The mitochondrial kinase PINK1, stress response and Parkinson's disease

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Abstract Mitochondrial dysfunction is well documented in presymptomatic brain tissue with Parkinson's disease (PD). Identification of the autosomal recessive variant PARK6 caused by loss-of-function mutations in the mitochondrial kinase PINK1 provides an opportunity to dissect pathogenesis. Although PARK6 shows clinical differences to PD, the induction of alpha-synuclein "Lewy" pathology by PINK1-deficiency proves that mitochondrial pathomechanisms are relevant for old-age PD. Mitochondrial dysfunction is induced by PINK1 deficiency even in peripheral tissues unaffected by disease, consistent with the ubiquitous expression of PINK1. It remains unclear whether this dysfunction is due to PINK1-mediated phosphorylation of proteins inside or outside mitochondria. Although PINK1 deficiency affects the mitochondrial fission/fusion balance, cell stress is required in mammals to alter mitochondrial dynamics and provoke apoptosis. Clearance of damaged mitochondria depends on pathways including PINK1 and Parkin and is critical for postmitotic neurons with high energy demand and cumulative stress, providing a mechanistic concept for the tissue specificity of disease.

Keywords PINK1 · Parkin · Mitochondria · Oxidative stress · Parkinson's disease

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Parkinson's disease and PARK6

Parkinson's Disease (PD) is the second most common neurodegenerative disorder after Alzheimer's Disease (AD), manifesting usually at old age without a family history, just like AD. The clinical course of PD starts with unspecific symptoms such as hyposmia, constipation, depression and sleep alterations that are attributed to degenerative changes in the olfactory bulb, the gastrointestinal nervous system and brainstem structures such as the dorsal motor vagal nucleus and the locus coeruleus neurons. The locomotor hallmark signs of PD develop later and present a deficiency in spontaneous movement initiation, cogwheel rigidity, impaired postural reflexes and rest tremor, caused mainly by the degeneration of dopaminergic neurons projecting from the midbrain substantia nigra to the striatum. The resulting deficit in dopaminergic signaling can be counteracted efficiently with pharmacological therapy or deep brain stimulation, postponing the immobility and dependence of PD patients by more than 5 years until usually cognitive deficits become limiting. A characteristic neuropathological feature of PD is the presence of multi-protein aggregates containing α-synuclein and ubiquitin in neuronal cell bodies and processes, the so-called Lewy bodies and Lewy neurites, which highlight the progression of the disease through affected cell populations from the gut and the olfactory bulb to the cerebral cortex (Braak et al. 2006). The typical biochemical features of the affected brain tissue include signs of respiratory complex I inhibition, signs of oxidative stress as e.g. lipid peroxidation and DNA damage, together with altered stress response pathways such as the glutathione system.

Despite similarities in the diagnostic motor syndrome, different forms of PD vary in the onset age as well as progression severity and the presence of accessory signs.

This is not only due to the different genetic background and random life experiences of each patient but can be also related to the specific factors that cause PD. These factors include different neurotoxins inhibiting respiratory complex I such as MPTP and pesticides (Winklhofer and Haass 2009), but also divalent ions like manganese (Gitler et al. 2009). In addition, mutations in different genes such as α-synuclein (chromosomal gene locus PARK1/PARK4), Parkin (PARK2), UCH-L1 (PARK5), PINK1 (PARK6), DJ-1 (PARK7), LRRK2 (PARK8), ATP13A2 (PARK9), Omi1/HtrA2 (PARK13), PLA2G6 (PARK14) and FBXO7 (PARK15) can result in PD (for a recent review see Gasser 2009).

Studying consanguineous PD families with early manifestation around 30–40 years of age and particularly mild progression, the autosomal recessive PD variant PARK6 was demonstrated to be caused by loss-of-function mutations in the protein PTEN induced putative kinase 1 (PINK1) (Valente et al. 2004). PARK6 patients also differ from idiopathic PD patients, since the therapeutic benefit from dopamine substitution appears to last (Kessler et al. 2005), and since olfactory, autonomic and cognitive deficits, as well as postural tremor are rare, while drug-induced dyskinesia is frequent. Therefore, a purely mitochondrial pathogenesis in such autosomal recessive patients was claimed to contrast with protein aggregation pathomechanisms in sporadic idiopathic and autosomal dominant forms of PD (Ahlskog 2009; Nishioka et al. 2009). However, the recent documentation of a first PARK6 brain autopsy confirmed the occurrence of Lewy pathology (Samaranch et al. 2009, personal communication), transient knock-down of PINK1 in neuroblastoma cells induced aggregation of recombinant alpha-synuclein, and PARK6 patient fibroblasts as well as PINK1-KO mice showed dysregulated expression of endogenous alpha-synuclein (Hoepken et al. 2008; Gispert et al. 2009), supporting the hypothesis that protein degradation/aggregation and synaptic pathology may occur in PARK6 just as in idiopathic PD. Thus, the pathogenesis of different PD forms may converge in common pathways of mitochondrial dysfunction, oxidative stress and protein aggregation.

PINK1 loss-of-function induces mitochondrial dysfunction

To understand the pathogenesis of PARK6, it is essential to elucidate the consequences of PINK1 loss-of-function mutations. PINK1 contains 581 amino acids including a N-terminal mitochondrial targeting sequence and the sequence of a serine-threonine kinase (Nakajima et al. 2003; Silvestri et al. 2005) (Fig. 1). The endogenous
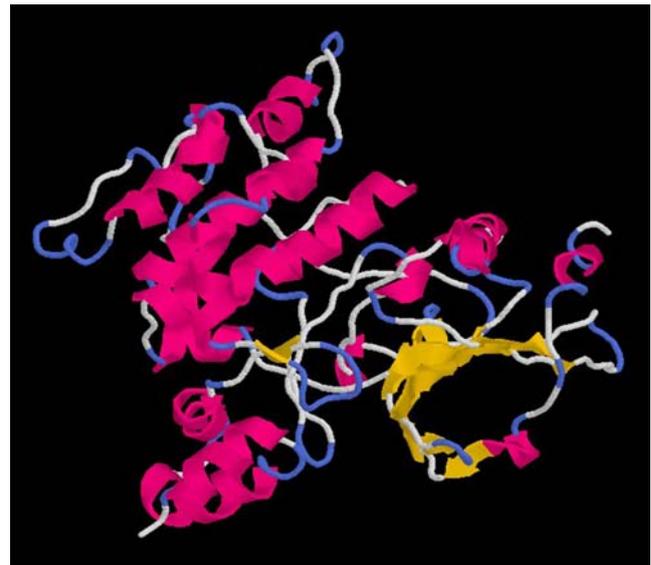
Fig. 1 Putative 3D model of the PINK1 kinase domain. In view of the homology of PINK1 sequences from the protein center onwards except the C-terminus versus pak1 sequences representing the kinase domains, the known x-ray structure of pak1 was used as template. The 3D model is tilted to show the putative regulatory loops (*left, in pink*), the putative ATP channel (*center, in yellow*) and the loop containing the pathogenic G309D missense mutation which led to the identification of PINK1 as disease protein (*center right*). Missing from the model are the N-terminal sequences which mediate mitochondrial import (*lower left*), as well as the C-terminal sequences thought to decide substrate specificity (*upper right*). The model was created using Composer with the SYBYL 6.9 from Tripos (compare Grudzinska et al. 2005)

physiological targets of PINK1 phosphorylation activity are unknown, but two Parkinson' disease proteins with partial mitochondrial localization were claimed on the basis of recombinant work, namely Parkin and Omi (indirect via p38 phosphorylation), as well as the mitochondrial chaperone Trap1 (Plun-Favreau et al. 2007; Pridgeon et al. 2007; Kim et al. 2008). PINK1 expression was shown to be quite ubiquitous, to occur in brain neurons rather than in glia (Blackinton et al. 2007) and to correlate to mitochondrial mass (Scheele et al. 2007). The cytoplasmic precursor of PINK1 is not immediately cleaved and imported into mitochondria, but may remain demonstrable together with the mature form visible as a doublet band in western blotting, while some experiments also suggested that mature PINK1 can be re-exported from mitochondria to the cytoplasm (Beilina et al. 2005; Haque et al. 2008;). A putative transmembrane domain was reported together with evidence localizing PINK1 in the mitochondrial outer membrane with the kinase domain facing the cytoplasm (Zhou et al. 2008), while independent studies provided evidence for PINK1 dimerization and association with the respiratory chain complexes (Liu

et al. 2009). Further, PINK1 was observed to regulate calcium efflux via the mitochondrial Na(+)/Ca(2+) exchanger (Gandhi et al. 2009) and was implicated in mitochondrial trafficking via a multiprotein complex containing Miro, Milton and Mitofilin (Weihofen et al. 2009).

To elucidate the downstream effects of PINK1 loss-of-function and to model PARK6 pathogenesis, different systems were employed such as *D. melanogaster, C. elegans, D. rerio* and *M. musculus* mutants, patient skin fibroblasts and recombinant cell lines with PINK1 knock-down/knockout or with overexpression of a defective kinase domain. The loss of functional PINK1 was found to result in increased reactive oxygen species (ROS) levels, enhanced lipid peroxidation, altered glutathione metabolism, enhanced MnSOD levels, impaired glucose import, a decrease of complex I respiration, ATP production, mitochondrial membrane potential and cristae length, a deficit in mtDNA synthesis and levels, an overload of calcium, uncontrolled cytochrome C release, elevated caspase-3 activity and GSK3beta activity (Wang et al. 2006, 2007; Yang et al. 2006; Hoepken et al. 2007; Anichtchik et al. 2008; Gautier et al. 2008; Piccoli et al. 2008; Wood-Kaczmar et al. 2008; Gandhi et al. 2009; Grünewald et al. 2009; Gegg et al. 2009; Gispert et al. 2009; Marongiu et al. 2009). Efficient rescue of this pathology was observed with drugs such as the mitochondrial permeability transition pore blocker cyclosporin A, the mitochondrial calcium influx blocker ruthenium red and the GSK3beta inhibitor LiCl (Anichtchik et al. 2008; Marongiu et al. 2009). The consequences of mitochondrial dysfunction for the organism include defective axonal outgrowth observed in PINK1 deficient *C. elegans* (Sämann et al. 2009). In PINK1-KO mice, specific neuronal dysfunction such as pathological neurotransmitter release, synaptic plasticity and altered postsynaptic receptor sensitivity was documented in the dopaminergic nigrostriatal pathway (Kitada et al. 2007; Martella et al. 2009), but neuronal cell death is not demonstrable in PINK1 knockout mice (Kitada et al. 2007, 2009; Gispert et al. 2009; Martella et al. 2009). These findings are compatible with established data that identified enhanced ROS levels and lipid peroxidation as events occurring before the degeneration of dopaminergic nigrostriatal neurons in the brain of PD patients (Jenner et al. 1992).

However, at present it remains unclear whether these mitochondrial alterations are upstream consequences of PINK1 loss-of-function, whether they are secondary to altered mitochondrial distribution dynamics affecting the physiological trafficking within neurons, or secondary to altered mitochondrial repair/clearance in response to random stimuli and stress events within neurons. Furthermore, mitochondrial dysfunction appears to be present in neuronal as well as peripheral cell types unaffected by PARK6, thus providing no satisfactory understanding for the preferential vulnerability of neurons, particularly of dopaminergic neurotransmission.

PINK1 loss-of-function alters mitochondrial dynamics

The morphology of mitochondria is dynamic and can vary from small, rounded, fragmented mitochondria via the more usual tubular mitochondria to interconnected mitochondrial networks (Bereiter-Hahn et al. 2008). The mitochondrial morphology is altered by physiological changes such as uncoupling (Lyamzaev et al. 2004), oxidative stress (Pletjushkina et al. 2006; Jendrach et al. 2008), or apoptosis (Perfettini et al. 2005).

In the *D. melanogaster* model, PINK1 knockout results in mitochondrial fragmentation and swelling (Deng et al. 2008; Poole et al. 2008; Yang et al. 2008), correlating well with the extensive cell damage in this fruit fly model. PINK1 was therefore interpreted to act like the known mitochondrial fission factors Drp1, Fis1 and MTP18.

In mammalian cells, the role of PINK1 for mitochondrial morphology remains controversial: In cortical neurons of PINK1 knockout mice no changes (Gispert et al. 2009) or a slight elongation of mitochondria (Gautier et al. 2008) were reported, suggesting that a compensatory mechanism maintains mitochondrial morphology quite stable in the murine models. While some groups demonstrated PINK1 to act also in human cells as a fission factor (Yang et al. 2008; Jendrach, unpublished data), other researchers observed increased mitochondrial fission shortly after a transient knockdown of PINK1 (Exner et al. 2007; Dagda et al. 2009), and concluded that PINK1 acts like the known fusion factors Mfn1, Mfn2 and Opa1. Three recent publications link altered mitochondrial fission in PINK1 deficient cells to increased Drp1 activity (Sandebring et al. 2009; Lutz et al. 2009; Park et al. 2009). Thus, alterations of mitochondrial fission/fusion balance are now hypothesized to be part of the autophagic process degrading dysfunctional mitochondrial fragments (Cherra et al. 2009, Chu 2009), and to depend on the specific stressor employed.

Role of PINK1 in stress response

The data presented above lead to the important question why no murine model, not even a mouse with a triple mutation (Parkin, DJ-1, PINK1) (Kitada et al. 2009), exhibits altered mitochondrial morphology, neuronal Lewy bodies or massive loss of dopamineric neurons, as are

typical for PD. A possible explanation could be the short life span of a mouse that lives only up to three years with the respective mutation, while a human has to cope much longer. In addition, laboratory mice live in a protected environment, lacking exposure to various kinds of stressors that humans encounter every day, and differ from humans in key metabolic features as e.g. the capacity to synthesize the antioxidant vitamin C.

This hypothesis is supported by a rising amount of data implicating PINK1 in cellular stress response. PINK1 expression is modulated by trophic stress such as serum deprivation, ischemia and oxygen-glucose deprivation, with PINK1 modulating intracellular stress/trophism signals such as Akt phosphorylation (Mei et al. 2009; Sakurai et al. 2009; Shan et al. 2009). Although mitochondrial morphology was not altered in the cortical neurons of PINK1 knockout mice and in PARK6 patient fibroblasts cultured with high glucose supplementation, altered mitochondrial morphology in comparison to controls was observed under low glucose culture for fibroblasts and after proteasomal stress in mouse primary neurons (Exner et al. 2007; Gispert et al. 2009). The use of 4E-BP transfection or the drug rapamycin to suppress protein synthesis, mimicking an important neuronal reaction to stress, effectively ameliorates mitochondrial defects induced by PINK1 deficiency (Tain et al. 2009).

The loss of functional PINK1 results in impaired tolerance to mitochondrial stress, e.g. enhancing the sensitivity of mitochondria to fragmentation upon exposure to the complex I inhibitor rotenone (Sandebring et al. 2009) and the vulnerability of dopaminergic neurons towards the complex I inhibitor MPTP (Haque et al. 2008). Although exposure to oxidative stress makes increased mitochondrial damage and enhanced apoptosis rates apparent in PINK1-deficient cells (Clark et al. 2006; Gautier et al. 2008; Haque et al. 2008; Jendrach, unpublished data), murine models in contrast to D. melanogaster show no discernible signs of apoptosis in the unstressed state (Park et al. 2006; Clark et al. 2006; Gautier et al. 2008; Gispert et al. 2009). Conversely, overexpression of PINK1 in the neuronal cell line PC12 protected cells against oxidative stress induced apoptosis, an effect mediated by the direct phosphorylation of TRAP1 (TNF receptor-associated protein 1) by PINK1 (Pridgeon et al. 2007). TRAP1 is a mitochondrial localized chaperone that has been shown to reduce ROS directly in mitochondria (Hua et al. 2007). Other chaperones such as Cdc37/Hsp90 have also been shown to interact with PINK1 (Weihofen et al. 2008). This role of PINK1 during and after oxidative stress could also explain the protective effects of PINK1 overexpression observed in human neuroblastoma lines (Petit et al. 2005) and with murine primary cortical neurons (Haque et al. 2008).

Recent data indicate that the stress-protection role of PINK1 may be mediated via Parkin and may involve repair and clearance pathways. The ubiquitin E3 ligase parkin can bind selectively to damaged mitochondria and participates in the engulfment of damaged mitochondria in preautophagosomal structures (Narendra et al. 2008). PINK1-mediated phosphorylation of Parkin is a requirement for this translocation, and the interaction of PINK1 and Parkin has mutual effects on their solubility (Kim et al. 2008; Shiba et al. 2009; Um et al. 2009; Xiong et al. 2009). Consequently Parkin can rescue mitochondrial dysfunction after knockout of PINK1 in D. melanogaster (Park et al. 2006; Yang et al. 2006) and also in HeLa cells (Exner et al. 2007). A loss of parkin in D. melanogaster causes abnormal mitochondrial morphologies and neuropathological dysfunction (Greene et al. 2003; Whitworth et al. 2005). It has also been reported that PINK1 acts through phosphorylation of Omi/HtrA2 to preserve mitochondrial integrity (Plun-Favreau et al. 2007). The role of PINK1 in mitochondrial clearance is further supported by studies with primary cortical neurons of PINK1 knock-out mice. Here, an inhibition of proteasomal degradation led to strongly increased mitochondrial aggregation (Gispert et al. 2009). These data agree with the proposal of Narendra et al. (2008) that the PINK1/Parkin pathway is involved in mitochondrial quality control and affects mitochondrial clearance by autophagy. This is especially important for postmitotic nerve cells because this cell type is much more susceptible to cumulative oxidative damage than proliferating cells such as fibroblasts, and this concept might explain the selective vulnerability of dopaminergic nerve cells.

Taken together, the data presented here indicate that PINK1 is important for mitochondrial maintenance during and after stress. A loss of functional PINK1 results in an accumulation of damaged mitochondria, rendering cells more susceptible to oxidative stress and affecting neurotransmitter signaling. This explains why the pathology of PARK6 appears only cumulatively with age in postmitotic neurons. Further work is needed to elucidate the interaction between PINK1 and other PD-associated proteins in common molecular pathways, to understand the mechanisms which ensure mitochondrial quality control and distribution, and to analyze the trophic stimuli and stress events which determine synaptic strength.

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