Mitochondrial dysfunction has long been implicated in the etiopathogenesis of Parkinson's disease (PD), based on the observation that mitochondrial toxins can cause parkinsonism in humans and animal models. Research into the function and dysfunction of PD-associated genes revealed that at least some of these genes interface with pathways regulating various aspects of mitochondrial biology. Mutations in the parkin gene, encoding an E3 ubiquitin ligase, are responsible for the majority of autosomal recessive parkinsonism. Our previous work revealed that parkin is a stress-inducible protein with a wide neuroprotective capacity, preventing cell death under various stress conditions. We now present evidence that the acute stress-protective activity of parkin and its capacity to induce mitophagy are mediated by two separate and independent pathways. While a functional autophagic machinery and expression of the mitochondrial kinase PINK1 is required for parkin-induced mitophagy, these components are dispensable for the anti-apoptotic activity of parkin. We identified a signaling pathway that is essential for the anti-apoptotic activity of parkin but not for induction of mitophagy. In support of this concept, parkin seems to exert adaptive effects on mitochondria depending on the severity of mitochondrial damage. Parkin prevents stress-induced cell death under moderate stress conditions with only minor mitochondrial defects. However, when mitochondria are irreversibly damaged in response to severe stress, parkin can promote their elimination via mitophagy.

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9P1

Mitochondrial membrane potential decrease caused by lack of PINK1 is not due to proton leak, but to respiratory chain deficiency

Taku Amo1, Shigeto Sato2, Shinji Saiki2, Alexander M. Wolf3, Masaaki Toyomizu4, Clement A. Gautier5, Jie Shen5, Thomas Langer6, Daniel Krappmann4, Gunnar Dittmar2, Jörg Tatzelt1,2, Konstanze F. Winklhofer1,2
1Adolf Butenandt Institute, Ludwig Maximilians University, Munich, Germany
2German Center for Neurodegenerative Diseases, Munich, Germany
3Max Delbrück Center for Molecular Medicine, Berlin, Germany
4Institute of Toxicology, Helmholtz Center Munich, Germany
5Institute of Developmental Genetics, Helmholtz Center Munich, Germany
6Institute for Genetics, University of Cologne, Germany
E-mail: konstanze.winklhofer@med.uni-muenchen.de

Mutations in PTEN-induced putative kinase 1 (PINK1) cause a recessive form of Parkinson’s disease (PD). PINK1 is associated with mitochondrial quality control and its partial knock-down induces mitochondrial dysfunction including decreased membrane potential and increased vulnerability against mitochondrial toxins, but the exact function of PINK1 in mitochondria has not been investigated using cells with null expression of PINK1. Here, we show that loss of PINK1 caused mitochondrial dysfunction. In PINK1-deficient (PINK1−/−) mouse embryonic fibroblasts (MEFs), mitochondrial membrane potential and cellular ATP levels were decreased compared with those in littermate wild-type MEFs. However, mitochondrial proton leak, which reduces membrane potential in the absence of ATP synthesis, was not altered by loss of PINK1. Instead, activity of the respiratory chain, which produces the membrane potential by oxidizing substrates using oxygen, declined. H2O2 production rate by PINK1−/− mitochondria was lower than PINK1+/+ mitochondria as a consequence of decreased oxygen consumption rate, while the proportion (H2O2 production rate per oxygen consumption rate) was higher. These results suggest that mitochondrial dysfunctions in PD pathogenesis are caused not by proton leak, but by respiratory chain defects.

Reference

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9P2

The gender- and brain region-specific role of cytochrome c oxidase in hypoxia and neurodegeneration

S. Arnold
University Clinic of the Goethe University, Center of Biological Chemistry (ZBC), Molecular Bioenergetics, Theodor-Stern-Kai 7, Haus 26, D-60590 Frankfurt/Main, Germany
E-mail: samold2012@gmail.com

The selective loss of neural cells from a particular brain region is a common feature of neurodegenerative diseases. A failure of mitochondrial function seems to be a causative factor. Hypoxia [1,2] and toxins, such as 3-nitropropionic acid (3-NPA, [3–5]) and 1-methyl-4-phenylpyridinium (MPP+ [6,7]), affect mitochondrial function as well as neural cell viability and are known as inducers of stroke, Huntington’s and Parkinson’s disease, respectively.

We demonstrated that hypoxia and these neurotoxins affect mitochondrial gene expression, ATP and reactive oxygen species (ROS) production and that cytochrome c oxidase (COX), the terminal enzyme of the mitochondrial respiratory chain, appears to play a crucial role. The application of hypoxia [1,2], 3-NPA [3–5] and MPP+ [6,7] to cultured primary astrocytes and neurons from different brain regions of female and male mice caused an increase of COX isofrom IV-2 transcription and protein expression in neural cells from cortex (hypoxia), female/male striatum (3-NPA) and male midbrain (MPP+). A siRNA against COX IV-2 revealed that COX IV-2 is causally related to elevated intracellular ATP levels at the expense of increased mitochondrial ROS production and neural cell death.

Our data suggest that cell death in response to hypoxia, 3-NPA and MPP+ is primarily caused due to increased oxidative stress in neural cells in a brain region-specific and in case of MPP+ also in a gender-specific way. COX appears to take center stage of metabolic and cell survival control in stroke and neurodegeneration [8]. This work was supported by DFG (AR343/4-1).

References