Cell Tissue Res (2017) 367:1–3
DOI 10.1007/s00441-016-2533-4

EDITORIAL

Recent advances in mitochondrial biology - integrated aspects

Chris Meisinger[1] · **Carola Hunte**[1]

Published online: 17 November 2016

Mitochondria are still best known for their role as "the cell's powerhouse". However, it is now clear that this description is a harsh underestimation of the manifold functions of this versatile and highly fascinating organelle. We have detailed knowledge of the well-known mitochondrial functions that involve them in a plethora of metabolic pathways. Several important pathways and cellular programs have been uncovered in the last decades and placed mitochondria under a novel focus (Nunnari and Suomalainen 2012). Beside its role as a central inducer of programmed cell death we have started to learn how they can be selectively degraded by autophagic mechanisms, how they might be involved in aging or adapt their functions to cellular stress responses. Research on mitochondria has expanded accordingly with the result that several of the old paradigms on mitochondria had to be reassessed: Mitochondria were considered to be static organelles. Now we know that they are highly dynamic and elongated networks that constantly change by disassembly through fission and newly connect by fusion. Mitochondria with their origin from engulfed prokaryotes were also considered largely disconnected from cellular communication. Nowadays we know that mitochondrial functions are integrated in a large variety of cellular signalling pathways adapting their functions to the need of the cell (Shutt and McBride 2013; Opalinska and Meisinger 2015).

✉ Chris Meisinger
chris.meisinger@biochemie.uni-freiburg.de

✉ Carola Hunte
carola.hunte@biochemie.uni-freiburg.de

[1] Institute of Biochemistry and Molecular Biology, ZBMZ, Faculty of Medicine and BIOSS Centre for Biological Signalling Studies, University of Freiburg, Freiburg, Germany

Furthermore, the identification of a rapidly growing number of mutations that result in impaired mitochondrial proteins in patients with often pronounced neurological, neurodegenerative or (cardio)muscular phenotypes, but also in patients suffering from cancer or diabetes, has now implicated mitochondria in a huge number of human disorders. Decades of basic research to decipher the biogenesis, maintenance and functions of mitochondria can now be exploited to dissect the pathophysiological consequences of the identified mutations and will shed new light on the importance of this organelle on cellular integrity.

This Cell and Tissue Research special issue on "Recent Advances in Mitochondrial Biology" features the latest insights into cutting-edge mitochondrial research and points out the entanglement of the deciphered physiological mechanisms with the pathophysiological consequences in human diseases.

The extraordinary task and challenges of building up an organellar proteome encoded in two separate genomes is addressed by two reviews in this issue. The article by Mai et al. (2016) inspects mammalian mitochondrial gene expression and guides us from analysis of the structural peculiarities of the mitoribosome and regulation of mitochondrial translation also through pre- and post-translational events and gives an overview of the human genes in which recent identification of mutations have been associated with mitochondrial diseases. Involvement of mitochondrial translation in degenerative processes like ageing is also the focus of the article contributed by Suhm and Ott (2016) that analysed the recent progress in our understanding how defects in mitochondrial protein expression lead to the activation of cellular stress signalling pathways and how this is connected to organismal aging. Several mitochondria-to-nucleus signalling pathways have been identified in yeast, *Caenorhabditis elegans* and mammalian cells, however, the challenge remains to identify the exact mechanism by which this communication is executed.

While the mitochondrial genome only encodes a limited number of mitochondrial proteins the vast majority of the mitochondrial proteome is encoded in nuclear DNA, translated as preproteins on cytosolic ribosomes and imported into the organelle. The essential task of translocation across the mitochondrial membranes and sorting of these cytosolic precursor proteins into their final mitochondrial compartment requires a sophisticated protein import machinery. Manganas et al. (2016) describe our current knowledge of these different protein import pathways with a focus on targeting of preproteins by a redox-controlled pathway into the intermembrane space and discuss the link to general redox homeostasis by expanding their description to the redox-systems present in the ER and bacterial periplasm that play a crucial role in cellular physiology. Erdogan and Riemer (2016) complement this overview of the mitochondrial disulfide relay system by describing our current knowledge of the mammalian machinery and provide us with a comprehensive overview how dysfunctions in this machinery can affect Fe-S-cluster maturation, calcium uptake and respiratory chain activity and result in human diseases.

The focus of the article by Demishtein-Zohary and Azem (2016) is the major translocase for matrix proteins in the inner membrane, the TIM23 complex, for which a detailed mechanistic analysis of its various subunits was performed. The authors trace the translocation steps and their regulation from initial interaction with the precursor in transit over crossing through the TIM23 channel and pulling into the matrix. While most of the studies have been performed in the model system *Saccharomyces cerevisiae* the human TIM23 complex has attracted attention as it is also involved in a variety of pathological conditions including cancer, diabetes and neurodegenerative diseases.

While TIM23 is the central translocation pore in the inner membrane, a further protein complex in the inner membrane has only been identified recently, albeit its crucial function in formation and maintenance of the cristae structure: MICOS, the mitochondrial contact site and cristae organizing system. The article by Kozjak-Pavlovic (2016) gives a comprehensive overview of our current knowledge of the identified subunits of the human MICOS complex, discusses potential new subunits and analyses the connection of MICOS with mitochondrial protein import, mitochondrial DNA stability and respiration.

While mitochondrial protein biogenesis has been analysed in detail, the identification and analysis of quality control mechanisms that maintain and adapt the mitochondrial proteome and thereby mitochondrial function are a relatively new field in mitochondrial research. Poveda-Huertes et al. (2016) investigate the fate of imported precursors that carry cleavable presequences as targeting signals upon arrival in the mitochondrial matrix and describe the various proteases involved in presequence cleavage and degradation that are required to obtain mature, stable and functional proteins. But what happens when mitochondrial protein biogenesis is hampered resulting in an imbalance in mitochondrial proteostasis? Quality-control related mitophagy, the autophagic degradation of malfunctioning or superfluous mitochondria, plays an essential role in physiological homeostasis. Dengjel and Abeliovich (2016) describe the molecular events in yeast and mammalian cells that result in targeting, segregation and engulfment of mitochondria and also highlight experimental proteomic approaches that have led to the elucidation of regulatory aspects in mitophagy. The elimination of damaged mitochondria in mammalian cells by mitophagy is mediated by the Pink1/Parkin system. Rüb et al. (2016) discuss how Pink1 is activated by a decrease in the membrane potential across the inner membrane, accumulates and thereby labels damaged mitochondria for autophagic removal via recruitment and activation of Parkin. The largely neglected role of lipids in the mitochondrial membranes and how they might play important roles in neurodegeneration is featured by Aufschnaiter et al. (2016). And last but not least Fielden et al. (2016) highlight recent findings how mitochondria serve as key targets during bacterial infections thereby integrating host cell processes in human cells.

In summary, this issue provides an overview of recent developments in mitochondrial research and how discoveries of basic mechanisms and principles may play important roles in pathophysiology.

References

Aufschnaiter A, Kohler V, Diessl J, Peselj C, Carmona-Gutierrez D, Keller W, Büttner S (2016) Mitochondrial lipids in neurodegeneration. Cell Tissue Res. doi:10.1007/s00441-016-2463-1

Demishtein-Zohary K, Azem A (2016) The TIM23 mitochondrial protein import complex: function and dysfunction. Cell Tissue Res. doi:10.1007/s00441-016-2486-7

Dengjel J, Abeliovich H (2016) Roles of Mitophagy in cellular physiology and development. Cell Tissue Res. doi:10.1007/s00441-016-2472-0

Erdogan AJ, Riemer J (2016) Mitochondrial disulfide relay and its substrates: mechanisms in health and disease. Cell Tissue Res. doi:10.1007/s00441-016-2481-z

Fielden LF, Kang Y, Newton HJ, Stojanovski D (2016) Targeting mitochondria: how intravacuolar bacterial pathogens manipulate mitochondria. Cell Tissue Res. doi:10.1007/s00441-016-2475-x

Kozjak-Pavlovic V (2016) The MICOS complex of human mitochondria. Cell Tissue Res. doi:10.1007/s00441-016-2433-7

Mai N, Chrzanowska-Lightowlers ZMA, Lightowlers RN (2016) The process of mammalian mitochondrial protein synthesis. Cell Tissue Res. doi:10.1007/s00441-016-2456-0

Manganas P, MacPherson L, Tokatlidis K (2016) Oxidative protein biogenesis and redox regulation in the mitochondrial intermembrane space. Cell Tissue Res. doi:10.1007/s00441-016-2488-5

Nunnari J, Suomalainen A (2012) Mitochondria: in sickness and in health. Cell 148:1145–1159

Opalinska M, Meisinger C (2015) Metabolic control via the mitochodnrial protein import machinery. Curr Opin Cell Biol 33:42–48

Poveda-Huertes D, Mulica P, Vögtle N (2016) The versatility of the mitochondrial presequence processing machinery: cleavage, quality control and turnover. Cell Tissue Res. doi:10.1007/s00441-016-2492-9

Rüb C, Wilkening A, Voos W (2016) Mitochondrial quality control by the Pink1/Parkin system. Cell Tissue Res. doi:10.1007/s00441-016-2485-8

Shutt TE, McBride HM (2013) Staying cool in difficult times: mitochondrial dynamics, quality control and the stress response. Biochim Biophys Acta 1833:417–424

Suhm T, Ott M (2016) Mitochondrial Translation and cellular stress response. Cell Tissue Res. doi:10.1007/s00441-016-2460-4