18L.4 Multi-site control and regulation of mitochondrial energy production

G. Benard, N. Bellance, C. Jose, S. Melser,
K. Nouette-Gaulain, R. Rossignol
INSERM U688, Physiopathologie mitochondriale,
Université Victor Segalen-Bordeaux 2, 146 rue Léo-Saignat,
F-33076 Bordeaux Cedex, France
E-mail: rossig@u-bordeaux2.fr

With the extraordinary progress of mitochondrial science and cell biology, novel biochemical pathways have emerged as strategic points of bioenergetic regulation and control. They include mitochondrial fusion, fission and organellar motility along microtubules and microfilaments (mitochondrial dynamics), mitochondrial turnover (biogenesis and degradation), and mitochondrial phospholipids synthesis. Yet, much is still unknown about the mutual interaction between mitochondrial energy state, biogenesis, dynamics and degradation. Meanwhile, clinical research into metabolic abnormalities in tumors as diverse as renal carcinoma, glioblastomas, paragangliomas or skin leiomyomata, has designated new genes, oncogenes and oncometabolites involved in the regulation of cellular and mitochondrial energy production. Furthermore, the examination of rare neurological diseases such as Charcot–Marie–Tooth type 2a, Autosomal Dominant Optic Atrophy, Lethal Defect of Mitochondrial and Peroxisomal Fission, or Spastic Paraplegia suggested involvement of MFN2, OPA1/3, DRP1 or Paraplegin, in the auxiliary control of mitochondrial energy production. Lastly, advances in the understanding of mitochondrial apoptosis have suggested a supplementary role for Bcl2 or Bax in the regulation of mitochondrial respiration and dynamics, which has fostered the investigation of alternative mechanisms of energy regulation. Here, we discuss the regulatory mechanisms of cellular and mitochondrial energy production, and we emphasize the importance of the study of rare neurological diseases in addition to more common disorders such as cancer, for the fundamental understanding of cellular and mitochondrial energy production.

doi:10.1016/j.bbabio.2010.04.420

18L.5 Role of the mitochondrial kinase Pink1 in Parkin recruitment and mitophagy

Richard J. Youle
National Institutes of Health, Bethesda, MD, USA
E-mail: youler@ninds.nih.gov

Pink1 is mutated in some autosomal recessive forms of Parkinson's disease and has been linked genetically to Parkin activity and to mitochondrial dysfunction. Recently we found that Parkin, a cytosolic E3 ligase, translocates to mitochondria upon mitochondrial damage or uncoupling. How Parkin may sense mitochondrial uncoupling, however, was unknown. Pink1, a kinase located on the outer mitochondrial membrane is strictly required for Parkin translocation to mitochondria and for Parkin-mediated mitophagy. The mechanism of Pink1 activation upon mitochondrial damage occurs by an unexpected posttranslational induction process. We identified a constitutive proteolytic processing and rapid turnover of endogenous Pink1 leading to low basal expression on healthy mitochondria. Upon mitochondrial uncoupling or damage, Pink1 proteolysis is prevented leading to a dramatic upregulation of Pink1 expression on mitochondria. Furthermore, Pink1 upregulation occurs selectively on individual impaired mitochondria within a milieu of energetically functional mitochondria in individual cells. We thus identify a novel mechanism for detection of mitochondrial function in cells and propose that lesions in a mitochondrial quality control pathway may contribute to some forms of parkinsonism.

doi:10.1016/j.bbabio.2010.04.421

Posters

18P.1 Mitochondria, autophagy and nitric oxide are correlated and control myogenesis

Clara De Palma[1], Serena Pisoni[1], Sarah Pambianco[1], Sestina Falcone[4], Luca Scorrano[2], Silvia Brunelli[3], Emilio Clementi[1]
[1]*Unit of Clinical Pharmacology "Luigi Sacco" Hospital of Milano, Italy*
[2]*Department of Cell Physiology and Metabolism,*
University of Geneva, Switzerland
[3]*Department of Experimental Medicine, University of Milano Bicocca, Italy*
[4]*Inserm, Institute de Myologie Univ Paris 06, France*
E-mail: clara.depalma@guest.unimi.it

Mitochondrial morphology is regulated by the balanced processes of fission and fusion; whether these events play a role also in shaping cell functions is still not well understood. Here we provide evidence that during myogenic differentiation the short mitochondria of myoblasts change into the extensively elongated network observed in myotubes. We show that mitochondrial elongation is required for myogenesis to occur and that this event depends on the cellular generation of nitric oxide (NO). Inhibition of NO synthesis in myogenic precursor cells leads to inhibition of mitochondrial elongation and of myogenic differentiation. The specific target of NO action is Drp1. NO controls Drp1 translocation to mitochondria and its docking to the specific interactor Fis1; further, it controls the GTPase activity of the protein. In the presence of NO Drp1 functions are maintained at basal levels to allow mitochondria to create a fused network that enhances myogenic differentiation. The action of NO on Drp1 is mediated through a direct phosphorylation of the protein, induced by activation of PKG. Inhibition of the NO pathway leads to mitochondrial fission accounting for a latent mitochondrial dysfunction, reducing respiratory activity and OXPHOS ATP production. Despite the apoptotic features of these mitochondria, myoblasts do not undergo spontaneous apoptosis. They acquire sensitivity to apoptosis in the presence of 3-methyl-adenine, a general inhibitor of lysosomes degradation. In addition we found a decrease of mitochondrial number and DNA when NO generation was inhibited, accompanied by increases in LC3 positive autophagosomes and cleavage of LC3. These findings suggest that mitochondrial latent dysfunction is related to induction of a mitophagic prosurvival pathway. In this study we demonstrate a new regulation of Drp1 function mediated by NO and the fundamental role played by this regulation during myogenic differentiation. In addition we show how mitophagy can act as a protective factor in the absence of NO. These results unravel a fine control check of the myogenic differentiation programme dependent on metabolic signals.

doi:10.1016/j.bbabio.2010.04.422

18P.2 Imaging of mitochondrial network and mt nucleoids in β-cells of diabetic Goto Kakizaki rats

Andrea Dlasková[1], Tomáš Špaček[1], Lydie Plecitá-Hlavatá[1],
Jitka Šantorová[1], BerkovaZuzana Berková[2], Jan Saudek[2], Petr Ježek[1]
[1]*Institute of Physiology, Academy of Sciences of the Czech Republic, v.v.i, Czech Republic*
[2]*Institute of Clinical and Experimental Medicine, Czech Republic*
E-mail: dlaskova@biomed.cas.cz