Yoo *et al. Cell Communication and Signaling* (2025) 23:36
https://doi.org/10.1186/s12964-025-02032-2

Cell Communication and Signaling

REVIEW

Open Access

Role of cardiolipin in skeletal muscle function and its therapeutic implications

Youngbum Yoo[1†], MyeongHoon Yeon[1†], Mee-Sup Yoon[2,3*] and Young-Kyo Seo[1,4*]

Abstract

Cardiolipin, a unique phospholipid predominantly present in the inner mitochondrial membrane, is critical for maintaining mitochondrial integrity and function. Its dimeric structure and role in supporting mitochondrial dynamics, energy production, and mitophagy make it indispensable for skeletal muscle health. This review provides a comprehensive overview of cardiolipin biosynthesis, remodeling processes, and essential functions within mitochondria. We explore the influences of cardiolipin on the stability of the mitochondrial complexes, cristae formation, and calcium handling, all of which are vital for efficient oxidative phosphorylation and muscle contraction. Skeletal muscle, with its high energy demands, is particularly dependent on cardiolipin for optimal performance. We discuss the impact of aging on cardiolipin levels, which correlates with a decline in mitochondrial function and muscle mass, contributing to conditions such as sarcopenia. Furthermore, we examined the relationship between cardiolipin and endurance exercise, highlighting the effects of exercise-induced increase in cardiolipin levels on the improvement of mitochondrial function and muscle health. The role of *Crls1* in cardiolipin synthesis has been emphasized as a potential therapeutic target for the treatment of sarcopenia. Increasing cardiolipin levels through gene therapy, pharmacological interventions, or specific exercise and nutritional strategies holds promise for mitigating muscle atrophy and promoting muscle regeneration. By focusing on the multifaceted role of cardiolipin in mitochondria and muscle health, we aimed to provide new insights into therapeutic approaches for enhancing muscle function and combating age-related muscle decline.

Keywords Cardiolipin, Mitochondrial function, Skeletal muscle, Sarcopenia, Oxidative phosphorylation, *Crls1*, Exercise, Muscle atrophy

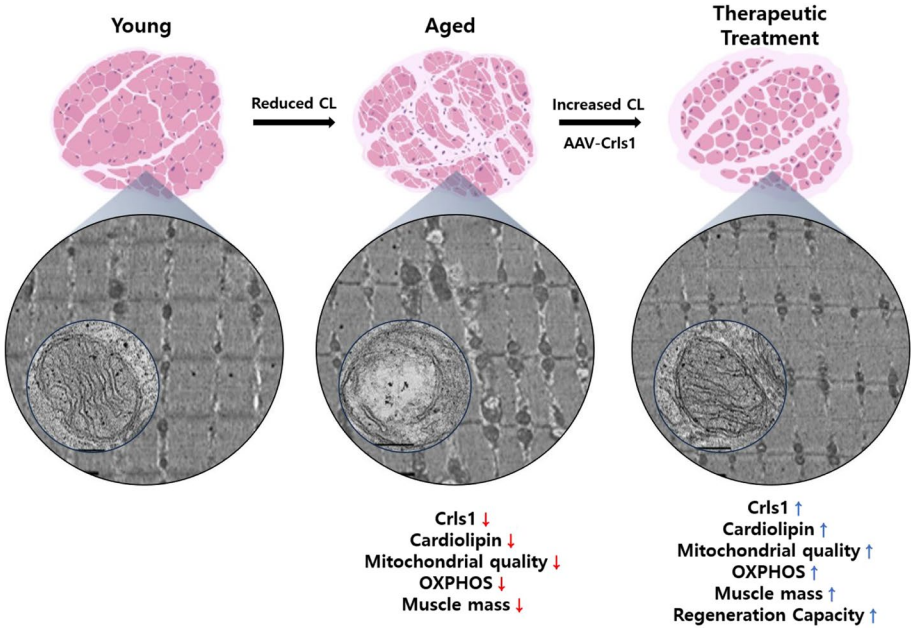
Graphical Abstract

Cardiolipin and Crls1 were reduced in aged skeletal muscle, contributing to mitochondrial dysfunction and muscle atrophy. In aged skeletal muscle, reduced CL levels are directly associated with impaired mitochondrial respiration capacity and structural degradation. Upregulating CL synthesis enhances mitochondrial function by stabilizing ETC proteins, increasing oxygen flux, and improving cristae architecture. Therapeutic strategies, including CL-targeting

†Youngbum Yoo and MyeongHoon Yeon contributed equally to this work.

*Correspondence:
Mee-Sup Yoon
msyoon@gachon.ac.kr
Young-Kyo Seo
ykseo@kribb.re.kr
Full list of author information is available at the end of the article

compounds like elamipretide and gene therapy, show promise for mitigating sarcopenia by improving mitochondrial bioenergetics and muscle regeneration.



Introduction

Mitochondria are indispensable organelles in eukaryotic cells that are primarily known for their role in energy production via oxidative phosphorylation (OXPHOS) [1]. The structural integrity and functionality of mitochondria are critically dependent on various representative phospholipids found in mitochondrial membranes, including phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), phosphatidic acid (PA), phosphatidylserine (PS), phosphatidylglycerol (PG), and cardiolipin (CL) [2].

CL, a unique dimeric phospholipid predominantly located in the inner mitochondrial membrane, is essential for maintaining mitochondrial membrane integrity and supporting the optimal function of enzymes involved in energy metabolism [3]. CL biosynthesis involves a multistep process beginning with the synthesis and transport of PA from the ER to mitochondria, underscoring the functional interplay between these organelles [4]. In skeletal muscle, characterized by high energy demand, CL is particularly critical due to its roles in mitochondrial dynamics, energy production, and overall muscle performance [5]. The mitochondrial content in skeletal muscle fibers ranges from 2–10% of cellular volume, depending on fiber type. This variability reflects the functional demands of oxidative (slow-twitch) fibers, which are relatively enriched in mitochondria to support sustained, energy-intensive muscle contractions through oxidative phosphorylation. Alterations in the levels and composition of mitochondrial phospholipids, including CL, profoundly influence muscle function and are linked to various muscle-related conditions. Exercise-induced increases in mitochondrial PC, PE, and CL correlate with enhanced mitochondrial efficiency and muscle health, whereas aging-associated declines in phospholipids, especially PE and CL are implicated in reduced aerobic capacity and muscle performance [6].

This review aims to elucidate the multifaceted role of CL in skeletal muscle physiology, with a particular emphasis on its contribution to mitochondrial dynamics, energy production, and muscle performance. By exploring the molecular mechanisms underlying CL function and its therapeutic potential, this work provides a framework for understanding its relevance in aging and muscle-related diseases. Advancing our understanding of CL's role in skeletal muscle health could pave the way for innovative treatments to combat age-related muscle decline and enhance muscle function across various clinical contexts.

Role of phospholipids in mitochondrial structure with a focus on cardiolipin

The mitochondria contain numerous phospholipids in various forms that support the structure and function of the organelle. The representative phospholipids of mitochondria, PC, PE, PI, PA, PS, PG, and CL [2], are present

in the outer and inner mitochondrial membranes, where they contact the ER and regulate mitochondrial dynamics, mitophagy, cristae formation, and the stability of mitochondrial complex proteins [7–10].

PI is involved in mitophagy and mitochondrial fission and is synthesized in the ER before being transported to the mitochondria [11]. PA is synthesized in the ER and then transferred to the mitochondria, where it is used as a precursor for cytidine diphosphate diacylglycerol (CDP-DAG) synthesis, or is primarily found at the OMM-IMM contact sites [12]. PS serves as a precursor for PE synthesis via PSD [13]. PC is primarily known to maintain the overall shape of the mitochondrial outer membrane. Recent studies have reported that the PC/PE ratio in muscles is associated with insulin sensitivity [14]. Additionally, exercise induces an increase in mitochondrial PC and PE contents [15, 16], which decreases with aging in skeletal muscles [17]. Mitochondrial PE plays a pivotal role in skeletal muscle energetics by promoting the formation of cristae, specialized structures that host electron transport system (ETS) enzymes. The conical shape of PE enables optimal cristae curvature, facilitating respiratory enzyme activity and enhancing oxidative phosphorylation and ATP production. Studies, including Heden et al. [16], highlight the correlation between increased mitochondrial PE levels and improved aerobic capacity, while reductions in PE impair respiratory efficiency and muscle function.

CL is a unique phospholipid that plays a crucial role in the structure and function of several cellular components, including mitochondrial membranes. It is a unique phospholipid characterized by its dimeric structure, comprising two phosphatidyl groups linked by a glycerol molecule, which distinguishes it from other phospholipids. This structure results in four fatty acid chains, making CL highly flexible and capable of forming a cone-like shape that is essential for its function in the mitochondrial membrane. The specific fatty acid composition of CL can vary, although it predominantly contains linoleic acid in mammalian cells, contributing to its unique properties.

This high concentration of CL in the IMM is critical for the structural organization and functional optimization of the mitochondrial membrane. Its distribution is not uniform; it is highly enriched in regions of high curvature, such as the cristae, which are the invaginations of the IMM. This specific localization is crucial for its role in maintaining mitochondrial architecture and function.

Biosynthesis and remodeling of cardiolipin

De novo CL biosynthesis in mammals is a multi-step process that begins with the synthesis and transport of PA from the ER to mitochondria (Fig. 1). CL biosynthesis and remodeling occur primarily in the mitochondrial inner membrane (MIM). PA is imported from the ER and translocated across the inner membrane space via the protein complex PRELID–TRIAP1 [18, 19], which potentially inhibits apoptosis by interacting with cytoplasmic Hsp70 and Apaf1 [20]. CDP–DAG synthase TAMM41 activates PA [21], allowing phosphatidylglycerol phosphate synthase (PGS1) to convert CDP–DAG to phosphatidylglycerol phosphate (PGP) [22]. Subsequently, phosphatase protein-tyrosine phosphatase mitochondrial 1 (PTPMT1) converts PGP to PG. CL synthesis is completed when cardiolipin synthase (CRLS1) uses a second molecule of CDP–DAG to produce CL [23]. CL interacts with numerous proteins, enzymes, and metabolite transporters within the IMM and can be remodeled when one of its four fatty acid chains is deacylated by calcium-independent phospholipase A2-gamma (iPLA2-gamma) to form mono-lysocardiolipin, which is then reacylated by TAFAZZIN to form mature CL [24]. This remodeling process significantly impacts mitochondrial function and optimal mitochondrial activity (Fig. 1).

Importance of cardiolipin in mitochondrial function

CL is crucial for mitochondrial function and ensuring structural integrity by facilitating the tight packing of lipids necessary for cristae formation, which supports the arrangement of respiratory chain complexes and enhances OXPHOS [25–30]. The structural properties of CL significantly contribute to cristae formation [31], with CL accounting for approximately 18% of the inner mitochondrial membrane (IMM) mass [32] (Table 1 and Fig. 2). This distribution is crucial for its role in maintaining mitochondrial architecture and function.

CL plays a critical role in maintaining mitochondrial cristae structure by regulating the stability of the mitochondrial contact site and cristae organizing system (MICOS) and mitochondrial complex proteins, both essential for proper cristae formation and function [33]. These structural and functional attributes of cristae, including their length and abundance, are closely linked to the efficiency of energy production in mitochondria, highlighting the importance of CL in optimizing mitochondrial bioenergetics [12, 34, 35]. In addition to its role in energy production, CL supports the mitochondrial protein dynamics. It interacts with and stabilizes key enzymes such as cytochrome c oxidase and ATP synthase, maintaining their conformation and activity for efficient ATP production. Furthermore, CL stabilizes proteins involved in mitochondrial dynamics, such as mitofusins (Mfn1/2) and dynamin-related protein 1 (Drp1) [4], which are essential for mitochondrial quality control and adaptation to cellular energy demands.

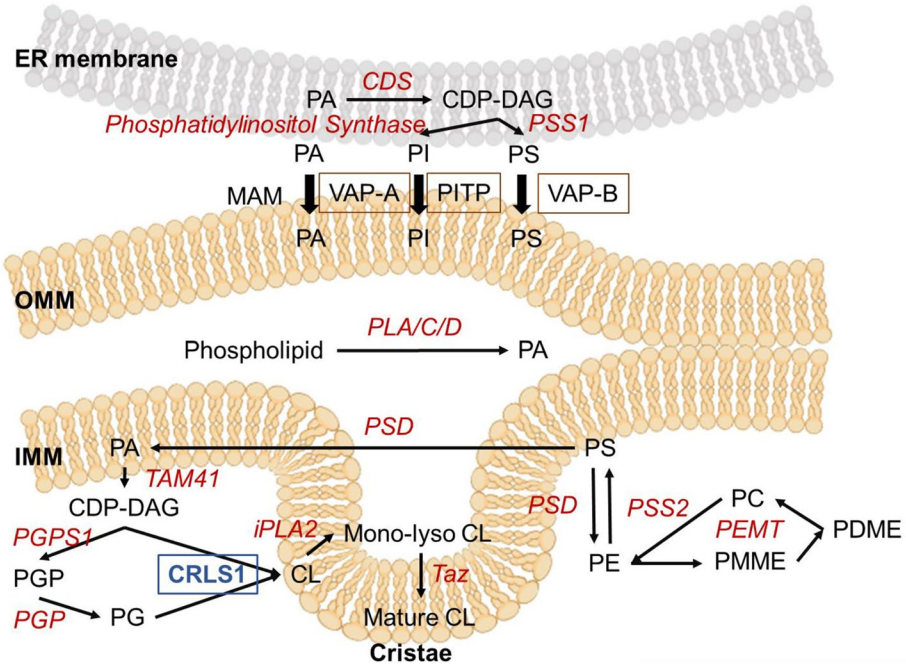


Fig. 1 Synthesis of Phospholipids in association of ER to mitochondria. The endoplasmic reticulum (ER) and mitochondria share many proteins and lipids. The phospholipids of the mitochondria are supplied from the ER or synthesized and degraded within the mitochondria. Phospholipids, phosphatidic acid (PA), phosphatidylserine (PS), and phosphatidylinositol (PI) from the ER membrane, move into mitochondrial membranes via the mitochondrial-associated membrane (MAM). Cardiolipin Highlight the synthesis pathway for and its remodeling process, including enzymes like TAM41, PGPS1, iPLA2, CRLS1, and Taz. Abbreviations: PITPs; phosphatidylinositol transfer proteins, CDS; CDP-diacylglycerol synthase, PGP; phosphatidylglycerophosphate phosphatase, PGPS1; phsophatidylgylcerophosphate synthase1, CRLS1; cardiolipin synthase1, PSD; phosphatidylserine decarboxylase, PEMT; phosphatidylethanolamine N-methyltransferase, PSS1/2; phosphatidylserine synthase 1/2, VAP; vesicle-associated membrane protein-associated protein, iPLA2; calcium independent phospholipase 2-gamma), Taz; tafazzin. CDP-DAG; cytidine diphosphate diacylglycerol, PGP; phosphatidyl-glycerophosphate, PMME; phosphatidyl mono-methylethanolamine, PDME; phosphatidyl di-methylethanolamine

Table 1 Composition of phospholipid in inner membrane of mitochondria

Phospholipid	Composition	Exercise	Aging	Ref
Phosphatidylinositol	5%	-	-	
Phosphatidylserine	3%	-	-	
Phosphatidylcholine	40%	↑	-	78, 79
Phosphatidylethanolamine	34%	↑	↓	78–81
Cardiolipin	18%	↑	↓	13, 67, 79, 80

Beyond energy production, CL is a key regulator of mitophagy, the selective removal of damaged mitochondria. During this process, CL is externalized to the outer mitochondrial membrane, acting as a signal for the recruitment of autophagic machinery, such as LC3A/B/C. This regulatory function ensures cellular homeostasis by preventing the accumulation of dysfunctional organelles [36, 37].

Mitochondrial dysfunction is a key driver of cellular senescence, with alterations in CL playing a central role. CL is critical for maintaining the structural integrity of mitochondrial membranes and stabilizing electron transport chain (ETC) supercomplexes [38]. Depletion of CL disrupts mitochondrial cristae organization, impairs ETC efficiency, and increases reactive oxygen species (ROS) production. Elevated ROS levels induce oxidative damage, activate DNA damage response pathways, and trigger the release of pro-apoptotic factors like cytochrome c, collectively promoting senescence-associated phenotypes and accelerating cellular aging.

Therapeutic strategies targeting CL have shown promise in mitigating mitochondrial dysfunction and cellular senescence. For example, Elamipretide, a tetrapeptide that binds to CL, prevents its oxidation, stabilizes ETC supercomplexes, and restores mitochondrial bioenergetics. This compound has demonstrated efficacy in improving mitochondrial oxygen flux, reducing oxidative damage, and protecting against ischemia/reperfusion (I/R) injury. Similarly, melatonin, a potent antioxidant, preserves mitochondrial integrity by scavenging ROS and preventing CL oxidation. By inhibiting mitochondrial permeability transition pore (mPTP) opening and

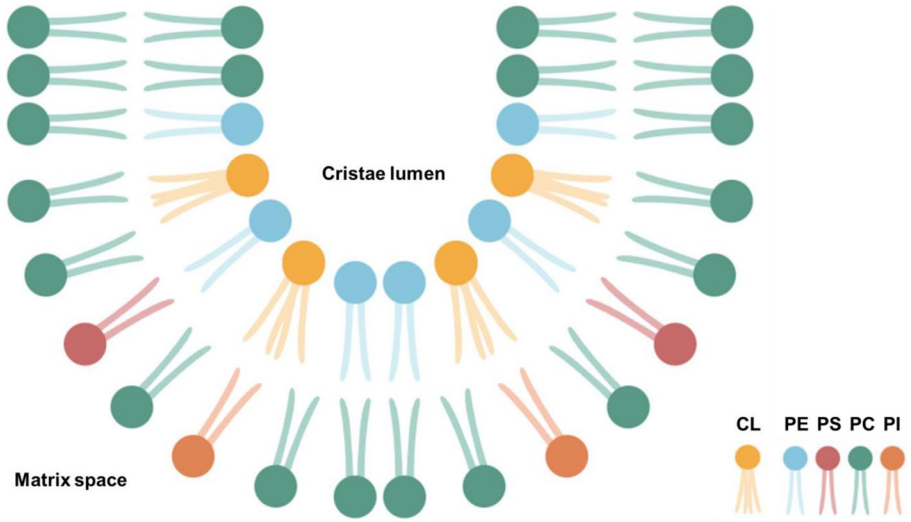


Fig. 2 Cardiolipin in mitochondrial cristae. Phospholipids of inner mitochondrial membrane are composed of PE, PS, PC, PI, and CL. CL is a major phospholipid, mainly distributed in the cristae lumen of the inner mitochondrial membrane

cytochrome c release, melatonin reduces oxidative stress and delays senescence onset. These interventions highlight the therapeutic potential of preserving CL integrity to combat aging-related mitochondrial dysfunction.

In aged skeletal muscle, reduced CL levels are directly associated with impaired mitochondrial respiration capacity and structural degradation. Studies have shown that upregulating CL synthesis enhances mitochondrial function by stabilizing ETC proteins, increasing oxygen flux, and improving cristae architecture [39]. This regulation suppresses protein degradation mechanisms and promotes muscle strength, underscoring the connection between CL homeostasis and the prevention of senescence-associated decline in skeletal muscle.

The critical roles of CL in energy production and mitochondria quality control underscores its significance in mitochondria-rich tissues like skeletal muscle, which rely heavily on efficient ATP generation for muscle contraction. Dysregulation of CL metabolism has been implicated in several muscular disorders, including Duchenne muscular dystrophy, sarcopenia, and mitochondrial myopathies [40–43].

Cardiolipin in muscle atrophy

Skeletal muscle, accounting for 30–40% of body weight, is a critical system for motility and metabolism, primarily deriving its energy through glycolysis and OXPHOS [44, 45]. Owing to their high energy demands, skeletal muscles are densely packed with mitochondria. Muscle atrophy, characterized by a loss of muscle mass and strength, can result from reduced protein synthesis and increased protein degradation, often exacerbated by mitochondrial dysfunction associated with aging [46–48].

Age-related muscle loss is driven by inadequate protein intake and diminished energy production efficiency, both linked to mitochondrial dysfunction [49–51]. Enhancing mitochondrial quality and function is essential to counteract this decline. CL plays an essential role in mitochondrial enhancement, and elevated levels of CL; moreover, CL synthase has been proven to be effective in preventing muscle atrophy [39]. CL, abundant in the inner mitochondrial membrane, is crucial for maintaining the structure and function of protein complexes involved in OXPHOS and ATP production [40, 52]. This process highlights the significant ATP requirement for skeletal muscle contraction, with CL enhancing mitochondrial function and ATP production [53].

Mitochondrial dysfunction, including CL dysregulation, is a critical contributor to sarcopenia. CL is essential for maintaining mitochondrial membrane integrity and function, with its depletion linked to impaired bioenergetics, increased oxidative stress, and muscle atrophy. Targeted therapeutic approaches, such as cardiolipin-targeting agents (e.g., Elamipretide), have shown promise in preclinical studies. These interventions aim to restore mitochondrial function, reduce oxidative stress, and support muscle regeneration. However, these strategies must be part of a comprehensive approach that also addresses other contributors to sarcopenia, such as chronic inflammation, hormonal imbalances, neuromuscular degradation, and lifestyle factors.

In skeletal muscles, energy production occurs primarily through OXPHOS [54], which is efficient in ATP

production [55]. Enhancing OXPHOS efficiency is a key strategy to prevent muscle atrophy [56]. This process is mediated by mitochondrial complex proteins located in the inner mitochondrial membrane, whose stability and function are influenced by CL levels [57]. Increasing CL levels enhance both the function and expression of these mitochondrial proteins, making CL a promising target for sarcopenia treatment.

Previous studies demonstrated that enhancing OXPHOS improves regeneration efficiency in aged mice [43]. Elevated CL levels improve the function, expression, and stability of mitochondrial complex proteins, thereby supporting muscle regeneration and mitigating atrophy. Induction of CL synthesis, particularly via the cardiolipin synthase protein Crls1, is a key marker for muscle regeneration. Myogenesis, the process of muscle cell formation, is associated with increased expression of Crls1 and elevated CL synthesis [39]. Conversely, a reduction in factors like PTPMT1 and Crls1 leads to decreased CL levels, closely associated with muscle atrophy [59].

CL also regulates the function of calcium-handling proteins by modulating the curvature and dynamics of skeletal muscle cell membranes, thereby enhancing calcium regulation critical for muscle contraction and relaxation. The expression of CL in skeletal muscle was significantly reduced under conditions of muscle atrophy (Table 2). Exercise training alters the content, composition, and distribution of CL, improving mitochondrial function and metabolic capacity of skeletal muscles [60, 61]. These findings suggest that CL is integral to skeletal muscle improvement and a potential target for treating muscle-related diseases or enhancing exercise performance (Fig. 3).

Stability of sarcoplasmic reticulum and mitochondrial membrane proteins in skeletal muscles

Muscle tissue stores calcium ions in the sarcoplasmic reticulum (SR) and releases them in response to action potentials, leading to muscle contraction [62]. Dysfunction of SR proteins may be caused by CL deficiency, resulting in problems with calcium ion release and uptake in the SR. CL deficiency induces abnormal endoplasmic reticulum (ER) activation, with CL mutations leading to ER dysfunction and age-related reductions in the binding and functionality of mitochondrial membrane proteins to the ER in skeletal muscle [63, 64]. The relationship between the SR and mitochondria is crucial, with SR primarily influencing the function of the neuromuscular junction [65]. The SR responds to stimulation from nerve cells; moreover, enhancing the functions of the SR and mitochondria simultaneously may be necessary when proposing treatment methods through nerve cell improvement [66].The decline in SR function in response to nerve cell stimulation is linked to overall muscle dysfunction that occurs during aging [67]. Although there is no comprehensive research on improving CL to increase signals from nerve cells, validating whether improving CL can modify the structure and mass of the SR is critical. This appears to be closely related to muscle strength, which decreases with aging.

The age-dependent changes in the mitochondrial-associated membrane (MAM) induced by CL loss was illustrated in Fig. 4. The schematic representation highlights the structural and functional alterations in mitochondria from young to old cells, emphasizing the role of CL in maintaining mitochondrial integrity and function. In young cells, mitochondria exhibit well-defined cristae structures, adequate levels of CL, and efficient ATP production by the electron transport chain which is organized within the cristae. Robust MAM connections facilitate effective communication and lipid transfer between the ER and mitochondria.

As cells age, several changes occur with CL depletion, subsequent cristae disruption, and decreased ATP production. The MAM structure in aged mitochondria alters the association between the ER and mitochondria, possibly becoming less efficient in lipid transfer and signaling. Electron microscopy images highlight the following

Table 2 Cardiolipin abnormalities in animal model (tissues)

Tissues	Conditions	Amount of Cardiolipin	Refs
Brain	17- old mouse; Brain mitochondrial active oxygen species production	21% decrease of total CL	[82]
	24-old rat; Mitochondrial dysfunction in rat brain with aging	31% decrease of total CL	[83]
	20-old rat; cardiolipin depletion in aged rat brain mitochondria	25% decrease of total CL	[84]
Skeletal Muscle	chronic muscle activity	48% CL content increase	[85]
	Chronic muscle disuse	About 40% CL decreased	
	Chronic electrical stimulation	3.7fold increase of mitochondrial CL level than those of control	[86]
	Two weeks denervation	54 ± 13% of CL contents than those of control	[87]
	22-month-old mouse, Total cardiolipin levels in the mitochondria of TA muscle	20% decrease of total CL	[39]

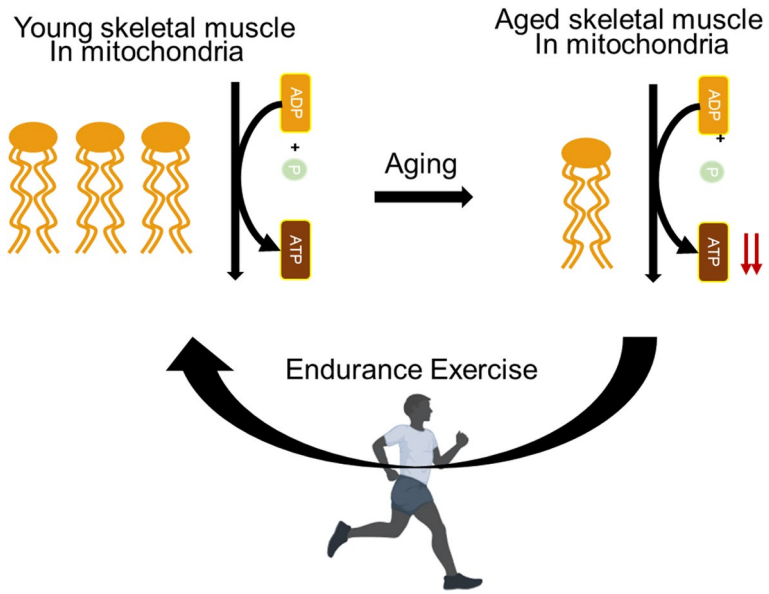


Fig. 3 Roles of *Crls1* and Cardiolipin in exercise and skeletal muscle. An increase in *Crls1* expression and CL levels can improve sarcopenia. Age-dependent decrease in CL level causes mitochondrial dysfunction. Mitochondrial dysfunction induces muscle atrophy and weakness; however, endurance exercise increases CL levels in aged skeletal muscles

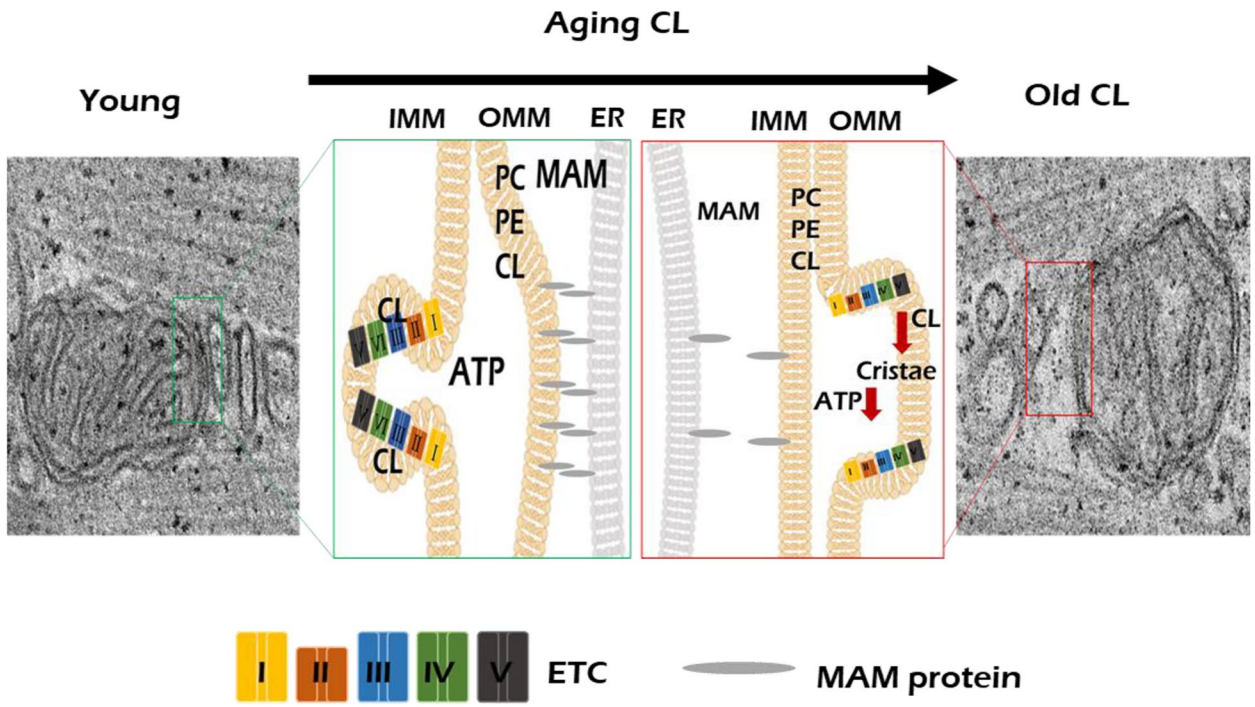


Fig. 4 Aged-dependent dysfunction of mitochondrial-associated membrane (MAM) was induced by cardiolipin (CL) loss. The young skeletal muscle (left panel) shows a cross-section of mitochondria with healthy mitochondrial membranes. CL is well-distributed, supporting efficient interactions between the inner mitochondrial membrane (IMM), the outer mitochondrial membrane (OMM), and the endoplasmic reticulum (ER) via MAM regions. While the old skeletal muscle (right panel) shows significant loss of CL, disruption in mitochondrial cristae, and severely impaired interactions between mitochondrial membranes and MAM. CL is involved in mitochondrial dynamics and the contact of mitochondria with the ER. The illustration shows the increase in the distance between the mitochondrial membrane and ER membrane and the amount of CL in between young and old skeletal muscle. Figure partially created with BioRender.com. Abbreviations: PC; Phosphatidylcholines, PE; phosphatidylethanolamine, CL; Cardiolipin, ETC; Electron Transport Chain, MAM; Mitochondrial-Associated Membrane

ultrastructural changes: in young mitochondria, cristae are tightly packed and well-organized, whereas in aged mitochondria, cristae appear swollen and less defined, reflecting the structural damage and functional decline associated with aging. The decrease in CL and subsequent cristae disruption plays a critical role in the decline of mitochondrial function with age, impacting cellular energy metabolism and leading to reduced ATP production. Changes in MAM structure may affect lipid metabolism and calcium signaling between the ER and mitochondria, further contributing to cellular aging. Therefore, maintaining or restoring CL levels in the IMM could be a potential therapeutic strategy to preserve mitochondrial function and mitigate age-related cellular decline (Fig. 4) [39].

Cardiolipin and endurance exercise in skeletal muscle

Endurance exercises require substantial energy and oxygen, and are characterized by high presence of mitochondria, blood vessels, and myoglobin [61, 68, 69]. To enhance mitochondrial quantity and energy production, the function of the electron transport chain must increase, leading to a proliferation of mitochondria cristae as an adaptative response [70]. In muscle tissues, particularly red muscles (slow-twitch fibers), the expression of *Crls1* remains stable with aging, which explains their resistance to muscle loss [39, 71]. In contrast, white muscles (fast-twitch fibers) exhibit a decline in *Crls1* expression with aging, making them more susceptible to sarcopenia. Endurance exercise induces a switch from fast-twitch to slow-twitch muscle fibers, promoting an increase in mitochondrial cristae density and CL content, thereby enhancing mitochondrial function [72]. This process is important for increasing CL levels, which are crucial in preventing age-related muscle loss in red muscles. Similarly, increasing CL in white muscles can prevent muscle loss and promote muscle regeneration [39]. While white muscles have fewer mitochondria compared to red muscles, they store substantial energy and heavily rely on mitochondrial energy production [72]. Energy demand in white muscles can lead to protein breakdown under energy deficiency. However, increased CL enhances mitochondrial function, delaying or inhibiting protein breakdown and preventing white muscle atrophy [39].The exact mechanism underlying exercise-induced *Crls1* expression remains unclear, but it is well known that exercise increases CL levels. Increased mitochondrial activity owing to exercise leads to the accumulation of ROS, which is cleared through processes such as mitophagy and mitochondrial dynamics [37, 73–75], with CL assisting in these processes. During endurance exercise, mitochondrial performance directly determines overall endurance capacity, with exercise enhancing the activity of mitochondrial complex proteins, thereby increasing both the quantity and functionality of slow-twitch muscle mitochondria [76, 77]. An exercise-induced increase in CL enhances mitochondrial activity, leading to improved muscle function and overall muscle health. This increase, along with elevated expression of *Crls1*, can mitigate age-related deficiencies, making CL and *Crls1* promising therapeutic targets for addressing conditions such as sarcopenia.

Targeting *Crls*1 expression and cl metabolism for sarcopenia treatment

Sarcopenia, characterized by age-related muscle loss and functional decline, poses a significant challenge in aging populations. Although research on the therapeutic potential of CL in sarcopenia is still in its early stages, understanding the role of CL in muscle health is critical. CL is integral to regulating mitochondrial activity in skeletal muscle, directly influencing muscle function and overall health. Emerging evidence suggests that exercise can increase CL levels [61], offering a potential avenue for mitigating sarcopenia, even though direct upregulation of *Crls*1 expression through exercise has yet to be demonstrated. These findings highlight the importance of CL in developing exercise interventions to counteract sarcopenia effectively.

Enhancing *Crls1* expression offers a promising therapeutic approach to combat sarcopenia. By upregulating *Crls1* potentially replicating the beneficial effects of exercise on mitochondrial function. Beyond exercise-based interventions, several targeted strategies focusing on CL modulation have emerged as viable options for addressing mitochondrial dysfunction in skeletal muscle.

One promising strategy involves CL supplementation. For example, Elamipretide, a tetrapeptide that binds to CL, has been shown to prevent its oxidation, stabilize ETC supercomplexes, and improve mitochondrial bioenergetics. Preclinical studies have demonstrated its efficacy in enhancing mitochondrial oxygen flux, reducing oxidative stress, and supporting muscle regeneration. These findings position Elamipretide as a potential pharmacological treatment for age-related muscle decline.

Another approach under investigation is gene therapy targeting *Crls1* expression to restore endogenous CL synthesis. Experimental models indicate that increasing *Crls1* expression can enhance mitochondrial stability, reduce oxidative damage, and improve muscle strength, particularly in aged skeletal muscle. This strategy directly addresses the age-related decline in CL synthesis and its impact on mitochondrial function.

Additionally, the activation of tafazzin, an enzyme responsible for CL remodeling, represents another

promising avenue. Tafazzin plays a critical role in optimizing CL functionality by supporting mitochondrial cristae structure and dynamics. This process is essential for maintaining efficient ATP production and ensuring the structural integrity of mitochondria.

These strategies collectively highlight the therapeutic potential of modulating CL levels to restore mitochondrial function and mitigate sarcopenia. While still in the research phase, they provide valuable insights into future directions for clinical applications aimed at preserving muscle health in aging populations. Graphical abstract illustrates how reduced CL levels and *Crls1* expression in aged skeletal muscle impair mitochondrial respiration and structure. Upregulating CL synthesis improves mitochondrial function by stabilizing ETC proteins, increasing oxygen flux, and enhancing cristae architecture, offering a viable pathway to mitigate sarcopenia.

Future studies should focus on identifying the mechanisms underlying the interaction between the ER and mitochondria, which are disrupted by CL deficiency. Addressing these issues could pave the way for novel therapeutic strategies to combat sarcopenia. In addition, exploring the combined effects of exercise and pharmacological therapies on *Crls1* expression and CL synthesis may provide a comprehensive approach to managing sarcopenia. Staying up to date with the latest research trends in sarcopenia treatment and seeking expert advice will be essential for developing effective presentive and therapeutic measures. By targeting *Crls1* expression and CL metabolism, future strategies could revolutionize sarcopenia treatment and improve muscle health in aging populations.

Conclusion and future perspectives

CL plays a crucial role in maintaining mitochondrial integrity and supporting essential functions such as energy production, mitochondrial dynamics, and mitophagy, all of which are vital for muscle health. Exercise-induced increases in CL levels enhance mitochondrial efficiency and muscle function, while age-related declines in CL contribute to muscle deterioration. Gaining a deeper understanding of CL's role could lead to therapeutic strategies for muscle-related diseases like sarcopenia. Approaches aimed at modulating CL levels could significantly benefit muscle health, particularly in aging populations.

The gene Crls1 has emerged as a promising therapeutic target for sarcopenia, offering potential applications in gene therapy, drug development, and the regulation of calcium signaling in muscle cells. Exploring Crls1 expression could also provide valuable insights for designing exercise-based interventions to preserve muscle health in older adults. However, practical applications of these strategies are still in the early stages of research.

Continued research efforts are essential for translating these preliminary findings into viable therapeutic strategies for sarcopenia. Considering the pivotal role of CL in mitochondrial function, several directions for future research may be proposed. Priority should be given to developing gene therapy techniques to enhance the expression of *Crls1*, which is crucial for CL synthesis. Additionally, investigating pharmacological agents that can increase CL levels or mimic its function is essential. Studying the effects of dietary supplements and specific exercise regimens in increasing CL levels in the skeletal muscles and understanding the interplay between nutrition, exercise, and CL synthesis could lead to practical strategies for maintaining muscle health. Investigating the role of CL in mitochondrial dynamics, such as fusion, fission, and mitophagy, is critical for ensuring mitochondrial quality control and adapting to energy demands, particularly in aging muscle tissues. Furthermore, understanding how CL impacts calcium homeostasis in muscle cells is essential, as calcium plays a pivotal role in muscle contraction and relaxation. Such studies could uncover innovative approaches to improving muscle function and mitigating age-related sarcopenia. Moreover, detailed research on MAM proteins and phospholipids in the context of age-related sarcopenia is necessary. By conducting in-depth studies on the structural and functional changes in MAMs caused by CL loss, we can improve our understanding of the impact of these changes on lipid metabolism and calcium signaling between the ER and mitochondria. To evaluate the effectiveness of therapies targeting CL in treating sarcopenia, it is imperative to transition from laboratory research to clinical trials. Collaborative efforts between researchers, clinicians, and pharmaceutical companies will be crucial in translating these findings into real-world treatments. This knowledge will unveil new therapeutic targets, research directions and provide new possibilities for the treatment and improvement of sarcopenia.

Therefore, future research can provide a deeper understanding of the role of CL in muscle health and develop effective strategies for combating sarcopenia and other muscle-related diseases.

Acknowledgements

This research was supported by grants from the National Research Foundation of Korea (NRF) (No. OGM6512312), National Research Council of Science & Technology (NST) Aging Convergence Research Center (NTC0132312), and the Ministry of Health and Welfare of Korea (BGC1502312, HV22C0128).

Authors' contributions

YKS and MSY designed and directed the project. YBY and MHY prepared Figs. 1, 2, 3 and 4. All authors wrote and reviewed the manuscript and consented to the description of author's contribution.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Author details
[1]Aging Convergence Research Center, Korea Research Institute of Bioscience and Biotechnology (KRIBB), Daejeon 34141, Republic of Korea. [2]Department of Molecular Medicine, College of Medicine, Gachon University, Incheon 21999, Republic of Korea. [3]Department of Health Sciences and Technology, GAIHST, Gachon University, Incheon 21999, Republic of Korea. [4]School of Medicine, Sungkyunkwan University, Suwon 16419, Republic of Korea.

Received: 11 September 2024 Accepted: 7 January 2025
Published online: 21 January 2025

References
1. Chen W, Zhao H, Li Y. Mitochondrial dynamics in health and disease: mechanisms and potential targets. Signal Transduct Target Ther. 2023;8:333.
2. Heden TD, Neufer PD, Funai K. Looking beyond structure: membrane phospholipids of skeletal muscle mitochondria. Trends Endocrinol Metab. 2016;27:553–62.
3. Zuccaro KE, et al. Cardiolipin clustering promotes mitochondrial membrane dynamics. bioRxiv. 2024;2005(2021):595226. https://doi.org/10.1101/2024.05.21.595226.
4. Kameoka S, Adachi Y, Okamoto K, Iijima M, Sesaki H. Phosphatidic acid and cardiolipin coordinate mitochondrial dynamics. Trends Cell Biol. 2018;28:67–76.
5. Paradies G, Paradies V, Ruggiero FM, Petrosillo G. Role of cardiolipin in mitochondrial function and dynamics in health and disease: molecular and pharmacological aspects. Cells. 2019;8:728.
6. Faber C, et al. Cardiolipin profiles as a potential biomarker of mitochondrial health in diet-induced obese mice subjected to exercise, diet-restriction and ephedrine treatment. J Appl Toxicol. 2014;34:1122–9.
7. Green DE, Fleischer S. The role of lipids in mitochondrial electron transfer and oxidative phosphorylation. Biochim Biophys Acta. 1963;70:554–82.
8. Nguyen TT, Voeltz GK. An ER phospholipid hydrolase drives ER-associated mitochondrial constriction for fission and fusion. Elife. 2022;11:e84279.
9. Kojima R, Endo T, Tamura Y. A phospholipid transfer function of ER-mitochondria encounter structure revealed in vitro. Sci Rep. 2016;6:30777.
10. Mejia EM, Hatch GM. Mitochondrial phospholipids: role in mitochondrial function. J Bioenerg Biomembr. 2016;48:99–112.
11. Lordan R, Tsoupras A, Zabetakis I. Phospholipids of animal and marine origin: structure, function, and anti-inflammatory properties. Molecules. 1964;2017:22.
12. Horvath SE, Daum G. Lipids of mitochondria. Prog Lipid Res. 2013;52:590–614.
13. Steenbergen R, et al. Disruption of the phosphatidylserine decarboxylase gene in mice causes embryonic lethality and mitochondrial defects. J Biol Chem. 2005;280:40032–40.
14. Lee S, et al. Skeletal muscle phosphatidylcholine and phosphatidylethanolamine respond to exercise and influence insulin sensitivity in men. Sci Rep. 2018;8:6531.
15. Newsom SA, et al. Skeletal muscle phosphatidylcholine and phosphatidylethanolamine are related to insulin sensitivity and respond to acute exercise in humans. J Appl Physiol. 2016;1985(120):1355–63.
16. Heden TD, et al. Mitochondrial PE potentiates respiratory enzymes to amplify skeletal muscle aerobic capacity. Sci Adv. 2019;5:eaax8352.
17. Pollard AK, Ortori CA, Stoger R, Barrett DA, Chakrabarti L. Mouse mitochondrial lipid composition is defined by age in brain and muscle. Aging (Albany NY). 2017;9:986–98.
18. Gaigg B, Simbeni R, Hrastnik C, Paltauf F, Daum G. Characterization of a microsomal subfraction associated with mitochondria of the yeast, Saccharomyces cerevisiae. Involvement in synthesis and import of phospholipids into mitochondria. Biochim Biophys Acta. 1995;1234:214–20.
19. Kannan M, Lahiri S, Liu LK, Choudhary V, Prinz WA. Phosphatidylserine synthesis at membrane contact sites promotes its transport out of the ER. J Lipid Res. 2017;58:553–62.
20. Potting C, et al. TRIAP1/PRELI complexes prevent apoptosis by mediating intramitochondrial transport of phosphatidic acid. Cell Metab. 2013;18:287–95.
21. Blunsom NJ, Gomez-Espinosa E, Ashlin TG, Cockcroft S. Mitochondrial CDP-diacylglycerol synthase activity is due to the peripheral protein, TAMM41 and not due to the integral membrane protein, CDP-diacylglycerol synthase 1. Biochim Biophys Acta Mol Cell Biol Lipids. 2018;1863:284–98.
22. Muller F, Frentzen M. Phosphatidylglycerophosphate synthases from Arabidopsis thaliana. FEBS Lett. 2001;509:298–302.
23. Dudek J. Role of cardiolipin in mitochondrial signaling pathways. Front Cell Dev Biol. 2017;5:90.
24. Xu Y, Malhotra A, Ren M, Schlame M. The enzymatic function of tafazzin. J Biol Chem. 2006;281:39217–24.
25. Joshi AS, Zhou J, Gohil VM, Chen S, Greenberg ML. Cellular functions of cardiolipin in yeast. Biochim Biophys Acta. 2009;1793:212–8.
26. Schlame M, Ren M. The role of cardiolipin in the structural organization of mitochondrial membranes. Biochim Biophys Acta. 2009;1788:2080–3.
27. Lewis RN, McElhaney RN. The physicochemical properties of cardiolipin bilayers and cardiolipin-containing lipid membranes. Biochim Biophys Acta. 2009;1788:2069–79.
28. Xu Y, et al. Assembly of the complexes of oxidative phosphorylation triggers the remodeling of cardiolipin. Proc Natl Acad Sci U S A. 2019;116:11235–40.
29. Osellame LD, Blacker TS, Duchen MR. Cellular and molecular mechanisms of mitochondrial function. Best Pract Res Clin Endocrinol Metab. 2012;26:711–23.
30. Ren M, Phoon CK, Schlame M. Metabolism and function of mitochondrial cardiolipin. Prog Lipid Res. 2014;55:1–16.
31. Muhleip A, McComas SE, Amunts A. Structure of a mitochondrial ATP synthase with bound native cardiolipin. Elife. 2019;8:e51179.
32. Chupin V, Leenhouts JM, de Kroon AI, de Kruijff B. Cardiolipin modulates the secondary structure of the presequence peptide of cytochrome oxidase subunit IV: a 2D 1H-NMR study. FEBS Lett. 1995;373:239–44.
33. Harner ME, et al. Aim24 and MICOS modulate respiratory function, tafazzin-related cardiolipin modification and mitochondrial architecture. Elife. 2014;3:e01684.
34. Anand R, Reichert AS, Kondadi AK. Emerging roles of the MICOS complex in cristae dynamics and biogenesis. Biology (Basel). 2021;10:600.
35. Mejia EM, Cole LK, Hatch GM. Cardiolipin metabolism and the role it plays in heart failure and mitochondrial supercomplex formation. Cardiovasc Hematol Disord Drug Targets. 2014;14:98–106.
36. Iriondo MN, et al. LC3 subfamily in cardiolipin-mediated mitophagy: a comparison of the LC3A, LC3B and LC3C homologs. Autophagy. 2022;18:2985–3003.
37. Chu CT, et al. Cardiolipin externalization to the outer mitochondrial membrane acts as an elimination signal for mitophagy in neuronal cells. Nat Cell Biol. 2013;15:1197–205.
38. Paradies G, Paradies V, De Benedictis V, Ruggiero FM, Petrosillo G. Functional role of cardiolipin in mitochondrial bioenergetics. Biochim Biophys Acta. 2014;1837:408–17.
39. Yoo Y, et al. Age-dependent loss of Crls1 causes myopathy and skeletal muscle regeneration failure. Exp Mol Med. 2024;56:922–34.
40. 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.
41. Claypool SM, Oktay Y, Boontheung P, Loo JA, Koehler CM. Cardiolipin defines the interactome of the major ADP/ATP carrier protein of the mitochondrial inner membrane. J Cell Biol. 2008;182:937–50.
42. Korzeniewski B. Regulation of ATP supply during muscle contraction: theoretical studies. Biochem J. 1998;330(Pt 3):1189–95.
43. Hong X, et al. Mitochondrial dynamics maintain muscle stem cell regenerative competence throughout adult life by regulating metabolism and mitophagy. Cell Stem Cell. 2022;29:1506–8.
44. Frontera WR, Ochala J. Skeletal muscle: a brief review of structure and function. Calcif Tissue Int. 2015;96:183–95.
45. Febbraio MA, Dancey J. Skeletal muscle energy metabolism during prolonged, fatiguing exercise. J Appl Physiol. 1999;1985(87):2341–7.
46. Bodine SC, et al. Identification of ubiquitin ligases required for skeletal muscle atrophy. Science. 2001;294:1704–8.

47. Cohen S, Nathan JA, Goldberg AL. Muscle wasting in disease: molecular mechanisms and promising therapies. Nat Rev Drug Discov. 2015;14:58–74.
48. Cadena SM, et al. Skeletal muscle in MuRF1 null mice is not spared in low-gravity conditions, indicating atrophy proceeds by unique mechanisms in space. Sci Rep. 2019;9:9397.
49. Beaudart C, et al. Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. Osteoporos Int. 2017;28:1817–33.
50. Anton SD, et al. Nutrition and Exercise in Sarcopenia. Curr Protein Pept Sci. 2018;19:649–67.
51. Ferri E, et al. Role of Age-Related Mitochondrial Dysfunction in Sarcopenia. Int J Mol Sci. 2020;21:5236.
52. Abrigo J, Simon F, Cabrera D, Vilos C, Cabello-Verrugio C. Mitochondrial dysfunction in skeletal muscle pathologies. Curr Protein Pept Sci. 2019;20:536–46.
53. Sherratt HS, Turnbull DM. Mitochondrial oxidations and ATP synthesis in muscle. Baillieres Clin Endocrinol Metab. 1990;4:523–60.
54. Hargreaves M, Spriet LL. Skeletal muscle energy metabolism during exercise. Nat Metab. 2020;2:817–28.
55. Korzeniewski B. Effects of OXPHOS complex deficiencies and ESA dysfunction in working intact skeletal muscle: implications for mitochondrial myopathies. Biochim Biophys Acta. 2015;1847:1310–9.
56. Sartori R, Romanello V, Sandri M. Mechanisms of muscle atrophy and hypertrophy: implications in health and disease. Nat Commun. 2021;12:330.
57. Sousa JS, D'Imprima E, Vonck J. Mitochondrial respiratory chain complexes. Subcell Biochem. 2018;87:167–227.
58. Wagatsuma A, Sakuma K. Mitochondria as a potential regulator of myogenesis. Scient World J. 2013;2013:593267.
59. Zheng H, et al. Loss of Ptpmt1 limits mitochondrial utilization of carbohydrates and leads to muscle atrophy and heart failure in tissue-specific knockout mice. Elife. 2023;12:RP86944.
60. Larsen S, et al. Biomarkers of mitochondrial content in skeletal muscle of healthy young human subjects. J Physiol. 2012;590:3349–60.
61. Mendham AE, et al. Exercise training improves mitochondrial respiration and is associated with an altered intramuscular phospholipid signature in women with obesity. Diabetologia. 2021;64:1642–59.
62. Diaz-Vegas AR, et al. Mitochondrial calcium increase induced by RyR1 and IP3R channel activation after membrane depolarization regulates skeletal muscle metabolism. Front Physiol. 2018;9:791.
63. Lee RG, et al. Deleterious variants in CRLS1 lead to cardiolipin deficiency and cause an autosomal recessive multi-system mitochondrial disease. Hum Mol Genet. 2022;31:3597–612.
64. Lu X, et al. Ultrastructural and proteomic profiling of mitochondria-associated endoplasmic reticulum membranes reveal aging signatures in striated muscle. Cell Death Dis. 2022;13:296.
65. Gonzalez-Freire M, de Cabo R, Studenski SA, Ferrucci L. The neuromuscular junction: aging at the crossroad between nerves and muscle. Front Aging Neurosci. 2014;6:208.
66. Anagnostou ME, Hepple RT. Mitochondrial mechanisms of neuromuscular junction degeneration with aging. Cells. 2020;9:197.
67. Hunter SK, Pereira HM, Keenan KG. The aging neuromuscular system and motor performance. J Appl Physiol. 2016;1985(121):982–95.
68. Mitranun W, Deerochanawong C, Tanaka H, Suksom D. Continuous vs interval training on glycemic control and macro- and microvascular reactivity in type 2 diabetic patients. Scand J Med Sci Sports. 2014;24:e69-76.
69. Takakura H, et al. Endurance training facilitates myoglobin desaturation during muscle contraction in rat skeletal muscle. Sci Rep. 2015;5:9403.
70. Nielsen J, et al. Plasticity in mitochondrial cristae density allows metabolic capacity modulation in human skeletal muscle. J Physiol. 2017;595:2839–47.
71. Menshikova EV, et al. Calorie restriction-induced weight loss and exercise have differential effects on skeletal muscle mitochondria despite similar effects on insulin sensitivity. J Gerontol A Biol Sci Med Sci. 2017;73:81–7.
72. Glancy B, Balaban RS. Protein composition and function of red and white skeletal muscle mitochondria. Am J Physiol Cell Physiol. 2011;300:C1280-1290.
73. Jezek J, Cooper KF, Strich R. Reactive oxygen species and mitochondrial dynamics: the yin and yang of mitochondrial dysfunction and cancer progression. Antioxidants (Basel). 2018;7:13.
74. Tilokani L, Nagashima S, Paupe V, Prudent J. Mitochondrial dynamics: overview of molecular mechanisms. Essays Biochem. 2018;62:341–60.
75. Stepanyants N, et al. Cardiolipin's propensity for phase transition and its reorganization by dynamin-related protein 1 form a basis for mitochondrial membrane fission. Mol Biol Cell. 2015;26:3104–16.
76. Silva LA, et al. Physical exercise increases mitochondrial function and reduces oxidative damage in skeletal muscle. Eur J Appl Physiol. 2009;105:861–7.
77. Bori Z, et al. The effects of aging, physical training, and a single bout of exercise on mitochondrial protein expression in human skeletal muscle. Exp Gerontol. 2012;47:417–24.
78. Gardocki ME, Jani N, Lopes JM. Phosphatidylinositol biosynthesis: biochemistry and regulation. Biochim Biophys Acta. 2005;1735:89–100.
79. Dudkina NV, Sunderhaus S, Boekema EJ, Braun HP. The higher level of organization of the oxidative phosphorylation system: mitochondrial supercomplexes. J Bioenerg Biomembr. 2008;40:419–24.
80. Kim YJ, Guzman-Hernandez ML, Balla T. A highly dynamic ER-derived phosphatidylinositol-synthesizing organelle supplies phosphoinositides to cellular membranes. Dev Cell. 2011;21:813–24.
81. Wojtczak L, Baranska J, Zborowski J. Transport of phosphatidic acid within the mitochondrion. Biochim Biophys Acta. 1990;1044:284–7.
82. Lores-Arnaiz S, Lombardi P, Karadayian AG, Cutrera R, Bustamante J. Changes in motor function and brain cortex mitochondrial active oxygen species production in aged mice. Exp Gerontol. 2019;118:88–98.
83. Petrosillo G, Matera M, Casanova G, Ruggiero FM, Paradies G. Mitochondrial dysfunction in rat brain with aging Involvement of complex I, reactive oxygen species and cardiolipin. Neurochem Int. 2008;53:126–31.
84. Sen T, et al. Depolarization and cardiolipin depletion in aged rat brain mitochondria: relationship with oxidative stress and electron transport chain activity. Neurochem Int. 2007;50:719–25.
85. Ostojic O, et al. The effects of chronic muscle use and disuse on cardiolipin metabolism. J Appl Physiol. 2013;1985(114):444–52.
86. Takahashi M, Hood DA. Chronic stimulation-induced changes in mitochondria and performance in rat skeletal muscle. J Appl Physiol. 1993;1985(74):934–41.
87. Wicks KL, Hood DA. Mitochondrial adaptations in denervated muscle: relationship to muscle performance. Am J Physiol. 1991;260:C841-850.

Publisher's Note