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Commentary

The search for genetic mouse models of prodromal Parkinson's disease

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ABSTRACT

Parkinson's disease is characterized and diagnosed by bradykinetic motor symptoms caused by the loss of dopamine neurons in the substantia nigra. The pathological and non-motor behavioral changes that occur prior to degeneration are less well characterized, although changes in gait, olfaction and cognition have been recognized in familial Parkinson's disease subjects. Gene mutations associated familial Parkinson's disease give rise to mitochondrial changes, altered energy homeostasis and intracellular trafficking deficits, and these can be modeled in transgenic mice. Here we discuss the recent finding of prodromal behavioral disturbances in a PINK1 deficient mouse that manifest prior to dopaminergic cell death and correlate to 5-HT fiber losses and mitochondrial morphological changes. We discuss the representation of the PINK1 deficient mouse and other genetic models to accurately recapitulate early Parkinson's disease. Prodromal symptoms and underlying pathology modeled in mice and cell lines from human subjects may have wide implications for earlier diagnosis. Current and emerging therapies need to be tailored to target both early cognitive and late stage motor symptoms.

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Signs of prodromal Parkinson's disease

Parkinson's disease (PD) is a multisystem neurodegenerative disorder classically characterized by cardinal motor symptoms, including resting tremor, bradykinesia, freezing and postural instability. These behaviors occur when greater than 50% of the dopamine neurons of the substantia nigra (SN) are lost, and are currently the only features used for diagnosis for the idiopathic form of the disease (reviewed in Savitt et al., 2006).

PD patients often have additional widespread 'non-motor' problems originating beyond the basal ganglia, including gastrointestinal dysfunction, mood swings, proprioception abnormalities, sleeping pattern changes and psychiatric problems (Grinberg et al., 2010). It has now been established that psychiatric disturbances, gait and other symptoms precede motor dysfunction. In a recent retrospective analysis of 93 patients an average 7.6 different non-motor symptoms were recorded per patient, 10 years prior to diagnosis (Gaenslen et al., 2011). Further, within a five-year period before the onset of motor features of PD, a higher proportion of males were treated for anxiety and depression than in the general population (Jacob et al., 2010). The incidence of anxiety, sleep disturbance and depressive symptoms are correlated with impaired olfactory discrimination (Morley and Duda, 2011; Morley et al., 2011; Siderowf et al., 2012). A specific association with executive function, speed of information processing, and verbal fluency with olfactory deficits has also been found in early stage patients (Parrao et al., 2012). Gait disturbances also manifest long before other motor symptoms in PD patients, decreased stride length and irregular stepping to metronome timing have been observed in non-medicated individuals (Ebersbach et al., 1999a, 1999b).

Many of these prodromal and early disturbances are likely to arise from dysregulation of specific non-nigral and 5-HT specific nuclei of the brainstem, (Grinberg et al., 2010; Jellinger, 2011), which represents the initial region of pathology according to Braak staging (Braak et al., 2000, 2003). However, this topological and chronological progression through nuclei may be oversimplified, as the model cannot account for all prodromal abnormalities. Recent studies have reinforced 5-HT neuron dysfunction as an initial step in PD pathogenesis. A decrease in SERT binding was seen in the orbitofrontal cortex, caudate–putamen and midbrain of early stage patients (Guttman et al., 2007). PET scans have also been used effectively to correlate depression, tremor, weight fluctuations and visual problems with changes in SERT and 5-HT_{1A}/5-HT_{2B} receptors (reviewed in Politis and Loane, 2011).

PD is not typically considered to be a strongly genetic disease, and genetic variants make up only about 5% of all cases. However, relatively rare genetic variants can be exploited to explore early PD symptomatology, where diagnosis is determined by genetic test. Mutations in specific genes which cause mitochondrial dysregulation and energy disturbances have in many cases been conclusively shown to cause PD. These genes code for α-synuclein, parkin, leucine-rich repeat kinase 2 (LRRK2),

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PTEN-induced putative kinase 1 (PINK1), DJ-1 and ATP13A2 (reviewed in Nuytemans et al., 2010). There are over 30 recorded mutations of the PINK1 gene alone, many causing autosomal recessive PD with a robust phenotype (Ibanez et al., 2006). PINK1 mutation carriers display atrophy of hippocampus, parahippocampus, frontal cortex and cingulate (Reetz et al., 2008), confirming the notion of widespread dysfunction. PINK-1 homozygous mutations are associated with early onset PD and affected individuals have a slow disease progression (Bonifati et al., 2005). The intracellular changes that proceed cell death in PD are plentiful, yet distinguishing causative changes is difficult; genetic forms of early PD provide a platform on which to study these mechanisms. It is hoped that a greater insight into mechanisms of early PD will be found after the characterization of early stage and slow disease progression models, which show extra-striatal and nigral changes.

Modeling of prodromal symptomatology in PD

Robust measures of cognition have thus far been tested on MPTP and 6-OHDA models, representing late stage PD (reviewed in Dunnett and Lelos, 2010; Fox and Brotchie, 2010). Nevertheless, it is necessary to distinguish between cognitive behavioral aspects that are present at the prodromal stage, those that are present throughout the disease course, and those that only manifest specifically in late stage disease. Partial dopamine cell depletion produces cognitive, sensory-motor and motor symptoms (Chagniel et al., 2012; Courtiere et al., 2011; Dowd and Dunnett, 2005a, 2005b; Dowd et al., 2005; Dunnett et al., 1987; Fornaguera et al., 1994; Heuer et al., 2012; Smith et al., 2012); however, there are few models of early PD that show symptomatology that are the result of early neurotransmitter disturbances in other basal ganglia circuits that precede cell death entirely. Parkin knock out, DJ-1-deficient and α synuclein overexpressing mice all show subtle parkinsonian phenotypes including gait disturbance, olfactory dysfunction, anxiety, impaired exploration and circadian rhythm changes (Chandran et al., 2008; Fleming et al., 2008; Rodriguez-Navarro et al., 2007; Ubeda-Banon et al., 2012; Zhu et al., 2007), recapitulating early PD. At the early stages of the disease in α-synuclein over-expressing mice, α-synuclein depositions are more widespread in the olfactory nucleus, olfactory tubercle, piriform cortex and lateral entorhinal cortex than in the SN (Ubeda-Banon et al., 2012), indicating that pathways involved in these earlier symptoms are the most vulnerable to pathophysiological changes. The neuropathological mechanisms for these prodromal symptoms are currently lacking. It has recently been shown that aged PINK1 deficient mice show prodromal deficits, a preferential loss of serotonin (5-HT) innervation and a minor loss of dopamine cells (Glasl et al., 2012), which may be critical to symptoms of this nature. DJ-1 deficient mice display less dopamine neurons in the ventral tegmental area (VTA) at late stage and display a diminished rearing response (Pham et al., 2010). In contrast, LRRK2 and α-synuclein overexpressing mice initially have increases in dopamine release and hyperactivity (Li et al., 2010; Magen et al., 2012; Melrose et al., 2010), with specific enhancement of acetylcholine in the latter model (reviewed in Magen and Chesselet, 2010). Parkin null mice show a loss of neurons of the locus coeruleus, associated with forebrain norepinephrine depletion and a reduced startle response (Von Coelln et al., 2004). In addition, the combination of three recessive mutations in a single mouse model does not have a cumulative effect to cause dopaminergic cell death, and no cells were lost in either the SN or locus coeruleus at 24 months (Kitada et al., 2009b). Equally, reduced dopamine release and post-synaptic plasticity abnormalities were no-more severe than that reported in PINK1 deficient mice (Kitada et al., 2007).

It has recently been shown that the PINK1 mouse model had clear prodromal symptoms, including olfactory and gait disturbances (Glasl et al., 2012), enabling the discovery of dopamine and non-dopamine mechanistic clues, which could impact on diagnosis and treatment strategies. Firstly it is important to note that the PINK1 deficient mouse has and early onset and slow disease progression mimicking the human form (Bonifati et al., 2005) and also recapitulates well-documented deficits in humans. Patients carrying mutations in PINK1 and Parkin have clear deficits on the Pennsylvania Smell discrimination test (Eggers et al., 2010; Ferraris et al., 2009; Kertelge et al., 2010), non-motor deficits (Ephraty et al., 2007; Reetz et al., 2008) and gait abnormalities (Atsumi et al., 2006; Ephraty et al., 2007). Further clues into the mechanism of these symptoms may be found using induced pluripotent stem cells (iPSCs) differentiated towards neuronal subtypes taken from effected mutation carrying individuals, thereby representing a means of studying pathology in vitro (Piccoli et al., 2008; Sanchez-Danes et al., 2012). LRRK2 and sporadic iPSCs differentiated toward a dopaminergic phenotype show accumulation of autophagic vacuoles and a reduced number of neurites in comparison to healthy subject controls (Sanchez-Danes et al., 2012). Although cell death in these models is limited, the cell stress caused by the mutations, make them extremely vulnerable to additional toxins that may otherwise be sub-threshold in healthy models and cell lines. Certainly sub-threshold doses of 6-OHDA can cause dopaminergic cell death in vivo, only if previously primed with lipopolysaccharide (bacterial mimic) or polyinosinic:polycytidylic acid (viral mimic) (Deleidi et al., 2010; Koprich et al., 2008). In the same manner, transgenic mice and patient-derived iPSCs from familial PD patients may have a heightened vulnerability to neurotoxins and endotoxins, which may trigger neurodegeneration, disease progression and the presence of robust motor deficits. DJ-1 deficient mice have increased vulnerability to oxidative stress (Kim et al., 2005), which can be directly translated in vitro (Martinat et al., 2004). Peripheral lipopolysaccharide injections into PINK1 −/− mice cause a greater increase in pro-inflammatory cytokines IL-1β, IL-12 and IL-10 in the striatum, compared to wild-type littermate controls (Akundi et al., 2011). Enhanced inflammatory responses of mouse models in which regular mitochondrial function is already compromised may trigger neurodegeneration and motor symptom onset if the right dose is given. It would be interesting to monitor how cognitive, gait and olfaction symptoms progress following increased cell death in the same model. A limitation of the current model, without initiating cell death by additional means, is that robust cell death did not occur even at late stage and therefore if the prodromal period is present until death, how well does this model the prodromal phase alone? Cell death and motor features are associated with PINK1 mutations at late stage in the human form (Bonifati et al., 2005). Therefore prodromal comparisons in the PINK1 deficient mouse should be made on behavioral and, neuronal and intracellular phenotypes, rather than time points in disease progression. Furthermore, PINK1 knockdown mice may not show all the dysfunction that maybe caused by mutations of the gene, as some deficits are likely to be caused by gain-of-function mechanisms.

Validating the PINK1 model is problematic, as no autopsies have been reported thus far. Further, it will be extremely rare to examine the brain of an individual with a PINK1 mutation that may die of other non-PD related causes, prior to robust motor symptom onset, which may truly represent genetic prodromal PD.

Mitochondrial dysfunction

The question of whether there is an initial, cell-specific pathway at fault to cause neuronal changes that lead to olfactory function, gait changes and neuropsychiatric problems in early PD is beginning to be answered. PINK1, parkin and DJ-1 genes can translocate to the mitochondria and other organelles to influence their function. PINK1 is a highly conserved gene, and encodes a protein containing a mitochondrial-binding motif (Valente et al., 2004a, 2004b), localized on the inner and outer mitochondrial membranes. Under normal conditions, PINK1 is likely to promote mitochondrial fission by interacting with mitochondrial morphology machinery (reviewed in Yang and Lu, 2009). The consequences of this to the normal cell are twofold: firstly, mitochondrial fission would cause movement of the mitochondria to the synapse, thereby supplying energy for function and integrity; secondly, it would promote pro-survival mechanisms in the cell, i.e. preservation of mitochondrial

DNA and reduction in oxidative stress (reviewed by Perez-Pinzon et al., 2012). PINK1 mutations in cultured neurons from PINK1 −/− mice are confined to the kinase domain, yet cause impaired mitochondrial membrane potentials and an inefficiency to inhibit the formation of reactive oxygen species (Wang et al., 2011a). PINK1 mutations also cause a reduction in the action of electron transport chain enzymes I and V, and reduced ATP synthesis (Liu et al., 2011; Wang et al., 2011c). These mitochondrial dynamics are directly related to mitochondrial function and morphology. Fission and fusion properties of mitochondria are changed with mutant forms of PINK1 in vitro, such that an enhancement in fusion and/or decrease in fission prevails (reviewed Yang and Lu, 2009).

The PINK1 −/− mouse model of early PD shows robust changes in mitochondrial morphology and a reduction in small fragmented subtypes, indicative of enhanced fusion and/or reduction in fission (Glasl et al., 2012). Mitochondrial fission can be enhanced by overexpressing the GTPase dynamin related protein-1 to rescue mitochondrial homeostasis in a *drosophila* model of PINK1 deficiency (Liu et al., 2011). Similar metabolic disturbances have been reported from other mutations associated with familial PD (reviewed in Cardoso, 2011), yet there has been little characterization in animal models. Although metabolic deficits are present at the prodromal phase, the later preferential loss of dopaminergic A9 neurons of the SN pars compacta (SNc), compared to A10 neurons of the VTA, may also stem from mitochondrial-related mechanisms. Mitochondria in SNc neurons occupy 40% less space that those of the VTA and mitochondria are smaller in size compared to other cell types (Liang et al., 2007), which may make them more vulnerable to other cellular insults. Prior to death, reduction in the number of mitochondria, lack of axonal transport of remaining mitochondria and lowered ATP supply is directly related to the loss of synapses and spines (Li et al., 2004), which may account for signaling problems and non-motor symptoms. In accordance cognitive decline in Alzheimer's disease models is related to synaptic clearance by deficits in energy dependent mechanisms (Calkins et al., 2011).

A fundamental question that remains is whether oxidative damage, mitochondrial fission/fusion imbalances and morphology changes also occur in sporadic cases of PD, and, if so, does this contribute to prodromal symptoms. Patient-specific iPSCs from familial and idiopathic PD patients show similar metabolic disturbances and mitochondrial changes (Sanchez-Danes et al., 2012). Altered energy homeostasis is likely to be a primary event in several pathways and systems to cause prodromal symptoms in PD. Similar correlations have recently been made in experiments modeling Huntington's disease in transgenic mice. Mitochondrial fragmentation and motility deficits are seen in the YAC128 mouse model at 6 months of age at which no robust motor deficits or cell death is observed (Song et al., 2011), yet cognitive deficits in learning and set shifting paradigms are apparent (Brooks et al., 2011a, 2011b).

5-HT dependent mechanisms for prodromal symptoms

Psychiatric problems such as sleep disturbance and depression have long been associated with the 5-HT system (reviewed in Fox et al., 2010). The recent paper by Glasl and colleges also implicated the 5-HT system in olfactory dysfunction as the result of PINK1 deficiency (Glasl et al., 2012). Although many other investigators using genetic models convey the prodromal aspects of the disease, the 5-HT system is often overlooked, even though its dysfunction is key to symptomology in early PD patients (reviewed in Politis and Loane, 2011). Olfactory perception and/or processing deficits may relate to the loss of 5-HT innervation directly, or may precede 5-HT loss. In the neonatal rat it has been recognized that the depletion 5-HT levels by 53% causes deficits in olfactory recognition, such that natural orientation toward the mother ceases (Dulcy et al., 2010). It has been determined that 5-HT specifically modulates glomerular cells, where odor information is initially processed. Excitation of 5-HT_{2A} receptors on external tufted cells causes their depolarization by a channel-mediated inward current (Liu et al., 2012). Therefore 5-HT innervation may co-ordinate the frequential bursting of these neurons with the timing frequency of exploratory smelling of the environment to facilitate the coding of smells before they are processed by higher centers (Liu et al., 2012). Thus this deficit found in humans and the PINK1 −/− mouse may not be neuropsychiatric in origin but arise early in the sensory coding process. 5-HT sprouting is closely regulated by BDNF and the TrkB receptors; therefore, lack of olfactory innervation may occur via an indirect consequence of the lack of modulation of neurotrophic support on this system. At this stage it cannot be ruled out that the 5-HT innervation losses are a secondary event to the death of mitral cells. Mitral cell loss in the olfactory bulb and misrouting of olfactory projection fibers occurs in the general population with aging (Hoogland et al., 2003), and therefore defective mitral cells in patients with PD and aged PINK-1 knock down mice may contribute to other pathological processes, such that the 'combined hit' leads to mitral cell death. Certainly olfactory deficits in the PINK1 −/− mice were only noted in aged mice (27 months; Glasl et al., 2012). Loss of bulbar projection cells alone causes a decrease in 5-HT innervation in mice, without reduction of the numbers of 5-HT cell bodies in the raphé nucleus (Gomez et al., 2012).

Although preferential intracellular abnormalities clearly occur in 5-HT and dopaminergic neurons that contain recessive PD-linked mutations (Glasl et al., 2012), the mutated protein likely has an effect on all cells. Robust mitochondrial morphological changes were seen in cultured hippocampal neurons derived from the PINK1 −/− mouse (Glasl et al., 2012). An interesting notion is that the mitochondrial disturbances and subsequent oxidative stress characterized here cause the preferential damage of vulnerable enzymes such as tryptophan hydroxylase 2 (TPH2) in 5-HT neurons. It has been shown in vitro that cellular stress leads to an increase in the propensity of TPH2 to form insoluble membrane bound aggregates, effecting 5-HT biogenesis (Kuhn et al., 2011). The vulnerability of TPH2 arises from the capacity of any of the cysteine residues to cross-link upon oxidation, causing misfolding of the protein, such that the catalytic site no longer functions. The consequence of this particular protein misfolding is likely to have broader implications for the cell, over and above the primary biogenesis of 5-HT. TPH2 phosphorylation associates with the cytoskeleton protein tubulin (Yamauchi and Fujisawa, 1984), it is found ubiquitously throughout the cell soma and dendrites, and it is a major component of intracellular trafficking (Joh et al., 1975). Disruption of protein trafficking is highly associated with cellular dysfunction and death in neurodegenerative disease (reviewed in Burke, 1990). It is possible that synaptic dysfunction and the autophagic system occur as a secondary event to TPH2 oxidation in 5-HT neurons, to cause prodromal symptoms.

Dopamine and cholinergic dependent dysregulation in early PD

Gait problems associated with early PD are thought to be partly driven by deficits in executive function, caused by alterations in prefrontal and anterior cingulate cortex processing (Malouin et al., 2003), which are innervated extensively by dopamine, as opposed to the classical hypothesis that gait is purely an automated motor activity (Yogev et al., 2005). PD patients have attentional deficits when performing additional tasks while walking (Bond and Morris, 2000; Camicioli et al., 1998; Plotnik et al., 2011; Yogev et al., 2005), regardless of the use of anti-parkinsonian medication (Camicioli et al., 1998). PD patients appear to have underlying deficits in prioritization of tasks. Certainly, dendritic deficits, dopamine turnover changes and synaptic dysfunction precede cell death in dopamine cells (Chung et al., 2009), which may account for such observations. Dopamine dysfunction in the dorsal fronto-striatal pathway may underlay gait and other cognitive problems, as these circuits tightly control motivation and executive function (Lodge, 2011; Ravizza et al., 2012). Cholinergic innervation has been associated with neuropsychiatric problems and may specifically exacerbate gait and postural instability reviewed in (reviewed in Yarnall et al., 2011). Sleep disturbances in PD have also been linked to cholinergic denervation (Kotagal et al., 2012).

The lack of dopamine cell loss in early PD models does not protect from the dysregulation of medium spiny neurons in some instances, as the reduction of dopamine release from synaptic vesicles in the striatum and corticostriatal plasticity abnormalities has been shown (Kitada et al., 2007), which may contribute and exacerbate early phenotypic disturbances. However it is unclear whether dopaminergic changes can be translated to the PINK1 −/− knock down mouse as striatal dopamine measurements were not conducted past the 6 month time point and hence changes in the corticostriatal pathway may have been missed. Nevertheless, striatal plasticity deficits have been seen in other PINK1 −/−, Parkin deficient and α-synuclein overexpressing mouse models (Kitada et al., 2007, 2009a; Tozzi et al., 2011) and this represents an interesting area of investigation for future studies in other genetic PD models. Abnormalities in corticostriatal connectivity (Joshi et al., 2009) emerge at the same time as cognitive deficits in other rodent models of neurodegenerative diseases (Brooks et al., 2011a, 2011b; Fielding et al., 2011; Joshi et al., 2009; Trueman et al., 2011), and motor deficits in models of late stage PD (Centonze et al., 1999; Picconi et al., 2003), yet has not yet been yet been associated with prodromal symptoms of PD.

Early diagnosis benefits and clinical perspectives

Prodromal diagnosis cannot be made on psychiatric deficits alone. However, it is hopeful that continued research in this area will give rise to new behavioral 'biomarkers' of early PD. This may be critical for the efficiency of past and emerging neuroprotective and anti-inflammatory strategies. Those implemented after diagnosis, based on the manifestation of motor symptoms, have thus far shown little efficacy in clinical trials (reviewed in Whitton, 2010), but may have enhanced neuro-protective and beneficial effects at the prodromal stage. Diagnosis of early behavioral changes in PD may therefore enhance the efficiency of interventions and pharmacotherapy. Clear changes in the structure of the olfactory bulb, olfactory sulcus and anterior olfactory region can be found in PD patients by diffusion tensor and magnetic resonance imaging (Rolheiser et al., 2011; Wang et al., 2011b). Mild stages in gait have been found in patients using biometric engineering methods and treadmills (Barth et al., 2011; Park et al., 2011). These are promising strategies but efforts should also be made to measure executive function and attention-deficit gait components. A strategy which may unfold into the clinical setting is the dual testing of gait with other cognitive tasks to determine executive function deficits. Verbal fluency, walking with a tray, reciting of words and button pressing have all been used effectively to hinder gait in PD patients, in contrast to good synchrony in healthy controls (Bond and Morris, 2000; Camicioli et al., 1998; Plotnik et al., 2011; Yogev et al., 2005). A comparative study of gait in PD patients, cerebella ataxia, and subcortical arteriosclerotic encephalopathy, highlighted that PD patients had no problems changing the velocity of walking, unlike other groups (Ebersbach et al., 1999b), so general tests for gait across diseases should be avoided. It can be assumed that new diagnostic strategies involving a combination of olfactory imaging, objective measurements of gait (with executive function testing paradigms) and neuropsychiatric tests will emerge in the near future to identify prodromal PD.

It is controversial whether current and emerging therapeutics in PD have any effect on cognition. L-DOPA has little impact on cognition based on classic frontal tests such as the Wisconsin Card Sorting Task (Jubault et al., 2009), and is typically given many years after cognitive symptoms first become manifest, although some improvement in cognition by L-DOPA may be found with patients who have high cognitive impairment at baseline (Mattis et al., 2011). Bilateral STN stimulation improves cerebral blood flow to the dorsal premotor cortex; parahippocampal gyrus and lateral cerebellum and decreases blood flow to the orbito-prefrontal cortex and supplementary motor areas. These changes are associated with improvement in learning when off medication (Mure et al., 2012), and are not seen by dopamine pharmacotherapy alone. In contrast, there is a wealth of evidence to suggest that deep brain stimulation of either GPi or STN may actually worsen cognition, or that initial improvements are transient in expression (Alberts et al., 2008; Mikos et al., 2011; Okun et al., 2009; Zahodne et al., 2011). Improvement of gait may also be seen upon stimulation of the pedunculopontine nucleus (Thevathasan et al., 2011); however, these effects were only achieved by a reduction of freezing. It is hoped that synaptic connections and dopaminergic reinnervation caused by the transplantation of fetal dopamine cells into the caudate putamen may cause cognitive improvements; however, initial studies indicate that cognition is only improved marginally (Sass et al., 1995). 5-HT losses, continuing even at latter stages, are increasingly coming to light, and represent a problem which currently cannot be treated by otherwise promising cell-based therapies (Politis et al., 2012). There have been recent pre-clinical data to suggest that stem cells over-expressing choline acetyltransferase improve memory in a kainic acid memory deficit model (Park et al., 2012). The migratory aspects of stem cells and their bioengineering potential makes them a key candidate to treat both motor and non-motor symptoms in PD in the future.

Early intervention strategies could be focused on reducing oxidative stress, mitochondria fission/fusion problems to normalize energy metabolism and hence vesicle trafficking, and synapse maintenance to broadly manipulate dysregulation throughout the brain, impacting on both neuropsychiatric and motor disturbances. The kinase pathway, and its specific targets such as Jun N-terminal kinase and Akt pathways are promising targets for oxidative therapeutics (Greggio et al., 2007), in which preclinical research would be well matched to be carried out the PINK1 −/− and LRRK2 −/− mouse models. This may have significant implications for the wider PD population, as similar dysfunction is observed in idiopathic patient-derived iPSCs (Sanchez-Danes et al., 2012). Interestingly, the licensed and popular dopamine agonist, pramipexole, diminishes some non-motor symptoms and cognitive deficits in mid-late stage PD (Costa et al., 2009; Levin et al., 2009), effects that may partly stem from the antioxidant properties of the drug, decreasing the amount of harmful mitochondrial reactive oxygen species (Ferrari-Toninelli et al., 2010). Coenzyme Q10, creatine and other novel antioxidants have been shown to decrease lipid peroxidation and α-synuclein deposits in MPTP treated mice (Yang et al., 2005, 2009); however, dosing disparities between tolerance and optimal activity may represent a problem translating these treatments to the clinic. Nevertheless, gene therapy approaches that target mitochondrial specific transcription factors to intracellular mitochondria could be utilized to improve cell respiration and mitochondrial movement velocities. This strategy has shown promising results in vitro (Keeney et al., 2009) and could be translated to prodromal PD models by use of appropriate viral vectors. Oxidative stress in peripheral tissues may also be utilized as a biomarker for early PD to aid diagnosis. At late stage oxidative stress can be measured in isolated lymphocytes from blood samples in idiopathic and familial PD patients (Hoepken et al., 2007; Prigione et al., 2009), but it remains unclear how early this can be detected and what the threshold levels of key proteins will be.

In addition to the causative familial mutations, other gene mutations such as glucocerebrosidase (GBA), the protein of which is involved in lysosomal storage, have a higher risk of developing PD (Lill et al., 2012). GBA mutation carriers had equivalent early deficits in mini-mental state examination tests, memory and visuospatial tests compared to those with parkin and LRRK2 mutations (Alcalay et al., 2010, 2012), which provides the first evidence of relevance of cognition to intracellular lysosomal storage capacity.

Conclusions

Cognitive disturbances are likely to occur prior to cell death as the result of altered energy metabolism, trafficking, vesicle release, neurotransmitter level reduction and fiber innervation, summarized in Fig. 1. The combined evaluation of cognitive, olfactory, gait and other non-motor features of prodromal PD may provide a means for

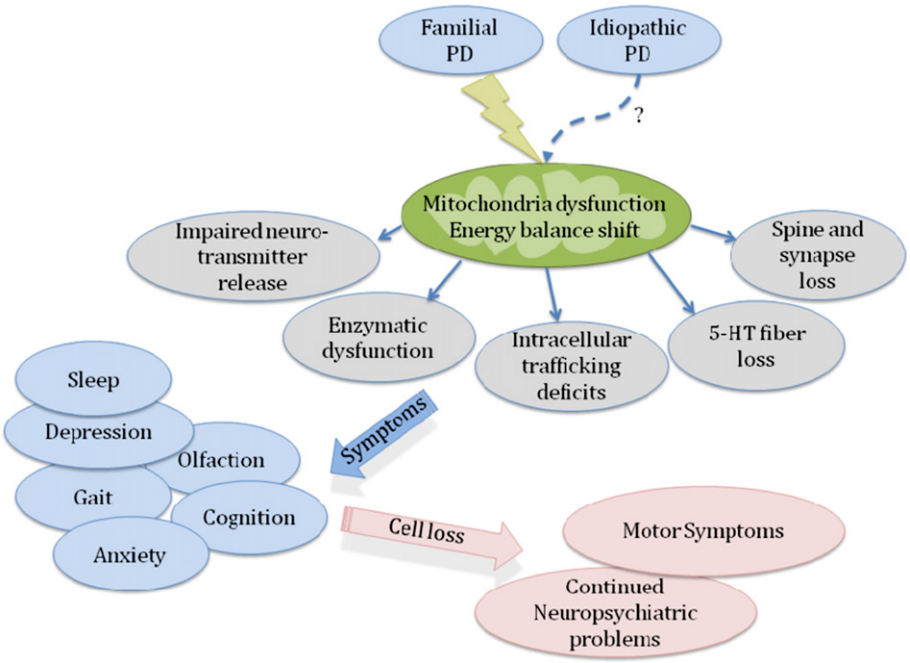

Fig. 1. The cascade of intracellular events which lead to early neuro-psychiatric, motor and olfactory deficits in prodromal PD.

earlier diagnosis of the familial form, at risk mutation carriers and for other neurodegenerative diseases. Greater mechanistic insights into cognitive disturbances may also lead to new and/or combined motor-psychiatric therapeutic strategies.

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