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Editorial

Editorial: Mitophagy in physiology and pathology

Mitophagy targets selectively damaged or superfluous mitochondria for lysosomal degradation. Accumulating evidence indicates that the efficient removal of dysfunctional organelles is crucial for development and the maintenance of cellular and organismal health. Alterations in mitophagy contribute to developmental defects, ageing and age-associated pathologies such as cancer, cardiovascular diseases, metabolic syndrome and neurodegenerative disorders, among others. This special issue of *Mechanism of Ageing and Development* presents a series of articles that discuss recent advances and current challenges in the field, which need to be addressed before modulation of mitophagy can be considered for therapeutic intervention.

Mitophagy serves a housekeeping function to ensure elimination of old and damaged mitochondria under physiological conditions or help cells adapt to their specific developmental programs. Under stress conditions, induction of mitophagy contributes to preservation of cellular energy homeostasis promoting stress resistance and survival. Recent studies have revealed that defects in mitophagy accelerate the ageing process and are implicated in many pathological conditions including cancer, metabolic disease, cardiovascular diseases and neurodegeneration disorders, supporting the contribution of mitophagy to health and disease (Palikaras et al., 2018).

To highlight recent discoveries and open questions in the field, we present this Special issue, which includes nine articles focusing on the regulation and functional aspects of mitophagy and its relationship with mitochondrial dynamics, DNA repair mechanisms and iron homeostasis. The last two articles discuss the emerging role of mitophagy in neuronal homeostasis whose dysregulation accelerates ageing and increases susceptibility to age-associated neurodegeneration. An outline of the major topics covered in this issue is presented below.

A review by Babbar and colleagues surveys the signaling pathways that regulate DNA damage and repair and their links to mitophagy regulation. Furthermore, the authors discuss the complex interplay between mitochondrial dysfunction and genomic instability, with respect to normal ageing and the pathophysiology of cancer, diabetes and neurodegeneration. Finally, they consider the therapeutic potential of combinational approaches targeting DNA repair and mitophagy to battle various pathological conditions in humans (Babbar et al., 2020).

The article by Aman and co-authors highlights the roles of nicotinamide adenine dinucleotide (NAD^+) in modulating ageing. NAD^+ levels decline with age and depletion of NAD^+ has been shown to accelerate ageing and the onset of age-associated diseases. The authors explore the cellular and molecular underpinnings of this phenomenon placing emphasis on mammalian ageing. In this context, they highlight the important contribution of NAD^+ to mitochondrial homeostasis through coordination of the opposing processes of mitochondrial biogenesis and mitophagy. Moreover, they discuss the therapeutic potential of boosting endogenous NAD^+ levels as a means to induce mitophagy in an effort to combat neurodegenerative disorders, including Alzheimer's disease. Finally, the authors discuss the potential use of artificial intelligence to provide new mechanistic insight into how perturbations of the NAD^+ - mitophagy axis may drive ageing and age-associated pathologies (Aman et al., 2020).

In a methods article, Montava-Garriga and colleagues briefly discuss various methodologies to detect mitophagy placing special emphasis on the mito-QC reporter, which bears a tandem mCherry-GFP tag fused to the mitochondrial targeting sequence of the outer mitochondrial membrane protein FIS (amino acids 101–152). Then, the authors describe in detail an image analysis tool, the so called mito-QC Counter, for mitophagy quantitation. This newly developed macro for FIJI allows the reliable semi-quantitative mitophagy assessment in different cell lines and upon various stimuli as well as in tissues of the mito-QC transgenic mice. Therefore, the mito-QC Counter macro for FIJI is very useful in quantifying mitophagy both *in vivo* and *in vitro* (Montava-Garriga et al., 2020).

The next article addresses the role of mitochondrial dynamics in promoting ageing and age-associated diseases. In this review, Liu and colleagues describe the conserved proteins and mechanisms that govern mitochondrial fusion and fission. Furthermore, the authors discuss recent findings that link these processes to specific hallmarks of ageing including cell viability, senescence, mitochondrial function and mitochondrial quality control mechanisms. Connections to nutrient and energy sensing pathways are also mentioned. Finally, the authors discuss emerging observations suggesting that imbalanced mitochondrial dynamics contribute to various human pathologies such as cardio-metabolic disorders and neurodegenerative diseases, among others (Liu et al., 2020).

In their review, Leboulet and colleagues survey the mechanisms that govern mitophagy and the available tools and methods for monitoring *in vivo* this process in the model organism *Caenorhabditis elegans*. Moreover, the authors discuss the physiological roles of mitophagy in the context of development, ageing and adaptation to various intrinsic and extrinsic stimuli. Finally, they discuss the powerful platform that *C. elegans* offers to model human diseases and study the role of impaired mitophagy in neurodegeneration (Leboutet et al., 2020).

A research article by Henkel and co-authors examines the roles of sorting nexin ATG24/SNX4 in regulating general autophagy and selective forms of autophagy, mainly pexophagy and to a lesser extent mitophagy, with important consequences for development and ageing in the filamentous fungus *Podospora anselina*. This organism has been previously established as a model to study the molecular basis of healthy ageing (Henkel et al., 2020).

In their review, Zhang and co-authors discuss the essential functions of mitophagy in the heart within physiological and pathological contexts and the underlying molecular mechanisms. A growing body of

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evidence indicates that cardiac ageing is associated with impaired mitophagy leading to accumulation of dysfunctional mitochondria. Moreover, the authors discuss recent studies suggesting that mitophagy is transiently induced and then is reduced in the heart in response to cardiac stress and that excessive mitophagy may be detrimental. The final section is devoted to the potential cardioprotective effects of some mitophagy- inducing natural compounds (i.e. urolithin A, spermidine etc.), which have been shown to be beneficial in model organisms (Zhang et al., 2020).

The last two articles discuss the contribution of mitophagy to neuronal health and the emerging observations that link several neurological and psychiatric pathologies to mitophagy defects. Palikaras and Tavernarakis discuss the importance of healthy mitochondria in maintaining synaptic activity and plasticity focusing on the vital role of mitophagy in mediating the elimination of dysfunctional organelles from pre- and post-synaptic endings (Palikaras and Tavernarakis, 2020). Finally, a review by Schiavi, Strappazzon and Ventura discusses the basic molecular mechanisms that regulate mitophagy and iron homeostasis and how their perturbations accelerate the ageing process and the onset of age-related neurodegenerative diseases with emphasis on Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. Finally, the authors discuss emerging observations suggesting the existence of a cross talk between mitophagy and iron metabolism, which influences lifespan and health. Indeed, impaired mitophagy and iron overload accelerate ageing and increase the risk of age-related neuronal pathologies (Schiavi et al., 2020).

In closing this Editorial, we would like to thank all the authors and referees, for their efforts and contributions, towards compiling this special issue on the topic of mitophagy, and hope that it will provide a useful point of reference for the biomedical research community.

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Maria Markaki
Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas, Heraklion, 70013, Crete, Greece

Nektarios Tavernarakis[a,b,*]
[a] *Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas, Heraklion, 70013, Crete, Greece*
[b] *Department of Basic Sciences, School of Medicine, University of Crete, Heraklion, 70013, Crete, Greece*
E-mail address: tavernarakis@imbb.forth.gr.

[*] Corresponding author at: Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology-Hellas, Heraklion, 70013, Crete, Greece.