

Editorial

Mitochondria and Ageing

Christiaan Leeuwenburgh,¹ Reinald Pamplona,² and Alberto Sanz³

¹ Division of Biology of Aging, Department of Aging and Geriatric Research, College of Medicine, Institute on Aging, University of Florida, Gainesville, FL 32611, USA

² Department of Experimental Medicine, Faculty of Medicine, University of Lleida-IRBLleida, 25008 Lleida, Spain

³ Mitochondrial Gerontology and Age-Related Diseases Group, Institute of Biomedical Technology and Tampere University Hospital, University of Tampere, 33014 Tampere, Finland

Correspondence should be addressed to Alberto Sanz, alberto.sanz@uta.fi

Received 26 May 2011; Accepted 26 May 2011

Copyright © 2011 Christiaan Leeuwenburgh et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

During the last two decades, interest relating to mitochondria in the field of aging has grown exponentially. Nowadays, it is known that mitochondria are more than just the powerhouses of the cell. They participate in almost every aspect of metabolism. The more we learn about mitochondria, the more fascinating they become and the more they seem to be implicated in aging. Originally, the gerontological community became interested in mitochondria due to their role in the generation of reactive oxygen species (ROS). D. Harman proposed his renowned free radical theory of aging in 1956 [1], reformulating it 16 years later as the mitochondrial free radical theory of aging (MFRTA) [2] in order to emphasise the fact that mitochondria were simultaneously both the main generators and the main targets of free radicals. Since then, many laboratories have published an extensive volume of data both supporting and refuting the MFRTA. Presently, new theories have been put forward suggesting a role for mitochondria in aging which is independent of the generation of ROS. For example, it has been proposed that aging is caused by the accumulation of mutations and large-scale deletions in mitochondrial DNA (mtDNA), which may partly arise from the inherent error rate of mtDNA polymerase gamma rather than oxidative damage [3]. It has also been proposed that aging can be caused by an alteration of the redox homeostasis, since mitochondria regulate the relative levels of NADH/NAD⁺, NADPH/NADP⁺, and GSH/GSSG [4].

The considerable attention that mitochondria have attracted is well represented in this special issue. Different authors present new discoveries from their laboratories or

review the latest advances in their fields of expertise. The role of mtDNA in aging and cancer is a popular and highly debatable topic. This is illustrated by three articles in the “Mitochondria and Aging” special issue. Specifically, R. Gredilla in “DNA damage and base excision repair in mitochondria and their role in aging” describes the substantial progress that has been achieved in understanding the repair mechanisms relevant to mtDNA. It is currently known that mtDNA has a sophisticated repair system adapted to the particular needs of an environment characterised by high levels of ROS. C. Desler et al. in “The importance of mitochondrial DNA in aging and cancer” and A. M. Czarnecka and E. Bartnik in “The role of the mitochondrial genome in ageing and carcinogenesis” analyse the contribution of mitochondria to both the origin and progression of cancer. Several interesting correlations are revealed; however, further research is needed before more definite conclusions can be reached. This will require the implementation of new techniques to measure every aspect of mitochondrial function in detail in combination with high-throughput screening. L. Staunton et al. in “Proteomic profiling of mitochondrial enzymes during skeletal muscle aging” describe how proteomic profiling can help to achieve this, whereas E. Barbieri et al. in “Morpho-functional and biochemical approaches for studying mitochondrial changes during myoblasts differentiation” demonstrate a practical application of the techniques in the study of cellular fate. Although the role of mitochondria in cell differentiation is not yet understood, available data indicate that they play a major role and that certain changes in mitochondrial function are essential to complete cellular differentiation.

Dietary restriction (DR) is the most widely used intervention to extend lifespan. Currently, numerous laboratories worldwide are searching for genetic targets that will allow an increased lifespan without reducing the number of calories. It is well established that mitochondria are major contributors to the cellular adaptations needed to prolong lifespan during DR. However, the mechanisms or pathways involved have yet to be completely elucidated. Organisms with a short lifespan, such as yeast, offer an excellent opportunity for screening. B. Li et al. in "*Identification of potential calorie restriction-mimicking yeast mutants with increased mitochondrial respiratory chain and nitric oxide levels*" use this approach to identify new genes implicated in lifespan extension by DR. For example, they show evidence that nitric oxide produced by complex IV triggers changes that elicit lifespan extension. Several mechanisms have been proposed to underlie the increase in lifespan by DR, an increase in the deacetylase activity of sirtuins and an augmentation of mitochondrial biogenesis being two of them. G. R. Wagner and R. M. Payne in "*Mitochondrial acetylation and diseases of aging*" discuss the role of mitochondrial deacetylases in aging. The importance of mitochondrial sirtuins has recently been documented by articles describing their essential role in the activation of protection against oxidative damage during DR [12, 13]. Mitochondrial biogenesis is another leading topic in aging research. One of the major regulators of this process is peroxisome-proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α). T. Wenz in "*Mitochondria and PGC-1 α in aging and age-associated diseases*" discusses the alteration of mitochondrial biogenesis in aging and how PGC-1 α can be used as a novel therapy. New treatments are needed to protect against neurodegenerative diseases, one of the most devastating consequences of aging. Calcium is a key player in the intercommunication of different cellular organelles as reviewed by J. P. Decuypere et al. in "*IP₃ receptors, mitochondria, and Ca²⁺ signaling: implications for aging*." Upon intercommunication damage, cellular homeostasis is lost, resulting in cellular death or transformation. R. Kumar and H. Atamna in "*Therapeutic approaches to delay the onset of Alzheimer's disease*" propose two complementary approaches to delay the onset of Alzheimer's disease. Boosting mitochondrial metabolism should decrease amyloid- β peptide accumulation. Coincidentally, exercise increases mitochondrial function and decreases the concentration of markers of Alzheimer's disease [16]. Deregulation of metal transition homeostasis is increasingly recognized as a major problem during aging [17].

If the past is described as good and the present as promising, then the future will likely be very bright. However, there are many challenges that must be overcome to understand completely the role of mitochondria in aging and enable the development of new therapeutic approaches. The development of new techniques to study mitochondrial function *in vivo* is of the utmost priority. Most of our knowledge about how mitochondria work is based on data from isolated organelles. As *in vitro* systems are prone to artifacts, an *in vivo* approach would prove much more reliable. Cell culture offers an alternative approach, but is restricted by the fact that oxygen pressure is a major determinant of mitochondrial

function and levels used are often not representative of physiological concentrations. For success, we must aim for excellence. Therefore, we must strive for the situation which enables the quantification of measurements in model organisms and human patients *in vivo*. Difficult? Maybe. Possible? Yes. In summary, for all of us interested in understanding these fascinating organelles, we are living in exciting times. But if we work hard, the future will be even more promising.

Christiaan Leeuwenburgh
Reinald Pamplona
Alberto Sanz

References

- [1] D. Harman, "Aging: a theory based on free radical and radiation chemistry," *Journal of Gerontology*, vol. 11, no. 3, pp. 298–300, 1956.
- [2] D. Harman, "The biologic clock: the mitochondria?" *Journal of the American Geriatrics Society*, vol. 20, no. 4, pp. 145–147, 1972.
- [3] A. Trifunovic and N. G. Larsson, "Mitochondrial dysfunction as a cause of ageing," *Journal of Internal Medicine*, vol. 263, no. 2, pp. 167–178, 2008.
- [4] D. P. Jones, "Radical-free biology of oxidative stress," *American Journal of Physiology*, vol. 295, no. 4, pp. C849–C868, 2008.
- [5] R. Gredilla, "DNA damage and base excision repair in mitochondria and their role in aging," *Journal of Aging Research*, vol. 2011, Article ID 257093, 9 pages, 2011.
- [6] C. Desler, M. L. Marcker, K. K. Singh, and L. J. Rasmussen, "The importance of mitochondrial DNA in aging and cancer," *Journal of Aging Research*, vol. 2011, Article ID 407536, 9 pages, 2011.
- [7] A. M. Czarnecka and E. Bartnik, "The role of the mitochondrial genome in ageing and carcinogenesis," *Journal of Aging Research*, vol. 2011, Article ID 136435, 10 pages, 2011.
- [8] L. Staunton, K. O'Connell, and K. Ohlendieck, "Proteomic profiling of mitochondrial enzymes during skeletal muscle aging," *Journal of Aging Research*, vol. 2011, Article ID 908035, 9 pages, 2011.
- [9] E. Barbieri, M. Battistelli, L. Casadei et al., "Morphofunctional and biochemical approaches for studying mitochondrial changes during myoblasts differentiation," *Journal of Aging Research*, vol. 2011, Article ID 845379, 16 pages, 2011.
- [10] B. Li, C. Skinner, P. R. Castello et al., "Identification of potential calorie restriction-mimicking yeast mutants with increased mitochondrial respiratory chain and nitric oxide levels," *Journal of Aging Research*, vol. 2011, Article ID 673185, 16 pages, 2011.
- [11] G. R. Wagner and R. M. Payne, "Mitochondrial acetylation and diseases of aging," *Journal of Aging Research*, vol. 2011, Article ID 234875, 13 pages, 2011.
- [12] S. Someya, W. Yu, W. C. Hallows et al., "Sirt3 mediates reduction of oxidative damage and prevention of age-related hearing loss under caloric restriction," *Cell*, vol. 143, pp. 802–812, 2010.
- [13] X. Qiu, K. Brown, M. D. Hirschey, E. Verdin, and D. Chen, "Calorie restriction reduces oxidative stress by SIRT3-mediated SOD2 activation," *Cell Metabolism*, vol. 12, no. 6, pp. 662–667, 2010.
- [14] T. Wenz, "Mitochondria and PGC-1 α in aging and age-associated diseases," *Journal of Aging Research*, vol. 2011, Article ID 810619, 12 pages, 2011.

- [15] R. Kumar and H. Atamna, "Therapeutic approaches to delay the onset of Alzheimer's disease," *Journal of Aging Research*, vol. 2011, Article ID 820903, 11 pages, 2011.
- [16] K. Y. Liang, M. A. Mintun, A. M. Fagan et al., "Exercise and Alzheimer's disease biomarkers in cognitively normal older adults," *Annals of Neurology*, vol. 68, no. 3, pp. 311–318, 2010.
- [17] J. Xu, E. Marzetti, A. Y. Seo, J. S. Kim, T. A. Prolla, and C. Leeuwenburgh, "The emerging role of iron dyshomeostasis in the mitochondrial decay of aging," *Mechanisms of Ageing and Development*, vol. 131, no. 7-8, pp. 487–493, 2010.
- [18] J.-P. Decuypere, G. Monaco, L. Missiaen, H. De Smedt, J. B. Parys, and G. Bultynck, "IP₃ receptors, mitochondria, and Ca²⁺ signaling: implications for aging," *Journal of Aging Research*, vol. 2011, Article ID 920178, 20 pages, 2011.

