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Mitochondrion quality control for longevity promotion

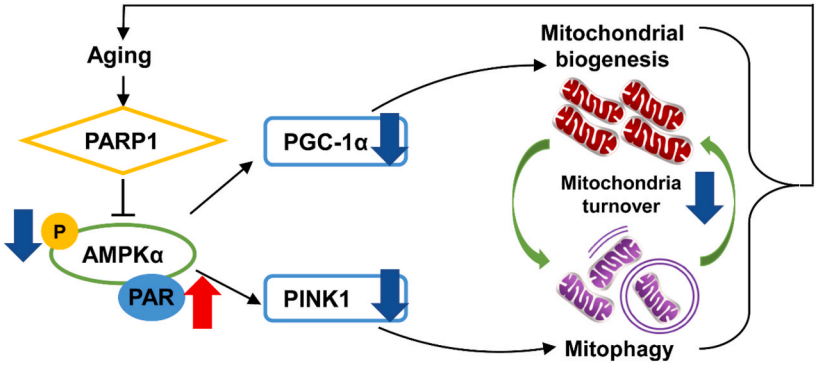
Aging is a complex process that involves a number of mechanisms, including deregulated autophagy, telomere shortening, oxidative stress, systemic inflammation, and metabolic dysfunction [1]. Mitochondria play a vital role in cell physiology, but it is still unclear how their functions are affected during aging and which cell types specifically relate to pro-longevity through mitochondrial states.

It has been previously reported that PARP1 acts in several aging mechanisms, functioning as a longevity assurance factor at a younger age [2] and as an aging-promoting factor at an older age [3]. Currently, PARP1 inhibitors are being used as antitumor drugs in clinical settings [4]. However, it is still necessary to clarify whether the reduction of PARP1 can delay the aging process and what role of the PARP1-linked signaling network plays in the aging process. Recently a research article published in Proceedings of the National Academy of Sciences of the United States of America titled "Muscle PARP1 inhibition extends lifespan through AMPKα PARylation and activation in Drosophila", Guo et al. elucidated the function of PARP1 in longevity through AMPKα, providing a theoretical basis for drug development and application [5]. Moreover, the authors also unveiled that PARP1 could interact with AMPKα and then regulate it via PARylation and the inhibition of PARP1 increases the activity of AMPKα, mitochondrial turnover and promote longevity.

Previous study has demonstrated that the activation of AMP-activated protein kinase (AMPK) exerted pro-longevity effects in diverse species, including *C. elegans* and *Drosophila* [6,7]. Pharmacological activation *via* metformin treatment promoted health span in mice [8,9]. AMPK has been explored for its involvement in controlling mitochondrial biogenesis and dynamics [10,11], as well as energy expenditure through modifying NAD + metabolism [12], but its requirment for regulating mitochondrial homeostasis during aging is still unknown.

In this new study, the authors first observed that PARP1 activity is induced in the skeletal muscle of different species, including mice, *Drosophila*, and human, during aging. To investigate the role of PARP1 in aging and longevity in vivo, Guo et al. generated PARP1 global knockdown in *Drosophila,* which has a longer lifespan and better climbing ability, suggesting that PARP1 may be involved in the muscle during aging process. To this end, PARP1 specific knockdown in *Drosophila* muscle was generated, which demonstrated that it increases lifespan by preserving mitochondrial biogenesis and function during aging. Further studies suggested that PARP1 could interact with AMPKα, and then regulate it via PARylation at residues E155 and E195, as well as inhibit its phosphorylation. The PARP1 and AMPKα double knockdown *Drosophila* proved that AMPKα is the cause of PARP1 inhibition-induced longevity. PARP1 and AMPKα double knockdown *Drosophila* also showed impaired mitophagy functions for mitochondrial turnover. Moreover, the authors demonstrated that the maintenance of mitophagy is necessary for PARP1 inhibition-mediated lifespan because the effects of knocking down the mitophagy-regulating gene PINK1 were reversed.

Taken together, this study identifies that the knockdown of PARP1, specifically in muscle, extended the lifespan of *Drosophila*. In addition, AMPKα and dynamic mitochondrial homeostasis were required to show the effects of PARP1 inhibition. Biochemical analysis indicated that muscle PARP1 exerted pro-aging effects on *Drosophila* through the regulation of AMPKα PARylation and activity, followed by manipulation of mitochondrial homeostasis. Findings in this research may contribute to the development of new therapeutic approaches for anti-aging.



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Summary scheme: Model depicting that the inhibition of PARP1 induces activation of AMPKα and then regulates mitochondrial biogenesis and PINK1-mediated mitophagy in aged flies, eventually manipulating longevity.

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Declaration of competing interest

No conflict of interest to disclose.

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