PADUA DAYS ON MUSCLE AND MOBILITY MEDICINE 2026

International Conference

March 3rd to 6th Euganean Thermae and Padua, Italy

BASICS IN AGING

ROLE OF PROHIBITIN ISOFORMS IN MITOCHONDRIAL FUNCTION WITH AGING AND EXERCISE

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Skeletal muscle is a highly metabolic and adaptable tissue that is reliant on an adequately-sized pool of healthy mitochondria to sustain its function (1,2). While mitochondrial integrity is continuously required throughout our lifespan, the importance of this organelle increases with age, as it has been reported that aged muscle exhibits a marked reduction in mitochondrial content and function (3,4). This altered mitochondrial profile has been postulated to contribute to muscle aging through several mechanisms (1), suggesting that mitochondria play a pivotal role in governing muscle health with age. Chronic exercise is a potent intervention for the enhancement of the mitochondrial reticulum, as it induces the activation of several mitochondrial quality control (MQC) pathways which ultimately improve mitochondrial function in both young and aged individuals (1,4,5). To investigate novel exercise-responsive regulators of mitochondrial function, two Prohibitin isoforms were evaluated. Situated within the inner mitochondrial membrane, Prohibitin 1 (PHB1) and Prohibitin 2 (PHB2) form a unique complex which together mediate several aspects of mitochondrial health (6), including cristae stabilization (7), OXPHOS capacity (8), mitophagy (9), and biogenesis (10). While the importance of PHBs in mediating mitochondrial homeostasis is beginning to emerge, their role during aging and exercise remains unknown. To evaluate this, PHB1 and PHB2 content was measured in young (6-8 mo) and aged (22-23 mo) mice following 6-weeks of voluntary wheel running (VWR). Importantly, with age there was a marked decline in mitochondrial PHBs, suggesting a reduced capacity to drive various mitochondrial quality control (MQC) pathways with age. While VWR was able to increase the relative abundance of PHBs, mitochondrially-localized PHBs remained unchanged following training within aged muscle, indicating that the localization of this complex may be altered. To investigate the functional significance of PHBs during exercise, PHB1 and PHB2 expression was inhibited using short-interfering RNA within C2C12 myotubes and electrically stimulated for four days to induce chronic contractile activity (CCA). Myotubes were then collected for various biochemical analyses, including respiration, confocal microscopy, flow cytometry, and protein measurements. Following a 56% reduction in PHB expression, there was a significant decline in biogenesis-related protein markers and oxygen consumption. This was accompanied by an elevation in mitochondrial ROS, fragmentation of the reticulum, and an increase in protein markers related to the integrated stress response, including eif2α and CHOP. A 3-fold increase in PINK1 protein suggests that the cellular stress observed may be mitochondrial-specific. Importantly, CCA-induced mitochondrial adaptations were ablated with knock-down of PHB2, indicating that PHB2 is required for the activation of MQC pathways commonly activated with contraction. These findings demonstrate a critical role for PHB2 in regulating MQC, thereby providing novel insight into the molecular mechanisms underpinning mitochondrial maintenance and adaptations observed in muscle with exercise.

Keywords: *Prohibitins, mitochondria, integrated stress response, aging, skeletal muscle.*

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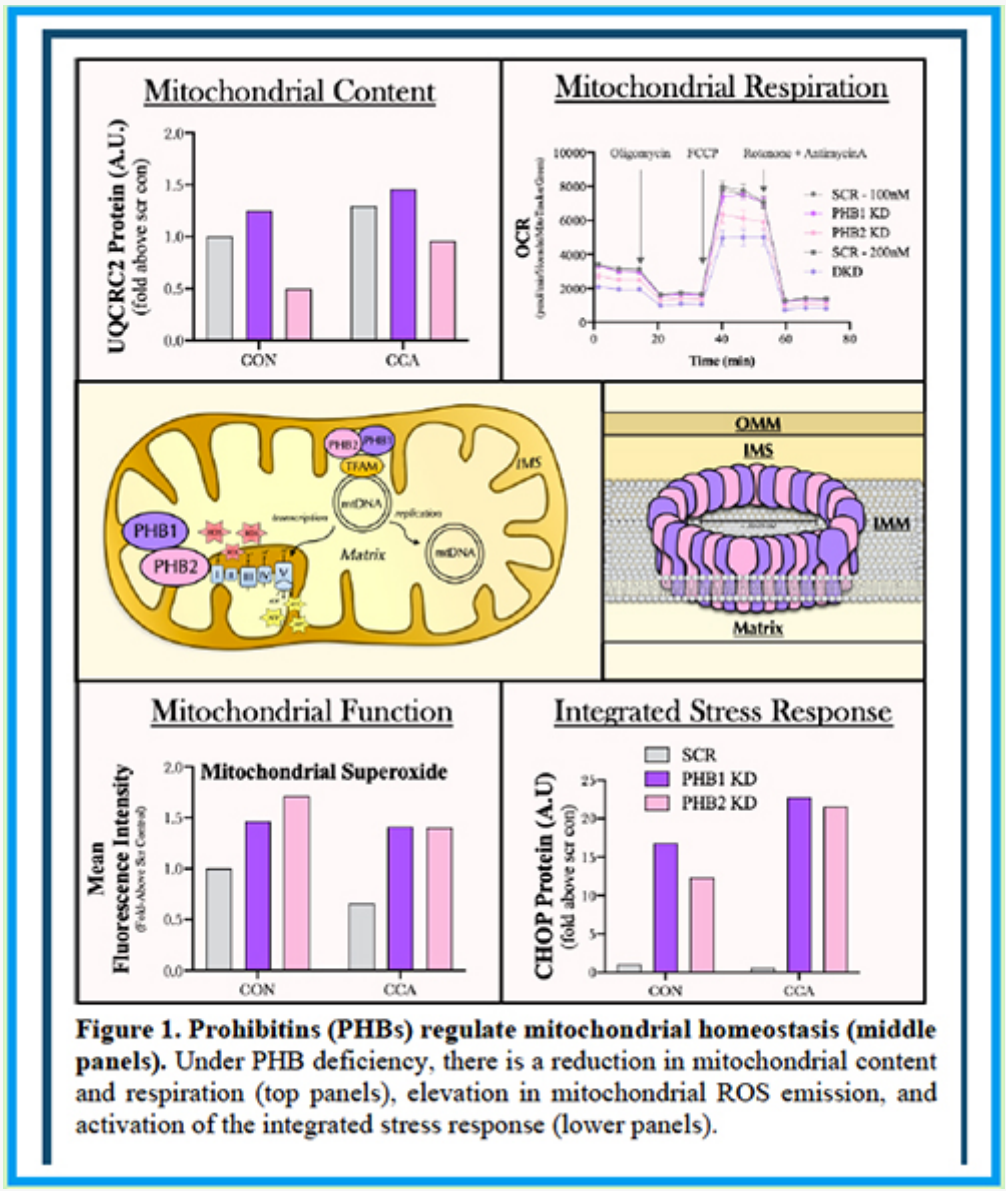

Figure 1. Prohibitins (PHBs) regulate mitochondrial homeostasis (middle panels). Under PHB deficiency, there is a reduction in mitochondrial content and respiration (top panels), elevation in mitochondrial ROS emission, and activation of the integrated stress response (lower panels).