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Review Article

The effect of exercise on autophagy receptors and ubiquitin-dependent mitophagy pathway: Narrative review

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Abstract

Most of the intracellular and extracellular factors that play a vital role in regulating energy metabolism and determining cell fate converge in the mitochondria. To promote or hinder cell survival through regulating the function and maintaining the mitochondrial structure. The decline of mitochondrial function and homeostasis with aging is the basis of the pathogenesis of aging-related diseases, especially in skeletal muscles. One of the important components of mitochondrial quality control that helps maintain the homeostasis of myocytes is autophagy, which is an important biological and evolutionary process, and its vital function is the removal of defective organelles. Although it has been proven that regular sports activities act as autophagy stimulators and play a role in maintaining the cellular homeostasis of skeletal muscle fibers and regulating intracellular metabolism. However, cellular autophagic responses to exercise in skeletal muscle appear to be different in different exercise protocols and disease models. How exercise activity modulates autophagy in skeletal muscle and how the effect of exercise is regulated by the autophagy signaling pathway are still poorly understood. The importance of understanding the obscure angles of this process can be an important goal in preventing the pathology of age-related diseases in skeletal muscle.

Key Words: **Aging, Exercise training, Mitochondrial, Autophagy, Mitophagy**

Introduction

Autophagy is a cellular recycling process that breaks down and reuses damaged or unnecessary components (Parzych, K. R., & Klionsky, D. J, 2014). This self-degradative mechanism plays a crucial role in maintaining cellular health and energy balance. Autophagy involves the formation of double membrane structures called autophagosomes, which engulf cytoplasmic material and fuse with lysosomes for degradation. Mitophagy, a specialized form of autophagy, specifically targets mitochondria for removal. This process is essential for mitochondrial quality control, as it eliminates damaged or dysfunctional mitochondria that could otherwise harm the cell (Glick, D., Barth, S., & Macleod, K. F, 2010). Mitophagy has an impact on cellular health by preventing the accumulation of reactive oxygen species and maintaining mitochondrial function. In skeletal muscle, autophagy and mitophagy are particularly important for adapting to exercise-induced stress and promoting muscle health. Mitophagy also contributes to cellular bioenergetics by recycling mitochondrial components to provide building blocks for the synthesis of biomolecules (Chatzinikita, E et al., 2023). By preserving mitochondrial function, mitophagy helps limit inflammation and maintain tissue function during aging. The connection between autophagy, particularly mitophagy, and exercise has a significant influence on cellular health and overall well-being. Through physical activity, our bodies activate crucial pathways that boost mitophagy, helping to clean up damaged mitochondria and maintain a healthy cellular environment. This process plays a key role in adapting to exercise-induced stress, promoting muscle health, and potentially slowing down age-related decline (Triolo, M., et al 2022).

Given that aging is a complex process characterized by progressive disorders in several systems of the body, in this condition the person will be prone to an increasing risk of negative consequences (Dharmarajan, 2021; Maldonado et al., 2023; Ziaaldini et al., 2017). Also, it is difficult to define it at different levels, for example, molecular, cellular, physiological and psychosocial. The most accepted physiological definition of

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aging includes the reduction of physiological reserves, while still supporting acceptable performance in a steady state and not it can adapt to any additional stress, even physiological. Therefore, aging itself is associated with progressive homeostatic/homeodynamic disorder, which causes the organism to decrease and lack flexibility (Fulop et al., 2010; Pomatto & Davies, 2017; Tenchov et al., 2023). As aging is accompanied by complex changes in the musculoskeletal system, including loss of muscle mass and strength, these changes often cause serious and life-threatening injuries and disabilities, and in many cases, for older people, these changes lead to It will be related to problems in a person's functional skills, disability and loss of independence (Larsson et al., 2019; Najafi et al., 2018; Volpi et al., 2004). Also, studies show that aging muscle is associated with structural and functional deterioration of mitochondria, but how the aging process changes the quality and quantity of skeletal muscle mitochondria is still not well understood (Ferri et al., 2020; Seo et al., 2016). To deal with the loss of mitochondrial function and homeostasis, cells have a number of quality control mechanisms designed to reduce the burden of damage and promote health (B.-H. Liu et al., 2024; Sedlackova & Korolchuk, 2019). In fact, mitochondrial quality control (MQC) is performed through the coordination of mitochondrial proteostasis, biogenesis, dynamic processes and autophagy. Also, studies conducted on gene expression profiling have shown that the role of mitochondria in aging has tissue specificities and is especially related to tissues such as brain, heart and skeletal muscle, these tissues are strongly related to oxidative metabolism. Since neurons and myocytes are not able to remove their damaged organelles through cell division due to their post-mitotic nature, they rely only on the efficiency of MQC in maintaining mitochondrial homeostasis. The occurrence of any disorder at any level of MQC can simply result in mitochondrial dysfunction, lack of energy and ultimately the complete loss of cell viability. However, the functional consequences of these interactions with muscle physiology have not yet been fully identified. Therefore, investigating the relationships between MQC pathways and metabolic regulation of muscle mass may provide more information to discover new pathways, pathways that can be used to devise preventive and therapeutic interventions against muscle aging (Q. Chen et al., 2023; D. Liu). et al., 2021; Picca, Mankowski, et al., 2018; Scheibye-Knudsen et al., 2015a, 2015b). It is impaired with aging (Cardoso et al., 2018). But myocyte autophagy is like a double-edged sword, because its excessive activation causes muscle atrophy, while its defective function causes weakness and degeneration. Theoretically, the timing of these conflicting events is crucially different. In fact, defective autophagy has long-term pathological consequences such as aging, which is caused by the progressive accumulation of damaged proteins and dysfunctional organelles in muscle fibers. In addition, loss of basal autophagy disrupts cell-ular homeostasis, while short-term intensification of autophagy flux during muscle disuse causes atrophy. Further understanding of the molecular events that regulate stress-induced autophagy and basal autophagy in myocytes, as well as modulating the activity of autophagy receptors in the mitochondrial outer membrane, to design therapeutic strategies that exploit the homeostatic function of this cellular pathway and the deleterious effects of activation It is essential that they are not accompanied by too much (Calvani et al., 2013). Since doing regular sports activities is one of the important and basic things to prevent chronic diseases and functional disorders. Therefore, sports exercises play a key role in achieving a healthy lifestyle in the elderly population (Nascimento et al., 2019). The benefits of various sports exercises on the function and structure of aged myocytes have been proven, but the cellular and molecular mechanisms involved in the occurrence of such effects have not yet been fully identified (Ney, 2015). In the following, a summary of the research results regarding the role of regular physical activity in modulating mitochondrial protein levels during the aging process is presented in Table 1.1. The aim of this study will be to summarize and review recent advances in our understanding of the molecular mechanisms of autophagy receptors in the mitochondrial outer membrane, as well as the effect and role of exercise on this pathway.

Mitochondria as the base of cell power and aging

Mitochondria are important and essential organelles that produce energy to maintain muscle function (Heden et al., 2016; Oliveira & Hood, 2019a). In other words, mitochondria are the powerhouses that consume oxygen in cells and create an environment for the synthesis of many essential molecules. It also provides the possibility of producing energy with high efficiency through oxidative phosphorylation. But these vital organelles are like a dynamic network whose morphology and function are constantly changing and adapting according to the needs of the cell (Scheibye-Knudsen et al., 2015a). These organelles are abundant in most cells, and constitute approximately 40% to 10% of the cell volume (Hamacher-Brady & Brady, 2016). Importantly, mitochondria have their own DNA. The human mitochondrial genome (mtDNA) is a small circular molecule with an approximate length of 16.6 kilobases, which is located inside the matrix space and is connected to the mitochondrial inner membrane. In humans, mtDNA encodes 13 polypeptides, 22 tRNAs, and two ribosomal genes that are essential for oxidative phosphorylation. Structurally, mitochondria are composed of an outer membrane, an intermembrane space, a highly folded inner membrane (crista) and matrix space (Figure 1) (Scheibye-Knudsen et al., 2015a). The place of energy production in mitochondria is in the inner mitochondrial membrane (IMM). Cristae are microcompartments that form as a result of IMM folding in response to metabolic cues or external st-

Table 1. The role of regular physical activity in modulating mitochondrial protein levels during the aging process.

Reference	Tissue	Subject	Comparative	Training	Results
(Drummond, M.et al.,2014)	Muscle	Humans	Sedentary elderly, Active elderly	Without exercise intervention	↑ (mRNA): Bnip3; Drp1; Parkin; beclin1 NS (mRNA): Mfn2; PINK1; LC3 NS: beclin1
(Ogborn, D.I.et al.,2015)	Muscle	Humans	Youths/elderly	Single bout of resistance training (4 sets of rept. at 75% 1RM with 2 min rest between sets)	↑ (mRNA): PGC-1α (3 h); TFAM (24 h); LC3II (3 h) ↑: LC3II (48 h) NS (mRNA): Nix; Bnip3 NS: Parkin; PINK1; VDAC1; beclin1
(Zampieri, S.et al ,2015)	Muscle	Humans	Youths and active and sedentary elderly	Without exercise intervention	↓: Bnip3 NS: PGC-1α; beclin1
(Fealy, C. E., et al.2014)	Muscle	Humans	Elderly	12 weeks of aerobic exercise for 60 min (20 min cycle ergometer and 40 min treadmill walking) at 80–85% HRmax 5 days/week	↑ (mRNA): OPA1; Drp1 ↓: phosphorylated Drp1 NS (mRNA): Mfn1; Mfn2; Fis1; PINK1; Parkin
(Tanner, R. E., et al 2015)	Muscle	Humans	Youths/elderly	5 days of bed rest and 8 weeks of high intensity resistance exercise	↑: LC3II/I NS: beclin1
(Lira, V. A., et al 2013)	Muscle	Mice	plantaris muscle/ mixed fiber types	Voluntary wheel-running exercise (third day,) and 2 day with wheels locked	↑: autophagy flux, LC3-II/LC3-I ratio and LC3-II levels, mitophagy protein Bnip3 expression in tonic oxidative muscle compared to muscles of either mixed fiber types
(Sun, Y., et al 2016)	Muscle	Mice	Control group/ Voluntary wheel running	run on wheels freely for 8 weeks	↑: mRNA expression of NRF1, BIM and Bcl-XL

stimuli. The length and width of the cristae determine the effectiveness of the electron transport chain (ETC) (Sedlackova & Korolchuk, 2019). In fact, the bioenergetic role of mitochondria includes the oxidation of Acetyl-CoA in the tricarboxylic acid (TCA) cycle to produce NADH and FADH2, these two The molecule transfers electrons to the electron transport chain to create an electrochemical gradient across the inner mitochondrial membrane (IMM) and use it to produce ATP (Figure 2). Finally, the electrons are transferred to molecular oxygen (O2) and reduced to the form of H2O molecules. The combination of these two processes is called oxidative phosphorylation, or in other words cellular respiration. Due to the leakage of electrons from complex I or III of the electron transport chain, the O2 molecule can be incompletely reduced and produce superoxide anion, which is the precursor of most reactive oxygen species (ROS). Low levels of ROS have physiological roles, while high levels and/or prolonged persistence of ROS can cause oxidation of proteins, lipids and nucleic acids, and this event leads to cell dysfunction and programmed cell death (Hamacher-Brady & Brady, 2016).

Dysfunction of mitochondria is one of the signs of aging, with features such as disorder in mitochondrial morphology, insufficient ATP production, accumulation of DNA mutations, mitochondria (mtDNA), increased production of reactive oxygen species (ROS) and oxidative damage caused by It is described as nucleic acids, proteins and lipids. Autophagy is a mitochondrial quality control mechanism that is capable of breaking down damaged and excess mitochondria and thus prevents their destructive effects on the cell, and also maintains cell homeostasis in response to stress. To date, there have been many evidences about significant disruption in the process of mitophagy and the occurrence of numerous pathologies in humans, including aging and related diseases such as neurodegenerative disorders, cardiovascular pathologies and cancer. Although the relationship between autophagy and aging has been fully established as an important mitochondrial quality control mechanism, its role in aging and aging-related disorders has remained unknown for a long time. However, recent studies have shown that autophagy can also play an essential role in delaying aging and aging-related disorders (G. Chen et al., 2020b, 2020a; Kauppila et al., 2017; Lane et al., 2015; Srivastava, 2017). In the continuation of this article, we will update the contents related to the mechanisms

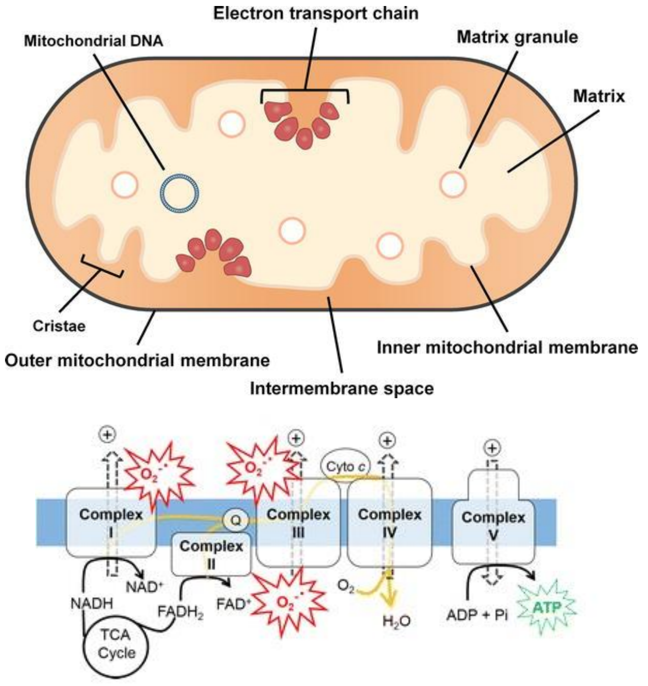

Figure 1. Mitochondria are composed of an outer membrane, an intermembrane space, a highly folded inner membrane (crista) and matrix space.

of autophagy and its role in aging, as well as the inhibition of this mechanism to prevent disorders related to aging, muscle atrophy.

Autophagy and the role of LC3

The Nobel Prize for the research on lysosomes was awarded to Christian de Devoe, who used the term autophagy for the first time in 1963. He used this word to describe the phenomenon in which vesicles with a single or double membrane contain cytoplasm contents, such as organelles for digestion (Zarringol, 2018). Also, Japanese biologist Yoshinori Ohsumi won the Nobel Prize on October 3, 2016. receive physiology due to the discovery of the autophagy-dependent pathway. The word autophagy is derived from the Greek word autophagositos, which means self-eating, and also autophagy exists in the genome of every eukaryotic organism and is a fundamental event in the life of eukaryotes (Levine & Klionsky, 2017). Based on the available evidence, autophagy is considered as a natural and regulated and sometimes destructive mechanism in cells, which plays a key role in removing unnecessary compounds and recycling dysfunctional organs (Ho et al., 2006). The important point is that autophagy is highly conserved from yeast to humans, proteins and organelles are surrounded by a two-layer membrane called phagophore. Then this membrane is stretched and closed, and a vesicle with a double-layered membrane called autophagosome is formed, which separates the contents of the cytoplasm. Finally, the autophagosome combines with acidic lysosomes, and the cytosolic contents in the autophagosome will be broken down by the hydrolytic enzymes of the lysosome (Zarringol, 2018). On the other hand, in some cases, autophagy can cause cell survival and in other cases, cell death. The proteins involved in autophagy are known as Atg, which were first discovered in yeast (Wesselborg & Stork, 2015). According to research, yeast Atg1kinase plays an important role in inducing autophagy, and in addition, autophagy is promoted by AMPK, but autophagy is inhibited by mTOR (mammalian target of rapamycin) (J. Kim et al., 2011). One of the important regulators of autophagy is mTOR, which inhibits autophagy when nutrients are available (Zarringol, 2018). The important morphological feature known for autophagy is the creation of a double-layered membrane called autophagosome, and by enclosing cytosol cargoes, it prepares them for degradation to lysosomes (Kimura et al., 2017). The formation of autophagosome is mainly by means of phosphatidyl inositol. - 3-kinase class (PI3K) III and also (Atg6) Autophagy related gene are controlled (Zarringol, 2018). Also, autophagy is induced after the cell is exposed to environmental stresses such as nutritional deficiency, hypoxia, and oxygen free radicals, and with an adaptive or adaptive process, by providing energy-generating metabolites, it sustains the cell's survival. So that in recent studies, by removing the key genes of the autophagy process, an increase in cell death has been observed. In a similar study, it was reported that by inhibiting autophagy in cells, apoptosis increases. Autophagy is known as a vital process in the cell, which plays a role in biological development, aging, immune system and cell death, and is effective in fatal disorders such as nervous system breakdown, autoimmune diseases and types of cancers. Autophagy has a double function, on the one hand, it increases the duration and rate of cell survival, and on the other hand, in advanced stages, it causes cell death.

However, so far no agreement has been reached regarding the role of autophagy in the process of cell death, and the heterogeneity in the results of many studies has been a matter of discussion (Hosseini et al., 2013). Approximately 30 genes regulate the autophagy process, all of which have been discovered in yeast. And 16 of their homologues have been identified in humans. Meanwhile, Beclin-1 and LC3 genes play a pivotal role in autophagy. Beclin-1 is involved both in signaling pathways and in the initiation phase of autophagosome formation where interaction with PI3PK and hvp34 is necessary. LC3 gene is located at chromosomal position 17q21. This gene encodes a protein with a linear sequence of 450 amino acids, which has a weight equal to 60 KDa. LC3 is found in cytoplasmic structures such as the endoplasmic reticulum, mitochondria, membrane and nucleus, and is a specialized molecule that plays a multifunctional role in the cell, including a direct role in the initiation of autophagy, and includes a soluble form of LC3I (with a molecular weight of 18 Kb) and It is a lipid called LC3II (with a molecular weight of 16 Kb) and it is expressed as 3 isoforms (LC3C, LC3B, and LC3A) in mammalian tissue, of which LC3B is related to autophagy. A variety of stressors upregulate LC3 into its cytosolic form and increase the interaction of the cytosolic form of LC3I with phosphatidylethanolamine to form the LC3II form that is specifically localized to the autophagosome, as well as LC3II has been considered as the most reliable autophagy marker so far (Akbari-Kelishomi et al., 2018; Zare Karizi et al., 2017).

Mitochondrial quality control and mitophagy

Mitochondria are vulnerable to oxidative damage, and efficient cleaning mechanisms are needed to remove dysfunctional mitochondria from the organelle complex. These mechanisms are particularly important for the high energy demand in post-mitotic cells and neurons, as the regenerative capacity of neurons is low and mitochondrial damage leads to cell death. One of the key cellular mechanisms mediating the removal of dysfunctional mitochondria is autophagy. Autophagy is a vesicle-mediated catabolic pathway that leads to the identification, capture, and delivery of damaged cargo to the lysosome for degradation and release of nutrients. The selective destruction of damaged mitochondria through autophagy is called mitophagy (Sedlackova & Korolchuk, 2019). Basically, the goal of mitophagy is to limit the production of ROS and maintain cell homeostasis and ultimately maintain its health (Picca, Calvani, et al., 2018). This process occurs by mitochondrial depolarization, proteotoxic stress, dysregulation of calcium signaling, absence of molecular oxygen (hypoxia) or as a programmed event. The field of mitophagy is not fully understood and has been of interest due to the link between mitochondrial dysfunction and neurodegeneration. This relationship was determined following the discovery of two proteins involved in the pathology of Parkinson's disease, namely PINK1 and Parkin in mitochondrial destruction (Sedlackova & Korolchuk, 2019). In fact, to date, the best understood mitophagy system is the one controlled by the serine/threonine kinase PINK1 (putative PTEN-inducible kinase #1) and the E3 ligase Parkin 1, which acts as a sensor of mitochondrial polarization state. These proteins facilitate ubiquitin-dependent mitophagy of depolarized organelles (Hamacher-Brady & Brady, 2016). The initial discovery of ubiquitination-dependent mitophagy mediated by these proteins was followed by the investigation of specific events of ubiquitin-independent mitophagy (Sedlackova & Korolchuk, 2019). In the following, we will examine the BNIP3, NIX-dependent mitophagy that has been discovered so far.

Ubiquitin-dependent mitophagy and the role of autophagy receptors

Stress-induced mitophagy pathways proceed independently of ubiquitin-mediated cargo delivery and require a different set of autophagy receptors. Lack of oxygen or hypoxia leads to increased expression of three autophagy receptors, which are located in mitochondria (Sedlackova & Korolchuk, 2019) (Figure 2). Factor1 contains the second FUN14 (FUNDC1), a mitochondrial outer membrane protein that has three transmembrane domains, and in C elegans is involved as a receptor in the process of mitophagy by unpaired proteins, hypoxia, and clearance of parental mitochondria (G. Chen et al., 2020b). In fact, FUNDC1 is a hypoxia-responsive autophagy receptor that connects to the OMM through its three membrane-spanning regions, and the N-terminus region containing its LIR is exposed to the cytoplasm. FUNDC1-mediated regulation of mitophagy in hypoxia has two aspects. First, hypoxia leads to increased expression of FUNDC1 through the negative regulation of microRNA-137 (miR-137) involved in the repression of FUNDC1 translation. Second, hypoxia causes the dephosphorylation of a tyrosine sequence in its LIR motif and then increases the recruitment of LC3 mediated by FUNDC1 (Sedlackova & Korolchuk, 2019). Evidence also shows that PGAMA5 molecule dephosphorylates phosphorylated CK2 at serine 13 position in response to hypoxia or mitochondrial unpaired proteins and thus activates the LC3 binding process. In addition, ULK1 phosphorylates the LIR motif in the FUNDC1 molecule at serine 17 and this event results in increased LC3 binding (Hamacher-Brady & Brady, 2016). In addition to FUNDC1, two members of the BCL-2 protein family initiate mitophagy. They adjust in response to hypoxia. BCL-2 and the adenoviral E1B-19 kDa proteins (BNIP3) and BNIP3L (NIX) are BH3-only pro-apoptotic members (Figure 2) that are involved in the regulation of cell death at the level of the mitochondrial OMM and the endo/sarcoplasmic reticulum. Both BNIP3 and NIX have the ability to homodimerize and associate with the OMM through the membrane-spanning zyglycine region, interact with LC3, and indirectly initiate autophagy by inhibiting the binding of BCL-2 to Beclin1 (an autophagy inducer). The role of NIX in mitophagy was determined in NIX-deficient mice with erythroid maturation defect. NIX-deficient mouse erythrocytes retain their mitochondria due to a defect in mitochondrial targeting in the autophagy-exocytosis pathway. BNIP3-dependent mitophagy was first described in chemotherapy- and arsenic trioxide-induced ceramide-induced tumor cell death and confirmed in studies of hypoxia-induced mitophagy. The expression of BNIP3 and NIX also increases in hypoxia. Therefore, BNIP3 and NIX promote development-specific mitophagy and stress-induced ubiquitin-independent mitophagy. However, the role of BNIP3 and NIX in basal mitophagy and the precise nature of mitophagy initiation and execution under stress remain unclear. Increased oxidative stress induces mitophagy by acting on CL (a mitochondrial IMM phospholipid). CL consists of one glycerol molecule coupled with two phosphatidyl moieties and four acyl chains. In healthy mitochondria, CL is confined to the inner half of the IMM, where it is made and, due to its unique structure, shapes it by increasing the fluidity of the IMM. A recent study sho-

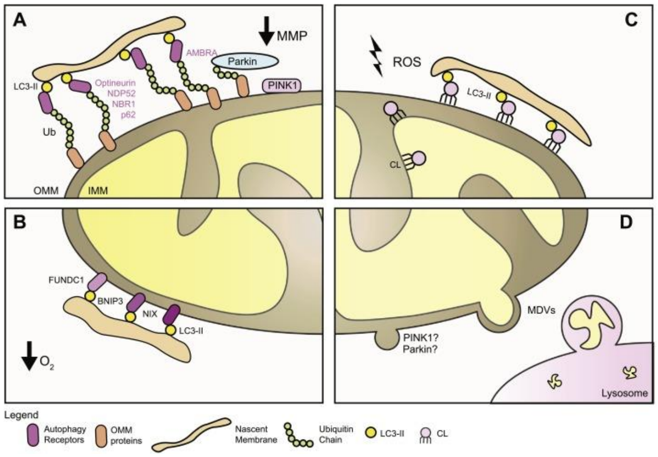

Figure 2. Expression of three autophagy receptors at levels of mitochondria.

-wed that in response to oxidation, CL is bound to IMM/OMM contact sites and transferred from IMM to OMM by phospholipid scramblase 3.

Translocation of CL to the OMM acts as a mitophagy signal, as LC3 contains CL-binding sequences and has been observed to bind to CL at the OMM and invoke the autophagy machinery (Figure C3) (Sedlackova & Korolchuk, 2019). Also Evidence shows that the BH3 domains of BNIP3 and NIX proteins play a role in pre-death events to some extent, but often this activity and role is mediated by the transmembrane domain. One of the important insights into this mechanism is through the explanation that BNIP3 causes cell death without cytochrome c release or caspase activation. In this study, it was shown that BNIP3 activates MPT, which is associated with increased ROS production and excessive autophagy. In contrast, NIX does not induce MPT activation despite cytochrome c release. In fact, BNIP3 and NIX proteins are associated with the induction of autophagy, and there are several potential mechanisms in this context. The first mechanism is through mitochondrial dysfunction, BNIP3 or NIX probably increase ROS production and can activate autophagy. The second mechanism is the competition between BNIP3 or NIX to bind to BCL2 (or an associated protein), which can release Beclin1 from BCL-2 complexes and activate autophagy. In the third mechanism, BNIP3 binds to Rheb and prevents its activity. Rheb is the upstream activating molecule of mTOR or the target molecule of rapamycin in mammals; Therefore, BNIP3 probably activates autophagy through suppression of mTOR. Thus, BNIP3 and NIX proteins regulate two main cell activities, namely cell death and autophagy (Ney, 2015).

The role of BCL-xL protein in the process of aging and autophagy

Very large B-lymphocyte lymphoma (BCL-xL) is a molecule involved in longevity and successful aging, suggesting its role in regulating cell survival pathways. In addition to fully describing the role of BCL-xL as an inhibitor of apoptosis and inhibitor of cytochrome C release, the indirect relationship of this molecule with autophagy and aging pathways has also been determined. However, there is a dual role for BCL-xL indirectly related to autophagy and senescence, which takes the form of activation or inactivation depending on the cell type and specific conditions. Collectively, all these findings indicate the exact mechanism of the role of BCL-xL in the interrelationship between apoptosis, autophagy and the aging process, and thus promote the process of cell survival or death (Borrás et al., 2020). In other words, BCL-xL acts as critical and decisive nodes in complex networks to integrate information and make the final decision in the field of cell life/death (Zhou et al., 2011). In fact, BCL-xL can regulate autophagy through indirect metabolic circuits because (i) it controls the efficiency of mitochondrial ATP production, (ii) the exchange of vital bioenergetic metabolites (e.g. ATP and ADP) by affecting PTPC components, (iii) reducing intracellular levels of Acetyl-CoA and (iv) interacting with the cytoplasmic pool of p53. Hence, BCL-xL expression levels may affect autophagy flux under steady-state, as opposed to adapted, conditions. This aspect of the cross-talk between BCL-xL and autophagy warrants further investigation. Hence, BCL-xL seems to act in important centers for the coordinated control of several cellular functions, including the three-step switch between homeostatic metabolism, adaptive responses to stress, and cell death (Michels et al., 2013).

Pathophysiology of mitophagy dependent on BNIP3, NIX and the role of BCL-Xl

Although it may be oversimplified, BNIP3 and NIX proteins have the potential to cause disease through two mechanisms. Stress-induced excessive expression of any of these two proteins can directly lead to mitochondrial dysfunction and cell death. In another way, dysfunction of BNIP3 and NIX can lead to dysfunction of mitochondrial quality control and finally dysfunction of mitochondria and cell death. The best described models of disease mediated by BNIP3 and NIX to date relate to the heart. BNIP3 protein is regulated by hypoxia. Experiments performed in Dorn's laboratory have shown that forced expression of NIX in mice causes lethal peritonal cardiomyopathy in these animals, while the absence of NIX protects mice against Gαq-induced cardiomyopathy and increased pressure overload (Ney, 2015). In a study, lipotoxicity, which is a form of cellular stress and is caused by the accumulation of lipids. It led to mitochondrial dysfunction and insulin resistance in muscle, and finally, the NIX mitophagy receptor reacted to lipotoxicity and accumulated in response to high-fat feeding (da Silva Rosa et al., 2020). In addition, the expression of BNIP3 and NIX proteins is usually disrupted in cancer. In the condition of hypoxia and in the peripheral areas of necrotic tumor, the translation process of both

BNIP3 and NIX proteins increases (Hamacher-Brady & Brady, 2016). It has also been reported that the expression of the BNIP3 coding gene in different types of cancer, such as hematological malignancies, lung cancer, breast, stomach, pancreas, liver is correlated with the aggressiveness and metastasis of cancer (G. Chen et al., 2020b). In this regard, Oversa et al. (2015) showed in their study that both BNIP3 and NIX show an increasing trend They show cancer cachectic patients (Aversa et al., 2016). But in the liver tissue, starvation induces the expression of BNIP3 in the liver. On the other hand, the lack of BNIP3 is associated with the accumulation of dysfunctional mitochondria in the liver, and this event is related to the formation of an abnormal metabolic profile. In the absence of BNIP3, reactive oxygen species (ROS), inflammation and symptoms of steatohepatitis are increased. Therefore, the reduction of BNIP3 leads to the dysfunction of mitochondria in the liver and failure of metabolic homeostasis (Ney, 2015). Considering the effect of aging on the expression of BNIP3, the results of the articles do not seem to be decisive. Some studies have shown that this protein may increase in the muscles of sedentary elderly people. A possible explanation may be that induction of BNIP3 compensates for loss of mitochondrial autophagy and minimizes mitochondrial damage. Conversely, BNIP3 decreased in the heart of aged mice, while it remained unchanged in the muscle of aged humans. Effects of aging on NIX, and subsequently on autophagy and mitochondrial clearance, in skeletal muscles are rarely known. It has been reported that the expression of NIX is increased in the skeletal muscles of aged mice. This observation, while consistent with research showing an increase in autophagy markers in aged muscle, is in contrast to other authors who have reported an age-related decrease in mitophagy. Considering these data, it can be concluded that the age-related increase of both BNIP3 and NIX may indicate a failure in the mitophagy mechanism. Probably, the accumulation of BNIP3 and NIX can prevent these proteins from performing their function in the mitophagic process (Moreira et al., 2017). To become cancerous, the cell needs to overcome a number of immune mechanisms in the face of disorders. In this condition, the cell must escape processes such as apoptosis and autophagy to survive. In the occurrence of cancers, Bcl-2 family proteins such as Bcl-2 and Bcl-xL are often overexpressed. These two molecules prevent apoptosis by binding to Bax or Bak. Also, by conducting studies, it has been clearly established that Bcl-2 and Bcl-xL have anti-autophagy capabilities. Long-term food deprivation can stimulate autophagy; autophagy is a process conserved in evolution to break down cytoplasmic components such as large molecules. and organs. To prolong cell survival, autophagy is first induced, but its induction beyond normal causes cell death (Zhou et al., 2011). Computational, biochemical, and genetic evidence also showed that Bcl-xL reduces the useless ion flux across the mitochondrial inner membrane to prevent wasteful depletion of cellular resources, thereby preventing an energetic crisis during stress (Y. Chen et al. al., 2009). In summary, the main role of BCL-xL is to promote cell survival by inhibiting apoptosis or autophagy (or both). In addition, it has been described that a certain level of senescence is required for successful aging, including cell reprogramming. Therefore, high levels of BCL-xL can have a beneficial effect on maintaining senescent cells during the aging process (Borrás et al., 2020).

Autophagy/mitophagy and the role of exercise

Skeletal muscle shows age-dependent oxidative damage in biomolecules based on increased mitochondrial DNA mutations, addition of carbonyl group to proteins and lipid peroxidation. Oxidative stress can cause damage to mitochondrial DNA (mtDNA), which leads to mitochondrial dysfunction and an incomplete cycle. Decreased oxidative capacity and dysfunction of mitochondria have been associated with the pathogenesis of old age disabilities (Nascimento et al., 2019). Muscle mitochondria show signs of dysfunction with aging. These signs include increased ROS and decreased membrane potential, these two signs are factors that stimulate mitophagy. Increased mitophagy has also been observed in aged skeletal muscle, which is associated with increased LC-II on mitochondria (Oliveira & Hood, 2019b). For a long time, exercise has been known as a factor promoting health in old age and reducing susceptibility to related diseases, which is probably related to the induction of autophagy. Also, mitophagy may play a role in the beneficial effects of exercise (G. Chen et al., 2020b). But the findings obtained from the results of research on the effect of exercise activities on autophagy/mitophagy systems are contradictory and require more studies. to understand these effects (Y. Kim et al., 2017). Recent evidence in young animals has shown that an acute bout of endurance exercise increases markers of autophagy/mitophagy and may contribute to the removal of defective mitochondria after exercise. Whether or not successive bouts of exercise continue to stimulate autophagy and mitochondrial remodeling has not been well elucidated. One month of treadmill training led to an increase in the expression ratio of LC3-II to LC3-I and a decrease in p62, which indicates active autophagy. However, long-term exercise resulted in a decrease in total LC3 and no change in the ratio of active to inactive form. These data suggest that large changes in autophagy occur initially with an exercise stimulus. When sufficient adaptation has occurred, the need for autophagy is likely to be reduced, which may be due to the presence of a healthier population of organelles. Therefore, participation in exercise for the elderly is likely to increase mitochondrial benefits by reversing the attenuated rate of mitophagy evident with age or by stimulating the removal of damaged organelles. However, this is an area that needs considerable clarification, especially given the effects of exercise and the possible sex-specific differences that exist (Carter et al., 2015). C57BL/6 males who swam 1 hour daily five times a week for 8 weeks. In order to measure the autophagy flux in skeletal muscle, rats were treated with or without 0.4 mg/kg/day intraperitoneal colchicine (blocking the destruction of autophagosomes) after swimming exercise. The evaluation of autophagic flux showed that swimming training leads to an increase in autophagic flux (100% increase in LC3-II) in rat skeletal muscles, which indicates the important role of autophagy in mitochondrial biogenesis, which plays a key role in cellular adaptation to endurance exercise (Ju et al., 2016). Kwon et al. (2018) in a study on male Wistar rats with resistance training on the deep flexor muscles of the fingers concluded that in parallel with the increase in the anabolic signaling pathway (phosphorylation AKT, mTOR, and p70S6K) there is a significant decrease in autophagy (LC3-II/LC3-I ratio), which in the absence of changes in key autophagy proteins: Phosphorylation of ULK1, BECLIN1 and BNIP3. It happens, which indicates muscle hypertrophy caused by strength training along with enhancing anabolism and limiting catabolism caused by autophagy (Kwon et al., 2018). Additionally, the research findings imply that a single bout of resistance training can activate mitophagy in human skeletal muscle, potentially through the mechanism of mitochondrial ejection. BNIP3L/NIX is suggested as a reliable indicator for measuring mitophagy flux in this context (Díaz-Castro, F., et al.,2024). Recent studies have revealed that Bcl2 plays a crucial role in mediating autophagy induced by exercise, as well as in the skeletal muscle adaptations that occur in response to training while on a high-fat diet. Notably, the mitochondrial adaptations resulting from a treadmill exercise training regimen in mice, regardless of whether they were fed a low-fat or high-fat diet, did not necessitate the activation of autophagy through Bcl2. Instead, the training regimen led to an increase in protein synthesis rates and basal autophagy in Bcl2AAA mice, while acute exercise triggered the activation of autophagy through the mitochondrial-specific mediators BNIP3 and Parkin. This indicates that exercise activates these mitochondrial-specific autophagy mediators as alternative pathways for mitochondrial clearance (Ehrlicher, S. E., et al.,2020).

Also, the findings demonstrate that moderate exercise training can elevate PINK1 expression and promote autophagy, which plays a vital role in preserving skeletal muscle homeostasis. Conversely, under conditions of adverse stress, an abnormal rise in PINK1 levels may trigger excessive autophagy, disrupt mitochondrial function, and lead to diminished cell viability. Altogether, PINK1 expression is instrumental in triggering mitophagy, thereby enabling the clearance of dysfunctional mitochondria and providing protection to skeletal muscle cells. However, during periods of strenuous exercise, the integrity and quantity of skeletal muscle mitochondria are adversely affected, leading to the accumulation of autophagosomes. At this juncture, the levels of PINK1 and Parkin within the mitochondria rise significantly, resulting in an excessive activation of mitophagy that can cause further mitochondrial damage in skeletal muscle (Li, Y. Q., et al.,2021).

Along with reducing the amount of mitochondrial stress, it will lead to an increase in the health, viability and longevity of the cell, tissue and organism, or in other words mitohormesis. However, identifying all processes regulating autophagy/mitophagy and mitochondrial dynamics, determining the mechanisms of oxidative stress and understanding the link between mitohormesis (systemic adaptation) and the adaptive response to exercise in old age and related diseases require more research. A better understanding of the signaling pathways is important (Melouane et al., 2020).

Joint analysis of all studies does not allow establishing a clear trend on the effect of physical activity in relation to the type of exercise, volume, or intensity. Overall, aerobic or combined chronic long-term training (more than 12 weeks) seems to be the type of exercise most effective to counteract the age-related damage at the mitochondrial level. Therefore, it seems that exercise stimulates dynamics, and mitophagic capacity, although there is not a consensus about the behavior of different proteins in response to a physical stimulus. Future studies should focus on investigating the effects that different protocols of physical exercise can cause on the expression of mitochondrial proteins, as well as whether exercise practice could prevent mitochondrial damage and the effects on the dysfunctional mitochondria (Moreira, O. C., et al.2017).

Conclusion

It seems that the protection of mitochondria is an important and fundamental factor in order to prevent age-related diseases, especially in skeletal muscle and to prevent its atrophy. In the meantime, autophagy as an evolutionarily protected biological process can It has a vital role for the recovery of protein density and defective organelles. Because doing regular physical activities as a stimulus for the autophagy mechanism in skeletal muscles can help to regulate the metabolism of myocytes in addition to modulating this mechanism. In other words, doing physical activity can help the muscle cell's ability to remove mitochondria with impaired function and maintain the synthesis capacity of healthy mitochondria and prevent muscle wasting. An increase in autophagy will result. However, regular exercise will be a solution to regulate this process and ultimately improve the adaptation of skeletal muscles to exercise.

What is already known on this subject?

Autophagy is a cellular recycling process that breaks down and reuses damaged or unnecessary components. Theses procese can activate with different exercise training.

What this study adds?

Because doing regular physical activities as a stimulus for the autophagy mechanism in skeletal muscles can help to regulate the metabolism of myocytes in addition to modulating this mechanism.

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