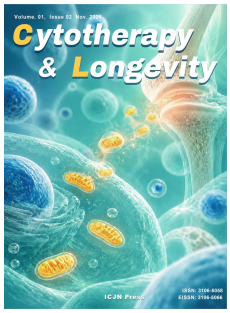
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REVIEW

Therapeutic Potential of Mitochondrial Transfer and Transplantation in Orthopaedic Diseases

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Abstract

Mitochondria are dynamic organelles that can move between cells, but endogenous mitochondrial transfer and therapeutic mitochondrial transplantation are distinct processes. Endogenous transfer describes mitochondrial movement between donor and recipient cells through contact-dependent structures such as tunneling nanotubes and specialized cell processes, or through contact-independent extracellular vesicles and released mitochondria. Connexin 43 (Cx43)-associated gap-junctional communication can regulate transfer in some models, although gap-junction pores cannot carry intact mitochondria; cell fusion is an adjacent phenomenon rather than a transfer route. Mitochondrial dysfunction is implicated in osteoarthritis, rheumatoid arthritis, osteoporosis, sarcopenia, myopathy, and intervertebral disc degeneration. This narrative review extends the discussion beyond bone and joint conditions to skeletal muscle, tendon and ligament, intervertebral disc, and spinal cord. It compares endogenous transfer with therapeutic delivery of isolated mitochondria, organizes evidence by tissue and donor-recipient pair, and relates beneficial or adverse outcomes to mitochondrial quality, route, and disease context. Most therapeutic findings remain preclinical. Standardized product characterization, tissue-appropriate delivery, functional outcomes, and long-term safety will be needed to assess clinical potential.

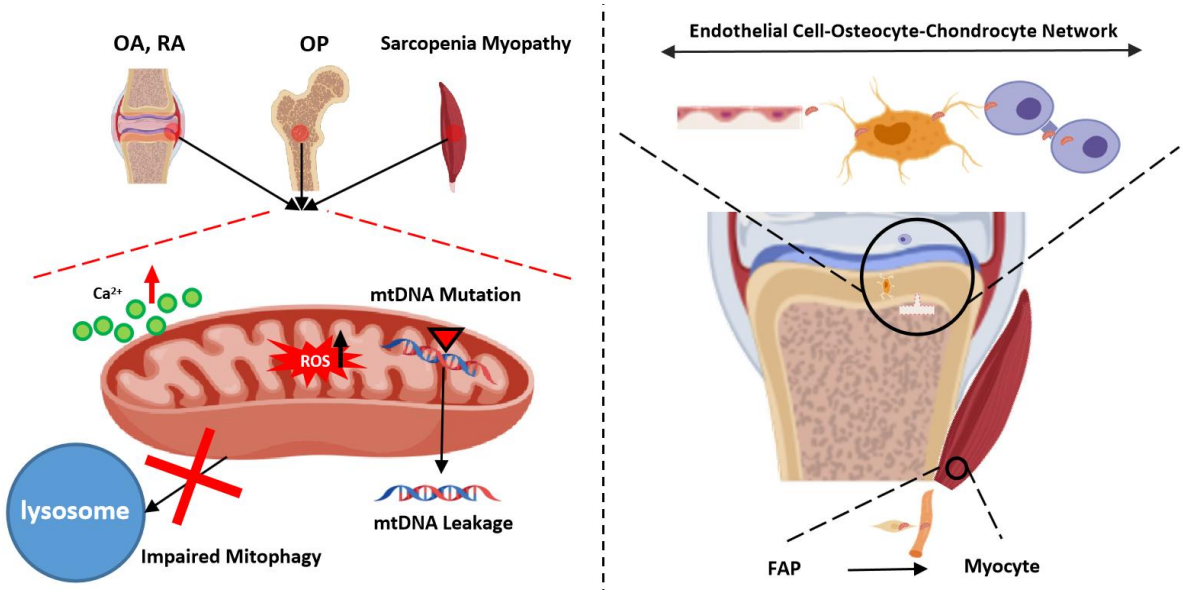
Keywords

Mitochondria transfer; Orthopaedic disease; Musculoskeletal system; Therapeutic strategy

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Graphical Abstract



NOTE: OA: osteoarthritis; RA: rheumatoid arthritis; OP: osteoporosis; ROS: reactive oxygen species; FAP: fibroadipogenic progenitor; mtDNA: mitochondrial deoxyribonucleic acid.

Highlights

- Distinguishes endogenous mitochondrial transfer from therapeutic transplantation.
- Summarizes mitochondrial transfer mechanisms across musculoskeletal tissues.
- Reviews therapeutic applications in bone, cartilage, muscle, tendon, and spinal disorders.
- Highlights the context-dependent beneficial and detrimental effects of mitochondrial transfer.
- Identifies key challenges in mitochondrial delivery, product standardization, and clinical translation.

1. Introduction

Mitochondria are multifunctional organelles in eukaryotic cells[1]. They are best known for their role in oxidative phosphorylation, but also participate in metabolic signaling, redox regulation, calcium homeostasis, immune modulation, and biosynthetic pathways[2]. Over the past decades, mitochondria have been found to play roles in additional cellular processes, including cell signaling, mitophagy, apoptosis, and other regulatory pathways[3]. Owing to their central role in cellular homeostasis, mitochondrial dysfunction is associated with a wide range of diseases[3]. In the musculoskeletal system, mitochondrial dysfunction has been increasingly recognized as a key pathological mechanism underlying various orthopaedic disorders, including osteoarthritis, osteoporosis, and intervertebral disc degeneration[4,5]. Two related but conceptually distinct processes form the foundation of this review. Mitochondrial transfer refers to the naturally occurring intercellular movement of mitochondria between donor and recipient cells through mechanisms such as tunneling nanotubes (TNTs), extracellular vesicles (EVs), gap junction channels, and dendritic structures[6]. In contrast, mitochondrial transplantation denotes the deliberate isolation and delivery of exogenous mitochondria as a therapeutic intervention. We adopt the nomenclature framework recently proposed by Brestoff *et al.* which distinguishes physiological mitochondrial transfer, experimental mitochondrial transfer, mitochondrial transplantation, and cell fusion-related mitochondrial mixing[7]. Throughout this review, these terms are used with precision: "transfer" for endogenous intercellular processes and "transplantation" for therapeutic delivery of isolated mitochondria.

Approximately two decades ago, mitochondria were found to be transferable between cells[8,9]. Under certain conditions, healthy mitochondria can be transferred from donor cells to stressed or injured recipient cells. Although the underlying mechanisms are not yet fully understood, cellular stress, inflammation, and reactive oxygen species (ROS) have been proposed as key triggers of mitochondrial transfer *in vivo*[10]. Importantly, endogenous mitochondrial transfer observed in physiological and pathological contexts provides the biological rationale for developing mitochondrial transplantation as a therapeutic approach.

The earliest evidence of mitochondrial transfer between mammalian cells was reported in 1982[11], when Clark and Shay demonstrated that exposure to isolated mitochondria or co-culture with donor cells could confer antibiotic resistance to cancer cells. In 2005, Koyanagi *et al.* first visualized mitochondrial transfer from rat cardiomyocytes to human endothelial progenitor cells via TNTs using time-lapse video microscopy *in vitro*[12]. Subsequently, in 2006, Prockop *et al.* confirmed that mitochondrial transfer could rescue aerobic respiration in recipient cells *in vitro*[8]. In 2009, McCully *et al.* reported the first application of mitochondrial transplantation as a therapeutic strategy in an animal disease model[13]. In 2011, Rebbeck *et al.* provided evidence suggesting mitochondrial transfer as a pathological process in a canine transmissible cancer *in vivo*[14]. Since then, mitochondrial transfer has attracted increasing attention, and numerous studies and translational trials are ongoing, driven by its potential to emerge as a

novel therapeutic approach in the future.

Recent reviews have discussed the mechanisms and therapeutic applications of mitochondrial transfer in various scenarios. In particular, Wu *et al.* reviewed mitochondrial transfer in bone-related diseases, focusing on bone and joint conditions and delivery strategies, and also discussed mitochondrial transfer from mesenchymal stromal cells to nucleus pulposus cells[15]. This review extends the scope to skeletal muscle, tendons and ligaments, and spinal cord injury. It expands the discussion of intervertebral disc degeneration to include direct intradiscal transplantation and engineered approaches to mitochondrial delivery and incorporates evidence linking mitochondrial transfer to transcortical angiogenesis. Across tissues, we distinguish endogenous intercellular transfer from therapeutic delivery and compare donor-recipient pairs, transfer routes, and functional outcomes to assess how tissue architecture and disease context shape delivery constraints and the potential for benefit or harm.

It is important to distinguish between "mitochondrial transfer" and "mitochondrial transplantation," as these terms are often used interchangeably but denote distinct concepts. Following the nomenclature recommendations proposed by Brestoff *et al.* mitochondrial transfer refers to the naturally occurring intercellular movement of mitochondria between cells, encompassing both physiological and experimental mitochondrial transfer[7]. In contrast, mitochondrial transplantation denotes the active, therapeutic delivery of isolated mitochondria into target cells or tissues. Natural mitochondrial transfer mechanisms serve as the biological foundation that inspires therapeutic mitochondrial transplantation strategies. This review adopts these definitions throughout and uses each term according to the nature of the process being described.

2. Mitochondrial Transfer Type

Mitochondrial transfer can be broadly categorized into contact-dependent and contact-independent mechanisms. Contact-dependent transfer is mediated by direct cell-cell interactions, including TNTs, dendritic structures, and gap junction channel (GJC) dependent pathways, whereas contact-independent transfer occurs via EVs or the release of free mitochondria[6,7,16]. Different investigators have described these transfer modes from distinct perspectives, and the underlying mechanisms remain incompletely understood. Although mitochondrial transfer has been observed to depend on TNTs, dendritic structures, or GJC-related proteins, these pathways are not necessarily mutually exclusive. Instead, multiple transfer mechanisms may operate concurrently within the same biological context. For example, Norris *et al.* demonstrated that GJCs can induce the internalization of annular gap junction vesicles[17]. Moreover, donor cells may deliver mitochondria to recipient cells through different pathways depending on cellular context and mitochondrial status[18].

The mechanisms of mitochondrial transfer exhibit tissue-specific patterns in the musculoskeletal system. In bone, osteocytes utilize their extensive dendritic network for mitochondrial transport driven by Mitofusin 2 (Mfn2) and Vesicle-associated membrane protein-associated protein B/C (VAPB) tethering proteins[19,20]. In cartilage, chondrocytes form cytoplasmic arms and gap junction-mediated connections that facilitate intercellular communication and mitochondrial exchange[21]. In muscle, fibroadipogenic progenitors and myogenic cells engage in bidirectional mitochondrial transfer sensitive to mechanical and metabolic stimuli[22]. Understanding these tissue-specific functional adaptations is essential for designing targeted mitochondrial transplantation strategies for orthopaedic diseases (**Figure 1**).

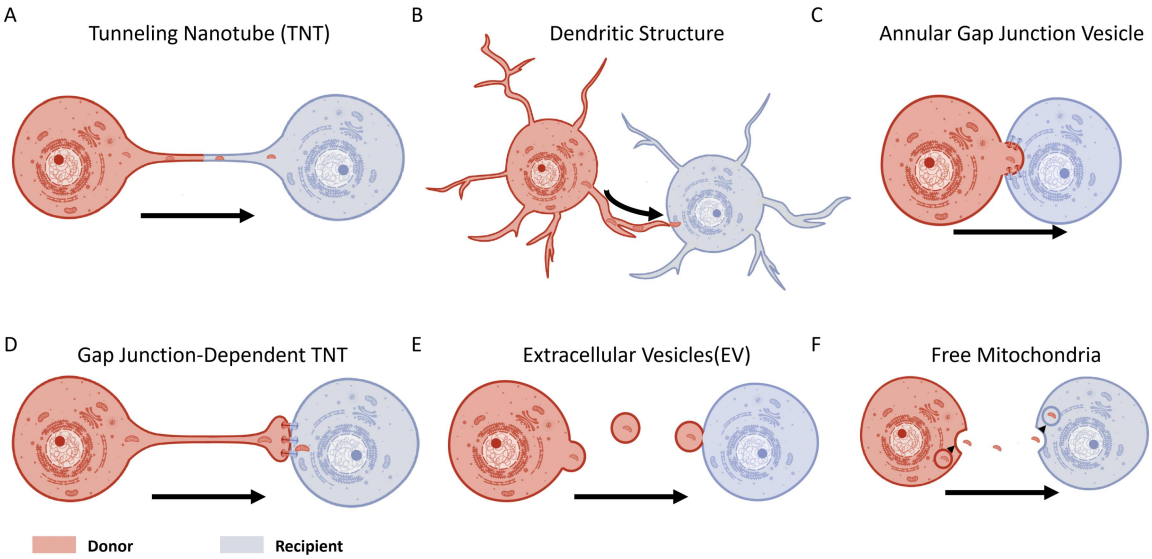


Figure 1. Mechanisms of mitochondrial transfer. (A) Tunneling nanotubes (TNTs): thin membranous conduits (50−200 nm diameter) that directly connect the cytoplasm of adjacent cells, allowing the passage of mitochondria, other organelles, and signaling molecules. TNT formation may involve cell dislodgment, membrane protrusion from a single cell, or coordinated protrusions from both interacting cells; (B) Dendritic structures: specialized cellular processes that form an interconnected network; in bone, osteocyte dendritic networks mediate mitochondrial transfer via endoplasmic reticulum-associated tethering, while in cartilage, chondrocyte cytoplasmic arms extend through the extracellular matrix; (C) Annular gap junction vesicle internalization: connexin-based gap junction channels between adjacent cells can be internalized as double-membrane vesicles containing cytoplasmic contents, including mitochondria; (D) Gap junction-dependent TNT stabilization: gap junction proteins (connexins) contribute to TNT formation and stability; inhibition of gap junction channels disrupts but does not abolish TNT-mediated mitochondrial transfer; (E) Extracellular vesicles (EVs): mitochondria or mitochondrial fragments encapsulated within EVs are released by donor cells and taken up by recipient cells; this mechanism operates over longer distances than contact-dependent transfer; (F) Free mitochondria: naked mitochondria released directly into the extracellular space or circulation without vesicular encapsulation; this mode is both naturally occurring and the basis for artificial mitochondrial transplantation via homogenization of donor cells. (Some elements created with BioGDP.com[23])

2.1 Contact-Dependent Transfer

2.1.1 Tunneling Nanotube

TNTs were first described in 2004 by Rustom and colleagues as thin, membranous structures with diameters ranging from 50 nm to 200 nm[9]. These structures were initially shown to mediate lysosomal transfer between cells, leading to the prediction that other organelles could also be transported via TNTs. In 2005, mitochondrial transfer through TNTs was directly visualized from rat cardiomyocytes to human endothelial progenitor cells using time-lapse video microscopy[12]. The mechanisms underlying TNT formation are heterogeneous and may involve cell dislodgment, membrane protrusion from a single cell, or coordinated membrane protrusions from both interacting cells[24] (**Figure 1A**).

In the musculoskeletal system, TNTs have been observed connecting osteocytes within the lacunar-canalicular network, chondrocytes across the articular cartilage matrix, and forming endothelial cell-osteocyte-chondrocyte communication networks within joints[19,25,26]. These TNT networks are increasingly recognized as conduits for intercellular mitochondrial trafficking that supports tissue homeostasis and stress responses in skeletal tissues.

2.1.2 Dendritic Structure

Dendritic structures represent another form of intercellular conduit for mitochondrial transfer. To date, dendritic structure-mediated mitochondrial transfer has been observed *in vivo* primarily in the nervous system and in osteocytes[19,25,27]. Owing to the limited number of studies, it remains unclear whether dendritic structures should be considered a specialized subtype of TNTs or a distinct transfer mechanism. Further investigations are required to elucidate the structural characteristics, molecular regulation, and functional significance of dendritic structure-mediated mitochondrial transfer (**Figure 1B**).

In orthopaedic contexts, osteocyte dendritic networks are the most extensively characterized mitochondrial transfer conduits, with Mfn2 and VAPB serving as key tethering proteins at endoplasmic reticulum-mitochondria contact sites[19]. Chondrocyte cytoplasmic arms extending through the cartilage matrix represent a morphologically analogous structure[21], suggesting that dendritic mitochondrial transfer may be a conserved mechanism across skeletal cell types.

2.1.3 Adhesion via Gap Junctional Channel

GJCs are protein complexes composed of connexin (Cx) subunits embedded in the cell membrane[28,29]. When the Cx complex of one cell interacts with the Cx complex of a neighboring cell, the two cells form direct adhesion. Previous studies have shown that modulators of GJCs, including enhancers or inhibitors, can significantly influence intercellular mitochondrial transfer[18,30]. However, the pore diameter of GJCs is only 1.50−2 nm, whereas mitochondria are typically 0.50−1 μm in diameter, indicating that GJCs cannot function as a direct conduit for mitochondrial passage. Instead, alternative mechanisms exist: Norris *et al.* demonstrated that GJCs can induce the internalization of annular gap junction vesicles[17] (**Figure 1C**). Other studies found that inhibiting GJC formation disrupted, but did not completely prevent, mitochondrial transfer through TNTs[31,32] (**Figure 1D**). In summary, GJC proteins primarily facilitate cell adhesion and intercellular signaling. The available evidence indicates that their role in mitochondrial transfer is indirect or regulatory rather than serving as physical conduits for intact mitochondria. Instead, GJCs likely contribute to mitochondrial transfer by stabilizing tunneling nanotube (TNT) structures and mediating annular gap junction vesicle internalization, as described above.

In musculoskeletal tissues, connexin 43 (Cx43) is the predominant gap junction protein expressed in osteocytes, chondrocytes, and synovial fibroblasts. Cx43-mediated gap junction communication has been shown to facilitate mitochondrial transfer from mesenchymal stem cells (MSCs) to chondrocytes *in vitro*, and pharmacological inhibition of Cx43 significantly reduces transfer efficiency[33], highlighting the translational relevance of this mechanism for orthopaedic cell therapy.

Contact-dependent mitochondrial transfer may be more complex than previously thought, with multiple transfer mechanisms potentially coexisting within the same biological process. Some studies have shown that inhibiting GJC formation partially impairs TNT-mediated mitochondrial transfer[31,32], suggesting that GJCs may contribute to or interact with TNT-mediated transfer. However, the precise relationship between these structures remains unclear. In addition, studies on dendritic structure-mediated mitochondrial transfer remain limited and have largely been conducted independently of research on TNTs[24-27]. Based on their morphological descriptions, dendritic structures share several characteristics with TNTs, raising the question of whether they represent distinct structures or different forms of the same intercellular connection. Further research is needed to clarify their structural differences, functional roles, and potential relationships in mitochondrial transfer.

2.2 Contact-Independent Transfer

2.2.1 Extracellular Vesicles

EVs represent a heterogeneous group of extracellular particles that differ in size, composition, and biogenesis. Mitochondria-associated extracellular particles reported in the literature span a broad size range, reflecting the heterogeneity of the structures described, including EVs containing mitochondrial components, mitochondria-derived vesicles (MDVs), and larger particles associated with intact mitochondria[7]. These entities should not be considered a single vesicle subtype, and their classification depends on their structural characteristics and mode of formation. Accordingly, size alone is insufficient to distinguish these populations, and the terminology used to describe mitochondrial cargo should reflect the evidence available in each study.

In addition to transferring intact mitochondria, EVs may also carry MDVs. For instance, osteoblasts release both mitochondria and MDVs within EVs in a cluster of differentiation (CD)38-dependent manner. These released EVs have been shown to promote the differentiation of osteoprogenitor cells into osteoblasts, thereby enhancing bone formation in a positive-feedback loop[34] (**Figure 1E**). In bone, Suh *et al.* reported that osteoblasts release mitochondria-associated extracellular particles, including mitochondria and mitochondria-derived vesicles, through a CD38-dependent process. These extracellular particles promoted osteoprogenitor differentiation, suggesting a role for mitochondrial secretion in coupling osteoblast activity to new bone formation[34]. However, this mechanism should be interpreted in the context of the cell type and experimental conditions investigated in the original study. Whether CD38 regulates similar mitochondrial release processes in other musculoskeletal cell populations remains to be established.

Macrophage-derived mitochondria-rich EVs have been shown to influence bone marrow mesenchymal stem cell (BMSC) mitochondrial dynamics in both osteogenic[35] and osteolytic[36] contexts, demonstrating that EV-mediated mitochondrial transfer plays context-dependent roles in bone remodeling.

2.2.2 Free Mitochondria

Cells can also release mitochondria that are not encapsulated within vesicles. Extracellular mitochondria have been detected in synovial fluid and circulation[37,38], and can be extruded without carriers[39]. Platelet-derived free mitochondria have submicron dimensions[37], Mitovesicles, extracellular vesicles of mitochondrial origin, have also been characterized in the brain[40,41]. Unlike other forms of mitochondrial transfer, free mitochondria can be generated artificially. Recent studies on mitochondrial transfer therapies commonly produce free mitochondria by homogenizing donor cells[42,43] (**Figure 1F**).

Free mitochondrial transplantation has been directly applied in orthopaedic preclinical models: isolated mitochondria from autologous muscle, allogeneic MSCs, or xenogeneic sources have been injected locally into injured rotator cuff[42], osteoarthritic joints[44], and intervertebral discs[45], demonstrating the translational feasibility of this approach for musculoskeletal indications.

The contact-independent approaches described above have been widely used for mitochondrial transplantation in various studies, as discussed in Section 4 of this review. Despite their promise for clinical translation, several challenges remain, largely due to the unique biological properties of mitochondria as therapeutic agents, which will be discussed in Section 5 of this review.

2.3 Cell Fusion

Cell fusion has been discussed in many reviews as a potential mechanism of mitochondrial transfer[16,24,46]. However, its classification remains controversial. A recent consensus statement by Brestoff *et al.* argued that cell fusion lacks a clearly definable donor or recipient cell and proposed that it should instead be considered a form of reversed vertical inheritance of mitochondria rather than a horizontal transfer mechanism[7]. Consistent with this emerging view, we consider the evidence for cell fusion-mediated mitochondrial mixing as distinct from the transfer/transplantation framework that is the focus of this review. Nevertheless, fusion-based mitochondrial exchange may have relevance in specific musculoskeletal contexts, such as osteoclastogenesis (monocyte-macrophage fusion) and myogenesis (myoblast fusion), and is noted here for completeness.

3. Orthopaedic Diseases Related to Mitochondrial Dysfunction

The pathology of orthopaedic diseases is complex. Degenerative and inflammatory conditions are commonly associated with dysfunction of local tissues. Various cell types, including chondrocytes, synovial cells, macrophages, osteoblasts, and myocytes, have been shown to exhibit mitochondrial dysfunction under pathological conditions (**Table 1**).

Table 1. Diseases in musculoskeletal system related with mitochondrial dysfunction

Disease	Mitochondria Dysfunction	Cellular Dysfunction	Pathway	Ref.
OA	Calcium homeostasis, ROS	Chondrocytes pyroptosis	TRPV4-Drp1-HK2	[47]
OA	Mitophagy	Chondrocytes autophagy, apoptosis	N/A	[48]
OA	Mitophagy	MSCs mitophagy	Wnt/β-catenin	[49]
OA	Potential change, ROS	Chondrocytes mitophagy, apoptosis	PINK1/Parkin	[50]
OA	Calcium homeostasis, potential change	Chondrocytes apoptosis, endoplasmic reticulum stress	IP3R-GRP75-VDAC1	[51]
RA	DNA mutation	N/A	N/A	[52]
OP	Atrophy, shrunken, loss of cristae	Osteoblasts ferroptosis	YAP1	[53]
OP	ROS	BMSCs adipogenesis	N/A	[54]
OP	Mitochondrial staining, ROS	BMSC senescence	Sirt1/PGC-1α	[55]
OP	Oxidative stress, potential change, morphology, dynamics	Osteoblasts apoptosis	N/A	[56]
OP	ROS	Osteocytes, osteoblasts, and osteoclasts mitophagy	AMPK/mTOR, PINK1/Parkin	[57]
OP	Mitophagy,	Osteoblasts mitophagy	PGC-1α/FoxO3a	[58]
Sarcopenia	Mitophagy, ROS	Myocyte mitophagy	N/A	[59]
Sarcopenia	Morphology, ROS	NMJ morphogical change, myocyte apoptosis	N/A	[60]
DMD	Dynamics	~~NA~~ N/A	N/A	[61]
Myopathy (RYR1)	Calcium homeostasis	Calcium homeostasis	N/A	[62]
Myopathy (MTM1)	Dynamics, location, morphology	Myocyte cytoskeletal change	N/A	[63]
IIM	ROS	Myoblasts, myocytes oxidative stress	N/A	[64]

NOTE: OA: osteoarthritis; OP: osteoporosis; RA: rheumatoid arthritis; DMD: Duchenne muscular dystrophy; RYR1: Ryanodine receptor 1; MTM1: Myotubularin 1; IIM: idiopathic inflammatory myopathy; ROS: reactive oxygen species; MSCs: mesenchymal stem cells; NMJ: neuromuscular junction; N/A: not applicable; TRPV4: transient receptor potential cation channel subfamily V member 4; Drp1: dynamin-related protein 1; HK2: hexokinase-2; PINK1: PTEN-induced kinase 1; GRP75: Glucose-related protein 75; VDAC1: voltage-dependent anion-selective channel 1; YAP1: yes-associated protein 1; AMPK: 5' AMP-activated protein kinase; mTOR: mammalian target of rapamycin; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator-1α; FoxO3a: forkhead box protein O3a; BMSC: bone marrow mesenchymal stem cell.

3.1 Osteoarthritis

Osteoarthritis (OA) affects cartilage, subchondral bone, and synovium[65]. Chondrocyte mitochondria contribute to calcium homeostasis and ROS control[66], both of which can be disrupted by chronic loading or inflammatory mediators. In lipopolysaccharide (LPS)-exposed cells, transient receptor potential cation channel subfamily V member 4 (TRPV4)-dependent calcium overload increased mitochondrial ROS and pyroptosis; TRPV4 inhibition improved outcomes after anterior cruciate ligament transection (ACLT) in mice[47]. Mechanical overload activates Piezo1 and suppresses mitophagy, linking mitochondrial dysfunction to chondrocyte apoptosis[48]. Calcium overload is also reported in OA-derived MSCs, where impaired mitophagy permits dysfunctional mitochondria to accumulate in subchondral bone[49]. Together, these findings connect mechanical and inflammatory stress with mitochondrial quality control in OA.

Preclinical interventions target these distinct stress pathways. FGF18 restores membrane potential and fusion-fission balance through PI3K-Akt[67], while Sirtuin 6 (SIRT6) modulates nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and 5' AMP-activated protein kinase (AMPK) signaling to reduce inflammatory ROS[65]. Chondrocyte-targeted clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 editing of forkhead box protein O3 (FoxO3) activates PINK1/Parkin mitophagy and restores mitochondrial homeostasis[50]. OPTN overexpression also regulates endoreticulum (ER)-mitochondrial calcium transfer and protects against apoptosis[51]. The approaches target different nodes — redox balance, mitochondrial turnover, and calcium flux — rather than one validated disease mechanism.

3.2 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune polyarthritis in which synovial fibroblasts and macrophages drive inflammation and joint damage[68]. Somatic mtDNA mutations accumulate in RA fibroblasts and are associated with impaired oxidative phosphorylation and excess ROS; extracellular mtDNA may also act as a damage signal[52,69]. Mitochondrial dynamics shift toward Drp1-mediated fission, linked to inflammatory, invasive, and tumor-like fibroblast behavior[70]. Impaired mitophagy can retain damaged, ROS-generating mitochondria and is associated with *NACHT*, leucine-rich repeat (*LRR)* and pyrin domain (*PYD)* domains-containing protein 3 (NLRP3) inflammatory signaling[70]. Altered ER-mitochondrial calcium transfer may affect bioenergetics and apoptotic sensitivity[70]. Single-cell analyses identify fibroblast and macrophage subsets with distinct mitochondrial phenotypes[68]. Hexokinase 2 (HK2) upregulation supports a glycolytic, hyperproliferative fibroblast state; preclinical HK2 inhibition attenuated synovial inflammation and joint destruction[71]. These interacting changes vary by cell state, so RA should not be treated as one uniform mitochondrial phenotype. Much of this evidence comes from patient-derived cultures or preclinical models; it remains unclear whether mitochondrial changes initiate, compensate for, or follow synovitis. Cell-resolved and longitudinal studies are needed to clarify that relationship. This heterogeneity limits extrapolation across disease stages[68]. The studies discussed here characterize RA-associated mitochondrial dysfunction and immune metabolism; they do not establish therapeutic mitochondrial transfer in RA.

3.3 Osteoporosis

Osteoporosis (OP) is characterized by reduced bone mass, weakened microarchitecture, and increased fracture risk[72]. Healthy remodeling depends on a balance between osteoblast formation and osteoclast resorption. When antioxidant defenses fail, excess ROS can injure osteoblasts and osteocytes while also enhancing osteoclast activity, shifting remodeling toward bone loss[73,74].

Postmenopausal OP is associated with loss of estrogen support for mitochondrial and bone-cell homeostasis. Estrogen receptor α (ERα) signaling promotes osteoblast maturation and mitochondrial gene expression[75], whereas estradiol attenuates oxidative phosphorylation and adenosine triphosphate (ATP) production in early osteoclast precursors[76]; estrogen can also regulate osteoblast mitophagy through G protein-coupled estrogen receptor (GPER)/ extracellular-signal regulated kinase (ERK) 1/2[77]. These lineage-specific effects caution against assuming a uniform response. Estradiol-associated changes in p53 and osteoclast mitochondrial metabolism have also been reported[78]. In ERα-blocked rats, osteoblast cyclooxygenase (COX) I/II expression fell[79]; ovariectomized mice showed reduced glutathione peroxidase 4 (GPX4) and osteoblast mitochondrial injury, with GPX4 loss linked to ferroptosis[53]. In another ovariectomy model, oxidative stress drove BMSC adipogenesis, while mito-TEMPO reduced ROS and bone loss[54]. Resveratrol enhanced mitochondrial staining and osteogenesis, reduced oxidative stress and senescence in human BMSCs, and attenuated vitamin D insufficiency-associated bone loss in mice[55]. Young-cell mitochondria also replenished aged periodontal-ligament stem cells and improved bone repair, an aging model rather than direct OP evidence[80]. Because these models differ in age, ovarian status, mitochondrial assays, and cell-specific endpoints, their results are not directly equivalent; translation remains untested in these experimental systems.

Diabetic osteoporosis (DOP) adds hyperglycemia-associated mitochondrial injury to impaired bone remodeling. Elevated glucose increases electron-transport-chain and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase ROS, damaging mtDNA, proteins, and lipids in osteoblasts and osteocytes[56,57]. Oxidative stress can open the mitochondrial permeability-transition pore, collapse membrane potential, release cytochrome c, and trigger osteoblast apoptosis[74]; advanced glycation end products (AGE)-receptors for advanced glycation end products (RAGE) signaling further amplifies mitochondrial apoptosis[56]. Insulin resistance may impair peroxisome proliferator-activated receptor gamma coactivator (PGC)-1α-linked biogenesis, and hyperglycemia disrupts osteocyte dendritic networks that support cell communication. In osteoclast precursors, glucose and oxidative stress enhance Receptor activator of nuclear factor kappa-B ligand (RANKL) signaling and mitochondrial biogenesis, increasing resorption[57]. Antioxidant, mitophagy-targeting, and mitochondrial-transplantation approaches partially rescued bone-cell function in preclinical models[53,54,58], but efficacy and durability remain model-specific. These studies measure different cell and structural endpoints; it is not yet known whether restored respiration consistently predicts fracture protection.

3.4 Sarcopenia and Myopathy

Sarcopenia is characterized by myofiber atrophy and loss of myofibers and is strongly associated with aging. Aging in both muscle cells and motor neurons contributes to the development of sarcopenia[81]. In aged muscle, mitochondrial deoxyribonucleic acid (mtDNA) and mitochondrial morphology are altered due to accumulated damage. mtDNA mutations progressively accumulate over time, increasing mitochondrial abnormalities[82]. Compared with younger individuals, the protein abundance of key mitochondrial fusion and fission regulators is reduced in older adults[83]. Mfn2, a mitochondrial outer membrane protein that mediates mitochondrial fusion and clustering, is downregulated in aged muscle. Mfn2

deficiency induces mitochondrial dysfunction and muscle atrophy, accompanied by impaired mitophagy and ROS accumulation[59]. At the neuromuscular junction (NMJ), mitochondria near the NMJ in superoxide dismutase (SOD1)-knockout oxidative stress mouse models appear dilated and structurally abnormal, accelerating sarcopenia and promoting myocyte apoptosis[60]. Similar to estrogen's role in osteoporosis, 17β-estradiol has been shown to modulate mitochondrial membrane microviscosity and improve bioenergetic function in muscle[84]. Additionally, testosterone can influence mitochondrial function in myocytes through multiple mechanisms[85].

Duchenne muscular dystrophy (DMD) is a genetic neuromuscular disorder caused by mutations in the dystrophin protein. Alterations in mitochondrial homeostasis and dynamics have been observed at early stages in DMD mouse models. Obestatin treatment was shown to improve mitochondrial homeostasis and prevent muscle dystrophy in these models[61]. Other studies have highlighted the link between congenital myopathies and secondary mitochondrial oxidative phosphorylation (OXPHOS) dysfunction[62]. Myotubularin (MTM1), a cytoskeletal protein mutated in X-linked centronuclear myopathy (XLCNM), affects mitochondrial localization, dynamics, and morphology in myocytes, leading to mitochondrial dysfunction[63]. Ryanodine receptor 1 (RYR1), a calcium channel that mediates calcium release from the sarcoplasmic reticulum, also contributes to mitochondrial dysfunction when mutated, as disruption of calcium homeostasis leads to various myopathies depending on the specific mutation[62].

Idiopathic inflammatory myopathies (IIM) are rare autoimmune disorders characterized by muscle weakness and systemic inflammation. Basualto-Alarcon *et al.* reported increased ROS levels in myoblasts and myocytes isolated from IIM patients, along with altered mitochondrial respiratory capacity[64]. More recently, Markowska and Tarnacka comprehensively reviewed the molecular mechanisms underlying IIM pathogenesis, highlighting the central role of mitochondrial dysfunction, including impaired oxidative phosphorylation, disrupted mitophagy, and elevated oxidative stress in muscle tissue[86]. While exercise interventions have shown benefits in IIM management, a detailed discussion of exercise physiology falls outside the scope of this mitochondrially focused review[87].

4. Mitochondrial Transfer/Transplantation in the Musculoskeletal System

Mitochondrial transfer occurs in a variety of tissues and involves three key components: the donor cell, the recipient cell, and the mode of transfer[6,7]. In addition to naturally occurring processes, mitochondrial transfer can be artificially induced both *in vivo* and *in vitro*, a phenomenon commonly referred to as mitochondrial transplantation[16] (**Table 2**).

Table 2. Mitochondrial transfer related to the musculoskeletal system

Donor	Recipient	*In Vivo*/*In Vitro*	Transfer Type	Effect	Key Protein/Pathway	Ref.
BMSC	Neuron	*In vitro*	TNT, GJC, unattached method	Decrease apoptosis of neuron	CX32, CX43	[18]
Osteocyte	Endothelial cells	*In vivo*, *in vitro*	Dendritic structure	Regulate transcortical vessels vascularization	RHOT1	[25]
Osteocyte	Osteocyte	*In vivo*	Dendritic structure	Improve stressed osteocyte	Mfn2, VAPB	[19,20]
MSC	Chondrocyte	*In vitro*	Free mitochondria	Decrease apoptosis, reduce ROS	N/A	[43]
Osteolineage Cell	Osteoclastic lineage	*In vivo*	Contact dependent	Inhibit bone resorption	MIRO1	[88]
Osteocyte	Cancer cell	*In vivo*	TNT	Antitumor immunity	cGAS/STING innate immune pathway	[89]
MG63	MSC	*In vitro*	liposome	Switch respiratory pattern, increase	BMP2-Wnt/β-catenin-calcium import axis	[90]
Macrophage	BMSC	*In vivo*, *in vitro*	N/A	Promote osteogenesis	N/A	[35]
BMSC	BMSC	*In vitro*	TNT	Decrease ROS, facilitate osteogenesis	MIRO1	[91]
Osteolineage Cell	Myeloid cell	*In vivo*	N/A	Myeloid-biased hematopoiesis	Mfn2	[92]
Macrophage (M1)	BMSC	*In vivo*	free mitochondria, EV, and TNT	Inhibit osteogenesis	TNF-α, NF-κB, oxidative phosphorylation, Hif-1α, and Toll-like signaling pathway	[93]
Macrophage	BMSC	*In vivo*	EV	Inhibiting osteogenesis	LCN2, OMA1, OPA1	[36]
Macrophage	BMSC	*In vitro*	EV, TNT	Promote osteogenesis	Drp1, CD200R-CD200 signalling axis	[94]
BMSC	Chondrocyte	*In vitro*	TNT, EV; isolated mitochondria	Increase DNA content and proteoglycan deposition	N/A	[95]
BMSC	Chondrocyte	*In vitro*	GJC	N/A	Cx43, GJA1-20k	[33]
Umbilical Cord-Derived MSC	Chondrocyte	*In vitro*, *in vivo*	TNT, free mitochondria	Improve metabolism, prevent cartilage degradation	N/A	[96]
BMSC (OA)	Chondrocyte	*In vitro*	Free mitochondria	Increase ROS, promote proliferation, osteogenesis, inhibit chondrogenesis	N/A	[97]

Table 2. Mitochondrial transfer related to the musculoskeletal system (continued)

Donor	Recipient	*In Vivo*/*In Vitro*	Transfer Type	Effect	Key Protein/Pathway	Ref.
Chondrocyte (OA)	BMSC	*In vitro*	Free mitochondria	Decrease ROS, promote osteogenesis, inhibit chondrogenesis	N/A	[97]
FAP	Myoblast	*In vivo*, *in vitro*	N/A	Recover injured muscle fiber	N/A	[22]
Muscular Cells	Myoblast, fibroblast	*In vitro*	Free mitochondria	Restore respiration and lysosomal function	N/A	[98]
BMSC	Tenocyte	*In vitro*, *in vivo*	TNT	ECM composition, anti-inflammation	N/A	[99,100]
Cardiomyocyte	Nucleus pulposus cell	*In vivo*, *in vitro*	Free mitochondria	Delay intervertebral disk degeneration	mtDNA/SPARC-STING signaling pathway	[45]
Macrophage (M2)	Nucleus pulposus cell, neuron	*In vitro*	TNT	Repair damaged recipient cell	N/A	[101]

NOTE: BMSC: bone marrow-derived mesenchymal stem cell; MSC: mesenchymal stem cell; OA: osteoarthritis; FAP: fibroadipogenic progenitor; TNT: tunnel nanotube; EV: extracellular vesicles; GJC: gap junctional channel; ROS: reactive oxygen species; ECM: extracellular matrix; N/A: not applicable; MIRO1: mitochondrial Rho GTPase 1; cGAS: cyclic GMP-AMP synthase; STING: stimulator of interferon genes; LCN2: lipocalin-2; OPA1: optic atrophy 1; Drp1: dynamin-related protein 1; CD200: cluster of differentiation 200; Cx: connexin; Mfn2: Mitofusin 2; TNF: tumor necrosis factor; VAPB: Vesicle-associated membrane protein-associated protein B/C; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; OMA1: overlapping mitochondrial activities.

4.1 Bone

Osteocytes exchange mitochondria along dendritic networks: Mitofusin-2 (Mfn2)-VAPB tethering at endoplasmic-reticulum-mitochondrial contacts supports transport, and adenosine diphosphate (ADP) released by stressed osteocytes activates P2Y2/P2Y6 receptors on healthy neighbors[19,20]. Osteocyte dendrites also deliver mitochondria to endothelial cells through mitochondrial Rho GTPase 1 (MIRO1), encoded by RHOT1, supporting angiogenesis of transcortical vessels[25]. In other bone-cell pairs, osteolineage-to-myeloid transfer can restrain osteoclastogenesis and bone resorption[88], whereas increased transfer after Receptor-interacting serine/threonine-protein kinase 4 (RIPK4) loss alters myeloid hematopoiesis; human RIPK4 mutations cause Bartsocas-Papas syndrome[92]. Osteocyte-to-cancer-cell transfer can instead activate mtDNA-cyclic GMP-AMP synthase (cGAS)/stimulator of interferon genes (STING) antitumor immunity[89].

Mature osteoblasts also secrete mitochondria and mitochondria-derived vesicles during osteogenesis through CD38/cyclic ADP-ribose (cADPR)-associated remodeling; these extracellular products promote osteoprogenitor differentiation and bone regeneration in mice[34]. In therapeutic models, MG63-derived mitochondria delivered in cationic liposomes enhanced MSC osteogenesis and bone-defect repair; the absence of changes in selected oncogenic markers in that experiment is not a long-term safety assessment[90]. Melatonin-loaded microspheres promoted TNT-associated transfer between senescent BMSCs and improved bone-defect healing in aged rats[91]. An immunoresponsive scaffold and an engineered MIRO1-targeting hydrogel each coupled macrophage-to-BMSC transfer with bone repair[35,102]. Mitochondrial replenishment also improved osteogenesis of senescent human periodontal-ligament stem cells and oral bone repair in a preclinical periodontal model[80]. Erythrocyte carriers loaded with mitochondria (MiLEs) supplied mitochondria and oxygen to macrophages and reduced inflammatory bone destruction in mice[103].

Transfer can also be harmful. In ovariectomy-associated osteoporosis, mitochondria from inflammatory macrophages reached BMSCs through extracellular, EV-associated, and TNT-associated routes; uptake was endocytosis-sensitive, and the transferred cargo promoted abnormal succinate accumulation and impaired osteogenesis[93]. Periodontitis-associated macrophage EVs disrupted BMSC mitochondrial dynamics through lipocalin-2 (LCN2)/overlapping mitochondrial activities (OMA1)/optic atrophy 1 (OPA1) signaling and contributed to bone loss[36]. By contrast, mechanical strain promoted Drp1-associated mitochondrial EV release and macrophage-to-BMSC signaling through CD200R/CD200, with *in vitro* and tibial-injection evidence of enhanced osteogenesis[94]. Together, these results show that donor state and local stimulus can reverse the effect of transfer; they do not establish a dominant route or therapeutic effect in human bone.

4.2 Cartilage and Chondrocytes

Mayan *et al.* described cytoplasmic arms, approximately 200 nm wide, extending between chondrocytes and distant lacunae in human and porcine cartilage. They observed Cx43 contacts and transfer of glucose, amino acids, and oligonucleotides, but did not demonstrate passage of intact mitochondria; the journal publication was in 2015 (online in 2013)[21]. In injured bovine cartilage, MSC processes penetrated matrix cracks to more than 100 μm, and donor mitochondria were detected in chondrocytes over 50 μm from the crack, including cells without direct MSC contact[104]. Ma *et al.* reported an osteocyte-endothelial-chondrocyte TNT network in mouse knees[26]. Morphology and small-molecule exchange alone therefore should not be interpreted as proof of organelle passage.

Korpershoek *et al.* demonstrated BMSC-to-chondrocyte mitochondrial transfer in human cell cultures; delivery of isolated BMSC mitochondria increased DNA content and proteoglycan deposition in three-dimensional chondrocyte cultures[95]. Irwin *et al.* found that t-BHP-induced oxidative stress increased transfer from MSCs to human OA chondrocytes, mainly through direct contact. Cx43 was enriched on actin-positive extensions containing mitochondria: Cx43 knockdown reduced transfer, whereas overexpression of GJA1-20k increased it[33]. These data implicate connexins in regulation, not passage of intact mitochondria through the GJC pore. Equine MSC-chondrocyte co-cultures provide additional *in vitro* evidence[104].

Cell-free approaches include isolated mitochondria and mitochondria-rich EVs from umbilical cord, synovial fluid, and Wharton's jelly MSCs[43,96,105]. Fusogenic liposomes improved mitochondrial delivery to chondrocytes and reduced cartilage injury in OA models[44]. In a mouse OA model, intra-articular umbilical cord - mesenchymal stem cell (UC-MSC) mitochondria protected cartilage and reduced synovial inflammation[96]. These transplantation findings are distinct from endogenous cell-to-cell transfer: isolated organelles, liposome-encapsulated mitochondria, and EV-associated cargo are different products whose mitochondrial content and potency require separate characterization.

The donor state can reverse the apparent effect. *In vitro*, OA-BMSC mitochondria increased ROS in recipient human chondrocytes without changing membrane potential; they promoted proliferation and osteogenic differentiation while suppressing chondrogenesis. Conversely, mitochondria from healthy or OA chondrocytes reduced ROS in rat MSCs and favored osteogenesis over chondrogenesis[97]. This bidirectional study indicates that disease state and recipient lineage both shape the response; mitochondria from diseased donors cannot be assumed equivalent to those from healthy MSCs.

Overall, cartilage studies combine endogenous transfer across cell processes, Cx43-associated regulation, co-culture rescue, and isolated-mitochondria or EV delivery. These are different interventions with different evidence: small-molecule passage through chondrocyte contacts does not prove mitochondrial passage, and successful cell-free treatment in an animal model does not establish a shared mechanism across donors or OA stages[21,33,43,96,104,105]. Most results remain *in vitro*, *ex vivo*, or in small-animal models; biodistribution, repeat dosing, and long-term cartilage function have not been compared across platforms. The available studies also differ in injury induction, donor-cell age, recipient phenotype, and outcome measurement, limiting direct comparison of reported efficacy. Reporting donor state, dose, and injury timing would improve comparisons across disease stages.

4.3 Muscle

Chi *et al.* observed mitochondrial transfer from fibroadipogenic progenitors (FAPs) to injured muscle fibers in a mouse model of rotator cuff tear. In a co-culture system, they further demonstrated that β-agonist treatment enhanced mitochondrial transfer from murine FAPs to C2C12 myoblasts[22]. These findings suggest that FAPs may contribute to mitochondrial exchange in injured skeletal muscle and that this process can be modulated by pharmacological stimulation. Compared with bone and cartilage tissues, skeletal muscle contains a relatively sparse extracellular matrix, and myofibers are densely aligned and closely packed. These structural characteristics may limit the formation or visualization of tunneling nanotubes (TNTs) in muscle tissue. Furthermore, *in vitro* studies of skeletal muscle mitochondrial transfer largely rely on C2C12 cells, in which mature myofibers are generated through myogenic differentiation. Given that differentiated myofibers form extensive cell-cell contacts, GJCs may represent a more physiologically relevant mechanism to investigate mitochondrial exchange in myofibers, whereas TNT-mediated transfer may be less readily detectable in this experimental context.

Yulong Shi's group has extensively investigated mitochondrial transplantation as a potential therapeutic strategy for rotator cuff muscle degeneration. In rat models of rotator cuff transection, the group examined the effects of administering mitochondria from different sources into injured rotator cuff muscles[42,106-108]. Mitochondrial transplantation improved muscle quality, as indicated by increased wet muscle mass and reduced fibrosis and fatty infiltration. Notably, both mitochondria-rich EVs derived from bone marrow mesenchymal stromal cells (MSCs)[106] and isolated skeletal muscle mitochondria[42] promoted macrophage polarization toward the M2 phenotype in muscle tissue, suggesting that transplanted mitochondrial preparations may exert therapeutic effects partly through modulation of the local immune microenvironment. Bhattacharya *et al.* investigated the transfer of isolated mitochondria from murine skeletal muscle to murine myoblasts and human fibroblasts. They found that the transferred mitochondria promoted mitochondrial network elongation and improved the bioenergetic profiles of recipient cells. Mitochondrial uptake by recipient myoblasts involved multiple mechanisms, including EV-mediated endocytosis, actin polymerization-dependent uptake, gap junctional communication, and macropinocytosis[98].

4.4 Tendon and Ligament

Wei *et al.* cultured BMSCs with hydrogen peroxide-treated tenocytes and observed mitochondrial transfer from BMSCs to tenocytes. This transfer restored mitochondrial membrane potential and attenuated oxidative stress and inflammation in tenocytes. In a collagenase type I-induced Achilles tendinopathy rat model, administration of cytochalasin B, a TNT inhibitor, abrogated the therapeutic effects of MSC injection, including improvements in ECM composition and anti-inflammatory responses[99]. Similar findings were reported by Lee *et al.* using mitochondria derived from umbilical cord MSCs in a rat collagenase type I-induced Achilles tendinopathy model[100]. Lo *et al.* transplanted mitochondria isolated from human adipose-derived MSCs into the site of partial anterior cruciate ligament (ACL) tears in a rabbit model. The transferred mitochondria were retained within ACL tissue and enhanced its collagen synthesis capacity. In addition, ACL cells isolated eight weeks after injury exhibited increased collagen synthesis and upregulated vascular endothelial growth factor (VEGF) gene expression following *in vitro* treatment with free mitochondria[109].

While these studies collectively demonstrate the feasibility of mitochondrial transplantation in tendon and ligament repair, several important limitations warrant consideration. First, the majority of studies have employed collagenase-induced injury models, which may not fully recapitulate the degenerative processes observed in chronic human tendinopathy. Second, the optimal timing of mitochondrial delivery relative to injury remains poorly defined: early-stage intervention may maximize tenocyte rescue, whereas delayed delivery may be insufficient to reverse established fibrosis. Third, comparative analyses of different mitochondrial sources, BMSCs, adipose-derived MSCs, umbilical cord MSCs, and autologous tenocyte-derived mitochondria, in tendon and ligament applications have not been systematically performed. Fourth, the durability of therapeutic effects beyond the acute post-injury period has not been rigorously assessed. Addressing these knowledge gaps through standardized comparative studies will be critical for advancing mitochondrial transplantation toward clinical application in tendon and ligament injuries.

4.5 Intervertebral Disc and Spinal Cord

Yang *et al.* isolated mitochondria from rat cardiomyocytes and incubated them with ROS-treated nucleus pulposus cells, which restored mitochondrial membrane potential in the recipient cells. In a rat model of intervertebral disc degeneration, intranuclear pulposus

injection of isolated mitochondria also delayed the progression of disc degeneration. This treatment was associated with reduced cytosolic mtDNA accumulation and suppression of inflammation involving the mtDNA/SPARC–STING pathway[45]. M2 macrophages have likewise been reported to donate mitochondria to nucleus pulposus cells and neurons through TNTs, which improved the viability and repair of injured recipient cells[101].

Li *et al.* reported mitochondrial transfer from BMSCs to primary cortical neurons in both direct co-culture and BMSC-conditioned medium systems. Consistent with these *in vitro* findings, administration of either BMSCs or isolated BMSC mitochondria in a rat model of spinal cord injury led to mitochondrial uptake by neurons and improved locomotor recovery. Isolated mitochondria also reduced neuronal apoptosis after oxygen-glucose deprivation *in vitro*[18].

Despite these encouraging findings, several issues need to be addressed before mitochondrial transplantation can be effectively applied to intervertebral disc degeneration or spinal cord injury. The degenerating nucleus pulposus presents an unfavorable environment characterized by hypoxia, low pH, limited nutrient availability, and substantial mechanical stress. It remains unclear whether exogenous mitochondria can preserve their membrane potential and oxidative phosphorylation capacity after delivery into this environment. In spinal cord injury, another major concern is whether transplanted mitochondria can reach neurons within the injured region, particularly in the presence of a dense glial scar. In addition, the functional recovery observed after mitochondrial transplantation may result from more than one mechanism. Direct restoration of neuronal mitochondrial function and secondary effects on the inflammatory microenvironment have not yet been clearly separated. Cell-specific mitochondrial tracing combined with functional measurements will therefore be important for determining where the transferred mitochondria ultimately localize and how they contribute to tissue repair.

An increasing body of evidence suggests that mitochondrial transfer may form interconnected communication networks involving multiple cell types and tissues in the musculoskeletal system. The knee joint provides an illustrative example. An osteocyte-endothelial cell-chondrocyte TNT network has been identified in mouse joints, providing a potential anatomical route for mitochondrial exchange between bone, blood vessels, and cartilage[26]. Bone regeneration provides another example, in which mitochondrial exchange between macrophages and BMSCs appears to influence the regenerative response. The effect may depend on the functional state of the donor macrophages, which can alter the osteogenic behavior of recipient BMSCs. Thus, damage to donor mitochondria, inefficient transfer, or reduced ability of recipient cells to utilize transferred mitochondria could all disturb this form of intercellular communication. Further work is needed to identify the molecules that regulate these exchanges and to determine whether impaired mitochondrial communication is a cause or a consequence of musculoskeletal disease.

Comparison across musculoskeletal tissues also indicates that mitochondrial transfer follows some common principles while retaining tissue-specific features. TNTs and related cytoplasmic extensions have been described in bone, cartilage, and skeletal muscle, including osteocyte dendritic processes, chondrocyte cytoplasmic extensions, and connections between FAPs and muscle fibers. These structures may provide physical routes for mitochondrial movement in tissues exposed to continuous mechanical and metabolic demands. Nevertheless, the regulatory mechanisms are not uniform. In osteocytes, mitochondrial transfer is associated with Mfn2 and VAPB-dependent ER-mitochondrial interactions, whereas Cx43 has been implicated in chondrocyte cytoplasmic extensions. In skeletal muscle, β-adrenergic signaling appears to regulate interactions between FAPs and myofibers. The biological consequences of mitochondrial transfer also vary among tissues. In bone and cartilage, it has mainly been linked to cellular homeostasis and tissue repair, while in skeletal muscle it may participate in metabolic adaptation and fiber-type regulation. The donor cell is another important variable. For example, macrophage-to-BMSC mitochondrial transfer can produce different effects depending on macrophage polarization. These differences suggest that mitochondrial transplantation should not be regarded as a uniform therapeutic approach; instead, the choice of donor cells, mitochondrial preparation, delivery route, and target cells may need to be tailored to the specific musculoskeletal disease.

4.6 Cross-Tissue Comparative Analysis of Mitochondrial Transfer

Three cross-tissue patterns emerge. First, route and access follow tissue architecture: osteocyte dendrites support exchange within mineralized bone, cartilage studies describe cell processes crossing matrix or TNT-like connections, and disc studies rely on local delivery into a confined compartment[19,21,25,26,45]. Second, evidence differs by intervention. Bone and cartilage include endogenous transfer, secretion, EV delivery, and transplantation, whereas muscle and tendon studies increasingly test injury-triggered exchange or direct local delivery[22,34,42,44,98-102,104-109]. These interventions differ in donor cells, cargo, and exposure and should not be pooled as one treatment class.

Third, biological context can reverse the direction of an effect. Healthy or mechanically conditioned donors can support repair, while inflammatory macrophage mitochondria can aggravate bone pathology[35,36,93,94]. The macrophage-to-BMSC axis illustrates this state dependence: scaffold or mechanical cues accompany pro-osteogenic effects, whereas osteoporosis and periodontitis models report impaired osteogenesis or bone loss[35,36,93,94]. Recipient lineage and disease stage therefore matter alongside donor quality and route.

Finally, evidence maturity is uneven. Bone studies include endogenous signaling and multiple animal repair models; cartilage studies combine cell and animal work across direct transfer, EVs, and isolated mitochondria; muscle and tendon intervention studies remain largely small-animal injury models; and disc or spinal-cord findings rely on a limited set of local-delivery experiments[18,19,22,25,42,45,98-102,104-109]. Differences in dose units, follow-up, and functional outcomes limit direct efficacy ranking. Cross-tissue comparison is most informative when it contrasts biological context, product type, recipient engagement, and tissue-level function rather than presenting a single universal mechanism.

5. Challenge and Future Direction

Clinical translation requires a defined product, dose, and safety framework. Adult somatic mitochondrial therapy is distinct from germline mitochondrial replacement; donor screening, informed consent, allogeneic immune risk, and long-term surveillance remain essential[110,111]. Dose units also need harmonization, because protein mass, particle count, and functional activity are not interchangeable.

Efficacy should be judged with tissue-specific function as well as mitochondrial assays: joint pain and function, bone

strength/fractures, muscle strength, tendon/ligament mechanics, and disc structure or pain are relevant examples. Avascular cartilage, mechanically loaded bone and tendon, and the confined disc may require different delivery, retention, and monitoring strategies. Preclinical studies should report target engagement and meaningful functional outcomes.

5.1 Mitochondrial Sources and Product Characterization

Potential sources include autologous tissue, screened allogeneic donors, and selected or engineered cells. Donor age, disease state, and cell type can affect mitochondrial quality and recipient response. Emerging approaches include CD38-enriched mitochondria-rich EVs[112] and nanomaterial stimulation of donor-cell mitochondrial production[113]. MG63-derived mitochondria have also been used to promote MSC osteogenesis; this tumor-derived source warrants product-specific safety evaluation[90]. Germline mitochondrial replacement and donation provide a regulatory precedent but are distinct from adult somatic mitochondrial transplantation[110,111].

Manufacturing and product characterization should be considered together. A 2026 methods study compared a rapid, detergent-free isolation protocol taking about 30 minutes with a commercial kit taking about 80 minutes. Mitochondria from proximal tubular cells isolated by the rapid protocol showed higher transfer to HEK293T recipients, greater oxygen-consumption activity, preserved dynamics, and lower oxidative stress; short-term dimethyl sulfoxide (DMSO)-based cryopreservation retained functional readouts after thawing[114]. This is protocol-specific manufacturing evidence using renal donor cells and HEK293T recipients. It does not establish performance in orthopaedic tissues.

Release criteria should extend beyond particle or protein quantity to identity, purity, membrane integrity and potential, respiration, ATP-generating capacity, uptake or fusion competence, mtDNA integrity, sterility, and a validated potency assay[114,115]. Cryopreservation and storage conditions should be validated for each source and intended product; post-thaw function, dose units, and batch consistency need standardized reporting before cross-study comparison or clinical manufacturing[115].

5.2 Administration

Most musculoskeletal transplantation studies use local delivery: intra-articular for OA, intramuscular for rotator-cuff injury, intratendinous or peri-ligamentous for tendon/ACL injury, and intradiscal for disc degeneration[42,44,45,99,100,107-109]. Local injection can improve access but does not guarantee retention or recipient-cell uptake. Systemic approaches require biodistribution and off-target assessment. Candidate carriers include fusogenic liposomes, hydrogels, mitochondria-rich EVs, and erythrocyte carriers loaded with MiLEs[35,44,102,103,106,112].

Carrier choice should match target tissue, cell type, exposure, and mitochondrial preservation. In a mouse inflammatory-bone-loss model, MiLEs supplied both mitochondria and oxygen to macrophages, promoted an M1-to-M2 shift, and suppressed osteoclast differentiation[103]. This is an early preclinical carrier result. Comparative studies should quantify dose, release, tissue persistence, cellular uptake, and potency rather than infer successful delivery from carrier presence alone.

5.3 Mechanistic Questions and Mitochondrial Fate

Mechanistic claims should distinguish physical transfer routes from their regulators. TNTs, osteocyte dendrites, and cartilage-cell processes have been observed in selected skeletal settings[19,21,26]. Cx43 and gap-junctional communication may regulate cell adhesion, signaling, or uptake, but the pore cannot transport an intact mitochondrion[7,17,18,30,33,104]. Cell fusion should be excluded from transfer claims unless lineage-resolved evidence demonstrates distinct donor and recipient cells[7]. Three-dimensional imaging and cell-specific tracing can help verify organelle movement *in vivo*[116].

After uptake, donor mitochondria may integrate with the recipient network, remain transient, or be removed by mitophagy[117]. MFN2 has been implicated in selected transfer-related models[19,59], but determinants of persistence, functional contribution, and recipient response remain unresolved. Longitudinal tracing combined with respiration, ATP, membrane potential, mtDNA, and mitophagy measurements is needed to establish fate rather than infer it from fluorescence alone[117].

Safety studies should assess innate immune activation, biodistribution, and off-target uptake alongside tissue efficacy. Circulating mitochondria promoted allograft rejection in an organ-donor model[118], while orthopaedic models report context-dependent inflammatory signaling after transfer[36,93]. The allograft finding is adjacent immunological evidence, not a demonstrated complication of musculoskeletal mitochondrial therapy; it supports testing immune responses and dose tolerance in the intended product and tissue.

6. Conclusion

Mitochondrial transfer and transplantation are being studied across bone, cartilage, muscle, tendon, ligament, intervertebral disc, and spinal cord, but the routes, products, and evidence maturity differ by tissue. Endogenous transfer can support repair or transmit stress signals depending on donor state, mitochondrial integrity, recipient cell, route, and disease environment. Therapeutic transplantation has shown activity in preclinical models, while standardized products and clinical efficacy remain to be established.

Priority studies should compare tissue-matched sources and delivery routes, define dose and potency, trace mitochondrial fate, and measure durable tissue function and safety in relevant models before clinical claims are made.

Abbreviations List

ACL: anterior cruciate ligament
ACLT: anterior cruciate ligament transection
ADP: adenosine diphosphate
AMPK: 5' AMP-activated protein kinase
BMSC: bone marrow–derived mesenchymal stem cell
CD200: cluster of differentiation 200
cGAS: cyclic GMP-AMP synthase
Cx: connexin
DMD: Duchenne muscular dystrophy
DMM: destabilization of the medial meniscus
DMSO: dimethyl sulfoxide
Drp1: dynamin-related protein 1
ECM: extracellular matrix
ERα: estrogen receptor α
EV: extracellular vesicle
FoxO3a: forkhead box protein O3a
GJC: gap junction channel
GRP75: Glucose-related protein 75
HK2: Hexokinase 2

IIM: idiopathic inflammatory myopathies
iPSC: induced pluripotent stem cell
LCN2: lipocalin-2
LPS: lipopolysaccharide
LRR: leucine-rich repeat
MDV: mitochondria-derived vesicles
Mfn2: Mitofusin 2
MIRO1: mitochondrial Rho GTPase 1
MSC: mesenchymal stem cells
mtDNA: mitochondrial deoxyribonucleic acid
MTM1: Myotubularin
mTOR: mammalian target of rapamycin
NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells
NMJ: neuromuscular junction
OA: osteoarthritis
OMA1: overlapping mitochondrial activities
OP: osteoporosis
OPA1: optic atrophy 1
OXPHOS: oxidative phosphorylation
PGC-1α: peroxisome proliferator-activated receptor gamma coactivator-1α
PINK1: PTEN-induced kinase 1
PMOP: postmenopausal osteoporosis
PYD: pyrin domain
RA: rheumatoid arthritis
ROS: reactive oxygen species;
RYR1: Ryanodine receptor 1
SOD: superoxide dismutase
STING: stimulator of interferon genes
t-BHP: tert-butyl hydroperoxide
TNF: tumor necrosis factor
TNT: tunneling nanotube
TRPV4: transient receptor potential cation channel subfamily V member 4
UC-MSC: umbilical cord - mesenchymal stem cell
VAPB: Vesicle-associated membrane protein-associated protein B/C
VDAC1: voltage-dependent anion-selective channel 1
XLCNM: X-linked centronuclear myopathy
YAP1: yes-associated protein 1

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ChatGPT (OpenAI) was used solely for language editing and proofreading to improve the clarity, grammar, and readability of the manuscript. The authors reviewed and edited all AI-assisted suggestions and take full responsibility for the content, accuracy, and integrity of the final manuscript.

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Not applicable.

Conflicts of Interest

The authors declare no competing financial interests.

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