

New insights on Parkinson's disease genes: the link between mitochondria impairment and neuroinflammation

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Abstract Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor disturbances, appearance of Lewy bodies and dopaminergic neuronal death. The etiology of PD is unknown, although aging and neurotoxins are established risk factors. The activation of glial cells in the brain is the first defense mechanism against pathological events in neurodegenerative diseases, and neuroinflammation is suggested to play an important role in PD disease progression leading to dopaminergic neuronal degeneration. Gene mutations in several PD-related genes may affect up to 15 % of the PD cases. These gene mutations can cause either loss or gain of function in their respective proteins leading to autosomal recessive and autosomal dominant PD, respectively. Most of the identified genes play a role in mitochondrial activity and integrity, and this was demonstrated mostly in neuronal cells. In this review, we aim to describe the link between PD-related genes, which are involved in mitochondrial function, and deleterious neuroinflammation.

Keywords Inflammation · PD genes · Microglia · Astrocytes

Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by resting tremor, muscular rigidity and gait disturbances (Fahn et al. 1998; Mayeux 2003), affecting more than 1 % individuals over 55 years old and more than 3 % of those over the age of 75 years (Mayeux 2003). PD pathology is characterized by the progressive loss of dopaminergic neurons in the substantia nigra (SN) pars compacta and their termini in the dorsal striatum (Thomas 2009). The pathological hallmark of PD is the presence of intracellular inclusions of aggregated α -synuclein known as Lewy bodies (Croisier et al. 2005; Spillantini et al. 1998). The etiology of PD is unknown, although neurotoxins and older age are known risk factors. In recent years, several genes and susceptibility factors have been identified, implicating abnormal handling of misfolded proteins by the autophagy–lysosomal and ubiquitin–proteasome systems, mitochondrial and lysosomal dysfunctions, increased oxidative stress and other pathogenic dysfunctions, as contributing factors for PD (Lesage and Brice 2009). Neuroinflammatory mechanisms might contribute to the cascade of events leading to neuronal degeneration (Hirsch and Hunot 2009), and several reports suggest an important role of neuroinflammation in triggering dopaminergic neuronal death in PD (Hirsch 2000; Jenner 2003; Koutsilieri et al. 2002).

Interestingly, while the cause of sporadic PD is still unclear, the percent of gene mutation in PD can reach to approximately 15 % with genes still being identified (Wood-Kaczmar et al. 2006; Xiromerisiou et al. 2010). To date, 17 genes have been identified as related to PD (Singleton et al. 2013) including α -synuclein and several mitochondrial genes (see Fig. 1), and 10–25 % of patients with early onset (before age 50) PD carry

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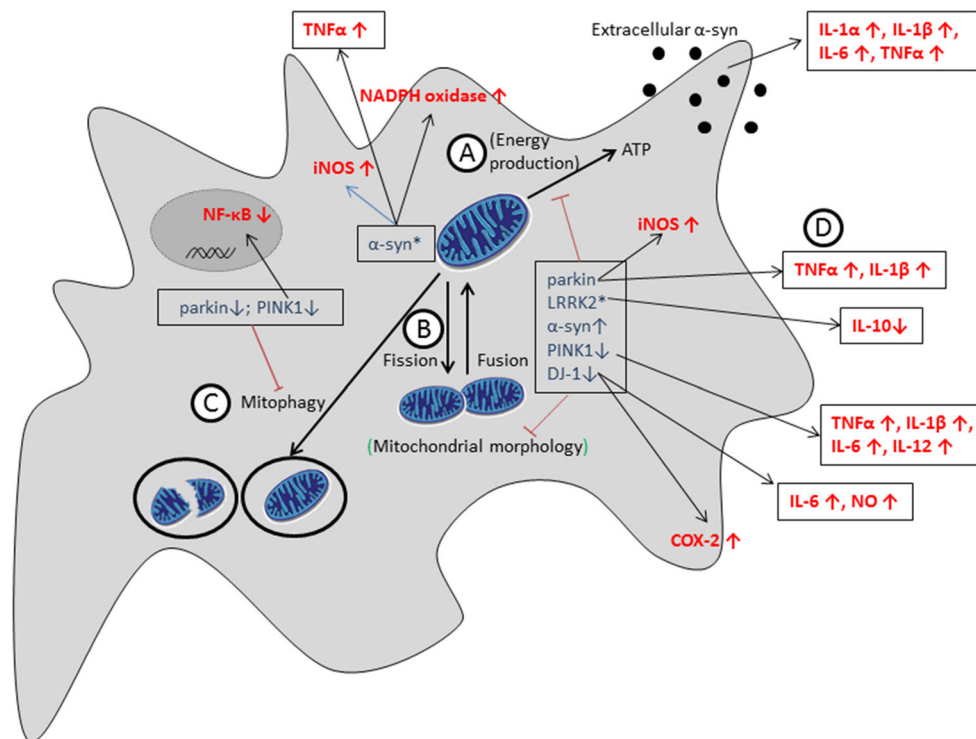


Fig. 1 PD gene mutations impair mitochondrial activity and might increase pro-inflammatory response. **A** Mitochondrial energy production is impaired by α Syn over-expression, by down-regulation or loss of function of parkin, PINK1 or DJ-1, and by expression of mutant LRRK2. **B** Mitochondrial morphology, controlled by fission and fusion, is disrupted by α Syn over-expression; by down-regulation or loss of function of parkin or PINK1; and by expression of mutant

LRRK2 or over-expression of wild-type LRRK2. **C** Turnover of mitochondria through mitophagy is affected by down-regulation or loss of function of parkin and PINK1. **D** Expression of pro-inflammatory cytokines, such as TNF α , IL-1 β and IL-6 as well as oxidative stress markers, such as iNOS, NO and NADPH oxidase, due to differential expression of PD-related genes, is marked with arrows to the respective genes

mutations in these genes. These gene mutations can cause either loss or gain of function in their respective proteins, and can result in autosomal recessive and autosomal dominant PD (Wood-Kaczmar et al. 2006; Xiomerisiou et al. 2010).

In this review, we will address evidence of the involvement of mitochondria and neuroinflammation in PD pathology. Furthermore, we will discuss the different genes identified as causing genetic forms of PD, and how they affect mitochondrial activity and inflammation in the CNS. Finally, we will describe links between mitochondrial activity and neuroinflammation, as a result of gene mutation, in the pathology of PD.

Mitochondria and reactive oxygen species in PD

Mitochondria are the organelles that constitute a cell's major source of adenosine triphosphate (ATP) production, the chemical energy of the cell. Within mitochondria, ATP is produced via the action of four respiratory complexes (I, II, III, IV) in the matrix, and ATP synthase in the mitochondrial inner membrane (Haelterman et al. 2014).

Mitochondrial mechanisms have been implicated in a variety of human disorders (Vafai and Mootha 2012) including PD (Haelterman et al. 2014).

Animal models for PD are usually based on administration of toxins to produce PD-related pathology and symptomatology. A common feature of all toxin-induced models is their ability to induce mitochondrial damage and to cause cell death in dopaminergic neuronal cells that reflect what is seen in PD (Blesa et al. 2012). This first led to focusing the research on mitochondrial dysfunction in PD.

Defects in mitochondrial complex-I lead to increased free radical stress and reactive oxygen species (ROS), and increased neuronal vulnerability to glutamate excitotoxicity (Sherer et al. 2002). Studies of human post-mortem brains indicate that ROS and abnormal complex-I function play an important role in the pathogenesis of PD (Orth and Schapira 2002; Schapira et al. 1998). The activity of complex-I, a major component of the electron transport chain, is decreased in the substantia nigra (Schapira et al. 1990) and frontal cortex (Parker et al. 2008) in patients with PD.

Oxidative damage to lipids, proteins and DNA (Dexter et al. 1989; Zhang et al. 1999) as a result of mitochondrial

dysfunction, as well as a decrease in the levels of antioxidant glutathione (Perry and Yong 1986), has been detected in autopsy tissue from the brains of individuals with PD. This abnormality is predicted to render cells more vulnerable to apoptosis, and possibly contributes to the dysfunction and eventual death of cells during the PD disease process (Henchcliffe and Beal 2008).

There are also findings that provide a link between oxidative damage and formation of the Lewy body protein aggregates that are characteristic of PD, as oxidative damage induces α Syn aggregation and impairs proteasomal ubiquitination and degradation of proteins (Jenner 2003). Oxidative stress may cause the oxidation of dopamine to the quinone products, which are believed to be damaging to brain mitochondria (Jenner 2003; Koutsilieri et al. 2002; McGeer and McGeer 2008), suggesting positive feedback of damaged mitochondria, oxidative stress and quinone production, resulting in PD pathology and dopaminergic cell death.

Inflammation and Parkinson's disease

Neuroinflammatory mechanisms might contribute to the cascade of events leading to neuronal degeneration (Hirsch and Hunot 2009). Several reports suggest the important role of neuroinflammation in triggering dopaminergic neuronal death in PD (Hirsch 2000; Jenner 2003; Koutsilieri et al. 2002).

There is evidence of elevated levels of proinflammatory cytokines, such as interleukin- 1β (IL- 1β), tumor necrosis factor- α (TNF α) and IL-6, which leads to increased production of inducible nitric oxide synthase (iNOS), secretion of nitric oxide (NO), oxidative stress, neuronal stress, and further neuronal dysfunction and death in postmortem PD brains (McGeer et al. 1988; Mogi et al. 1994a, b) and PD models (Hirsch and Hunot 2009). As key components of the innate immune response in the brain, glial cells, and in particular microglia and astrocytes, can function as a double-edged sword, with both neurotoxic and neurotrophic effects (Block et al. 2007).

Most proposed etiologies of PD, including environmental toxins (Sherer et al. 2003), and bacterial and viral exposure (Carvey et al. 2006), induce inflammatory activation. For example, lipopolysaccharide (LPS), endotoxin from gram-negative bacteria, is a potent inducer of inflammation and presents diverse effects on microglia and astrocytes (Benveniste 1992). Interestingly, inflammatory activation by intracerebral LPS administration into the cortex, hippocampus, striatum or SN of mice and rats enhances the death of only dopaminergic neurons in the SN (Castano et al. 1998; Herrera et al. 2000), which is in

accordance with the inflammatory response reported in PD. In addition to infectious responses, non-infectious inflammatory response were also linked to PD. High mobility group box 1 (HMGB1), a type of damage-associated molecular pattern molecule (DAMP), is increased following exposure of microglia to several PD-inducing toxins, such as rotenone and toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), (Gao et al. 2011b). HMGB1 was also shown to create a non-infectious inflammatory response, through secretion and paracrine activation of TLRs.

It was recently shown that human microglia express dopamine receptors (Mastroeni et al. 2009) and exposure to dopamine may increase secretion of proinflammatory cytokines (Rogers et al. 2007; Trudler et al. 2014). Indeed, increase sensitivity of microglia to dopamine was previously suggested to trigger neurotoxicity to dopaminergic neurons (Trudler et al. 2014). Activated microglia can produce large amounts of superoxide radicals, which may be the major source of the oxidative stress responsible for dopaminergic cell death in PD (McGeer and McGeer 2008).

Astrocytes maintain brain plasticity and protect the brain from injuries (Sofroniew 2005) by secreting protective neurotrophic factors and toxic inflammatory mediators (Segev-Amzaleg et al. 2013). In most cases of PD, there is an elevation in glial fibrillary acidic protein (GFAP) expression that marked astrocytes activation (Cabezas et al. 2013). In experimental models of the toxin such as MPTP, there is marked increase in proliferation and activation of astrocytes in the striatum and substantia nigra (Kohutnicka et al. 1998). Astrocytes activation may mediate neuroinflammatory response towards dopaminergic neurons by secretion of proinflammatory cytokines, generation of ROS and lipid peroxidation (Cabezas et al. 2013). This astrocytic activation was also shown to be accompanied by increased expression of nuclear factor erythroid 2 [NF-E2]-related factor 2 (NRF2) and Wnt1, which exerted neuroprotective effects on dopaminergic neurons (Chen et al. 2009; L'Episcopo et al. 2011). This may suggest that astrocytes activation may also play a neuroprotective role in PD.

Peripheral immune cells such as T-cells also appear to play a role in the pathology of PD. In PD patients' brains, there is an increase in CD4+ and CD8+ T-cells, which appears to be specific to the substantia nigra (Brochard et al. 2009). MPTP model in CD4 knockout resulted in higher survival of dopaminergic neurons and markedly reduced activation of microglia (Brochard et al. 2009). In this review, however, we will focus on the role of CNS resident cells in mediating inflammatory processes in PD.

Genetic links between mitochondrial activity and neuroinflammation in PD

Several genes have been identified to cause monogenetic forms of PD. Most of these genes are involved in mitochondrial activity, some of which also play a part in the inflammatory process in the CNS. In this section, we will review these genes and discuss the involvement in those processes (see Fig. 1).

Alpha synuclein

Alpha synuclein (α Syn) is the major component of PD Lewy bodies and clinically, patients with mutated α Syn have relatively young age of onset, rapid progression, and high prevalence of dementia, psychiatric, and autonomic disturbances (Xiromerisiou et al. 2010). The normal function of α Syn is poorly understood, but it is implicated in the regulation of vesicle dynamics at the presynaptic membrane, and is important in learning and neuronal plasticity (Sidhu et al. 2004).

α Syn can localize to the mitochondria via an N-terminal targeting motif (Shavali et al. 2008). α Syn can also impair the normal dynamics of mitochondria and this effect is more substantial in A53T mutant (Xie and Chung 2012). α Syn overexpression in neurons results in abnormal mitochondrial function and impaired complex-I activity, specifically in the dopaminergic neurons of the nigrostriatal pathways (Subramaniam et al. 2014). Overexpression of the A53T mutant of α Syn resulted in accumulation of α Syn in the mitochondria, in correlation with complex-I inhibition and aging (Chinta et al. 2010). Elevated expression levels of α Syn in the brain can lead to the development of PD (Miller et al. 2004; Singleton et al. 2003). This enhanced expression increases the deposition of soluble α Syn into insoluble aggregates (Miller et al. 2004). Pathogenic mutations in α Syn (notably A53T) have increased rates of self-assembly and fibrillization, and are considered gain of function mutations, resulting in autosomal dominant inheritance (Conway et al. 2000). Furthermore, it was recently suggested that cell–cell transmission of α Syn pathology is the basis for disease spreading between interconnected areas in the brain. However, while several brain regions, such as the thalamus and cortical regions, exhibit formation of Lewy bodies after injection of α Syn, the neurodegeneration appears to be selective to dopaminergic neurons in the substantia nigra (Luk et al. 2012).

Watson et al. (2012) have demonstrated that in α Syn overexpressing mice, despite the presence of high levels of α Syn in other brain regions, there was a selective early inflammatory response in regions of the nigrostriatal pathway. They suggested that specific factors, that may

involve an increase in the expression of Toll-like receptors (TLRs), mediate α Syn-induced inflammatory responses in the SN, which could explain the selective vulnerability of dopaminergic neurons in PD (Watson et al. 2012). Transgenic mice overexpressing of human α Syn exhibited increased vulnerability of dopaminergic neurons to LPS-induced inflammation, and this inflammatory response led to the accumulation of insoluble α Syn aggregates and the formation of cytoplasmic α Syn inclusions bodies within dopaminergic neurons (Gao et al. 2008). LPS-challenged transgenic mice expressing mutant α Syn (A53T) showed nitration and aggregation of α Syn and degeneration of dopaminergic neurons. Furthermore, those Tg mice have prolonged microglial activation, expressing iNOS and NADPH oxidase enzymes which generate nitric oxide and superoxide, respectively (Gao et al. 2011a). This finding suggests that microglia-dependent oxidative stress is a causative factor in α Syn accumulation and toxicity. It has been suggested that α Syn has a role in neuroinflammation and microglial activation in PD (Meulener et al. 2005). Microglial cells that were exposed to extracellular α Syn show increased proinflammatory phenotype, with increased IL1 α , IL1 β , TNF α and IL6 secretion (Alvarez-Erviti et al. 2011; Roodveldt et al. 2010). In addition, nitrated α Syn was shown to increase the expression of HMGB1 in microglia (Reynolds et al. 2008) suggesting that the microglial activation pattern following exposure to aggregated α Syn shows similarities to other non-infectious inflammatory responses. Finally, when microglia was treated with the A53T mutation of α Syn, this effect was exacerbated (Alvarez-Erviti et al. 2011; Roodveldt et al. 2010) (see Fig. 1).

α Syn stimulates human astrocytes as well as human U-373 MG astrocytoma cells to up-regulate IL-6 and inflammatory mediator intercellular adhesion molecule-1 (ICAM-1). The mutated forms of α Syn are more potent stimulators than the WT forms (Klegeris et al. 2006). Moreover, mice that selectively express mutated α Syn in astrocytes developed an early onset movement disability, and demonstrated dysfunctional astrocytes. These astrocytes were able to activate microglia and induce neurodegeneration (Gu et al. 2010).

A possible mechanism underlying the effect of α Syn on immune activation is Nurr1, a transcription factor belonging to the orphan nuclear receptor family. The expression of Nurr1 is reduced in α Syn expressing cells, as demonstrated in mice (Lagace-Wiens et al. 2008), and PD patients (Frohman et al. 2005). Nurr1 is a potential regulator of cytokine and growth factor action through regulating the inflammatory response (Lev et al. 2009). Moreover, Nurr1 has a neuroprotective effect because of its capability to inhibit the production of inflammatory mediators in microglia by interaction with CoREST, an NF- κ B repressor,

and by the promotion of the bound formation with NF- κ B subunit p65 resulting in reduction of TNF α secretion (Saijo et al. 2009).

Microglial activation following phagocytosis of aggregated α Syn also enhanced dopaminergic neurodegeneration through production of ROS, in a NADPH oxidase dependent manner (Zhang et al. 2005b). These results suggest that damage to neurons in the substantia nigra may release aggregated α Syn to the substantia nigra, promoting microglia to produce proinflammatory mediators, thereby further inducing nigral neurodegeneration in PD (Zhang et al. 2005b). The extent of microglial activation was correlated with the degree of dopaminergic neurotoxicity induced by both wild-type and mutant α Syn. Exposure to mutated α Syn also induced greater production of reactive oxygen species (ROS) than WT α Syn. These results demonstrated that microglia have an important role in mediating the enhanced neurotoxicity induced by mutant forms of α Syn (Zhang et al. 2007). Interestingly, recent results suggest that passive immunization with monoclonal antibodies against α Syn may be of therapeutic relevance in patients with PD (Masliah et al. 2011), providing further evidence for the involvement of immune activity in disease progression (see Fig. 1).

Leucine-rich repeat kinase 2 (LRRK2)

LRRK2 is a large gene that consists of 51 exons. It encodes the 2527 amino acid cytoplasmic protein leucine-rich repeat kinase 2 (LRRK2) that consists of a leucine-rich repeat towards the amino terminus of the protein, and a kinase domain toward the carboxyl terminus with various conserved domains in between (Klein and Westenberger 2012). There are more than 50 different missense and nonsense mutations reported in *LRRK2* to date (Nuytemans et al. 2010), and at least 16 of them are pathogenic, with gain of function attributes, and the G2019S mutation has been extensively researched (Klein and Westenberger 2012; West et al. 2005). However, the pathogenic mechanism leading to PD caused by LRRK2 mutations is still uncertain. LRRK2 is a large protein with many domains capable of protein–protein interactions, and thus it is plausible that changes in these domains would influence the LRRK2's relationship with other proteins (Berger et al. 2010; Klein and Westenberger 2012; Venderova et al. 2009).

LRRK2 can localize to the outer membrane of the mitochondria (Biskup et al. 2006). LRRK2 mediated mitochondrial fragmentation and dysfunction, which is exacerbated in the G2019S mutation, leading to neurotoxicity (Wang et al. 2012). Fibroblasts acquired from LRRK2 mutated patient (G2019S), showed decreased

mitochondrial membrane potential and intracellular ATP levels (Mortiboys et al. 2010). This was also demonstrated recently with induced pluripotent stem cells (iPSC) from PD patients carrying LRRK2 mutations. Mutant LRRK2 iPSCs demonstrated mitochondrial dysfunction and mitochondrial DNA damage (Cooper et al. 2012; Sanders et al. 2014), further supporting the role of LRRK2 in mitochondrial function.

High LRRK2 expression has been discovered in macrophages and monocytes (Thevenet et al. 2011), as well as T-cells (Hakimi et al. 2011), leading to the speculation of a functional role for LRRK2 in the immune system (see Fig. 1).

Moehle et al. (2012) have shown that microglial activation triggers LRRK2 expression, and that LRRK2 inhibition, by either small-molecule kinase inhibitors or shRNA, attenuates microglial proinflammatory response and reduces TNF α and NO levels following LPS activation (Moehle et al. 2012). This suggests that LRRK2 plays an important role in mediating proinflammatory responses in microglia cells. Recently, it was demonstrated that LRRK2 acts through regulation of p38 MAPK and NF- κ B signaling pathways to stimulate microglial inflammatory responses. p38 MAPK plays a crucial role in regulating oxidative stress-induced cell death and survival (Runchel et al. 2011). LRRK2 knockdown attenuated the inflammatory response to LPS and reduces cytokine and NO secretion, and LRRK2 overexpression increased the response (Kim et al. 2012). Furthermore, mutated LRRK2 microglia showed a decrease in IL-10 production in response to LPS stimuli, as compared to WT (Gillardon et al. 2012).

In a small cohort of patients carrying LRRK2 mutations, patients showed neuronal degeneration in substantia nigra, and some of the patients exhibited Lewy body pathology (Zimprich et al. 2004). Similarly, double mutant mice carrying mutated α Syn and mutated LRRK2 showed increased striatal neurodegeneration, compared to mice carrying only mutated α Syn (Lin et al. 2009), suggesting a possible connection between LRRK2 and α Syn pathologies.

Taken together, these results suggest that LRRK2 mutations, which are gain of function mutations, could change the microglia towards a proinflammatory phenotype, which changes the microenvironment of brain, and thereby triggers and/or enhances the pathogenesis of PD.

Parkin

Parkin is a 465 amino acid protein with a molecular mass of 52 kDa, which is highly expressed in heart, testis, brain and skeletal muscle (Kitada et al. 1998). Parkin was identified to have E3 ubiquitin ligase activity (Shimura

et al. 2000), and *parkin* mutations in patients resulted in the loss of E3 activity (Imai et al. 2000). Parkin also has a role in the mitochondrial activity and integrity (Abou-Sleiman et al. 2006), and in mammalian cells, parkin was shown to be recruited to the dysfunctional mitochondria, where it mediates the engulfment and degradation of deficient mitochondria, a process known as mitophagy (Narendra et al. 2008). Parkin-null *Drosophila* demonstrate disordered mitochondria (Greene et al. 2003), *parkin*^{-/-} mice showed decreased mitochondrial respiratory capacity and increased oxidative stress (Palacino et al. 2004). Mitochondrial quality control is important for vital energy production processes, and was also linked to apoptosis-related processes such as the release of cytochrome c (Youle and van der Bliek 2012), suggesting that impairments in mitophagy could have detrimental effects on cells. In similar experiments using *parkin*^{-/-} mice, however, there was no significant loss of dopaminergic neurons in the substantia nigra and inclusion bodies (Goldberg et al. 2003). Interestingly, *Parkin*^{-/-} mice bearing mutated α Syn, did not show a more severe phenotype compared to mice carrying only mutated α Syn, regarding Lewy bodies deposition and neurodegeneration (von Coelln et al. 2006). These findings suggest that parkin-mediated toxicity is not necessarily synuclein-dependent, and may require additional factors to induce marked neurodegeneration.

Parkin is abundantly expressed in microglia, and *parkin*-null mice have increased number of microglia, as measured by immunocytochemical analysis (Casarejos et al. 2006). Additionally, parkin loss of function in microglia resulted in enhanced toxicity to dopaminergic neurons after rotenone treatment (Casarejos et al. 2006).

A possible mediator for the effect of parkin on inflammation is TNF- α receptor-associated factor (TRAF) 2/6 signaling pathway. TRAF2 and TRAF6 are essential mediators of cytokine signaling by regulating c-Jun N-terminal kinase (JNK) and nuclear factor- κ B (NF- κ B) signaling. Parkin expression is inversely related to TRAF2/6 expression, and it promotes the proteasomal degradation of TRAF2/6 and protects inflammatory signaling in response to cytokine activation. These results suggest that TRAF2/6 may be a physiological target of parkin, and they provide an explanation for why loss of parkin is detected in PD (Chung et al. 2013), and how it relates to the neuroinflammation observed in PD. This indicates that the loss of parkin may induce an inflammatory response in PD (see Fig. 1).

Parkin levels are reduced in microglia in response to LPS of TNF α activation, in an NF- κ B dependent manner. In addition, activated macrophages from *Parkin*-null mice expressed increased levels of TNF α , IL-1 β , and iNOS mRNA compared to WT macrophages (Tran et al. 2011). Moreover, loss of parkin function increases the

vulnerability of dopaminergic neurons in the SN to inflammation-related degeneration, that was triggered by i.p. injection of low dose LPS (Frank-Cannon et al. 2008).

These reports indicate that parkin serves as an anti-inflammatory factor, suggesting that reduced parkin levels, or mutated parkin which has a loss of function phenotype, may be proinflammatory, and increase the neuronal death attributed to inflammation.

PTEN induced putative kinase 1 (PINK1)

PINK1 gene encodes a 581 amino acid protein with an N-terminal mitochondrial targeting motif and a highly conserved kinase domain homologous to the serine/threonine kinases of the Ca²⁺/calmodulin family (Gandhi et al. 2006). PINK1 is crucial for the intact function of cells, and is involved in cell respiration (Gandhi et al. 2009), protein folding and degradation (Dagda et al. 2009; Moriwaki et al. 2008), and in several mitochondrial functions, such as fission/fusion dynamics (Deng et al. 2005; Poole et al. 2008), trafficking (Weihofen et al. 2009) and calcium signaling (Marongiu et al. 2009). In addition, PINK1 is required for recruitment of parkin to the mitochondria with impaired membrane potential (Narendra et al. 2010; Vives-Bauza et al. 2010). PINK1 loss of function impairs the mitochondrial respiratory chain and ATP production, and induces neuronal aggregation of α Syn (Liu et al. 2009). Conversely, PINK1 overexpression can rescue α Syn-induced neuronal degeneration in a fly model (Todd and Staveley 2008), as well as α Syn-induced mitochondrial fragmentation in a *Caenorhabditis elegans* model (Kamp et al. 2010). These reports emphasize the important role of PINK1 in modulation of mitochondrial activity under normal conditions, as well under disease conditions.

PINK1 can interact with several chaperone proteins and such interaction may affect both its stability and its neuroprotective effects (Deas et al. 2009). PINK1 has been shown to protect cells against oxidative stress (Deas et al. 2009) by phosphorylating the mitochondrial protein TRAP1 (chaperone tumor necrosis factor receptor-associated protein 1) (Pridgeon et al. 2007).

Mutations in PINK1 gene account for 1–8 % of the early onset autosomal recessive PD cases (Klein et al. 2007; Xiromerisiou et al. 2010). PINK1 deficiency, results in calcium overload within mitochondria, causing ROS production in the mitochondria and cytosol (Gandhi et al. 2009). Moreover, PINK1 knockdown induced mitophagy, i.e., lysosomal degradation of mitochondria, a decrease in mitochondria levels within cells (Dagda et al. 2009).

PINK^{-/-} embryonic fibroblasts showed decreased basal and inflammatory cytokine-induced NF- κ B activity. In addition, PINK^{-/-} mice had increased levels of IL-1 β , IL-

12 and IL-10 in the striatum after peripheral stimulation with LPS (Akundi et al. 2011) (see Fig. 1). Kim and colleagues (2013) have shown that in organotypic cultures, PINK1^{-/-} slices expressed higher mRNA levels of TNF α , IL1 β and IL-6 compared to those of WT slices. These results indicate that PINK1 deficiency increases the production of proinflammatory cytokines, leading to a neurotoxic effect. The observed effect was mediated by reduced serine/threonine kinase Akt activation and enhanced I κ B degradation in response to brain injury (Kim et al. 2013). Another possible mechanism for the effect is that PINK1 directly interacts with two members of the IL-1 β -mediated downstream signaling pathway, TRAF6 and transforming growth factor β activated kinase-1 (TAK1), and positively regulates their activation leading to enhanced IL-1 β -mediated cytokine production (Lee et al. 2012). These reports demonstrate that PINK1 plays a role in the proinflammatory response in PD, possibly through interactions with the mitochondria.

DJ-1

DJ-1 encodes a small 189 amino acid protein that is ubiquitously expressed and highly conserved throughout diverse species (Bandopadhyay et al. 2004; Nagakubo et al. 1997). DJ-1 is localized to the cytoplasm, nucleus (Bader et al. 2005; Nagakubo et al. 1997) and mitochondria (Zhang et al. 2005a) of the cells, and it has been suggested that oxidation promotes the mitochondrial localization of DJ-1 (Blackinton et al. 2005). It was shown that the loss of functional DJ-1 causes 1–2 % of autosomal recessive early onset PD cases (Abou-Sleiman et al. 2003; Bonifati et al. 2003).

Several hypotheses have been introduced to explain the mechanism of DJ-1 involvement in PD pathogenesis. It has been suggested that DJ-1 plays a role in maintenance of mitochondrial complex-I activity (Hayashi et al. 2009) as well as in maintenance of mitochondrial morphology through fission/fusion dynamics (Irrcher et al. 2010), and that loss of DJ-1 function impairs nigrostriatal dopaminergic function (Chen et al. 2005; Goldberg et al. 2005; Kim et al. 2005). Of note, similarly to PINK1, DJ-1 overexpression can also rescue α Syn-induced mitochondrial fragmentation in a *C. elegans* model (Kamp et al. 2010). Neuronal cells that carry mutant forms of DJ-1, become more susceptible to death in parallel with the loss of oxidized forms of DJ-1 (Taira et al. 2004; Yokota et al. 2003), and are more sensitive to toxins (Lev et al. 2008). Moreover, DJ-1^{-/-} mice are more vulnerable to several toxicity models of PD, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment (Kim et al. 2005), 6-hydroxydopamine (6-OHDA), and rotenone toxicity without α Syn pathology (Lev et al. 2008, 2013). In all of the above

models, DJ-1^{-/-} induced a greater loss of dopaminergic neurons in these mice. It was demonstrated that ROS production, induced by bisphenol A (BPA) compromised mitochondrial function and elevated the expression and oxidization of DJ-1. DJ-1 was found to maintain the complex-I activity against BPA-induced oxidative stress after the localization in mitochondria. Furthermore, it was suggested that DJ-1 plays a role in the prevention of mitochondrial injury-induced cell death (Ooe et al. 2005).

It has been previously reported that DJ-1 is important for the proinflammatory response in astrocytes, and that DJ-1^{-/-} astrocytes have neurotoxic properties, with increased NO production and enhanced induction of COX2 and IL-6 (Waak et al. 2009). Moreover, recent research demonstrated that DJ knockout attenuates astrocytes neuroprotection against 6-OHDA toxicity (Lev et al. 2013), suggesting a protective role for astrocytes in the 6-OHDA model for PD, which depends on DJ-1 activation. When DJ-1 is knocked out, the protective effect is diminished, suggesting that DJ-1 is important for the neuroprotective ability of astrocytes, and that mutated DJ-1 reduces the neuroprotection.

Stimulation of macrophages with LPS induced an elevation in the DJ-1 protein levels (Mitsumoto and Nakagawa 2001). We have recently demonstrated that DJ-1-deficient microglia have increased monoamine oxidase (MAO) activity which resulted in elevation of intracellular ROS, NO, and proinflammatory cytokines, leading to increased dopaminergic neurotoxicity. This phenotype was ameliorated by rasagaline, a MAO inhibitor which is approved for treatment in PD patients. Those results demonstrate the important role of DJ-1 in immune activation in Parkinson's disease (Trudler et al. 2014).

Conclusion

There is increasing evidence that connects neuroinflammation and PD progression. PD gene mutations were previously suggested to lead to neuronal dysfunction leading to neuronal death. Here, we described the potential role of PD genes in mediating brain inflammation, as well as their effect on mitochondrial structure and function. Furthermore, we suggest that PD genes may trigger neuroinflammation to dopaminergic neurons either as a result of neuronal stress or by direct activation of glia cells in the microenvironment towards the dopaminergic neurons. This phenomenon supports the notion of a non-cell-autonomous mechanism in PD. Further understanding of the mechanisms underlying impairment of microglia or astrocyte activity, which are linked to PD genes, may provide new avenues for the etiology of PD and new therapeutic approaches.

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