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# Mitochondrial Paths to Sarcopenia – A Refined Short Review

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**Abstract:** The current revision aims to report on the geriatric syndrome, well known as sarcopenia, specifically the communication between sarcopenia and mitochondrial pathways. It is predicted that pervasiveness of sarcopenia in community-dwelling elderly people is around 25%, and there is a 5% loss of muscle mass per decade of life from the fourth decade onwards, possibly progressing after the age of 65 years. Muscular mass usually supplies up to ~50% of total body weight in grown-ups but drops to 25% with aging at 75-80 years old. In the past, several molecular mediators contributing to sarcopenic muscle loss involves ubiquitin proteasomes, inflammatory molecules, and autophagy. Currently, the central roles of mitochondria in the management of sarcopenia are underpinned. However, the collection of scientific evidence suggests that mitochondria have built both direct and indirect physiological implications in controlling muscle physiology and muscle mass in both healthy and diseased conditions, specifically in sarcopenia, the role of mitochondrial pathways epitomize an assuring area of exploration. It is advisable to have an overview of latest discoveries highlighting the mitochondrial function in sarcopenia to generate innovative remedies that can aid to enhance, manage or slow down age-related muscle loss. In the current review, we discuss relevant scientific studies delineating mitochondrial roles and pharmacological therapeutics of sarcopenia.

**Keywords:** Skeletal muscle, Ageing, Sarcopenia, Muscle wasting, Atrophy, Mitochondrial Quality Control, Mitochondrial dysfunction, Mitophagy and Proteostasis.

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## INTRODUCTION

Severe muscle loss creates adverse outcomes not only on the function of skeletal muscle but on the quality of life of victims who suffer from it. Four familiar yet different states distinguished by muscle loss are disuse atrophy, sarcopenia, cachexia and muscular dystrophies. Wasting of muscle mass is an unavoidable component of sarcopenia and involuntary loss of skeletal muscle mass or strength linked with aging [1, 2]. Some disadvantageous consequences such as inability to move / walk, poor quality of life, and enhanced risk of death makes sarcopenia a significant clinical dilemma in public health of older people [3, 4]. It is predicted that the generality of sarcopenia in community-dwelling elderly adults is around 25% [5-7] and there is a 5% loss of muscle mass per decade of life from the fourth decade onwards, possibly progressing after the age of 65 years [8-10]. Sarcopenia first appears after the age of 40. The progressive loss of muscle begins from 8% and muscle strength at 10-15% loss per decade until the period of 70 years, increases to 15% muscle loss and 25% to 40% muscle per decade [11-13]. Muscular mass usually suppl--ies up to ~50% of total body weight in grown-ups but drops to 25% with aging at 75–80 years old [14, 15]. Histologically, decreased muscle fiber number and size features sarcopenic muscle wasting. Molecularly, fiber type switch and impaired satellite cell functions are hallmarks of age-related muscle loss [1, 16].

Noteworthy to mention that sarcopenia is correlated with reduced protein synthesis but, no significant change in the activity of the proteolytic system [1, 16]. Also, modified proteostasis, declined motor unit number, abnormal hormonal levels, high amounts of inflammatory cytokines, and mitochondrial dysfunction are the commonly attributed tools underlying muscle degeneration in sarcopenia (Figure 1). Even though various molecular mediators (ubiquitin proteasomes, inflammatory molecules, and autophagy) contributing to sarcopenia are known, yet it has been difficult to classify physiological victims to develop novel anti-sarcopenic therapeutics in humans. In spite of a more recent stage II clinical trial shows that anti-myostatin antibody (ATA 842) attenuates sarcopenia with improved muscle mass, strength, age associated

energy expenditure and insulin sensitivity, many pharmaceutical and supplemental compounds fail to inhibit this [17].

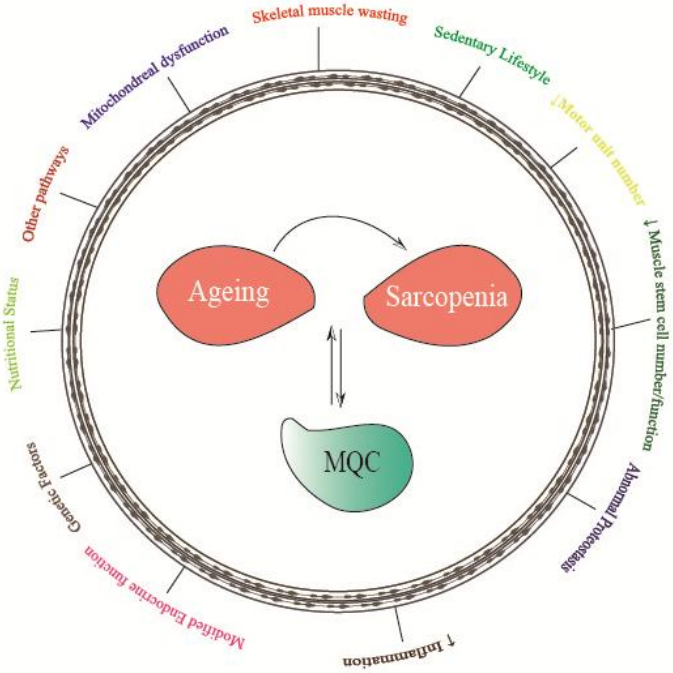


**Figure 1: Mitochondrial Abnormality Is A Cause or A Consequence of Aging** - Illustration of relationship between aging and age associated muscle loss (Sarcopenia). The outer listed factors contribute in the regulation of the sarcopenia and Mitochondrial Quality Control (MQC) in muscles during ageing. It is unclear whether mitochondrial defects cause sarcopenia or sarcopenia provokes mitochondrial dysfunction in ageing.

In our body, muscles are the only tissues harboring highest mitochondrial content to provide massive amounts of ATP for muscle-related activities like movement and exercise. Maintenance of mitochondrial integrity during muscle degeneration considered as the prerequisite factor in muscle cells [18]. Taking into account the fundamental functions like homeostasis, cell death, energy production and cellular quality control by mitochondria, defects in mitochondrial function can be considered as a prime motivator to trigger muscle loss in sarcopenia and other muscle wasting conditions. We aim to offer the possibility of targeting particular mitochondrial signaling mechanisms to obtain a curable profit in sarcopenia.

## Mitochondrial Abnormality Is A Cause or A Consequence of Aging

Prior discoveries established a direct cause-and-effect relationship between mitochondrial DNA (mtDNA) mutations and sarcopenia, demonstrated premature aging combined with sarcopenia and reduced lifespan of mice bearing polymerase γ (PolG) with proofreading-deficiency of mitochondrial DNA [19-21]. Studies also reported that mutations in mitochondrial DNA displayed premature aging phenotypes in mice [22, 23]. Mice with PolG expression displayed systemic mitochondrial dysfunction, reduced respiratory chain pathway, stimulated apoptosis and impaired mitochondrial quality control (MQC) [24-26]. In addition to mitochondrial dysfunction, increased oxidative stress does seem to happen in aged human muscle tissues [27].

**Quick Notes:**

- Aging is a natural form of pathology associated with disability, frailty, falls and decline in proper function.
- Sarcopenia is a condition commonly linked with loss of muscle mass and physical function of older adults.
- Sarcopenia invites secondary disease states including malnutrition, inflammation, defective neuromuscular junctions, and alterations in mitochondria quality control, oxidative stress and apoptosis.
- Clinical investigations recommend lifestyle changes such as extra nutritional supplements and exercise due to lack of pharmaceutical therapeutics.

Noteworthy to mention, that PolG mice display premature aging because of mitochondrial dysfunction alone, as these mice never had abnormal oxidative stress levels. However, data from Lopez-Otin et al. and Calvani et.al., support the notion that irrespective of mitochondrion - generated reactive oxygen species (ROS) mechanism, mitochondrial dysfunction alone considered as the hallmarks of aging and sarcopenia [18, 28]. On the other hand, studies from Lewis et al. conducted with naked mole-rats highlighted that presence of higher amounts of ROS levels even at the young age had no effect on aging and related phenotypes since the mole-rats lived for the ancient period due to unknown cytoprotective mechanisms [29]. A debate is going on the fact that whether ROS mediated mtDNA dysfunction is a fundamental cause of aging or not. Together, these conclusions show that mtDNA mutations may jeopardize cell functioning and survival independent of oxidative damage during aging.

Anderson and Weindruch reported that brain, heart, and muscles are highly sensitive to mitochondria-mediated aging, as these tissues solely depend on mitochondria-mediated removal of defective organelles. Hence efficient MQC is needed to maintain mitochondrial homeostasis in the brain, heart, and skeletal muscle tissues. Defects at any path of MQC

(Figure 2) can bring great responses such as energy shortage, mitochondrial dysfunction, and cell death [30]. Cells can achieve MQC under healthy conditions via systematisation of various mitochondrial related pathways (Figure 2), majorly through mitochondrial biogenesis, dynamics, proteostasis and autophagy [31]. Defects in skeletal muscle MQC linked with sarcopenia and aging. Substantial experimental evidence supported a role for mitochondrial dysfunction and disordered MQC in fiber loss during sarcopenia. In vivo studies using transgenic mice with loss of autophagy-related protein-7 (Atg7) exhibited muscle loss, weakness, oxidative stress, apoptosis, and aggregations of atypical giant damaged mitochondria [32].

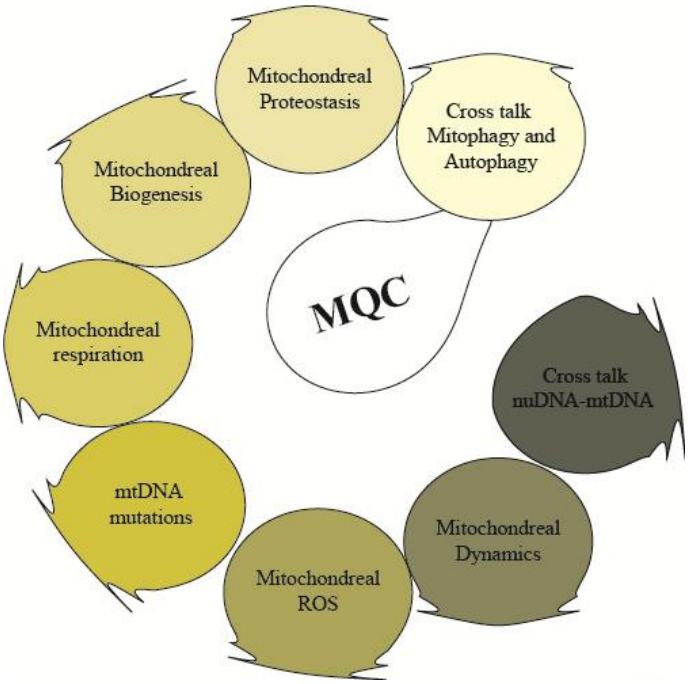


**Figure 2: Pleiotropy of Mitochondrial Quality Control:** Schematic representation of interrelated signaling pathways that are part of mitochondrial quality control of the cell. Imbalance at any stage of mitochondrial homeostasis severely affects the pathophysiology of cell or organism.

Preclinical and clinical data from aged rats, primates, and humans show that in most of the muscle fibers, loss of succinate dehydrogenase hyperactivity (SDH++) and cytochrome C oxidase activity (COX-) seen. COX- and SDH++ - two essential intermediates of electron transport chain (ETC) that occurs in mitochondria [33-35]. Besides, Wanagat et al. demonstrated that mitochondrial DNA deletion mutations resulted in muscle wasting, fiber splitting, and oxidative damage in sarcopenia. Furthermore, importantly, mtDNA deletion mutations colocalize with ETC abnormalities and eventually cause loss of ETC activity [33-36]. Alken J et al. suggested a molecular basis i.e mtDNA deletion and ETC abnormalities for muscle fiber loss with age, a process originating with the mtDNA deletion and ending with muscle fiber breakage and damage [37].

## Mitochondrial Quality Control In Sarcopenia

A collection of interdependent cellular processes as described in Figure 2, includes mitochondrial biogenesis, proteostasis, autophagy, and dynamics that guarantees the preservation of operative mitochondrial pool [38]. Mitochondrial homeostasis is one of the critical processes to maintain muscle cell stability, and the importance of MQC regulation and its abnormalities in muscles have been vigorously explored [39-41].

## Mitochondrial Biogenesis And Sarcopenia:

The growth and multiplication of existing mitochondria are known as "Mitochondrial biogenesis." Being bacterial origin mitochondria has its own genomic DNA and can auto-replicate. Nearly, a thousand genes involved from both nuclear DNA (nuDNA) and mtDNA with co-operation of many transcriptional coactivators creation of new mitochondria. Physiological states, exercise, starvation, oxidative stress, and inflammation trigger mitochondrial biogenesis [42]. Nuclear genes with the help of RNApol II interaction encodes 95% of mitochondrial proteins whereas mtDNA codes proteins of the ETC, mitochondrial tRNAs, and rRNAs. Numerous studies reported the involvement of several transcription factors and co-activators in mitochondriogenesis [42]. Peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1) family members (PGC-1α and PGC-1β), nuclear respiratory factor family members (NRF-1 & NRF-2), and the estrogen-related receptor alpha (ERRα) gained popularity as transcriptional regulators of mitochondrial biogenesis via activating the expression of mitochondrial proteins encoded from nuclear DNA. Virbasius JV et al. demonstrated that transcription of NRF1 and NRF2 from nuclear DNA promotes the expression of mitochondrial transcription factor A (TFAM) and mitochondrial transcription factors B1 and B2 (TFB1M and TFB2M), these factors can bind, drive transcription and replication of mtDNA [43].

Clinical evidence suggests that in aged people low levels of PGC-1α and its intermmediate targets were seen in skeletal muscles [26, 44-46]. Even though PGC-1α cannot bind to mtDNA directly, it can shuttle from the cytosol to both the nucleus and mitochondria, expediting mitochondrial biogenesis, mtDNA repair, and nuclear-mitochondrial crosstalk [47, 48]. In the past, research findings reported a reduction in PGC-1α mRNA levels during denervation, unloading and aging [49-51]. Further, a definite association between PGC-1α levels, oxidative potential, and functional status were observed in low

functioning aged individuals [26]. Presence of higher amounts of PGC-1α in atrophying muscle models (sarcopenia, hind limb suspension, cachexia, denervation, and fasting) demonstrated improved mitochondrial turnover and prevented muscle loss [49, 50]. Not only PGC-1α but also its homolog PGC-1β displayed overlapping functions with PGC-1α in maintaining healthy mitochondrial function in skeletal muscles through sharing a shared pool of target genes. Deletion of PGC-1α/β in skeletal muscles demonstrated mitochondrial structural derangements and biogenic defects with fusion-fission errors [52, 53]. In 2012, Ruas et al. discovered the presence of a novel PGC-1α gene splice variant named PGC-1α4 in muscles underwent post-resistance training, associated with maintenance of muscle hypertrophy. In the same study, PGC-1α4 overexpression protected muscle loss induced via hind-limb suspension and cancer cachexia [54]. Later, Ydfors et al. reported the increased expression of muscle PGC-1α4 in young individuals enduring both endurance training and resistance exercise [55, 56]. However, currently, the biological functions of PGC-1α4 in human muscles remain unclear and debatable, since PGC-1α4 levels did not associate with exercise-induced human muscle hypertrophy and all PGC-1α isoforms appear to be expressed for a little while in response to acute exercise and regardless of the mode. There is an immediate need for further investigation to identify the potential applications of PGC-1α4 in muscle maintenance and mitochondrial function in humans.

Many cellular and molecular signaling events lead to progression of the transcriptional cascade in mitochondria. A physiological stimulus including exercise, diet, starvation and disease conditions can trigger a series of molecular events to cope with the situation. AMP-activated protein kinase (AMPK) is a primary manager of mitochondrial biogenesis and regulates energy metabolism in response to acute energy crises [57]. Chronic pharmacological AMPK activation in the muscle of rats exhibited significant mitochondrial biogenesis through PGC-1α and the NRF [58]. Reznick et al. further confirmed that chronic activation of AMPK using AMPK-alpha (2) activity by 5'-aminoimidazole-4-carboxamide-1-beta-D-ribofuranoside (AICAR), or β-guanadinopropionic acid (β-GPA) and exercise failed to activate AMPK-α2 in old rats. Inactivation of AMPK-α2 post-stimulation diminished mitochondrial biogenesis in aged rats, indicating that AMPK activity reduces with aging and that it may be an essential causative factor in mitochondrial dysfunction during aging [59]

NAD+-dependent deacetylases sirtuins (SIRTs) modulate PGC-1α levels in muscles in response to diet and exercise. Among SITRs involved in muscle maintenance, SIRT3 (mitochondrial) expression was lower with sedentary-aged individuals but equally increased despite age in trained individuals [60]. SIRT3 acts downstream to PGC-1α to promote mitochondrial biogenesis and reduced ROS production in muscle cells (Kong et al., 2010). Lagouge M et al. reported that pharmacological activation of SIRT1-PGC-1α path improves mitochondrial biogenesis and protects against metabolic diseases in muscles [61]. In 2013, an alternate PGC-1α/β-independent pathway of nuclear-mitochondrial communication that is induced by a drop in NAD(+) and the build-up of hypoxia-inducible factor 1α (HIF-1α) negatively affected mitochondrial function with age [62]. Further, raising NAD+ levels with poly (ADP-ribose) polymerase (PARP) inhibitor guarding against muscle dysfunction provoked by mitochondrial dysfunction [63]. Insulin-like growth factor 1 (IGF-1)/ATP citrate lyase (ACL) is another pathway regulating mitochondrial metabolism in aging. In aged mice skeletal muscles, ACL activity is decreased, and improved ACL levels stimulate ETC activity and oxygen usage, which suggests that age-induced reductions in IGF-1 concentrations may impair mitochondrial ETC activity via ACL [64]. Das et al. proposed activation of the IGF-1/ACL pathway in muscles attenuated mitochondrial dysfunction and sarcopenia [65]. PGC-1 -mediated degradation of proteins through autophagic-lysosomal and the ubiquitin-proteasome system is one of the critical signalling paths in controlling mitochondrial function and sarcopenia. Both isoforms namely PGC-1α and β prevented protein degradation and muscle wasting via blocking the expression of forkhead box O3 (FoxO3) and nuclear factor κB (NF-κB) targets [52]. Since muscle wasting in aging is one the potential factor that needs therapeutic attention to improve aging experience [66].

## PROTEOSTASIS OF MITOCHONDRIA AND SARCOPENIA

A team of experts at Geroscience Initiative identified seven extremely interdependent “pillars of aging” that are crucial for evaluating and attending the process of aging [67]. Proteostasis was one of the seven pillars of aging classified. Relatively mitochondrial protein homeostasis considered one of the critical mechanism to maintain the functional integrity of the mitochondrial proteome during normal and disease conditions. Proteostasis of mitochondria involves turn-over of proteins, deterioration of mutated, misfolded or oxidized proteins. The degradation and functioning of mitochondrial proteostasis require allocation of mitoproteases (mitochondrial) and ubiquitin-proteasome system (UPS) [68]. Latest advancements in mitochondrial biology reported the occurrence of proteolytic enzymes called mitoprotease. Mitoprotease modulates mitochondrial function, biochemical activities including

the maturation of proteins imported from outside of mitochondria, the housekeeping of protein quality via degrading damaged proteins and the control of mitochondrial gene expression and biogenesis by regulating essential targets of these pathways [69]. A group of nine individual mitoprotease identified so far and classified based on their structure and locality within mitochondria [69]. Four ATP-dependent proteases (Intermembrane ATPases associated with diverse cellular activities (AAA) protease (iAAA protease), matrix AAA (mAAA) protease, Lon protease homologue (LONP) and ATP-dependent Clp protease proteolytic subunit (ClpP), two ATP-independent (mitochondrial inner membrane protease Atp23 homologue (ATP23) and Ser protease HTRA2 and/or OMI) and oligopeptidases (presequence protease PITRM1 and/or HPREP and mitochondrial oligopeptidase M MEP and/or neurolysin) currently known [69]. A mitoprotease-mediated quality check is the first line of resistance against any damage and requires the degradation of non-assembled proteins that result from mitonuclear irregularity and proteins that are misfolded or damaged as a result of stress [69]. Protein turnover inside the mitochondrial matrix mediated by Lon, ClpP, and m-AAA [70]. The membrane-bound i-AAA, Yme1L1, OMA1 and presenilins-associated rhomboid-like protein (PARL) guarantees protein quality at inter-membrane space [69]. Relatively mitochondrial protein homeostasis considered one of the critical mechanism to maintain the functional integrity of the mitochondrial proteome during normal and disease conditions. Recent discoveries demonstrated that LonP expression and activity dropped with age and improving LonP expression levels provided immunity over oxidative stress and aging [71]. Lack of Htra2 /Omi provoked pre-mature aging of mice characterized by raised activity in clonal expansion of mitochondrial DNA (mtDNA) deletions [72]. Numerous studies reported that absence of certain mitoproteases including AGF3L2, ClpP, and PARL could create mitochondrial dysfunction which eventually affected the lifespan of mice which experienced cachexia [73-75]. Moreover, Single nucleotide polymorphism of gene AGF3L2 associated with improved cognitive abilities and longevity of aged cohorts [76]. Taken, together, the above-discussed discoveries imply that mitoproteases play a crucial role in the aging process.

## MITOPHAGY AND SARCOPENIA

Macroautophagy or autophagy means an evolutionarily conserved degradative process that aids in protein degradation and removal of cellular debris via autophagosomes [77-79]. Autolysosomes are formed when autophagosomes fuse with lysosomes, where the encapsulated material degraded. Mitophagy was first reported by Rodriguez-Enriquez et al. and said the presence of depolarised mitochondria colocalized with lysosomes expressing GFP-LC3-positive autophagosomes and coined the term 'mitophagy.' Rodriguez-Enriquez et al. describe mitophagy as a selective degradative process for mitochondrial proteins only [80]. Several studies aimed to explore the relationship of autophagy and aging in various experimental models. In 2003, Del Roso A et al. observed reduced macroautophagy in aged rats [81]. Enhanced autophagy in mice shown to improve life-span [82]. Pharmacological activation of mitophagy in aged mouse demonstrated enhanced mediators of mitochondrial quality control including PGC1α, SIRT3, Parkin, and BCL2 interacting Protein 3 (BNIP3) [83]. Sustained activation of mammalian rapamycin complex 1 (mTORC1) targets and perturbed mitophagy regulators has been seen in skeletal muscles of old mice undergone fasting [84].

Similarly, age-related increases in sarcoplasmic reticulum stress possibly linked to diminished autophagy as evidenced by LC3II/I conversion ratio [85]. Impaired mitogenesis, poor functioning of mitochondria and decline in muscle mass and strength witnessed in the aged population [26]. Further, investigatory study point that impaired mitochondrial fusion and mitophagy correlated with sarcopenia in hip fractured seniors [40]. A significant notice that absence of fusion protein mitofusin-2 (Mfn2) ties age-related sarcopenia and undermined autophagy to activation of an adaptive mitophagy pathway [86]. Impaired autophagy triggers the accumulation of cellular wastes, and excessive functioning brings stress and catabolic activity of the cell. For example, deletion of PTEN-induced putative kinase 1 (PINK1) and Parkin, critical players of mitophagy causes mitochondrial dysfunction and muscle degeneration [87]. Deletion of AMPK in muscles alone demonstrated muscle weakness and mitochondrial dysfunction [88].

A continued presence of mTORC1 produces late-onset myopathy related to impaired autophagy with dysfunctional mitochondria in skeletal muscle [89]. In rats, Cui et al. demonstrated that calorie restriction improves senescence markers, increased mitophagy, and less mitochondrial degeneration [90]. Very recently, in muscle stem cells, it has been reported that during aging mitophagy is damaged [91]. These observations open roads for therapeutic approaches aimed toward autophagy-related muscle diseases.

## MITOCHONDRIAL NETWORK AND SARCOPENIA

Mitochondria frequently shift appearance during the coupled motions fission and fusion, sometimes travel

along cytoskeletal courses. Fission and Fusion (F&F) determine the length and the extent of the mitochondrial network and are affected by cellular environment, metabolic stress and pathological status of the mitochondria. Mitochondrial fusion and fission processes are well-known for genetic complementation, organelle function, and proper sorting of newly manufactured mitochondria in splitting cells.

Mitochondrial fusion provides interconnected organelles through assuring mtDNA associating within the artery, blocking focal deposition of mutant mtDNA and shielding mtDNA integrity [31]. Rearrangements and reshaping of mitochondria play notable roles in mitophagy and apoptosis. Pieces of evidence support the notion that misshaped mitochondrial network in muscle cells often associated with aging [86]. The abnormal network of mitochondria is tightly governed by Mfn1 and Mfn2, optic atrophy protein 1 (Opa1), dynamin-related protein 1 (Drp1), and fission protein 1 (Fis1) [26, 92]. It has recently been shown that the expression of Drp1 and Mfn2 transcripts are reduced in aged muscle [92]. Disturbed expression levels of Fis1 displayed abnormal mitochondria, exaggerated expression of the same gene prevented cell senescence [93, 94]. In addition, declined protein levels of Mfn2 observed in muscles from old hip-fractured patients with sarcopenia [40]. Current discoveries propose an unusual connection among aging, muscle atrophy, and mitochondrial dynamics. However, in humans, further investigations are required to understand the complexity of molecular pathways involved in mitochondrial quality control and sarcopenia.

## Clinical Importance derived from Mitochondrial Quality Control for Sarcopenia

The discovery of novel roles of mitochondrial quality control, including mitoproteases may have sustainable clinical outcomes for sarcopenia. Some of the pharmaceutical drugs which are under process of clearing clinical approval are stated in Table 1. There are chances to consider clinical applications of anti-atrophy drugs to treat elderly peoples. Use of angiotensin-converting enzyme (ACE) inhibitors including perindopril improved muscle strength and walking speed in 641 aging disabled women as well as 130 older adults [95-97]. In 2011, Burks TN et al. reported that losartan, angiotensin II receptor antagonist, repairs skeletal muscle remodeling and guards against disuse atrophy in sarcopenic mice model [98]. Currently, clinical trial titled, "A Study of Muscle Strength Maintenance in Older Adults under the supervision of Jeremy Walston from Johns Hopkins University undergoing that evaluating the effects of losartan. A clinical trial testing the effectiveness of metformin in blocking the progress of sarcopenia in older adults with prediabetes might bring enlightenment to the current scenario. Investigations in mice have shown shrinkage in proteolysis and muscle atrophy with the use of rosiglitazone [99, 100].

**Table 1: Future Pharmacological Therapeutic of Sarcopenia**: In the below table a list of future pharmacological therapeutic drugs to treat Sarcopenia are stated. The molecular component and brand names of the drugs are listed. ActRIIB – Activin receptor type – 2B, AT2R – Angiotensin type 2 receptor, GH – Growth Hormone, PPAR-gamma – Peroxisome proliferator-activated receptor gamma; NSAID – Non-steroidal anti-inflammatory drugs; AICAR – 5-Amino imidazole-4-carboxamide ribonucleotide:

| S.No | Pharmacological drugs of Sarcopenia | Clinical Trails |
|---|---|---|
| 1. | Unsaturated fatty acids-Omega-3 | Phase I |
| 2. | Anabolic steroid- MK-0773 | Phase II |
| 3. | Antibody (ActRIIB) -BYM338 (Bimagrumab) | Phase II |
| 4. | Antibody (myostatin) - REGN1033 (SAR391786) | Phase II |
| 5. | AT2R antagonist -Losartan | Phase II |
| 6. | Estrogen synthesis inhibition - Anastrozole | Phase II |
| 7. | Hunger hormone - Ghrelin | Phase II |
| 8. | Medical food mixture-AN777 | Phase III |
| 9. | GH releasing peptide -MK-677 | Phase III |
| 10. | Androgen precursor - Dehydroepiandrosterone | Phase III |
| 11. | PPAR-γ agonist - Pioglitazone (Actos) | Phase IV |
| 12. | Cationic ammonium compound - Cetylpyridinium chloride | Investigator trials |
| 13. | NSAID - Acetaminophen | Investigator trials |
| 14. | Ursolic Acid | Pre-clinical studies |
| 15. | Proteasome Inhibitors- Bortezomib | Pre-clinical studies |
| 16. | Cyclophilin D Inhibitor- Debio-025 | Pre-clinical studies |
| 17. | AICAR | Pre-clinical studies |

Xanthine oxidase inhibitor such as allopurinol able to counter muscle atrophy or even sarcopenia. Medication with allopurinol in rats with extremities suspended for 14 days prevented the atrophy of the soleus [101]. More recently, Beveridge et al. reported allopurinol treatment showed greater functional gains in older rehabilitation patients [102]. Just recently, Fujii, Miyashita, et al. demonstrated that 100 weeks old mice treated with 5-aminolevulinic acid (ALA) stimulated muscle mitochondria, improved muscle mass by the increase of branched-chain amino acids (BCAAs) contents, enhanced muscle strength and endurance [103]. Other treatments for sarcopenia also includes testosterone, growth hormone, dehydroepiandrosterone (DHEA) and myostatin-associated drugs, that are known

to improve muscle strength and mass in aged individuals [104].

In 2014, deubiquitinase USP30 inhibitor was recommended to treat Parkinson disease, since USP30 inhibitors can promote mitophagy, improve mitochondrial network via fusion and increases oxidative respiration in mice deficient of mitofusins [105]. There are also circumstances in which the clinical applications can be based on the restoration of the activity of mitoproteases that are modulated in certain pathologies, including many hereditary diseases of mitochondrial proteolysis [106-108]. Mitochondrial dysfunctions caused by excess ROS are present in few neurodegenerative disorders. Moreover, the excess damage mediated by reactive oxygen species that is observed in some neurodegenerative disorders can be neutralized by antioxidants like Vitamin E or N- acetylcysteine [109]. In the case of proteolytic alterations in cancer, the increased levels of some mitoproteases that have been observed in certain tumours suggests a need for inhibition-based therapies. Mitochondrial fission has been found to be amplified in some neurodegenerative diseases, hence of mitochondrial fission inhibitors may retain hope as therapeutic targets to treat patients with neurodegenerative diseases such as Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD) and Amyotrophic Lateral Sclerosis (ALS) [110]. Over the last 5 years inhibitors of mitochondrial fission discovered namely Mdivi [111], P110 [112], and Dynasore [113], which provided healthy mitochondrial function in neurons affected by AD, HD, and PD [110].

The identity, validation, and application of therapeutics to prevent age-associated muscle loss seem far away. Although scientifically we made progress in claiming some of the pathological conditions associated with sarcopenia, there is a need for better and simple therapeutics. Till today, the physiological conditions that appear first and the molecular triggers of muscle loss in aging are poorly understood. All the discoveries made so far demonstrate a central role for mitochondrial degeneration in age-related muscle atrophy. It will be critical to obtain more perceptions about the relationship between the function and dysfunction of MQC paths to acknowledge these effects in human diseases. It is understood that mitochondria can initiate and maintain sarcopenia. Currently, MQC have been identified to build direct or indirect connections with other cellular components (e.g. endoplasmic reticulum, peroxisomes, and lysosomes/vacuoles) as well as the extracellular environment through mitochondria-derived vesicles secretion. However, the beneficial importance of these inner-communications in muscle physiology is not yet fully appreciated and poses an obstacle in the progression. In fact, the metabolites generated in mitochondria can travel within the cell, investigating the connection between metabolic functions of muscle mass and MQC might provide new strategies to devise precautionary and healing mediations against muscle aging. Further, clinical studies needed to test whether exercise and nutrition might be useful to improve MQC and overcome sarcopenia in aged individuals. Targeting dysfunctional mitochondria and increasing healthy mitochondria muscle tissues provide the best strategy for reducing sarcopenia.

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