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Commentary Open Access

Exercise and TFAM: Protectors of Skeletal Muscle

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Commentary

"Your blood pressure is too high, your cholesterol is out of range, and your bodyweight is out of control you need to exercise." Large numbers of people may hear this or something similar as the rebuttal to an all but smooth checkup at doctor's offices around the world. The statement is true: you do need to exercise. The closest thing we have to a miracle drug that can be grossly applied to improve, at the least, some aspect of most health issues is putting the human body in motion through physical activity or, more simply, exercising. While exercise is heavily studied as corrective and preventative medicine, scientists have only recently begun to look at the precise cellular signaling mechanisms leading to the positive benefits of movement. Furthermore, the scope of the application of exercise may be preached too broadly at times leaving us with missed opportunities to prevent and correct negative health consequences during specific, acute periods.

On a translational level, decades of empirical evidence guide us to support the idea of exercising to assist in our goal of achieving ideal health outcomes [1]. This leads many M.D.s, Ph.D.s, nurses, physical therapists, personal trainers, your co-worker, mother-in-law, and new puppy to tell you to "exercise to be healthy". We accept this as universal knowledge now. But currently there may be a gap in data pertaining to a specific time to prescribe exercise. More specifically, when someone knowingly enters a period of disuse or unloading of skeletal muscle, the time period prior to muscle disuse may be crucial to prescribe exercise to improve recovery and the quality of life.

This scenario occurs in many forms: limb immobilization, bedrest, microgravity, and sedentary periods. When someone has elective surgery that will require immobilization of a limb post-surgery for an extended period, they enter a known time frame of unloading and disuse of their body. Many physicians prescribe bedrest orders in certain situations during a pregnancy in which women will inevitably experience disuse. Even astronauts going into space enter a setting in which, because of a reduction in gravity, the skeletal muscle tissue is not used or loaded normally. One of the common negative consequences of each of these scenarios is skeletal muscle atrophy.

Skeletal muscle atrophy is caused by different factors including disease, injury, aging, nutritional decrements, as well as unloading and disuse [2]. It is characterized by a decrease in the cross-sectional area of the muscle, a decline in force generative capabilities, decrease in functional proteins of the muscle mass, and a loss of oxidative ability making the tissue less resistant to fatigue. There is a clear link between the dysfunction of the mitochondria and skeletal muscle atrophy [3]. The cause of both depends on originating factors like aging, disuse, etc., (Figure 1).

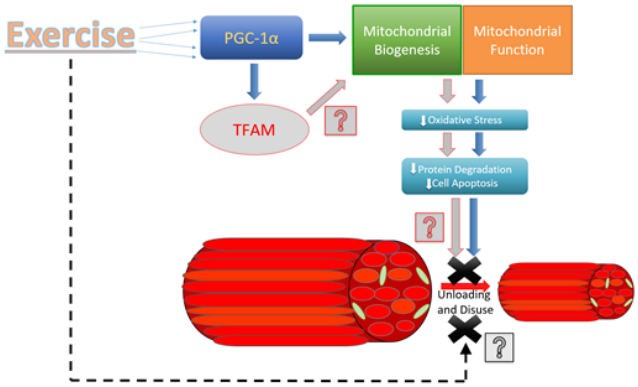

Figure 1: Hypothesis: Exercise increases TFAM and prevents skeletal muscle atrophy during disuse

Ultimately, the lack of muscle contraction and lack of stimuli loading the muscle encompasses disuse. Activation of protein signaling pathways by reactive oxygen species (ROS) leads to protein degradation (ubiquitin-proteasome, IKK, Nf-κB) and cell apoptotic (Caspase-9 to Caspase- 3 executioner) pathways that arise with corresponding downregulation of protein synthesis pathways (PI3K-Akt, mTORC1) when muscle is abnormally disused [4]. When protein degradation exceeds protein synthesis over time, atrophy and decreased mitochondrial function are observed.

When muscle fibers shrink and the function of the mitochondrion organelle produces energy for the cell and is involved in the regulation of oxidative stress decreases, quality of life declines. As this decrease in function occurs, we lose the ability to perform work and symptoms of fatigue arise. One can imagine cases of skeletal muscle atrophy rendering a previously abled body now unable to get out of bed on their own or walk to the bathroom without help. Alternatively, someone has trouble walking up a flight of stairs. But what if there was a treatment to prepare ourselves for the disuse of our muscles that diminished the protein degradation and mitochondrial dysfunction that normally occurs when you stop loading and contracting your muscle tissue? What if that "treatment" could be, monetarily, free? Insert M.D. here: "You need to follow this exercise protocol before you go into surgery."

Preliminary data from our laboratory suggests only fourteen exercise sessions in under 3 weeks performed before unloading the hindlimbs of mice for seven consecutive days results in significantly less skeletal muscle atrophy of the lower hindlimbs. While mice that did not exercise experienced losses of skeletal muscle weight and size between 20-28% after unloading, mice that exercised before unloading

their hindlimbs only experienced 7-8% reductions in muscle mass. From a mechanistic view, exercising prior to unloading reveals greater blood flow in the hindlimbs, reduced oxidative stress, and increased mitochondrial biogenesis signaling protein markers compared to unloading only. Specifically, the master regulator peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) and mitochondrial transcription factor A (Tfam) are observed to be increased.

Cannavino et al. conducted a study overexpressing PGC-1α in a transgenic mouse model undergoing hindlimb suspension. Results from wild type hindlimb suspension revealed decreased levels of PGC-1α and increased protein degradation and mitochondrial dysfunction markers. Overexpressing PGC-1α protected muscle mass from atrophy induced by unloading. Sandri et al. similarly diminished skeletal muscle atrophy caused by denervation in mice by overexpressing PGC-1α [5]. Moreover, PGC-1α co-activates nuclear respiratory factors (NRF-1, NRF-2) to transcribe directly the nuclear expression of TFAM mRNA. Therefore, our laboratory is further investigating the effects of TFAM overexpression in mice during muscle unloading and disuse. Preliminary results suggest this overexpression of TFAM in a transgenic mouse model further diminishes skeletal muscle atrophy over 7 days of hindlimb unloading, as compared to wild type mice that experienced the same unloading protocol. TFAM's role is to not only initiate transcription of mitochondrial DNA (mtDNA) to increase mitochondrial function, but also protect mtDNA from degradation by excessive oxidative stress [6]. As exercise increases PGC-1α to increase mitochondrial function and also Tfam to protect mtDNA and increase its transcription [7], we observe a mechanism in which exercise and this important molecular pathway works during a setting such as muscle disuse to ameliorate atrophy. While these current unpublished results are specific to skeletal muscle health, the implications to apply this prescription to encompass other areas of health in this specific time frame are worth further investigation.

The power of exercise strikes again. The response to exercise is through many physiologic factors beginning with an abundance of cell-signaling cascades leading to conditioning the skeletal muscle tissue, improving cardiovascular function, modifying bioenergetics, and even improving cognition [8]. These factors are all simply adaptations to prepare for the stress of movement. In the scenario of entering a known atrophic setting (think: having elective surgery in a month), forcing these adaptations can be analogous to putting on a heavy armor sheath of health as you enter the sedentary, atrophic arena. You are inducing protective mechanisms that can save time, money, and quality of life during the atrophic setting and after as you enter rehabilitation. Yes, we all know we need to exercise from a broad scope. But, there may be times when it is more important. So, the next time you go to the International Space Station for a few days or, more likely, choose to repair that damaged meniscus from your high school tennis days, tell your orthopedic surgeon your mother-in-law said you need to exercise first.

References

1. Kemi OJ, Wisloff U (2010) High-intensity aerobic exercise training improves the heart in health and disease. J Cardiopulm Rehabil Prev 30: 2-11.
2. Bodine SC, Baehr LM (2014) Skeletal muscle atrophy and the E3 ubiquitin ligases MuRF1 and MAFbx/atrogin-1. Am J Physiol Endocrinol Metab 307: E469-E484.
3. Kang C, Yeo D, Ji LL (2016) Muscle Immobilization Activates Mitophagy and Disrupts Mitochondrial Dynamics in Mice. Acta physiologica (Oxf).
4. Theilen NT, Kunkel GH, Tyagi SC (2017) The Role of Exercise and TFAM in Preventing Skeletal Muscle Atrophy. J Cell Physiol 232: 2348-2358.
5. Cannavino J, Brocca L, Sandri M, Bottinelli R, Pellegrino MA (2014) PGC1-alpha over-expression prevents metabolic alterations and soleus muscle atrophy in hindlimb unloaded mice. J Physiol 592: 4575-4589.
6. Kukat C, Davies KM, Wurm CA, Spåhr H, Bonekamp NA, et al. (2015) Cross-strand binding of TFAM to a single mtDNA molecule forms the mitochondrial nucleoid. Proceedings of the National Academy of Sciences 112: 11288-11293.
7. Campbell CT, Kolesar JE, Kaufman BA (2012) Mitochondrial transcription factor A regulates mitochondrial transcription initiation, DNA packaging, and genome copy number. Biochimica et biophysica acta 1819: 921-929.
8. Radak Z, Kaneko T, Tahara S, Nakamoto H, Pucsok J, et al. (2001) Regular exercise improves cognitive function and decreases oxidative damage in rat brain. Neurochem Int 38: 17-23.