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□ Hormesis plays a critical role in producing some major benefits derived from physical exercise. However whether these known cellular mechanisms are applicable to ameliorate age-related deterioration of muscle function is not entirely clear. The present communication proposes that antioxidant adaptation, the peroxisome proliferator-activated receptor gamma coactivator (PGC)-1α activated mitochondrial biogenesis, and eccentric contraction-induced, cytokine-propelled muscle inflammation could be important redox-sensitive pathways by which exercise-induced disturbance in oxidant-antioxidant hemeostasis may serve as a heretic stimulus to promote adaptations that help healthy aging and improve the quality of life.

Keywords: aging, exercise, hormesis, muscle, reactive oxygen species,

After decades of intensive research it becomes widely accepted among scientific community that reactive oxygen species (ROS) play a significant role in aging. Furthermore, ROS are generated during physical exercise in both animals and human and increased ROS production can modify intracellular oxidant-antioxidant homeostasis and possibly aging (Powers and Jackson 2008). However, while there are still unanswered basic scientific questions, gerontologists and the general public alike are interested in the implication of exercise in modulating aging, and especially, how hormesis could be involved in exercise-induced health-promoting benefits. Some of the frequently asked questions are "Why does exercise generate free radicals and causes oxidative damage, but we are still advised to exercise more often?" "Does participation in regular exercise extend life span in human?" "How much exercise is good for the body when one gets older?" "Do old people who are physically active need to take antioxidant supplementation?" Answering these questions not only requires understanding of the dynamic nature of interactions between oxidants and antioxidants, but also a multidisciplinary approach to analyze the specific conditions involved. The term *Hormesis* has been adopted to explain how a mild oxidative stress associated with exercise can result in favorable adaptations that protect the body against more severe stresses and disorders derived from physical stress or other etiological origin (Ji et al. 2009). While some authors have now advocated that "exercise is antioxi-

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dant" (Gomez-Cabrera et al. 2008), American College of Sports Medicine is already carrying the slogan "exercise is medicine". This brief communication intends to address several topics fundamental to exercise-induced hormetic effects based on basic research derived from cell biology, exercise physiology and free radical chemistry. Every effort has been made to relate discussions to 'real world' problems.

(1) DOES EXERCISE INCREASE LIFE SPAN?

Rodent studies show that rats involved in life-time long voluntary running had a significant prolongation of average longevity even though they had greater food intake compared to sedentary rats, but the runners did not show any increase in maximal life span (Holloszy 1993). There is no data in human showing that exercise can affect longevity. However, in human population, morbidity is concentrated in the last two decades of life, beginning on the average at age 55 and increasing in frequency until the average age of death at 75 with an increase of approximately two years in longevity in physically active people as compared to less active people (Paffenbarger et al. 1993). This at first may seem to add to the health care problem in that more people would be living longer with chronic illness, but that is not the case. A longitudinal study noted that disability levels in a vigorously exercising population remained below that of non-exercisers and significant increases in disability were delayed by approximately 15 years (Fries 1996). These data indicate that engaging in regular physical activity would increase the age of onset of chronic illness and shorten the time between the onset of morbidity and death. This compression of the period of morbidity as a result of physical exercise would represent a significant improvement in the quality of life of the elderly and result in major reductions in the cost of treating the medical conditions of the elderly. Despite these clear benefits, the adaptive mechanisms involved and the time period where major protection offered by exercise occurs are still unclear.

(2) WHY IS EXERCISE AN ANTIOXIDANT AND MEDICINE?

There is clear evidence that an acute bout of heavy exercise generates sufficient ROS to challenge the body's antioxidant defense system (Powers and Jackson 2008). However, a review of literature reveals that we are not in agreement as to how ROS generation could impact on the physiological function of muscle and other organs. Some research suggests that exercise-induced ROS could retard muscle energy production and contractile function, whereas others found ROS are actually required for optimal performance (Reid 2001). One of the most important findings of free radical chemistry of exercise was that muscle contraction can activate redox-sensitive signal transduction pathways to stimulate the

expression of certain gene products that function to restore ROS homeostasis (Goodyear et al. 1996, Hollander et al. 2001). The pathways that are sensitive to ROS include nuclear factor kappa (NF) κB, mitogen-activated protein kinase (MAPK), and heat shock proteins (HSP) (Allen and Tresini 2000). Recently, peroxisome proliferator-activated receptor gamma coactivator (PGC)-1α activated signaling pathway has been added to the list (Handschin & Spiegelman, 2008). Activation of redox-sensitive pathways usually results in gene products that would restore intracellular oxidant-antioxidant hemeostasis and protection from potential oxidative stress. These products include (1) antioxidant enzymes (e.g. manganese superoxide dismutase [MnSOD], glutathione peroxidase [GPX], γ-glutamyl cysteine synthetase); (2) transcription factors and co-factors required for nuclear binding (e.g. c-fos, activating transcription factor [ATF]-2, PGC-1α); (3) molecules controlling redox status, (e.g. thioredoxin, glutathione); and (4) a wide range of proteins that could influence metabolic status and thus ROS production, such as uncoupling proteins (UCP), enzymes in fatty acid and glucose metabolism, and mitochondrial fusion and fission proteins (Ji et al. 2009). Because the above mentioned effects are "health-promoting", we support the views that exercise is indeed an antioxidant and medicine. It has been recently shown that oral administration of antioxidants and inhibition of intracellular ROS source could adversely affect antioxidant enzyme adaptation, mitochondrial biogenesis and insulin sensitivity in animal and human skeletal muscle in response to exercise clearly demonstrating that ROS play a key role in exercise hormesis (Gomez-Cabrera et al. 2008, Kang et al. 2009a, Ristow et al. 2009).

(3) DOES PGC-1α-INDUCED MITOCHONDRIAL BIOSYNTHESIS PREVENTS SARCOPENIA?

Skeletal muscle undergoes loss of mass and functionality with aging, a process known as *sarcopenia* (Morley et al. 2001). Despite decades of intensive research, the mechanisms for sarcopenia and potential clinical measures for its prevention are still lacking. Recent research reveals that mitochondria participate in almost all important cellular biological functions such as metabolic trafficking, regulating ROS homeostasis, signal transduction and apoptosis, and that decreased mitochondrial biosynthesis may underlie the mechanism for sarcopenia (Chan 2006).

Mitochondrial biogenesis is largely controlled by PGC-1α, which (1) interacts with nuclear respiratory factors (NRF)-1/2 to control nuclear encoded mitochondrial proteins involved in electron transport chain (ETC) complexes, metabolic pathways for fatty acid and glucose metabolism, UCP expression and apoptosis, and (2) promotes mitochondrial transcription factor A (Tfam) expression thus regulating mitochondrial DNA (mtDNA) replication and gene expression of mtDNA-encoded pro-

teins (Kelly and Scarpulla 2004). Moreover, mitochondrial morphology (size, shape and motility) can be regulated by controlled expression of mitochondrial fusion and fission protein (Chan 2006). Finally, PGC-1 controls most of the enzymes and proteins affecting oxidant-antioxidant balance such as UCP2/3, MnSOD and GPX expression (St-Pierre et al. 2006).

Several studies have shown that an acute bout of endurance exercise and stimulated muscle contraction can upregulate PGC-1α and activate mitochondrial protein synthesis and proliferation (Baar et al. 2002). Furthermore, repeated exercise bouts (exercise training) could result in accumulation of PGC-1α, NRF-1, and Tfam protein levels. These observations were thought to play an important role in mediating mitochondrial adaptation to exercise, such as elevated respiratory activity (oxygen consumption), increased expression of Krebs cycle and ETC enzymes, enhanced fatty acid oxidation and mitochondrial morphological changes. We recently showed that ROS generation during acute sprinting exercise can activate PGC-1 pathway and stimulate mitochondrial biosynthesis, because reducing ROS generation with allopurinol to inhibit xanthine oxidase (XO), the main ROS source of this type of exercise, attenuated PGC-1α expression and PGC-1α -controlled signaling pathway (Kang et al. 2009a).

Does aging attenuate PGC-1α-controlled mitochondrial biosynthesis? Could age-related changes in mitochondrial biosynthesis be a reason for sarcopenia? These questions still await research in this area (Corton and Brown-Borg 2005). Our preliminary data indicate that aged (24 mo) rats had significantly lower gene expression in the PGC-1α signaling pathways, shown by decreased mRNA and protein contents for PGC-1α, Tfam and cytochome c compared to young (4 mo) rats (Kang et al. 2009b). Furthermore, phosphorylation of the upstream enzymes AMP kinase and p38 MAPK, as well as cAMP response element (CRE) nuclear binding, was down-regulated. However, these changes were reversed or partially prevented by chronic treadmill running for 8 weeks. Thus, exercise training is a powerful tool to prevent mitochondrial deterioration with aging and perhaps sarcopenia.

(4) IS MUSCLE INFLAMMATION A REQUIRED PROCESS FOR HORMESIS?

In older people, muscle stretch injury and subsequent inflammatory response represent a serious threat to health and quality of life. Weakened muscles are also a main etiological reason for fall, which is the 14th leading cause of death in the United States with annual death rate increasing by 55% from 1993-2003 among the elderly. Research evidence up to date suggests that pre-conditioning with eccentric contraction (EC) is an effective method to improve muscle strength and prevent future stretch injury (Maruhashi et al., 2007). Thus, eccentric exercise could be a means to reduce fall and thus decrease mortality in older people.

Exercise and hormesis

Compared to concentric (shortening) contraction, EC causes more structural damage to the myocyte and oxidative damage to myofibril proteins and enzymes (Reid 2001, Ji et al. 2009). After the initial injury blood-borne leukocytes (mainly polymorphoneutrophils, PMN) infiltrate the damaged muscle sites due to the attraction by the adhesion molecules (e.g. vascular cell adhesion molecule-1 [VCAM-1]) on cell surface. Subsequently, there is a "respiratory burst" caused by the activation of NADPH oxidase to generate large amounts of superoxide radicals and H_2O_2. There is clear evidence that NFκB and MAPK are activated after eccentric contraction leading to greater expression of inflammatory cytokines such as tumor necrosis factor (TNF)α, interleukin (IL)-1, 6 and VCAM-1 and escalated ROS production via a vicious cycle. Nevertheless, this inflammation enhances blood perfusion due to nitric oxide (NO) production by inducible NO synthase (iNOS), raises temperature to speed up reactions, and increases hormonal exposure to damaged tissues, all or which are important for healing of damaged tissues. Moreover, gene expression of antioxidant enzymes are also upregulated so that cells undamaged by EC, but affected by the PMN infiltration, are more capable of resisting future indiscriminative attacks. Thus, after the initial injury and oxidative damage, the muscle not only recovers but also becomes bigger, stronger and more capable of handling elevated functional demand. However, whether or not old muscles are capable of responding to hormetic stimulus is still controversial (Ji 2008). It was recently demonstrated that EC training impairs NFκB activation and overexpression of inflammation-related genes induced by acute EC in the elderly (Jiménez-Jiménez et al., 2008).

Interestingly, muscle inflammation and subsequent activation of NFκB could negatively influence the expression of PGC-1α and its effect on mitochondrial biogenesis. Chronic inhibition of NFκB via the pharmacological agent pyrolidine dithiocarbamate (PDTC) was found to increase PGC-1α level suggesting inactivity might down-regulate PGC-1α due to elevated NFκB activity (Feng et al. 2009). Furthermore, suppression of NFκB via polyphenols such as curcumin can reduce inflammation and attenuate muscle atrophy (Alamdari et al. 2009). Handschin and Spiegelman (2008) recently highlighted the role of PGC-1α as to "control muscle plasticity, suppress a broad inflammatory response and mediate the benefits of exercise".

In conclusion, although exercise does not directly extend life span in human, it induces several major health benefits such as upregulation of antioxidant defense, stimulating mitochondrial biogenesis, and prevention of injury. These are important elements for improving muscle health and reducing sarcopenia, hence delivering clear benefits for healthy aging.

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