The role of mitochondria in the pathogenesis of sarcopenia: a concise review

Chiara Greggi[1], Umberto Tarantino[1,2]

[1] Department of Clinical Sciences and Translational Medicine, University of Rome "Tor Vergata", Rome, Italy
[2] Department of Orthopaedics and Traumatology, "Policlinico Tor Vergata" Foundation, Rome, Italy

ABSTRACT

The aging process results in progressive loss of muscle mass and strength, a condition known as sarcopenia. At biological-molecular level, this condition is characterized by numerous changes that occur in the muscle cell, such as increased protein degradation, apoptosis, altered autophagy process, impaired myogenic pathway, and mitochondrial dysfunction. The purpose of this concise review is to provide a brief overview of the involvement of mitochondria in the pathogenesis of sarcopenia, highlighting the potential involvement of carnitine palmitoyl transferase 1, an enzyme localized in the outer mitochondrial membrane, involved in the transport of long-chain fatty acids into the mitochondrion for β-oxidation. This protein is a potential new player in the pathogenesis of sarcopenia, since it may be responsible for the accumulation of fat mass and the development of insulin resistance in the muscle tissue of affected subjects, thus suggesting a new pathway underlying the onset and progression of the disease.

KEYWORDS

Sarcopenia, mitochondria, muscle, mitochondrial dysfunction, energy metabolism.

Biological-molecular aspects of sarcopenia

Skeletal muscle is a highly plastic tissue that can adapt its mass, structure, and metabolic capacity in response to changes in mechanical loading [1]. During aging, skeletal muscle exhibits a progressive loss of mass, strength, and function, which collectively is termed sarcopenia, a condition that can increase the risk of frailty and morbidity, and result in an overall worsening of the quality of life [2]. This loss of muscle mass and strength and concomitant increase in body fat are physiological phenomena that occur in older adults, partly as a consequence of metabolic changes associated with a sedentary lifestyle [3]. This condition is characterized by atrophy and loss of muscle fibers, caused by a state of chronic inflammation that leads to protein degradation, apoptosis, impaired autophagy, and decreased myogenic potential [4]. In addition, profound metabolic changes occur in myofibers during aging, including mitochondrial dysfunction that contributes to altered cellular anabolism and reduced contractile force generation, leading to loss of muscle mass and strength [5]. Bone-muscle crosstalk is considered an important element in the pathophysiology of sarcopenia [6]. Indeed, there are numerous molecules that play a role in both the maintenance of bone and muscle tissue homeostasis. Among them, emerging evidence points to the involvement of bone morphogenetic proteins (BMPs), members of the transforming growth factor-β (TGF-β) family, which orchestrate various biological processes related to cell proliferation, differentiation, morphogenesis, homeostasis, and regeneration [7]. It has recently been shown that molecular pathways involving BMPs also play a role in the control of satellite cell function [8]. Indeed, a close association was found between the expression of BMP-2, BMP-4, and BMP-7 and satellite cell activity, in particular, between the expression of BMPs and the number of myogenin and CD44-positive satellite cells [9]. In addition, BMP expression can induce satellite cells to differentiate into osteoblasts, contributing to important pathophysiological phenomena such as fracture healing: under stimulation of BMPs, muscle cells located near bone fracture sites are able to provide osteoprogenitor cells in cases where the periosteum is unable to efficiently provide for this need, and furthermore, muscle osteoprogenitors appear to possess osteogenic potential similar to that of periosteum-derived cells [10]. Thus, the cellular and molecular impairment that occurs in sarcopenic muscle tissue also contributes to delayed fracture healing [9]. Other potential regulatory factors of sarcopenia include myostatin. This protein is also a member of the TGF-β superfamily, and it acts as a potent negative regulator of skeletal muscle growth: in fact, *in vitro* experiments have shown that myostatin blocks the proliferation of myoblasts and satellite cells by upregulating the MyoD gene, competing for binding to the BMP receptors and impairing muscle regeneration [11]. Thus, the balance between myostatin and BMPs-mediated signaling strongly influences muscle quality [9]. Among the myokines that have gained popularity as potential biomarkers of sarcopenia there is irisin, a

Article history
Received 20 Mar 2023 – Accepted 19 May 2023

Contact
Chiara Greggi; chiara.greggi@gmail.com
Department of Clinical Sciences and Translational Medicine, University of Rome "Tor Vergata", Rome, Italy

hormone-like myokine produced in abundance by skeletal muscle in response to exercise, in both mice and humans [12]. This myokine has recently been shown to affect skeletal metabolism *in vivo*: mice with induced hind limb atrophy, when treated with recombinant irisin, showed improvements in cortical bone mass, geometry, and bone tissue strength. In the same mice, treatment with recombinant irisin resulted in protection against muscle mass decline, as shown by the maintenance of muscle fiber cross-sectional area. These data reveal for the first time that this molecule can mediate the recovery of bone mass loss induced by muscle disuse and atrophy [13,14].

Mitochondrial dysfunction and sarcopenia

The pathophysiological mechanisms that contribute to the onset of frailty and sarcopenia represent the hallmarks of aging and encompass numerous biological processes including maintenance of genomic and epigenetic stability, autophagy, cellular senescence, intracellular signaling, regulation of intra- and extracellular mechanical properties, microbiome homeostasis, and mitochondrial activity [15]. Indeed, mitochondria play a key role in several key cellular processes including energy production, calcium-mediated pathways, reactive oxygen species (ROS) generation, and cell death. Dysregulation of any of these processes can affect the quantity and/or quality of mitochondria and, potentially, trigger a cascade of damaging events within the cell [16]. Such events are what occur in the case of aging skeletal muscle, where a chronic increase in oxidative stress over time can cause cumulative and irreversible damage to mitochondrial proteins, lipids, and nucleic acids [17]. The role of mitochondrial abnormalities and oxidative stress in the etiology of sarcopenia has been extensively characterized. The "mitochondrial theory of aging" states that the aging proce

ss is modulated by toxicity due to ROS, leading to mitochondrial DNA (mtDNA) deletions and mutations, macromolecular oxidation, electron transport chain (ETC) dysfunction, senescence, and cell death [18]. In fact, muscle tissue from older adults shows: (1) increased abnormalities in the mitochondrial ETC, (2) the accumulation of fibers negative for cytochrome c oxidase and positive for succinate dehydrogenase, (3) increased expression of oxidative stress markers, (4) accumulation of somatic mtDNA mutations, and (5) gene transcription indicative of mitochondrial dysfunction [3]. Several studies in the literature have also shown that with aging, there is a decrease in mitochondrial protein synthesis and a decrease in adenosine triphosphate (ATP) production in muscle tissue [19]. Indeed, the impact of mitochondrial bioenergetic decline on muscle aging is shown by the existence of a correlation between ATP synthesis/O_2 consumption and walking speed in healthy elderly people [20]. Another mechanism linking mitochondrial dysfunction to sarcopenia is the possible impact of ATP deficiency on protein synthesis, which is reflected in the concomitant decrease in the body's bioenergetics and muscle protein anabolism in the course of aging [21]. The bioenergetic decline of aged muscle could thus be the result of a vicious cycle involving oxidant production, mtDNA damage and depletion, and a defective mitochondrial quality control system [20]. The increased mitochondrial oxidative stress is assumed to be necessary to stimulate muscle protein degradation by activating autophagy mediated by lysosomes and the ubiquitin-proteasome system; also, energetic stress, i.e., reduced ATP production, may activate the adenosine monophosphate protein kinase (AMPK)-FoxO3 pathway, leading to increased protein degradation [22,23]. According to recent evidence, overexpression of peroxisome proliferator gamma coactivator 1 (PGC-1α), a key factor in mitochondrial biogenesis, may also protect muscle mass from acute atrophy due to immobilization or disuse, but it has also been reported that overexpression of this factor in muscle tissue can result in uncoupling of cellular respiration, leading to a decrease in ATP synthesis, and thus to a state of atrophy, especially of muscles rich in type 2 fibers [24]. Taken together, this body of evidence suggests a central role of mitochondrial energy metabolism in the regulation of muscle mass, and therefore possibly in the recovery of muscle mass after a period of disuse [2]. It is also notable that loss of mitochondrial function can be partially reversed by exercise [25]. Mitochondria can adapt to changes in the cell's energy requirements by adjusting their size and distribution. Even a single exercise can stimulate changes in mitochondrial morphology [26]. Indeed, early studies investigating changes in mitochondrial morphology showed that type I muscle fibers contain a mitochondrial pool with higher fusion rates than those found in type II muscle fibers [27]. Regular exercise may indeed result in a shift in the mitochondrial morphological profile toward that of an oxidative type muscle fiber [28] (Table I). In accordance with the literature, therefore, aging is primarily responsible for increased levels of oxidative stress and ROS production; this in turn leads to the occurrence of cellular damage, such as oxidation of macromolecules, DNA damage, triggering of apoptosis, and mitochondrial dysfunction. As mentioned above, alteration of the morphology and function of mitochondria results in a consequent and inevitable decrease in the amount of intracellular ATP, which is one of the main features of a senescent cell. Accordingly, as some studies report, mitochondrial dysfunction may in fact contribute to the onset of a senescent cell phenotype, due to damage to the ETC, which in turn causes increased superoxide anion and hydrogen peroxide production, AMP/ATP ratios, release of mitochondrial damage-associated molecular patterns, and reduced NAD+/NADH ratios. These changes have been shown to contribute to both senescent cell cycle arrest and senescent-associated secretory phenotype regulation via multiple signaling pathways [29]. Therefore, the reduction in ATP levels typical of a senescent cell and brought about by mitochondrial dysfunction could potentially be responsible for the reduction in muscle protein anabolism, which is followed by reduction in muscle contractile activity, resulting in the onset of muscle atrophy and sarcopenia (Figure 1).

Carnitine palmitoyl transferase 1 (CPT1)

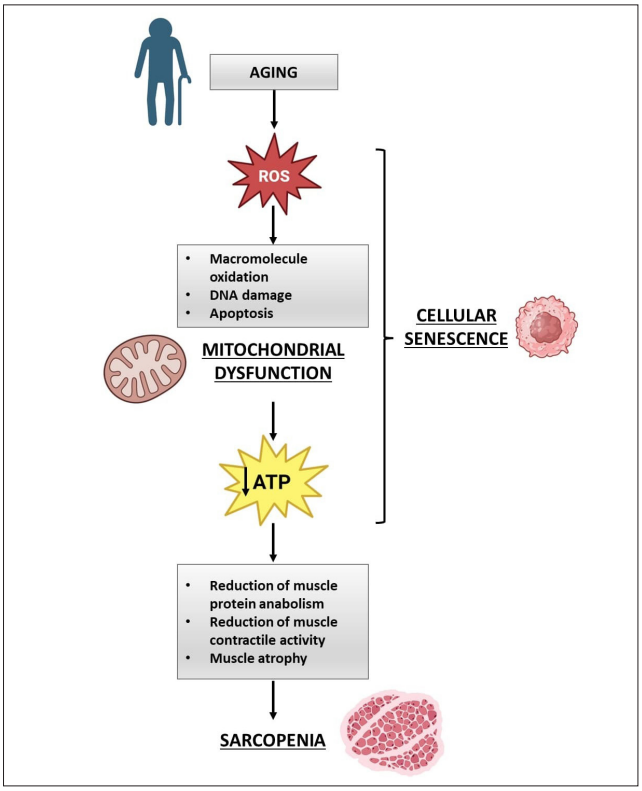
Carnitine palmitoyl transferase 1 (CPT1) resides in the outer mitochondrial membrane and is involved in intracellular regulation of metabolism by transporting long-chain fatty acids into the mitochondria for β-oxidation [30].

Table I *In vivo* and *in vitro* studies exploring the correlation between mitochondrial dysfunctions, CPT1 and sarcopenia.

STUDIES	MODEL	METHODS	OUTCOME	REFERENCE
In vivo	Mouse	Transgenic mice expressing a proofreading-deficient version of mtDNA polymerase gamma, characterized by a high rate of mitochondrial mutations	Transgenic model exhibited elevated mtDNA mutation rates, mitochondrial dysfunction, and premature aging; muscles from mtDNA mutator mice also showed higher levels of mitochondrial fission and autophagy, which contribute to the sarcopenic phenotype.	17
	Human	Measurement of mitochondrial protein synthesis rate in needle biopsy skeletal muscle samples, from subjects aged 20-92 years	A decline in the rate of mitochondrial protein synthesis in skeletal muscle of older subjects was observed, associated with a decrease in skeletal muscle oxidative capacity and mitochondrial function.	19
	Mouse	CD1 mice; muscle atrophy was induced by denervation or fasting	A disorganized mitochondrial network was observed in atrophic muscles; activation of AMPK results in remodeling of the mitochondrial network, contributing to muscle atrophy, also through activation of FoxO3.	22
	Mouse	D-line mice expressing 10-fold higher PGC-1α mRNA and E-line mice expressing 13-fold higher PGC-1α mRNA in skeletal muscle	Muscle tissue of transgenic mice showed increased energy expenditure, uncoupling of oxidative phosphorylation, and decreased ATP content.	24
	Mouse	In vivo electrotransfer technology to express, in tibialis anterior of male C57BL/6J mice, a mutated CPT1 form (CPTmt)	The muscle of mice expressing CPTmt was characterized by an increased percentage of oxidative fibers, higher glycogen content, increased muscle capillarity, and increased resistance to fatigue.	35
	Human	Metabolomic analysis of plasma samples obtained from hip fracture patients of both sexes undergoing surgery	Metabolite set enrichment analysis showed CPT deficiency in sarcopenic subjects compared with non-sarcopenic subjects.	41
In vitro	Cell culture	Transient transfection on HEK293 FT, MEF cells and C2C12 myogenic cell line	AMPK activation upregulated FoxO3 expression, inducing expression of atrophy-related genes, mitochondria alteration and protein breakdown.	22

mtDNA: mitochondrial DNA; **PGC-1α**: peroxisome proliferator gamma coactivator 1; **mRNA**: messenger RNA; **ATP**: adenosine triphosphate; **AMPK**: adenosine monophosphate protein kinase; **FoxO3**: Forkhead box O3; **CPTmt**: mutated CPT.

Figure 1 Possible correlation between mitochondrial dysfunction, cellular senescence, and sarcopenia.



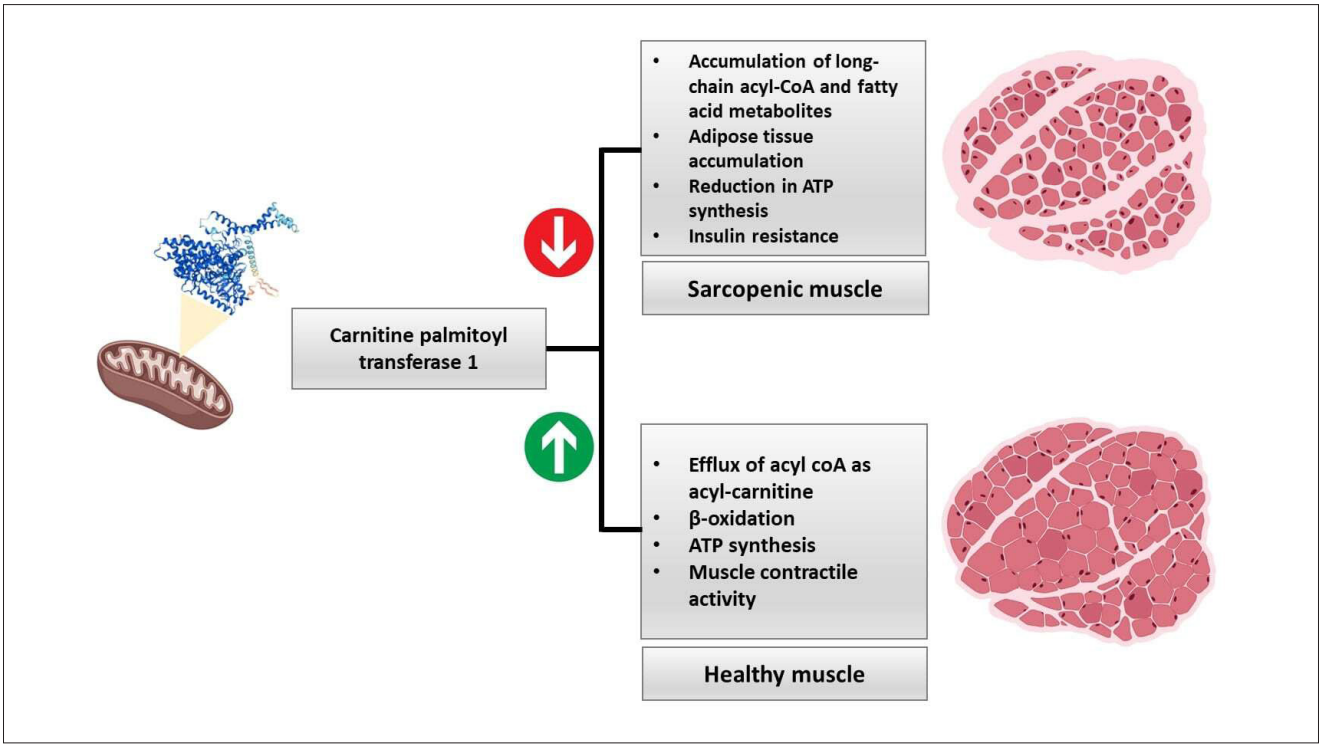
Three different proteins belonging to the CPT1 family have been identified: CPT1A (or L-CPT1), CPT1B (or M-CPT1), and the most recently described variant, CPT1-C. While CPT1B is expressed only in brown adipose tissue, muscle, and heart, and CPT1C in the endoplasmic reticulum of neurons, CPT1A shows broader expression, and is found to be more localized in liver, pancreas, kidney, brain, blood, and embryonic tissues [31]. Compared with the muscle protein CPT1B, CPT1A shows higher affinity for its substrate (carnitine) and lower affinity for the physiological inhibitor malonyl-CoA [32]. In recent years, CPT1A has generally been studied in correlation with several types of cancer, particularly breast and liver cancer, but according to recent evidence, this protein may be involved in the dysregulation of bone metabolism underlying the onset of osteoporosis [31]. Several studies have indeed identified many genetic loci associated with osteoporosis, but the functional mechanisms underlying these associations have rarely been investigated. In this regard, Liu *et al*. performed integrative analyses, using publicly available databases and resources. In their study, 128 single nucleotide polymorphisms (SNPs) associated with osteoporosis were analyzed: among them, 8 SNPs exert cis-regulatory effects on 11 target genes, and 2 SNPs in particular (RPL31 rs2278729 and LRP5 rs3736228) were confirmed to affect the expression of three genes, including CPT1A, which were differentially expressed in human subjects characterized by high and low bone mineral density (BMD) [33]. From the numerous studies in the literature, moreover, it is

known that osteoporotic patients also suffering from muscular atrophy are characterized by a greater amount of adipose tissue: in these subjects, given their inability to perform physical activity, lean mass is progressively replaced by fat mass, thus suggesting a potential involvement of CPT1 in the pathogenesis of sarcopenia [34]. β-oxidation of fatty acids is the main source of energy for muscle, especially during the performance of endurance and high-intensity physical activity, so CPT1 plays a key role in this context. Accordingly, the study by Hénique *et al*., highlights precisely how CPT1 represents a key regulatory enzyme of muscle energy metabolism, as mice transgenic for a mutated form of CPT, active but insensitive to its physiological inhibitor, were characterized by muscle remodeling. In fact, the muscle of these mice showed an increased percentage of oxidative fibers (+28%), higher glycogen content, increased muscle capillarity, and, overall, increased resistance to fatigue [35]. Carnitine is an amine obtained mainly from meat or dairy products or synthesized from lysine and methionine in the liver or kidney [36]. More than 95% of the body's total carnitine is stored within skeletal muscle as free or acyl carnitine [37]. Carnitine plays an essential role in energy metabolism because it serves as a substrate for CPT1, mediating the transport of long-chain fatty acids into the mitochondrial matrix for β-oxidation [38]. According to some clinical studies, carnitine treatment improved insulin sensitivity in patients with obesity and diabetes, enhancing mitochondrial function by promoting the influx of fatty acids for oxidation and the efflux of long-chain coenzyme A (acyl-CoA) from the mitochondria as acyl-carnitine [38,39]. This prevented the accumulation of long-chain acyl-CoA and other fatty acid metabolites intracellularly, a phenomenon that impairs insulin signaling and contributes to the development of insulin resistance in skeletal muscle [40]. In agreement with previous studies, Marques and colleagues, in an interesting study, suggest a link between mitochondrial dysfunction and sarcopenia, having identified a correlation between disease severity and long-chain fatty acid levels. In addition, metabolomic analysis showed a deficiency of CPT in sarcopenic patients compared with healthy subjects, suggesting a potential new pathway involved in the onset of sarcopenia, with a primary role played by CPT1 [41] (Table I).

Discussion and conclusion

The aging process is characterized by loss of muscle tissue mass, strength, and function, collectively identified as sarcopenia, a condition that can increase the risk of frailty and morbidity, and result in an overall worsening of the quality of life of those affected [42]. This condition results in a number of cellular changes, such as reduced protein synthesis, apoptosis, impaired autophagy, and reduced myogenic potential, which together result in muscle fiber atrophy [43]. During the aging process, muscle cells are also characterized by dysregulation of mitochondrial activity, which contributes to altered cellular anabolism and reduced contractile force generation, thus leading to loss of muscle mass and strength [18]. In fact, mitochondria play a key role in several physiological processes not strictly related to energy metabolism alone, dysregulation of which can trigger a number of damaging events within the cell [44]. CPT1, a protein residing in the outer mitochondrial membrane and involved in the intracellular regulation of metabolism, transports long-chain fatty acids into the mitochondria for β-oxidation, thus playing a primary role in the regulation of energy metabolism [31]. Studies in the literature have shown that this protein may

Figure 2 Potential involvement of CPT1 in the pathogenesis of sarcopenia.



potentially be involved in the onset of osteoporosis, its expression being correlated with BMD levels, but its possible role in the pathogenesis of sarcopenia has not been excluded. First, it has been reported that treatment with carnitine, a substrate of CPT1, appears to enhance mitochondrial activity, preventing the accumulation of long-chain acyl-CoA and other fatty acid metabolites intracellularly, a phenomenon that contributes to the development of insulin resistance in skeletal muscle [38,39]. This finding suggests that possible dysregulation of CPT1 may potentially be involved in the progressive replacement of lean mass by fat mass, a phenomenon typically observed in sarcopenic subjects (Figure 2). Indeed, in agreement with these studies, a correlation between elevated levels of long-chain fatty acids and degree of disease severity in sarcopenic patients has recently been identified, concomitant with CPT deficiency in these subjects [41]. Therefore, mitochondrial dysfunction represents not only potential new molecular pathways underlying the onset and progression of sarcopenia, but also a field to be further investigated in order to identify potential new diagnostic markers or therapeutic targets, which may allow early diagnosis and targeted treatment of this disease.

References

1. Guimarães-Ferreira L, Nicastro H, Wilson J, Zanchi NE. Skeletal muscle physiology. ScientificWorldJournal. 2013;2013:782352.
2. Zhang X, Trevino MB, Wang M, et al. Impaired mitochondrial energetics characterize poor early recovery of muscle mass following hind limb unloading in old mice. J Gerontol A Biol Sci Med Sci. 2018;73(10):1313-22.
3. Safdar A, Hamadeh MJ, Kaczor JJ, Raha S, Debeer J, Tarnopolsky MA. Aberrant mitochondrial homeostasis in the skeletal muscle of sedentary older adults. PLoS One. 2010;5(5):e10778.
4. Bonaldo P, Sandri M. Cellular and molecular mechanisms of muscle atrophy. Dis Model Mech. 2013;6(1):25-39.
5. Tarantino U, Scimeca M. Bone morphogenetic proteins, satellite cells, and sarcopenia: perspective in translational medicine. J Gerontol A Biol Sci Med Sci. 2018;73(12):1591-3.
6. Tarantino U, Greggi C, Visconti VV, et al. Sarcopenia and bone health: new acquisitions for a firm liaison. Ther Adv Musculoskelet Dis. 2022;14:1759720X221138354.
7. Rahman MS, Akhtar N, Jamil HM, Banik RS, Asaduzzaman SM. TGF-β/BMP signaling and other molecular events: regulation of osteoblastogenesis and bone formation. Bone Res. 2015;3:15005.
8. Friedrichs M, Wirsdöerfer F, Flohé SB, Schneider S, Wuelling M, Vortkamp A. BMP signaling balances proliferation and differentiation of muscle satellite cell descendants. BMC Cell Biol. 2011;12:26.
9. Scimeca M, Piccirilli E, Mastrangeli F, et al. Bone morphogenetic proteins and myostatin pathways: key mediator of human sarcopenia. J Transl Med. 2017;15(1):34.
10. Beederman M, Lamplot JD, Nan G, et al. BMP signaling in mesenchymal stem cell differentiation and bone formation. J Biomed Sci Eng. 2013;6(8A):32-52.
11. Baczek J, Silkiewicz M, Wojszel ZB. Myostatin as a biomarker of muscle wasting and other pathologies-state of the art and knowledge gaps. Nutrients. 2020;12(8):2401.
12. Colaianni G, Cinti S, Colucci S, Grano M. Irisin and musculoskeletal health. Ann N Y Acad Sci. 2017;1402(1):5-9.
13. Colaianni G, Mongelli T, Colucci S, Cinti S, Grano M. Crosstalk between muscle and bone via the muscle-myokine irisin. Curr Osteoporos Rep. 2016;14(4):132-7.
14. Colaianni G, Mongelli T, Cuscito C, et al. Irisin prevents and restores bone loss and muscle atrophy in hind-limb suspended mice. Sci Rep. 2017;7(1):2811.
15. Picca A, Calvani R, Coelho-Júnior HJ, Marini F, Landi F, Marzetti E. Circulating inflammatory, mitochondrial dysfunction, and senescence-related markers in older adults with physical frailty and sarcopenia: a BIOSPHERE exploratory study. Int J Mol Sci. 2022;23(22):14006.
16. Kausar S, Wang F, Cui H. The role of mitochondria in reactive oxygen species generation and its implications for neurodegenerative diseases. Cells. 2018;7(12):274.
17. Joseph A-M, Adhihetty PJ, Wawrzyniak NR, et al. Dysregulation of mitochondrial quality control processes contribute to sarcopenia in a mouse model of premature aging. PLoS One. 2013;8(7):e69327.
18. Calvani R, Joseph AM, Adhihetty PJ, et al. Mitochondrial pathways in sarcopenia of aging and disuse muscle atrophy. Biol Chem. 2013;394(3):393-414.
19. Rooyackers OE, Adey DB, Ades PA, Nair KS. Effect of age on in vivo rates of mitochondrial protein synthesis in human skeletal muscle. Proc Natl Acad Sci U S A. 1996;93(26):15364-9.
20. Marzetti E, Calvani R, Cesari M, et al. Mitochondrial dysfunction and sarcopenia of aging: from signaling pathways to clinical trials. Int J Biochem Cell Biol. 2013;45(10):2288-301.
21. Paez HG, Pitzer CR, Alway SE. Age-related dysfunction in proteostasis and cellular quality control in the development of sarcopenia. Cells. 2023;12(2):249.
22. Romanello V, Guadagnin E, Gomes L, et al. Mitochondrial fission and remodelling contributes to muscle atrophy. EMBO J. 2010;29(10):1774-85.
23. Greer EL, Oskoui PR, Banko MR, et al. The energy sensor AMP-activated protein kinase directly regulates the mammalian FOXO3 transcription factor. J Biol Chem. 2007;282(41):30107-19.
24. Miura S, Tomitsuka E, Kamei Y, et al. Overexpression of peroxisome proliferator-activated receptor gamma co-activator-1alpha leads to muscle atrophy with depletion of ATP. Am J Pathol. 2006;169(4):1129-39.
25. Miljkovic N, Lim JY, Miljkovic I, Frontera WR. Aging of skeletal muscle fibers. Ann Rehabil Med. 2015;39(2):155-62.
26. Sorriento D, Di Vaia E, Iaccarino G. Physical exercise: a novel tool to protect mitochondrial health. Front Physiol. 2021;12:660068.
27. Mishra P, Varuzhanyan G, Pham AH, Chan DC. Mitochondrial dynamics is a distinguishing feature of skeletal muscle fiber types and regulates organellar compartmentalization. Cell Metab. 2015;22(6):1033-44.
28. Hood DA, Memme JM, Oliveira AN, Triolo M. Maintenance of skeletal muscle mitochondria in health, exercise, and aging. Annu Rev Physiol. 2019;81:19-41.
29. Habiballa L, Salmonowicz H, Passos JF. Mitochondria and cellular senescence: implications for musculoskeletal ageing. Free Radic Biol Med. 2019;132:3-10.
30. Lee K, Kerner J, Hoppel CL. Mitochondrial carnitine palmitoyltransferase 1a (CPT1a) is part of an outer membrane fatty acid transfer complex. J Biol Chem. 2011;286(29):25655-62.
31. Pucci S, Zonetti MJ, Fisco T, et al. Carnitine palmitoyl transferase-1A (CPT1A): a new tumor specific target in human breast cancer. Oncotarget. 2016;7(15):19982-96.
32. Mazzarelli P, Pucci S, Bonanno E, Sesti F, Calvani M, Spagnoli LG. Carnitine palmitoyltransferase I in human carcinomas: a novel role in histone deacetylation? Cancer Biol Ther. 2007;6(10):1606-13.
33. Liu K, Tan LJ, Wang P, et al. Functional relevance for associations between osteoporosis and genetic variants. PLoS One. 2017;12(4):e0174808.
34. Di Pietro G, Scimeca M, Iundusi R, et al. Differences between muscle from osteoporotic and osteoarthritic subjects: in vitro study by diffusion-tensor MRI and histological findings. Aging Clin Exp Res. 2020;32(12):2489-99.

35. Hénique C, Mansouri A, Vavrova E, et al. Increasing mitochondrial muscle fatty acid oxidation induces skeletal muscle remodeling toward an oxidative phenotype. FASEB J Off Publ Fed Am Soc Exp Biol. 2015;29(6):2473-83.
36. Bremer J. Carnitine--metabolism and functions. Physiol Rev. 1983;63(4):1420-80.
37. Brass EP. Pharmacokinetic considerations for the therapeutic use of carnitine in hemodialysis patients. Clin Ther. 1995;17(2):176-185; discussion 175.
38. Kerner J, Hoppel C. Fatty acid import into mitochondria. Biochim Biophys Acta. 2000;1486(1):1-17.
39. Ringseis R, Keller J, Eder K. Role of carnitine in the regulation of glucose homeostasis and insulin sensitivity: evidence from in vivo and in vitro studies with carnitine supplementation and carnitine deficiency. Eur J Nutr. 2012;51(1):1-18.
40. Cooney GJ, Thompson AL, Furler SM, Ye J, Kraegen EW. Muscle long-chain acyl CoA esters and insulin resistance. Ann N Y Acad Sci. 2002;967:196-207.
41. Marques J, Shokry E, Uhl O, et al. Sarcopenia: investigation of metabolic changes and its associated mechanisms. Skelet Muscle. 2023;13(1):2.
42. Larsson L, Degens H, Li M, et al. Sarcopenia: aging-related loss of muscle mass and function. Physiol Rev. 2019;99(1):427-511.
43. Vainshtein A, Sandri M. Signaling pathways that control muscle mass. Int J Mol Sci. 2020;21(13):4759.
44. Camara AKS, Lesnefsky EJ, Stowe DF. Potential therapeutic benefits of strategies directed to mitochondria. Antioxid Redox Signal. 2010;13(3):279-347.