Directions in Science
TheScientificWorldJOURNAL (2009) 9, 250–254
ISSN 1537-744X; DOI 10.1100/tsw.2009.33

TheScientificWorldJOURNAL
www.thescientificworld.com

Impact of Mitochondrial Dynamics on Organismic Aging

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Received February 3, 2009; Revised March 27, 2009; Accepted March 29, 2009; Published April 1, 2009

KEYWORDS: mitochondria, mitochondrial dynamics, fusion, fission, *Podospora anserina*, aging, autophagy, reactive oxygen species

Biological aging is accompanied by progressive and irreversible impairments of physiological functionality with concomitant increases in morbidity and mortality. Aging is governed by an intricate network of various molecular pathways that affect the cell. In many eukaryotic organisms studied so far, the powerhouses of the cell, mitochondria, are, on the one hand, mandatory to keep the cell alive due to a number of metabolic activities. On the other hand, these organelles were found to play a crucial role in processes like apoptosis and aging. While the former is initiated by the release of death-inducing factors like cytochrome-c, "apoptosis-inducing factor" (AIF), endonuclease G, and Smac/DIABLO from the mitochondria[1], reactive oxygen species (ROS) formed during respiratory activity are among the key factors that contribute to cellular aging, according to the "Mitochondrial Theory of Aging"[2]. Therefore, mitochondria have been the target of dedicated research in order to understand the cellular pathways these organelles effect and how their functionality is regulated[3,4].

An important regulatory factor of mitochondrial function is the dynamic morphology transitions of these organelles. Spherical mitochondria can be conveniently distributed within a cell and segregated to daughter cells. Mitochondrial fusion is essential during embryonic development and biogenesis of sperm cells in *Drosophila melanogaster*[5], and is important for content mixing of mitochondria[6]. Compounds such as metabolites, oxygen, proteins, lipids, and mtDNA can be efficiently transferred in the mitochondrial compartment. Mitochondrial fusion was shown to enable the complementation of mtDNA defects[7,8]. Moreover, the inner membrane potential ($\Delta\Psi_M$) can also be transmitted between fusing mitochondria, allowing "electric coupling" and efficient transfer of energy[9]. Groundbreaking insights into how mitochondrial morphological transitions are regulated have been gained from research on baker's yeast *Saccharomyces cerevisiae*[10,11]. In yeast, fission is mainly performed by Dnm1p, Mdv1p, and Fis1p[12,13,14,15,16]. Fis1p is located in the outer mitochondrial membrane and interacts with Mdv1p. Mdv1p binds to Dnm1p via a WD40 domain. Dnm1p is a large GTPase, which is regarded as the "master regulator of mitochondrial fission" in yeast[10]. Homologs of Dnm1p have been identified in various organisms, including nematodes[17], flies[18], and mammals[19], suggesting an evolutionarily conserved mechanism of mitochondrial division. The molecular machinery executing mitochondrial fusion in yeast consists of Fzo1p, Ugo1p, and Mgm1p, in addition to regulatory proteins. Fzo1p is a large GTPase situated in the outer mitochondrial membrane, which is needed for tethering and outer-membrane

fusion of juxtaposed mitochondria[20,21,22,23,24]. The exact role of the outer membrane protein Ugo1p in the fusion process has not been clearly elucidated so far. Mgm1p belongs to the class of large GTPases and has been shown to be needed for inner membrane fusion and remodeling of the cristae membranes[22,25]. The human orthologue of Mgm1, OPA-1, is known to have different splice variants that can be proteolytically processed at different sites to generate different isoforms[26,27,28,29,30,31]. Importantly, OPA-1 deficiency and mutation, respectively, are associated with a number of diseases (e.g., ADOA [autosomal dominant optic atrophy], ataxia, deafness, multiple sclerosis–like disorders)[32,33,34,35].

Mitochondrial morphology transitions have been recently shown to affect the aging of fungal model systems such as yeast and the filamentous ascomycete *Podospora anserina,* which has been a convenient model organism for the study of aging for more than 50 years[36,37,38].

The *P. anserina* mutant *PaDnm1*::ble, which is impaired in mitochondrial fission due to the deletion of the fission gene *PaDnm1*, has been characterized in recent studies[39,40]. Interestingly, in contrast to most other *P. anserina* longevity mutants, *PaDnm1*::ble does not display phenotypic defects (e.g., slow growth rate, reduced fertility, sterility). Therefore, the healthy period of the lifetime, the health span, is extended in *PaDnm1*::ble. In *PaDnm1*::ble, the normally short filamentous mitochondria appear to be highly elongated and in some cases interconnected[39]. On standard complex growth medium, *PaDnm1*::ble isolates benefit from a highly increased mean lifespan (244 vs. 22 days wild-type). Factors proposed to be responsible for the beneficial effect on aging are (1) a stabilized mitochondrial genome, (2) delayed fragmentation of mitochondria, (3) decreased ROS generation, and (4) increased resistance to apoptosis stimulation[39,40]. The last point suggests that the activation of recently identified apoptotic components like metacaspases in the terminal stage of the *P. anserina* life[41,42] is also delayed in this particular mutant. Significantly, elevated resistance against apoptotic stimulation has also been demonstrated in Dnm1/Drp1 mutants of yeast[43], *Caernorhabditis elegans*[44], *D. melanogaster*[45,46], and mammalian cell lines[47,48,49,50] in which the gene that encodes the corresponding PaDNM1 orthologue has been deleted or down-regulated. Collectively, the studies show that *PaDnm1*::ble not only displays an extended life span, but also a prolonged health span, underlining that *P. anserina* is a suitable model organism to study molecular pathways leading to healthy aging.

In addition to apoptosis regulation, the control of mitochondrial dynamics has recently been identified to be important for processes that might also play vital roles for aging, autophagy of dysfunctional mitochondria (mitophagy), and resistance to ROS, respectively. Mitophagy is regarded as a pathway to recycle dysfunctional or damaged mitochondria[51]. Therefore, mitophagy plays an important role for the quality control of mitochondria. Recently, mitochondria were found to divide asymmetrically in a Drp1-dependent manner[52]. One mitochondrion retained its normal membrane potential and was able to fuse with other mitochondria, whereas the other had a lowered $\Delta\Psi_M$ and decreased levels of the fusion protein OPA-1[52]. This way, the damaged mitochondrion was removed from the mitochondrial population, increasing the chance for its degradation by the autophagosome. At present, it is unclear whether this intriguing mechanism is decreased during aging and if this could also account for increased levels of dysfunctional mitochondria in old cells.

The *C. elegans* homologue of OPA-1, EAT-3, was identified as an essential factor for resistance against ROS[53]. If in loss-of-function mutants of *eat3,* the *sod2* gene, encoding a mitochondrial superoxide dismutase, is down-regulated, phenotypic defects like decreased brood size are enhanced. Moreover, the *eat3* mutants are also much more sensitive to the addition of a metabolic generator of superoxide anions[53]. In a mammalian cell line, it was shown that transient treatment with the ROS H_2O_2 impairs mitochondrial dynamics and that in response to this stress, an up-regulation of various fusion and fission genes at the transcript level was found[54]. These intriguing results connect the regulation of mitochondrial morphology to the defense against oxidative stress, which might constitute a new link in the complex network that regulates aging at the cellular level.

The identification and characterization of novel cellular pathways that might bear the potential to increase the healthy period of life is one of the desired aims of experimental aging research. Mitochondrial dynamics regulation has emerged as a candidate for achieving this goal, at least in two

fungal model systems, *S. cerevisiae* and *P. anserina*. It will certainly be interesting to see whether or not these molecular pathways also play similar roles in higher biological systems.

ACKNOWLEDGMENTS

The author wishes to thank Prof. Dr. Heinz D. Osiewacz (Johann W. Goethe University, Frankfurt, Germany) for his support. The experimental research of the author was funded by the European Commission via the Integrated Project with the acronym MiMage (LSHM-CT-2004-512020).

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This article should be cited as follows:

Scheckhuber, C.Q. (2009) Impact of mitochondrial dynamics on organismic aging. *TheScientificWorldJOURNAL* **9**, 250–254. DOI 10.1100/tsw.2009.33.