Skeletal muscle adaptation to exercise: can we call it “Sarcohormesis”?

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More than eighty years ago, the process of adaptation of the human body in response to a specific stressor to return to normal homeostasis was termed “general adaptation syndrome”[1]. The concept was then broadened to what it is now referred to as the hormesis theory[2]. The idea of hormesis has been recently adapted to the mitochondria and has been named mitohormesis[3,4]. The term refers to an adaptive response mediated by mitochondria in which exposure to a low to mild level of stress culminates in increased stress resistance over time[3]. Usually, the main cause of this stress is the production of reactive oxygen species (ROS) (ie, oxidative stress). Noteworthy, physical exercise increases mitochondrial metabolism and ROS formation, which triggers this adaptive response leading not only to increased stress resistance (i.e. antioxidant defense), but also to a plethora of physiological adaptations that eventually culminates in extended life span [3].

Merry and Ristow [2] have recently reviewed this topic and summarized the evidence that mitohormesis is a significant adaptive-response signaling pathway that is precipitated by exercise. They suggest that mitohormesis plays a key role in mediating exercise induced adaptations. In addition to ROS, the authors state that there are other potential mitochondrial signal emitters acting to mediate adaptation in physical exercise, such as mitochondrial derived peptides (*mitokines*). Of note, both ROS and *mitokines* may elicit mitochondrial and systemic adaptations that protect the body against metabolic disturbances[2].

In another review [5], authors highlight that ROS produced as a consequence of muscle contraction may serve as signaling molecules to stimulate adaptations due to the activation of redox sensitive signaling pathway. Some of the most important redox sensitive pathways implicated in skeletal muscle adaptations are nuclear factor κB (NFκB), mitogen-activated protein kinases (MAPK) and peroxisome proliferator-activated receptor γ co-activator 1α (PGC-1α)[5]. It’s argued that they play a role in mitochondrial biogenesis, antioxidant defense, inflammation and protein turnover[5]. Thus, redox signaling may be one of the most relevant molecular mechanisms of exercise induced adaptive response (i.e. hormesis/mitohormesis) that leads to improved skeletal muscle health, once skeletal muscle is the major source of ROS during exercise[6].

Interest is emerging with regard to strategies that apply stress to muscle before, during or after exercise in order to stimulate a greater adaptation. These include restricted carbohydrate intake, blood flow restricted exercise, mechanical overload or even heating the muscles passively[7]. Indeed, with or without those strategies, physical exercise can expose skeletal muscles to distinct kinds of

stress including thermal, metabolic, oxidative, hypoxic or mechanical stress[7]. Type, volume, intensity and duration of exercise, and type of contraction activity (i.e. aerobic, resistive, concentric, eccentric, etc.) will dictate the predominant form of exercise stress. Also, stress coming from an exercise session may activate a variety of biochemical messengers that are not limited to mitochondrial ROS. For instance, high or repetitive forces over skeletal muscle (ie, mechanical overload) leads to disruption of the sarcolemma, basal lamina and active myofibrillar proteins. Literature refers to this as exercise induced muscle damage (EIMD) and is well documented in previous research[6,8]. EIMD triggers an inflammatory response mediated by neutrophils (i.e. phagocytic cells) that migrate to the trauma area and induce secretion of other agents to facilitate repair and regeneration[8]. In this scenario, ROS can be one of the agents produced by neutrophils and start adaptation signaling (i.e. a secondary source of ROS acting on skeletal muscle)[6]. However, other anabolic agents are synthetized within skeletal muscle that can mediate adaptation and muscle growth (i.e. hypertrophy) such as cytokines (*myokines*). Numerous myokines were identified including interleukins (i.e. IL-6, IL-10, etc.) that contribute to hypertrophic signaling in an autocrine-paracrine fashion[8]. In addition, mechanical stimuli alone can initiate other anabolic pathways such as muscle swelling, quiescent satellite cell proliferation and insulin-like growth factor-1 (IGF-1), the latter being considered the major extracellular mediator of skeletal muscle growth [8]. Hence, structural damage to muscle cells activate a series of relevant adaptation pathways via mechanotransduction that may be linked or not with ROS.

For the sake of these arguments, it would not be inappropriate that we extend the concept of hormesis beyond mitochondria. In this sense, "*sarcohormesis*" would be a candidate term to identify skeletal muscle adaptation to stress, particularly the stress coming from physical exertion. In other words, "*sarcohormesis*" could finely represent the compensation/supercompensation response of skeletal muscle cells to the transient homeostasis disturbances caused by exercise. Noteworthy, regarding mechanotransduction pathways, resistance exercise would be the most suitable stimuli to emblematize "*sarcohormesis*". Nevertheless, future appraisal of the term is pertinent and welcome.

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Competing interests
None declared

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