

Mitochondrial Transplantation: A Paradigm Shift in Osteoporosis Therapy

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Abstract: Osteoporosis, a global health crisis marked by compromised bone mineral density and heightened fracture susceptibility, demands innovative therapeutic strategies beyond conventional anti-resorptive approaches. Mitochondrial dysfunction, characterized by impaired bioenergetics, oxidative stress overload, and calcium dysregulation, has emerged as a central driver of osteoblast-osteoclast imbalance. Recent breakthroughs in mitochondrial transplantation (MT)—a revolutionary modality involving the transfer of functional mitochondria to metabolically compromised cells—have demonstrated unprecedented efficacy in preclinical osteoporosis models, restoring bone mass, microarchitecture, and mechanical strength. This review synthesizes cutting-edge insights into mitochondrial dynamics in bone homeostasis, dissects the molecular cascades linking mitochondrial failure to osteoporotic pathogenesis, and critically evaluates MT's potential to redefine osteoporosis management. We also discuss novel mechanisms of intercellular mitochondrial trafficking within the osteocyte dendritic network, explore bioengineered delivery platforms (eg, immunomodulatory hydrogels, nanoparticle-encapsulated mitochondria), and address emerging challenges in clinical translation, including donor source optimization, immune compatibility, and CRISPR-engineered mitochondrial genomes. By integrating single-cell omics data and AI-driven mitochondrial viability predictors, this work charts a roadmap for personalized mitochondrial medicine, positioning MT as a cornerstone of next-generation osteoporosis therapeutics.

Keywords: osteoporosis, mitochondrial transplantation, mitochondrial disease, mitochondrial transfer

Introduction

Osteoporosis, a systemic skeletal disorder characterized by diminished bone mineral density (BMD) and microarchitectural deterioration, represents a significant global health burden. This condition arises from an imbalance between bone resorption by osteoclasts and bone formation by osteoblasts, leading to increased fracture risk and associated morbidity, particularly in postmenopausal women and the elderly.¹ Despite advancements in therapeutic interventions, including antiresorptive agents (eg, bisphosphonates) and anabolic drugs (eg, teriparatide), current treatments often fail to fully restore bone homeostasis and are associated with side effects, high costs, and limited long-term efficacy.^{2,3} Consequently, there is an urgent need for innovative therapeutic strategies that address the underlying pathophysiology of osteoporosis.

Mounting evidence establishes mitochondrial dysfunction as central to osteoporosis pathogenesis. As essential organelles, mitochondria critically regulate osteoblast and osteoclast activity by governing bone remodeling through

energy production, redox homeostasis, and calcium signaling.⁴ Consequently, deciphering mitochondrial involvement in these processes may enable therapeutic strategies to modulate mitochondrial activity—promoting osteoblast differentiation while suppressing osteoclastogenesis to preserve bone health. Mitochondrial transfer, involving delivery of donor mitochondria to recipient cells, alters bioenergetic profiles and functional states in recipient populations.⁵ This capability suggests therapeutic promise for restoring homeostasis in compromised bone cells. Osteocytic dendritic networks facilitate mitochondrial transfer, supporting metabolic recovery.⁶ Recent work identifies mitochondrial transplantation—direct transfer of functional mitochondria to impaired cells—as a strategic approach to boost osteoblastic ATP generation, enhance respiratory capacity, and dampen osteoclastogenic cytokine expression, thereby reducing bone loss in preclinical osteoporosis models.⁷

This review delineates the multifaceted contributions of mitochondria to bone homeostasis and evaluates their therapeutic targeting potential via specific mitochondrial pathways to modulate osteoblast/osteoclast dynamics in osteoporosis. It synthesizes current mechanistic insights into mitochondrial dysfunction pathogenesis, advances in mitochondrial transfer techniques, and preclinical/clinical evidence for mitochondrial transplantation as a therapeutic intervention. Furthermore, we address the challenges and future directions for translating this approach into clinical practice, highlighting requirements to optimize delivery systems, ensure long-term safety, and mitigate immune responses.

Osteoporosis: A Growing Global Health Burden

Epidemiology and Current Therapies

Osteoporosis, a systemic bone disease characterized by reduced bone mineral density (BMD) and microstructural deterioration, significantly increases the risk of fractures. This condition disproportionately affects women and older adults, where osteoporotic fractures contribute substantially to disability and mortality. Osteoporosis affects over 200 million people worldwide, with osteoporotic fractures contributing significantly to disability, mortality, and healthcare costs.^{8–10} The growing global elderly population exacerbates the high prevalence of osteoporosis and its associated healthcare burden. Despite this pervasive impact and ongoing research into promising new areas like the gut-bone axis, osteoporosis remains an incurable condition with significant unmet clinical needs.^{11,12} This reality underscores the urgent need for novel therapeutic strategies, especially considering the substantial limitations of existing treatments.

Current pharmacotherapy for primary osteoporosis encompasses bone anabolic agents, anti-resorptives, dual-action compounds, and adjunctive metabolic modulators.^{13–15} However, these agents exhibit significant clinical limitations that constrain therapeutic efficacy and patient adherence. Regarding efficacy, many demonstrate limited capacity to increase BMD, with monotherapy typically yielding only modest gains.^{16,17} Furthermore, their therapeutic effects are site-specific and provide incomplete protection against certain fracture types. For example, alendronate demonstrates no significant reduction in non-vertebral fracture risk among women with osteopenia without prevalent vertebral fractures, nor significant fracture risk reduction in individuals without fracture history or for hip fractures specifically.^{16–19} Furthermore, long-term benefits are constrained: skeletal protection wanes with extended use, and treatment cessation may accelerate bone loss.^{16,20,21} Safety concerns include notable adverse events. Bisphosphonate therapy associates with gastrointestinal disturbances and 63 reported cases of osteonecrosis of the jaw (ONJ), indicating potential risk elevation.^{18,22,23} Prolonged bisphosphonate use increases atypical femoral fracture (AFF) risk, while agents like raloxifene elevate thrombosis risk.^{16,20,24} Additional constraints encompass cost and narrow therapeutic indications. These agents demonstrate suboptimal cost-effectiveness and target limited patient subsets. Critically, osteoporosis remains incurable.^{16,18,19,25–27} Current therapies—including calcium/vitamin D supplementation, estrogen replacement, and anti-osteoporotic agents—may attenuate disease progression but fail to restore bone remodeling homeostasis; consequently, lifelong management is requisite.²⁸

Mitochondrial Dysfunction in Osteoporosis

Osteoporosis is characterized by an imbalance in osteoblast and osteoclast activity. Under normal physiological conditions, mitochondria play a crucial role in regulating bone metabolism and maintaining bone homeostasis. However,

mitochondrial dysfunction disrupts this delicate balance, leading to intracellular abnormalities and cellular dysfunction. This disruption, in turn, affects the balance between osteoblast and osteoclast activity, contributing to the development of osteoporosis. Key features of mitochondrial dysfunction in osteoporosis include: 1. Impaired oxidative phosphorylation: Reduced ATP production compromises osteoblast differentiation and bone formation. 2. Elevated ROS production: Excessive ROS disrupts cellular signaling pathways, leading to osteocyte apoptosis and increased osteoclast activity. 3. Defective mitophagy: Impaired clearance of damaged mitochondria exacerbates cellular dysfunction and bone loss.²⁹ Recent studies suggest that mitochondrial dysfunction specifically in osteocytes may impair their normal function and compromise their ability to maintain bone homeostasis, potentially leading to osteoporosis.³⁰ Given the pervasive role of mitochondrial dysfunction and its associated ROS production in bone cells, it is crucial to examine how these factors specifically influence the distinct functions of osteoclasts and osteoblasts.

Impact of Mitochondrial Dysfunction on Osteoclasts: The ROS-NF- κ B Axis

Mitochondrial dysfunction in osteoporosis elevates reactive oxygen species (ROS)—a pathological hallmark—driving osteoclast-mediated NF- κ B activation that dysregulates bone remodeling. This mechanism integrates oxidative stress with inflammatory signaling. NF- κ B transcription factors coordinate osteoclast differentiation, survival, and osteoclastogenic cytokine expression (eg, TNF- α , IL-1 β).^{31–34} In quiescent cells, cytoplasmic NF- κ B complexes with inhibitory I κ B proteins. Following stimulation, I κ B undergoes IKK-induced phosphorylation and ubiquitin-mediated degradation, permitting NF- κ B nuclear translocation and target gene transactivation. Osteoclast ROS primarily derive from NADPH oxidases (NOX) and the mitochondrial electron transport chain. Elevated ROS activate NF- κ B through covalent IKK complex modification. This multi-subunit complex comprises IKK α , IKK β , and NEMO, undergoing direct oxidative alterations that potentiate its activity.^{35–37} ROS including H₂O₂ oxidize specific IKK β cysteine residues (Cys179), triggering conformational activation that enables I κ B α phosphorylation at Ser32/36 degradation motifs.^{38–41} Phosphorylated I κ B α is then ubiquitinated and degraded, releasing NF- κ B (eg, p65/p50 heterodimers) into the nucleus.^{42,43} ROS also inhibit I κ B phosphatases (eg, PP2A) through oxidative modification of catalytic metal ions or active-site cysteine residues, compromising phosphatase activity and consequently potentiating I κ B phosphorylation, degradation, and NF- κ B activation.^{44–51} ROS directly activate osteoclast surface receptors (TNFR, IL-1R) and integrin signaling, initiating TAK1-dependent IKK activation. This occurs through enhanced TAK1-NEMO scaffolding within the IKK signalosome, potentiating kinase activity. Mitochondrially generated ROS modulate NF- κ B signaling through dual mechanisms: impairing core mitochondrial functions (ATP synthesis, calcium handling) and inhibiting intrinsic antioxidant defenses like manganese superoxide dismutase (MnSOD). This establishes a self-amplifying oxidative cycle that sustains NF- κ B activation.^{52–56} Physiologically, ROS function as second messengers that potentiate RANKL-induced osteoclastogenesis via NF- κ B pathway activation, thereby supporting bone remodeling homeostasis.^{57–59} Pathological ROS elevation (eg, during inflammation or redox imbalance) induces constitutive NF- κ B activation, driving osteoclast hyperactivation and prolonged lifespan that underlie osteoporosis and rheumatoid arthritis pathogenesis.^{60–62} In postmenopausal osteoporosis, estrogen deficiency promotes pathological ROS accumulation that potentiates osteoclastogenesis via NF- κ B signaling, driving accelerated bone loss.^{63–66} Elevated osteoclastic ROS drive NF- κ B pathway activation through direct IKK oxidation, I κ B phosphatase suppression, and upstream signaling modulation. This mechanism maintains physiological bone remodeling while underpinning pathological resorption. Therapeutic targeting of the ROS-NF- κ B axis through antioxidant agents or IKK inhibitors constitutes a rational approach for managing osteolytic disorders. While osteoclast activity mediates bone resorption, osteoblast function—specifically osteogenic differentiation and matrix deposition—is equally essential for osteogenesis and critically dependent on mitochondrial integrity and redox homeostasis.

Impact of Mitochondrial Dysfunction on Osteoblasts: The OXPHOS-Runx2 Axis

Mitochondrial integrity and redox homeostasis critically govern osteoblastic differentiation and bone formation—distinct from osteoclast-activating roles—primarily through master transcription factor modulation (eg, Runx2). Runx2 maintains high expression during osteoblast differentiation and is indispensable for this process.⁶⁷ It orchestrates bone matrix protein synthesis at differentiation onset while sustaining preosteoblast populations, thereby inhibiting terminal

maturation.⁶⁸ Bioenergetic regulation involves oxidative phosphorylation (OXPHOS)—coupling electron transport chain (ETC) flux to ATP synthase activity—which powers cellular functions.⁶⁹ Glutathione (GSH) scavenges reactive oxygen species (ROS) and maintains osteoblast viability.^{70,71} During BMSC osteogenic differentiation, GSH levels elevate preferentially in osteoblast versus adipogenic progenitors.^{72,73} Metabolic coupling links enhanced OXPHOS to intracellular GSH elevation, enabling mitochondrial ROS clearance and redox homeostasis preservation.⁷⁴ OXPHOS dysfunction (eg, mitochondrial impairment) disrupts ROS-scavenging equilibrium, causing pathological ROS accumulation.⁷⁵ Pathological consequences: ROS covalently modify Runx2 cysteines, inducing conformational disruption and 20S proteasomal degradation that compromise Runx2 stability/activity.⁷⁶ OXPHOS failure reduces ATP output, elevating AMP/ATP ratios and activating AMPK.⁷⁷ AMPK phosphorylates RUNX2-Ser118.⁷⁸ Diabetic context: AMPK/PGC-1 α downregulation correlates with diminished Runx2 expression,⁷⁹ suggesting accelerated RUNX2 degradation may constitute a mitochondrial safeguard by limiting glucose utilization, suppressing OXPHOS, and attenuating ROS generation.⁷⁴

Regarding Stem Cell Aging and Differentiation

COL6A3 overexpression enhances bone marrow mesenchymal stem cell (BMSC) differentiation and survival in inflammatory milieu by promoting mitochondrial autophagy (mitophagy) and preserving cristae architecture, indicating its therapeutic potential for stem cell-based osteoporosis interventions.⁸⁰ Conversely, *Lrrc17* knockdown activates mTOR/PI3K-mediated mitophagy, reprogramming BMSC differentiation from adipogenic to osteogenic lineages and implicating its role in aging-related differentiation shifts. In aged murine models, BMSC-specific *Lrrc17* knockdown attenuates ovariectomy-induced bone loss.⁸¹ Hematopoietic stem cell transplantation (HSCT) preconditioning regimens induce MSC mitochondrial dysfunction and mitophagy impairment, consequently diminishing MSC functionality and predisposing to osteopenia/osteoporosis.⁸²

Addressing Metabolic Regulation and Antioxidant Capacity

NAB therapy activates Nrf2 to augment mitochondrial antioxidant defenses, improve energy metabolism, and preserve trabecular architecture with calcium homeostasis. It concurrently stimulates osteogenesis via the Nrf2-GSK-3 β axis, upregulating PGC-1 α and TFAM. At physiological concentrations, NAB protects MC3T3-E1 osteoblasts against H₂O₂-induced oxidative stress, promoting differentiation and maintaining bone metabolic homeostasis.⁸³

Focusing on Mitochondrial Quality Control and Autophagy

PINK1—a mitochondrial serine/threonine kinase regulating mitophagy—is essential for osteoblast differentiation, as evidenced by impaired differentiation in PINK1 knockout mice. This function likely involves mitochondrial homeostasis maintenance and ROS suppression.⁸⁴

Collectively, these findings suggest that targeting mitochondrial dysfunction and promoting mitochondrial health may be promising therapeutic approaches for osteoporosis.

Mitochondrial Donor Sources and Compatibility Considerations

Diverse Mitochondrial Sources and Their Therapeutic Implications in Osteoporosis

Osteoporosis fundamentally stems from an imbalance between bone formation and resorption. Mitochondria, as central regulators of energy metabolism and signaling pathways, directly govern osteoblast and osteoclast activity. Mitochondria derived from distinct sources exhibit unique therapeutic profiles for osteoporosis—encompassing mechanisms, indications, advantages, and limitations—all rooted in their core metabolic functions. Skeletal muscle mitochondria function as the primary ATP source for contraction through oxidative phosphorylation (OXPHOS). Exercise induces myokine secretion (eg, irisin) from skeletal muscle, which enhances osteoblast function and bone formation via endocrine pathways.⁸⁵ Their calcium-buffering capacity contributes to systemic calcium homeostasis, thereby regulating bone mineralization. Clinically, functional enhancement via exercise or pharmacotherapy promotes myokine secretion, augments osteoblast proliferation and matrix deposition, and increases mechanical loading on bone.^{86–91} These properties make them optimally indicated for disuse osteoporosis (prolonged immobilization or microgravity exposure) and age-related primary osteoporosis.^{92–94} Key advantages include non-pharmacological intervention and musculoskeletal co-

benefits. Limitations involve suboptimal efficacy in advanced disease and dependence on patient-specific factors such as adherence and functional capacity.⁸⁶ Impaired skeletal muscle mitochondrial function reduces mechanical loading and exacerbates bone loss, whereas enhanced activity improves bone health through myokine signaling.^{95–97} Hepatic mitochondria regulate systemic energy metabolism—including gluconeogenesis and fatty acid β -oxidation—and catalyze vitamin D activation, thereby establishing calcium-phosphate homeostasis to modulate bone health.⁹⁸ Hepatocytes synthesize bone metabolism-related proteins to sustain nutrient supply and maintain bone tissue metabolic balance.⁹⁹ Clinically, enhancing hepatic mitochondrial function improves vitamin D activation and calcium-phosphate homeostasis, indirectly promoting mineralization while mitigating lipid-induced osteotoxicity via lipid metabolism regulation.¹⁰⁰ These agents are particularly suitable for secondary osteoporosis (eg, hepatic vitamin D deficiency or obesity-associated pathologies), as they concurrently address systemic metabolic derangements and benefit metabolic syndrome. Limitations comprise indirect mechanisms, requirement for sustained intervention, and limited direct microstructural restoration. Hepatic dysfunction impairs vitamin D activation, diminishes calcium absorption, and precipitates secondary osteoporosis; conversely, hepatic metabolites modulate bone formation by regulating osteoblastic energy metabolism.^{98,101–104} Mesenchymal stem cell (MSC) mitochondria drive osteogenic differentiation and critically determine pre-osteoblast fate through mitochondrial biogenesis (eg, PGC-1 α pathway) and ROS signaling (low-level ROS promotes osteogenesis). MSCs additionally serve as mitochondrial donors, restoring dysfunctional bone cell mitochondria via exosomal transfer or direct transplantation, thus improving the local osteogenic microenvironment. Clinically, mitochondrial augmentation—through transplantation or pharmacological activation—enhances osteoblast differentiation and repairs compromised bone cells via exosome-mediated mitochondrial delivery.^{105–108} These therapies are particularly indicated for postmenopausal and glucocorticoid-induced osteoporosis, providing direct correction of impaired bone formation, efficient anabolic effects, and site-specific intervention.^{102,106,107} Limitations include requirements for sophisticated in vitro culture systems and transplantation protocols, immune rejection risks, and substantial costs.^{107,109} Crucially, MSC mitochondrial function critically regulates osteogenic differentiation: dysfunction impairs osteoblast generation and reduces bone mass, whereas augmentation substantially enhances bone-forming capacity.¹⁰⁵

Genomic and Physiological Factors Influencing Mitochondrial Function and Compatibility

Mitochondrial DNA (mtDNA) is a covalently closed circular molecule devoid of protein-coding capacity, with a compact organization spanning 16,569 base pairs in humans. This double-stranded genome encodes 37 tightly packed genes: 22 transfer RNAs (tRNAs), two ribosomal RNA subunits (12S and 16S rRNA), and 13 polypeptides essential for the assembly and function of oxidative phosphorylation complexes.^{110,111} An mtDNA haplogroup denotes a phylogenetically defined cluster of mtDNA polymorphisms accumulated through maternal inheritance over evolutionary time.¹¹² These variations modulate mitochondrial oxidative phosphorylation (OXPHOS) functional capacity, metabolic efficiency, and oxidative stress signaling.¹¹³ Mounting evidence linking mtDNA haplogroups to disease susceptibility highlights the significance of mitochondrial genetics in human health. These associations involve complex interactions among bioenergetics, redox homeostasis, immune modulation, and nuclear-mitochondrial crosstalk. As mechanistic insights advance, mtDNA haplogroups emerge as valuable precision medicine biomarkers for predicting disease risk, therapeutic responsiveness, and longevity. Realizing this potential necessitates addressing current technical and ethical constraints while adopting integrative analytical frameworks. Genomically, mitochondrial function is regulated via estrogen receptor α/β (ER α /ER β) activation by 17 β -estradiol (E2), which stimulates nuclear respiratory factor 1 (NRF1) transcription.^{114,115} Estrogen (E2) upregulates transcription of nuclear-encoded electron transport chain proteins via NRF1 activation, which subsequently induces Mitochondrial Transcription Factor A (TFAM) expression, thereby activating transcription of mtDNA-encoded genes.^{116,117} NRF-1 dimerically binds DNA response elements, recruiting coactivators PGC-1 α , PGC-1 β , and PRC to modulate target gene transcription in a cell-type-specific manner.¹¹⁸ Mitochondrially localized ER α /ER β directly regulate mtDNA gene transcription and mitochondrial function, reflecting their tissue-specific distribution patterns.¹¹⁹

Aging constitutes a multifactorial process characterized by progressive functional decline, with mitochondria serving as central mediators of this deterioration.^{120–124} Mitochondria constitute the primary bioenergetic source essential for maintaining tissue homeostasis and supporting repair mechanisms, while their functional capacity undergoes progressive age-associated impairment.¹²⁵ Aging is associated with reduced expression of mitochondrial OXPHOS genes.^{126,127} Building upon mitochondria's central role in redox regulation, the Mitochondrial Free Radical Theory of Aging postulates that reactive oxygen species (ROS)-mediated oxidative damage to mtDNA initiates mitochondrial dysfunction, establishing a self-propagating cycle of escalating ROS production that ultimately disrupts cellular homeostasis.¹²⁸ Among the 13 mtDNA-encoded polypeptides examined by Short et al in physiologically aging humans, nine exhibited significant reductions in elderly subjects. Critically, diminished expression of cytochrome c oxidase subunits 3 and 4 (COX3/COX4) quantitatively correlated with attenuated ATP synthesis capacity.¹²⁹ ATP synthesis was assessed using Complex I-specific (glutamate/malate) and Complex II-specific (succinate + rotenone) substrates, revealing an approximately 8% decline per decade per gram tissue, or a 5% decrease normalized to mitochondrial protein content. Concomitantly, mitochondrial DNA and RNA abundance declined proportionally with ATP production in physiologically aging humans. Complementary quantitative mass spectrometry by Stauch et al of brain mitochondria from 5- (young), 12- (middle-aged), and 24-month-old (aged) mice demonstrated altered expression of catabolic pathway proteins and metabolite levels, indicating age-dependent metabolic demands influence proteomic profiles.¹³⁰ Aging drives accumulation of somatic mutations and large-scale deletions in mitochondrial DNA.^{131,132} Concomitantly, mtDNA defects induce compensatory increases in mitochondrial DNA copy number (mtDNAcn) to mitigate functional loss from impaired mitochondria.^{133,134}

Donor sex modulates immune cell subtype distribution, thus impacting immunological compatibility. Sex-specific disparities in immune cell proportions are evident: males demonstrate lower CD4⁺ naive T cell frequencies but elevated natural killer (NK) cell and monocyte counts compared to females, whereas females exhibit higher platelet counts.¹³⁵ These disparities contribute to alterations in global immune competence, consequently affecting immunological compatibility. Immunosenescence involves age-dependent remodeling of immune cell composition and functionality, substantially impacting immunological compatibility. Notably, CD8⁺CD45RA⁺ naive T cell abundance declines in aged individuals, whereas CD4⁺ effector memory and CD8⁺ central memory T cell frequencies rise with aging.^{136–138} These alterations may affect the immune system's capacity to recognize and respond to allogeneic tissues, thereby influencing immunological compatibility. Concomitantly, age-associated mitochondrial dysfunction may also play a role in modulating immunological compatibility. With advancing age, diminished mitochondrial function may compromise the energy supply and metabolic pathways in immune cells, consequently impairing their functional capacity and altering immunological compatibility. Importantly, certain tissues demonstrate age- and sex-specific patterns of responsiveness. Sex serves as a critical biological variable that influences multiple aspects of physiology and pathophysiology.¹³⁹ Sex hormones modulate mitochondrial function.^{119,140,141} Studies employing young or ovariectomized animal models demonstrate that gonadal steroids regulate mitochondrial energy production via transcriptional and post-transcriptional mechanisms.¹⁴⁰ Ovariectomy abolished the mitochondrial metabolic advantage in young female mice, whereas orchectomy exerted no significant effect on mitochondrial function in males. These findings indicate that ovarian steroids constitute the critical factor sustaining the mitochondrial advantage observed in females.¹⁴⁰ Sex-specific differences in mitochondrial performance are primarily mediated by endogenous estrogens, particularly estradiol (E₂), acting through their cognate receptors (ER α , ER β , GPER1) via tissue-specific and cell-type-dependent mechanisms. As transcription factors, ER α and ER β bind estrogen response elements (EREs) in nuclear DNA, activating transcription of nuclear respiratory factor 1 (NRF-1). Evidence indicates that mammalian mtDNA inheritance is predominantly maternal, facilitated by the active degradation of paternal mitochondria post-fertilization. For instance, sperm mitochondria undergo ubiquitination and subsequent elimination. This mechanism ensures mtDNA genetic stability and minimizes pathological dysfunction arising from genetic conflicts.¹⁴² Recent murine studies have elucidated sexually dimorphic patterns in age-related mitochondrial dysfunction. In male mice, aging was associated with augmented mitochondrial activity in metabolically active tissues including cardiac muscle, skeletal myocytes, and testicular parenchyma. Conversely, age-dependent reductions in mitochondrial function were observed in female mice within thermogenic brown adipose tissue and neural components of the cerebral cortex. These findings suggest that sex-specific regulation of

mitochondrial bioenergetics and reactive oxygen species homeostasis may differentially modulate immune system homeostasis through tissue-specific metabolic reprogramming.¹²⁵ The observed divergence in mitochondrial adaptation to aging across sexes implies potential mechanisms underlying gender-based disparities in age-related immune dysfunction and oxidative stress susceptibility.

Challenges and Ethical Considerations in Non-Maternal Mitochondrial Transplantation

Non-maternal mitochondrial transplantation confronts multiple and complex challenges, with core conflicts centered on immunogenicity, epigenetic interference, and ethical controversies. At the immunological level, exogenous mtDNA activates the mitochondrial-specific Toll-like receptor 9 (mtDNA-TLR9), triggering an innate immune response characterized by type I interferon release and inflammasome assembly. Clinical data indicate that approximately 23% of transplant recipients develop high-titer anti-mtDNA IgG antibodies within 7 days post-transplantation, which exhibit significant positive correlation with graft dysfunction ($r=0.82$, $p=0.003$).^{143,144} Crucially, heterologous mitochondrial membrane proteins TOM40 and TIM23 may function as neoantigens, inducing T cell-mediated immune rejection.¹⁴³ At the epigenetic level, the introduction of non-maternal mtDNA disrupts the homeostatic equilibrium established through nuclear-mitochondrial coevolution. Specifically, fluctuations in the mitochondrial metabolite α -ketoglutarate concentration inhibit TET methylcytosine dioxygenase activity, leading to abnormal hypermethylation of the IGF2-H19 imprinting control region,^{145,146} Concurrently, retrograde signaling dysregulation significantly reduces SIRT1 deacetylase activity, silencing the expression of nucleus-encoded mitochondrial genes such as TFAM and PGC-1 α .¹⁴⁶ The focus of ethical controversy lies in the risk that CRISPR-edited “universal donor” mitochondria pose for germline chimerism, potentially resulting in permanent alterations to the human genetic lineage.¹⁴⁷ Furthermore, the cross-generational transmission of non-maternal mtDNA contravenes the principle of natural maternal inheritance, and modeling studies predict a potential reduction in mitochondrial haplotype diversity within the population.^{144,148} Addressing technical bottlenecks necessitates the development of haplotype matching systems integrating deep sequencing (coverage $\geq 1000\times$) with artificial intelligence prediction (eg, the AlphaFold-MITO model) to circumvent efficiency losses in ATP synthesis caused by defects in OXPHOS complex assembly.¹⁰⁶

Mitochondrial Transplantation: Mechanisms and Techniques

Mitochondrial transfer refers to the endogenous intercellular movement of mitochondria through physiological conduits (eg, tunneling nanotubes [TNTs], extracellular vesicles [EVs], or cell fusion), primarily induced by cellular stress or metabolic imbalance to restore cellular function. In contrast, mitochondrial transplantation specifically denotes therapeutic procedures involving the isolation of functional mitochondria from donor cells and their exogenous administration into recipient cells. These two processes diverge substantively in methodology, biocompatibility, ethical implications, and clinical translatability. Herein, mitochondrial transfer is rigorously defined as the endogenous intercellular exchange of mitochondria mediated by TNTs, EVs, or osteocyte dendritic networks. Conversely, mitochondrial transplantation denotes the exogenous delivery of mitochondria utilizing techniques such as microinjection, nanocarrier encapsulation, or hydrogel-based loading. This conceptual distinction is mechanistically and clinically substantiated by studies contrasting natural mitochondrial trafficking^{6,149–152} with engineered transplantation methodologies.^{153–157} Having established this conceptual framework, we now examine the pivotal role of mitochondrial function in maintaining bone homeostasis and the contribution of its dysregulation to skeletal disorders.

The Critical Role of Mitochondrial Function in Bone Health

In eukaryotic cells, mitochondria orchestrate essential cellular processes, including oxidative phosphorylation, calcium homeostasis, and lipid and amino acid metabolism. They further regulate apoptotic and necrotic pathways.¹⁵⁸ This pivotal role in cellular metabolism establishes mitochondrial dysfunction as a determinant of impaired cellular homeostasis and disease pathogenesis.¹⁵⁹ Although mitochondrial dysfunction drives multisystem disorders, its cell-specific manifestations—such as in osteocytes and osteoblasts—increasingly contribute to distinct pathology.¹⁶⁰

Historically, mitochondrial disease research has predominantly focused on severe multisystem disorders such as MELAS syndrome and Leigh syndrome,^{161,162} characterized by complex multisystem manifestations. However, subtle or

localized mitochondrial dysfunction can critically impair organ-specific and cell-type-specific physiological functions. Within the bone microenvironment, mitochondrial impairment in osteoblasts, osteoclasts, and bone marrow mesenchymal stem cells (BMSCs) perturbs the tightly regulated bone remodeling equilibrium, underpinning pathologies including osteoporosis.¹⁶³

Although nutritional supplements and vitamin complexes are widely utilized for general health support, their efficacy in modifying disease progression or symptom severity of mitochondrial dysfunction—particularly as therapeutics for skeletal pathologies—remains limited.³⁰ Despite proliferating therapies targeting molecular defects in mitochondrial disorders, most confront limitations arising from etiological complexity. This inherent pathobiological intricacy frequently renders symptomatic management insufficient for arresting underlying disease progression.¹⁶⁴ Emerging research, including mitochondrial transplantation studies, identifies novel strategies to restore mitochondrial integrity. Adaptation of these approaches to correct mitochondrial dysfunction in bone cells constitutes a viable clinical avenue for preventing and treating skeletal disorders.¹⁶⁵ This conceptual refocusing shifts emphasis from systemic mitochondrial disorders toward mechanisms governing mitochondrial function in bone cells and skeletal integrity. Advancing mechanistic comprehension of intrinsic mitochondrial exchange processes within the bone niche is prerequisite for evaluating both endogenous reparative pathways and targeted therapeutic interventions.

Mechanisms of Intercellular Mitochondrial Transfer in Bone Homeostasis

This section examines endogenous mechanisms governing mitochondrial exchange among bone cells—a naturally occurring intercellular process. Mitochondrial transfer (MT) constitutes an evolving research domain investigating the dynamic translocation of functional mitochondria from donor to recipient cells. This translocation enables mitochondrial internalization and subsequent integration into the recipient's metabolic architecture (Figure 1a). MT directly modifies bioenergetic parameters, metabolic plasticity, and phenotypic consequences in recipient cells.¹⁴⁹ These mechanistically diverse processes represent specialized intercellular signaling modalities essential for maintaining tissue homeostasis and

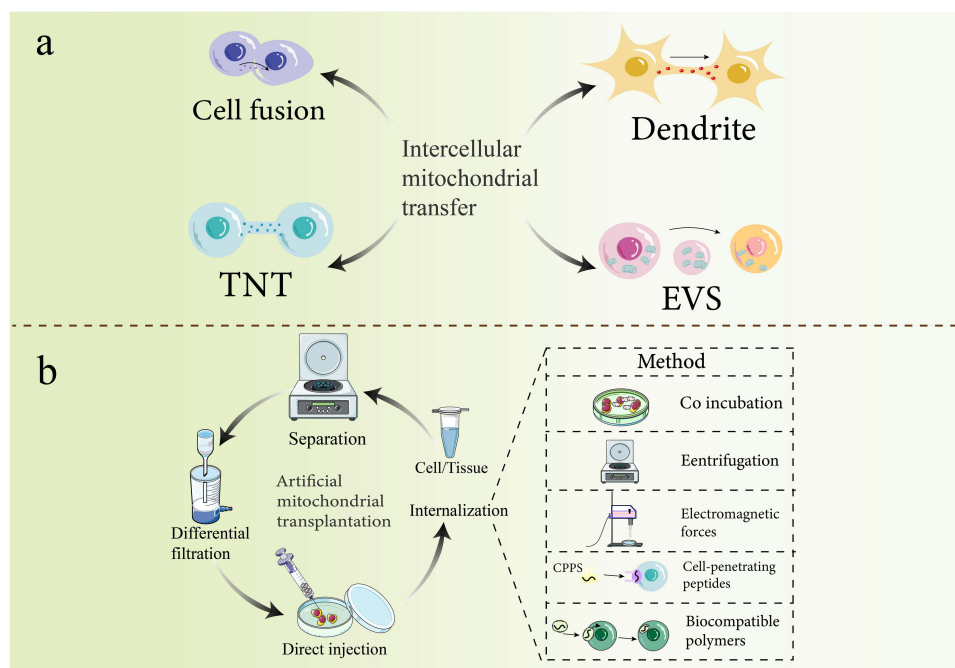


Figure 1 Methods of mitochondrial transfer and artificial mitochondrial transplantation.

Notes: (a) The established intercellular material transport mechanisms for mitochondrial transfer encompass cell fusion, dendritic transfer, tunneling nanotubes (TNTs), and vesicle transport. (b) Artificial mitochondrial transplantation involves several steps. Cells or tissues are centrifuged, filtered, and differentiated before direct injection of mitochondria into aculture dish containing mesenchymal stem cells for subsequent internalization. Internalization methods include centrifugation, magnetic transfer, cell-penetrating peptides, and biocompatible polymers to facilitate complete mitochondrial transplantation.

coordinating stress responses within osseous microenvironments. Current MT classification systems reflect distinct structural configurations and operational principles.

Direct Cell-to-Cell Connections for Mitochondrial Delivery

Tunneling nanotubes (TNTs): Transient, F-actin-based membrane protrusions forming direct intercellular connections. These structures mediate efficient intercellular communication and direct translocation of macromolecular cargo—including organelles such as mitochondria—between donor and recipient cells.^{150,151} Mitochondrial transfer via TNTs mitigates stress-induced cellular dysfunction and rescues cells during early apoptotic stages, demonstrating their functional role in cellular resilience. TNTs facilitate long-range organelle transport, enabling targeted mitochondrial delivery across cellular networks.¹⁵²

Cell Fusion: Cell fusion entails permanent integration of adjacent heterotypic cells, resulting in complete sharing of cytoplasmic components and organelles, including mitochondria.^{166,167} Although less commonly observed than TNT-mediated transfer, cell fusion constitutes a distinct mechanism for extensive mitochondrial integration, contributing to metabolic reprogramming in recipient cells.

Vesicle-Mediated Mitochondrial Packaging and Delivery

Extracellular vesicles (EVs)—including exosomes and microvesicles—constitute a principal pathway for mitochondrial delivery. These membrane-bound structures encapsulate intact mitochondria or mitochondrial constituents prior to extracellular release. Recipient cells internalize mitochondrion-containing EVs via endocytosis or membrane fusion, facilitating integration of transferred mitochondrial cargo.¹⁶⁸ EV-mediated mitochondrial transfer constitutes an adaptable mechanism enabling both localized and systemic mitochondrial delivery, contributing to paracrine signaling pathways and therapeutic applications.

Relevance in Bone Tissue

While mechanistic understanding of mitochondrial transfer continues to advance across biological systems, accumulating evidence establishes its essential role in bone homeostasis. Contemporary experimental approaches have enabled direct visualization and functional validation of this process within the osseous niche. Critically, mitochondrial transfer between bone cells occurs via osteocyte dendritic networks—elaborate cellular projections extensively interconnected throughout the mineralized matrix—as experimentally demonstrated.

Photoactivatable mitochondria (PhAM) studies in primary murine osteocytes and MLO-Y4 cell lines demonstrate mitochondrial transfer within dendritic networks using high-resolution confocal microscopy. Functional osteocytes transfer mitochondria to neighboring metabolically compromised osteocytes, restoring metabolic function through ER-mitochondrial axis coordination. This process specifically involves mitochondrial fusion proteins including mitofusin-2 (Mfn2), essential for osteocyte homeostasis.⁶

Beyond osteocyte-to-osteocyte transfer, evidence demonstrates mitochondrial transfer across additional bone cell lineages. Macrophages within the osseous niche donate mitochondria to mesenchymal stem cells (MSCs), promoting osteogenic differentiation through essential metabolic crosstalk.¹⁶⁹ This mitochondrial transfer regulates recipient cell fate and function, critically influencing bone formation and repair processes. Under osteoporotic conditions, macrophages exhibiting phenotypic alterations release oxidatively damaged mitochondria, compromising MSC osteogenic differentiation.¹⁶⁹

Collectively, these findings position intercellular mitochondrial transfer as a fundamental process governing homeostatic regulation in skeletal biology and pathology. Current research aims to characterize the scope and functional consequences of distinct mitochondrial transfer mechanisms in bone formation, resorption, and skeletal integrity. Given the established role of endogenous mitochondrial transfer in bone homeostasis, the following section examines emerging mitochondrial transplantation (MT) strategies for therapeutic mitochondrial restoration.

Techniques for Mitochondrial Transfer

In light of the demonstrated benefits of mitochondrial exchange, both naturally occurring transfer and therapeutically engineered transplantation, the field has progressed to develop methodologies for the artificial delivery of mitochondria.

The field of mitochondrial transfer (MT) emerged in 1982 with Clark and Shay's pioneering technique of "mitochondrial transformation", sparking further research despite initial uncertainties regarding the transfer mechanism.¹⁵³ Artificial MT involves several steps: separation and purification of mitochondria, their transmission, and internalization by recipient cells (Figure 1b). Table 1 provides a detailed overview of the current methodologies employed in mitochondrial transplantation, outlining their key contributions and improvements in the field. Separation and purification are the most critical steps, requiring a suitable mitochondrial source. In clinical settings, autologous skeletal muscle offers advantages due to its reduced immunogenicity and ease of access.^{176–178} Differential and density gradient centrifugation are common separation techniques, but achieving both high yield and high purity can be challenging. Therefore, personalized centrifugation protocols may be necessary for mitochondria from different tissues. A promising approach by McCully et al utilizes differential filtration for rapid and efficient separation of highly purified, functional mitochondria, potentially meeting the time constraints of clinical applications (separation time < 30 minutes).¹⁵⁴ Exogenous, isolated mitochondria have been successfully delivered to recipient cells in various in vitro and in vivo models. MT can be classified as in vitro or in vivo delivery. Both models often employ direct injection via microinjection or needles, a method also used in some clinical trials.^{155,179} For in vitro applications, researchers have explored methods beyond simple co-incubation to enhance mitochondrial internalization. These methods include centrifugation, magnetic transfer, cell-penetrating peptides, and biocompatible polymers.¹⁸⁰ However, compared with CO incubation, invasive technologies

Table 1 Overview of Current Mitochondrial Transplantation Methods and Key Improvements

Technical Name	Classification	Application Method	Core Mechanism	Advantages	Limitations
Differential filtering method ¹⁵⁴	\	Rapid purification	Filtering technology to quickly separate high-purity mitochondria	Short separation time (<30 minutes), high purity	Parameters need to be optimized to adapt to different tissue sources.
Microinjection method/needle direct injection method ¹⁵⁵	Intravenous administration	Physical injection	Physical penetration of the cell membrane to directly deliver mitochondria	Efficient; straightforward	Traumatic, potentially damaging to cells/tissues
Co-incubation ¹⁷⁰	Administration by non-intravenous route	Simple co-culture	Rely on the spontaneous endocytosis of the cell	<ul style="list-style-type: none"> Enhance aerobic respiration Protect cardiomyocytes from oxidative stress injury Inhibit left ventricular dilation and myocardial fibrosis 	Safety issues such as microcirculation blockage and arrhythmia
Photothermal nanoknife ¹⁷¹	In vitro/in vivo administration	Photothermal perforation	Laser-induced transient pore in the cell membrane	High cutting precision, suitable for high-precision operations	<ul style="list-style-type: none"> Targeted cells and potential damage to the recipient cells High operation special equipment; high mitochondrial damage risk; limited transplantation cell number.
Fluid dynamics ¹⁷²	Intravenous administration	High pressure injection	Use high pressure to promote mitochondria into the vascular system	Fast distribution	Targeted cells and potential damage to the recipient cells
Cell-penetrating peptide ^{173–175}	In vitro/in vivo administration	Chemically mediated	Peptide molecules promote mitochondrial transmembrane transport	<ul style="list-style-type: none"> Low operability increases the uptake ability of target cells PP (mainly cationic) can penetrate the membrane and then be internalized into the cell Low cell toxicity, as they degrade into amino acids 	The first-generation CPP has low selectivity for cells, tissues, and organs.
Hydrogel scaffold ¹⁵⁷	In vitro/in vivo administration	Material mediated	Promote the targeted transfer of mitochondria between cells	<ul style="list-style-type: none"> Immune reactivity Adapt to the environment of bone regeneration Has good biocompatibility 	More clinical trials are needed to verify its safety and effectiveness

such as photothermal nanoknife, non-injection, and hydrodynamics may be less popular due to limited targeting of cells and the potential damage to recipient cells. Studies have shown that successful mitochondrial internalization requires intact outer membranes and active mitochondria within recipient cells.^{181,182} Mitochondrial uptake may involve a variety of mechanisms, including actin-mediated endocytosis, macropinocytosis, and caveolin-dependent endocytosis.^{183,184} It is worth noting that the internalized mitochondria can avoid the lysosomal system in the cell and fuse with the host mitochondrial network.¹⁸⁵ Further research is needed to fully elucidate the mechanisms of mitochondrial internalization, as recipient cells likely employ a combination of these pathways. To further enhance the precision, efficiency, and safety of mitochondrial delivery, advanced strategies have emerged, including exosome-mediated transfer and biomimetic coating technologies.

Exosome-Mediated Mitochondrial Transfer

Exosomes are membrane-bound extracellular vesicles with a diameter of 30–150 nm, encapsulating a diverse array of molecular cargo, including proteins, lipids, and nucleic acids. These naturally occurring nanovesicles mediate intercellular communication, modulate osteocyte activity, and exhibit favorable biocompatibility with minimal immunogenic potential.^{186–188} Mitochondria act as central metabolic hubs in osteocytes, orchestrating three critical physiological processes: (1) ATP generation via oxidative phosphorylation to meet cellular energy demands; (2) calcium ion buffering to maintain intracellular signaling; and (3) reactive oxygen species regulation to preserve redox equilibrium. Dysregulation of these mitochondrial functions disrupts skeletal homeostasis and represents a fundamental pathophysiological mechanism underlying osteoporotic bone loss.^{189–192} In response to cellular stress signals (eg, oxidative stress and bioenergetic dysfunction), donor cells (eg, mesenchymal stem cells) selectively package functional mitochondria into exosomal vesicles for intercellular transfer. Exosomes undergo cellular internalization via membrane fusion or receptor-mediated endocytosis, subsequently delivering functional mitochondrial cargo to replenish the impaired mitochondrial network in recipient cells.^{193–196} The exogenously delivered mitochondria functionally integrate into the metabolic networks of recipient cells, exhibiting three key biological activities: (1) restoration of ATP production through oxidative phosphorylation; (2) attenuation of reactive oxygen species (ROS) generation; and (3) modulation of calcium signaling dynamics. The exosomal payload, comprising mitochondrial DNA (mtDNA) and associated regulatory proteins (eg, mitochondrial transcription factor A, TFAM), enhances mitochondrial biogenesis and functional recovery in recipient cells, thereby reestablishing cellular bioenergetic homeostasis.^{197–199} Exosomes mediate the intercellular regulation of mitochondrial quality control through their molecular cargo (eg, miRNAs, cytokines), which modulates key signaling pathways (including AMPK/mTOR) in recipient cells. This coordinated action simultaneously enhances: (1) mitophagic clearance of dysfunctional mitochondria; and (2) de novo mitochondrial biogenesis, collectively optimizing cellular bioenergetic efficiency.^{200–203} In the therapeutic management of osteoporosis, stem cell-derived exosomes (eg, bone marrow mesenchymal stem cell exosomes) facilitate the intercellular transfer of functional mitochondria to osteoblasts, resulting in three key therapeutic effects: (1) restoration of oxidative phosphorylation capacity; (2) upregulation of osteogenic transcription factors (eg, Runx2) and bone-specific proteins (eg, osteocalcin); and (3) enhanced bone matrix deposition and mineralization.^{29,36} Exosome-mediated mitochondrial transfer exerts multimodal inhibitory effects on osteoclast activity through three complementary mechanisms: (1) attenuation of intracellular ROS accumulation; (2) suppression of NF- κ B signaling pathways; and (3) miRNA-dependent (eg, miR-21-5p) downregulation of RANKL expression, collectively reducing osteoclastogenesis and bone resorptive capacity.^{204–206} Exosome-facilitated mitochondrial transfer confers cytoprotective and metabolic benefits to bone marrow stromal cells through three synergistic mechanisms: (1) augmentation of endogenous antioxidant defenses; (2) attenuation of pro-inflammatory cytokine secretion (eg, TNF- α , IL-6); and (3) metabolic reprogramming that promotes osteogenic differentiation while suppressing adipogenic commitment, thereby preserving skeletal homeostasis.^{102,207–209} Preclinical studies using ovariectomized rat models have demonstrated that mitochondrial-enriched mesenchymal stem cell exosomes elicit four significant therapeutic effects: (1) increased bone mineral density ($p < 0.01$); (2) restored trabecular microarchitecture; (3) elevated osteoblast counts; and (4) reduced osteoclast numbers, confirming their osteoprotective efficacy.^{210,211} Exosome therapy offers advantages such as favorable biological safety (being cell-derived secretions with low immunogenicity, minimal risk of rejection, and low toxicity), strong targeting and permeability (enabling accurate delivery of mitochondria to

osteocytes, penetration of biological barriers, and overcoming limitations of traditional drugs), and high modifiability (allowing modification to load specific components such as miR-146a for enhanced therapeutic specificity).^{212–218} Notwithstanding these advantages, critical challenges remain in clinical translation, including (1) optimization of scalable production and purification protocols; (2) incomplete elucidation of underlying molecular mechanisms; and (3) insufficient clinical validation through large-scale trials.^{219–221} Future clinical translation will require (1) refinement of scalable production methodologies; (2) mechanistic elucidation of mitochondrial transfer processes; (3) development of nanotechnology-enabled targeted delivery systems; and (4) rigorous multicenter clinical evaluation.

Mitochondria-Mimetic Coating-Based Immune-Evasive Enveloping Technology

Recent developments in biomimetic mitochondrial membrane engineering have yielded immunologically inert nanovehicles, marking a transformative advancement in precision therapeutics. This bioinspired approach offers two synergistic benefits: (1) superior immune evasion through molecular camouflage of surface epitopes, and (2) enhanced mitochondrial specificity via evolutionary conserved organelle targeting sequences, collectively optimizing treatment efficacy. Zheng et al established that rationally designed mitochondrial nanocarriers can reconstitute mitochondrial biogenesis pathways, effectively reversing neuronal bioenergetic deficits.²²² The CSCCT nanoparticle system utilizes a hierarchical targeting approach combining blood-brain barrier (BBB) translocation with neuronal mitochondrial accumulation. Surface functionalization with DSPE-PEG₂₀₀₀-TPP confers: (1) mitochondriotropic specificity through triphenylphosphonium cation-mediated potential gradient recognition, (2) reduced opsonization through steric stabilization, and (3) prolonged plasma residence time by minimizing reticuloendothelial system clearance. The inherent biocompatibility of native cell membranes confers both immunotolerance and enhanced circulatory stability. The DSPE-PEG₂₀₀₀-TPP-modified macrophage membrane coating mediates dual functionality: (1) potentiated immune evasion through self-marker retention, and (2) selective targeting of compromised neurons via inflammation-dependent integrin-VCAM-1 molecular recognition. Focused ultrasound-mediated blood-brain barrier (BBB) disruption enables transient and reversible nanoparticle extravasation into brain parenchyma, facilitating site-specific accumulation at pathological foci. The bioengineered NC@PPN core-shell system demonstrates tumor cell-selective internalization and mitochondria-targeted delivery through coordinated surface ligand-receptor interactions and membrane fusion mechanisms. Clathrin-dependent endocytic trafficking and cholesterol-mediated cellular internalization synergistically enhance mitochondrial delivery efficiency.²²³ The outer shell incorporates somatostatin (SST) ligands that exhibit high-affinity binding to somatostatin receptor subtype 2 (SSTR2), which is overexpressed on MCF-7 breast cancer cell membranes, thereby mediating tumor-selective cellular recognition. The system exploits tannic acid's (TA) polyphenolic architecture to facilitate mitochondrial localization via high-affinity interactions with voltage-dependent anion channels (VDACs) on the outer mitochondrial membrane. Quantitative colocalization analysis revealed significant spatial correlation between NC@PPNs and mitochondrial markers (Pearson's $r > 0.85$), confirming targeting specificity. Peng et al developed an integrated targeting platform combining small-molecule ligands with natural biomembrane coatings. TPP-functionalized gold nanoparticles (TPP-GNPs) exploit electrostatic potential-driven interactions with mitochondrial membranes, achieving both enhanced organelle-specific accumulation and surface plasmon resonance-mediated nanoparticle assembly.²²⁴ The cancer cell membrane (CCM) encapsulation strategy forms a protective biointerface around GNA, shielding its structural integrity from biological degradation while extending its plasma half-life. Homotypic membrane fusion facilitates direct nanoparticle cytosolic entry, circumventing endolysosomal sequestration and subsequent degradation. This mechanism enables efficient TPP-mediated mitochondrial trafficking, substantially improving cellular internalization kinetics.

Programmable Nanorobots or Magnetically Guided Delivery Systems

Engineered DNA nanostructures and magnetically responsive delivery systems represent groundbreaking developments in precision mitochondrial medicine. DNA origami-based nanocarriers (eg, tetrahedral frameworks and tubular transporters) achieve cell-specific mitochondrial delivery through programmable molecular interactions and three-dimensional spatial targeting.^{225–228} Cell-type selective targeting is accomplished via TXNDC5 antibody-conjugated aptamer arrays immobilized on delivery substrates,^{229–231} A key innovation utilizes the acidic osseous milieu ($\text{pH} \leq 6.5$) to trigger i-motif structural transitions, facilitating subsecond mitochondrial release,^{232–235} while ensuring nanocarrier biodegradation

prevents tissue accumulation.²³⁶ Preclinical evaluation in a validated osteoporosis model revealed that a single treatment regimen increased bone mineral density by 32%, demonstrating statistically significant improvement over conventional delivery approaches ($p < 0.001$).²³⁶ Magnetogenetic delivery systems utilizing IONP-tagged mitochondria show enhanced intercellular transfer efficiency under controlled magnetic guidance.²³⁷ The integrated platform combines magnetothermal therapy, where AMF-activated SPIONs produce localized hyperthermia, simultaneously stimulating vascularization and bone regeneration through coupled mechanisms.²³⁶ SPIONs additionally permit longitudinal, quantitative tracking of mitochondrial engraftment via MRI.²³⁸ Notwithstanding these advances, clinical implementation faces notable challenges: (1) depth-dependent magnetic field attenuation requiring high-field systems ($\geq 3\text{T}$) for deep tissue applications ($> 10\text{cm}$), and (2) hepatotoxicity risks from persistent SPION retention.²³⁹

Application of Mitochondrial Transplantation in the Treatment of Osteoporosis

Mitochondrial Transfer in Bone Homeostasis Regulation and Osteoporosis Intervention

Accumulating evidence demonstrates that mitochondrial transfer (MT) constitutes a fundamental regulatory axis in bone homeostasis, mediating intercellular crosstalk and functional synchronization across osteogenic cell populations (Figure 2). This biological process critically regulates bone formation, remodeling kinetics, and reparative processes, thereby revealing potential therapeutic targets for osteoporosis intervention (Figure 3).

The skeletal matrix demonstrates substantial accumulation of mitochondrial components, reflecting their active engagement in osteoblast maturation and mineral homeostasis regulation, likely facilitated by regulated extracellular vesicle trafficking.^{240–242} Biochemical and genetic studies confirm that fully differentiated osteoblasts actively export intact mitochondria and mitochondrial-derived vesicles (MDVs), which subsequently potentiate the osteogenic programming of mesenchymal stem cell precursors.^{240,243,244} Recent advances have uncovered a fundamental interdependence between mitochondrial morphological plasticity and osteogenic differentiation, whereby differentiation signals provoke mitochondrial network fragmentation and annular reorganization, ultimately leading to CD38/cADPR-dependent extracellular discharge.^{240,244} Experimental modulation of mitochondrial fusion-fission balance - through either fusion suppression (eg, OPA1 knockout) or fission activation (eg, Fis1 transgenic expression)—markedly amplifies mitochondrial export capacity, yielding increased extracellular mitochondrial abundance and enhanced osteogenic potential.²⁴⁰ These data collectively establish that the unique structural specialization of mature osteoblasts' mitochondrial networks supports the regulated extracellular deployment of bioactive mitochondria and MDVs, which function as critical determinants of osteoblast lineage progression and bone matrix biosynthesis.²⁴⁰ Deciphering these regulatory circuits provides a molecular basis for therapeutic mitochondrial transfer strategies designed to stimulate bone formation and prevent osteoporosis-associated skeletal degeneration.

Osteocytes, the terminally differentiated cells embedded within the mineralized bone matrix and interconnected via an extensive canalicular network, serve as an exemplary biological system for studying mitochondrial transfer mechanisms and their role in maintaining skeletal homeostasis.^{6,245,246} The osteocyte lacunar-canalicular system functions as a critical mechanosensory apparatus that precisely regulates bone remodeling through paracrine communication with osteoblasts and osteoclasts.^{6,245,246} In this context, intercellular mitochondrial transfer represents an essential cytoprotective strategy for these long-lived cells, protecting against progressive cellular damage while maintaining their functional capacity to preserve bone structural integrity.^{30,247} Metabolically stressed osteocytes demonstrate the ability to internalize mitochondria from surrounding functional osteocytes, restoring bioenergetic homeostasis and maintaining their regulatory functions in bone metabolism.²⁴⁷ Current evidence indicates that this transfer process depends on specialized ER-mitochondria membrane contact sites, which facilitate directional mitochondrial transport through the canalicular network.⁶ Notably, Mitofusin 2 (Mfn2), a key mediator of mitochondrial dynamics, establishes ER-mitochondria tethering and promotes intercellular mitochondrial exchange.^{6,248,249} Experimental data show that VAPB knockdown significantly attenuates mitochondrial transfer, impairing metabolic recovery in dysfunctional osteocytes, suggesting that ER-mediated mitochondrial distribution involves coordinated actions of Mfn2 and VAPB-containing protein complexes.⁶

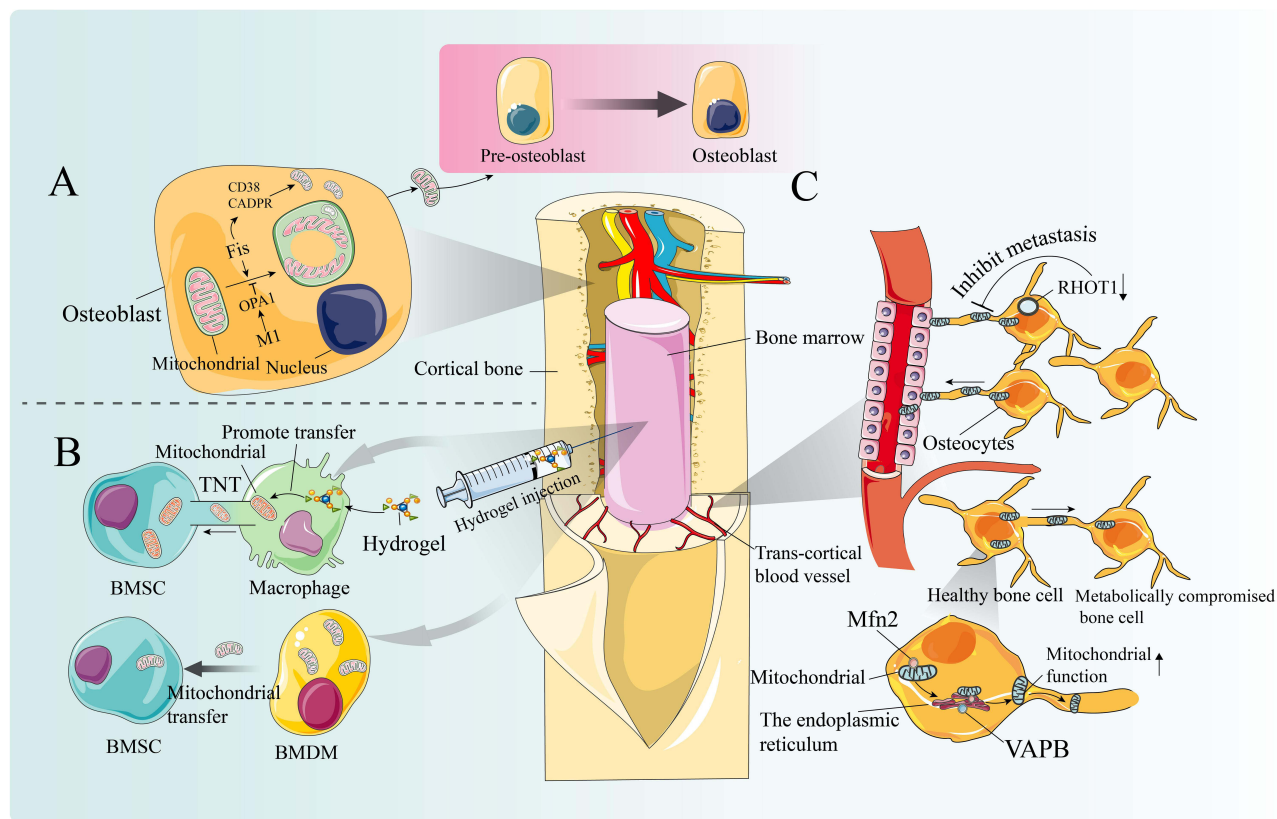


Figure 2 The role of mitochondrial transfer in bone cell communication and function.

Notes: (A) Mature osteoblasts actively release mitochondria and mitochondrial-derived vesicles (MDVs) to facilitate the differentiation of osteoblast precursor cells. Osteogenesis induction triggers mitochondrial fragmentation, donut formation, and subsequent secretion via CD38/cADPR signaling. Disrupting mitochondrial fusion (OPA1 knockout) or enhancing fission (Fis1 overexpression) can accelerate these processes, resulting in increased mitochondrial secretion and accelerated osteogenesis. (B) The injection of an engineered hydrogel with immunoreactivity can adapt to the bone regeneration environment and promote targeted intercellular mitochondrial transfer. Macrophages can restore mitochondrial bioenergetics in bone marrow mesenchymal stem cells (BMSCs) by continuously supplying mitochondria, fundamentally addressing the issue of insufficient energy support in BMSCs caused by local inflammation during bone repair and regeneration. Another novel 3D biomimetic hydrogel scaffold with immunomodulatory properties can promote the migration of macrophage mitochondria to BMSCs, thereby stimulating osteoblastic differentiation. (C) Bone cells are interconnected through an extensive dendritic network. Mitochondrial fission protein 2 (Mfn2), aGTPase, facilitates this transfer by bridging the endoplasmic reticulum (ER) to mitochondria. Knockdown of the endoplasmic reticulum mitochondrial binding protein vesicle-associated membrane protein B (VAPB) impedes mitochondrial transfer, reducing the ability to salvage damaged cellular metabolic function (Upward black arrows indicate an increase in mitochondrial function.). The transcortical vascular system (TCV) promotes communication between the bone marrow vascular system and the external circulation. Conditional knockout of the RHO1 gene (Downward black arrows indicate a decrease in RHO1), encoding MIRO1, disrupts mitochondrial transfer in bone cells, leading to TCV network degradation and subsequent impairment of cortical bone healing.

Age-related declines in Mfn2 expression are associated with defective mitochondrial transport and reduced transfer efficiency within the osteocyte network.⁶ These deficits contribute to osteocyte apoptosis, metabolic dysfunction, and ultimately promote osteoporosis development by disrupting mechanotransduction pathways and impairing the bone's adaptive repair capacity.⁶

Mitochondrial transfer mechanisms involve multiple cell types beyond osteocytes, with MIRO1 (Mitochondrial Rho GTPase 1) emerging as a central regulator of microtubule-associated mitochondrial transport.^{250,251} The transcortical vascular system functions as a principal interface mediating molecular exchange between bone marrow vasculature and the systemic circulatory system.²⁵² Recent investigations reveal that viable osteocytes maintain vascular integrity through mitochondrial transfer to endothelial cells, thereby preserving microvascular structure and function.²⁵² Experimental osteocyte depletion leads to progressive deterioration of transcortical vasculature.²⁵² Targeted deletion of Rho1 (encoding MIRO1) in osteocytes impairs mitochondrial transport and induces vascular degeneration, establishing MIRO1-mediated transfer as essential for vascular homeostasis.²⁵² Endothelial cells receiving osteocyte-derived mitochondria show restored functionality, increased angiogenic potential, and enhanced capacity for bone repair.²⁵² Collectively, these findings delineate a critical osteocyte-vascular axis, revealing novel therapeutic avenues for mitochondrial transfer-based

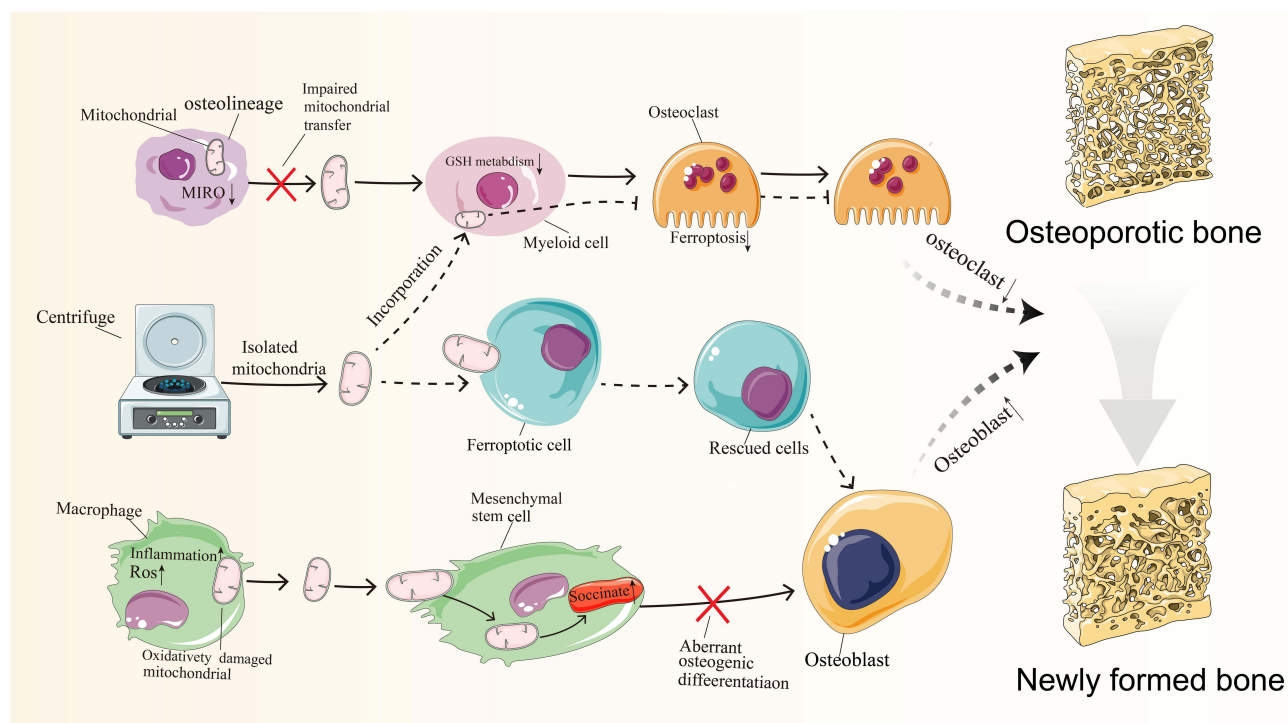


Figure 3 The therapeutic potential of mitochondrial transplantation in osteoporosis.

Notes: Decreased Miro1 expression in osteoblasts impairs mitochondrial transfer, leading to altered glutathione metabolism, protection of osteoclast lineage cells from iron-induced apoptosis, and promotion of osteoclast activity. In osteoporosis, macrophages with altered phenotypes and metabolic states release oxidatively damaged mitochondria, and increased mitochondrial transfer results in succinic acid accumulation, causing metabolic dysregulation in bone marrow mesenchymal stem cells. Succinic acid accumulation is a pivotal factor in abnormal osteogenic differentiation. Recent research findings suggest that mitochondrial transplantation could be a promising novel approach for preventing and treating osteoporosis. Mitochondrial transplantation could be a promising novel approach for preventing and treating osteoporosis. Mitochondria isolated through centrifugation can be merged with cells exhibiting metabolic abnormalities, effectively protecting and repairing cellular damage, thereby restoring bone metabolic balance and promoting osteogenic differentiation. The dashed line in the figure represents the proposed hypothesis. (Black upward arrows indicate an increase in substance or expression, while black downward arrows indicate a decrease in substance or expression).

interventions in skeletal disorders associated with vascular compromise, including osteoporosis and impaired fracture healing.

Optimal bone regeneration, critical for osteoporotic fracture healing and skeletal integrity, requires tightly controlled immune regulation and efficient metabolic adaptation within the fracture callus.²⁵³ As central regulators of cellular energetics and metabolic pathways, mitochondria represent attractive therapeutic targets, with mitochondrial transfer emerging as a viable strategy for functional recovery.^{254,255} Recent developments in biomaterial engineering have produced immunologically active graded hydrogels specifically designed to integrate with the bone regeneration micro-environment and promote targeted mitochondrial delivery between cells.¹⁵⁶ A prime example is the dependence of bone marrow mesenchymal stem cells (BMSCs), crucial mediators of bone repair, on mitochondrial transfer from macrophages to sustain their bioenergetic requirements. This cellular crosstalk alleviates inflammatory-mediated metabolic suppression of osteogenesis, highlighting its therapeutic potential for improving bone regeneration in osteoporosis.¹⁵⁶ The newly engineered 3D bionic GAD/Ag PIO hydrogel platform demonstrates significant immunomodulatory capacity and promotes BMSC osteogenic differentiation through macrophage-mediated mitochondrial transfer in experimental models.¹⁵⁷ Preclinical animal studies further validate this scaffold's ability to enhance fracture healing.¹⁵⁷ Together, these results position mitochondrial transfer-enabled scaffolds as a novel treatment approach for boosting bone formation and fracture repair, with important clinical implications for osteoporosis and bone regeneration therapies.¹⁵⁷

The Therapeutic Potential of Mitochondrial Transfer From Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) have emerged as promising therapeutic agents for tissue regeneration, owing to their triad of biological properties: immunomodulatory capacity, reactive oxygen species scavenging activity, and pro-regenerative potential.²⁵⁶ A fundamental mechanism mediating these therapeutic effects involves intercellular

mitochondrial transfer from MSCs to recipient cells, which has been experimentally demonstrated in both animal models and cell culture systems.²⁵⁷ The biological significance of MSC-mediated mitochondrial transfer (MSC-MT) underscores its therapeutic potential for disorders characterized by mitochondrial impairment. Future investigations should focus on mechanistic elucidation, optimization of transfer efficacy, and development of clinically translatable therapeutic approaches.¹⁵³

MSCs as Mitochondrial Donors for Tissue and Organ Repair

Bone marrow-derived mesenchymal stem cells (BM-MSCs), representing a paradigm of mesenchymal stem cell populations, exert their therapeutic effects post-transplantation via three principal mechanisms: (1) direct intercellular signaling, (2) paracrine mediator secretion, and (3) extracellular vesicle-mediated communication (encompassing both exosomes and microvesicles).²⁵⁸ Accumulating experimental data demonstrate that mitochondrial transfer from BM-MSCs promotes functional restoration in damaged tissues.²⁵⁹ This biological process assumes particular importance in disorders characterized by mitochondrial dysfunction, where BM-MSC-originated mitochondrial transfer to compromised cells can ameliorate tissue pathology. A well-documented instance involves the uptake of BM-MSC mitochondria by alveolar epithelial cells, providing cytoprotection against pulmonary injury induced by endotoxin exposure or cigarette smoke inhalation.^{260,261} Importantly, BM-MSC senescence, manifested as progressive functional deterioration, constitutes a major etiological factor in age-related osteoporosis. These mechanistic insights have led to the hypothesis that controlled mitochondrial transfer *in vitro* could enhance BM-MSC osteogenic potential, thereby offering a novel therapeutic approach for osteoporosis intervention.

Intercellular Mitochondrial Transfer Modulating MSC Function in Bone Homeostasis

In addition to serving as mitochondrial donors, MSCs exhibit functional plasticity that is modulated by mitochondrial acquisition from other cell populations, particularly macrophages. Under physiological conditions, macrophage-derived mitochondrial transfer enhances MSC osteogenic potential, contributing to skeletal homeostasis. However, in osteoporotic states, metabolically compromised macrophages predominantly release oxidatively impaired mitochondria. The subsequent uptake of these dysfunctional mitochondria, especially from pro-inflammatory M1-polarized macrophages, induces redox imbalance and succinate accumulation in recipient MSCs. This metabolic perturbation disrupts osteogenic differentiation capacity through pathological remodeling of MSC metabolism. Collectively, these observations establish bidirectional mitochondrial transfer between macrophages and MSCs as a critical metabolic checkpoint in bone homeostasis, revealing therapeutic opportunities for osteoporosis through targeted modulation of this intercellular crosstalk.²⁶²

The Role of Ferroptosis in Osteoporosis and the Potential of Mitochondrial Transplantation

Ferroptosis, an iron-dependent programmed cell death pathway driven by membrane lipid peroxidation, represents a key pathogenic mechanism in osteoporosis-related bone deterioration.²⁶³ Preserving mitochondrial integrity has emerged as a promising therapeutic strategy to counteract ferroptosis-mediated cellular damage.²⁶⁴ However, translating this approach into clinical applications remains challenging due to unresolved mechanistic aspects of mitochondrial dysregulation and uncertainties regarding optimal therapeutic windows. Pharmacological suppression of mitochondrial superoxide production restores bioenergetic competence and may protect against ferroptosis-induced cell death.²⁶⁵

Mitochondrial Transfer Regulating Ferroptosis in Bone Cells

Mitochondrial transfer (MT) serves as a critical regulatory node governing ferroptosis within the bone microenvironment.²⁶⁶ Substantial experimental data confirm that osteoprogenitor cells actively engage in mitochondrial donation to myeloid lineage cells. Targeted deletion of MIRO1 in osteogenic precursors impairs mitochondrial trafficking, promoting excessive osteoclast differentiation and subsequent bone loss. At the molecular level, impaired mitochondrial transfer disrupts glutathione-mediated redox balance, a key determinant of ferroptotic vulnerability, consequently inhibiting programmed cell death in osteoclast precursors while potentiating their resorptive capacity. Bidirectional mitochondrial exchange between skeletal and hematopoietic systems significantly influences glucocorticoid-induced

osteoporosis pathogenesis, the most common secondary osteoporosis variant. This intercellular communication mechanism drives glutathione depletion while ameliorating disease advancement.²⁶⁶ Collectively, these findings establish that skeletal homeostasis depends on precise osteo-immune mitochondrial crosstalk, while identifying ferroptosis pathway modulation as a promising therapeutic strategy for glucocorticoid-associated bone loss.

Mitochondrial Transplantation as a Therapeutic Approach for Ferroptosis

Mitochondrial transplantation exhibits therapeutic efficacy in attenuating ferroptosis across diverse biological contexts, highlighting its potential application for osteoporosis management. In neurodegenerative models, transplanted mitochondria demonstrate functional engraftment within murine cortical neurons, effectively preventing ferroptosis-associated neuronal damage. Neurodegenerative disease studies further confirm that exogenously administered mitochondria integrate into neuronal networks, exerting protective effects against ferroptotic synaptic degeneration.²⁶⁷

Future Directions and Challenges in Mitochondrial Transplantation

Mitochondrial transplantation (MT) has emerged as a promising therapeutic strategy, demonstrating efficacy across various models, from cellular and animal studies to early human trials. These models utilize both autologous and non-autologous mitochondria. Preclinical animal studies consistently show that MT restores mitochondrial function and enhances cellular energy metabolism.¹⁴⁶ Clinically, MT has proven effective in treating conditions like myocardial ischemia-reperfusion injury and cardiogenic shock after ischemia-reperfusion.^{176,268} Notably, autologous MT is a particularly attractive therapeutic approach for various diseases due to its ability to avoid significant increases in inflammatory markers like TNF- α , IL-6, and high-sensitivity C-reactive protein.¹⁷⁹ This personalized approach, where mitochondria are processed in vitro and reintroduced into the same patient, inherently minimizes the risk of immune rejection, aligning well with principles of precision medicine. The process of mitochondrial isolation and transplantation is generally considered straightforward, time-efficient, and boasts a high success rate, offering better controllability, stability, and effectiveness compared to other enhancement strategies.¹⁰⁶

Overcoming Translational Hurdles

Despite its considerable promise, the widespread clinical application of MT faces several uncertainties and obstacles. The primary challenge involves not only the efficient and specific delivery of functional mitochondria to target cells in vivo but also establishing the long-term stability and efficacy of transplanted mitochondria within host cells. Researchers are actively pursuing novel methods to address these issues. For instance, CRISPR gene editing technology offers the potential to correct mutations associated with mitochondrial diseases by modifying the DNA of transplanted mitochondria. Moreover, to overcome the difficulties of targeting mitochondria to specific cells in vivo, mitochondria can be encapsulated within nanoparticles for precise delivery. The development of innovative technologies such as nanoparticle-mediated delivery and CRISPR gene editing has instilled hope for the advancement of novel therapies for mitochondrial diseases.¹⁴⁷

Mitochondrial Sourcing, Storage, and Immune Response

Although mitochondrial transplantation holds promising potential, several challenges remain for its clinical application, including mitochondrial storage, transplant rejection, and ethical considerations.¹⁴⁵ Given the critical role of mitochondrial quality in transplantation, meticulous selection of the mitochondrial source is paramount. While autologous transplantation is generally preferred for treating mitochondrial diseases due to its ability to avoid inflammation and rejection, it is not feasible for patients with congenital mitochondrial disorders. In these cases, mitochondria derived from compatible allogeneic donors within the same species are required. To significantly expand the clinical applicability of mitochondrial transplantation, further research is essential to elucidate the immune response and associated mechanisms. The immune response remains a critical, yet understudied, aspect of mitochondrial replacement therapy.¹⁴⁷ Mitochondria used in transplantation often originate from either autologous or allogeneic sources. While allogeneic mitochondria offer greater clinical practicality, particularly for patients with mtDNA mutations, in vitro studies have reported immune

responses following their transplantation.¹⁴³ Conversely, continuous injection of allogeneic mitochondria in mice has demonstrated safety.¹⁴⁴ These conflicting findings necessitate further investigation into the underlying mechanisms.

Moreover, the limited time window for mitochondrial isolation restricts the applicability of mitochondrial transplantation. Mitochondrial activity rapidly declines following removal from the host.²⁶⁹ Currently, there is no effective method for long-term mitochondrial preservation, necessitating immediate use after extraction. Isolated mitochondria are susceptible to internal and external membrane damage, leading to significant decreases in function and activity.²⁷⁰ While refrigeration and cryopreservation are being explored as potential solutions,²⁶⁹ these strategies can stabilize the mitochondrial membrane but are unable to preserve normal bioenergetic functions. Consequently, the development of an effective mitochondrial storage solution is urgently needed to broaden its practical applications.²⁶⁹ Therefore, establishing the optimal method for separating and transplanting mitochondria is crucial for obtaining complete and feasible mitochondria for clinical treatment.²⁷¹

Alternative Delivery Methods and Future Research Directions

Cell-mediated mitochondrial transfer provides a potentially safer approach compared to direct mitochondrial transplantation, eliminating the need for laborious mitochondrial isolation and the challenges associated with *in vitro* mitochondrial preservation. However, transfer efficiency remains a significant hurdle for cell-mediated mitochondrial transfer. Despite advancements, translating targeted mitochondrial transmission from the laboratory to clinical practice continues to face substantial challenges. The integration of functional cells can complicate the evaluation of therapeutic efficacy in cell-mediated mitochondrial transfer. Furthermore, the process of selecting donor cells and delivering mitochondria to target sites requires further standardization. Future research should prioritize the development of efficient mitochondrial storage solutions and transport methods.²⁷²

Advances in tools and technologies for measuring mitochondrial transfer *in vivo*, coupled with the recognition of mitochondria's pivotal role in pathological states, have spurred rapid growth in the field of intracellular mitochondrial transfer. Despite progress, the molecular mechanisms underlying mitochondrial transfer between different cells remain largely elusive. Further research is needed to evaluate the effectiveness, stability, and safety of artificial mitochondrial transplantation technology in human trials.¹⁴⁷ So far, only a small number of clinical trials with varying results have been conducted, and while the safety and effectiveness of mitochondrial transplantation have been validated to a certain extent, this does not necessarily indicate long-term safety and effectiveness.¹⁴⁷ Furthermore, the effectiveness and safety of exogenous mitochondria need to be further explored in human trials.¹⁴⁷ Future research should address several critical questions, including: the efficiency and long-term viability of mitochondria during isolation and delivery; strategies to mitigate the potential immune response to allogeneic mitochondria; the mechanisms governing fusion between transplanted mitochondria and the host cell mitochondrial network; and the preservation of unique characteristics by transplanted mitochondria within host cells. The answers to these questions, while potentially influenced by cell type, tissue, and environment, could fundamentally transform our understanding of mitochondrial biology and uncover promising avenues for therapeutic and diagnostic applications¹⁶⁰ (Figure 4).

Conclusion

Osteoporosis, a systemic skeletal disorder characterized by progressive bone loss and microarchitectural deterioration, represents a major global health challenge necessitating therapeutic strategies beyond conventional anti-resorptive approaches. Emerging evidence implicates mitochondrial dysfunction as a central pathophysiological mechanism underlying the disrupted bone remodeling balance in osteoporosis. This review critically evaluates contemporary data demonstrating that mitochondrial quality control serves as a critical determinant of skeletal homeostasis, wherein subtle disturbances in mitochondrial function can significantly impair bone turnover processes and accelerate osteoporotic progression.

Recent progress in mitochondrial transplantation (MT)—a novel regenerative strategy involving the precise administration of functional mitochondria to cells with bioenergetic deficits—has demonstrated significant therapeutic effects in preclinical osteoporosis models, including reversal of bone mass depletion, reconstruction of trabecular networks, and enhancement of bone mechanical competence. This comprehensive review assesses various mitochondrial donor sources

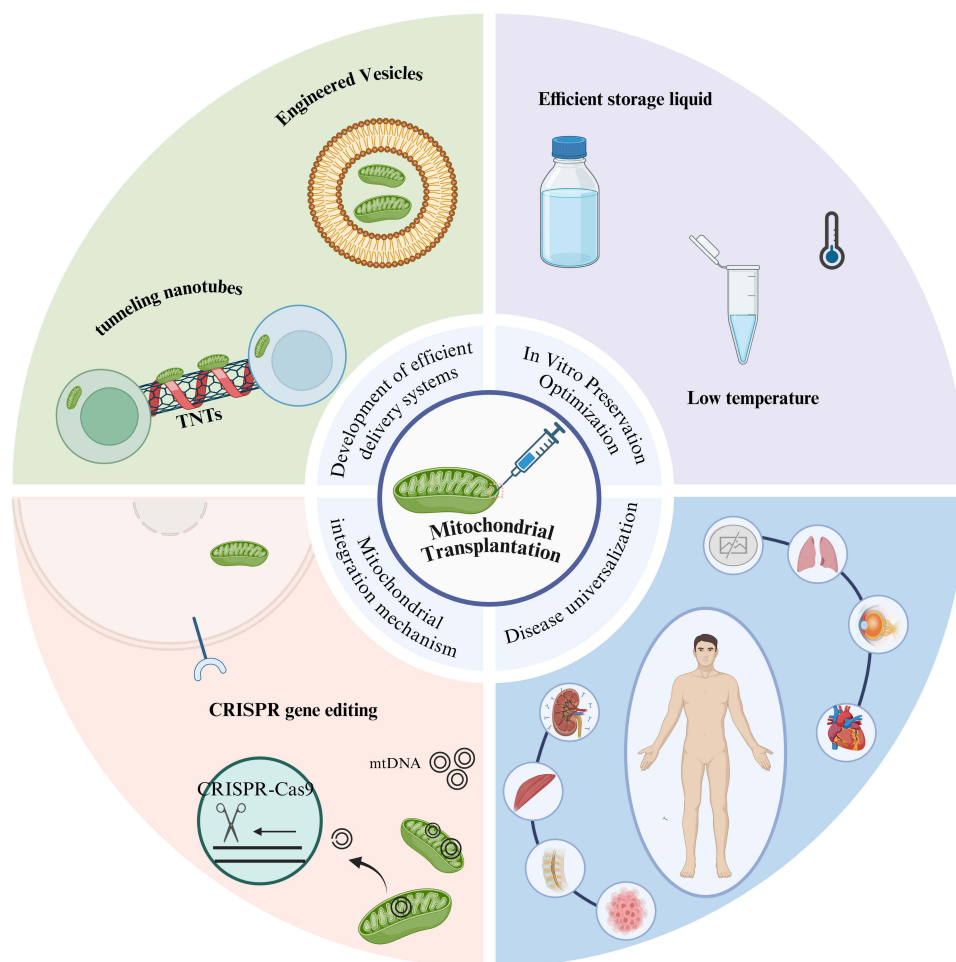


Figure 4 The future direction of mitochondrial transplantation.

Notes: Future mitochondrial transplantation can advance through the development of efficient delivery systems, optimization of invitro preservation techniques, and innovation of mitochondrial integration mechanisms, while also being applied to various diseases.

—particularly skeletal muscle, hepatocyte, and mesenchymal stem cell-derived mitochondria—each possessing unique therapeutic attributes for osteoporosis intervention. Of particular note, mitochondria isolated from mesenchymal stem cells exhibit pronounced osteogenic specificity, effectively restoring bone-forming capacity through both exosomal transfer pathways and direct mitochondrial incorporation.

Intercellular mitochondrial transfer occurs through phylogenetically conserved mechanisms, including tunneling nanotube-mediated transport, extracellular vesicle encapsulation, and fusogenic cellular interactions. In skeletal tissue, this process assumes particular physiological significance as osteocytes employ their extensive canalicular networks to distribute mitochondria throughout the osseous matrix, thereby maintaining metabolic homeostasis.

Despite its considerable therapeutic promise, mitochondrial transplantation faces substantial challenges in clinical implementation. Principal technical obstacles involve: (1) developing efficient methodologies for tissue-specific mitochondrial delivery, (2) ensuring sustained bioenergetic competence following cellular integration, and (3) preventing adverse immune recognition. Further limitations stem from the transient viability of isolated mitochondria and inadequate cryopreservation techniques for mitochondrial banking.

From an ethical perspective, allogeneic mitochondrial transfer necessitates careful evaluation, with particular attention to potential germline incorporation and incompatibilities between donor mitochondria and recipient nuclear genomes. Future research should prioritize the development of optimized mitochondrial preservation techniques and enhanced delivery methodologies. Emerging strategies such as CRISPR-mediated mitochondrial genome engineering and

nanoparticle-facilitated mitochondrial transfer may address current technological limitations. Combining single-cell multi-omics analyses with computational models of mitochondrial function could facilitate personalized mitochondrial therapies, positioning MT as a groundbreaking approach for osteoporosis intervention. A comprehensive understanding of mitochondrial transfer mechanisms, supported by rigorous clinical evaluation, is essential for advancing mitochondrial transplantation toward clinical application in osteoporosis treatment.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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