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Mitohormesis in exercise training

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ABSTRACT

Hormesis is a process whereby exposure to a low dose of a potentially harmful stressor promotes adaptive changes to the cell that enables it to better tolerate subsequent stress. In recent years this concept has been applied specifically to the mitochondria (mitohormesis), suggesting that in response to a perturbation the mitochondria can initiate and transduce a signal to the nucleus that coordinates a transcriptional response resulting in both mitochondrial and non-mitochondrial adaptations that return and maintain cellular homeostasis. In this review we summarize the evidence that mitohormesis is a significant adaptive-response signaling pathway, and suggest that it plays a role in mediating exercise-induced adaptations. We discuss potential mitochondrial emitters of retrograde signals that may activate known exercise-sensitive transcription factors to modulate transcription responses to exercise, and draw on evidence from mitochondrial dysfunction animal models to support a role for mitohormesis in mitochondrial biogenesis. Studies directly linking mitohormesis to the exercise training response are lacking, however mounting evidence suggests numerous signals are emitted from the mitochondria during exercise and have the potential to induce a nuclear transcription response, with reactive oxygen species (ROS) being the primary candidate.

1. Hormesis and exercise

Exercise training involves the repeated exposure to an acute increase in metabolic, thermoregulatory, hypoxic, oxidative and mechanical stress. It is this exposure that stimulates compensatory physiological adaptations that improve tolerance to subsequent similar stressors [1]. Achieving such adaptation is the purpose of undertaking regular exercise, and underpins the protective nature of exercise against the development of various chronic diseases [2]. The process by which an organism adapts to a specific stress in an effort to return the body to normal homeostasis was initially termed 'general adaptation syndrome' [3], before being broadened to what we now refer to as the hormesis theory [4,5]. The premises of this theory is that exposure to low continuous or higher intermittent sub-lethal doses of a stressor, that would otherwise be harmful at larger or chronic doses, promotes favorable biological adaptations which protect against greater subsequent stress. Hormesis diverges from the traditional liner response, where increasing exposure to potentially harmful stressors results in increasing levels of damage, and is best represented by a J- or bell-shaped curve indicating that very low exposure or very high exposure is detrimental, while moderate exposure is advantageous or even necessary (Fig. 1).

The principle of hormesis dates back to the 16th century when Paracelsus stated *sola dosis facit venenum*, i.e. only the dose would make the poison [6]. The term hormesis was coined later following the observation that very dilute doses of poisonous substances stimulate the growth of plants or yeast [7,8], and appears to apply directly to the exercise training response [9]. For example, endurance exercise depletes muscle glycogen and increases core temperature, and in response to training muscle glycogen storage are increased and thermoregulation is improved. If these stressors are further elevated by initiating exercise in a glycogen depleted state or training in the heat, exercise training induced improvements in muscle glycogen storage [10] and thermoregulation [11] are further enhanced. Conversely, extreme exposure to exercise heat-stress can lead to heat exhaustion [11], and chronic depletion of muscle glycogen through excessive exercise training contributes to central and peripheral fatigue associated with overtraining

Abbreviations: AMPK, 5′ adenosine monophosphate-activated protein kinase; CaMK, Ca^{2+}/calmodulin-dependent; CIT2, citrate (Si)-synthase; clk-1, clock-1; COQ7, Coenzyme Q7 homolog, ubiquinone; COX, cytochrome oxidase; ETC, electron transport chain; GLUT, glucose transporter; HIF-1, hypoxia inducible factor; JNK, c-Jun N-terminal kinases; HSF, heat shock factor; HSP, heat shock protein; MAPK, mitogen-activated protein kinases; Mckl, murine clock; mTOR, mechanistic/mammalian target of rapamycin; mtTFA, mitochondrial transcription factor A; mtDNA, mitochondrial DNA; MOTS-c, mitochondrial open reading frame of the 12S rRNA-c; NFE2l2, nuclear factor erythroid 2-related factor 2; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NNMT, Nicotinamide N-Methyltransferase; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1α; ROS, reactive oxygen species; Rtg, Retrograde regulation protein; RXRα, retinoid X receptor alpha; UPR^{mt}, mitochondrial unfolded protein response

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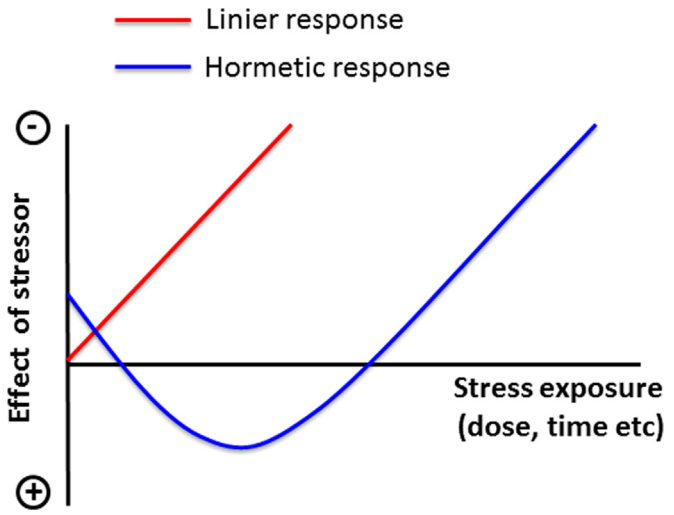

Fig. 1. Hormetic and theoretical liner response to stress. Theoretically the exposure of a cell to a stressor results in detrimental effects in cellular function which are proportional to the level of exposure (liner response). Hormesis refers to a response where a low exposure to a stressor results in beneficial adaptions which improve the function of the cell, but once a threshold level of exposure is surpassed further exposure leads to cellular damage (hormetic response). Potentially no or very little exposure to stressors may also be a disadvantage to the homeostatic function of the cell.

syndrome [12]. Therefore, and in line with the hormesis concept, increasing exercise stress can enhance cellular adaptations to an extent; however, once a threshold level of stress is exceeded exercise stress can have detrimental affects on cellular function.

2. Mitohormesis

In recent years the hormesis theory has been extended specifically to the mitochondria (mitohormesis) [13–16], with the concept being that mild perturbations in mitochondrial homeostasis coordinate a nuclear and cytosolic response that leaves the whole cell less susceptible to future perturbation. Such responses are not limited to acute cytoprotective mechanisms but can induce long-term metabolic alterations and stress resistance. During exercise mitochondria metabolism in increased to meet the energy demands of the exercise task. Therefore, if the mitochondria are capable of regulating their own, as well as cell-wide and possibly system-wide, responses to changes in homeostasis it stands to reason that mitohormesis signaling would be a central mechanism regulating exercise-mediated adaptation. In this article we will review the evidence that mitohormesis is contributing to the signaling of exercise adaptation, and postulate potential mediators of the mitohormetic response.

3. Mitochondrial retrograde signaling

The mitochondrial genome encodes for only a handful of proteins associated with the oxidative phosphorylation system, with the majority of mitochondrial proteins being encoded in the nucleus [17]. In order for the cell to respond to changes sensed by the mitochondria, signals must be transduced in a reverse or 'retrograde' direction from the mitochondria to the cytoplasm and nucleus (Fig. 2). The majority of work to identify mitochondrial retrograde signals has come from budding yeast models (*Saccharomyces cerevisiae*), where mitochondrial DNA (mtDNA) can be removed or mutated without dramatically affecting the normal function of the cell. Early studies showed that removal of mtDNA alters the genome-wide response to comprised mitochondria in a perturbation-specific manner, effectively establishing the existence of a signal transduction pathway between the mitochondria and nucleus [18–20]. The CIT2 gene was then observed to be the major nuclear target of mitochondrial perturbation in yeast [21], and this allowed for identification of retrograde regulatory proteins (Rtg) 1, 2 and 3 as transcription factors targeting CIT2 [22,23]. In yeast Rtg2 appears to be the upstream sensor for mitochondrial perturbations and acts via Rtg1 and Rtg3 to coordinate a nuclear response [20,24]. Importantly, Rtg2 activity is regulated by metabolites such as glutamate and ammonium [19], and is susceptible to inhibition by the nutrient-sensing kinases TOR (target of rapamycin) [25], thus providing a potential mechanism whereby changes in the mitochondria can affect cell-wide responses.

The Rtgs are now generally accepted to be the major transducers of retrograde (and potentially mitohormetic) signals in yeast, however, identifying candidates in mammalian cells has proven to be more complex. Through the varied manipulation of mtDNA content in cells, Chae et al. [26] has recently identified more than 70 transcription factors that are potentially involved in mitochondrial retrograde signaling. Primary candidates include those transcriptions factors that are also responsive to perturbations in mitochondrial respiration and include peroxisome proliferator-activated receptor gamma, coactivator 1 alpha (PGC1α), hypoxia inducible factor (HIF-1), mitochondrial transcription factor A (mtTFA), nuclear factor erythroid 2-like 2 (NFE2L2), nuclear factor

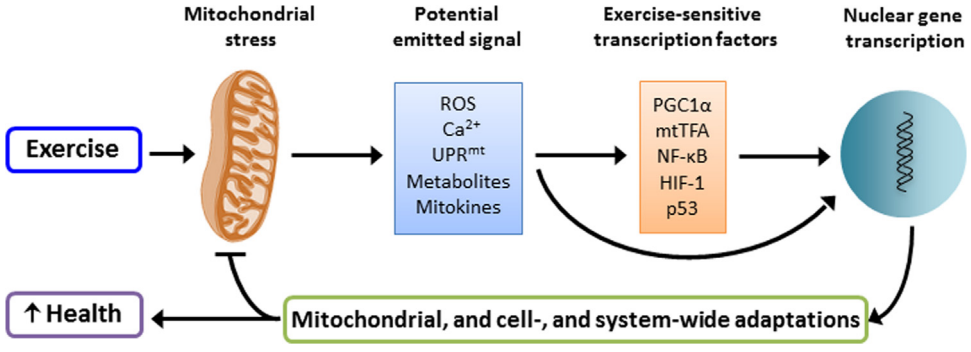

Fig. 2. Potential mitohormetic response to exercise. Exercise induces mitochondrial stress and as a result signals are sent from the mitochondrion to the nucleus to induce mitochondrial specific, cell- and potentially system-wide adaptive responses which protect the cell against subsequent stress (mitohormesis). Potential signals emitted by mitochondria during or immediately following exercise may include, but are not limited to, changes in ROS, Ca^{2+}, UPR^{mt}, metabolic metabolites and mitokine levels. These may act directly to initiate a transcriptional response in the nucleus or via signaling intermediates such as protein kinases (not depicted in this figure but may include AMPK, mTOR, CaMK's and MAPK's) and exercise-sensitive transcription factors. AMPK, 5′ adenosine monophosphate-activated protein kinase; CaMK, Ca^{2+}/calmodulin-dependent; HIF-1, hypoxia inducible factor; MAPK, mitogen-activated protein kinases; mTOR, mechanistic target of rapamycin; mtTFA, mitochondrial transcription factor A; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1α; ROS, reactive oxygen species.