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Review Article

Calcium Dysregulation and Mitochondrial Dysfunction Form A Vicious Cycle in Parkinson's Disease

J Tabitha Hees[1]* and Angelika B Harbauer[1,2]

[1]*Max-Planck-Institute for Neurobiology, Germany*

[2]*Institute of Neuronal Cell Biology, Technische Universität München, Germany*

***Corresponding author:** Angelika B Harbauer, Max-Planck-Institute for Neurobiology, Institute of Neuronal Cell Biology, Technische Universität München, Munich, Germany.

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Abstract

Mitochondria are not only the "power houses of the cell" but also function as a major Ca^{2+} buffer in the cell. Mitochondrial dynamics respond to the level of Ca^{2+} in the cell in order to maintain a beneficial feedback cycle between Ca^{2+} buffering and mitochondrial dynamics that allows adaption of mitochondrial to the cellular (sub) environment. Mutations in proteins linked to Parkinson's disease (PD) are linked to both mitochondrial dysfunction and Ca^{2+} dysregulation, which can trap the cell in a vicious cycle. The high energetic demands and high Ca^{2+} of dopaminergic neurons may explain why this cell type is the most vulnerable to mutations in PD related genes.

Introduction

Neurons depend on a healthy pool of mitochondria, as they require large amounts of energy and Ca^{2+} buffering, yet their highly extended, complex structures and long axons [1] make maintaining and distributing mitochondria a challenging task [2]. Parkinson's disease (PD has long been linked to mitochondrial dysfunction [3], yet why specifically dopaminergic neurons degenerate first remains to be elucidated.

Regulation of mitochondrial dynamics

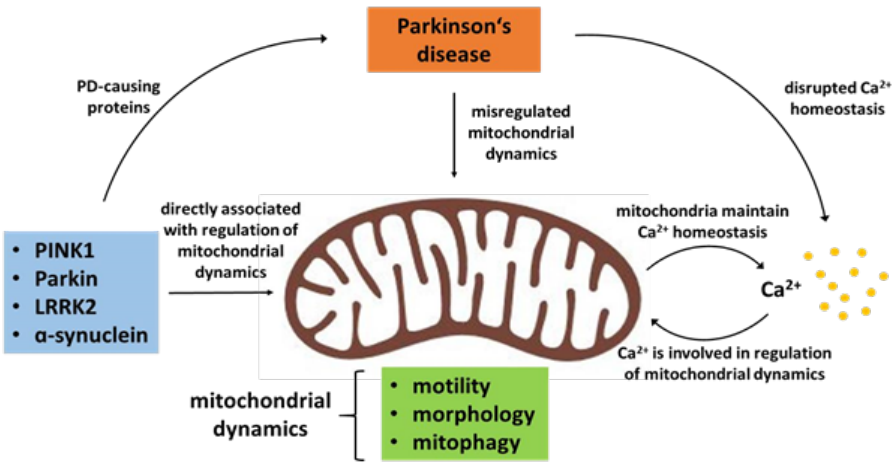

Figure 1: PD-causing proteins and Ca^{2+} in the context of mitochondrial dynamics and PD.

The blue box lists those proteins found mutated in PD, which directly influence one or more aspects of mitochondrial dynamics and Ca^{2+} handling. The aspects of mitochondrial dynamics regulated are listed in the green box. The beneficial feedback cycle between Ca^{2+} and mitochondrial dynamics that allows adaption of mitochondrial dynamics to the cellular (sub)environment is depicted on the right. Upon misregulation of either side of the feedback loop a vicious cycle ensues that exacerbates both mitochondrial dysfunction and disrupted Ca^{2+} signalling in PD.

Mitochondrial maintenance and proper axonal distribution in neurons are possible due to the highly dynamic nature of these organelles. Almost all mitochondrial proteins are post-translationally imported into the organelle [4] and mitochondrial trafficking distributes them along the cytoskeleton across the cell [5,6]. Changes in mitochondrial morphology by fusion and fission events further adjust their functionality [7,8] and finally clearance of damaged mitochondria via mitophagy, a specific form of autophagy, contributes to maintaining a pool of healthy mitochondria [9-11]. All these processes are highly regulated to ensure proper mitochondrial function in response to the (sub-)cellular environment (Protein import: [4,12]; Trafficking: [9,13-16]; Fission/fusion: [17-19]; Mitophagy: [20-22]. While mitophagy has received a lot of attention as two of the main players are mutated in hereditary PD (PINK1/Parkin) [23,24], several signalling pathways disrupted in PD also alter mitochondrial trafficking (Figure 1).

A central target of these pathways is the mitochondrial outer membrane protein Miro (also RHOT1/2) which couples the organelle to the cytoskeleton via the adaptor protein Milton (also TRAK1/2) [25-28]. Miro gets phosphorylated by the kinase PINK1 and consecutively ubiquitinated by the E3-Ligase Parkin [20-22], which leads to its degradation and mitochondrial arrest [14,29].

A parallel pathway leading to Miro degradation seems to involve LRRK2 kinase [30]. Likewise, accumulated a-synuclein also dysregulates Miro on several levels. It affects Miro subcellular distribution and limits transport of healthy mitochondria into axons [31]. Furthermore, it also prevents Miro degradation in response to mitochondrial damage [32]. Finally, cytosolic Ca^{2+} directly binds to the EF hands in Miro, leading to a conformational change that also arrests mitochondrial movement [13,33-35].

Calcium signalling in PD

Ca^{2+} is essential for cellular signalling, as it allows cells to quickly adapt and respond to the local microenvironment. The failure to control Ca^{2+} has devastating consequences for the cell, eventually leading to cell death [36]. Neuronal mitochondria are especially needed to buffer cytosolic Ca^{2+} transients elicited by neuronal activity [37]. In this way, they both prolong the signals and protect neurons from the possibly detrimental Ca^{2+} spikes. Hence, it is not surprising that disruption of Ca^{2+} homeostasis is a pathological feature of several neurodegenerative diseases including PD [38]. Several PD-causing proteins are involved in controlling Ca^{2+} homeostasis such as PINK1, Parkin, LRRK2 and a-synuclein [39-42]. Ca^{2+}_{mito} uptake, mainly mediated by the mitochondrial calcium uniporter (MCU), is required for maintaining Ca^{2+} homeostasis [43,44]. Furthermore, the mitochondrial inner membrane Ca^{2+}/H+ antiporter LETM1 is involved in Ca^{2+}_{mito} uptake. PINK1 phosphorylates LETM1, thereby regulating mitochondrial Ca^{2+} levels [42]. Loss of PINK1 has been shown to result in disrupted mitochondrial Ca^{2+} transport and make neurons more vulnerable to stress [42,45].

Miro at the center of mitochondrial calcium regulation

Miro, the mitochondrial outer membrane protein involved in mitochondrial transport, has recently also been reported to be involved in Ca^{2+} -related processes: Regulation of Ca^{2+} uptake at ER mitochondria encounter structures (ERMCS) and control of mitochondrial shape in response to Ca^{2+}.

The Ca^{2+} uptake into mitochondria mainly takes place at ERMCS [46]. Miro has been found to be involved in regulating Ca^{2+} transfer from ER to mitochondria independent of its function in mitochondrial transport and morphology. Its yeast homolog Gem1p is translocated to ERMCS regulating the number and the size of these complexes [47]. This localization is conserved in mammalian Miro [47]. A more recent study confirms the role of Miro in controlling Ca^{2+}_{mito} homeostasis at ERMCS [48]. Once Miro is translocated to ERMCS, it interacts with ERMCS components modulating the Ca^{2+} transfer and the integrity of the complex. The localization of Miro to ERMCS is promoted by Polo kinase-mediated phosphorylation of Miro. Loss of Miro results in Ca^{2+}_{mito} depletion and overexpression in Ca^{2+}_{mito} overload [48] revealing the importance of the Polo/Miro signalling pathway in the regulation of Ca^{2+}_{mito} uptake. Furthermore, this study shows that both PINK1 and LRRK2 are involved in this process. They function upstream of Miro and seem to control the Ca^{2+}_{mito} homeostasis through Miro. In *Drosophila* PINK1 and $LRRK2_{G2019S}$ mutants, Ca^{2+}_{mito} homeostasis is dysregulated and characterized by elevated Ca^{2+}_{mito} levels. Upregulated Miro levels have been found to be responsible for the dysregulation in the PD models [48]. This is in line with the fact that both PINK1 and LRRK2 are involved in pathways that result in degradation and thus downregulation of Miro [14,30]. The increased Ca^{2+}_{mito} levels, present in PINK1 and LRRK2 mutants, lead to mitochondrial swelling and eventually neuronal death.

Finally, mitochondria undergo a morphology change called MiST mediated by Miro sensing Ca^{2+} [49]. Miro-dependent MiST is involved in mitochondrial quality control as it is required for autophagy and mitophagy. Considering the disrupted Ca^{2+} homeostasis in PD, MiST may be mistakenly triggered by pathologically increased cytosolic Ca^{2+} levels, thereby contributing to mitochondrial dysfunction.

Why are dopaminergic neurons so susceptible?

It has been shown that, with age, the amount of Ca^{2+} dysregulation increases [50]. Ca^{2+} dysregulation, however, is not ubiquitous but restricted to specific cell types. Dopaminergic neurons, the main cell type affected in PD, are autonomous pacemakers relying on L-type Ca^{2+} channels. It has been shown that aging is associated with increased reliance of dopaminergic neurons on these Ca^{2+} channels accompanied by sustained increase in cytosolic Ca^{2+} levels [51]. With the need to pump Ca^{2+} out of the cell come higher energy demands and thus an increased oxidative phosphorylation (OXPHOS) rate. The increased need to buffer Ca^{2+} and therefore elevat-

ed Ca^{2+}_{mito} as well as the increased OXPHOS rate result in elevated mitochondrial oxidative stress [52,53]. Ca^{2+}_{mito} overload may even directly trigger opening of the permeability transition pore (PTP) leading to the release of proapoptotic factors and even more Ca^{2+} into the cytosol [54]. This further exacerbates the mitochondrial phenotype due to Ca^{2+} dependent arrest in a vicious cycle (Figure 1) and will eventually lead to programmed cell death [55,56]. This, along with the need to feed an extensively branched axonal arbor [57], may be one of the reasons why dopaminergic neurons are particularly susceptible in PD.

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