

EDITORIAL FOCUS

Respiratory resilience as form fades: skeletal muscle mitochondrial adaptation in aging

 John Noone^{1,2,3,4,5}

¹Department of Physical Education and Sport Sciences, Faculty of Education and Health Sciences, University of Limerick, Limerick, Ireland; ²Physical Activity for Health Research Cluster, University of Limerick, Limerick, Ireland; ³Sport and Human Performance Research Centre, University of Limerick, Limerick, Ireland; ⁴Limerick Digital Cancer Research Centre, University of Limerick, Limerick, Ireland; and ⁵Health Research Institute, University of Limerick, Limerick, Ireland

Mitochondrial adaptation with aging has been long debated. Challenges in study design, methodological variability, comorbidities, and laboratory-to-laboratory inconsistencies make interpretation of mitochondrial adaptation notoriously difficult, untangling such can feel like navigating a complex web, or fittingly, a reticulum. A major source of this inconsistency has stemmed from imprecise or misapplied terminology. As emphasized in the timely perspective by Monzel et al. (1), adopting precise language to delineate facets of mitochondrial biology is essential for interpreting adaptations, whether to exercise, disease, therapeutics, or aging.

In this journal, Leija et al. (2) add important depth to this debate with their article “Resilience of the Mitochondrial Reticulum in Aging.” The Brooks laboratory, long recognized for advancing our understanding of lactate metabolism in exercise, now challenges the dogma of inevitable mitochondrial decline with aging. Using a hind-limb mixed muscle (MM) approach, the authors compared mitochondrial energetics (oxidative phosphorylation), structural features (morphology), and behavior (fusion-fission dynamics) between young (4 mo) and older (24 mo) male and female NIA C57BL/6JN mice. Although translating these findings to human aging remains complex and sometimes controversial, the murine model provides valuable insight. By carefully managing biological and behavioral variability, the use of such helps to underscore the influence of the abovementioned factors on mitochondrial properties, advancing our understanding of how aging shapes the nature of this organelle.

Along with other integral factors, from reactive oxygen species (ROS) emission, calcium regulation, and adaptation of mitochondrial membrane potential, the controversy surrounding skeletal muscle mitochondrial adaptation with age has often centered on respiratory capacity, particularly in humans. Some studies report clear declines in skeletal muscle mitochondrial energetics with age (3), whereas others argue that observed changes are largely shaped by factors ranging from mitochondrial abundance and the use of supraphysiological substrate concentrations, to the age-related loss of muscle mass, aerobic capacity, and power output (4, 5). In this context, findings from Leija et al. (2) are noteworthy: following isolation of MM mitochondria, authors observed no significant age-related difference in

mitochondrial coupling efficiency (ADP:O) when assessed under physiological substrate concentrations. However, they did report a significant decrease in the respiratory control ratio (RCR; state 3/state 4 oxygen consumption) in older mice, a finding consistent with human observations by Porter et al. (6), indicative of diminished mitochondrial integrity in aged muscle. Interestingly, Leija et al. (2) further illustrated that mitochondrial content remained unchanged between young and old mice. However, older mice did express declination in protein abundance of mitochondrial substrate transporter proteins (mMCT1, mPC1, CPT1b, CPT2, and HADH), multienzyme complex activity (LDH and PDH), and protein expression of key regulators of mitochondrial dynamics (DRP1, FIS1, and MFN1), suggestive of structural remodeling of the mitochondrial reticulum, without change in mitochondrial abundance. Supporting this phenotypic adaptation with age, both two-dimensional (2-D) and 3-D confocal microscopy revealed significant reductions in branch length, diameter, area, and mitochondrial form factor in older skeletal muscle. Taken together, these comprehensive findings suggest that age-related alterations in skeletal muscle mitochondrial biology may be driven more by structural and dynamic features, such as the locality of ATP synthesis, than by direct impairments in the process of ATP homeostasis itself.

Aging imposes considerable strain on the body, manifested through primary, antagonistic, and integrative hallmarks. Among these, mitochondria, owing to their sensitivity to damage, have been implicated as a central driver, with so-called “dysfunction” (or more precisely, adapted function) recognized as a key antagonistic hallmark of aging (7). Yet, whether these functional adaptations arise from impaired proton and electron transfer or from structural disruptions within the mitochondrial reticulum remains unresolved, a classic “chicken-and-egg” scenario. By carefully controlling covariates that shape mitochondrial adaptation (sex, body composition, physical activity, comorbidities, and socioeconomic status) through the use of NIA C57BL/6JN mice, Leija et al. (2) suggest attention should be directed to organelle form as opposed to functionality, prompting a reevaluation of the mitochondrial theory of aging and the need for extrapolation in humans. Mitochondrial dynamics, regulated by the interplay of fusion, fission, and mitophagy, are



Correspondence: J. Noone (john.noone@ul.ie).
Submitted 25 August 2025 / Revised 26 August 2025 / Accepted 26 August 2025



central to determining phenotype (8), and these processes are themselves strongly influenced by cardiovascular health and muscle mass. In line with this, authors propose that performance decrements in aged mice are driven primarily by alterations in mitochondrial structure and dynamics, rather than by energetic decline.

Although integral to advancing our understanding of mitochondrial physiology with aging, this work also underscores the pressing need for further study, particularly in humans. Like humans, mitochondria are highly complex with many integrated and influential processes, which were not explored, including mitochondrial autophagy (mitophagy), ROS emission, changes to membrane potential, and calcium regulation. To fully appreciate the global mitochondrial shifts imposed by aging, a comprehensive investigation of all these processes is also necessary. Given the multifaceted nature of human biology and substantial interindividual variability, addressing these questions will demand carefully designed, longitudinal randomized controlled trials. Though costly, such efforts are essential to determine where therapeutic or/and behavioral strategies directed at mitochondrial physiology should be targeted to improve overall health outcomes with aging.

Ultimately, this work may help resolve the decade-long debate surrounding mitochondrial adaptations with aging in humans—are the changes driven by mitochondrial activity, architecture, abundance, or an amalgamation of the three? The findings of Leija et al. (2) provide critical insight here, demonstrating that age-related changes in skeletal muscle mitochondria of mice are shaped more by structural features and dynamic behavior than by declines in energetic function.

DISCLAIMERS

The content and any opinions expressed in this article are those of the authors and do not necessarily represent the views of the American Physiological Society.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

J.N. drafted manuscript; edited and revised manuscript; approved final version of manuscript.

REFERENCES

1. Monzel AS, Enríquez JA, Picard M. Multifaceted mitochondria: moving mitochondrial science beyond function and dysfunction. *Nat Metab* 5: 546–562, 2023. doi:10.1038/s42255-023-00783-1.
2. Leija RG, Vázquez-Medina JP, Brooks GA. Resilience of the mitochondrial reticulum in aging. *Am J Physiol Endocrinol Metab* 329: E477–E494, 2025. doi:10.1152/ajpendo.00110.2025.
3. Joseph AM, Adhihetty PJ, Buford TW, Wohlgemuth SE, Lees HA, Nguyen LM, Aranda JM, Sandesara BD, Pahor M, Manini TM, Marzetti E, Leeuwenburgh C. The impact of aging on mitochondrial function and biogenesis pathways in skeletal muscle of sedentary high- and low-functioning elderly individuals. *Aging Cell* 11: 801–809, 2012. doi:10.1111/j.1474-9726.2012.00844.x.
4. Distefano G, Standley RA, Dubé JJ, Carnero EA, Ritov VB, Stefanovic-Racic M, Toledo FG, Piva SR, Goodpaster BH, Coen PM. Chronological age does not influence ex-vivo mitochondrial respiration and quality control in skeletal muscle. *J Gerontol A Biol Sci Med Sci* 72: 535–542, 2017. doi:10.1093/gerona/glw10.
5. Gonzalez-Freire M, Scalzo P, D'Agostino J, Moore ZA, Diaz-Ruiz A, Fabbri E, Zane A, Chen B, Becker KG, Lehrmann E, Zukley L, Chia CW, Tanaka T, Coen PM, Bernier M, de Cabo R, Ferrucci L. Skeletal muscle ex vivo mitochondrial respiration parallels decline in vivo oxidative capacity, cardiorespiratory fitness, and muscle strength: The Baltimore Longitudinal Study of Aging. *Aging Cell* 17: e12725, 2018. doi:10.1111/accel.12725.
6. Porter C, Hurren NM, Cotter MV, Bhattarai N, Reidy PT, Dillon EL, Durham WJ, Tuvdendorj D, Sheffield-Moore M, Volpi E, Sidossis LS, Rasmussen BB, Børsheim E. Mitochondrial respiratory capacity and coupling control decline with age in human skeletal muscle. *Am J Physiol Endocrinol Physiol* 309: E224–E232, 2015 [Erratum in *Am J Physiol Endocrinol Physiol* 309: E884, 2015]. doi:10.1152/ajpendo.00125.2015.
7. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: an expanding universe. *Cell* 186: 243–278, 2023. doi:10.1016/j.cell.2022.11.001.
8. Wai T, Langer T. Mitochondrial dynamics and metabolic regulation. *Trends Endocrinol Metab* 27: 105–117, 2016. doi:10.1016/j.tem.2015.12.001.