Mitochondria in Muscles

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mechanotransduction mitochondria athletic performance stress response manual therapy calcium ions bioenergetic metabolism

1. The Mitochondria at the Center of the Organism

Mitochondria are the cellular organelles that produce adenosine triphosphate (ATP), the primary energy substrate for the human organism. Derived from bacteria engulfed by what became the first eukaryotic cell, mitochondria contain their DNA (mtDNA) and are involved in many metabolic processes[1][2][3]:

- amino acids, nucleotides, porphyrin, cholesterol, steroid hormones, glutathione and nitric oxide synthesis [2][3];
- antioxidant and ROS production and regulation[1][2];
- intra- and extracellular signaling through the release of Ca^{2+} and ROS[1][2][3];
- cell survival regulation, since mitochondria affect apoptosis[1][2].

Researchers have recognized mitochondria among the main factors that allow the organism to face environmental stimuli through the stress response, whether local or systemic[3][4][5]. Indeed, mitochondria can regulate the organic adaptation by affecting both homeostasis—the maintenance of physiological parameters within a determined range beyond which irreversible damages and death would occur—and allostasis—the spontaneous and proactive change of physiological parameters to face environmental stressors[3][4][5].

The most recent research on stress pathophysiology has highlighted that mitochondria can mediate how adverse psychosocial experiences impact on cellular and subcellular functions such as the stimulation and inhibition of immune and inflammatory response, oncogenic processes, gene regulation, and telomere maintenance[5]. In

particular, mitochondria seem to have a double role in translating the effects of the stressful experience, an example being physical training. On the one hand, mitochondria could be the main target of the stress response; on the other hand, they could affect subsequent cellular or molecular alterations, thus acting as mediators of the stress response [3][4][5]. Mitochondria play a central role in the stress response due to their ability to produce energy[4]. The more the energy produced, the better the brain can redistribute it to each organ or system that needs it to face the stressors efficiently. Indeed, this energy helps organs and cells change their structure and function based on the neuroendocrine molecules released during the stress response[4][3][5].

2. Mitochondria and Physical Activity

Among environmental stressors, surely physical activity represents one of the stimuli that may strain the organism the most, both physically and psychologically—think about the high pressure that athletes, in particular elite ones, need to endure during training or the athletic performance [6]. At the muscular level, mitochondria may go through rapid and peculiar modifications—changing in volume, protein expression, and used substrate—based on muscle activity and cell environmental conditions, such as concentrations of nutrients, ROS, or lactic acid[7][8]. Indeed, skeletal muscle tissue requires a different amount of oxygen based on the sustained physical load, and mitochondria undergo the modifications mentioned above accordingly to provide muscles with the necessary oxygen[9].

In fact, mitochondia can create dynamic networks throughout the cytoplasm to allow cells to adapt efficiently. In particular, mitochondria can connect to create more prominent cellular structures—mitochondrial fusion—or split in smaller organelles—mitochondrial fission. In addition, mitochondria may die—mitophagy—or be born anew—biogenesis—based on the stimuli received from the environment and, especially, from the cell nucleus [2][4][10].

Mitochondrial biogenesis is among the biological processes that physical activity influences the most. Indeed, a prolonged physical exercise characterized by high oxygen consumption requires a great increase in the number of available mitochondria, which must also show a heightened oxidative enzymatic capacity for producing the required energy[10].

Whereas several factors regulate mitochondrial biogenesis during physical activity, others may induce mitophagy during immobilization[10]. These factors are molecules and intracellular signaling pathways involved in different cellular responses that can influence the cellular energetic metabolism[10]. Specifically:

- in the case of muscular contraction, biogenesis is promoted by an increase in ROS, intracellular Ca^{2+} flux, the kinases p38-MAPK and AMPK[1][10]. These are central to regulating the hunger–satiety balance and the consumption and creation of glucose/glycogen reserve. They also can activate or inhibit the intracellular messenger cyclic adenosine monophosphate (cAMP), which is induced by many hormones and neuropeptides, including catecholamines[10]. Biogenesis is also upregulated by an increased expression of sirtuins, which are

proteins related to longevity, and CREB transcription factor, which is involved in neuronal plasticity and memory formation[11][10]. All these factors induce the synthesis of the peroxisome proliferation factor PGC-1α that, as a consequence, stimulates mitochondrial biogenesis[11][10]. It is worth noting that peroxisomes—the other organelles whose generation can be promoted by PGC-1α—interact strongly with mitochondria to carry out several vital cellular functions [12]. Indeed, they cooperate in the disposal of toxins or metabolic waste, in the regulation of ROS production, in the activation of immune response, and in the cholesterol metabolism, and in the β-oxidation of fatty acids[11][12];

- in case of immobilization, mitophagy is promoted by a reduction in the synthesis of PGC-α, sirtuins, AMPK and insulin-like growth factor 1 (IGF-1)[11][10]. As a result, the forkhead box O-class (FOXO) transcription factors become active and induce a cascade of several intracellular pathways that lead to protein degradation and mitophagy [10].

It is worth noting that during high-intensity training, FOXO factors interact with a high AMPK production to assure the processes of protein degradation and mitochondrial biogenesis could work together for allowing muscles the best possible remodeling and growth[10]. On the contrary, too much physical effort makes protein degradation prevail over biogenesis, thus weakening musculature[10].

Endurance training, which is mainly aerobic, represents the kind of physical activity that affects mitochondrial biogenesis the most by stimulating especially the activator protein 1 (AP-1) transcription factor, which is involved in oxidation, inflammation and apoptosis[9]. Endurance training also enables the expression of AMPK, PGC-1α and the peroxisome proliferator-activated receptors α and γ (PPAR-α and PPAR-γ), both of which regulate cellular oxidation[9][10][13]. On the other hand, resistance or anaerobic training leads mainly to muscular hypertrophy, that is, an increase in muscle volume due to a higher synthesis of muscle fibers, collagen fibers, and other proteins paramount for muscular metabolism. Muscular hypertrophy is regulated by different cellular pathways, in particular, by the anabolic PI3K–Akt–mTOR pathway[13]. Despite these different consequences, both aerobic and anaerobic exercises share several metabolic pathways and, as a result, even anaerobic training may increase the PGC-1α synthesis[14].

Regarding endurance training, the available literature suggests that the cellular factors mentioned above could also induce the transcription of proteins involved in the Krebs cycle and respiratory chain, thus influencing energy production[9]. Nonetheless, since these factors participate in several cellular responses, they could be induced either by metabolic stimuli—diet (i.e., antioxidants, fasting and carbohydrates, proteins or fat consumption), inflammation, cellular growth factors and stress hormones—or mechanical stimuli[1][3][9][10].

3. Mitochondria as Mechanosensitive Organelles

Among the mechanical stimuli that could affect the cellular factors involved in mitochondrial biogenesis, we may include muscle contractions and stretching, the stiffness or elasticity of the extracellular matrix (ECM), and the mechanical forces created by other cells and organelles[1]. All these mechanical stimuli may be transmitted to the

mitochondrial network through the cytoskeleton and its components, that is, actin filaments, microtubules and intermediate filaments[1][9]. Indeed, the cytoskeleton sustains, connects and shapes each cellular structure—without the cytoskeleton, cells and organelles would break apart [1][9].

Mitochondria are linked with the cytoskeleton in several ways. For instance, mitochondria contain tubulin, a protein included in the structure of cytoskeletal microtubules; they are attached to vimentin, another protein that composes intermediate filaments, without which they would disintegrate; lastly, they move on actin filaments[1].

The forces applied on the cytoskeletal filaments could thus induce a spatial remodeling that moves mitochondria closer to or away from each other[1][9]. As a result, mechanical forces facilitate mitochondria fusion or fission, whose alternation is paramount to regulating muscle metabolism finely and allowing muscles to consume the energy needed for facing the actual stressor[1][9]. Furthermore, a correct balance between fusion and fission favors biogenesis: on the one hand, fission facilitates the mitophagy of defective mitochondria[1][15]; on the other hand, fusion facilitates Ca^{2+} influx, which constitutes one of the most critical signals for the birth of new functional mitochondria[1](Figure 2). The correct balance between fusion and fission also allows cells to distribute their mitochondria to their daughter cells during mitosis[1][9][10][15].

As reported in the scientific literature over the last years, changes in the cytoskeletal mechanical tension could affect mitochondria since these organelles and their ionic channels—the same channels that make Ca^{2+} enter the mitochondrial matrix—are mechanosensitive structures[16][17][18]. In fact, due to changes in mechanical tension, the channels located in the mitochondrial membrane can open or close and, as a result, alter the cellular metabolism [19][16][17][18].

In addition, cytoskeletal filaments are not merely attached to the mitochondrial membrane: they are linked directly with the ionic channels lying in the mitochondrial membrane, in particular, with the voltage-dependent anion channels (VDACs)[1]. VDACs allow the flux of ATP, adenosine diphosphate (ADP), pyruvate, malate, and other molecules paramount for the energetic metabolism[20]. VDACs also determine the mitochondrial membrane potential, a characteristic that can influence the mitochondrial function heavily[1]. Therefore, changes in the cytoskeletal tension can alter the mitochondrial membrane potential, directly impacting mitochondria life and death[1][20].

The mechanical stimuli that occur in the body include transient, monotonous and fluctuation (e.g., muscle contractions, heartbeat and breathing) stress[1]. All these mechanical stimuli can affect mitochondrial structure and function: on the one hand, both transient and monotonous mechanical stretches can increase ROS production and facilitate mitochondrial fission. On the other hand, fluctuations in shear stress or cycle-by-cycle stretch can modify the cytoskeletal architecture, bioenergetic metabolism and expression of intracellular signaling pathways[1].

Analyzing ATP production by vascular smooth muscle cells (VSMCs), researchers found an almost linear correlation between mechanical stress, mitochondrial fractal dimension (FD) and ATP production[1]. FD is an index that measures mitochondria's ability to occupy space: the higher the FD, the more complex the mitochondrial network and the more energy produced. In particular, it was found that[1]:

- under no mechanical stress, FD and ATP production are both low;
- under continuous monotonous stress (e.g., 4 h of static cellular stretch), both FD and ATP increase;
- under variable stress (e.g., 4 h of cyclic stretch of variable intensity), FD increases considerably, as proof of mitochondrial fusion and biogenesis, and ATP production may rise even to 10 times the resting value (i.e., when mechanical stress is absent).

4. The Role of Ca^{2+}-signaling in Mitochondria and Muscles

Among all intracellular signaling pathways, Ca^{2+} signaling undoubtedly plays a central to the muscle tissue.

Whereas voltage-gated calcium channels (Ca_V) are located in the membrane of many different cells, skeletal muscle cells express a particular channel that behaves differently compared to all other Ca_Vs: the channel $Ca_V1.1$[21]. This channel does not induce Ca^{2+}influx in the cell when activated; instead, whether activated by an electric or mechanical stimulus, $Ca_V1.1$ induces the release of the intracellular Ca^{2+} stored in the sarcoplasmic reticulum to begin muscle contraction[21].

Concerning the muscle sarcoplasmic reticulum, it is worth noting that it constitutes a system similar to the endoplasmic reticulum (ER) of the other eukaryotic cells[22][23]. ER has been found to have a peculiar link with mitochondria due to being distant just a few nanometers from them. Indeed, ER and mitochondria communicate through contact sites called mitochondria-associated ER membranes (MAMs)[22][23]. MAMs allow a direct passage for molecules to travel between ER and mitochondria: as a result, mitochondrial activity is finely regulated[22][23]. In addition, MAMs allow Ca^{2+} flux inside mitochondria whenever needed, thus facilitating muscle contraction, and regulating several cellular processes, such as mitochondrial fission, inflammasome formation (a particular protein complex released when cells sense potentially dangerous substances) and cellular autophagy[1][22][23]. The ER constitutes thus a paramount reservoir for Ca^{2+} ions that can be released upon electric, chemical or mechanical stimulation.

Ca^{2+} flow allows the neural control of skeletal muscle fibers: upon sensing a nerve impulse, Ca_Vs increase Ca^{2+} influx to generate an action potential that propagates along the cell membrane. Consequently, skeletal muscle contraction begins[24]. Ca^{2+} intracellular concentration also regulates intracellular processes such as the actin–myosin coupling required for muscle contraction, protein synthesis and degradation, and the fiber type shifting between fast-twitch and slow-twitch phenotypes[24]. The fiber type shifting is mediated, in particular, by Ca^{2+}-

sensitive proteases and transcription factors. Even mitochondrial respiration, plasticity and adaptations are affected by changes in Ca^{2+} concentration[24] (Figure 3).

The regulation of Ca^{2+} influx in muscle cells affects the contraction–relaxation cycle of muscle fibers, with significant consequences on the functions of many tissues, including blood vessels and bronchi[25][26]. Ca^{2+} influx also affects muscle tissue development since it influences neuromuscular junction formation and their functionality through muscle nicotinic acetylcholine receptors (nAChRs)[27]. The role Ca^{2+} ions play for skeletal muscle tissue integrity has been deemed so important that several studies investigated the correlation between Ca^{2+} signaling, muscle growth or hypertrophy (even in the heart) and muscle stem cells proliferation in both health and disease[28][29][30].

Ca^{2+} signaling affects ROS production inside muscle cells since ROS are formed during normal metabolic activity and muscle contractions[31]. Ca^{2+} ions also seem to be involved in glycolysis regulation as they influence the catalysis rate of some enzymes central to glycolysis. By modulating the energetic metabolism, Ca^{2+} ions can thus coordinate the beginning of muscle contractions[24]. Ca^{2+} influx in mitochondria increases the ability of these organelles to produce ATP by affecting mitochondrial crests and, thus, the electron transport chain. As a result, during muscle contraction, energetic homeostasis may be maintained more efficiently[24].

Lastly, Ca^{2+} ions participate in skeletal muscle hypertrophy, as this phenomenon represents an adaptive response subsequent to mechanical load. Although the mechanisms of action behind this effect have not yet been completely discovered, the main actors seem to be the molecule calcineurin and the ratio between extracellular ATP and intracellular Ca^{2+}[24][32]. Calcineurin is an intracellular Ca^{2+}-dependent molecule that can affect the differentiation of skeletal muscles satellite cells (i.e., muscle stem cells) through epigenetic mechanisms. The satellite cell differentiation is vital for regenerating muscle fibers after lesions and guaranteeing hypertrophy in the long-term[24]. Concerning the ratio between extracellular ATP and intracellular Ca^{2+}, an increase in plasmatic ATP (such as during physical activity) elicits a Ca^{2+} influx that induces the activation of the mTOR pathway and some MAPKs through complex signaling cascades central to cellular growth[32][33][34].

Even though Ca^{2+} channels have been usually viewed as dependent on chemical and electric stimuli, mechanobiology has shown that Ca^{2+} signaling is a mechanosensitive and mechano-dependent pathway[28][30]. Indeed, mechano-dependent Ca^{2+} channels are abundantly expressed in muscles during their whole development, hence fulfilling a crucial role for every muscle cell, whether cardiac, skeletal or smooth[28][30].

Ca^{2+} performs a pivotal role in transducing mechanical stimuli into intracellular signals as mechanical forces can change the cytosolic Ca^{2+} concentration and, as a result, induce the effects described in the previous paragraphs[30]. Indeed, mechanical tensions can affect the state of the membrane Ca^{2+}-dependent channels by acting on the physical connections between the ECM, cytoskeleton and cell membrane (e.g., by stretching cytoskeletal

filaments). Changes in intracellular Ca^{2+} concentration allow cells to acquire information about the external environment and to respond promptly by modifying their metabolism, gene expression and protein synthesis[28].When undergoing mechanical stress, cells may change their cytoskeleton structure by remodeling actin filaments, whose functionality depends on Ca^{2+} availability. The cytoskeleton may facilitate Ca^{2+} influx through the opening of mechanosensitive stretch-activated ion channels (SACs): this event may then activate the membrane Ca^{2+} channels, with all due consequences. Therefore, the cytoskeleton could be viewed as a controller of cellular Ca^{2+} entry due to its mechanosensitivity and influence on SACs[28].

Lastly, among the several types of Ca^{2+} channels inside muscle cells, there are also the transient receptor potential (TRP) channels. TRPs have been vastly researched over the years due to their prominent role in mediating high threshold stimuli—TRP channels are central to nociception. In fact, they are also involved in mechanotransduction in many different tissues and cells: TRPs are sensitive to various mechanical forces, such as fluid shear stress and cell membrane stretching[28]. In particular, Ca^{2+} entry through TRP channels seems to be the main stimulus able to regulate the signaling pathways involved in muscle tissue regeneration and reparation[24].

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