# Mitochondria-associated endoplasmic reticulum membranes in degenerative musculoskeletal disorders: Mechanistic evidence and therapeutic perspectives (Review)

SHILONG MENG[1*], XINLEI FU[2*], YAWEI XU[1*], ZHILIANG PENG[1], XU ZHANG[1], YANGUANG CAO[3], BINBIN TANG[3], XIAOLIN SHI[3] and KANG LIU[3]

[1]The Second Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou, Zhejiang 310053, P.R. China; [2]Department of Tuina, The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, Zhejiang 310006, P.R. China; [3]Second Department of Orthopedics and Traumatology, The Second Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, Zhejiang 310005, P.R. China

Received May 27, 2026; Accepted August 28, 2026

DOI: 10.3892/mmr.2026.14020

**Abstract.** Mitochondria-associated endoplasmic reticulum membranes (MAMs) are specialized endoplasmic reticulum (ER) membrane domains at ER-mitochondrial contact sites that coordinate $Ca^{2+}$ transfer, lipid exchange, mitochondrial quality control and cellular stress responses. In osteoporosis, intervertebral disc degeneration, osteoarthritis and sarcopenia/skeletal muscle atrophy, altered ER-mitochondrial communication has been linked to recurrent disturbances in $Ca^{2+}$ homeostasis, mitochondrial function, ER stress, inflammatory signaling and cell fate. However, evidence for MAM involvement varies markedly in directness and biological context. This narrative review compares these evidence patterns and their therapeutic implications across degenerative musculoskeletal disorders. Direct structural and causal evidence is most developed in intervertebral disc degeneration and selected osteoarthritis models; osteoporosis is supported mainly by studies of MAM-associated regulators and functional pathways, whereas sarcopenia-specific mechanisms remain largely informed by aging muscle and related experimental models. The direction and consequences of contact remodeling also vary with cell type, metabolic state and disease stage, arguing against a uniform gain- or loss-of-contact model. Interventions targeting contact-site regulators or MAM-related $Ca^{2+}$ and mitochondrial pathways have shown preclinical benefit, but MAM-specific target engagement and human validation remain limited. Progress will require paired structural and functional assessment together with validation in clinically characterized human tissues and patient-derived systems.

*Correspondence to:* Professor Kang Liu, Second Department of Orthopedics and Traumatology, The Second Affiliated Hospital of Zhejiang Chinese Medical University, 318 Chaowang Road, Gongshu, Hangzhou, Zhejiang 310005, P.R. China
E-mail: liukang1982@163.com

*Contributed equally

*Abbreviations:* ASC, apoptosis-associated speck-like protein containing a CARD; ATF4, activating transcription factor 4; BAP31, B-cell receptor-associated protein 31; BCL2L13, BCL2-like 13; BiP, binding immunoglobulin protein; BK channel, large-conductance $Ca^{2+}$-activated $K^+$ channel; cZFP609, circular RNA ZFP609; DRP1, dynamin-related protein 1; ED-71, eldecalcitol; ER, endoplasmic reticulum; E-Syt1, extended synaptotagmin 1; Fis1, mitochondrial fission 1 protein; FKBP8, FK506-binding protein 8; FUNDC1, FUN14 domain-containing protein 1; GRP75, glucose-regulated protein 75; IMM, inner mitochondrial membrane; IP3R, inositol 1,4,5-trisphosphate receptor; IRE1α, inositol-requiring enzyme 1α; ITPR1, inositol 1,4,5-trisphosphate receptor type 1; IVDD, intervertebral disc degeneration; LRRK2, leucine-rich repeat kinase 2; MAMs, mitochondria-associated endoplasmic reticulum membranes; MCU, mitochondrial calcium uniporter; MERCs, mitochondria-endoplasmic reticulum contact sites; MFN2, mitofusin 2; MITOL, mitochondrial ubiquitin ligase; NFATc1, nuclear factor of activated T cells 1; NLRP3, NLR family pyrin domain containing 3; NLRX1, NLR family member X1; OA, osteoarthritis; OMM, outer mitochondrial membrane; OPA1, OPA1 mitochondrial dynamin-like GTPase; OPTN, optineurin; ORP5/8, oxysterol-binding protein-related proteins 5 and 8; PACS-2, phosphofurin acidic cluster sorting protein 2; PDZD8, PDZ domain-containing protein 8; PERK, protein kinase RNA-like endoplasmic reticulum kinase; PINK1, PTEN-induced kinase 1; PRKN, parkin RBR E3 ubiquitin protein ligase; PSD, phosphatidylserine decarboxylase; PSS, phosphatidylserine synthase; PTPIP51, protein tyrosine phosphatase-interacting protein 51; PTPN1, protein tyrosine phosphatase non-receptor type 1; RANKL, receptor activator of nuclear factor-κB ligand; REEP5, receptor accessory protein 5; ROS, reactive oxygen species; S1P, site-1 protease; SERCA, sarco/endoplasmic reticulum $Ca^{2+}$-ATPase; Sig-1R, sigma-1 receptor; SIRT3, sirtuin 3; SLC25A5/ANT2, solute carrier family 25 member 5/adenine nucleotide translocator 2; SLC39A7, solute carrier family 39 member 7; SP1, specificity protein 1; SR, sarcoplasmic reticulum; SYNJ2BP, synaptojanin 2 binding protein; TRα, thyroid hormone receptor α; VAPB, vesicle-associated membrane protein-associated protein B; VDAC1, voltage-dependent anion channel 1

*Key words:* mitochondria-associated endoplasmic reticulum membranes, ER-mitochondrial contacts, organelle communication, musculoskeletal degeneration, mitochondrial dysfunction, endoplasmic reticulum stress, ferroptosis

**Contents**

1. Introduction
2. MAM biology in disease
3. Role of MAMs in degenerative musculoskeletal disorders
4. Therapeutic perspectives
5. Conclusions

## 1. Introduction

Aging is accompanied by progressive deterioration of musculoskeletal tissue homeostasis, contributing to chronic pain, impaired mobility, fragility and loss of physical independence (1-5). Osteoporosis, intervertebral disc degeneration, osteoarthritis (OA) and sarcopenia arise in distinct tissues and differ markedly in clinical presentation, yet several cellular abnormalities recur across these disorders, including disrupted $Ca^{2+}$ homeostasis, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, oxidative stress, inflammatory dysregulation and altered cell fate (6-10). This convergence has focused increasing attention on communication between intracellular organelles as a component of musculoskeletal degeneration.

Mitochondria-associated endoplasmic reticulum membranes (MAMs) are specialized ER membrane domains located at sites of close apposition to mitochondria, where they coordinate $Ca^{2+}$ transfer, lipid exchange, mitochondrial metabolism and quality control, and stress signaling (11,12). Studies have implicated MAM-associated molecules and ER-mitochondrial communication in osteoclast and osteoblast function, nucleus pulposus cell degeneration, chondrocyte homeostasis, and age-related skeletal muscle dysfunction (13-17). These findings place the ER-mitochondrial interface within several pathways relevant to musculoskeletal degeneration.

Current evidence is heterogeneous in both directness and biological context. Certain studies directly assessed ER-mitochondrial contact architecture or manipulated contact-site regulators (14,17,18), whereas others inferred MAM involvement from $Ca^{2+}$ transfer, mitochondrial dysfunction or ER stress without measuring the interface itself (15,19-21). Contact remodeling may also differ in direction and biological consequence according to cell type, metabolic state and disease stage (15,16,22-24), and human mechanistic evidence remains limited. The pathological significance of MAM dysregulation may therefore lie less in a simple increase or decrease in ER-mitochondrial contact than in loss of context-appropriate homeostasis. The present narrative review critically compares mechanistic evidence across osteoporosis, intervertebral disc degeneration, OA/cartilage degeneration and sarcopenia/skeletal muscle atrophy, with emphasis on the directness of evidence, cross-disease differences, unresolved questions and therapeutic implications.

*Literature search*. Literature searches were conducted in PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Web of Science (https://www.webofscience.com/) from database inception through to August 15, 2026. Search terms combined 'mitochondria-associated endoplasmic reticulum membrane(s)', 'MAM(s)', 'ER-mitochondrial contact(s)' and 'MERC(s)' with 'osteoporosis', 'intervertebral disc degeneration', 'osteoarthritis', 'sarcopenia' and 'skeletal muscle atrophy'. Peer-reviewed studies examining MAM structure, MAM-associated molecules or ER-mitochondrial communication in relevant cellular, animal or human tissue models were prioritized. Studies outside the musculoskeletal scope, duplicate reports and articles with only peripheral relevance to ER-mitochondrial communication were excluded. Reference lists of key articles were also screened for additional relevant studies.

## 2. MAM biology in disease

*Core structural and functional features relevant to disease interpretation*. MAMs are dynamic ER membrane domains located at sites of close apposition to mitochondria. Their extent, spacing and molecular composition vary across cell types and physiological states (25-30). ER-mitochondrial contacts are organized by multiple tethering and regulatory systems, including mitofusin 2 (MFN2), vesicle-associated membrane protein-associated protein B-protein tyrosine phosphatase-interacting protein 51, mitochondrial fission 1 protein-B-cell receptor-associated protein 31 and PDZ domain-containing protein 8 (31-37), while the inositol 1,4,5-trisphosphate receptor (IP3R)-glucose-regulated protein 75 (GRP75)-voltage-dependent anion channel 1 (VDAC1) complex provides a major route for $Ca^{2+}$ transfer from the ER to mitochondria (38,39).

$Ca^{2+}$ transfer at these interfaces couples intracellular signaling to mitochondrial metabolism and stress responses (19,38,39). Excessive transfer can produce mitochondrial $Ca^{2+}$ overload, oxidative stress, loss of membrane potential and cell injury (19,40). MAMs also support non-vesicular phospholipid exchange between the two organelles. Phosphatidylserine synthesized in the ER is transferred to mitochondria for conversion to phosphatidylethanolamine, while oxysterol-binding protein-related proteins 5 and 8 and extended synaptotagmin 1 participate in lipid transfer and the maintenance of mitochondrial membrane composition and respiration (41-45). Direct evidence linking this lipid-transfer machinery to musculoskeletal degeneration remains sparse. The major structural and signaling modules of MAMs are summarized in Fig. 1.

ER-mitochondrial contacts also participate in mitochondrial fission, mitophagy and stress signaling. Dynamin-related protein 1 (DRP1), phosphofurin acidic cluster sorting protein 2 (PACS-2)/receptor accessory protein 5 and FUN14 domain-containing protein 1 link contact-site organization to mitochondrial dynamics and quality control (46-50), whereas Sigma-1 receptor (Sig-1R), inositol-requiring enzyme 1α (IRE1α)/mitochondrial ubiquitin ligase and protein kinase RNA-like endoplasmic reticulum kinase (PERK)/MFN2 connect the interface to ER stress responses (51-53). Autophagosome formation can initiate at ER-mitochondrial contacts, and disturbances at these sites have also been linked to apoptosis and ferroptosis (54-56).

ER-mitochondrial stress is also coupled to inflammasome activation. During NLR family pyrin domain containing 3 (NLRP3) activation, NLRP3 and the adaptor apoptosis-associated speck-like protein containing a CARD

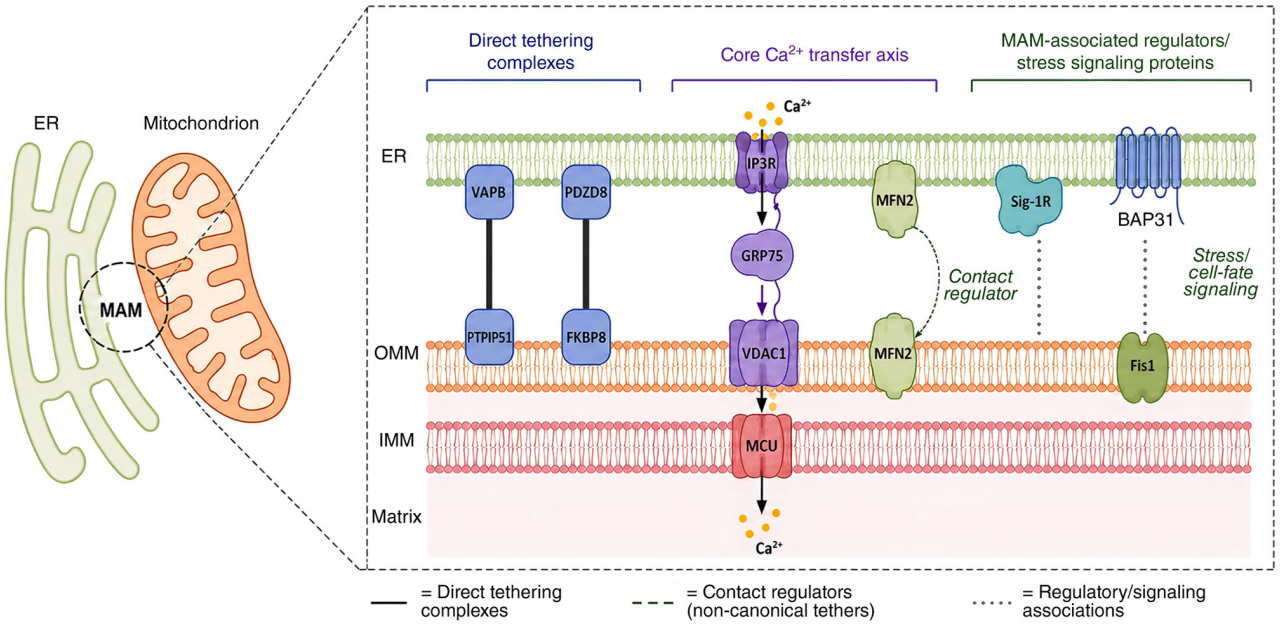


Figure 1. Molecular organization of MAMs. MAMs are specialized ER domains closely apposed to mitochondria that coordinate inter-organelle communication. The enlarged interface illustrates representative tethering and regulatory modules, including VAPB-PTPIP51 and PDZD8-FKBP8, the IP3R-GRP75-VDAC1-MCU $Ca^{2+}$ transfer axis, MFN2-mediated contact regulation, and MAM-associated Sig-1R and BAP31-Fis1 signaling. Solid lines denote direct tethering interactions, dashed lines denote contact regulation and dotted lines denote regulatory or signaling associations. BAP31, B-cell receptor-associated protein 31; ER, endoplasmic reticulum; Fis1, mitochondrial fission 1 protein; FKBP8, FK506-binding protein 8; GRP75, glucose-regulated protein 75; IMM, inner mitochondrial membrane; IP3R, inositol 1,4,5-trisphosphate receptor; MAMs, mitochondria-associated endoplasmic reticulum membranes; MCU, mitochondrial calcium uniporter; MFN2, mitofusin 2; OMM, outer mitochondrial membrane; PDZD8, PDZ domain-containing protein 8; PTPIP51, protein tyrosine phosphatase-interacting protein 51; Sig-1R, sigma-1 receptor; VAPB, vesicle-associated membrane protein-associated protein B; VDAC1, voltage-dependent anion channel 1.

redistribute toward ER-mitochondrial regions, while mitochondrial reactive oxygen species (ROS) and $Ca^{2+}$ signaling contribute to inflammasome assembly and activation (57,58). Direct evidence linking MAMs to NLRP3 activation in degenerative musculoskeletal tissues remains limited. The core MAM-associated modules relevant to musculoskeletal degeneration are summarized in Table I (59-62).

*Direct MAM evidence vs. MAM-related functional inference*. Evidence for MAM involvement varies depending on how directly ER-mitochondrial contacts are examined. Structural or biochemical assessment of contact sites by ultrastructural imaging, MAM fractionation or contact-site proteomics provides the most direct evidence, particularly when combined with perturbation of tethering or contact-site regulators and corresponding phenotypic changes (13,14,18,25,63). Studies of MAM-resident or tethering proteins also provide mechanistic evidence, but changes in these proteins do not establish contact-site remodeling unless MAM architecture is measured. Other studies infer MAM involvement from ER-to-mitochondrial $Ca^{2+}$ transfer, mitochondrial $Ca^{2+}$ overload, ER stress or mitochondrial dysfunction (15,19-21). These processes are closely linked to the ER-mitochondrial interface but are not specific measures of MAM structure.

Disease-specific causal evidence is most developed in intervertebral disc degeneration (IVDD), where disrupted MAM integrity and phenotypic rescue have been linked to synaptojanin 2 binding protein (SYNJ2BP) and PACS-2 (14,18). In osteoporosis, the strongest data concern MFN2- and Sig-1R-dependent regulation of osteoclast function, with additional evidence from osteoblast and vascular models (15,64-67). OA studies now include direct assessment of abnormal ER-mitochondrial contacts (17,68), although the number of mechanistic studies remains small. Aging skeletal muscle has been examined using ultrastructural and proteomic approaches (13,69,70); evidence specific to clinical sarcopenia, however, still largely comes from aging, hereditary myopathy and metabolic models (21-24,71-74).

## 3. Role of MAMs in degenerative musculoskeletal disorders

*Osteoporosis*. Osteoporosis is a systemic skeletal disorder characterized by low bone mass and deterioration of bone microarchitecture, resulting in increased bone fragility and fracture risk (8). Current MAM-related evidence is concentrated in osteoclast biology, with additional findings from osteoblast-lineage cells and the bone vascular microenvironment.

Jung *et al* (15) showed that MFN2 promotes receptor activator of nuclear factor-κB ligand (RANKL)-induced osteoclast differentiation through the $Ca^{2+}$-calcineurin-nuclear factor of activated T cells 1 (NFATc1) axis. Ballard *et al* (65) further showed that its tethering function is required for this effect: *Mfn2* deficiency impaired store-operated $Ca^{2+}$ entry, reduced NFATc1 activation and increased bone mass. Wei *et al* (64) identified a related mechanism involving the MAM-localized Sig-1R, which suppresses osteoclastogenesis by promoting ER-associated degradation of sarco/endoplasmic reticulum $Ca^{2+}$-ATPase 2 (SERCA2); deficiency of the gene encoding

Table I. Core structural and functional modules of MAMs relevant to musculoskeletal degeneration.

| Core MAM-associated module | Representative molecules/complexes | Principal function at the ER-mitochondrial interface | Relevance to musculoskeletal degeneration | (Refs.) |
|---|---|---|---|---|
| Contact organization and tethering | MFN2; VAPB-PTPIP51; PDZD8; Fis1-BAP31 | Maintain ER-mitochondrial proximity and organize contact-site architecture | Altered contact organization can disrupt inter-organelle signaling and stress adaptation | (31-37) |
| $Ca^{2+}$ transfer and metabolic coupling | IP3R-GRP75-VDAC1; MCU; SERCA | Couple ER $Ca^{2+}$ release to mitochondrial uptake and metabolic responses | Dysregulated $Ca^{2+}$ transfer contributes to mitochondrial $Ca^{2+}$ overload, oxidative stress and cell injury | (19,38-40,59-62) |
| Lipid transfer and metabolic coordination | PSS/PSD; ORP5/8; E-Syt1 | Mediate phospholipid exchange and support mitochondrial membrane composition and respiration | Direct evidence linking this machinery to musculoskeletal degeneration remains sparse | (41-45) |
| Mitochondrial dynamics and quality control | DRP1; PACS-2/REEP5; FUNDC1 | Coordinate mitochondrial fission, distribution, mitophagy and contact-site remodeling | Disturbance of these processes is associated with mitochondrial fragmentation, impaired quality control and reduced stress tolerance | (46-50) |
| Stress, cell-fate and inflammatory signaling | Sig-1R; IRE1α/MITOL; PERK/MFN2; NLRP3/ASC (activation-associated recruitment) | Integrate ER stress with autophagy, apoptosis, ferroptosis and inflammasome signaling | Connect ER-mitochondrial stress with degenerative cell responses and inflammatory signaling | (51-58) |

ASC, apoptosis-associated speck-like protein containing a CARD; BAP31, B-cell receptor-associated protein 31; DRP1, dynamin-related protein 1; ER, endoplasmic reticulum; E-Syt1, extended synaptotagmin 1; Fis1, mitochondrial fission 1 protein; FUNDC1, FUN14 domain-containing protein 1; GRP75, glucose-regulated protein 75; IP3R, inositol 1,4,5-trisphosphate receptor; IRE1α, inositol-requiring enzyme 1α; MAMs, mitochondria-associated endoplasmic reticulum membranes; MCU, mitochondrial calcium uniporter; MFN2, mitofusin 2; MITOL, mitochondrial ubiquitin ligase; NLRP3, NLR family pyrin domain containing 3; ORP5/8, oxysterol-binding protein-related proteins 5 and 8; PACS-2, phosphofurin acidic cluster sorting protein 2; PDZD8, PDZ domain-containing protein 8; PERK, protein kinase RNA-like endoplasmic reticulum kinase; PSD, phosphatidylserine decarboxylase; PSS, phosphatidylserine synthase; PTPIP51, protein tyrosine phosphatase-interacting protein 51; REEP5, receptor accessory protein 5; SERCA, sarco/endoplasmic reticulum $Ca^{2+}$-ATPase; Sig-1R, sigma-1 receptor; VAPB, vesicle-associated membrane protein-associated protein B; VDAC1, voltage-dependent anion channel 1.

Sig-1R (*Sigmar1*) aggravated bone loss in ovariectomized mice. PTEN-induced kinase 1 (PINK1) has also been linked to MAM-dependent $Ca^{2+}$ signaling in osteoclasts, although these data were obtained in periodontitis-associated bone loss rather than osteoporosis (75).

In osteolineage cells, *Mfn2* deletion produced a different skeletal phenotype. Osteolineage-specific *Mfn2* depletion increased cortical bone formation in female mice and enhanced oxygen consumption and mineralization during early osteogenic differentiation (16). The contrasting effects of MFN2 in osteoclasts and osteolineage cells argue against a uniform skeletal role across bone-cell compartments. In diabetic osteopenia, BK channel activation preserved osteoblast function and reduced bone loss through regulation of mitochondrial $Ca^{2+}$ and solute carrier family 25 member 5/adenine nucleotide translocator 2-PINK1-parkin RBR E3 ubiquitin protein ligase-mediated mitophagy (66). ER-mitochondrial contact remodeling, however, was not directly examined in this study.

MAM-associated regulation also extends to the bone vascular compartment. Wang *et al* (67) reported that eldecalcitol (ED-71) preserved mitochondrial $Ca^{2+}$ homeostasis in type H vascular endothelial cells, reduced glucocorticoid-induced senescence and improved angiogenesis-osteogenesis coupling. Mechanistic support in osteoporosis is currently strongest in osteoclasts. Direct structural evidence of MAM remodeling remains sparse and several supporting studies derive from periodontitis-, diabetes- or glucocorticoid-associated bone-loss models.

*IVDD*. IVDD is characterized by progressive loss of nucleus pulposus cell homeostasis, extracellular matrix breakdown, cellular senescence and cell death. Evidence for MAM involvement includes both altered ER-mitochondrial ion transfer and direct changes in contact-site integrity.

In nucleus pulposus cells exposed to excessive mechanical compression, Lin *et al* (20) found increased ER stress and ER-mitochondrial $Ca^{2+}$ transfer. Inhibition of ER stress or blockade of the IP3R-GRP75-VDAC1 axis reduced mitochondrial $Ca^{2+}$ overload and poly(ADP-ribose) polymerase-apoptosis-inducing factor-associated programmed necrosis. Zheng *et al* (76) showed that site-1 protease deficiency caused ER distension and increased ER-mitochondrial contacts, while disrupting ER-to-mitochondrial $Ca^{2+}$ transfer and accelerating nucleus pulposus cell senescence and disc degeneration.

Song *et al* (14) observed disrupted MAM integrity in degenerative disc tissue and tert-butyl hydroperoxide-treated nucleus pulposus cells. SYNJ2BP deficiency was associated with mitochondrial $Zn^{2+}$ overload and cellular senescence, whereas SYNJ2BP overexpression promoted MAM formation, stabilized the NLR family member X1 (NLRX1)-solute carrier family 39 member 7 (SLC39A7) complex, restored mitochondrial $Zn^{2+}$ homeostasis and attenuated disc degeneration.

Kang *et al* (18) reported impaired MAM integrity and reduced PACS-2 expression in degenerative human and rat disc tissues and in nucleus pulposus-derived stem cells exposed to an acidic microenvironment. PACS-2 preserved ER-mitochondrial contacts through the specificity protein 1 (SP1)/leucine-rich repeat kinase 2 (LRRK2)/MFN2 axis, reduced ER stress and mitochondrial dysfunction and limited stem-cell apoptosis. Loss of PACS-2 aggravated disc degeneration, whereas its restoration improved the reparative effect of transplanted cells. Human degenerative disc tissues support the presence of MAM disruption, while causal rescue has so far been demonstrated mainly in experimental models.

*OA/cartilage degeneration*. OA is characterized by progressive articular cartilage degeneration and impaired chondrocyte homeostasis. Studies in OA have identified MAM-related transcriptional signatures and experimentally linked ER-mitochondrial communication to chondrocyte dysfunction (17,68,77,78).

Li *et al* (77) identified MAM-related genes associated with OA and cellular senescence, including protein tyrosine phosphatase non-receptor type 1 and inositol 1,4,5-trisphosphate receptor type 1. ER-mitochondrial contacts were not directly assessed in this study. Hou *et al* (17) showed that loss of MFN2 impaired mitochondrial function and cartilage matrix metabolism, with fewer mitochondrial-ER junctions also observed in damaged human cartilage. Sirtuin 3 stabilized MFN2, while MFN2-mediated mitochondrial-ER junctions supported $Ca^{2+}$ homeostasis and reduced chondrocyte senescence. Intra-articular delivery of MFN2 mRNA attenuated cartilage degeneration in experimental OA models.

ER-mitochondrial $Ca^{2+}$ transfer has also been linked to chondrocyte apoptosis. In temporomandibular joint OA, optineurin deficiency enhanced $Ca^{2+}$ transfer through the IP3R-GRP75-VDAC1 complex, increased mitochondrial $Ca^{2+}$ loading and promoted apoptosis (78). Pharmacological inhibition of this pathway reduced $Ca^{2+}$ overload and apoptosis.

Song *et al* (68) showed that inflammatory stress increased aberrant ER-mitochondrial contacts in chondrocytes. Circular RNA ZFP609 (cZFP609) stabilized oligomeric binding immunoglobulin protein (BiP), attenuated IRE1α-associated ER stress, reduced aberrant ER-mitochondrial contacts and suppressed lipid peroxidation and ferroptosis. Intra-articular cZFP609 delivery also reduced cartilage degeneration in an experimental OA model. Human cartilage provides structural evidence of altered ER-mitochondrial contacts, whereas causal rescue and therapeutic testing remain predominantly preclinical.

*Sarcopenia/skeletal muscle atrophy*. Sarcopenia is an age-related skeletal muscle disorder characterized by progressive loss of muscle mass and function. Most structural evidence concerning the ER-mitochondrial interface comes from aging skeletal muscle rather than clinically defined sarcopenia.

Lu *et al* (13) identified age-related changes in MAM ultrastructure and protein composition in striated muscle using electron microscopy and proteomic profiling. Allen *et al* (69) likewise detected early alterations in ER-mitochondrial contacts and MAM protein composition in aging skeletal muscle, changes that were prevented by exercise. Unten *et al* (70) reported increased mitochondria-ER contact sites (MERCs) in myoblasts from older human donors. MERCs denote the physical contacts between the two organelles, whereas MAMs more specifically refer to the membrane domains and molecular components associated with these interfaces.

$Ca^{2+}$ transfer at these contacts has also been linked to age-related muscle atrophy. Shi *et al* (21) showed that age-related reduction of thyroid hormone receptor α increased IP3R type 1-mediated $Ca^{2+}$ transfer and MAM formation, leading to mitochondrial $Ca^{2+}$ overload, mitochondrial dysfunction and skeletal muscle atrophy in mice. Separately, Grepper *et al* (71) localized BCL2-like 13 to ER-mitochondrial contact sites and showed that its loss altered $Ca^{2+}$ dynamics and impaired skeletal muscle function, without changing the contact-site number.

Additional mechanisms have been identified in hereditary and metabolic muscle models. Selenoprotein N-related myopathy is associated with defective ER-mitochondrial contacts and impaired bioenergetics (72), whereas OPA1 mitochondrial dynamin-like GTPase deficiency increases ER-mitochondrial tethering through an activating transcription factor 4-dependent response (22). Metabolic studies have reported both reduced ER-mitochondrial coupling and excessive MAM formation in insulin-resistant skeletal muscle (23,24,74). Clinical validation in well-characterized sarcopenia populations remains limited.

*Cross-disease synthesis*. Recurrent abnormalities in $Ca^{2+}$ signaling, mitochondrial function and ER stress occur across the disorders discussed above, but they do not imply a uniform MAM defect. ER-to-mitochondrial $Ca^{2+}$ transfer has been directly interrogated in several disease models (20,21,78), whereas mitochondrial dysfunction or ER stress alone cannot establish altered contact-site organization. The common molecular pattern therefore reflects convergence on organelle stress pathways more clearly than a uniform structural defect at the ER-mitochondrial interface.

The direction of MAM remodeling also varies by cellular context. MFN2 promotes osteoclast differentiation through $Ca^{2+}$-dependent signaling, whereas osteolineage-specific *Mfn2* depletion enhances cortical bone formation (15,16,65). In

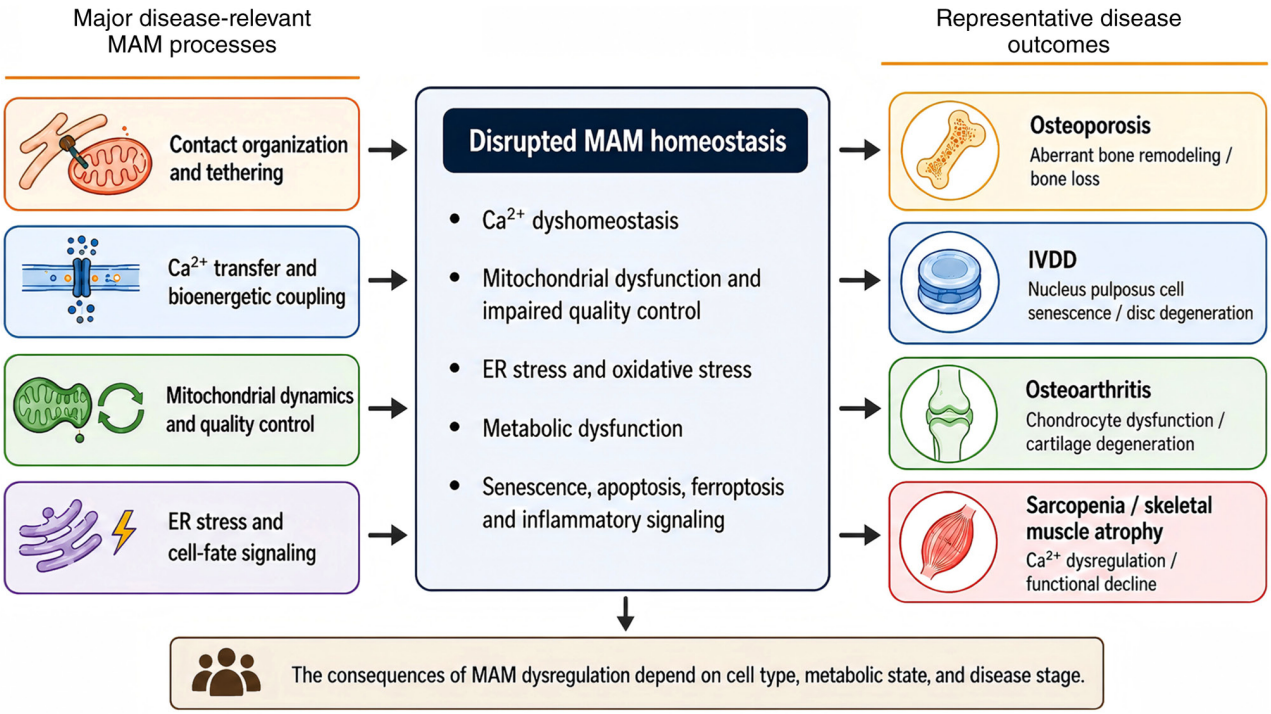


Figure 2. Disease-oriented framework of MAM dysregulation in degenerative musculoskeletal disorders. Major disease-relevant MAM processes, including contact organization and tethering, $Ca^{2+}$ transfer and bioenergetic coupling, mitochondrial dynamics and quality control, and ER stress/cell-fate signaling, converge on disrupted MAM homeostasis. Shared downstream consequences include $Ca^{2+}$ dyshomeostasis, mitochondrial dysfunction, impaired quality control, ER and oxidative stress, metabolic dysfunction and senescence- or cell death-related signaling. These alterations are linked to representative disease outcomes in osteoporosis, intervertebral disc degeneration, osteoarthritis and sarcopenia/skeletal muscle atrophy. The consequences of MAM dysregulation are context-dependent and vary with cell type, metabolic state, and disease stage. ER, endoplasmic reticulum; IVDD, intervertebral disc degeneration; MAM, mitochondria-associated endoplasmic reticulum membrane.

skeletal muscle, both loss of contact integrity and stress-associated increases in ER-mitochondrial tethering have been reported (13,22-24), while endurance exercise can reduce ER-mitochondrial contacts (79). Contact abundance alone is therefore an inadequate marker of dysfunction. These observations point to cell type, metabolic state and disease stage as key determinants of whether contact remodeling is adaptive or maladaptive.

Translational evidence remains uneven across disorders. Direct structural and causal evidence is concentrated in IVDD and selected OA models, whereas osteoporosis and skeletal muscle studies rely more heavily on molecular or functional readouts and preclinical systems. Human interventional validation remains limited, particularly in clinically defined sarcopenia.

Taken together, these observations support a disease-oriented framework in which distinct MAM-associated processes converge on disrupted MAM homeostasis and shared downstream consequences, while giving rise to tissue-specific outcomes across osteoporosis, intervertebral disc degeneration, OA and sarcopenia/skeletal muscle atrophy (Fig. 2). A comparative summary of disease-specific evidence strength, directness and translational status is provided in Table II.

## 4. Therapeutic perspectives

*Modulation of MAM structure and contact-site regulators.* MAM organization can be modified through contact-site regulators, membrane composition and MAM-resident proteins. Genetic restoration of contact-site regulators has been examined in IVDD models. SYNJ2BP overexpression promoted MAM formation and NLRX1-SLC39A7 complex assembly, restored mitochondrial $Zn^{2+}$ homeostasis and reduced nucleus pulposus cell senescence and disc degeneration (14). PACS-2 restoration similarly preserved MAM integrity through the SP1/LRRK2/MFN2 pathway, reduced apoptosis of nucleus pulposus-derived stem cells and improved the reparative efficacy of transplanted cells (18).

Contact organization can also be altered without directly manipulating classical tethering proteins. In OA models, cZFP609 stabilized oligomeric BiP, attenuated IRE1α-associated ER stress, reduced aberrant ER-mitochondrial contacts, and suppressed chondrocyte ferroptosis and cartilage degeneration (68). In palmitic acid-exposed nucleus pulposus cells, phosphatidylcholine increased ER-mitochondrial interactions, restored mitochondrial phosphatidylcholine content and fatty-acid oxidation and alleviated lipotoxic injury (80).

Pharmacological modulation of a MAM-resident protein has been demonstrated in experimental bone-loss models. Sig-1R activation suppressed osteoclastogenesis by promoting ER-associated degradation of SERCA2, whereas *Sigmar1* deficiency aggravated bone loss (64). Local *Sigmar1* overexpression and treatment with the Sig-1R agonist dimemorfan preserved bone mass in experimental models.

*Pharmacological modulation of MAM-related functions.* Beyond direct manipulation of contact-site organization,

Table II. Comparative evidence for MAM involvement in degenerative musculoskeletal disorders.

| Disorder | Principal cells/ tissues | Representative MAM-related molecules/ pathways | Contact-site/ structural evidence | Functional/ mechanistic evidence | Human evidence/ translational status | (Refs.) |
|---|---|---|---|---|---|---|
| Osteoporosis | Osteoclasts; osteoblast-lineage cells; type H vascular endothelial cells | MFN2; Sig-1R/ SERCA2; PINK1; SLC25A5/ANT2-PINK1-PRKN | Direct structural assessment of MAM remodeling remains limited; most studies examine MAM-associated proteins or $Ca^{2+}$-related functions | MFN2-dependent $Ca^{2+}$-NFATc1 signaling regulates osteoclastogenesis; Sig-1R suppresses osteoclast differentiation; MAM-related $Ca^{2+}$ and mitochondrial quality-control pathways have also been implicated in osteoblast and vascular models | Evidence remains predominantly preclinical and includes ovariectomy-, periodontitis-, diabetes- and glucocorticoid-associated bone-loss models; direct human validation is limited | (15,16,64-67,75) |
| Intervertebral disc degeneration | Nucleus pulposus cells; nucleus pulposus-derived stem cells | SYNJ2BP; PACS-2; S1P; IP3R-GRP75-VDAC1; NLRX1-SLC39A7; SP1/ LRRK2/MFN2 | Altered MAM integrity has been demonstrated in degenerative disc tissues and experimental models; SYNJ2BP and PACS-2 manipulation modifies contact-site integrity | Abnormal ER-mitochondrial $Ca^{2+}$/$Zn^{2+}$ handling is linked to ER stress, mitochondrial dysfunction, senescence and apoptosis | Human degenerative disc tissues show MAM abnormalities; causal rescue and therapeutic testing remain mainly preclinical | (14,18,20, 76) |
| Osteoarthritis/ cartilage degeneration | Articular chondrocytes; human cartilage; temporomandibular joint chondrocytes | MFN2/SIRT3; OPTN; IP3R-GRP75-VDAC1; cZFP609/BiP-IRE1α; PTPN1; ITPR1 | Altered mitochondrial-ER junctions have been observed in damaged human cartilage and experimental OA; inflammatory stress can induce aberrant ER-mitochondrial contacts | MFN2-dependent contact regulation affects chondrocyte homeostasis; abnormal $Ca^{2+}$ transfer promotes apoptosis; cZFP609 regulates ER stress, ferroptosis and contact remodeling | Human cartilage provides structural evidence; causal rescue and therapeutic intervention remain predominantly preclinical | (17,68, 77,78) |
| Sarcopenia/ skeletal muscle atrophy | Skeletal muscle fibers; myoblasts | TRα/IP3R1; BCL2L13; OPA1/ATF4 | Aging skeletal muscle shows ultrastructural and proteomic remodeling of MAMs/MERCs; altered | Age-related MAM $Ca^{2+}$ transfer contributes to mitochondrial $Ca^{2+}$ overload and muscle atrophy; hereditary and | Human evidence derives mainly from aging skeletal muscle and myoblast studies; mechanistic | (13,21-24, 69-74) |

Table II. Continued.

| Disorder | Principal cells/ tissues | Representative MAM-related molecules/ pathways | Contact-site/ structural evidence | Functional/ mechanistic evidence | Human evidence/ translational status | (Refs.) |
|---|---|---|---|---|---|---|
| | | | contacts have also been observed in aged human myoblasts | metabolic models show both reduced and excessive ER-mitochondrial coupling | evidence specific to clinically defined sarcopenia remains limited | |

Evidence strength and directness differ across musculoskeletal disorders. Direct structural and causal evidence is most developed in intervertebral disc degeneration and selected osteoarthritis models; osteoporosis is supported mainly by studies of MAM-associated regulators and functional pathways, whereas sarcopenia-specific evidence remains largely derived from aging skeletal muscle and related experimental models. Recurrent pathological axes across these conditions include $Ca^{2+}$ dyshomeostasis, mitochondrial dysfunction, endoplasmic reticulum stress and altered cell-fate regulation. ATF4, activating transcription factor 4; BCL2L13, BCL2-like 13; BiP, binding immunoglobulin protein; cZFP609, circular RNA ZFP609; ER, endoplasmic reticulum; GRP75, glucose-regulated protein 75; IP3R, inositol 1,4,5-trisphosphate receptor; IRE1α, inositol-requiring enzyme 1α; ITPR1, inositol 1,4,5-trisphosphate receptor type 1; IVDD, intervertebral disc degeneration; LRRK2, leucine-rich repeat kinase 2; MAM(s), mitochondria-associated endoplasmic reticulum membrane(s); MERCs, mitochondria-endoplasmic reticulum contact sites; MFN2, mitofusin 2; NFATc1, nuclear factor of activated T cells 1; NLRX1, NLR family member X1; OA, osteoarthritis; OPA1, OPA1 mitochondrial dynamin-like GTPase; OPTN, optineurin; PACS-2, phosphofurin acidic cluster sorting protein 2; PINK1, PTEN-induced kinase 1; PRKN, parkin RBR E3 ubiquitin protein ligase; PTPN1, protein tyrosine phosphatase non-receptor type 1; S1P, site-1 protease; SERCA2, sarco/endoplasmic reticulum $Ca^{2+}$-ATPase 2; Sig-1R, sigma-1 receptor; SIRT3, sirtuin 3; SLC25A5/ANT2, solute carrier family 25 member 5/adenine nucleotide translocator 2; SLC39A7, solute carrier family 39 member 7; SP1, specificity protein 1; SYNJ2BP, synaptojanin 2 binding protein; TRα, thyroid hormone receptor α; VDAC1, voltage-dependent anion channel 1.

pharmacological studies have largely targeted functional processes coordinated at the ER-mitochondrial interface, particularly $Ca^{2+}$ handling and mitochondrial homeostasis. Ruthenium Red suppressed RANKL-induced ROS production and NFATc1 activation, inhibited osteoclastogenesis and reduced bone loss in ovariectomized mice (81). Mitochondria-targeted $Ca^{2+}$-regulating nanoparticles reduced mitochondrial $Ca^{2+}$ overload and pro-inflammatory macrophage polarization in experimental OA (82). In glucocorticoid-induced bone loss, ED-71 reduced GRP75-dependent MAM-mediated mitochondrial $Ca^{2+}$ overload in type H vascular endothelial cells and attenuated cellular senescence (67).

Proteins controlling $Ca^{2+}$ transfer and mitochondrial permeability have also been targeted in dystrophin-deficient muscle. MKT077 inhibited GRP75-dependent $Ca^{2+}$ transfer from the sarcoplasmic reticulum to mitochondria, reduced mitochondrial $Ca^{2+}$ overload and alleviated muscle pathology in mdx mice (83). Alisporivir improved mitochondrial $Ca^{2+}$ handling and mitochondrial homeostasis in dystrophin-deficient muscle (84), while VBIT-4, a voltage-dependent anion channel inhibitor, reduced mitochondrial $Ca^{2+}$ overload and partially improved muscle pathology in a severe Duchenne muscular dystrophy model (85). The relevance of these findings to sarcopenia remains indirect because the evidence derives from dystrophin-deficient muscle models.

Pharmacological evidence for MAM-linked ER stress signaling is less developed in degenerative musculoskeletal disease. PERK and IRE1α signaling pathways are closely associated with ER-mitochondrial stress communication, but most musculoskeletal studies have examined ER stress without directly assessing changes in MAM organization (86-88).

*Physiological and systemic modulation of ER-mitochondrial communication*. Beyond molecular and pharmacological interventions, ER-mitochondrial communication is also responsive to physiological and metabolic cues. Exercise provides the clearest example in skeletal muscle. Endurance exercise alters ER-mitochondrial contacts in a demand-dependent manner (79), and exercise prevented early age-related abnormalities in these contacts in aging muscle (69). In diabetic skeletal muscle, swimming also modified MAM-related ER stress and mitochondrial dysfunction (73). Exercise-related changes in ER-mitochondrial contacts therefore appear to form part of the broader metabolic adaptation of skeletal muscle.

Metabolic state itself can reshape the ER-mitochondrial interface. Reduced MAM integrity has been associated with skeletal muscle insulin resistance (23), whereas obesity-related activation of pyruvate dehydrogenase kinase 4 can increase ER-mitochondrial contact and impair insulin signaling (24). Muscle-specific p53 deletion likewise modifies MAM organization in diet-induced insulin resistance (74). A smaller number of bioactive interventions have been linked more directly to MAM-related functions. *Polygonatum sibiricum* polysaccharide improved skeletal muscle aging phenotypes by regulating MAM-mediated $Ca^{2+}$ homeostasis (89). Representative experimental interventions targeting MAM structure or MAM-related functions are summarized in Table III.

Table III. Representative experimental interventions targeting MAM structure or MAM-related functions relevant to degenerative musculoskeletal disorders.

| Intervention | MAM-related target or mechanism | Disease/model | Main reported effect | Evidence level and MAM directness | (Refs.) |
|---|---|---|---|---|---|
| SYNJ2BP overexpression | SYNJ2BP-dependent MAM formation; NLRX1-SLC39A7 complex; mitochondrial $Zn^{2+}$ homeostasis | IVDD; nucleus pulposus cells and experimental disc degeneration | Restored MAM formation and mitochondrial $Zn^{2+}$ homeostasis; reduced cellular senescence and disc degeneration | Cell + animal; direct contact-site evidence | (14) |
| PACS-2 overexpression | PACS-2-SP1/ LRRK2/MFN2 axis; MAM integrity | IVDD; degenerative disc tissues, nucleus pulposus-derived stem cells and experimental IVDD | Preserved MAM integrity; reduced ER stress, mitochondrial dysfunction and apoptosis; improved reparative efficacy | Human tissue association + cell/ animal intervention; direct contact-site evidence | (18) |
| cZFP609 delivery | BiP-IRE1α signaling; aberrant ER-mitochondrial contacts | OA; chondrocytes and experimental OA | Reduced aberrant contacts, ER stress, lipid peroxidation and ferroptosis; attenuated cartilage degeneration | Cell + animal; direct contact-site evidence | (68) |
| Phosphatidylcholine | ER-mitochondrial contact formation; mitochondrial phosphatidylcholine content and fatty-acid oxidation | IVDD; palmitic acid- exposed nucleus pulposus cells | Increased ER-mitochondrial interactions, restored mitochondrial lipid metabolism and reduced lipotoxic injury | Cell; direct contact modulation | (80) |
| Dimemorfan (Sig-1R agonist) | MAM-resident Sig-1R; SERCA2 degradation | Osteoclasts and experimental bone-loss models | Suppressed osteoclastogenesis and preserved bone mass | Cell + animal; MAM-resident target evidence | (64) |
| Ruthenium Red | Mitochondrial $Ca^{2+}$ uptake/MCU-associated pathway | Osteoclasts and ovariectomized mice | Reduced mitochondrial $Ca^{2+}$ uptake, ROS production and NFATc1 activation; inhibited osteoclastogenesis and bone loss | Cell + animal; MAM-related functional evidence | (81) |
| Mitochondrial $Ca^{2+}$ nanoregulators | Mitochondrial $Ca^{2+}$ homeostasis | OA; macrophages and experimental OA | Reduced mitochondrial $Ca^{2+}$ dysregulation and pro-inflammatory macrophage polarization; attenuated OA pathology | Cell + animal; MAM-related functional evidence | (82) |
| Eldecalcitol (ED-71) | GRP75-dependent MAM-mediated mitochondrial $Ca^{2+}$ homeostasis | Glucocorticoid-induced bone loss; type H vascular endothelial cells | Reduced mitochondrial $Ca^{2+}$ overload and endothelial senescence; preserved angiogenesis-osteogenesis coupling | Cell + animal; MAM-associated functional evidence | (67) |
| MKT077 | GRP75-dependent ER/SR-to-mitochondrial $Ca^{2+}$ transfer | Dystrophin-deficient mdx mice | Reduced mitochondrial $Ca^{2+}$ overload and skeletal muscle pathology | Animal; contact-associated functional evidence; indirect to sarcopenia | (83) |
| Alisporivir | Mitochondrial $Ca^{2+}$ handling and mitophagy | Dystrophin-deficient mice | Improved mitochondrial $Ca^{2+}$ handling and mitophagy and reduced muscle pathology | Animal; MAM-related functional evidence; indirect to sarcopenia | (84) |

Table III. Continued.

| Intervention | MAM-related target or mechanism | Disease/model | Main reported effect | Evidence level and MAM directness | (Refs.) |
|---|---|---|---|---|---|
| VBIT-4 | VDAC-dependent mitochondrial $Ca^{2+}$ handling | Severe Duchenne muscular dystrophy model | Reduced mitochondrial $Ca^{2+}$ overload and mitochondrial dysfunction; partially attenuated muscle pathology | Animal; MAM-related functional evidence; indirect to sarcopenia | (85) |
| *Polygonatum sibiricum* polysaccharide | MAM-mediated $Ca^{2+}$ homeostasis | Aging C2C12 and myotubes and aged mice | Modulated MAM formation $Ca^{2+}$ homeostasis; improved age-related skeletal muscle phenotypes | Cell + animal; MAM- related functional evidence in aging muscle | (89) |

Evidence level indicates the experimental system in which the intervention was evaluated, whereas MAM directness distinguishes direct assessment or manipulation of ER-mitochondrial contacts from interventions acting on MAM-associated molecules or functions. These categories describe the nature of the available evidence and do not constitute a formal methodological quality grading system. BiP, binding immunoglobulin protein; cZFP609, circular RNA ZFP609; ED-71, eldecalcitol; ER, endoplasmic reticulum; GRP75, glucose-regulated protein 75; IRE1α, inositol-requiring enzyme 1α; IVDD, intervertebral disc degeneration; LRRK2, leucine-rich repeat kinase 2; MAM, mitochondria-associated endoplasmic reticulum membrane; MCU, mitochondrial calcium uniporter; MFN2, mitofusin 2; NFATc1, nuclear factor of activated T cells 1; NLRX1, NLR family member X1; OA, osteoarthritis; PACS-2, phosphofurin acidic cluster sorting protein 2; ROS, reactive oxygen species; SERCA2, sarco/endoplasmic reticulum $Ca^{2+}$-ATPase 2; Sig-1R, sigma-1 receptor; SLC39A7, solute carrier family 39 member 7; SP1, specificity protein 1; SR, sarcoplasmic reticulum; SYNJ2BP, synaptojanin 2 binding protein; VDAC, voltage-dependent anion channel.

*Translational barriers, unresolved issues and future directions*. A major barrier to the field is the lack of a standardized approach for defining MAM remodeling. Transmission electron microscopy and electron tomography provide ultrastructural information on contact distance, extent and three-dimensional organization, whereas proximity ligation assays assess molecular proximity and genetically encoded contact reporters enable dynamic monitoring of ER-mitochondrial interactions. MAM fractionation characterizes the biochemical composition of contact-site fractions, while live-cell $Ca^{2+}$ imaging measures functional ER-to-mitochondrial signaling. These approaches interrogate different features of the interface and are not interchangeable. Changes in contact distance, abundance of a MAM-associated protein or $Ca^{2+}$ transfer alone cannot define the structural and functional state of the contact site. Combining structural and functional measurements within the same experimental system would improve comparison across tissues, models and disease stages (25,63,90).

Molecular profiling can add disease- and cell-specific context to these measurements. MAM-enriched and proximity-labeling proteomics can resolve changes in contact-site composition, whereas single-cell and spatial transcriptomic approaches can localize MAM-associated pathways to defined cell populations and tissue regions. Public transcriptomic datasets from aging and diseased skeletal muscle may also help prioritize candidate regulators and examine their associations with age, disease severity or treatment response. Because transcriptomic signatures do not demonstrate physical ER-mitochondrial contacts, candidates identified through these datasets require structural or functional validation (13,63,77,90).

Human validation remains limited. Most causal studies rely on cultured cells and animal models, whereas human evidence is derived largely from cross-sectional tissue analyses (14,18,23,70). Well-phenotyped patient-derived tissues and primary cells, together with stage-stratified and, where feasible, longitudinal sampling, could help determine whether MAM alterations precede tissue degeneration or arise during disease progression. Integration with clinically relevant phenotypes will also be necessary to establish the disease relevance of contact-site abnormalities across bone, cartilage, intervertebral disc and skeletal muscle.

Therapeutic translation is further constrained by target specificity. Many interventions discussed above modify $Ca^{2+}$ handling, mitochondrial permeability, ER stress or systemic metabolism without acting selectively at MAMs (67,81-85,89). Preclinical studies therefore need to demonstrate target engagement at the ER-mitochondrial interface rather than infer MAM correction solely from downstream mitochondrial or stress responses. Candidate interventions should link contact-site modulation to disease-relevant functional outcomes and ultimately be validated in human tissues or patient-derived systems.

## 5. Conclusions

Current evidence implicates MAMs in musculoskeletal degeneration, but the strength and directness of this evidence vary substantially across diseases and experimental settings. Direct structural and causal evidence is most developed in intervertebral disc degeneration and selected OA models, whereas evidence in osteoporosis derives mainly from MAM-associated regulators and functional pathways, and sarcopenia-specific mechanisms remain largely informed by aging muscle and related experimental models. These differences argue against a uniform MAM defect across musculoskeletal disorders and

indicate that the consequences of ER-mitochondrial contact remodeling depend on cell type, metabolic state and disease stage. Therapeutic modulation of contact-site regulators, $Ca^{2+}$ handling and mitochondrial homeostasis has shown preclinical effects, but MAM-specific target engagement and human validation remain limited. Determining whether MAM modulation can be translated into disease-modifying strategies will require integrated structural and functional assessment, standardized contact-site measurements, and validation in clinically characterized human tissues and patient-derived systems.

**Acknowledgements**

Not applicable.

**Funding**

This study was supported by the National Natural Science Foundation of China (grant no. 82274272) and the Zhejiang Chinese Medical University Institutional Key Research Support Program (grant no. 2025JKZDZC10). The funders had no role in the design of the review, analysis or interpretation of the literature or writing of the manuscript.

**Availability of data and materials**

Not applicable.

**Authors' contributions**

SLM, XLF and YWX drafted the manuscript. YGC, YWX and BBT conceived and designed the review. XZ and ZLP performed the literature search, information extraction and organization of the relevant data, and contributed to reviewing and revising the manuscript KL and XLS critically revised the manuscript and supervised the preparation of the review, providing overall quality control. Data authentication is not applicable. All authors have read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

**Use of artificial intelligence tools**

During the preparation of this work, AI tools were used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

**References**

1. Barone R and Szychlinska MA: Highlights in pathophysiology of the musculoskeletal system. Int J Mol Sci 24: 6412, 2023.
2. Zhang H, Gu W, Wu G and Yu Y: Aging and autophagy: Roles in musculoskeletal system injury. Aging Dis 16: 1438-1451, 2024.
3. De Luca K, Briggs AM, French SD, Ferreira ML, Cross M, Blyth F and March L: Disability burden due to musculoskeletal conditions and low back pain in Australia: Findings from GBD 2019. Chiropr Man Therap 30: 22, 2022.
4. Nguyen AT, Aris IM, Snyder BD, Harris MB, Kang JD, Murray M, Rodriguez EK and Nazarian A: Musculoskeletal health: An ecological study assessing disease burden and research funding. Lancet Reg Health Am 29: 100661, 2024.
5. Qiu K, Wang C, Mo X, Yang G, Huang L, Wu Y and Pan Z: The global macroeconomic burden of musculoskeletal disorders. Int J Surg 111: 7857-7866, 2025.
6. Jiang Y: Osteoarthritis year in review 2021: Biology. Osteoarthritis Cartilage 30: 207-215, 2022.
7. Mao X, Lv K, Qi W, Cheng W, Li T, Sun Y, Jin H, Pan H and Wang D: Research progress on sarcopenia in the musculoskeletal system. Bone Res 13: 78, 2025.
8. Morin SN, Leslie WD and Schousboe JT: Osteoporosis: A review. JAMA 334: 894-907, 2025.
9. Wen ZQ, Lin J, Xie WQ, Shan YH, Zhen GH and Li YS: Insights into the underlying pathogenesis and therapeutic potential of endoplasmic reticulum stress in degenerative musculoskeletal diseases. Mil Med Res 10: 54, 2023.
10. Wu K, Shieh JS, Qin L and Guo JJ: Mitochondrial mechanisms in the pathogenesis of chronic inflammatory musculoskeletal disorders. Cell Biosci 14: 76, 2024.
11. Hong H, Guo Z, Ge J and Li H: Mitochondria-associated endoplasmic reticulum membranes in health and diseases. MedComm (2020) 6: e70379, 2025.
12. Liu Y, Mao ZH, Huang J, Wang H, Zhang X, Zhou X, Xu Y, Pan S, Liu D, Liu Z and Feng Q: Mitochondria-associated endoplasmic reticulum membranes in human health and diseases. MedComm (2020) 6: e70259, 2025.
13. Lu X, Gong Y, Hu W, Mao Y, Wang T, Sun Z, Su X, Fu G, Wang Y and Lai D: Ultrastructural and proteomic profiling of mitochondria-associated endoplasmic reticulum membranes reveal aging signatures in striated muscle. Cell Death Dis 13: 296, 2022.
14. Song Y, Geng W, Zhu D, Liang H, Du Z, Tong B, Wang K, Li S, Gao Y, Feng X, *et al*: SYNJ2BP ameliorates intervertebral disc degeneration by facilitating mitochondria-associated endoplasmic reticulum membrane formation and mitochondrial Zn(2+) homeostasis. Free Radic Biol Med 212: 220-233, 2024.
15. Jung S, Kwon JO, Kim MK, Song MK, Kim B, Lee ZH and Kim HH: Mitofusin 2, a mitochondria-ER tethering protein, facilitates osteoclastogenesis by regulating the calcium-calcineurin-NFATc1 axis. Biochem Biophys Res Commun 516: 202-208, 2019.
16. Zarei A, Ballard A, Cox L, Bayguinov P, Harris T, Davis JL, Roper P, Fitzpatrick J, Faccio R and Veis DJ: Osteolineage depletion of mitofusin2 enhances cortical bone formation in female mice. Bone 148: 115941, 2021.
17. Hou M, Ma Y, Deng Y, Wu Y, Zhu Y, Liu Y, Li X, Yu L, He Z, Wang Y, *et al*: Therapeutic restoration of mitochondria-endoplasmic reticulum cross talk for osteoarthritis. Proc Natl Acad Sci USA 122: e2426992122, 2025.
18. Kang L, Wang J, Zhao C, Li Q, Zhang Z, Zhang H, Jia C, Zhou L, Wang Y, Chen Y, *et al*: PACS-2 mitigates NPSC apoptosis and intervertebral disc degeneration by preserving MAM integrity via the SP1/LRRK2/Mfn2 axis. Adv Sci (Weinh) 13: e11781, 2026.
19. De Ridder I, Kerkhofs M, Lemos FO, Loncke J, Bultynck G and Parys JB: The ER-mitochondria interface, where Ca(2+) and cell death meet. Cell Calcium 112: 102743, 2023.
20. Lin H, Peng Y, Li J, Wang Z, Chen S, Qing X, Pu F, Lei M and Shao Z: Reactive oxygen species regulate endoplasmic reticulum stress and ER-mitochondrial Ca(2+) crosstalk to promote programmed necrosis of rat nucleus pulposus cells under compression. Oxid Med Cell Longev 2021: 8810698, 2021.
21. Shi R, Zhang Y, Chen G, Zhang J, Liu J, Zhu H, Sun M and Duan Y: Ageing-dependent thyroid hormone receptor α reduction activates IP3R1-mediated Ca(2+) transfer in MAM and exacerbates skeletal muscle atrophy in mice. Cell Prolif 59: e70120, 2026.

22. Hinton A Jr, Katti P, Mungai M, Hall DD, Koval O, Shao J, Vue Z, Lopez EG, Rostami R, Neikirk K, *et al*: ATF4-dependent increase in mitochondrial-endoplasmic reticulum tethering following OPA1 deletion in skeletal muscle. J Cell Physiol 239: e31204, 2024.
23. Tubbs E, Chanon S, Robert M, Bendridi N, Bidaux G, Chauvin MA, Ji-Cao J, Durand C, Gauvrit-Ramette D, Vidal H, *et al*: Disruption of mitochondria-associated endoplasmic reticulum membrane (MAM) integrity contributes to muscle insulin resistance in mice and humans. Diabetes 67: 636-650, 2018.
24. Thoudam T, Ha CM, Leem J, Chanda D, Park JS, Kim HJ, Jeon JH, Choi YK, Liangpunsakul S, Huh YH, *et al*: PDK4 augments ER-mitochondria contact to dampen skeletal muscle insulin signaling during obesity. Diabetes 68: 571-586, 2019.
25. Csordás G, Renken C, Várnai P, Walter L, Weaver D, Buttle KF, Balla T, Mannella CA and Hajnóczky G: Structural and functional features and significance of the physical linkage between ER and mitochondria. J Cell Biol 174: 915-921, 2006.
26. Elbaz Y and Schuldiner M: Staying in touch: The molecular era of organelle contact sites. Trends Biochem Sci 36: 616-623, 2011.
27. Cohen S, Valm AM and Lippincott-Schwartz J: Interacting organelles. Curr Opin Cell Biol 53: 84-91, 2018.
28. Barazzuol L, Giamogante F and Calì T: Mitochondria associated membranes (MAMs): Architecture and physiopathological role. Cell Calcium 94: 102343, 2021.
29. Wu H, Carvalho P and Voeltz GK: Here, there, and everywhere: The importance of ER membrane contact sites. Science 361: eaan5835, 2018.
30. Fujimoto M and Hayashi T: New insights into the role of mitochondria-associated endoplasmic reticulum membrane. Int Rev Cell Mol Biol 292: 73-117, 2011.
31. Gomez-Suaga P, Paillusson S, Stoica R, Noble W, Hanger DP and Miller CCJ: The ER-mitochondria tethering complex VAPB-PTPIP51 regulates autophagy. Curr Biol 27: 371-385, 2017.
32. Yeo HK, Park TH, Kim HY, Jang H, Lee J, Hwang GS, Ryu SE, Park SH, Song HK, Ban HS, *et al*: Phospholipid transfer function of PTPIP51 at mitochondria-associated ER membranes. EMBO Rep 22: e51323, 2021.
33. Mórotz GM, Martín-Guerrero SM, Markovinovic A, Paillusson S, Russell MRG, Machado PMP, Fleck RA, Noble W and Miller CCJ: The PTPIP51 coiled-coil domain is important in VAPB binding, formation of ER-mitochondria contacts and IP3 receptor delivery of Ca(2+) to mitochondria. Front Cell Dev Biol 10: 920947, 2022.
34. Iwasawa R, Mahul-Mellier AL, Datler C, Pazarentzos E and Grimm S: Fis1 and Bap31 bridge the mitochondria-ER interface to establish a platform for apoptosis induction. EMBO J 30: 556-568, 2011.
35. Liu Y, Wei Y, Jin X, Cai H, Chen Q and Zhang X: PDZD8 augments endoplasmic reticulum-mitochondria contact and regulates Ca2+ dynamics and Cypd expression to induce pancreatic β-cell death during diabetes. Diabetes Metab J 48: 1058-1072, 2024.
36. Nakamura K, Aoyama-Ishiwatari S, Nagao T, Paaran M, Obara CJ, Sakurai-Saito Y, Johnston J, Du Y, Suga S, Tsuboi M, *et al*: Mitochondrial complexity is regulated at ER-mitochondria contact sites via PDZD8-FKBP8 tethering. Nat Commun 16: 3401, 2025.
37. Naón D, Hernández-Alvarez MI, Shinjo S, Wieczor M, Ivanova S, Martins de Brito O, Quintana A, Hidalgo J, Palacín M, Aparicio P, *et al*: Splice variants of mitofusin 2 shape the endoplasmic reticulum and tether it to mitochondria. Science 380: eadh9351, 2023.
38. Rizzuto R, Pinton P, Carrington W, Fay FS, Fogarty KE, Lifshitz LM, Tuft RA and Pozzan T: Close contacts with the endoplasmic reticulum as determinants of mitochondrial Ca2+ responses. Science 280: 1763-1766, 1998.
39. Szabadkai G, Bianchi K, Várnai P, De Stefani D, Wieckowski MR, Cavagna D, Nagy AI, Balla T and Rizzuto R: Chaperone-mediated coupling of endoplasmic reticulum and mitochondrial Ca2+ channels. J Cell Biol 175: 901-911, 2006.
40. Boehning D, Patterson RL, Sedaghat L, Glebova NO, Kurosaki T and Snyder SH: Cytochrome c binds to inositol (1,4,5) trisphosphate receptors, amplifying calcium-dependent apoptosis. Nat Cell Biol 5: 1051-1061, 2003.
41. Vance JE: Phospholipid synthesis in a membrane fraction associated with mitochondria. J Biol Chem 265: 7248-7256, 1990.
42. Rusiñol AE, Cui Z, Chen MH and Vance JE: A unique mitochondria-associated membrane fraction from rat liver has a high capacity for lipid synthesis and contains pre-Golgi secretory proteins including nascent lipoproteins. J Biol Chem 269: 27494-27502, 1994.
43. Yang X, Liang J, Ding L, Li X, Lam SM, Shui G, Ding M and Huang X: Phosphatidylserine synthase regulates cellular homeostasis through distinct metabolic mechanisms. PLoS Genet 15: e1008548, 2019.
44. Monteiro-Cardoso VF, Rochin L, Arora A, Houcine A, Jaaskelainen E, Kivela AM, Sauvanet C, Le Bars R, Marien E, Dehairs J, *et al*: ORP5/8 and MIB/MICOS link ER-mitochondria and intra-mitochondrial contacts for non-vesicular transport of phosphatidylserine. Cell Rep 40: 111364, 2022.
45. Sassano ML, Van Vliet AR, Vervoort E, Van Eygen S, Van den Haute C, Pavie B, Roels J, Swinnen JV, Spinazzi M, Moens L, *et al*: PERK recruits E-Syt1 at ER-mitochondria contacts for mitochondrial lipid transport and respiration. J Cell Biol 222: e202206008, 2023.
46. Friedman JR, Lackner LL, West M, DiBenedetto JR, Nunnari J and Voeltz GK: ER tubules mark sites of mitochondrial division. Science 334: 358-362, 2011.
47. Feng ST, Wang ZZ, Yuan YH, Wang XL, Sun HM, Chen NH and Zhang Y: Dynamin-related protein 1: A protein critical for mitochondrial fission, mitophagy, and neuronal death in Parkinson's disease. Pharmacol Res 151: 104553, 2020.
48. Li C, Li L, Yang M, Yang J, Zhao C, Han Y, Zhao H, Jiang N, Wei L, Xiao Y, *et al*: PACS-2 ameliorates tubular injury by facilitating endoplasmic reticulum-mitochondria contact and mitophagy in diabetic nephropathy. Diabetes 71: 1034-1050, 2022.
49. Ponneri Babuharisankar A, Kuo CL, Chou HY, Tangeda V, Fan CC, Chen CH, Kao YH and Lee AY: Mitochondrial Lon-induced mitophagy benefits hypoxic resistance via Ca(2+)-dependent FUNDC1 phosphorylation at the ER-mitochondria interface. Cell Death Dis 14: 199, 2023.
50. Chen S, Sun Y, Qin Y, Yang L, Hao Z, Xu Z, Björklund M, Liu W and Hong Z: Dynamic interaction of REEP5-MFN1/2 enables mitochondrial hitchhiking on tubular ER. J Cell Biol 223: e202304031, 2024.
51. Mori T, Hayashi T, Hayashi E and Su TP: Sigma-1 receptor chaperone at the ER-mitochondrion interface mediates the mitochondrion-ER-nucleus signaling for cellular survival. PLoS One 8: e76941, 2013.
52. Muñoz JP, Ivanova S, Sánchez-Wandelmer J, Martínez-Cristóbal P, Noguera E, Sancho A, Díaz-Ramos A, Hernández-Alvarez MI, Sebastián D, Mauvezin C, *et al*: Mfn2 modulates the UPR and mitochondrial function via repression of PERK. EMBO J 32: 2348-2361, 2013.
53. Takeda K, Nagashima S, Shiiba I, Uda A, Tokuyama T, Ito N, Fukuda T, Matsushita N, Ishido S, Iwawaki T, *et al*: MITOL prevents ER stress-induced apoptosis by IRE1α ubiquitylation at ER-mitochondria contact sites. EMBO J 38: e100999, 2019.
54. Hamasaki M, Furuta N, Matsuda A, Nezu A, Yamamoto A, Fujita N, Oomori H, Noda T, Haraguchi T, Hiraoka Y, *et al*: Autophagosomes form at ER-mitochondria contact sites. Nature 495: 389-393, 2013.
55. Li MD, Fu L, Lv BB, Xiang Y, Xiang HX, Xu DX and Zhao H: Arsenic induces ferroptosis and acute lung injury through mtROS-mediated mitochondria-associated endoplasmic reticulum membrane dysfunction. Ecotoxicol Environ Saf 238: 113595, 2022.
56. Rosa N, Ivanova H, Wagner LE II, Kale J, La Rovere R, Welkenhuyzen K, Louros N, Karamanou S, Shabardina V, Lemmens I, *et al*: Bcl-xL acts as an inhibitor of IP(3)R channels, thereby antagonizing Ca(2+)-driven apoptosis. Cell Death Differ 29: 788-805, 2022.
57. Zhou R, Yazdi AS, Menu P and Tschopp J: A role for mitochondria in NLRP3 inflammasome activation. Nature 469: 221-225, 2011.
58. Elliott EI, Miller AN, Banoth B, Iyer SS, Stotland A, Weiss JP, Gottlieb RA, Sutterwala FS and Cassel SL: Cutting edge: Mitochondrial assembly of the NLRP3 inflammasome complex is initiated at priming. J Immunol 200: 3047-3052, 2018.
59. De Vos KJ, Mórotz GM, Stoica R, Tudor EL, Lau KF, Ackerley S, Warley A, Shaw CE and Miller CCJ: VAPB interacts with the mitochondrial protein PTPIP51 to regulate calcium homeostasis. Hum Mol Genet 21: 1299-1311, 2012.

60. Wu S, Lu Q, Wang Q, Ding Y, Ma Z, Mao X, Huang K, Xie Z and Zou MH: Binding of FUN14 domain containing 1 with inositol 1,4,5-trisphosphate receptor in mitochondria-associated endoplasmic reticulum membranes maintains mitochondrial dynamics and function in hearts in vivo. Circulation 136: 2248-2266, 2017.
61. Maione AS, Faris P, Iengo L, Catto V, Bisonni L, Lodola F, Negri S, Casella M, Guarino A, Polvani G, *et al*: Ca(2+) dysregulation in cardiac stromal cells sustains fibro-adipose remodeling in arrhythmogenic cardiomyopathy and can be modulated by flecainide. J Transl Med 20: 522, 2022.
62. Guo X, Wang L, Xuan J, Chen T, Du Y, Qiao H, Zhang S, Sun Z, Wang J and Niu R: Fluoride induces spermatocyte apoptosis by IP3R1/MCU-mediated mitochondrial calcium overload through MAMs. J Hazard Mater 489: 137514, 2025.
63. Poston CN, Krishnan SC and Bazemore-Walker CR: In-depth proteomic analysis of mammalian mitochondria-associated membranes (MAM). J Proteomics 79: 219-230, 2013.
64. Wei X, Zheng Z, Feng Z, Zheng L, Tao S, Zheng B, Huang B, Zhang X, Liu J, Chen Y, *et al*: Sigma-1 receptor attenuates osteoclastogenesis by promoting ER-associated degradation of SERCA2. EMBO Mol Med 14: e15373, 2022.
65. Ballard A, Zeng R, Zarei A, Shao C, Cox L, Yan H, Franco A, Dorn GW II, Faccio R and Veis DJ: The tethering function of mitofusin2 controls osteoclast differentiation by modulating the Ca(2+)-NFATc1 axis. J Biol Chem 295: 6629-6640, 2020.
66. Jiang L, He H, Tang Y, Li J, Reilly S, Xin H, Li Z, Cai H and Zhang X: Activation of BK channels prevents diabetes-induced osteopenia by regulating mitochondrial Ca(2+) and SLC25A5/ANT2-PINK1-PRKN-mediated mitophagy. Autophagy 20: 2388-2404, 2024.
67. Wang X, Zhang W, Liu T, Rong X, Ren Q, Guan S and Li M: ED-71 prevents glucocorticoid-induced bone loss by inhibiting type H vascular endothelial cell senescence through maintaining mitochondria-associated membrane-mediated calcium homeostasis. Cell Signal 139: 112298, 2026.
68. Song Y, Luo JL, Zhang F, Shi J, Du S, Jiang HB, Zhang WD, Chen SY, Zhang DD, Kong P, *et al*: cZFP609 tethering BiP alleviates cartilage degradation in osteoarthritis via remedying aberrant ER-mitochondrial contacts. MedComm (2020) 6: e70405, 2025.
69. Allen RJ, Kronemberger A, Shi Q, Pope RM, Cuadra-Muñoz E, Son W, Song LS, Anderson EJ, Pereira RO and Lira VA: Altered relaxation and mitochondria-endoplasmic reticulum contacts precede major (mal)adaptations in aging skeletal muscle and are prevented by exercise. Aging Cell 24: e70137, 2025.
70. Unten Y, Takafuji K, Masukagami Y, Shiiba I, Horiuchi K, Husnik F, Yanagi S, Tateishi N and Suzuki T: Characterizing mitochondrial phenotypes and MERCS in aged human skeletal muscle myoblasts. PLoS One 21: e0343604, 2026.
71. Grepper D, Tabasso C, Zanou N, Aguettaz AKF, Castro-Sepulveda M, Ziegler DV, Lagarrigue S, Arribat Y, Martinotti A, Ebrahimi A, *et al*: BCL2L13 at endoplasmic reticulum-mitochondria contact sites regulates calcium homeostasis to maintain skeletal muscle function. iScience 27: 110510, 2024.
72. Filipe A, Chernorudskiy A, Arbogast S, Varone E, Villar-Quiles RN, Pozzer D, Moulin M, Fumagalli S, Cabet E, Dudhal S, *et al*: Defective endoplasmic reticulum-mitochondria contacts and bioenergetics in SEPN1-related myopathy. Cell Death Differ 28: 123-138, 2021.
73. Zhang Z, Cui D, Zhang T, Sun Y and Ding S: Swimming differentially affects T2DM-induced skeletal muscle ER stress and mitochondrial dysfunction related to MAM. Diabetes Metab Syndr Obes 13: 1417-1428, 2020.
74. Park S, Jung JK, Heo JY, Thoudam T, Jeong SY, Kang SH, Woo CH, Choi HC, Lee IK, Dan J, *et al*: Inducible skeletal muscle-specific p53 deletion alleviates high-fat diet-induced insulin resistance by modulating mitochondria-associated membrane in obese mice. Redox Biol 86: 103828, 2025.
75. Gou H, Wang T, Chen Y, Zhou Y, Li J and Xu Y: Role of Pink1 in regulating osteoclast differentiation during periodontitis. J Dent Res 104: 753-762, 2025.
76. Zheng B, Zhang X, Kong X, Li J, Huang B, Li H, Ji Z, Wei X, Tao S, Shan Z, *et al*: S1P regulates intervertebral disc aging by mediating endoplasmic reticulum-mitochondrial calcium ion homeostasis. JCI Insight 9: e177789, 2024.
77. Li HM, Wang C, Liu Q, Tong Z, Song B, Wei W and Teng C: Correlation between mitochondria-associated endoplasmic reticulum membrane-related genes and cellular senescence-related genes in osteoarthritis. ACS Omega 9: 19169-19181, 2024.
78. Zhang X, Liu H, Shi Y, Liu Z, Wang Y, Chen S, Yan X, Xu R, Ma J, Chen Q and Guo S: OPTN ameliorates chondrocyte apoptosis in temporomandibular joint osteoarthritis by modulating ER-mitochondria Ca(2+) transfer. Int Immunopharmacol 157: 114796, 2025.
79. Merle A, Jollet M, Britto FA, Goustard B, Bendridi N, Rieusset J, Ollendorff V and Favier FB: Endurance exercise decreases protein synthesis and ER-mitochondria contacts in mouse skeletal muscle. J Appl Physiol (1985) 127: 1297-1306, 2019.
80. Tu S, Dong Y, Li C, Jiang M, Duan L, Zhang W and Chen X: Phosphatidylcholine ameliorates palmitic acid-induced lipotoxicity by facilitating endoplasmic reticulum and mitochondria contacts in intervertebral disc degeneration. JOR Spine 8: e70062, 2025.
81. Wang Y, Li X, Zhou S, Li J, Zhu Y, Wang Q and Zhao F: MCU inhibitor Ruthenium Red alleviates the osteoclastogenesis and ovariectomized osteoporosis via suppressing RANKL-induced ROS production and NFATc1 activation through P38 MAPK signaling pathway. Oxid Med Cell Longev 2022: 7727006, 2022.
82. Lei X, Tan G, Wang Y, Chen L, Cao Y, Si B, Zhen Z, Li B, Jin Y, Wang W and Jin F: Mitochondrial calcium nanoregulators reverse the macrophage proinflammatory phenotype through restoring mitochondrial calcium homeostasis for the treatment of osteoarthritis. Int J Nanomedicine 18: 1469-1489, 2023.
83. Dubinin MV, Stepanova AE, Mikheeva IB, Igoshkina AD, Cherepanova AA, Talanov EY, Khoroshavina EI and Belosludtsev KN: Reduction of mitochondrial calcium overload via MKT077-induced inhibition of glucose-regulated protein 75 alleviates skeletal muscle pathology in dystrophin-deficient mdx mice. Int J Mol Sci 25: 9892, 2024.
84. Dubinin MV, Starinets VS, Mikheeva IB and Belosludtsev KN: Effect of Alisporivir on calcium ion transport and mitophagy in skeletal muscle and heart mitochondria in dystrophin-deficient mice. Bull Exp Biol Med 172: 695-700, 2022.
85. Dubinin MV, Stepanova AE, Mikheeva IB, Igoshkina AD, Kraeva EN, Cherepanova AA, Talanov EY, Polikarpova AV, Astashev ME, Loginov VA and Egorova TV: VBIT-4 rescues mitochondrial dysfunction and reduces skeletal muscle degeneration in a severe model of Duchenne muscular dystrophy. Int J Mol Sci 26: 8845, 2025.
86. Zito E: Targeting ER stress/ER stress response in myopathies. Redox Biol 26: 101232, 2019.
87. Casas-Martinez JC, Samali A and McDonagh B: Redox regulation of UPR signalling and mitochondrial ER contact sites. Cell Mol Life Sci 81: 250, 2024.
88. Zito E and Ferreiro A: Calcium and redox liaison: A key role of selenoprotein N in skeletal muscle. Cells 10: 1116, 2021.
89. Chen W, Shen Z, Dong W, Huang G, Yu D, Chen W, Yan X and Yu Z: Polygonatum sibiricum polysaccharide ameliorates skeletal muscle aging via mitochondria-associated membrane-mediated calcium homeostasis regulation. Phytomedicine 129: 155567, 2024.
90. Hung V, Lam SS, Udeshi ND, Svinkina T, Guzman G, Mootha VK, Carr SA and Ting AY: Proteomic mapping of cytosol-facing outer mitochondrial and ER membranes in living human cells by proximity biotinylation. Elife 6: e24463, 2017.