Review Article

Mitochondrial Dysfunction and Skeletal Muscle Atrophy: Causes, Mechanisms, and Treatment Strategies

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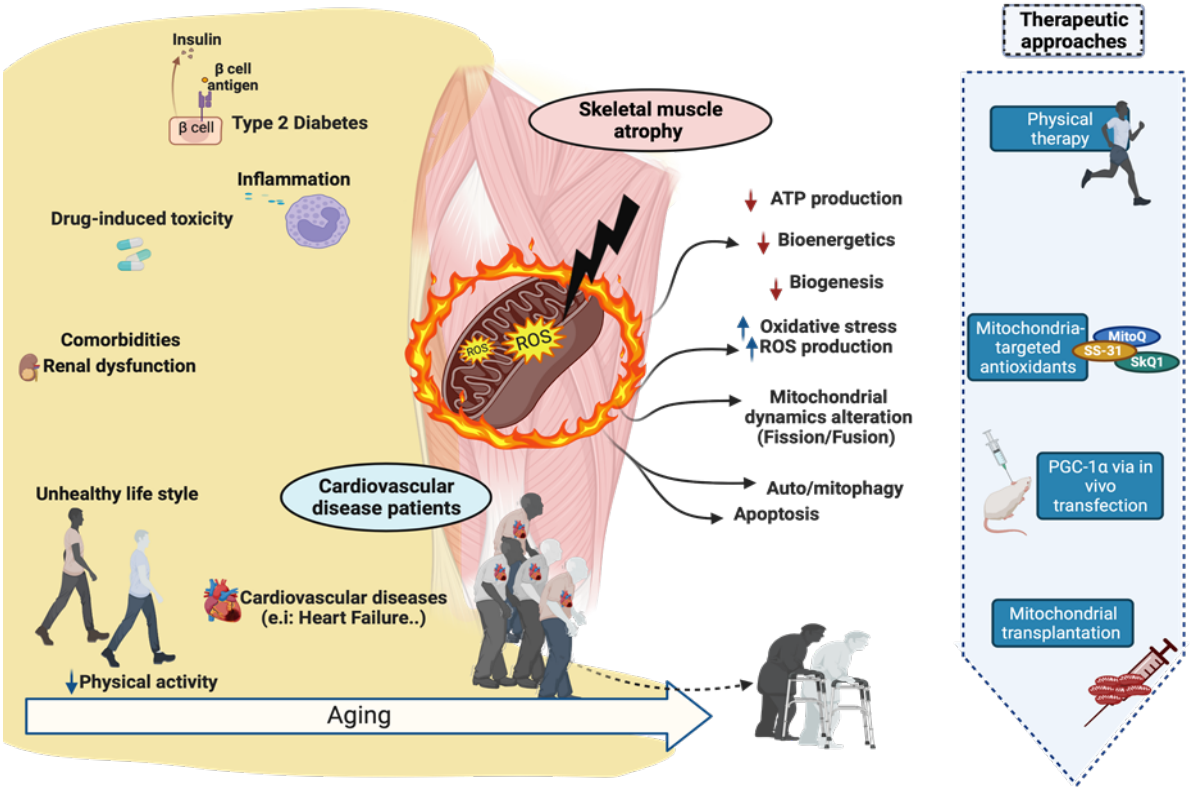
Abstract

Skeletal muscle, which accounts for approximately 40% of total body weight, is one of the most dynamic and plastic tissues in the human body and plays a vital role in movement, posture and force production. More than just a component of the locomotor system, skeletal muscle functions as an endocrine organ capable of producing and secreting hundreds of bioactive molecules. Therefore, maintaining healthy skeletal muscles is crucial for supporting overall body health. Various pathological conditions, such as prolonged immobilization, cachexia, aging, drug-induced toxicity, and cardiovascular diseases (CVDs), can disrupt the balance between muscle protein synthesis and degradation, leading to skeletal muscle atrophy. Mitochondrial dysfunction is a major contributing mechanism to skeletal muscle atrophy, as it plays crucial roles in various biological processes, including energy production, metabolic flexibility, maintenance of redox homeostasis, and regulation of apoptosis. In this review, we critically examine recent knowledge regarding the causes of muscle atrophy (disuse, cachexia, aging, etc.) and its contribution to CVDs. Additionally, we highlight the mitochondrial signaling pathways involvement to skeletal muscle atrophy, such as the ubiquitin-proteasome system, autophagy and mitophagy, mitochondrial fission-fusion, and mitochondrial biogenesis. Furthermore, we discuss current strategies, including exercise, mitochondria-targeted antioxidants, in vivo transfection of PGC-1α, and the potential use of mitochondrial transplantation as a possible therapeutic approach.

Keywords: Skeletal muscle atrophy, cardiovascular diseases, mitochondria, exercise, mitochondrial transplantation

Graphical abstract



The role of mitochondrial dysfunction in mediating skeletal muscle atrophy and therapeutic approaches

1. Introduction

Skeletal muscle, one of the largest organs in the human body, accounts for approximately 40% of body mass and serves as a highly active site for metabolic processes (Katare et al., 2022). Endurance and resistance exercises have been shown to improve skeletal muscle mass and function, while prolonged immobilization, chronic diseases, and certain medications used in clinical settings can lead to the loss of skeletal muscle mass and function (Egan and Sharples, 2023; Egan and Zierath, 2013). Furthermore, cardiovascular diseases (CVDs) are associated with an elevated prevalence and risk of skeletal muscle atrophy (He et al., 2021). Patients with CVDs often experience a decline in musculoskeletal and metabolic functions, which can result in conditions such as muscle atrophy, cardiac cachexia, and sarcopenia (Okoshi et al., 2013).

Skeletal muscle atrophy is characterized by a progressive loss of muscle mass and strength, leading to a reduced quality of life for individuals (Yin et al., 2021). The loss of skeletal muscle also contributes to metabolic abnormalities, including insulin resistance and type 2 diabetes, which can increase the risks of morbidity and mortality (Rubio-Ruiz et al., 2019). Recent evidence highlights the importance of mitochondria in maintaining skeletal muscle activity, as they play a crucial role in several vital processes such as ATP production, metabolic flexibility, functional integrity, and the regulation of the balance between reactive oxygen species (ROS) production and antioxidant systems (Nilsson and Tarnopolsky, 2019). Indeed, skeletal muscle has a mitochondrial density of approximately 52%, highlighting the crucial role of mitochondria in muscle function (Park et al., 2014). Therefore, mitochondrial dysfunction is considered a key factor contributing to the development of skeletal muscle atrophy (Hyatt and Powers, 2021).

This review offers a comprehensive overview of the role of mitochondrial dysfunction in mediating skeletal muscle atrophy and explores the underlying molecular mechanisms and cover recent findings on the factors contributing to skeletal muscle atrophy and the abnormalities of the skeletal muscle associated with mitochondrial dysfunction in CVDs. Additionally, we discuss current strategies that aim to counteract skeletal muscle atrophy. Finally, we review the potential therapeutic benefits of mitochondrial transplantation.

2. Mitochondria and skeletal muscle atrophy

Mitochondria are membrane-bound cell organelles that produce the majority of the chemical energy required to fuel the metabolic activities of cells. While the primary function of mitochondria is the aerobic synthesis of ATP in cells, these organelles also play a role in a variety of other crucial cellular processes, such as apoptosis and programmed cell death, as well as the generation of ROS (Brand et al., 2013). Skeletal muscle health is closely tied to the optimal functioning of mitochondria, which form an interconnected network with the sarcoplasmic reticulum and sarcolemma (Swalsingh et al., 2022). However, skeletal muscle atrophy is initiated by catabolic pathways that become activated as a result of mitochondrial dysfunction. These pathways ultimately impact the nucleus through a feedback mechanism (Romanello and Sandri, 2016).

Understanding the signaling network responsible for skeletal muscle atrophy is crucial for the development of effective therapeutic interventions. Mechanisms associated with mitochondria play a critical role in skeletal muscle atrophy, including the generation of ROS, disturbances in mitochondrial dynamics (fission and fusion), decreased mitochondrial biogenesis, impaired regulation of autophagy and mitophagy, and apoptosis (Hyatt and Powers, 2021). Particularly, mitochondrial ROS is considered a major contributing factor to skeletal muscle atrophy

(Powers et al., 2012b). Excessive ROS induces the oxidation of myofibrillar proteins, making them more vulnerable to proteolytic breakdown. Furthermore, elevated levels of ROS can impede the initial phase of mRNA translation, thereby inhibiting protein synthesis pathways (Lian et al., 2022). Additionally, oxidative stress in skeletal muscle can activate both calpain and caspase-3 (Powers et al., 2012a).

Mitochondria are dynamic organelles that undergo rapid fusion and fission processes to adapt their shape in response to the cellular environment's demands. Mitochondrial fusion is controlled by Mitofusin 1/2 (Mfn1/2) in the mitochondrial outer membrane and Optic atrophy 1 (OPA1) in the mitochondrial inner membrane, while mitochondrial fission is regulated by Dynamin related protein 1 (DRP-1), mitochondrial fission factor (Mff), and fission protein 1 (Fis1) (Tilokani et al., 2018). Muscular-specific ablation of Mfn1 and Mfn2 causes severe muscular atrophy (Romanello and Sandri, 2021). DRP-1 overexpression induces mitochondrial malfunction, mitophagy, and energy stress, which results in an atrophy via the adenosine monophosphate-activated protein kinase (AMPK)/Forkhead box O3 (FoxO3) pathway (Romanello et al., 2010). It has been demonstrated that genetic silencing Fis1 and DRP-1 in skeletal muscle prevents muscle loss induced by excessive production of transcription factor FoxO3 (Romanello et al., 2010). Inhibition of OPA1 leads to mitochondrial defects, generation of ROS, and release of mitochondrial DNA. These events trigger various transcription factors, including FoxO3, nuclear factor kappa B (NF-κB), and ATF4, which collaborate to coordinate the overexpression of genes related to muscle atrophy (Romanello and Sandri, 2021).

Mitophagy plays a vital role as a cellular autophagic process that specifically targets and removes damaged mitochondria. It is intricately linked with mitochondrial biogenesis, allowing for precise regulation of the quantity and quality of mitochondria. This coordinated process prepares the mitochondria for subsequent lysosomal breakdown, ultimately contributing to the restoration of cellular homeostasis in both healthy physiological conditions and challenging circumstances (Ma et al., 2020). Previous electron microscopy studies were the first to detect mitophagy in mammalian cells. These studies found enhanced mitochondrial sequestration in lysosomes following glucagon-stimulated hepatocyte catabolism (De Duve and Wattiaux, 1966). The Parkin E3 ligase and PINK1 (Phosphatase and tensin homolog (PTEN)-induced kinase 1) are the most widely studied pathways involved in mitophagy (Narendra et al., 2008). Activation of this pathway accelerates the clearance of defective mitochondria, preserving a healthy mitochondrial pool. However, it also reduces the total mitochondrial density in disuse skeletal muscle atrophy (Kang et al., 2016). Notably, significant mitophagy mediators, such as PINK1, Parkin, Mul-1, and microtubule-associated protein 1A/1B-light chain 3 (LC3II), were found to be increased in mouse TA muscle following disuse (Ji and Yeo, 2019). Sarcopenia, an age-related loss of muscle mass and strength, can be linked to inadequate Parkin-mediated mitophagy and elevated levels of mitochondrial ROS, resulting in the acceleration of skeletal muscle atrophy through MuRF-1 activation (Ito et al., 2022). The expression of Peroxisome proliferator-activated receptor gamma coactivator 1 (PGC-1) which serves as a master regulator of mitochondrial biogenesis, is reduced in skeletal muscle atrophy, while AMPK-activated PGC-1 promotes mitochondrial synthesis and facilitates the clearance of mitochondria through mitophagy (Cantó et al., 2009).

Apoptosis during muscle atrophy occurs in both myonuclear and other muscle cell types, leading to the elimination of unwanted, damaged, or defective cells. Bcl-2 family members play a role in mitochondrial-mediated apoptosis by facilitating the release of cytochrome c, AIF, and Endo G into the cytosol, subsequently activating caspases (Cheema et al., 2015). The pathophysiology of disuse muscle atrophy is believed to be primarily influenced by

mitochondria-mediated apoptotic signaling (Marzetti et al., 2010). The activation of caspase-3 to break down actomyosin complexes is a well-known consequence of inactivity-induced muscle atrophy (Smuder et al., 2010). Increased ROS triggers caspase-3 and promotes protein breakdown in skeletal muscle fibers (Powers and Schrager, 2022).

Consequently, the close interplay between mitochondria and skeletal muscle is crucial for maintaining muscle health and preventing atrophy. It is well established that mitochondrial dysfunction significantly contributes to skeletal muscle atrophy through multiple mechanisms. Gaining a deeper understanding of these mechanisms will provide valuable insights into the development of therapeutic interventions aimed at preserving muscle mass and function.

3. The causes of skeletal muscle atrophy

Skeletal muscle is a heterogeneous and multicellular tissue composed of various muscle fiber types with distinctly diverse metabolic and functional characteristics (Schiaffino and Reggiani, 2011). The classification of skeletal muscle types is based on myosin heavy chain (MHC) isoforms, as MHC exists in the forms of types I, IIa, and IIx and muscle fibers can contain either one or a combination of these isoforms (Gejl et al., 2021). These muscle fiber types can be broadly classified based on their contractile speed and aerobic or anaerobic characteristics, which include slow-oxidative (type I), fast oxidative-glycolytic (type IIa), and fast-glycolytic (type IIx) (Schiaffino and Reggiani, 2011; Smith et al., 2023). Slow-twitch muscle fibers primarily rely on aerobic metabolism, which is characterized by a high density of capillaries and oxidative enzymes. This metabolic profile enables them to exhibit greater resistance to fatigue. In contrast, fast-twitch muscle fibers have a higher rate of ATP hydrolysis compared to slow fibers and contract more readily due to their reliance on anaerobic metabolism, specifically glycolysis (Pereyra et al., 2022). While the contractile proteins actin and myosin play a significant role in contractile activity, key regulatory proteins such as troponin, tropomyosin, M-protein, beta-actin, gamma-actin, and C-protein also contribute to muscle function. Elastin, collagen, and reticulin are present in the sarcoplasm, and skeletal muscle also contains myoglobin, myogenin, myoalbumin, and x-globulin (Makovický et al., 2008).

Skeletal muscle serves as a source of amino acids for protein synthesis throughout the body (Argilés et al., 2016; Kamei et al., 2020). Protein synthesis in skeletal muscle is a dynamic process that plays a crucial role in muscle growth, repair, and maintenance. It involves a delicate balance between protein synthesis and degradation, which controls tissue function and mass (Hinde et al., 2021). Muscle atrophy occurs when the rate of protein degradation surpasses that of protein synthesis, leading to a decrease in the cross-sectional area of myofibers and a decline in muscle strength **(Figure 1).** The basic molecular mechanisms involved in skeletal muscle atrophy include the ubiquitin-proteasome system (UPS), autophagy, inflammation, the insulin-like growth factor 1 (IGF-1)/PI3K/Akt signaling pathway, and the myostatin pathway.

The UPS is believed to be responsible for the degradation of contractile proteins in skeletal muscle. This process involves a multistep reaction that includes the activation of an enzymatic cascade consisting of ubiquitin E1 (activating enzyme), E2 (conjugating enzyme), and E3 (ligase) enzymes. Various mechanisms are involved in the conjugation of ubiquitin, allowing the UPS to specifically target certain proteins for degradation (Khalil, 2018).

Another major mechanism for protein degradation is autophagy, which is required for the turnover of cellular components in both constitutive and responsive processes to various stimuli (Mizushima et al., 2008). Impaired autophagy in skeletal muscle can lead to cellular

abnormalities such as mitochondrial damage, endoplasmic reticulum stress, decreased turnover of sarcomeric proteins, and cell death, resulting in the development of various skeletal muscle disorders (Sandri, 2013). The FoxO3a protein is a key regulator of autophagy and ubiquitin-proteasome induction, and genetic stimulation of FoxO3a leads to skeletal muscle atrophy (Mammucari et al., 2007). Additionally, FoxO3a controls the transcription of autophagy-related genes, including LC3 and Bcl2 Interacting Protein 3 (Bnip3), and Bnip3 appears to mediate the effect of FoxO3a on autophagy (Mammucari et al., 2007; Sandri et al., 2004).

An important growth factor involved in regulating muscle hypertrophy is insulin-like growth factor 1 (IGF-1). IGF-1 stimulates the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway (Timmer et al., 2018). The UPS and autophagy are two mechanisms through which IGF-1 controls skeletal muscle protein synthesis and protein breakdown. However, the wide range of biochemical pathways controlled by IGF-1 makes it challenging to conduct studies specifically focused on IGF-1 in skeletal muscle (Yoshida and Delafontaine, 2020). In contrast to the role of IGF-1, myostatin has an opposite role in the regulation of skeletal muscle growth and size. Myostatin, a member of the transforming growth factor-β superfamily predominantly expressed in skeletal muscle, negatively regulates skeletal muscle growth by inhibiting protein synthesis and enhancing the activity of the ubiquitin-proteasome system, which leads to muscle atrophy (Rodriguez et al., 2014). From a mechanistic perspective, myostatin inhibits the Akt/mTOR/p70S6 pathway, which governs myoblast differentiation and myotube hypertrophy (Trendelenburg et al., 2009).

Recently, the activation of NF-κB has been suggested as a potential molecular mechanism for the loss of skeletal muscle. Once activated, NF-κB triggers the activation of proinflammatory cytokines, tumor-derived proteins, and other factors that contribute to muscle atrophy (Ji et al., 2022). NF-κB also upregulates the expression of several proteins in the ubiquitin-proteasome system and promotes the expression of inflammation-related molecules that directly or indirectly promote muscle wasting. Moreover, it can interfere with the process of myogenic differentiation (Li et al., 2008).

As a result, skeletal muscle comprises a heterogeneous tissue with a variety of muscle fiber types, each exhibiting distinctive metabolic and functional characteristics. Complex molecular mechanisms, including pathways associated with protein synthesis and degradation, are involved in the intricate regulation of skeletal muscle growth and maintenance. An understanding of these molecular processes is essential to unravel the complexities of skeletal muscle physiology and to develop strategies for the improvement of muscle health.

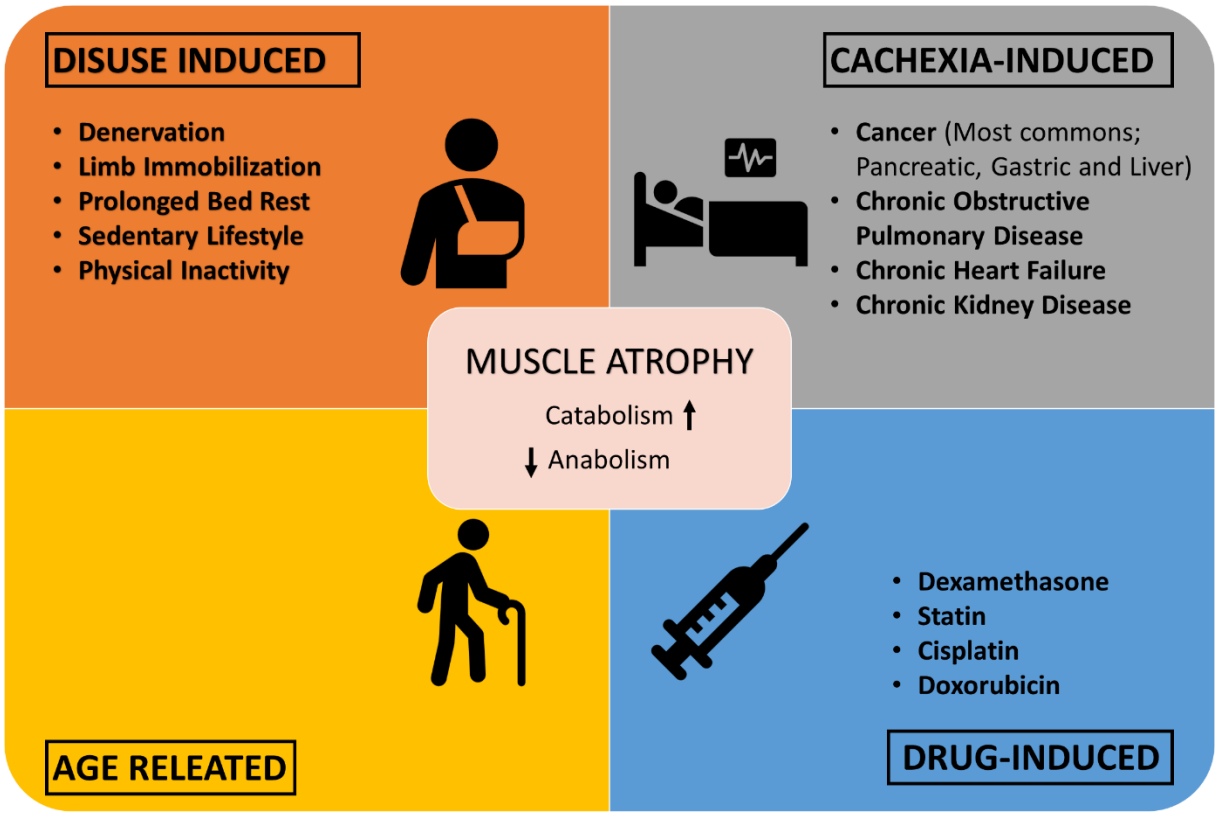


Figure 1: The causes of skeletal muscle atrophy.

3.1. Disuse-induced skeletal muscle atrophy

Skeletal muscle atrophy occurs as a consequence of the overall loss of proteins, organelles, and cytoplasm, typically associated with catabolic conditions such as inactivity or disuse (Sartori et al., 2021).The relationship between skeletal muscle mass and physical activity level is complex, and during periods of inactivity, body composition undergoes several changes, including an increase in fat mass and a decrease in muscle mass (Evans, 2010; Kuh et al., 2005). Several pathological conditions induce skeletal muscle atrophy, such as denervation, limb immobilization, prolonged bed rest, a sedentary lifestyle, spaceflight, microgravity, and physical inactivity (Timmons and Gallagher, 2016; Timmons et al., 2006). Previous studies have revealed that muscle immobilization leads to increased inflammation, oxidative stress, proteolysis, and metabolic dysfunction (Kandarian and Jackman, 2006).

Even after short-duration spaceflights, skeletal muscle atrophy is a prominent observation, evident both at the macroscopic level through a reduction in muscle size or volume, and at the microscopic level through a decrease in muscle fiber size (Lee et al., 2022). The twitch contractile characteristics of skeletal muscle are primarily determined by intracellular Ca2+ release and absorption by the sarcoplasmic reticulum (SR) (Qaisar et al., 2019). It has been observed that spending 6 days in space resulted in a considerable reduction in time to twitch peak force, a measure of SR Ca2+ release-uptake (Caiozzo, 1994).

The IGF-1/PI3K/Akt signalling pathway is critical for the regulation of protein synthesis via mTOR and glycogen synthase kinase 3 (GSK3) as well as protein degradation via modulation of FoxO transcription factors. Astronauts experience skeletal muscle atrophy and strength deficits after only a few weeks in space, mainly due to reduced protein synthesis as a result of unloading (Juhl et al., 2021). Both real and simulated microgravity conditions lead to an

increase in myostatin expression and a decrease in IGF-1 expression in skeletal muscle (Lalani et al., 2000). In a spaceflight experiment with gene knockout mice lacking MuRF1, skeletal muscle atrophy was observed under microgravity conditions (Nikawa et al., 2004). MuRF1-deficient animals were used in a spaceflight experiment using gene-knockout mice, and these mice exhibited muscular atrophy in microgravity (Cadena et al., 2019). Spaceflight experiments have demonstrated that exposure to microgravity leads to a decrease in skeletal muscle size, volume, cross-sectional area (CSA), and strength (Gao et al., 2018). Specifically, a study conducted over a 17-day space microgravity period revealed a 4-10% reduction in size in various muscle groups, including the quadriceps, soleus-gastrocnemius, and anterior calf (Tesch et al., 2005). While skeletal muscle atrophy occurs in all muscle groups, it is particularly prominent in muscles like the soleus, predominantly composed of slow-oxidative muscle fiber types (Gopalakrishnan et al., 2010). Furthermore, it is worth noting that the soleus and gastrocnemius muscles, which consist of type I and type II muscle fibers, exhibit the most significant degree of skeletal muscle atrophy during spaceflight (Fitts et al., 2010).

Disuse-induced skeletal muscle atrophy has been extensively researched in human bed rest studies and animal hind limb unloading models (Brocca et al., 2012; Wang et al., 2006b). In mouse models of inactivity and hindlimb unloading, decreased activation of Akt and mTORC1 has been seen in the soleus and medial gastrocnemius muscles (Kelleher et al., 2013). Disuse-induced atrophy may be significantly influenced by protein breakdown and the primary mechanism for intracellular protein breakdown is the UPS (Kitajima et al., 2020). Two significant ubiquitin E3 ligases specific to skeletal muscle, MuRF1 and MAFbx/atrogin-1, are involved in this process. Knockout studies have shown that MAFbx knockout mice exhibited reduced muscle mass loss after 7 and 14 days, while MuRF1 knockout mice showed a 36% greater muscle sparing 14 days following denervation (Bodine et al., 2001). However, some studies have reported no change or even a reduction in the expression of MuRF1 or atrogin-1 after 14 days or more of unloading (Suetta et al., 2012). The expression of Atrogin-1/MAFbx gene was found to be 2.5-fold increased after two weeks of limb immobilization (Chen et al., 2007). However, at 20 days after unloading, the mRNA levels in the vastus lateralis muscle did not show substantial alterations despite a significant reduction in muscle volume (Sakuma et al., 2009). Mechanical unloading, such as hindlimb suspension, can lead to reductions in mTOR signaling and protein synthesis (Kelleher et al., 2013). In humans, lower leg immobilization for 48 hours resulted in decreased Akt phosphorylation at Ser473 and Thr308, indicating a reduction in the protein synthesis pathway (Urso et al., 2006). Activation of Akt and mTORC1 has also been found to decrease in the soleus and medial gastrocnemius muscles of mouse models of immobilization and hindlimb unloading (Bodine, 2013). Zhang et al. demonstrated that hindlimb immobilization in animals led to a decrease in force capacity. This reduction in strength is attributed to a decrease in force per CSA and the size of the muscle fibers (Zhang et al., 2018). A two-week limb immobilization study showed a 9% reduction in quadriceps muscle volume, a 5-8% reduction in muscle CSA, and a 23% reduction in muscle strength (Glover et al., 2008).

Disuse is a common stressor that significantly affects the quantity and quality of mitochondria in skeletal muscle by promoting the generation of ROS, proinflammatory cytokines, and muscle proteolysis (Puthucheary et al., 2010). Muscle disuse leads to decreased muscle strength, down-regulation of myoglobin, reduced activity of oxidative phosphorylation complexes, and decreased citrate synthesis (Brocca et al., 2012). Normally, skeletal muscle regulates ROS levels through the use of endogenous antioxidant enzymes. However, during inactivity-induced oxidative stress, mitochondrial ROS generation becomes the primary source. Prolonged disuse results in the release of hydrogen peroxide (H_2O_2), which activates AMPK-mediated proteolytic

pathways, including the ubiquitin-proteasome and autophagy-lysosome systems. This leads to increased muscle protein breakdown and fiber atrophy (Liu et al., 2014a).

The elimination of defective organelles through mitophagy is a crucial aspect of maintaining muscle health during prolonged inactivity. Studies have observed that protein levels of Bnip3 reduced in the tibialis muscle after 7 days of hind limb immobilization, along with lower gene expression but higher protein levels of Bnip3L (Kang et al., 2016; Vainshtein et al., 2015) (Vainshtein et al., 2015). Furthermore, three days of hind limb suspension have been shown to decrease the expression of genes associated with mitochondrial biogenesis while increasing the expression of mitophagy genes such as Bnip3 and Bnip3L (Leermakers et al., 2019). Hindlimb denervation for one week resulted in increased expression of Parkin (an E3 ubiquitin ligase) and ROS, both of which play important roles in autophagy (Furuya et al., 2014).

Chronic muscular disuse disrupts the balance of the fission/fusion proteins on mitochondria and fission levels continue to be higher than those of fusion proteins (Memme et al., 2021). Muscle disuse causes mitochondrial dysfunction via reductions in gene and protein expression of the Mfn2 and OPA1 (Hyatt et al., 2021). In adult mouse skeletal muscle, knockdown of DRP-1 led to significant skeletal muscle atrophy (Dulac et al., 2020). Pro-apoptotic members of the Bcl-2 family co-localize with DRP-1 and Mfn2 and their activity can be modified by these apoptotic regulators (Cleland et al., 2011). Apoptosis was observed as early as 12 hours after hindlimb suspension, and before the increase in muscle atrophy F-box mRNA (Calvani et al., 2013). There is growing evidence indicating that chronic muscle inactivity causes mitochondrial damage and dysfunction, directly contributing to the skeletal muscle atrophy induced by disuse (Powers et al., 2011)

3.2. Cancer cachexia-induced skeletal muscle atrophy

Cachexia is common in various cancers, with liver and pancreatic cancer exhibiting rates of 41-45%, and head, neck, and lung cancer showing a rate of 30% (Anker et al., 2019). Furthermore, cachexia has been associated with chronic obstructive pulmonary disease, chronic heart failure (CHF), and chronic kidney disease (Kwan et al., 2019; Mak and Cheung, 2006; Valentova et al., 2020). The metabolic demands of cancer cells, particularly regarding the metabolism of glucose and amino acids, contribute to muscle cachexia (Penna et al., 2018). Another characteristic alteration in glucose metabolism in cancer cachexia is increased gluconeogenesis from lactate and alanine (Nipp et al., 2018). Both reduced amino acid availability and increased insulin levels block the mTOR-dependent anabolic pathway, which slows protein synthesis rates and promotes protein degradation in cancer cachexia (Argilés et al., 2014). It has been shown that the level of glutamine in the plasma of tumour-bearing rats is significantly lower than in healthy animals (Tessitore et al., 1993). The reduced availability of glutamine may lead to activation of the metabolic sensor AMPK (Roth and Oehler, 2010).

Cancer cachexia is a complex catabolic syndrome characterized by the involuntary loss of body mass due to severe skeletal muscle loss (Fearon et al., 2011). This condition can affect various aspects of muscle physiology, including muscle fiber structure, proteolysis (myostatin, UPS), protein synthesis pathways, lipid metabolism, inflammation, microRNAs, and mitochondrial metabolism (Chen et al., 2020; Dolly et al., 2020). The extent of muscle mass loss varies depending on the location of cancer, affecting 5-89% of cancer patients (Rier et al., 2016). Judge et al. demonstrated that patients with cachectic pancreatic cancer exhibited increased fibrosis and collagen in their skeletal muscles (Judge et al., 2018).

Inactivation of myostatin leads to skeletal muscle hypertrophy, while its overexpression results in skeletal muscle atrophy (Carnac et al., 2007; Rodriguez et al., 2014). Myostatin/activin A stimulate FoxO expression, leading to protein degradation through the upregulation of MuRF1 and MAFbx/Atrogin1 expression. Simultaneously, they inhibit protein synthesis by regulating the Akt/mTOR signaling pathway through suppressor of mothers against decapentaplegic 3 (SMAD3) (Setiawan et al., 2023). Toledo et al. reported that inhibiting myostatin with formoterol and the soluble myostatin receptor activin receptor type-2B (ActRIIB) reversed skeletal muscle wasting in tumor-bearing animals (Toledo et al., 2016). Experimental models indicate that the UPS plays a significant role in the degradation of muscle proteins in cancer cachexia (Chen et al., 2020; Fanzani et al., 2012). Muscle-specific ubiquitin ligases such MAFbx and MuRF1 expression levels are recognized as molecular indicators of increased proteasome-dependent proteolysis in cancer-related cachexia (Kitajima et al., 2020). The expression of MuRF-1, and MAFbx genes has been linked to various types of muscle atrophy, including cancer cachexia (Costelli et al., 2006). Cancer-related cachexia reduces protein synthesis and inhibits protein degradation through the regulation of mTOR, Akt, FoxO, and S6K (Schmitt et al., 2007).

Cancer cachexia is accompanied by an increase in inflammation primarily generated by immune cells in response to cancer. Patients with gastrointestinal cancer cachexia have been reported to exhibit higher levels of C-reactive protein (CRP) and pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and IL-8 (Riccardi et al., 2020). NF-κB is a transcription factor expressed in skeletal muscle (Hunter et al., 2002), and its activation triggers the release of inflammatory cytokines such as TNF-α (van de Vyver and Myburgh, 2012; Wyke et al., 2004). TNF-α has been demonstrated to have a direct catabolic impact on skeletal muscle, leading muscle atrophy inducing the UPS (Llovera et al., 1997). NF-κB inhibition reduces cytokine-induced skeletal muscle atrophy (Ladner et al., 2003). Kawamura et al. found that injecting NF-κB decoy oligonucleotides into cachectic mice with adenocarcinoma tumors significantly reduced muscle atrophy (Kawamura et al., 1999). Furthermore, IL-6 inhibits mTOR activity, and this suppression of mTOR is dependent on AMPK activation and occurs independently of the signal transducer and activator of transcription (STAT) signaling pathway (White et al., 2013).

Skeletal muscle atrophy associated with cancer cachexia is significantly influenced by dysregulation of mitochondrial metabolism, including increased fission, decreased fusion and or biogenesis, and reduced respiratory chain complexes (Fontes-Oliveira et al., 2013). Numerous studies have reported tumor-associated disruptions in the skeletal muscle mitochondria (Penna et al., 2020). For instance, the oxidative capacity of muscle and ATP synthesis are reduced in animals with cachexia (Ballarò et al., 2019a). Tumor patients with cachectic cancer and those with non-cachectic cancer had a similar number of mitochondrial DNA copies in their skeletal muscles (de Castro et al., 2019). However, mice with cachectic cancer exhibited a lower ratio of mitochondrial DNA to nuclear DNA than mice without cachectic cancer (Martin and Freyssenet, 2021). Mfn2, OPA1, Fis1, and DRP-1 were downregulated in the muscles of tumor-bearing mice (Barreto et al., 2016). In cachectic patients with gastric cancer, there was an increase in Fis1 transcript levels, but no difference in mitochondrial fusion (Mfn2 and OPA1), mitochondrial biogenesis (PGC1), and mitochondrial transcription factor (TFAM) (Marzetti et al., 2017). Another study found both reduced and unchanged PGC-1 protein levels in the skeletal muscle of animals with cachectic tumors (Ballarò et al., 2019b). Consistent with this study, De Castro et al. demonstrated an increase in Fis1 mRNA expression despite no change in fusion markers (Mfn2) and mitochondrial

biogenesis transcripts (TFAM and PGC-1) in patients with gastric or colorectal cancer (de Castro et al., 2019).

The role of autophagy in modulating the progression of cachexia and skeletal muscle atrophy is a topic of significant interest (Bowen et al., 2015). Activated FoxO3 reduces the activity of the IGF1/PI3K/Akt signaling pathway through mTOR and transcriptional-dependent pathways, suggesting that FoxO3 is the primary transcription factor that triggers autophagy and controls the expression of autophagy-related genes, including LC3 and Bnip3 (Mammucari et al., 2007). In skeletal fibers of cancer cachexia patients, there was an increase in LC3B II protein expression, while p62 expression showed no difference (Aversa et al., 2016). It is possible that mitochondrial dysfunction plays a central role in skeletal muscle atrophy in cancer cachexia, but whether it develops before or after muscle atrophy remains unclear.

3.3. Age-related skeletal muscle atrophy

Sarcopenia is defined as the loss of strength and mass of skeletal muscle during and can lead to an imbalance between muscle tissue anabolism and catabolism (Frontera et al., 1991; Larsson et al., 2019; Turkel et al., 2023). This imbalance ultimately results in muscle atrophy and a reduction in the size and number of type II muscle fibers (Cruz-Jentoft and Sayer, 2019). With increasing age, the loss of skeletal muscle begins and continues until the end of life. Between ages 20 and 80, there is a 30% loss in muscle mass and a 20% loss in CSA (Frontera et al., 2000). Age does not result in a shift to slow contractile characteristics in the male extensor digitorum longus (EDL) and female diaphragm (Hill et al., 2020). Brack et al. reported that older animals have a lower number of nuclei per unit length and a larger myonuclear field (Brack et al., 2005). Similarly, Wilkinson et al. reported that the mean total muscle size of the vastus lateralis is 18% smaller in older people. The same group observed a 40% decrease in total muscle size in people aged 20 to 80 years (Wilkinson et al., 2018). In another study, fiber subtypes were similarly reduced by 27% for type IIa and 31% for type IIx (Nilwik et al., 2013).

Satellite cells proliferate after being triggered by genes involved in cell cycle progression such as Pax7, myogenin and MyoD (Collins, 2006). Aging may result in a reduction in the number of satellite cells involved in muscle regeneration (Renault et al., 2002). However, some studies have found no decrease in satellite cell counts in aging skeletal muscle (Hikida et al., 2000). An anabolic growth factor known as IGF-1 can promote satellite cell proliferation and protein synthesis (Cassano et al., 2009). Skeletal muscle fiber size also decreases with age due to the reduction of satellite cell proliferation and growth factors such as IGFs (Chen et al., 2020). Myostatin can inhibit protein synthesis by decreasing Akt or enhance the degradation by increasing FoxO transcription, thus preventing satellite cell development (Bowen et al., 2015). Satellite cell activation declines with age due to a decrease in mitogen-activated protein kinase (MAPK) activity. This process increases growth factor-beta (TGF-b) levels and suppresses satellite cell activation (Carlson et al., 2009).

Some sarcopenia studies have indicated a reduction of protein synthesis in adult and elderly muscles, whereas others have found no difference (Francaux et al., 2016; Koopman et al., 2009). Additionally, conflicting findings have been reported on changes in the mTOR pathway with age (Sakuma et al., 2017). Although anabolic resistance is a problem in sarcopenia, activation of the Akt/mTOR pathway promotes sarcopenia (Ham et al., 2020). Akt overexpression in mice accelerated sarcopenia with protein breakdown in muscle quality maintenance (Sandri et al., 2013). Blocking of the PI3K/Akt/mTOR signaling pathway and inflammation induced on by aging can activate the UPS and cause a reduction in contractile

proteins (Peris-Moreno et al., 2021). Protein synthesis levels do not decline with age, but the sensitivity to anabolic stimulation is reduced (Dalle et al., 2017). Sedentary lifestyles and low testosterone levels, which are associated with aging, impair muscle protein synthesis (Ali and Garcia, 2014). Skeletal muscle protein synthesis is lower in elderly people than in younger people after protein consumption, which appears to be connected to insulin sensitivity (Rasmussen et al., 2006).

Furthermore, it has been established that the UPS plays a crucial role in facilitating skeletal muscle atrophy (Vainshtein and Sandri, 2020). There is debate about whether skeletal muscle UPS activity increases or decreases with age. Some studies suggest an increase, while others claim that aging muscles have decreased UPS activity. The muscles of older rats displayed various modifications indicating improved proteolysis by the UPS, which may enhance their capacity to remove misfolded proteins (Altun et al., 2010). The UPS and FoxO activity are probably less important in sarcopenia (Sandri et al., 2013). The FoxO pathway (MuRF-1 and MAFbx) does not significantly change or may even be downregulated with age (Larsson et al., 2019). However, it is considered that calpains and autophagy pathways have a larger effect during sarcopenia (Bowen et al., 2015). Calpain mRNA expression was higher in skeletal muscle elderly rats than in young rats (Dargelos et al., 2007; Samengo et al., 2012).

The potent mechanism of sarcopenia may be connected to increased generation of ROS derived from mitochondria and the activation of apoptotic cell death (Calvani et al., 2013). Elevated levels of ROS, such as H_2O_2, can hinder the phosphorylation of Akt, mTOR, and the downstream mTOR targets 4E-BP1 and p70S6K (Gomez-Cabrera et al., 2020). With age, cells produce more ROS from mitochondria (mtROS) and NADPH oxidase (NOX) (Damiano et al., 2019). Aging muscle, in general, experiences increased ROS production in both the interfibrillar and subsarcolemmal mitochondria (Boengler et al., 2017). This rise in ROS formation is triggered by the oxidation of ETC complex V and a decrease in ATP synthesis (Zorov et al., 2014). Mitochondrial DNA damage and reduced DNA repair systems are widespread in skeletal muscle with age (Joseph et al., 2016). Impaired mitophagy can also contribute to increase in ROS production (Carter et al., 2015). Aging-related reductions in mitochondrial content in skeletal muscle may be correlated with low gene and protein expression PGC-1 in both type I and type II muscle fibers (Joseph et al., 2012). PGC-1 reduces muscle protein degradation via the activity of NF-κB and FoxO3 (Sandri et al., 2006). In sarcopenic individuals, the expression profiles of PGC-1, estrogen-related receptors (ERRα) , and other coactivators have been found to be reduced (Migliavacca et al., 2019). Aging leads to increased mitophagy and fission while simultaneously reducing the amount of mitochondria in both slow and fast muscle fiber types (Murgia et al., 2017). Mitochondrial dysfunction in sarcopenia arises from the suppression of the genes and proteins regulating mitochondrial fusion and fission (Del Campo et al., 2018). Mfn2 levels decline with age as PGC-1 regulates Mfn2 expression, which is crucial for fusion dynamics and mitophagy (Chen and Dorn, 2013). Severe mitochondrial fragmentation, malfunction, ROS generation, ER stress, and suppression of autophagy contribute to skeletal muscle atrophy (Sebastián et al., 2016). Specific mitochondrial pathways play a role in aging-related sarcopenia and should be considered alongside other cellular pathways.

3.4. Drug-induced skeletal muscle atrophy

Skeletal muscle toxicity can occur due to various medications as a side effect of treatment or in response to therapy (Jones et al., 2014; Mor et al., 2011). Both endogenous and exogenous substances, including glucocorticoids, catecholamines, cytokines (such as TNF-α), and

glucagon, can contribute to skeletal muscle atrophy. Additionally, exogenous glucocorticoids, statins, cisplatin, and doxorubicin are among the most common causes of impaired muscle cell metabolism, leading to muscle toxicity and potential muscle atrophy (Jones et al., 2014).

Dexamethasone (Dex), a synthetic glucocorticoid, reduces the phosphorylation of the PI3K/Akt/FoxO3a pathway and activates atrogin 1 and MuRF1, leading to increased protein degradation and decreased protein synthesis (Gonnella et al., 2011; Wang et al., 2021a). Additionally, Dex treatment is associated with elevated myostatin mRNA and protein expression in rats, indicating its role in skeletal muscle atrophy (Qin et al., 2013). The deletion of the myostatin gene has been reported to prevent Dex-induced muscular atrophy in male mice (Gilson et al., 2007). When IGF-1 is overexpressed in myotube cultures treated with dexamethasone, it effectively counteracts the atrophy induced by Dex by reducing the levels of MuRF1 and MAFbx (Stitt et al., 2004). Furthermore, increased levels of atrogin-1/MAFbx and MuRF1 are associated with Dex-induced fast-twitch muscle atrophy (Jia et al., 2022). Dex treatment leads to decreased mTOR and Akt phosphorylation in mouse C2C12 myotubes and muscle tissues (Wang et al., 2022) , and it also decreases protein synthesis in rat gastrocnemius muscles through the mTOR/p70S6K pathway (Jhuo et al., 2023). The involvement of REDD1 (the repressor of mTORC1) has been observed in pathological conditions associated with skeletal muscle atrophy (Gordon et al., 2015). In the context of Dex treatment, it has been observed that REDD1 levels increase after 5 hours but return to baseline levels 24 hours later, whether it is a single dose or repeated doses of Dex (Britto et al., 2014).

Statin-induced muscle atrophy is significantly influenced by an increase in the expression of MAFbx and MuRF1 (Bodine and Baehr, 2014). Furthermore, statin therapy inhibits IGF-1 signaling promotes FoxO dephosphorylation, and enhances MAFbx gene transcription (Sandri et al., 2004). Additionally, statins increase the expression of myostatin in brown adipose tissue and skeletal muscle (Wang et al., 2021b). Moreover, statin-induced muscle damage affects fast-twitch muscles and impairs fatty acid oxidation (Goodman et al., 2015).

The cancer drug cisplatin has been found to induce skeletal muscle atrophy through various mechanisms including the UPS, inflammatory cytokines, disrupted calcium homeostasis, autophagy, mitochondrial biogenesis, oxidative stress, and lipid metabolism (Conte et al., 2020; Sakai et al., 2014). In models of cancer cachexia, cisplatin administration has been associated with weight loss and muscle atrophy (Conte et al., 2017). Activation of AMPK during cisplatin therapy does not improve glucose uptake but instead stimulates the ubiquitin-proteasome system, leading to skeletal muscle atrophy (Zhang et al., 2021). Mechanistically, cisplatin promotes severe muscular atrophy accompanied by increased expression of the ubiquitin ligases MAFbx/atrogin-1 and MuRF-1 (Huang et al., 2023; Sakai et al., 2014). Cisplatin treatment manifests symptoms of skeletal muscle atrophy, including a significant reduction in myotube diameter, suppression of Akt activity, and decreased mTOR protein expression In a model of cisplatin-induced muscle atrophy, elevated levels of LC3B II and p62 were observed while Akt was downregulated (Conte et al., 2017). Cisplatin administration also leads to decreased expression of MyoD and myogenin mRNA, which are markers of muscle differentiation (Wu et al., 2019). Furthermore, cisplatin treatment increases the mRNA levels of myostatin, p21, and promotes the phosphorylation of SMAD2 by downregulating the Mstn/ActRIIB signaling pathway (Sakai et al., 2014).

Doxorubicin is a commonly used chemotherapy drug in cancer treatment that can lead to skeletal muscle atrophy and increased production of ROS in humans. The development of muscle proteolysis, through heightened activity of the UPS, may be linked to a decrease in

PI3K/Akt signaling caused by doxorubicin-induced insulin resistance (Wang et al., 2006a). Kavazis et al. reported that doxorubicin injection enhanced the levels of MAFbx and MuRF-1 mRNA in soleus muscle (Kavazis et al., 2014). Moreover, doxorubicin treatment has been shown to induce severe glucose intolerance and muscular atrophy (de Lima Junior et al., 2016). Additionally, doxorubicin can reduce protein synthesis, and the mRNA expression of REDD1 was found to be significantly elevated in rats treated with doxorubicin (Nissinen et al., 2016).

The detrimental effects of certain medications on skeletal muscle atrophy are influenced by mitochondrial dysfunction. Dex treatment exacerbates oxidative stress and negatively impacts the redox state and mitochondrial function. Chen et al. observed higher levels of malondialdehyde (MDA), an indicator of oxidative stress and atrophy, in tissues treated with Dex, while glutathione (GSH) levels were lower (Chen et al., 2018). Increased caspase-3 immunoreactivity in the Dex group demonstrated the involvement of apoptosis in existing atrophy (Lim et al., 2018). Statin-induced muscle atrophy occurs independently of changes in PGC-1 protein and mitochondrial content (Vaklavas et al., 2009). Cisplatin administration leads to increased production of ROS, reduced mitochondrial membrane potential and ATP production (Matsumoto et al., 2022). Cisplatin treatment affects oxidative phosphorylation and decreases the respiratory capacity of cells (Inapurapu et al., 2017). Mitochondrial function impacts the LC3 II/I ratio and the levels of autophagy-related proteins in cisplatin-treated skeletal muscle (Seo et al., 2021). Mitochondrial dysfunction in cisplatin-treated animals affects mitochondrial fission proteins (Sirago et al., 2017). Cisplatin significantly decreases NRF2 expression, increases NADPH oxidase 4 (NOX4) expression, and enhances ROS levels, leading to mitochondrial dysfunction (Fan et al., 2020). Doxorubicin targets cardiolipin in the inner mitochondrial membrane to induce ROS production (Doerr et al., 2020). Doxorubicin induces oxidative stress, contractile and mitochondrial dysfunction, and activates proteolytic and apoptotic signaling pathways in skeletal muscle (Hiensch et al., 2020). ROS activation triggers proteolytic systems, including caspase-3 and the ubiquitin-proteasome pathway, for protein degradation in skeletal muscle (Gilliam et al., 2012). In animals treated with doxorubicin, PGC-1 expression is diminished, indicating reduced mitochondrial biogenesis in skeletal muscle (Hulmi et al., 2018). Doxorubicin administration enhances the levels of LC3-II/I ratio, autophagic vacuole formation, and autophagy-related proteins in the soleus of rats (Doerr et al., 2020). These findings underscore the significance of mitochondria in drug-induced muscle atrophy.

3.5. Cardiovascular diseases-induced skeletal muscle atrophy

CVDs are the leading cause of mortality worldwide and continue to pose a relevant burden to the health system (Roth et al., 2020). CVDs are positively associated with an enhanced prevalence and elevated risk of muscular atrophy. Individuals with CVDs experience metabolic and musculoskeletal dysfunction, which results in muscle atrophy, cardiac cachexia, and sarcopenia (Lena et al., 2020; Okoshi et al., 2013). As an example, the sarcopenia has been identified higher in CVDs patients ranged 61% in patients with acute decompensated heart failure (ADHF), 43% coronary heart disease (CHD), 43% in patients with coronary artery disease, 35% in congenital heart disease patients, 32% in CHF patients, 30% in cardiac arrhythmia (CA) patients, and 12% in other CVDs (Zuo et al., 2023).

Additionally, skeletal muscle deterioration is well recognized as a consequence of chronic disorders and continuous co-morbidity CVDs, such as CHF patients (Hunt et al., 2005). A total of 95% of chronic CHF patients exhibit clinical signs of muscle loss, including a lower left ventricular ejection fraction (LVEF), a worse ability for physical activity, and a lack of muscle

strength (Okoshi et al., 2013). Studies have shown that peripheral blood flow and skeletal muscle parameters including muscle metabolism are correlated highly in patients with heart HF (Middlekauff, 2010). Notably, up to 65% of HF patients experience muscular atrophy, and 20% of HF elderly suffer from sarcopenia, which is characterized by low muscle strength and progresses to cardiac cachexia (Campbell et al., 2015). Patients with HF and type 2 diabetes mellitus experience loss of muscle mass and strength (Wood et al., 2021). There is consensus that people with HF or type 2 diabetes have smaller fiber cross-sectional areas and a switch from type I to type II fiber muscles (Crossland et al., 2019). HF has also associated with hypertension-induced cardiac cachexia which subsequently leads to skeletal muscle atrophy (Nguyen et al., 2020).

The origin of HF associated with muscle loss is multifactorial and pathophysiological mechanisms are still unclear and need to be fully understood. However, it is suspected the involvement of the anabolic and catabolic signals dysregulation (Morciano et al., 2022). Increasing evidence has revealed the pathophysiology of systemic HF complications linked to muscle loss, as well as new therapeutic targets to improve survival (Tyrovolas et al., 2020). For instance, myostatin is a negative regulator of muscle growth, and, the myocardium releases myostatin into circulation, where it meets and suppresses skeletal muscle growth during an abnormal condition (Breitbart et al., 2011). Reduced skeletal muscle mass is associated with unchanged myostatin and decreased follistatin expression in CHF (Lima et al., 2010). On the other hand, inflammation frequently affects HF patients and has even been linked to skeletal muscle wasting in older HF patients. These patients exhibit a substantial increase in the inflammatory cytokines IL-6, 3-MH/Cr, BNP, and CRP, as well as a decrease in the muscle mass in their lower limbs (Koshikawa et al., 2020).

Calcium signaling is a key second messenger for signal transduction in cells and plays a crucial role in destiny and survival (Patergnani et al., 2020), which is a significant element that links skeletal muscle atrophy in HF patients. Sarcoplasmic reticulum (SR) contains T-tubules and stores calcium from skeletal muscle. For instance, changes in SR calcium handling have been found in skeletal muscle of CHF rats with myocardial infraction (Reiken et al., 2003). Additionally, a growing body of research has revealed that HF exhibits a differential expression of skeletal muscle proteins as well as mRNA for the isoform SERCA that is unique to skeletal muscle (Lunde et al., 2001).

Skeletal muscle mass loss is also associated with the prognosis and progression of elderly CHD, and it is a risk factor for atherosclerosis (Campos et al., 2017). However, the exact mechanism underlying the role of skeletal mass wasting and CHD is still unclear. Other pioneer studies have found a negative relationship between muscle mass and coronary heart calcification, which is a risk factor for CHD (Ko et al., 2016). A recent study has demonstrated the correlation of Matrix Gla-protein (MGP), an inhibitor of vascular calcification, with axial skeletal muscle and artery stiffness in hypertensive patients without HF (Vidula et al., 2022).

Taken together, further studies are required to better understand the pathophysiological mechanisms of skeletal muscle deterioration in CVDs patients, as well as, to focus on the causality correlations and the common risk factors between both skeletal muscle wasting and CVDs to facilitate the development of therapies and the quality of life.

3.5.1. The ubiquitin-proteasome system

The UPS fulfills a significant role in cellular homeostasis by degrading approximately 90% of proteins from all intracellular compartments (Kitajima et al., 2020). A growing number of studies have been administered on this degradative system in the field of cellular biology in general and cancer biology in particular. However, recent findings indicate that UPS is crucial for cardiac pathophysiologies such as atherosclerosis, cardiac hypertrophy, ischemic heart disease (IHD), HF, and myocardial ischemia/reperfusion injury (I/R).

To briefly summarize this process, target proteins are labeled with a chain of ubiquitin through a multistep enzymatic cascade of ubiquitination and are then recognized by the proteasome, a multiprotein complex responsible for the breakdown of these specific substrates (Kodroń et al., 2021). The E3 ubiquitin ligases are categorized based on their structural characteristics and regulate the specificity of the entire reaction (Pagan et al., 2013).

UPS is linked to mitochondrial homeostasis via a mechanism known as Mitochondrial Associated Degradation (MAD) and MAD is a quality control system at the mitochondrial outer membrane (OMM) (Wu et al., 2016). Additionally, UPS regulates the mitochondrial proteome and the channel protein Tom40 in the OMM facilitates the size-dependent retrograde transport of intermembrane space proteins (Wu et al., 2016). The status of the mitochondria and cellular homeostasis might be harmed by defects in this carefully calibrated mechanism, resulting in energy malfunction.

Two E3 ubiquitin ligases, MuRF1 and MAFbx have been associated with skeletal muscle atrophy (Bodine and Baehr, 2014). The expression of atrogenes, or atrophy-related genes, changes with the development of skeletal muscle atrophy. In particular, several of these atrogenes are crucial components of the complex UPS (Lecker et al., 2004). Skeletal muscle atrophy is characterized by increased protein degradation, while hypertrophy has a decreased degradation. This process is controlled by UPS. Notably, atrophic hearts revealed a decrease in the expression of both MAFbx/Atrogin-1 and MuRF-1. The gene expression of the other proteins involved in UPS is enhanced in hypertrophied and hypoxic hearts (Razeghi et al., 2006).

Skeletal muscle atrophy is a consequence of HF, and muscle strength in patients with severe congestive HF has been recommended as a predictor of long-term survival (Hülsmann et al., 2004). Following HF, preserved left ventricular ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) exhibit exercise intolerance. This intolerance is related to reduced metabolic and energetic performance (Adams et al., 2017; Weiss et al., 2017). A recent clinical trial reported that HFpEF and HFrEF groups presented increased proteolysis, such as MuRF-1 protein expression, levels of ubiquitinated proteins, and proteasome activity (Adams et al., 2021). The activation of UPS leads to muscle protein degradation following the activation of MuRF1 in CHF (Cohen et al., 2009). *In vivo* and *in vitro* experiments have demonstrated an involvement of the MAFbx/MuRF-1-dependent pathway in the degradation of troponin I in CHF (Adams et al., 2007). MuRF1 is only found in skeletal and cardiac muscle, where it regulates troponin I level through ubiquitylation and degradation, reducing cardiomyocyte contractility (Kedar et al., 2004). MuRF1 reduces cardiomyocyte death by targeting phosphor-c-Jun for proteasome degradation and inhibiting JNK signaling during cardiac I/R injury (Li et al., 2011). An improvement in mitochondrial energy production and mitochondrial homeostasis was observed in mice fed a MuRF1-interfering small molecule and subjected to myocardial infarction to induce CHF (Adams et al., 2019). However, the dual roles of MuRF1 in both CVDs and skeletal muscle atrophy has been documented in several studies. Indeed, other studies have reported the non-causative role of MuRF1 in skeletal muscle atrophy. While, heart-

specific MuRF1 overexpression stimulates HF instead of preventing cardiac hypertrophy, suggesting the involvement of other modulator factors in the mechanisms contributing in cardiac hypertrophy and skeletal muscle atrophy (Ferrandi et al., 2004; Milano et al., 2007; Peris-Moreno et al., 2020).

Rnf28 is another E3 ubiquitin ligase involved in the activation of UPS. Regular physical training demonstrated a reduction in Rnf28 expression in skeletal muscle in a randomized controlled trial of patients with advanced CHF (Höllriegel et al., 2013). Another study reported that the expression of MuRF1 normally increased in the skeletal muscle of patients with HF, but after 4 weeks of exercise training, MuRF1 mRNA levels decreased in CHF patients regardless of their age (Gielen et al., 2012).

Familial hypertrophic cardiomyopathy (FHC), an autosomal-dominant disease linked to mutations in genes encoding sarcomeric proteins such as cardiac myosin-binding protein C, is another cardiovascular disease in which UPS is involved (cMyBP-C) (Richard et al., 2003). MuRF1 controls the expression of cMyBP-C indirectly, and that Atrogin-1 plays a direct and specific role as an E3 ubiquitin ligase for the truncated form of the protein resulting from a mutation (Mearini et al., 2010). In response to pathological stimuli, atrogin-1 significantly reduces cardiac hypertrophy by mediating the ubiquitin-linked degradation of the protein calcineurin (Li et al., 2004). Furthermore, Atrogin-1 blocks physiological cardiac hypertrophic signaling by acting as a ubiquitin ligase on FoxO1 and FoxO3a, transcription factors that are downstream of the Akt pathway (Li et al., 2007).

The gene for desmin protein, the main intermediate filament expressed in muscles and essential for the proper cytoskeletal conformation, is mutated, resulting in desminopathy, a genetic disorder (Clemen et al., 2013). Skeletal muscle atrophy and cardiomyopathy are hallmarks of this condition, and at the cellular level, UPS is unable to break down misfolded desmin protein that accumulates inside cells (Liu et al., 2006).

3.5.2. Autophagy and Mitophagy

A balance between protein production and degradation is essential for maintaining skeletal muscle mass. The ubiquitin proteasomal pathway and the autophagic signaling pathway, as was previously discussed, play important roles in mediating protein degradation in skeletal muscle atrophy. The autophagy pathway is a highly conserved process that is crucial for energy production and consumption as well as for the turnover of macromolecules (Klionsky, Abdel-Aziz et al. 2021).

Autophagy is important for several intracellular pathways and to control the survival and the survival of the cells. At demonstration of this, autophagy has been found altered in several human related diseases, including cancer (Missiroli et al., 2016) (Patergnani et al., 2023), neurodegeneration (Patergnani et al., 2021b) (Castellazzi et al., 2019) (Shahmoradian et al., 2019), cardiovascular disease (Morciano et al., 2022) and skeletal muscle disorders (Carnio et al., 2014). The autophagy responses in the heart and skeletal muscle have been correlated with ameliorated glucose regulation resulting in beneficial effects on the CVDs (He et al., 2012). Acute autophagy repression preserves muscle mass, whereas chronic autophagy repression causes fiber atrophy, protein accumulation, and ultimately cell death induction (Carnio et al., 2014; Masiero et al., 2009).

This autophagy process is necessary for the removal of harmful proteins and organelles in response to cellular stress and starvation. Several protein factors are ULK and ATG proteins (ULK1/2, ATG13, ATG101, and FIP200/RB1CC1) (Hieke et al., 2015). Muscle atrophy advances as a result of the accumulation of damaged mitochondria, an uptick in oxidative stress and cell death (apoptosis), and the deletion of the essential autophagic protein ATG7 in skeletal muscle (Masiero et al., 2009). ATG7 inhibition causes severe contractility changes and myofiber dysfunction in cardiomyocytes (Li et al., 2016). While, ATG7 overexpression induces the autophagic process, improves cardiac performance, and reduces cardiac hypertrophy (Bhuiyan et al., 2013). Moreover, an excessive elevation of autophagic flux can be harmful to muscle homeostasis. For instance, Bnip3 and transcription factor FoxO3 overexpression affects negatively mitochondrial function and increases muscle atrophy (Mammucari et al., 2007). Indeed, FoxO3 protects against muscle loss when LC3 is genetically silenced (Mammucari et al., 2007).

A protective effect at the level of muscle mass has also been identified in mouse skeletal muscle when the expression of the key gene of mitochondrial biogenesis PGC-1α is increased via autophagy upregulation (Puigserver and Spiegelman, 2003). Another important and potent autophagic modulator is the AMPK. It leads to nuclear relocalization of the transcription factor FoxO3a to stimulate the autophagic proteins such as LC3B-II and Beclin1 (Sanchez et al., 2012). This potent autophagic activator protein protects the heart from HF and hypertrophy by stimulating autophagy (Li et al., 2018b). The deficits of the autophagic process in muscles cause cellular deterioration, including mitochondrial dysfunction, endoplasmic reticulum (ER) stress, and cell death, leading to the progression of multiple skeletal muscle disorders (Bonaldo and Sandri, 2013).

Notably, recent research has found that autophagy is significantly upregulated in response to intermittent hypoxia, resulting in increased skeletal muscle atrophy (Giordano et al., 2015). In the same study, intermittent exposure to hypoxia has resulted in a decrease in the autophagic-related protein LC3II in limb muscle (Giordano et al., 2015). Noteworthy, autophagy has been also documented to prevent heart deterioration enhanced by intermittent hypoxia and stimulates the turnover of damaged mitochondria (Maeda et al., 2013). Furthermore, cellular autophagy is dependently induced by hypoxia through a factor called hypoxia-inducible factor (HIF), which is a key sensor of hypoxia and controls numerous target genes in the human body (Bellot et al., 2009; Bouhamida et al., 2022). Recent research has revealed that the HIF-1 α subunit causes skeletal muscle fibrosis by activating several signaling pathways, such as the TGF and upregulating the expression of profibrotic cytokines (Valle-Tenney et al., 2020). HIF-1α also contributes to the pro-angiogenic process in skeletal muscle by activating the vascular endothelial growth factor (VEGF) gene during transcription activity (Olfert et al., 2010), which ameliorates the outcome and regeneration of skeletal muscle disorders (Valle-Tenney et al., 2020). However, studies reported the negative contribution of both HIF-1α and 2α subunit in the development of skeletal muscle. HIF-1α and HIF-2α co-deletion as well as with the use of pharmacological inhibitor (FM19G11) show a dependent and dispensable role in the development of skeletal muscle (Yang et al., 2017). Majmundar and colleagues found similar results in myogenic progenitor cells deleted HIF-1α, instead it modulates skeletal muscle regeneration via the Wingless-related integration (Wnt) repression (Majmundar et al., 2015). The contribution of HIF-1α as an activator of the autophagic process in cardiac cells to prevent hypoxic injury and enhance survival has been widely demonstrated in cardiovascular disease studies; however, its role is highly controversial depending on the duration of hypoxia and the persistence of HIF-1α stabilization (Bouhamida et al., 2022; Gui et al., 2016). Nevertheless, further studies are highly required to focus on the effective roles of HIF-1α and autophagy in

skeletal muscle abnormalities in CVDs patients. Although the autophagy-lysosome system plays a vital role in a variety of muscle atrophy, its relative relationship with cardiovascular disorders such as HF-enhanced skeletal muscle wasting needs to be defined (Mammucari et al., 2007).

A form of autophagy known as "mitophagy," is a selective form in which defective mitochondria are eliminated **(Figure. 2)** (Youle and Narendra, 2011). This catabolic process occurs as a crucial mechanism for mitochondrial quality control in both health and disease (Danese et al., 2022; Morciano et al., 2021; Patergnani et al., 2021a; Patergnani et al., 2021b; Saito et al., 2019) During this process, damaged mitochondria are first removed from the network, then engulfed by double-membrane vesicles known as autophagosomes and transported to the lysosome for proteolytic destruction (Twig et al., 2008) **(Figure.1)**. The E3 ligases Parkin and PINK1 are the most complex mitophagy pathways, but they can also function through Parkin-independent routes (Kane et al., 2014; Vives-Bauza et al., 2010). Additionally, this process can be achieved through other multiple proteins including p62/SQSTM, Bnip3, prohibitin 2 (PHB2), optineurin (Optn), and Nuclear dot protein 52 kD (NDP52) (Geisler et al., 2010; Hanna et al., 2012; Heo et al., 2015; Rikka et al., 2011; Wong and Holzbaur, 2014). For instance, CL has also been shown to induce mitophagy by translocating from the inner to the outer mitochondrial membrane, and it is abundant in both skeletal and heart muscles (Schlame et al., 2005). The FUN14 Domain Containing 1 (FUNDC1) protein, which interacts with LC3 and mediates mitophagy in response to hypoxia, is another mitophagy-related protein (Li et al., 2018a; Liu et al., 2012). Therefore, FUNDC1 maintains mitochondrial homeostasis and guards against IRI in the heart in mouse models (Zhang et al., 2017b). Skeletal muscle FUNDC1 knockout increases the release of hormone fibroblast growth factor 21 (FGF21), a mitokine ameliorating metabolic abnormalities(Flippo and Potthoff, 2021), thus inducing the mitochondrial unfolded protein response (UPRmt), and adipose tissue metabolic remodeling, thus ameliorating systemic metabolism (Fu et al., 2018; Guo et al., 2022). Additionally, the inactivation of FUNDC1 causes HF and suppresses mitophagy (Zhou et al., 2018). The induction of mitophagy flux during denervation has also been demonstrated, resulting in mitochondrial loss during disuse. LC3B-II, parkin, and p62 localize in mitochondria and elevate in response to denervation, thereby upregulating mitophagy (Vainshtein et al., 2015). PGC-1α, a metabolic regulator plays a major role in mitochondrial biogenesis and improves mitochondrial content and quality through the regulation of mitophagy and mitochondrial dynamics proteins (Soriano et al., 2006). Several mitophagy-related factors, such as mitochondrial ubiquitin ligase (Mul1) and Bnip3, are stimulated by the overexpression of PGC-1, including FoxO3, and this hinders the clearance of mitochondria when FoxO3 is inhibited (Kim et al., 2021). The repression of PGC-1α was reported to attenuate mitophagy in skeletal muscle . PGC-1 is also essential for maintaining cardiac homeostasis, and cardiac-specific overexpression of PGC-1 causes mitophagy (Zhu et al., 2019).

On the other hand, mitophagy in skeletal muscle is regulated by the transcriptional factor P53 in response to denervation-mediated disuse (Memme et al., 2022). The transcriptional regulator P53 is an important target for regulating mitochondrial content and acting as a modulator of skeletal muscle atrophy (Stocks et al., 2017). P53 mediates mitophagy repression and promotes heart dysfunction, targeting cytosolic p53 in the context of mitophagy (Hoshino et al., 2013). Hypoxia also significantly increases mitophagy, reduces ROS generation, and eventually leads to HIF-1 destabilization. Studies have shown the hallmark role of HIF-1α in the regulation of skeletal muscle atrophy through MYHC II, a skeletal muscle-specific contractile protein, and MyoG (Valle-Tenney et al., 2020).

A possible mechanism that is engaged during hypoxia is the mTOR, which is recognized to regulate the anabolic, catabolic mechanisms of skeletal muscle mass and is repressed in hypoxia. Studies have shown a major effect of mTOR in increasing the expression of MYHC beta (Myh7)(Binó et al., 2017). In addition, mTOR affects muscle fiber atrophy by suppressing protein synthesis and stimulating proteolysis (Bouhamida et al., 2022; Wu and Chen, 2015). Excessive and chronic mTORC1 upregulation results in muscle atrophy via muscle of the tumor suppressor tuberous sclerosis complex 1 (TSC1) (Castets and Rüegg, 2013). Similarly, hypoxia-induced mitophagy has been demonstrated in cardiomyocytes via the stabilization of HIF-1, which in turn regulates mitochondrial tagging via Bnip3 and NIX activation (Bruick, 2000).

Various research findings have shown that the expression of mitophagy proteins is reduced in aging rodent skeletal muscle (Li et al., 2018a; McMullen et al., 2009; Soriano et al., 2006). For instance, a decline in Parkin expression and subsequent malfunction of the mitophagy pathway has been shown in old mice and old rats (Goljanek-Whysall et al., 2020; Russ et al., 2014). A considerable decline in the Parkin/Voltage-dependent anion channel (VDAC) has been identified in the muscles of aged men as compared to young men as mitophagy dysfunction (Gouspillou et al., 2014). However, a different study has demonstrated contractile action in elderly skeletal muscle activates pre-lysosomal mitophagy (Carter et al., 2015).

The regulation of mitophagy in the skeletal muscle is poorly understood, despite the significance of the mitophagy process for tissue remodeling, quality control, and organelle turnover. Further research into the role of mitophagy in skeletal muscle atrophy in HF may reveal new molecular mechanisms and points for novel therapeutic approaches.

3.5.3. Mitochondrial fission-fusion

Mitochondria are highly dynamic organelles that can change continuously in terms of their size, shape, and distribution (Tilokani et al., 2018). These modifications are coordinated by two important alternating events that define mitochondrial dynamics: fission (mitochondrial separation) and fusion (adjacent mitochondrial fusion). Mitochondrial dynamics play a crucial role in maintaining mitochondrial functions and integrity, cell cycle regulation, and cell quality control (Liu et al., 2020) **(Figure.2)**. Furthermore, mitochondrial network morphology is modulated by the counterbalance between these processes that are strictly orchestrated by core machinery proteins (large guanosine triphosphates GTPases). These GTPases exhibit membrane-remodeling characteristics (Lee and Yoon, 2016).

The DRP-1, Mff, Fis1, and 49kD and 51kD mitochondrial dynamics proteins (Mid49/51) are important mitochondrial fission proteins in mammalian cells (Tong et al., 2020). Moreover, OPA1 and the Mfn1 and Mfn2 are three GTPase dynamin proteins that regulate mitochondrial fusion as opposed to OPA1. To preserve the health and physiological capabilities of the mitochondria as well as an intact mtDNA, it is crucial to sustain the mitochondrial dynamic process for increasing the energy generation capacity (Hoppins et al., 2007; Rambold et al., 2011).

The fission process provides quality control by separating defective mitochondria, as well as the formation of new mitochondrial networks (Youle and van der Bliek, 2012). Mitochondria undergo several fission cycles as a result of their inability to produce energy (Kang et al., 2016; Picard et al., 2015; Romanello et al., 2010). Excessive fission results in isolated mitochondria that are less efficient in producing energy because they need the energy to sustain their

membrane potential (Benard et al., 2006). As a result, if the mitochondria fail to provide enough energy for cardiac metabolism, HF may occur. As discussed in previous chapters, skeletal muscle atrophy is a common feature in HF patients, with an estimated 20% higher prevalence in elderly HF patients than in healthy elderly people (von Haehling et al., 2020). Furthermore, HF studies have revealed a decreased expression of mitochondrial fusion, and dysregulation of either mitochondrial fission or fusion (Hall et al., 2014).

Mitochondrial morphology and function have undergone significant modifications via mitochondrial fusion and fission in skeletal muscle atrophy (Leduc-Gaudet et al., 2015). Multiple signaling pathways are impacted by the instability of mitochondrial dynamics during skeletal muscle atrophy. Strong insights are supporting the causal link between mitochondrial fission and muscle maintenance (Romanello et al., 2010). For example, the mitochondrial fission protein DRP-1 is important in regulating skeletal muscle during mechanical activation and mitochondrial fission protein expression is reported to be decreased in various pathophysiological conditions of skeletal muscle (Nakano and Machida, 2022). Also, the mitochondrial fission DRP-1 protein is less expressed in skeletal and cardiac muscles in aged mice (Zhou et al., 2017). Recent research has demonstrated that muscle-specific DRP-1 deletion promotes muscle atrophy (Favaro et al., 2019). Consistently with the previous findings, reduction of DRP-1 expression in skeletal muscle fibers using the chemotherapeutic drug cisplatin results in increased skeletal muscle atrophy (Sirago et al., 2017). However, a study conducted by, Moore and colleagues founds no muscle atrophy when DRP-1 levels were reduced by 40% (Moore et al., 2019). Notably, overexpression of mitochondrial fission proteins in adult muscle is sufficient to cause muscular atrophy (Touvier et al., 2015). DRP-1 imbalance was linked to HF and myocardial injury, where its excessive elevation is harmful to heart function within the first 60 minutes (Disatnik et al., 2013). Heart-specific deletion of DRP-1 enhances significantly the accumulation of altered mitochondria which in return stimulates cell death (Givvimani et al., 2015). Accordingly, a different study found that high-fat dietary animals had lower levels of expression of the fusion protein Mfn 1/2 and the mitochondrial fission proteins DRP-1 and Fis1 (Liu et al., 2014b). Mfn1/2 muscle-specific deletion increases intense muscle loss and the repression of Mfn1 activity conducts in mitochondrial degradation and dysfunction in HF (Touvier et al., 2015). Heart and muscle tissues express Mfn2 more frequently than other tissues compared with Mfn1 (Santel and Fuller, 2001; Sebastián et al., 2012).

FoxO3 is well known as a key regulator of autophagy in the mitochondrial network and DRP-1 inhibition decreases FoxO3-mediated muscle atrophy (Romanello et al., 2010). Fis1 is a critical component of the mitochondrial fission machinery and is expressed in muscle atrophy. Interestingly, inhibiting Fis1 and Bnip3 harms the activation of ubiquitin-proteasome promoters such as atrogin-1 and MuRF-1 during fasting in mice (Romanello et al., 2010). In addition, Fis1 repression upregulates mitochondrion-associated protein aggregates (MAPAs) number suggesting that the formed MAPAs may be involved in the MAPAs' segregation from the mitochondria (Wang et al., 2023).

The mitochondrial fusion protein OPA1 requires Mfn1 to modulate the mitochondrial fusion in correlation with skeletal muscle loss (Tezze et al., 2017). Similarly, a decrease in the mitochondrial fusion protein OPA1 has recently been demonstrated in HF patients and animal models (Chen et al., 2009). OPA1 was found in heart-specific TFAM knockout mice cardiac tissue with mitochondrial cardiomyopathy, as well as skeletal muscle patients with mitochondrial myopathy (Duvezin-Caubet et al., 2006). Clinical studies have discovered that

specific OPA1 mutations increase the accumulation of mtDNA deletions in skeletal muscle patients (Yu-Wai-Man et al., 2010).

The maintenance of well-balanced mitochondrial fission and fusion processes is a hallmark to preserve muscle mass and subsequently prevent muscle loss. Nevertheless, the exact role of mitochondrial fission and fusion in muscle atrophy especially in patients with heart disorders remains to be uncovered and further research is needed to fully understand the molecular mechanisms.

3.5.4. Mitochondrial biogenesis

Nowadays, it is understood that individuals with CHF not only have skeletal muscle atrophy but also have diminished mitochondrial density in the peripheral muscle mass (Konishi et al., 2021). Since mitochondria cannot be synthesized de novo, mitochondrial homeostasis and mass are maintained by a regenerative process called mitochondrial biogenesis.

While mitochondria are being eliminated via mitophagy, mitochondrial biogenesis is activated in response to increased energy demand (Popov, 2020) **(Figure. 2)**. Even though mitochondria have their DNA, the majority of mitochondrial proteins are encoded by the nuclear genome (nuDNA) and are then imported into the mitochondria via the outer membrane translocase (TOM) and inner membrane translocases (TIM). On the other hand, the mitochondrial DNA (mtDNA) encodes only 13 subunits of the electron transport chain (ETC) complexes, along with 22 tRNA and 2 rRNA. Furthermore, mitochondrial genesis is a highly regulated process and requires a coordinated gene expression of both the nuclear and mitochondrial genomes, together with the replication of new mtDNA and mitochondrial phospholipids biosynthesis (Dorn and Kitsis, 2015; Scarpulla, 2008). The process is regulated by several transcription factors, among which the master regulator of mitochondrial biogenesis is the nuclear-encoded PGC-1α (Scarpulla et al., 2012). PGC-1 was discovered in brow fat as a coregulator of PPAR mediating adaptive thermogenesis, and it was later demonstrated to be a coactivator for a large number of mitochondrial biogenesis genes (Peng et al., 2017). PGC-1 is physiologically activated in response to ATP deficit during conditions like exercise, fasting, and cold weather, as well as in pathological states including HF and skeletal muscle atrophy (Kong et al., 2022). PGC-1 activation is promoted by several upstream pathways, including the calcium-dependent pathway, AMPK phosphorylation, and deacetylation of silent mating type information regulation 2 homolog-1 (SIRT1) (Cantó and Auwerx, 2009). Therefore, PGC-1α translocate into the nucleus binds different transcription factors including the NRF1/NRF2, which in turn promote regulate expression of the ETC subunits encoded by the nuDNA (Gureev et al., 2019). The ERRs stimulate the expression of genes involved in the generation of ATP, energy, and fat/glucose metabolism; in turn, these transcriptional factors trigger the NRF1/2-mediated induction of TFAM for the transcription and translation of mtDNA (Kelly and Scarpulla, 2004; Kong et al., 2022). PGC-1 also induces mitochondrial fusion via Mfn2 and mitochondrial breakdown via the autophagy-lysosome machinery, mediating mitochondrial turnover (Vainshtein et al., 2015). Recent research indicates that patients with severe HF or after a myocardial infarction experience skeletal muscle atrophy and loss of function (Jia et al., 2018; Zizola and Schulze, 2013). This process is linked to morphological changes in muscle fibers from type I to type II glycolytic, which are connected to changes in oxidative metabolism (Kennel et al., 2015). Consistent with this, skeletal mitochondrial content and oxidative metabolism are reduced in both rodent and human falling hearts which is also associated with decreased exercise capacity and metabolism (Karamanlidis et al., 2010; Lunde et al., 2001; Sihag et al., 2009). One study reported that decreased PGC-1 expression as well as that of its

downstream effectors NRF2 and TFAM linked to impaired respiratory chain performance (Mootha et al., 2003; Patti et al., 2003). PGC-1 deficiency in skeletal muscle causes exercises intolerance, which is also a feature of HF (Faerber et al., 2011; Zechner et al., 2010).

Additionally, the PGC-1α coordinates a large number of transcriptional process modulating the skeletal muscle response to exercise. PGC-1α has been reported as a critical regulator of HIF-2α in skeletal muscle (Rasbach et al., 2010). For instance, HIF-2α -muscle specific knockout enhances genes and proteins expression of fast-twitch fiber-type switch, indicating that HIF-2α is a downstream of PGC-1α modulating muscle-fiber (Rasbach et al., 2010). Other recent studies have been suggested the regulation of HIF-2α in adaptive response to exercise (Henderson et al., 2005; Nordsborg et al., 2010). However, it would be interesting to verify these finding in CVD's patients. Also, PGC-1α regulates the expression of multiple myokines including, myostatin, irisin/fibronectin type III domain-containing protein 5 (FNDC5), and brain-derived neurotrophic factor (BDNF) (Huh, 2018). Myokines are generated and secreted in muscle tissues by myocytes during contractions (Lee and Jun, 2019). Indeed, PGC-1α increases FNDC5 expression and stimulating its cleavage in response to exercise producing in return irisin that elevate the energy in muscle-specific PGC-1α overexpression mice (Boström et al., 2012).

Overexpression of PGC-1 reduces skeletal muscle atrophy in HF patients (Geng et al., 2011; Jia et al., 2018; Kang et al., 2015). The improvement of skeletal muscle energy deficit in HF patients is now known to occur with increased physical training (Rehn et al., 2012). It is unclear whether mitochondrial biogenesis impairment is directly related to HF disease or is a result of skeletal muscle atrophy, so more research is needed to pinpoint the precise mechanism involved in this cross-talk.

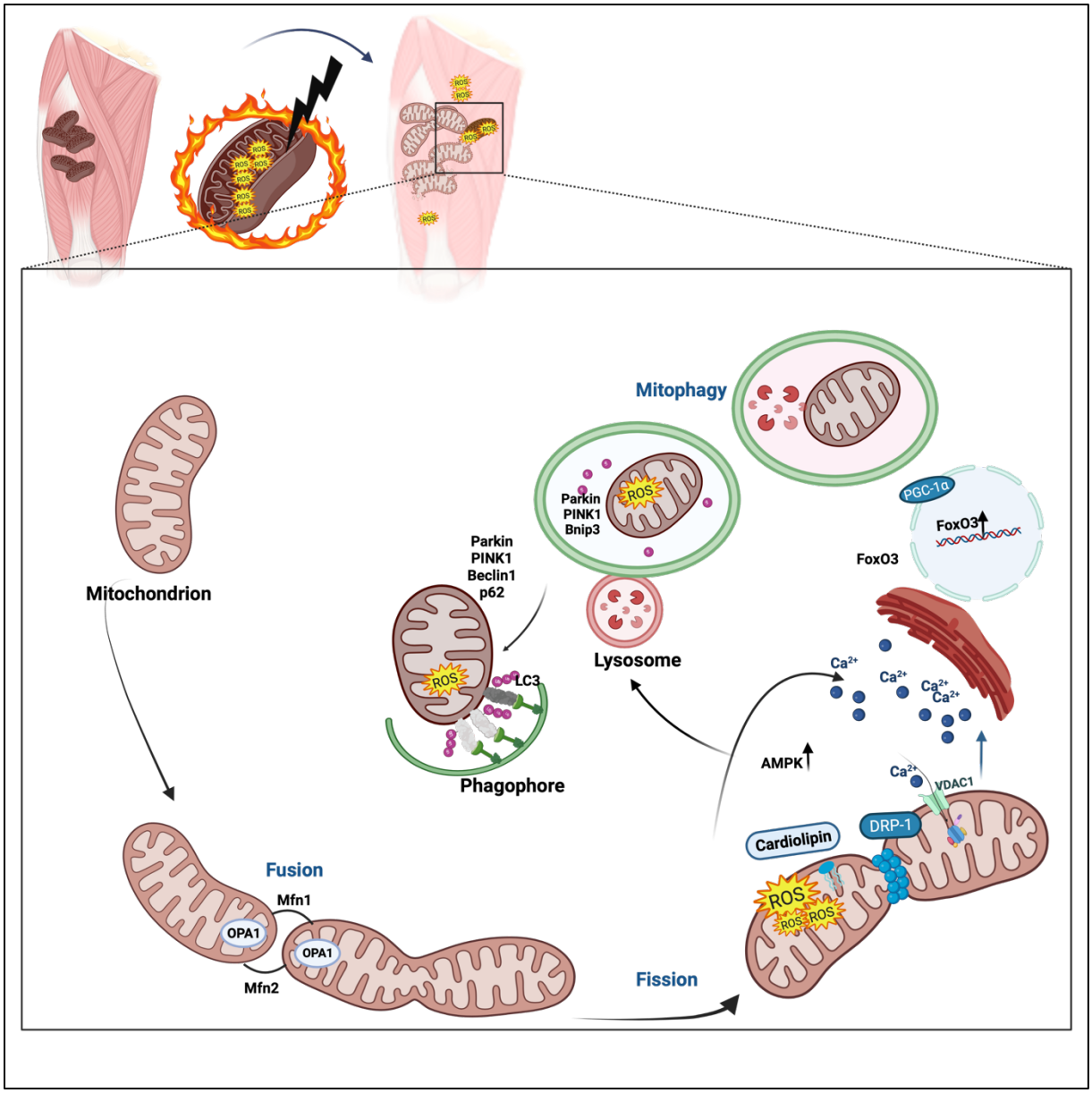


Figure 2: Mitochondrial dynamics and turnover in the skeletal muscle atrophy. An overview of a dynamic processes in which the mitochondria undergo morphological changes including, fusion, fission, and mitophagy. Balance of fission and fusion processes are needed to maintain normal mitochondrial function. An imbalance of fission/fusion leads mitochondrial dysfunction. Dynamin-related protein-1 (DRP-1), fission protein-1 (Fis1), mitofusin 1/2 (Mfn1 and Mfn2) optic atrophy 1(OPA1), PTEN-induced kinase 1 (PINK1), microtubule-associated protein 1A/1B-light chain 3 (LC3), forkhead box O3 (FoxO3).

4. Current therapeutic strategies

4.1. Exercise

Exercise is considered a cornerstone for longevity and disease prevention. Evidence suggests that, exercise is one of the most efficient therapeutic approach to prevent and cure metabolic and chronic disorders such as; T2D, cardiovascular diseases, metabolic syndrome and also skeletal muscle atrophy related conditions (Bassuk and Manson, 2005; Graham et al., 2021; LaMonte et al., 2005a; LaMonte et al., 2005b).

Exercise stimulates signaling pathways that significantly alter skeletal muscle physiology, contractile properties, and metabolism (Ferraro et al., 2014). Endurance exercise improves the ability of the body to transport and use oxygen to produce energy by increasing mitochondrial biogenesis and capillary density. (Joyner and Coyle, 2008). On the other hand resistance exercise increases muscle strength and power through neuromuscular adaptations and increases muscle CSA (Hughes et al., 2018). Further, exercise has a positive impact on mitochondria, increasing their size, number, and maximum oxygen uptake as well as the production of mitochondrial enzymes. Aerobic capacity is related to enhanced mitochondrial content and mitochondrial biogenesis in skeletal muscle, as well as cardiorespiratory variables (Holloszy, 1967; Porter et al., 2015). Also, exercise triggers a shift in fiber type, an increase in capillary and mitochondrial density, and an increase in CSA (Garatachea et al., 2015).The underlying mechanism of prevention from skeletal muscle atrophy is increased muscle protein synthesis and activation of signaling pathways that regulate muscle fiber metabolism and function. As a result, skeletal muscle atrophy can be treated or prevented through exercise (He and Ye, 2020; Shen et al., 2018).

Remarkably, there are few pivotal signaling pathways orchestrating the organismal response to exercise in terms of skeletal protein synthesis. IGF-1/Akt/mTOR pathway is the most studied pathway of all (Schiaffino et al., 2013; Schiaffino and Mammucari, 2011). The IGF-1/Akt/mTOR pathway is acutely stimulated to promote ribosomal biogenesis and translation to form proteins using these elongated ribosomes across the mRNA (Wen et al., 2016). Among its vital functions, mTOR is the master regulator of protein synthesis and maintaining muscle mass (Yoon, 2017). It has been shown that exercise triggers skeletal muscle protein synthetic response through mTOR activation (Song et al., 2017). Furthermore, both muscle contraction induced Akt and PGC-1 is shown to inhibits FoxO transcription factors thus activation of ubiquitin proteasome system and skeletal muscle atrophy (Sandri et al., 2006).

A study was conducted to investigate the effects of aerobic and resistance training on muscle mass recovery following short-term immobilization. The study revealed that aerobic exercise was effective in restoring the CSA of the plantaris muscle to its baseline level through the upregulation of PGC-1 expression and the downregulation of ubiquitin-proteasome activity. In contrast, the resistance exercise group did not exhibit any significant change (Vechetti-Junior et al., 2016). Another study involved two weeks of endurance training before a seven-day hindlimb suspension. The exercise group showed decreased levels of oxidative stress and elevated levels of SOD-1 and SOD-2 in the mitochondria as a marker of improved redox balance (Theilen et al., 2018). Moreover, mechanical ventilation in intensive care known to cause a disuse related atrophy of diaphgram muscle. For example, a study investigating the effects of 10-day exercise preconditioning before 12 hours of mechanical ventilation in rats reported that the exercise preconditioning group showed a decrease in H_2O_2 release and restored the mitochondria respiratory control ratio in mitochondria isolated from diaphragm muscle(Morton et al., 2019). Also, it has been known that cancer cachexia induces mitochondria dysfuntion related skeletal muscle atrophy, and exercise may attenuate it. A study, investigating exercise relation with cancer cachexia induced skeletal muscle atrophy found that mice with colon adenocarcinoma had low gastrocnemius and plantaris muscle weight. After, four weeks of voluntary exercise both gastrocnemius and plantaris muscle weights recovered. Furthermore, exercise attenuate the decrease in mitochondrial enzymes in skeletal muscle, such as citrate synthase and CytC oxidase. Mitochondrial Mfn2 and DRP-1 levels were lower in cancer cachexia skeletal muscle, but these levels improved with exercise, whereas 4-hydroxynonenal and protein carbonyls levels were lower. These findings indicate that exercise effectively prevents mitochondrial dysfunction, thereby reducing muscle wasting in cachexia

(Kitaoka et al., 2021). Obesity is associated with mitochondria-mediated apoptosis and skeletal muscle remodeling. Exercise has been related to skeletal muscle remodeling and apoptosis as a positive regulator. Heo et al. reported that treadmill exercise for 12 weeks after 20 weeks of feeding a high-fat diet reversed the obesity-induced increase in extra-myocyte space and the reduction in CSA of skeletal muscle in mice. The attenuation in skeletal muscle atrophy is attributed to decrease in mitochondria-mediated apoptotic factors such as Bax and Cytochrome C in skeletal mice gastrocnemius muscle (Heo et al., 2018).

Exercise has been shown to reduce age-related oxidative capacity loss. In one study, vastus lateralis biopsies were collected from young and old endurance athletes as well as sedentary men of the same age. Both young and elderly active subjects had shown higher mtDNA copies with increased oxidative phosphorylation related proteins (Balan et al., 2019). Further, it has been shown that lifelong exercise promotes better redox balance. For example, a study comparing lifelong exercised versus sedentary counterparts revealed that oxidative stress markers was reduced and antioxidant catalase expression was increased in older adults vastus lateralis muscle biopsies who exercised for a lifelong versus sedentary subjects (Bowen et al., 2015). Johnson et al observed an increase in muscle antioxidant defense in the elderly after eight weeks of endurance training (Johnson et al., 2015).

To sum up, exercise is the most studied therapeutic method to attenuate or reverse conditions related to skeletal muscle atrophy. One of the underlying mechanisms of prevention from skeletal muscle atrophy is the promotion of mitochondrial biogenesis to maintain the composition and function of mitochondria and activate a wide range of signaling pathways. This makes exercise an effective treatment for skeletal muscle atrophy due to a variety of causes. However, it is crucial to develop alternative treatment methods such as mitochondria-targeted antioxidants or mitochondrial transplantation instead of exercise therapy, especially for elderly bedrest patients and those with exercise tolerance.

4.2. Mitochondria-targeted antioxidants

Mitochondrial dysfunction is a critical regulatory process for the activation of atrophic programmes under muscle atrophy inducing conditions (Powers et al., 2011). Prolonged ROS exposure causes oxidative damage that can be detrimental to muscle function and causes muscle loss. Therefore, there is a rising interest in administering antioxidants to the mitochondria with the aim of avoiding or managing muscle dysfunction and damage caused by disease or injury. Numerous therapeutic agents have been used to improve mitochondrial function and energy metabolism (Penna et al., 2018) and acting specifically on mitochondria with antioxidant properties, which in return impact. The mitochondria-targeted antioxidants mainly acts on several transcription factors. The TFAM and NRF2 are one of the few pivotal transcription factors that mitochondria-targeted antioxidants have shown their therapeutic effects on mitochondrial health. Both of these factors are controlled by PGC-1 α, the master regulator, of mitochondrial quality control. Activation of PGC-1 α is known to inhibit oxidant damage and proteolytic activity in skeletal muscle thus attenuates skeletal muscle atrophy (Sandri et al., 2006).

A synthetic tetrapeptide known as SS-31 has been demonstrated to target and concentrate 1000 times more in the inner membrane of mitochondria (Zhao et al., 2005). It has been shown that SS-31 treatment on rats ameliorates immobilization-induced skeletal muscle atrophy through reducing mitochondrial ROS production and thereby oxidative stress and proteolytic activity (Min et al., 2011). Similarly, SS-31 treatment on old mice decreased glutathione redox status

and mitochondrial H_2O_2 emission in skeletal muscle. Further, age-related deficits in mitochondrial ATP synthesis, oxidative phosphorylation and energy status restored rapidly following SS-31 administration in old mice (Siegel et al., 2013). Moreover, antioxidant SS-31 was administered to C26 mice receiving chemotherapy to prevent mitochondrial dysfunction, and it also reversed the loss of the glycolytic myofiber area in skeletal muscle. SS-31 enhanced intracellular ATP levels and prevented mitochondrial loss and abnormal autophagy/mitophagy (Ballarò et al., 2021). In another study, SS-31-induced mechanical ventilation (MV) in the diaphragm of rats protected against MV-induced oxidative stress, mitochondrial dysfunction, diaphragm protease activation, and MV-induced contractile dysfunction and muscle atrophy (Powers et al., 2011). As a result, these studies show that SS-31 mitochondria-targeted antioxidants can help prevent skeletal muscle atrophy for a variety of reasons.

MitoQ, another mitochondria-targeted antioxidant, is another therapeutic agent used to prevent or ameliorate skeletal muscle atrophy. Pin et al. found that MitoQ treatment changed the levels of mitochondrial biogenesis markers, including Mfn2. Furthermore, MitoQ partially increased the levels of pyruvate dehydrogenase lipoamide kinase isozyme 4 (Pdk4) and cytochrome B (CytB), the genes involved in the regulation of mitochondrial metabolism and function, consistent with enzymatic modulation of pyruvate dehydrogenase, hexokinase, and SDH (Pin et al., 2022).

Similarly, compound XJB-5-131 is a mitochondrial-targeted antioxidant that accumulates in mitochondria and reduces oxidative damage to mitochondrial DNA (Robinson et al., 2018). XJB-5-131 has been shown to improve single fiber contractile function in rats by increasing the activity of electron transport chain complexes by reducing mitochondrial ROS and membrane depolarization (Javadov et al., 2015).

Astaxanthin (AX) has a molecular structure that enables it to attach via the lipid layer of cell membranes, producing stronger anti-oxidative and protective effects than other antioxidants like vitamin C, beta-carotene, and -tocopherol in the cell membrane (Yuan et al., 2011). For example, after 10 days of immobilization, animals receiving AX showed prevention in skeletal muscle atrophy in response to immobilization, and they also avoided the significant rise in Cu, Zn superoxide dismutase, cathepsin L, calpain, and ubiquitin production in atrophic muscle (Shibaguchi et al., 2016). AX is a carotenoid that exerts strong antioxidant activity and acts in the lipid bilayer. Sun et al. observed that AX injection ameroliated muscle mass loss and protected myofiber size in the soleus muscle after using tail suspension to induce muscular atrophy. Further, AX reversed the down-regulation of mitochondrial respiratory chain complexes II and III in the soleus muscle (Sun et al., 2021). AX may be effective in preventing skeletal muscle atrophy through mechanisms that increase energy production in mitochondria and thereby prevent oxidative stress.

Tocopherol and tocotrienols, two subgroups of vitamin E, have been suggested to promote myogenic differentiation during aging (Khor et al., 2016). These subgroups have been shown in studies to play a role in muscle regeneration during oxidative stress-induced premature aging, by increasing myoblast proliferation and protecting satellite cell regeneration (Lim et al., 2019). Vitamin E reduces the effect of hypoxia on mitochondrial function and apoptotic signaling pathways and decreased Bax expression in skeletal muscle (Magalhães et al., 2005). Servais et al. reported that 60 mg/kg of vitamin E given twice weekly prevented soleus muscle atrophy brought on by immobility or denervation via affecting calpains, caspases-3, 9, and 12, as well as the ubiquitin ligases MuRF-1 (Servais et al., 2007).

Mitochondria-targeted antioxidants have demonstrated reparative and protective effects in the treatment of mitochondrial ROS inhibition, cancer cachexia, aging, and muscle atrophy or dysfunction due to denervation-immobilization. However, these studies conducted on cell culture and rodent models. Further, more clinical human trials needed to be done for mitochondria-targeted antioxidants to used as a alternative therapy for mitochondria dysfunction associated skeletal muscle atrophy.

4.3. PGC-1α *in vivo* transfection

In recent years, it has become increasingly apparent that mitochondrial dysfunction is a key factor in skeletal muscle atrophy resulting from prolonged inactivity, ageing, cancer, and drug-induced atrophy (Hyatt et al., 2019; Sartori et al., 2021). As PGC-1α plays a crucial role in skeletal muscle function, in vivo transfection of PGC-1α has emerged as a promising therapeutic approach to counteract skeletal muscle atrophy and metabolic dysfunction by stimulating mitochondrial biogenesis and enhancing antioxidant defense (Benton et al., 2008; Geng et al., 2011; Lin et al., 2002; Selsby et al., 2012; Zhang et al., 2017a).

Animal studies have shown that in vivo transfection of PGC-1α can improve mitochondrial content and function, thereby enhancing endurance capacity and skeletal muscle quality (Calvo et al., 2008; Handschin et al., 2007; Kang et al., 2015; Kang and Ji, 2016; Lin et al., 2002; Sandri et al., 2006). For example, transfecting PGC-1α into the tibialis anterior muscle increased mitochondrial function and density, reduced oxidative stress, and increased fiber CSA in a model of immobilization-induced muscle atrophy (Kang et al., 2015). Another example of the role of PGC-1α in skeletal muscle atrophy is the suppression of proteolytic mechanisms that contribute to muscle atrophy. Overexpressing PGC-1α via in vivo transfection can lead to the suppression of transcription factors FoxO1 and FoxO3 and mitophagy markers such as Beclin-1, Bnip3, PINK1, and parkin in the tibialis anterior muscle of mice subjected to two weeks of immobilization followed by remobilization. Moreover, elevated PGC-1α expression significantly enhances oxidative enzyme activity and mitochondrial DNA proliferation, while reducing oxidative stress (Bax/Bcl2 ratio and caspase-3 activity) (Kang and Ji, 2016). Notably, ageing skeletal muscle exhibits a decrease in PGC-1α expression, suggesting that restoring PGC-1α levels could have a therapeutic effect on the onset and progression of age-related loss of muscle mass, known as sarcopenia (Anderson and Prolla, 2009; Wenz, 2011). A study by Yeo et al. demonstrated that transfecting PGC-1α into aged mouse tibialis muscle enhances mitochondrial oxidative function and antioxidant enzyme activities, decreases mitochondrial damage, and mitigates the effects of aging on skeletal muscle (Yeo et al., 2019). Furthermore, overexpression of PGC-1α inhibits age-related increases in mitophagy markers, including LC3II, p62, RheB, Beclin-1, and Mfn2 (Yeo et al., 2019). Although PGC-1α is critical for the maintenance of mitochondrial function, overexpression of PGC-1α did not protect against age-related loss of muscle mass and fiber size, suggesting that PGC-1α alone may not be sufficient to prevent skeletal muscle atrophy (Yeo et al., 2019). The authors also speculated that the transfection of PGC-1α into aged skeletal muscle may require a longer period of time to observe changes in skeletal mass and fiber size (Yeo et al., 2019). It is worth mentioning that introducing PGC-1α through transfection results in higher levels of PGC-1α protein production in the skeletal muscles of young animals compared to older ones (Yeo et al., 2019). This observation suggests that a reduction in PGC-1α expression resulting from in vivo electroporation in the skeletal muscles of aged mice may contribute less to the maintenance of skeletal muscle mass compared to young animals. Additionally, it is important to note that PGC-1α expression should remain within a physiological range to avoid negative consequences. For instance, overexpression of PGC-1α in cardiac myocytes of transgenic mice caused uncontrolled

mitochondrial proliferation, ultimately leading to the loss of sarcomeric structure and the development of dilated cardiomyopathy (Lehman et al., 2000; Russell et al., 2004).

From a methodological point of view, in vivo electroporation is a simple and effective technique for delivering plasmid DNA into skeletal muscle fibers, enabling the study of complex molecular interactions and morphological changes in skeletal muscle (Hughes et al., 2022; Kang et al., 2015). To maximize the efficiency of this method, it is critical to control key parameters, such as the practitioner's experience, plasmid concentration, and voltage (Hughes et al., 2022; Schertzer et al., 2006). Additionally, transfection efficiency is lower when applied to skeletal muscle and a greater transfection efficiency requires higher voltage during electroporation that will induce skeletal muscle damage (Benton et al., 2008; Schertzer et al., 2006). Undoubtedly, in vivo electroporation is a valuable tool that allows gain or loss of function studies of genes of interest for the elucidation of molecular pathways in skeletal muscle under both physiological and pathological conditions. However, it is essential to keep in mind that plasmid transfection may not occur in all fibers within the target muscle, which can limit the whole muscle analyses at the molecular and morphological levels (Benton et al., 2008; Hughes et al., 2022). Over the past decade, the CRISPR-Cas9 genome editing tool has become recognized as a highly efficient and time-saving technique, with a wide range of potential applications in the clinical setting (Jiang and Doudna, 2017; Jinek et al., 2012). Due to their high cellular uptake and editing efficiency, viral vectors may be an ideal option for in vivo delivery of CRISPR-Cas9 components, including guide RNA and Cas9 protein, to target specific genes and facilitate new discoveries in skeletal muscle physiology (Asmamaw Mengstie, 2022; Hughes et al., 2022). Despite the fact that the CRISPR-Cas9 system has been shown to be a powerful, efficient and reliable tool for gene editing in a wide range of organisms, there are many ethical and safety concerns that need to be addressed before it can be implemented (Caplan et al., 2015). Consequently, further studies are required to optimize efficient PGC-1α transfection in skeletal muscle of rodents and humans, and compare their advantages and disadvantages to evaluate their therapeutic potential for the treatment of skeletal muscle atrophy.

5. Possible therapeutic approaches

5.1. Mitochondrial transplantation

Skeletal muscle strength and mass can gradually decline due to various pathological conditions such as disuse/immobilization, diabetes, cancer, cardiovascular disease, and sarcopenia (Sandri et al., 2013). These conditions affect the skeletal muscle's ability to function properly by impairing mitochondrial content, morphology, and function, which in turn can lead to the production of reactive oxygen species and initiation of catabolic pathways (Romanello et al., 2010; Sartori et al., 2021). There is overwhelming evidence that mitochondrial transplantation has established a therapeutic role in treating various diseases in both preclinical and clinical experiments (Blitzer et al., 2020; Emani et al., 2017; Guariento et al., 2021; Kubat et al., 2021b; Ulger and Kubat, 2022; Ulger and Kubat, 2023; Wang et al., 2019; Zhou et al., 2022). A study by Kubat et al. reported that mitochondrial transplantation accelerated tubular regeneration, reduced protein accumulation in tubular cells, and improved the apoptotic-antiapoptotic balance in doxorubicin-induced nephrotoxicity (Kubat et al., 2021a). In a partial liver ischemia-reperfusion rat model, mitochondrial transplantation resulted in a reduction of hepatocyte necrosis, apoptotic TUNEL levels, cytosolic CytC expression, and caspase 9 expression (Lin et al., 2013). Another study showed that mitochondrial transplantation improved lung compliance and inspiratory capacity, and reduced neutrophil infiltration, interstitial edema, and apoptosis

in a lung ischemia-reperfusion model (Moskowitzova et al., 2020). Furthermore, in a Parkinson's disease model, mitochondrial transplantation increased electron transport chain function, and decreased levels of ROS, cellular apoptosis, and necrosis (Shi et al., 2017). Most studies focus on determining the protective effect of exogenous transplantation and the cellular functions derived from cells or tissues in organs such as the heart, liver, kidney, and brain (Alemany et al., 2023; Kubat et al., 2021a; Masuzawa et al., 2013; Ulger et al., 2021; Zhao et al., 2021). However, further research is needed to gain a more comprehensive understanding of how mitochondrial transplantation can be applied in response to skeletal muscle atrophy, ultimately aiming to translate these findings into clinical practice.

It is well established that mitochondrial transplantation may alleviate skeletal muscle atrophy by improving mitochondrial function and inhibiting muscle proteolytic signaling pathways (Liu et al., 2016). Kim and colleagues found that mitochondrial transplantation increased cell proliferation and ATP content as well as lowered mtROS levels in a dexamethasone-induced skeletal muscle atrophy model. Mitochondrial transplantation also dramatically restored PGC-1α expression, while significantly downregulating FoxO3 and MuRF-1 levels, following mitochondria transplantation (Kim et al., 2018). Moreover, mitochondrial transplantation significantly reduces infarct size and apoptosis, improves hindlimb function, increases ATP content, and decreases inflammation (Orfany et al., 2020). A study investigated the impact of mitochondrial transplantation on muscular myopathy. Isolated mitochondria from human umbilical cord mesenchymal stem cells were transplanted intravenously on days 1 and 7 in a Dex-induced skeletal muscle atrophy. Mitochondrial transplantation was found to reduce muscle inflammation and improve mitochondrial dysfunction by increasing mitochondrial activity, indicating its potential as a novel therapeutic approach for treating inflammatory myopathy (Kim J, 2019). A recent study described the beneficial effects of mitochondrial transplantation on muscle injury (Alway et al., 2023). Mitochondrial transplantation reduced non-contractile collagen deposition and dramatically enhanced the rate of gastrocnemius muscle fiber regeneration and force restoration, particularly between 7 and 14 days after injury. Mitochondrial transplantation also promoted regeneration selectively in Type IIB fibers (Alway et al., 2023). Indeed, mitochondrial transplantation mimics the natural intercellular transfer of mitochondria that occurs in organisms, and its success is being demonstrated by new publications (Leslie, 2022; Mokhtari et al., 2022; Sun et al., 2023). This technique is effective in restoring and preventing the loss of contractile elements in damaged or atrophied muscle cells. Additionally, introduction of exogenous mitochondria can increase the synthesis of extracellular proteins, such as collagen, thereby enhancing the structural integrity of the tissue (Alway et al., 2023).

Several mechanisms have been proposed for the protective effects of mitochondrial transplantation. (McCully et al., 2017; Yamada et al., 2020). The main function of mitochondria is to produce energy in the form of ATP, and mitochondrial transplantation can enhance the production of ATP by replacing healthy mtDNA with damaged mtDNA (Clemente-Suárez et al., 2023). Caicedo et al. demonstrated the interactions between human mesenchymal stem cells (hMSCs) and MDA-MB-231 cancer cells using the Mitoception method, and that endogenous mtDNA levels can be increased by mitochondrial transplantation, resulting in increased ATP production (Caicedo et al., 2015). Studies suggest that mitochondrial transplantation can enhance ATP synthesis, but the bioenergetic effect of transplanted mitochondria is transient and dose-dependent. For instance, in a limb ischemia model, Orfany et al. demonstrated a dose-dependent increase in ATP content following mitochondrial transplantation (Orfany et al., 2020). Furthermore, Zhang et al. showed that mitochondrial infusion may accelerate the elimination of ROS by improving ATP content and reducing the activation of apoptotic

pathways (Zhang et al., 2019). In normal cardiomyocytes, mitochondrial transplantation results in a transient improvement in bioenergetics, leading to a significant increase in baseline respiration and ATP generation. However, long-term experiments after transplantation have revealed that the bioenergetics of normal recipient cells eventually recover to physiological levels (Pour et al., 2020). Through actin-dependent endocytosis, transplanted mitochondria enter the cells, triggering the immune system and leading to the production of cytokines. These cytokines, in turn, can promote cell proliferation and growth (Yamada et al., 2020). In the injured spinal cords of mitochondrial transplanted rats, Lin et al. observed reduced levels of TNF, IL-6, and nitric oxide, indicating a decrease in inflammatory markers associated with mitochondrial transplantation (Lin et al., 2022). In contrast, Masuzawa et al. did not find a significant increase in blood inflammatory markers or the presence of anti-mitochondrial antibodies following mitochondrial transplantation in a rabbit model of ischemic cardiomyopathy (Masuzawa et al., 2013). Indeed, the analysis of inflammatory cytokines in the serum has shown that mitochondrial transplantation does not induce an immune or inflammatory response (Doulamis et al., 2022). Interestingly, Lin et al. discovered that exposure to mitochondria led to an increase in the expression of pro-inflammatory cytokines and chemokines (Lin et al., 2019). Highlighting an important aspect of mitochondrial transfer within the immune system, Jackson et al. demonstrated that mitochondrial transfer through nanotubes enhances phagocytic activity, while inhibiting TNT formation, which blocks mitochondrial transfer, impairs phagocytosis (Jackson et al., 2016). It is important to note that the exact mechanisms responsible for the cellular effects of mitochondrial transplantation are still to be elucidated. The beneficial effects mitochondrial transplantation may not solely rely on ATP production, and multiple signaling pathways and mitochondrial-derived peptides may also be involved. Furthermore, the inflammatory response in the context of mitochondrial transplantation is likely to be multifactorial. The transient nature of bioenergetic effects and potential immune responses induced by mitochondrial transplantation requires further research to optimize therapeutic potential and address these concerns.

Currently, there are no effective therapies for treating skeletal muscle atrophy, so any approach that focuses on improving mitochondrial function has the potential to slow down the loss of skeletal muscle quality and function. Some attempts have been made to enhance muscle strength, mass, and function by introducing exogenous mitochondria to restore mitochondrial function in skeletal muscle (Alway et al., 2023; Kim et al., 2018; Orfany et al., 2020). However, further research is necessary to fully understand its effects and underlying mechanisms. Specifically, it is essential to optimize the critical parameters of healthy mitochondria transplantation, such as storage, delivery route, and source of mitochondria. Furthermore, it is crucial to consider that when injecting mitochondria, all muscle fibers in the target muscle may not uptake the mitochondria equally. Such findings will provide new opportunities to develop possible interventions to restore mitochondrial function through mitochondrial transplantation, which could prevent and treat skeletal muscle atrophy.

6. Conclusion and future directions

Skeletal muscle atrophy occurs in a variety of conditions such as disuse, starvation, side effects of medication, aging, cancer cachexia, CVDs, and diabetes. Skeletal muscle atrophy is defined as the decrease of skeletal muscle mass caused by an imbalance in myofibrillar protein breakdown and synthesis.

Skeletal muscle mass and physical activity are linked, and body composition changes in a variety of ways during inactivity. Prolonged bed rest is one of the major factors for disuse muscle atrophy that have deleterious consequences on the musculoskeletal, CVDs, respiratory,

and cognitive systems. The relationship between disuse skeletal muscle atrophy and mitochondrial dysfunction leads to loss of muscle fiber CSA and reduction of myofilament proteins, decreased muscle strength, down-regulation of myoglobin, and decreased oxidative phosphorylation complex activity. As a result of CVDs, such as in individuals with CHF when the metabolic pathway is disrupted, skeletal muscle atrophy is now clearly understood (Hunt et al., 2009). Skeletal muscle anomalies and CVDs are tightly connected and this relationship has recently become a hot topic of new research.

Recent pieces of evidence revealed that mitochondrial dysfunction is a critical phenomenon in skeletal muscle atrophy. In this review, we discussed the causes of skeletal muscle atrophy, such as disuse and cachexia, as well as cardiovascular diseases, and demonstrated the primary mechanistic pathways affecting mitochondrial function in skeletal muscle atrophy. The manifestations of mitochondrial alteration are similar in numerous disorders more specifically in our latter muscle atrophy and CVDs. Several lines of evidence outlined the involvement of mitochondrial dysfunction in both muscle atrophy and CVDs and very few studies pointed out its major contribution, especially in the skeletal muscle of patients with CVDs. A deeper comprehension of the involvement of mitochondria-related mechanisms underlying skeletal muscle atrophy in CVDs such as HF is required to pave the way to endow and illustrate further potential therapeutic targets and preventative approaches.

Today, there are some effective treatments for preventing or treating skeletal muscle atrophy. Some of these include exercise, mitochondrial-targeting medications, and in vivo gene treatments. However, exercise cannot be employed in all circumstances, excessive doses of mitochondria-targeted drugs may cause negative effects such as cancer and stroke, and gene therapy is costly and heavily regulated by authorities.

Mitochondrial transplantation might be one of the possible therapeutic approaches for skeletal muscle atrophy. In addition to its effects such as reducing oxidative stress, increasing regeneration, and preventing necrosis, it seems likely that it can prevent mitochondrial damage mechanisms that occur in skeletal muscle atrophy. Although promising results have been reported in recent studies on the effects of mitochondrial transplantation in skeletal muscle, these effects need to be mechanistically supported by further studies.

The effectiveness of mitochondrial transplantation as a single or future therapeutic approach has some limitations. However, exercise, mitochondria-targeted antioxidants and PGC-1α via in vivo transfection are powerful inducers of mitochondrial biogenesis and mitochondrial function. Effective results can be obtained by combining these therapies with mitochondria transplantation.

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Table 1: Summary of current therapeutic strategies and possible therapeutic approaches

Therapeutic approach	Models	Result	Reference
Exercise	3 or 7 days aerobic or resistance training	Entire recovery of CSA, reduced the UPS and the upregulation in PGC-1α expression, inhibited the FoxO pathway.	Vechetti-Junior et al., 2016
Exercise	Short-term, concurrent exercise training, 2 weeks	Increased mitochondrial biogenesis and SMHC expression, and reduced Myh4, decreased ROS	Theilen, Jeremic, Weber, & Tyagi, 2018
Exercise	10 days treadmill running for 60 min/day	Reduced H_2O_2 release and lipid peroxidation production	Morton et al., 2019
Exercise	4 weeks voluntary exercise	Increased citrate synthase and CytC oxidase, improved Mfn2 and DRP-1, reduced 4-hydroxynonenal and protein carbonyls	Kitaoka, Miyazaki, & Kikuchi, 2021
Exercise	Treadmill exercise for 12 weeks	Ameliorated a decrease in the CSA, protected against increases in mitochondria-mediated apoptosis	Heo et al., 2018
Exercise	≥6 h training a week for at least 5 years	Increased fission and mitophagy	Balan et al., 2019
Exercise	8 weeks of exercise training	Reduced in the acetylation of isocitrate dehydrogenase 2, increased content of the mitochondrial deacetylase SIRT3, increased antioxidant defense	Johnson et al., 2015
Mitochondria-targeted antioxidants	14 days muscle immobilization SS-31 (1.5 mg/kg sc) daily for 14 days	Diminished mitochondrial ROS production and prevented oxidative stress, protease activation, myofiber atrophy	Min et al., 2011
Mitochondria-targeted antioxidants	Mitochondrial energetics aged or young mice intraperitoneal injection of 3 mg/kg SS-31	Reversed resting and maximal ATP production, improved oxidative phosphorylation and cell energy state	Siegel et al., 2013
Mitochondria-targeted antioxidants	Cachexia-chemotherapy muscle atrophy 2 mg/kg SS-31 treatment at day 4 or day 7	Prevented mitochondrial loss and abnormal autophagy/mitophagy	Ballarò et al., 2021
Mitochondria-targeted antioxidants	MV-induced diaphragm weakness i.p. injection with SS-31 every three hours for 12 hours.	Protected against MV-induced oxidative stress, mitochondrial dysfunction, protease activation, contractile dysfunction and muscle atrophy	Powers, Hudson, et al., 2011

Mitochondria-targeted antioxidants	Cancer cachexia induced skeletal muscle atrophy MitoQ administration 25 mg/kg in drinking water, daily	Increased the levels Pdk4 and CytB, with enzymatic modulation of pyruvate dehydrogenase, hexokinase, and SDH	Pin, Huot, & Bonetto, 2022
Mitochondria-targeted antioxidants	Aged or young mice XJB i.p. injection 3 mg/kg body weight for four weeks	Showed higher muscle contractility, high activity of the respiratory complexes I, III, and IV, reduced mitochondrial ROS	Javadov et al., 2015
Mitochondria-targeted antioxidants	10 days immobilization-skeletal muscle atrophy 0.04% AX diet and 0.2% AX diet 14 days before immobilization.	Reduced muscle atrophy, prevented the immobilization-induced increase in the expression of CuZn-SOD, cathepsin L, calpain, and ubiquitin	Shibaguchi et al., 2016
Mitochondria-targeted antioxidants	Ttail suspension skeletal muscle atrophy model AX-supplemented diets	Improved downregulation of mitochondrial respiratory chain complexes I and III, promoted mitochondrial biogenesis, suppressed mitochondrial ROS production, inhibited the activation of caspase 3	Sun et al., 2021
Mitochondria-targeted antioxidants	In vivo acute and severe hypobaric hypoxic insult vitamin E-supplemented 60 mg/kg ip, 3 times/wk for 3 wk	Reduced oxidative stress, prevented mitochondrial alterations	Magalhães et al., 2005
Mitochondria-targeted antioxidants	Immobilization or denervation muscle atrophy model 60 mg/kg twice-weekly vitamin E	Reduced calpains, caspases-3, -9, and -12, and ubiquitin ligases MuRF-1	Servais, Letexier, Favier, Duchamp, & Desplanches, 2007
Mitochondria-targeted antioxidants	Diet-induced-obesity and insulin resistance Resveratrol administration 4 g/kg	Protected mice against diet-induced-obesity and insulin resistance	Lagouge et al., 2006
PGC-1α via in vivo transfection	7, 14, 19 days immobilization-skeletal muscle atrophy plasmid DNA solution 2.5 μg/μl GFP, 2.7 μg/μl Flag-PGC-1α, or 2.5 μg/μl GFP-PGC-1α injection	Increased in PGC-1α content, mitochondrial CytC, TFAM, mitochondrial density, mDNA/nDNA ratio and CytC oxidase activity, ATP synthesis rate, and fiber CSA, SOD-2 activity NAD-dependent deacetylase SIRT3, reduced NF-kB-DNA binding and H_2O_2	Kang, Goodman, Hornberger, & Ji, 2015
PGC-1α via in vivo transfection	7- and 14-days immobilization, 5- and 10-days remobilization- skeletal muscle atrophy plasmid DNA solution (2.5 μg/μl GFP, 2.7 μg/μl Flag-PGC-1α) injection	Increased PGC-1α, oxidative enzyme activity, mitochondrial DNA proliferation and decreased FoxO1, FoxO3 activation, mitophagy markers, ubiquitination, Mfn2 degradation	Kang & Ji, 2016

PGC-1α via in vivo transfection	Age-related skeletal muscle atrophy plasmid DNA solution 2.5 μg/μl GFP, 2.7 μg/μl Flag-PGC-1α injection	Suppressed PINK and parkin protein levels, reduced the protein content of LC3II, p62, RheB, Beclin-1, Mfn2, Fis-1, DRP-1, increased mitochondrial oxidative function and antioxidant enzyme activities, reduced lipid peroxidation and inner membrane damage	Yeo, Kang, Gomez-Cabrera, Vina, & Ji, 2019
Mitochondrial transplantation	Dex-induced skeletal muscle atrophy 0.05, 0.5, and 5μg mitochondrial transplantation	Increased cell proliferation, ATP content, AMPK activation and decreased mROS level, downregulation of FoxO3α, MuRF-1	(Kim, Hwang, Yun, Lee, & Choi, 2018
Mitochondrial transplantation	Muscle I/R model 1×10^6, 1×10^7, 1×10^8, 1×10^9 mitochondrial transplantation	Reduced infarct size, apoptosis, improved hindlimb function increased ATP content and reduced inflammation	Orfany et al., 2020
Mitochondrial transplantation	Dex-induced polymyositis day 1 (0.67 ± 0.60), day 7 (0.75 ± 0.61) mitochondrial transplantation	Increased oxidative phosphorylation complex II, decreased inflammation and increased mitochondrial activity	Kim J, 2019
Mitochondrial transplantation	Muscle injury model 50 μg mitochondrial transplantation	Reduced non-contractile collagen deposition, improved the muscle fiber repair and restoration of force, and enhanced regeneration in Type IIB fibers and improved restoration of muscle function	Always et al., 2023

adenosine triphosphate (ATP), AMP-activated protein kinase (AMPK), astaxanthin (AX), cross sectional area (CSA), cytochrome B (CytB), cytochrome C (CytC), dexamethasone (Dex), dynamin-related protein 1 (DRP-1), forkhead box O (FoxO), green fluorescent protein (GFP), hydrogen peroxide (H_2O_2), ischemia reperfusion (I/R), mechanical ventilation (MV), mitochondrial transcription factor A (TFAM), mitofusin 2 (Mfn2), myosin heavy chain 4 (Myh4), nuclear factor-kappa B (NF-κB), nuclear respiration factor (NRF) 1-2, peroxisome proliferator-activated receptor gamma (PPAR) coactivator-1alpha (PGC-1α), pyruvate dehydrogenase lipoamide kinase isozyme 4 (Pdk4), reactive oxygen species (ROS), Sirtuin 3 (SIRT3), slow myosin heavy chain (SMHC), and ubiquitin-proteasome system (UPS).

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