial oxidative phosphorylation, autophagy-lysosomal metabolism, ubiquitin-proteasome protein degradation, and endoplasmic reticulum (ER) stress/unfolded protein response (UPR). The goal of this review is to provide insights into possible pathogenic mechanisms of PD at the cellular level, with a particular focus on rodent animal models.

Impairment of mitochondrial oxidative phosphorylation in PD and in animal models

Mitochondria are critical components of the eukaryotic cell due to their unique function – oxidative phosphorylation [154]. Oxidative phosphorylation is based upon two tightly connected components: the electron transport chain and chemiosmosis, which are orchestrated by five multi-subunit protein complexes localized on the inner mitochondrial membrane. The electron transport chain (complex I, II, III and IV) pass electrons from one subunit to another, and energy released in these electron transfers is used to form an electrochemical gradient (proton gradient). The chemiosmosis is the last step of oxidative phosphorylation, where ATP synthase (complex V) utilizes the proton gradient to produce ATP [154]. This is normal process of physiological respiration. However, the electron transport chain contains several redox centers that may leak electrons to molecular oxygen, leading to the production of superoxide. It has been reported that approximately 1% to 2% of the molecular oxygen consumed during normal physiological respiration is converted into reactive oxygen species (ROS) [31]. Production of ROS is markedly increased in a variety of pathologic conditions, including defects in one of the electron transport chain complexes [31]. Therefore, the mitochondrial oxidative phosphorylation system produces not only ATP essential for cell metabolism and other normal activities, but also incidental ROS that can lead to cell injury and death.

The role of mitochondrial dysfunction in PD includes evidence for reduced complex I activity and oxidation in various tissues of PD patients [173,136,99,151], and notable increases in complex I related oxidative damage in postmortem PD brain [93]. Mitochondrial deficits and subsequent oxidative stress are a leading hypothesis for dopaminergic neuron death in PD [60]. A number of PD-related genes are tightly associated with mitochondrial dysfunction [198,188,178], and there is increasing evidence of mutations or deletions in mitochondrial DNA in non-familial PD [75,81,166]. Given the wealth of this supporting evidence, it is not surprising that a number of well-established PD animal models are based upon “mitochondrial toxins,” such as MPTP and rotenone [124]. Meanwhile, molecular strategies aimed at producing mitochondrial deficits have also been employed in PD animal models (Table 2).

In addition to MPTP other neurotoxins have been used to model mitochondrial dysfunction in PD, including pesticides such as rotenone [8], paraquat [147], maneb [46] and trichloroethylene [61], as well as endogenous neurotoxins such as 6-hydroxy-dopamine (6-OHDA) [87,83] and homocysteine [101,17].

MPTP and rotenone, two potent inhibitors of complex I, are the most popular mitochondrial toxins for modeling PD in rodents [124]. MPTP neurotoxicity is relatively limited to the nigrostriatal dopaminergic pathway and is associated with a characteristic and quantifiable motor phenotype [134]. This model, as well as most other neurotoxin models, lacks α S pathology typical of PD [134], although isolated reports have shown ubiquitin and α S immunoreactive inclusions in mice treated with chronic low dose of MPTP [58]. In contrast, a number of rodent models with chronic rotenone treatment have α S-positive intracellular inclusions in parallel with degeneration of nigrostriatal dopaminergic neurons and motor

deficits. Phenotypic variability, high mortality rate and other non-PD related features are drawbacks of the rotenone model [34]. Paraquat is a weak inhibitor of mitochondrial complex I [165]. Some studies showed that it can induce motor dysfunction and loss of dopaminergic neurons in SN [24,127], and some studies have reported Lewy body-like structures in rodents treated with paraquat [120,54]. Interestingly, a combination of paraquat and an inhibitor of complex III – maneb [57] – significantly enhances SN neuronal loss in this model, indicative of synergistic effects of deficits in multiple subunits of the mitochondrial electron transport chain on neurodegeneration [193]. The relevance of paraquat to PD is questionable [135]. More recently, trichloroethylene, a complex I inhibitor [61], which has been used in PD animal models, has been epidemiologically linked to PD in humans who have been exposed to trichloroethylene-related products in the workplace [61,69,76]. Administration of trichloroethylene to rats induces SN neuron loss, dopamine depletion in the striatum, and behavioral deficits [112]. More importantly, accumulation of intraneuronal α S can be observed in this model.

In addition to environmental neurotoxins, mitochondrial deficits can also be induced by endogenous molecules, such as 6-hydroxydopamine (6-OHDA) [87,83] and homocysteine [101,17], which have been employed in animal models of PD. 6-OHDA is a hydroxylated analog of dopamine that can be detected in trace amounts in human brain and urine samples [87]. In fact, 6-OHDA was one of the earliest [197], and still widely used, neurotoxin models for PD, valued for its predictable degeneration of dopaminergic neurons and consistent behavioral phenotype [160,170]. The exact mechanism underlying its toxic effects is elusive, but recently, it was demonstrated that mitochondrial dysfunction is the primary cause of 6-OHDA-induced dopaminergic neuronal death [102]. Similar to MPTP, 6-OHDA rodent models lack Lewy-related pathology. Moreover, administration of 6-OHDA must be done by stereotaxic injection or direct infusion into the brain since it is impermeable to the blood brain barrier [18]. Homocysteine is another endogenous molecule that is toxic to dopaminergic neurons. It became a promising reagent for modeling PD in rodents due to its elevated level in plasma of PD patients and neurotoxicity to dopaminergic neurons in cell-based experiments [17]. Rats with unilateral intranigral infusion of homocysteine have inhibition of mitochondrial complex-I activity, reduced striatal dopamine, neurodegeneration of SN dopaminergic neurons, and impaired motor activity [17]. When applied to mice through other routes of administration homocysteine was not toxic; however, it was shown to enhance neurotoxicity of MPTP [47]. Therefore, sensitivity of rats or mice to homocysteine might account for the above discrepancy. It is worth noting that no α S pathology has been reported in homocysteine-induced rodent models.

Besides pharmacological approaches, genetic manipulations represent another strategy to generate mitochondrial dysfunction models. PTEN-induced putative kinase 1 (PINK1) is a mitochondrial serine/threonine-protein kinase, intimately involved in mitochondrial quality control. Mutations in PINK1, which are mostly loss of function mutations [198] or partial dominant negative mutations [161], are linked to autosomal recessive PD [199]. Several PINK1 knockout rodent models have been developed. One model established by Dave and coworkers has been well-characterized in a series of studies [39]. This model has significant mitochondrial proteomic alterations in the absence of mitochondrial functional changes at postnatal day 10; starts to show functional abnormalities at 4 months of age; and develops

rapidly progressive neurodegeneration between 4 and 8 months of age. The mice have a progressive movement disorder accompanied by loss of midbrain dopaminergic neurons, with 25% reduction at 6 months and 50% at 8 months of age [206,205]. An unexpected finding is 2 to 3 fold increase in both DA and 5-HT striatal content as late as 8 months of age [39].

Another PINK1 deficient mouse model has defects of key mitochondrial functions that correlate with an age-dependent and moderate decrease of striatal dopamine content. They have impaired locomotor activity; however, no dopaminergic neuronal loss is observed even at 18 months of age [64]. Other reported PINK1 knockout mice do not show observable gross motor dysfunction or alterations in the dopaminergic system, except for gait changes and olfactory dysfunction [65]. It is worth noting that none of the PINK1 models has α S pathology. A limited number of autopsies on PD with PINK1 mutations has shown mild Lewy-related pathology [159]. Given these observations, it has been suggested that PINK1 knockout mice may be used as models of prodromal PD [183].

Mitochondrial transcription factor A (TFAM) is a key activator of mitochondrial transcription that plays an essential role in maintaining mitochondrial integrity. A mouse model with significant mitochondrial dysfunction – MitoPark – was generated by disruption of TFAM in dopaminergic neurons [49]. MitoPark mice have reduced mtDNA expression and respiratory chain deficiency in midbrain dopaminergic neurons, associated with a motor phenotype, slowly progressive SN neurodegeneration, and formation of intra-neuronal inclusions. Further investigation in this model revealed that altered nigrostriatal function precedes the onset of motor dysfunction [73]. Loss of DA neurons also was associated with impairment in the circadian control of rest and activity [56]. Although MitoPark mice successfully recapitulate several characteristic features of PD, they do not have α S pathology.

There are several other genes that have been less frequently used to induce mitochondrial dysfunction. For example, mouse models with deficiency or abnormal expression of mitochondria function-related genes *Ndufs4* [185,95], *Hspd1* [118], *Aldh1a1/Aldh2* [209], *HtrA2* [26,152], *Twinkle* [186], and *dOTC* [137] have been generated. These mice show PD-related features to a varying degree. Interestingly, a mitochondrial targeted restriction endonuclease (Mito-PstI) has been used to develop a PD mouse model in which mitochondrial DNA double-strand breaks in dopaminergic neurons is induced by the expression of Mito-PstI conditionally controlled under dopamine transporter (DAT) promoter-driven tetracycline transactivator protein [156]. This model has mitochondrial dysfunction in dopaminergic neurons and many features of PD, including an L-DOPA reversible motor phenotype, progressive neurodegeneration of DA neurons, and striatal DA depletion [156]. While these models strongly implicate mitochondrial dysfunction in PD, none of them has α S pathology, which is true for both mitochondrial neurotoxin and genetic models. This raises the question of whether mitochondrial dysfunction would ever be sufficient for induction of α S pathology.

Impairment of autophagy-lysosomal system in PD and in animal models

The autophagy-lysosomal system is responsible for degrading and recycling unnecessary or damaged cytoplasmic molecules or organelles, an essential role in maintaining cellular energy and metabolic homeostasis [149]. Autophagy-lysosomal degradation is a delicately balanced and multistep process that involves orchestrated action of a large number of cellular factors. Autophagy includes three subtypes (macroautophagy, microautophagy and chaperone-mediated autophagy) that are distinguished by distinct routes for delivering targets to lysosomes [149]. Defects in any step or essential factor, such as formation of autophagosome or autophagolysosome, lead to accumulation of unwanted proteins (e.g., α S [208]) in neurons and possible neuron death. It has been suggested that this mechanism might be critical for Lewy-related pathology and neuronal loss in PD.

Support for this hypothesis is the mounting evidence of changes in autophagic vacuoles or autophagy-related markers in postmortem PD brains [5,212,43], as well as discoveries of autophagy-lysosomal related genetic abnormalities in familial PD [180,1,163]. Given the evidence that dysfunction of autophagy-lysosome system is crucial to PD, strategies aimed at compromising autophagy-lysosome system via genetic or pharmacological manipulations have been explored to develop PD animal models (Table 3).

As the final common pathway in the autophagy-lysosomal system, lysosomes have been the most frequent target for disruption in PD models. Genetic variants in certain lysosomal enzymes, such as glucocerebrosidase (GBA) and ATP13A2, are associated with familial PD [171,150]. Moreover, some lysosomal enzymes have been implicated in α -Syn degradation [177]. These enzymes have been targets for modeling PD in rodents. A mouse model with lysosomal function inhibition by administration of a potent, selective and irreversible competitive inhibitor of glucocerebrosidase – conduritol- β -epoxide – was associated with insoluble α S aggregates in the SN, as well as widespread neuroinflammation, as well as abnormalities in synapses, axonal transport, and cytoskeletal proteins [167]. Another mouse model with reduction in glucocerebrosidase activity in all tissues except the skin with mutations in GBA had rapid motor dysfunction associated with severe neurodegeneration and apoptotic cell death in the brain [51]. Further studies of this model revealed defective autophagic and proteasomal machinery and accumulation of p62/SQSTM1, ubiquitinated proteins and insoluble α S [145].

A mouse model of lysosomal enzyme cathepsin D deficiency showed impaired macroautophagy and proteasome activity, as well as extensive accumulation of endogenous α S as oligomeric and insoluble α S species [37,162]. In contrast to glucocerebrosidase and cathepsin D, ATP13A2 is a late endosomal/lysosomal P5-type transport ATPase that has no direct role in protein degradation. A mouse model lacking ATP13A2 shows accumulation of ubiquitinated protein aggregates, lipofuscinosis, and endolysosomal abnormalities, as well as age-related motor dysfunction [94]. Surprisingly, these phenotypes were independent of α S [94].

Another strategy for disruption of autophagy-lysosome degradation pathway is to impair autophagy. It has been reported that a mouse model with impairment of autophagy caused by

conditional deletion of Atg7, an E1-like activating enzyme that is essential for autophagy and cytoplasmic to vacuole formation, can recapitulate many pathological features of PD, including age-related loss of dopaminergic neurons, striatal dopamine reduction, α S accumulation and accumulation of ubiquitinated protein aggregates [2].

The most common genetic cause of late-onset PD, LRRK2 [214], is associated with defects in autophagy [121,71]. LRRK2 has been the target in a number of PD rodent models. Besides the changes of autophagic activity, some PD features, such as motor dysfunction, neuronal loss, dopamine depletion and axonal degeneration have been observed in different LRRK2 models [164,148,108,191]; however, none has α S pathology.

It is worth noting that a recent study shows that mice lacking IFN-beta-IFNAR function demonstrate motor and cognitive learning impairments, accompanied by reduction of dopaminergic neurons and defects of dopamine signaling in the nigrostriatal region, and formation of α S containing inclusions as well [48]. In-depth investigation of mouse brain revealed that the lack of IFN- β signaling caused defects in neuronal autophagy prior to synucleinopathy, which may be responsible for the observed PD features in this novel mouse model [48].

It is interesting to note that many rodent models with impaired autophagy-lysosomal system develop α S pathology without motor dysfunction. In contrast, models with genetic manipulation of ATP13A2 or LRRK2 show impaired motor function without α S pathology. This indicates that α S pathology and motor dysfunction may be independent processes in PD.

Impairment of ubiquitin proteasome system in PD and in animal models

The ubiquitin-proteasome system (UPS) is an essential and highly regulated mechanism for protein catabolism in the cytosol and nucleus that plays an important role in a variety of basic cellular processes [131]. The UPS degradation pathway starts with polyubiquitination of the target protein, which includes a series of ATP-dependent enzymatic steps and a series of necessary enzymes, ubiquitin-activating (E1), ubiquitin-conjugating (E2) and ubiquitin-ligase (E3) enzymes. The ubiquitinated protein is subsequently recognized by the 26S proteasome, and subjected to digestion into peptide fragments in its subunits (20S) after passing through the 19S subunit for the cleavage of polyubiquitin chain. Although 26S proteasome as an intact functional unit is the most common destination for protein degradation, its 20S subunit can also exist freely in mammalian cells to digest natively unfolded or damaged proteins in an ATP-independent manner. Under certain circumstances, the 20S proteasome can disassemble from the 26S and become a dominant degradation pathway [207]. Therefore, the 20S subunit is considered the final pathway of the UPS.

Since the UPS is a major route for α S degradation [208], it is conceivable that the blockage of this pathway could contribute to accumulation of α S and eventual Lewy-related pathology. Support for this hypothesis stems from a number of studies. Ubiquitinated α S coexists with proteasome subunits in Lewy bodies in PD [15], and both structural and functional defects in the 26/20S proteasome have been reported in PD brains [25,129]. In

addition, several components of the UPS, including proteasomal subunits, proteasomal activators, heat shock proteins, ubiquitin and ubiquitinated proteins have been identified as constituents of Lewy bodies [130]. Consequently, impairment in the UPS has been considered important PD pathogenesis.

In order to investigate proteasome dysfunction as a model for PD, the UPS can be altered with toxins or genetic manipulations (Table 4). Several proteasome inhibitors (e.g., lactacystin, PSI, MG and EXPO) have been administered to rodents. Lactacystin is the most often used proteasome inhibitor that is applied by stereotaxic infusion into medial forebrain bundle targeting the nigrostriatal pathology or directly into the SN. Almost all animals show varying degrees of neuronal loss at the injection site, there is variability related to dose used. Most also have striatal DA reduction, α S accumulation in SN, and motor impairment [16,204]. A major criticism of these models is the lack of specificity of this toxin. Surprisingly, a study from Lorenc-Koci and coworkers showed that lactacystin infusion into the SN caused reduction of α S expression locally, as well as neuronal loss and reduced DA, but no motor impairment [113]. Inhibitors of UPS suitable for systemic administration include Z-Ile-Glu(OtBu)-Ala-Leu-al [132,172], MG-132 and epoxomicin [132,189]. Results from these inhibitors have been inconsistent; some models recapitulate some features of PD pathology, while others have no effect at all [20]. These discrepancies are likely related to a number of experimental design issues, such dose and strain differences.

Genetic manipulations that perturb the UPS have also been developed for rodent models. Bedford and coworkers used a Cre/loxP system to establish a mouse model with conditional knockout of the proteasomal Psmc1 ATPase in neurons in different regions of the brain [12]. In this model, the 26S proteasome is disrupted due to failure of assembly of the 19S subunit, while 20S degradation remains functional. Mice in this model have significant loss of DA neurons and reduction of striatal dopamine [12,146]. More interestingly, the neurons that survive effects of 26S proteasome-depletion in both the forebrain and SN develop intraneuronal inclusions containing α S, ubiquitin and mitochondria, resembling pre-Lewy bodies [146,12].

Other rodent genetic models of UPS deficiency have targeted Parkin or UCH-L1. Parkin is an E3 ubiquitin ligase that plays an important role in UPS as well mitochondrial quality control [41]. Homozygous or compound heterozygous mutations in Parkin are associated with autosomal recessive juvenile onset Parkinsonism (ARJP), while heterozygous mutations may play a role in sporadic PD, as well [41]. Mutations in Parkin impair UPS protein degradation, leading to abnormal accumulation of proteins. Although it is well-established that parkin dysfunction disrupts mitophagy [141], this may also be an indirect consequence of impairment of the UPS because parkin-mediated proteasomal degradation of mitochondrial outer membrane proteins is an upstream determinant of mitophagy [28]. A number of parkin knockout mice have been reported; however, none of them has SN dopamine-related motor deficits, but mild reduction in DA without neuron loss has been observed in some models [66,123,213,153]. In contrast, a bacterial artificial chromosome transgenic mouse model expressing mutant parkin (Parkin-Q311X) in dopaminergic neurons demonstrated age-dependent neurodegeneration in the SN, significant reduction of striatal DA and motor deficits [114]. Moreover, this model had progressive accumulation of

proteinase K-resistant α S in the SN [114]. Another interesting parkin PD model is a rat model with adeno-associated virus (AAV)-mediated overexpression of p.T240R Parkin mutant and wild type human parkin. Overexpression of both forms of parkin were associated with progressive and dose-dependent dopaminergic neuronal loss and mild motor deficits [201].

UCHL1 is included in the discussion of models of UPS dysfunction because it is a member of a gene family whose products hydrolyze small C-terminal adducts of ubiquitin to generate ubiquitin monomers [122]. There are few rodent models for UCHL1 in part because disease-causing mutations (e.g. UCHL1 p.I93M) are extremely rare [107]. Transgenic mice with p.I93M UCHL1 mutation had significant reduction in SN neurons and decreased DA in the striatum, as well as decreased spontaneous, voluntary movements [176,210]. Another mouse model with UCHL1 knockout had early onset motor deficits, short lifespan and forebrain astrogliosis [179]. In these models, UCHL1 deficiency did not lead to changes in α S expression [176,210,179].

Of the various models for UPS dysfunction, lactacystin may be better than other proteasome inhibitors with respect to modeling the most important clinical and pathological features of PD. While genetic manipulation of Parkin or UCHL1 may induce SN neuronal degeneration and consequent motor deficits, α S pathology is not consistently observed in these models.

Impairment of endoplasmic reticulum (ER) stress and unfolded protein response (UPR) in PD and in animal models

The ER plays a key role in properly folding proteins and in protein quality control [133]. Under normal conditions, ER homeostasis is a tightly regulated process. ER homeostasis can be disrupted by a number of factors that lead to protein misfolding, abnormal protein maturation or ER calcium release, a process referred to as “ER stress.” ER stress triggers a physiologic protective response termed the unfolded protein response (UPR) [133]. The UPR is regulated by three major ER stress sensor proteins – activating transcription factor 6 (ATF6), inositol-requiring enzyme 1 (IRE1), and protein kinase RNA-like ER kinase (PERK). With activation of the UPR, cells restore ER balance by reducing ER stress and recovering ER homeostasis [133]. If the UPR becomes dysregulated, it can lead to defective ER proteostasis (e.g., accumulation of toxic misfolded proteins) associated with cell dysfunction and even cell death.

Since the accumulation of misfolded α S is a fundamental pathogenic process in PD [11], it is not surprising that ER stress and UPR can be observed in PD brains. There is compelling evidence that UPR activation markers (phosphorylated PERK and eIF2 α) are increased in the SN in PD [80]. In addition, ER stress-associated proteins, such as HERP, BIP and pPDI, are upregulated in SN of PD and some also co-localize with Lewy bodies [35,175,182]. Therefore, ER stress and UPR are likely involved in pathogenesis of PD; however, it is unclear if accumulation of aggregated α S is the cause or result of ER stress and disrupted UPR. Studies have showed that α S aggregation can induce ER stress and UPR [14] and vice versa [89].

Most studies of ER stress and the UPR in PD rodent models have focused on rescuing neuronal loss via alleviation of ER stress and regulation of UPR [133]. Only a few studies have produced ER stress via toxins or genetic manipulation to model PD in rodents (Table 5). An example is deletion of ATF6a gene in MPTP mice, which was associated with significantly increased neuronal loss and formation of ubiquitin-positive neuronal inclusions [79]. In a rat model overexpressing α S in the SN with AAV gene transfer, knockdown of GRP78 was shown to aggravate α S neurotoxicity, leading to significantly more neuronal loss and greater reduction of striatal DA; however, GRP78 knockdown had no influence on rat without α S overexpression [168]. As to PERK pathway in UPR, a recent study demonstrated that sustained up-regulation of ATF4 in the SN of rats via AAV mediated gene transfer produced motor dysfunction, neuronal loss and striatal DA reduction [77]. It is worth noting that none of the above models with perturbed UPR pathway had α S pathology. In contrast, a recently reported rat model using intranigral injection of a ER stress inducer – tunicamycin –not only had locomotor impairment and dopaminergic neuronal loss death, but also extensive α S oligomerization, activation of astroglia and increased expression of ER stress markers [36]. Missing from this report was description of whether they also had intra-neuronal α S inclusions.

It is clear that α S pathology is not a significant feature of rodent models with genetically induced ER stress or impairment of UPR, although they are associated with neuronal pathology and motor deficits. In contrast, administration of tunicamycin is a more robust method to model PD features, including α S pathology, by producing ER stress and perturbing the UPR.

Expression or deletion of PD-associated genes in PD models

Animal models based upon expression of PD genetic risk variants are useful for understanding the functional consequences of the variants and their role in the pathogenesis of PD. Some of these PD-related genes, such as Parkin and ATP13A2, have a clearly defined function in specific organelles or functional systems. Other genes do not fit well in this classification scheme. These include α S and DJ-1, neither of which seems to be directly related to mitochondrial stress, autophagy-lysosomal degradation, UPS or ER stress/UPR.

Alpha-synuclein in animal models of PD

α S is a major component of Lewy body, the pathological hallmark of PD [203,187]. Genetic coding region mutations, as well as duplication or triplication of the gene for α S (*SNCA*), are linked to autosomal dominant PD, suggesting that not only mutations, but also higher than normal levels of α S play a role in PD [203,53,181].

Transgenic rodent models overexpressing high level of wild type, mutant or truncated α S demonstrate regional expression of α S driven in part by mode of delivery and promoter, and most of them manifest a variety of pathologies and behaviors deficits. Several models have worth mentioning due to their robust phenotypes and development of features similar to those found in PD. Masliah et al. generated a wild type (WT) α S transgenic mouse model that had motor deficits and loss of dopaminergic terminals in the basal ganglia, as well as

α S- and ubiquitin-immunoreactive neuronal inclusions in the neocortex, hippocampus, and SN [125]. Another mouse model expressing WT α S had progressive PD-like motor deficits, progressive nigrostriatal pathology, and regionally specific proteinase K-resistant α S aggregates; however, no neuron loss was observed in this model [32]. Transgenic mice with bacterial artificial chromosome expressing wild-type α S from the complete human *SNCA* locus at disease-relevant levels had age-dependent loss of nigrostriatal dopamine neurons and motor dysfunction, but they had no observable α S pathology [86].

Several rodent models are based upon overexpression of mutant α S. Three transgenic models with A53T α S overexpression driven by mouse prion protein promoter have been generated. All three models had motor deficits [63,62,106], but only two of them had robust α S pathology and neuronal loss [62,106]. The other one had no α S pathology at all [63]. Another robust model is a mouse that conditionally expresses A53T in midbrain dopaminergic neurons. This model had profound motor disabilities, significant dopaminergic neuronal loss, reduction of dopamine release and α S pathology in both neuronal soma and axons of dopaminergic neurons [111]. Compared to the number of A53T models, there are only a few mice generated with overexpression of A30P. One notable model is one with high expression of A30P driven by hamster prion protein promoter. This mouse had progressive degeneration with gliosis and motor deficits, but without lesions in nigrostriatal dopaminergic neurons or α S pathology [70]. Double transgenic mouse models overexpressing both A53T and A30P have also been generated. One had not only accumulation of sarkosyl-insoluble α S and α S with pathologic posttranslational modifications (e.g., phosphorylation, ubiquitination and nitration), but also motor dysfunction and neuronal loss [84]; the other one had progressive decline in locomotor activity and loss of tyrosine hydroxylase-positive neurons, but no α S pathology [194]. Transgenic mouse models overexpressing other α S mutants have also been reported. For example, overexpression of E46K in mice is associated with age-dependent motor impairments and age-dependent neuronal inclusions that resemble Lewy bodies. Interestingly, this model also had abundant neuronal tau inclusions that resemble neurofibrillary tangles [50].

Transgenic mouse models have also been developed that express truncated forms of α S. Mouse overexpressing α S (1–119) driven by ROSA26 promoter had marked reduction of striatal dopamine yet no dopaminergic neuronal loss in SN or other PD features [38]. Transgenic mice with overexpression of α S (1–120) driven by rat tyrosine hydroxylase promoter had progressive reduction in spontaneous locomotion accompanied by reduction in striatal dopamine levels and formation of pathological inclusions in SN and olfactory bulb neurons [195]. In contrast, transgenic mice generated with the CamKII α promoter had expression in forebrain and formation of small granular neuronal cytoplasmic α S inclusions as well as memory deficits [78]; perhaps a better model for Lewy body dementia than for PD.

Although most transgenic α S rodent models have α S aggregates, there are some models with very subtle or no pathology throughout their life-span [52,126]. Moreover, marked differences can be also found in α S transgenic models generated in animals with similar genetic backgrounds and using identical promoters [63,62,106]. Therefore, unpredictable

effects of genomic integration site, epigenetic modifications and transgene copy numbers might play important roles in variability in transgenic rodent models.

In addition to transgenic technology, lentivirus or adeno-associated virus (AAV) infection-mediated overexpression of WT or mutant α S have been used to produce expression in particular brain regions through stereotaxic injection. Rats tend to be more often used with this type of model than mice, likely due to surgical technical challenges. It is interesting that in most viral models there is marked localized α S pathology, but variable neuronal loss and motor deficits [42,105,97]. This is probably a function of the high virus-mediated expression over a relatively short term, which does not allow neurons to adapt and to effectively degrade the overexpressed α S or to develop functional deficits from neurodegeneration.

It is worth noting that in order to test Braak staging hypothesis that posits that α S pathology progressively spreads by cells between interconnected brain regions, there are many rodent models which have been developed to demonstrate prion-like propagation of α S [116]. Some rodent models successfully recapitulate the distribution of α S pathology in brain regions vulnerable in PD, accompanied by neurodegeneration and motor impairment [115], which seems to fit with the hypothesis of pathologic α S propagation. On the other hand, a problem in these models is that the initial transmissible α S aggregates are supplied exogenously through inoculations that would be associated with disruption of tissue integrity at least at the site of implantation, rather than endogenously generated pathologic α S [90].

DJ-1 in PD models

Genetic studies have showed that missense, truncation and mutations in DJ-1 can cause autosomal recessive, early-onset familial PD [19]. Although the exact role of DJ-1 in PD pathogenesis is still unknown, studies on this gene suggest that it is mostly known as a redox-sensitive chaperone and as a sensor for oxidative stress, but associated with various cellular processes, including regulation of mitochondrial complex I activity, 20S proteasome function and autophagy [4,6,139].

Several mouse models with loss of DJ-1 function due to gene deficiency have been generated. The first mouse model generated by Goldberg et al. had altered dopaminergic neurotransmission, reduced sensitivity of nigral neurons to dopamine, and pronounced defects in locomotor activity [67]. Another DJ-1 knockout mouse line from Chandran et al. had progressive behavioral deficits, but no nigrostriatal dopaminergic neuronal loss [29]. A mouse model from Chen et al. had age-dependent and task-dependent impairment in motor behaviors with nigrostriatal dopaminergic dysfunction, but no dopaminergic neuronal loss [30]. Kim et al. and Manning-Bo et al., respectively, generated mouse models with DJ-1 function loss via different strategies. While both models had minimal PD-like changes, they both had enhanced vulnerability to PD-like pathology in response to MPTP [96,119]. Although dopaminergic neurodegeneration and motor impairment markedly vary in DJ-1 deficient mouse models, lack of α S pathology is consistently observed. Therefore, DJ-1 related PD may be independent of Lewy-related pathology. Unfortunately, autopsy findings in DJ-1-related PD have yet to be reported.

Other genes in PD models

Given the important role of nigrostriatal pathology in clinical manifestations of PD, several genes involved in development and maintenance of dopaminergic neurons have been targeted in PD rodent models. Conditional knockout of SHH in mouse DA neurons causes progressive loss of DA neurons, reduction of striatal dopamine and motor deficits [72]. Mice with heterozygous Nurr1 knockout, or conditional knockout, in DA neurons display the age-dependent decline in DA neurons and decreased DA signaling, but motor dysfunction was only apparent in heterozygous Nurr1 knockout (Nurr1^{+/-}) mice [91,211]. Pitx3-deficient aphakia mice display marked reduction in spontaneous locomotor activity and very low striatal DA levels due to progressive loss of mesencephalic dopaminergic neurons during fetal and postnatal development [82,200]. Mouse lacking one En1 allele have decreased mitochondrial complex I activity and progressive SN dopamine neuron degeneration in adulthood, but no observable motor deficits [142]. It is worth noting that none of models targeting dopaminergic neurons have α S pathology. In contrast, mice deficient of c-Rel factor or VMAT2 show not only progressive SN neurodegeneration, but also accumulated of α S [192,7]. It is unclear why some of these models (e.g., c-Rel, VMAT2) can induce α S aggregates in rodent models, while others do not. One possible reason is that the molecular interaction network of these genes might interface with pathways of α S degradation or expression.

Concluding comments

In order to completely recapitulate the major clinical and neuropathological characteristics of PD, an ideal animal model should exhibit age-dependent and progressive neurodegeneration, motor dysfunction and abnormal α S pathology. Neurodegeneration should include dopaminergic neuronal loss, striatal dopamine reduction and α S pathology in the form of neuronal and axonal inclusions (Lewy bodies and Lewy neurites). Motor dysfunction should include slowing (i.e. bradykinesia) that is responsive to dopaminergic therapy. With increasing recognition of the importance of non-motor symptoms of PD [174,155], ideal models would have involvement of central and peripheral autonomic nervous system and the olfactory bulb [128]. Although there are many rodent models generated over the past few decades, which have provided important insights into mechanisms of PD pathogenesis, none of the current models recapitulates all of the major features of PD.

In this review, inspired by advances in our understanding of the pathogenesis of PD at the cellular level, we attempted to evaluate how impairment of major cellular functional systems contributes to PD and how it can be exploited in rodent models. We note that neurotoxin models tend to be more efficient than genetic models in producing dopaminergic neurodegeneration; however, genetic models have the advantage of specifically disrupting cellular functions that are affected in PD. An obvious limitation of neurotoxin models is the unwanted side effects of a toxin [27], while genetic models have their own limitations related to whether they are based upon cDNA or genomic DNA, as well as effects of genetic background of the particular animal, as well as the integration site and copy number of the transgene.

In general, rodent models with impairment of mitochondrial oxidative phosphorylation system, ER stress and UPR system are best for modeling nigrostriatal degeneration accompanied by motor dysfunction, but they rarely have α S pathology. In contrast, models with impairment of autophagy-lysosomal system or ubiquitin-proteasome system more often have α S pathology (e.g., cathepsin D KO mice [37,162]), or α S pathology in addition to neuronal loss and motor deficits (e.g., PSMC1 KO [12] and Parkin-Q311X [114]). Genetic models with expression or deletion of PD-associated genes often have neurodegeneration with varying motor deficits, but only models based upon α S (with few exceptions - VMAT2 [192], c-Rel [7]) have α S pathology. Therefore, α S pathology seems closely associated with impairment of protein degradation systems or overexpression of α S, but independent of mitochondrial dysfunction, ER stress and impaired UPR. Overexpression of α S is expected to lead to aggregation if it is a concentration-dependent process [100]; however, it is less clear how cell models based upon mitochondrial dysfunction or perturbation of ER stress lead to α S pathology [89,92].

Our recent cell biological studies may provide some important clues. We found that α S aggregates can be rapidly formed in cultured neurons undergoing apoptosis by interaction between α S and proaggregant nuclear factors (e.g., histones) associated with disruption of nuclear envelope integrity. The role of nuclear factors in cellular models of PD draws attention to the number of genetic risk factors that are associated proteins that are in the nuclear compartment (Table 1). In our cellular model, high molecular weight aggregates were observed at later stages of apoptosis [90], and eventually, the aggregates spread to adjacent cells. We postulate that this may be a mechanism for formation of abnormal α S seeds that eventually contributes to cell-to-cell propagation [90] (Figure 1). It is possible that the α S aggregates observed in cell models cause by mitochondrial dysfunction could be secondary to loss of nuclear membrane integrity associated with apoptosis [90]. In cell culture experiments, apoptotic neurons can be observed with live cell imaging, and the process can be followed over time, permitting detection of a range of intracellular α S aggregates at different stages of apoptosis. In the brain, apoptotic neurons are rapidly cleared by the innate immune system, which includes intrinsic tissue phagocytes. It is conceivable that in normal individuals, toxin-associated neuronal apoptosis and initial α S aggregates are rapidly cleared by phagocytosis, while in PD aggregates are inefficiently cleared and become seeds for subsequent propagation of α S pathology. There is evidence to suggest that phagocytic activity is significantly reduced in PD [169,74,184]. Moreover, clearance of apoptotic cells can be impaired under chronic inflammatory conditions [190], such as those reported in PD [55]. If this hypothesis can be proven, phagocytic deficits may contribute to pathogenesis of PD. Augmenting innate immunity may be a novel therapeutic target to limit initiation and spread of α S pathology. The animal models described in this review have not used this approach. It is intriguing to postulate that apoptosis-associated α S seeds might be more readily detected in rodent models if they also had deficiency in phagocytosis. We schematically illustrate in Figure 2 mechanisms that might contribute to such a hypothetical model of PD pathogenesis.

The α S pathology observed in α S transgenic rodents varies in different models, and is also distinct from Lewy-related pathology in PD in terms of morphology, composition and biochemical properties. In addition to the models included in this review, there are a number

of other α S transgenic rodent models that do not show observable PD features throughout their lives [126,52,88]. The explanation for differences between various models remains unclear, but could be related to unpredictable effects related to genomic integration site, epigenetic modifications and transgene copy numbers. Future transgenic models will likely increasingly exploit ROSA26 locus targeted strategies to avoid those potential pitfalls [33].

In summary, many rodent models have been developed to study PD using genetic or toxin based strategies, but all have significant limitations. None of the available experimental rodent models recapitulate all the major pathologic and behavioral phenotypes of PD. Considering the role that aging plays in etiology and pathogenesis of PD, models that take these factors into consideration may address some of these deficiencies. As one suggestion, strategies that combine available genetic or toxin based strategies combined with induction of phagocytosis deficits may be worth exploring in future models of PD in rodents.

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Figure 1. Schema for role of proaggregant nuclear factors in α-synuclein aggregation

Filamentous αS aggregates can be rapidly formed in apoptotic neurons by interaction between αS and nuclear proaggregant factors associated with disruption of nuclear envelope. Such aggregates can be released from apoptotic bodies and taken up by surrounding healthy neurons as a potential seed for subsequent propagation.

Figure 2. Summary of cellular systems pathobiology in PD

Schematic hypothesis that PD rodent models with impairment of the four cell functional systems in neurons may form filamentous αS aggregates as potential seeds for propagation of αS pathology. Neurons with mitochondrial impairment (pathway 1) and ER stress/UPR (pathway 2) do not induce αS aggregation if apoptosis is not triggered (I.a), while neurons with impairment of autophagy-lysosomal (pathway 3) or ubiquitin proteasome system (pathway 4) normally induce αS aggregation (I.b) even without triggering apoptosis. If the impairment persists, apoptosis will be eventually triggered. In normal subjects with properly functioning immune system, apoptotic neurons are rapidly cleared by phagocytes (II); however, in PD apoptotic neurons may remain to form filamentous αS aggregates (III). Subsequently, they are released and taken up by surrounding healthy neurons as a potential seed for subsequent propagation (IV).

middle PD genetic loci and their cellular compartments

Table 1

Gene	O.R	P-value	Function	EC	PM	Nucl	Cyto	Skel	Mito	Lyso	Endo	Golgi	ER
<i>SNCA</i>	1.3	1.8 E-82	synaptic vesicle release	5	5	5	5	5	5	5		3	3
<i>MAPT</i>	0.8	6.1 E-49	microtubule associated protein		5	5	5	5					
<i>TMEM175</i>	1.3	6.0 E-41	endosome-lysosome potassium channel		3					5	5		
<i>ASH1L</i>	0.5	6.9 E-28	histone lysine N-methyltransferase	5		5						5	
<i>MCCCI</i>	0.8	5.5 E-22	mitochondrial enzyme				5		5				
<i>STK39</i>	1.2	1.7 E-20	kinase/cell stress response		3	5	5						
<i>LRRK2</i>	1.2	4.9 E-14	kinase/regulation of autophagy/lysosomes, Golgi & synaptic vesicle trafficking	5	4	5	5		5	5	5	5	5
<i>HLA-DQB1</i>	0.8	5.8 E-13	class II major histocompatibility complex		4 ₁								
<i>INPP5F</i>	1.8	1.29 E-11	inositol polyphosphate-5-phosphatase				3				5		

Select middle genetic loci with largest effect sizes from PDGene (showing their odds ratio for risk/protection for PD and their p-values) as well as the cellular compartments with which putative genes reside. O.R. = Odds ratio; EC = extracellular; PM = plasma membrane; Nucl = nucleus; Cyto = cytoplasm; Mito = mitochondrion; Lyso = lysosome; Endo = endosome; Golgi = Golgi apparatus; ER = endoplasmic reticulum. Color code = darker color indicates strength of evidence (5, 4 & 3) from *GeneCards@ Compartments*, which integrates data from literature curation, high-throughput microscopy-based screens, predictions from primary sequence, and automatic text mining

Table 2

Mitochondrial oxidative phosphorylation system in PD models

	Drug or gene modification	α S pathology	Neuronal loss		Striatal DA reduction	Motor behavior	Remarks
			SN	Other region			
Toxin	MPTP	No	Yes	No	Yes	Yes	Systematic administration
	6-OHDA	No	Yes	No	Yes	Yes	SN injection
	Paraquat/Maneb	Yes	Yes	No	Yes	Yes	Systematic administration
	Rotenone	Yes	Yes	No	Yes	Yes	Systematic administration
	Trichloroethylene	Yes	Yes	No	Yes	Yes	Systematic administration
	Homocysteine	Yes	Yes	No	Yes	Yes	SN injection
Genetic	PINK1 (KO)	No	Yes/No	No	Yes/No	Yes/No	Results vary in different animal models
	TFAM (KO)	No	Yes	No	Yes	Yes	Conditional knockout (DA only)
	Ndufs4 (KO)	No	No	No	Yes	No	
	Hspd1 (KO)	ND	ND	ND	ND	Yes	Heterozygous knock-out
	Aldh1a1/Aldh2 (KO)	ND	Yes	No	Yes	Yes	Knock-out of both isoforms
	HtrA2 (TM and TW)	ND	Yes (For TW only)	Yes	ND	Yes	
	Twinkle (TM)	ND	Yes	No	ND	Yes	
	dOTC (TM)	ND	Yes	No	Yes	Yes	

ND: not determined; KO: knockout; KD: knockdown; TM: Transgenic mutant gene; TW: Transgenic wildtype gene.

Table 3

Aumiddlehagy-lysosomal system in PD models

	Drug or gene modification	α S pathology	Neuronal loss		Striatal DA reduction	Motor behavior	Remarks
			SN	Other region			
Toxin	Conduitol- β -epoxide	Yes	No	Yes (Cortex)	ND	ND	Systematic administration
	Glucocerebrosidase (KO)	Yes	ND	Yes	ND	Yes	Conditional knockout
Genetics	Cathepsin D (KO)	Yes	ND	ND	ND	ND	
	ATP13A2 (KO)	No	No	No	ND	Yes	
	Atg7 (KO)	Yes	Yes	No	Yes	Yes	Conditional knockout
	Lrrk2 (MT)	No	Yes	No	Yes	Yes	
	Interferon- β (KO)	Yes	Yes	Yes	No	Yes	

ND: not determined; KO: knockout; KD: knockdown; TM: Transgenic mutant gene; TW: Transgenic wildtype gene.

Table 4

Ubiquitin-proteasome system in PD models

	Drug or gene modification	αS pathology	Neuronal loss		Striatal DA reduction	Motor behavior	Remarks
			SN	Other region			
Toxin	Lactacystin	Yes	Yes	No	Yes	Yes	SN injection
	PSI	Yes	Yes	ND	ND	Yes	Systematic administration
	MG-132	ND	Yes	No	Yes	No	SN injection
	Epoxomicin	ND	Yes	ND	Yes	Yes	Systematic administration
Genetics	PSMC1 (KO)	Yes	Yes	Yes	Yes	Yes	Conditional knockout
	Parkin (KO)	No	No	No	Yes	No	
	Parkin (TM)	Yes	Yes	No	Yes	Yes	Q311X, T240R mutant
	UCH-L1 (TM or KO)	No	Yes	No	Yes	Yes	

ND: not determined; KO: knockout; KD: knockdown; TM: Transgenic mutant gene; TW: Transgenic wildtype gene; PSI: Z-Ile-Glu(OtBu)-Ala-Leu-al.

Table 5

ER stress and UPR system in PD models

	Drug or gene modification	α S pathology	Neuronal loss		Striatal DA reduction	Motor behavior	Remarks
			SN	Other region			
Toxin	Tunicamycin	Yes	Yes	No	ND	Yes	SN injection
	ATF6a (KO)	No	Worse	No	ND	No	MPTP & probenecid injection
	GRP78 (KD)	Worse	Worse	No	Worse	No	α S expression
	ATF4 (TW)	No	Yes	No	Yes	Yes	rAAV expression in SN
Genetics							

ND: not determined; KO: knockout; KD: knockdown; TM: Transgenic mutant gene; TW: Transgenic wildtype gene.