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Mitochondrial quality control as a unifying regulatory platform in inflammatory bone diseases

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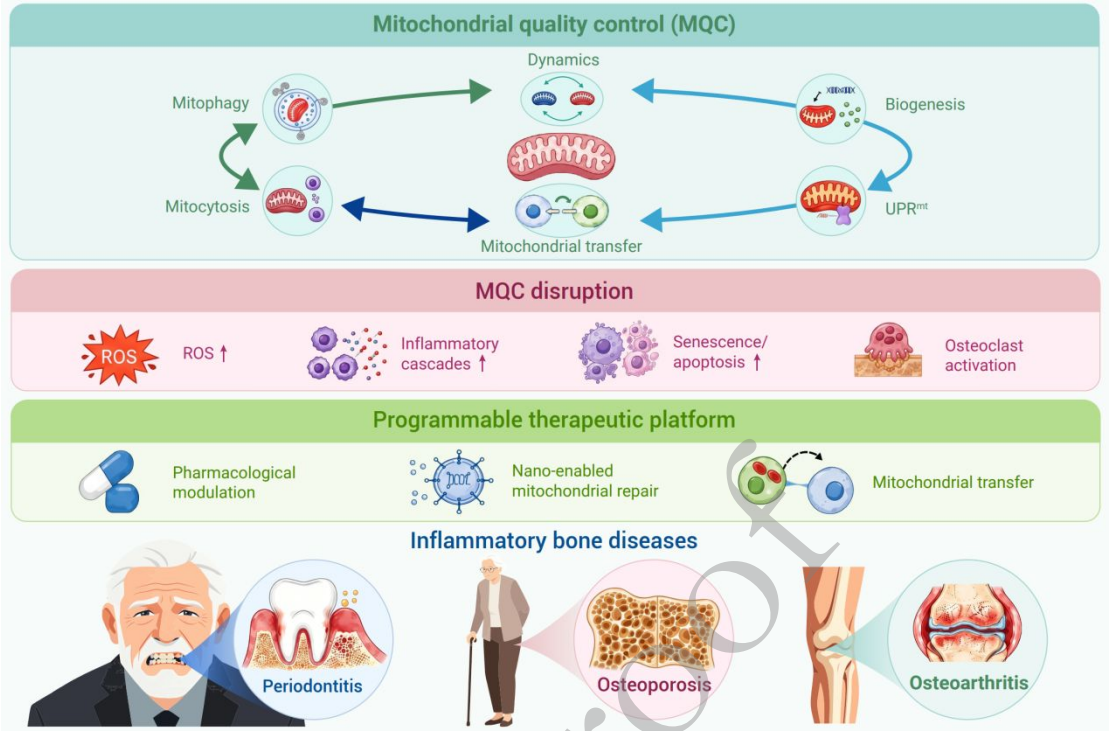
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

■ Mitochondrial quality control (MQC) maintains healthy mitochondria in bone and joint cells.

■ MQC failure amplifies oxidative stress and inflammation, driving bone loss and cartilage damage.

■ MQC-targeted therapies may restore mitochondrial function and support bone tissue repair.

ABSTRACT

Inflammatory bone diseases, including periodontitis, osteoporosis, and osteoarthritis, are traditionally investigated as distinct pathological entities, despite sharing common features of chronic inflammation and impaired tissue regeneration. A unifying regulatory framework that mechanistically links these conditions, however, remains largely undefined. Here, we propose mitochondrial quality control (MQC) as a unifying regulatory platform that integrates inflammatory signaling, cellular metabolic fitness, and fate determination within bone and joint microenvironments. MQC comprises coordinated processes that maintain mitochondrial homeostasis, including mitochondrial dynamics, mitophagy, biogenesis, and emerging mechanisms such as mitochondrial-derived vesicles, mitocytosis, mitochondrial unfolded protein response, and mitochondrial transfer. Disruption of these pathways amplifies oxidative stress and inflammatory cascades, promoting cellular senescence and apoptosis, thereby exacerbating bone loss and cartilage degradation. This review highlights MQC dysfunction as a shared pathological axis across inflammatory bone diseases rather than a disease-specific consequence. Importantly, we frame MQC as a programmable therapeutic platform and propose a stratified intervention paradigm, in which stage-dependent modulation of mitochondrial quality, ranging from pharmacological regulation to nanotechnology-enabled mitochondrial repair and mitochondrial transfer, may enable precision treatment. This framework positions MQC at the interface of inflammation, metabolism, and regeneration, offering a multidisciplinary perspective for the development of next-generation therapies for inflammatory bone diseases.

INTRODUCTION

Periodontitis, osteoporosis (OP), and osteoarthritis (OA) are common inflammatory bone diseases that impose a substantial global health burden.[1-4] Despite arising in distinct anatomical sites, they share convergent features: chronic inflammation, oxidative stress, metabolic dysfunction, and failed tissue regeneration.[5-7] This distinguishes them from other inflammatory bone diseases that arise from autoimmune processes (e.g., rheumatoid arthritis), infections (e.g., osteomyelitis), or biomaterial-driven reactions (e.g., periprosthetic osteolysis).[8-10] Emerging evidence indicates that mitochondrial dysfunction is not merely a downstream consequence of inflammation but a higher-order regulator that integrates metabolic stress, immune activation, and cell fate in bone and joint microenvironments.[11-15] In this context, mitochondrial quality control (MQC), the coordinated mechanisms that preserve mitochondrial integrity and adaptability, has emerged as a potential unifying framework linking inflammatory signaling to pathological bone remodeling.[16-17] Building on this concept, we propose that MQC functions as a central regulatory platform that integrates diverse pathological inputs—metabolic stress, oxidative damage, and inflammatory signals—to collectively dictate cell fate within bone and joint microenvironments. Recognizing MQC as a unifying regulatory platform may therefore enable a conceptual shift from disease-specific mechanisms toward a shared mitochondrial vulnerability underlying inflammatory bone diseases.

Mitochondria have long been recognized as central regulators of cellular bioenergetics; however, recent studies have substantially expanded their functional repertoire to include immune modulation, redox signaling, and stress adaptation.[18-19] Advances now indicate that cellular outcomes depend not solely on mitochondrial activity but on the dynamic capacity to preserve mitochondrial integrity and signaling competence under inflammatory stress.[20-21] This shift has led to the emergence of MQC as a higher-order regulatory system that governs how mitochondria sense, respond to, and recover from metabolic and inflammatory perturbations.[22-24] Unlike static measures

of mitochondrial dysfunction, MQC captures the coordinated regulation of mitochondrial turnover, remodeling, and inter-organelle communication, enabling cells to adapt to fluctuating inflammatory microenvironments.[25-27] Accumulating evidence shows that MQC disruption precedes irreversible tissue damage, positioning MQC failure as an early and targetable event in disease progression.[28-31] These insights provide a compelling rationale for reframing inflammatory bone diseases through the lens of MQC, particularly in light of recent methodological advances that enable direct manipulation of mitochondrial dynamics, mitophagy, and intercellular mitochondrial exchange.

Herein, we establish MQC as a unifying framework that integrates inflammatory signaling, metabolic fitness, and cell-fate determination across periodontitis, osteoporosis, and osteoarthritis. We first outline the core MQC pathways and their regulatory principles under inflammatory stress. We then examine how MQC dysregulation drives pathological responses in key bone-resident and immune cell populations. Finally, we discuss emerging MQC-targeted interventions, highlighting recent progress in pharmacological modulation, bioengineered nanotherapeutics, and intercellular mitochondrial transfer. By positioning MQC as a programmable platform, this review provides a roadmap for next-generation precision therapies in inflammatory bone diseases.

MOLECULAR MECHANISMS OF MITOCHONDRIAL QUALITY CONTROL

Maintaining mitochondrial integrity is critical for cellular function, especially in bone. Dysfunctional mitochondria accumulate damaged proteins, produce excessive reactive oxygen species (ROS), and trigger inflammation, all implicated in inflammatory bone diseases.[32-34] Cells counteract these threats through MQC mechanisms, including mitochondrial biogenesis, dynamics (fission/fusion),

mitophagy, mitochondrial-derived vesicles (MDVs), and the mitochondrial unfolded protein response (UPRmt) (Figure 1).[35]

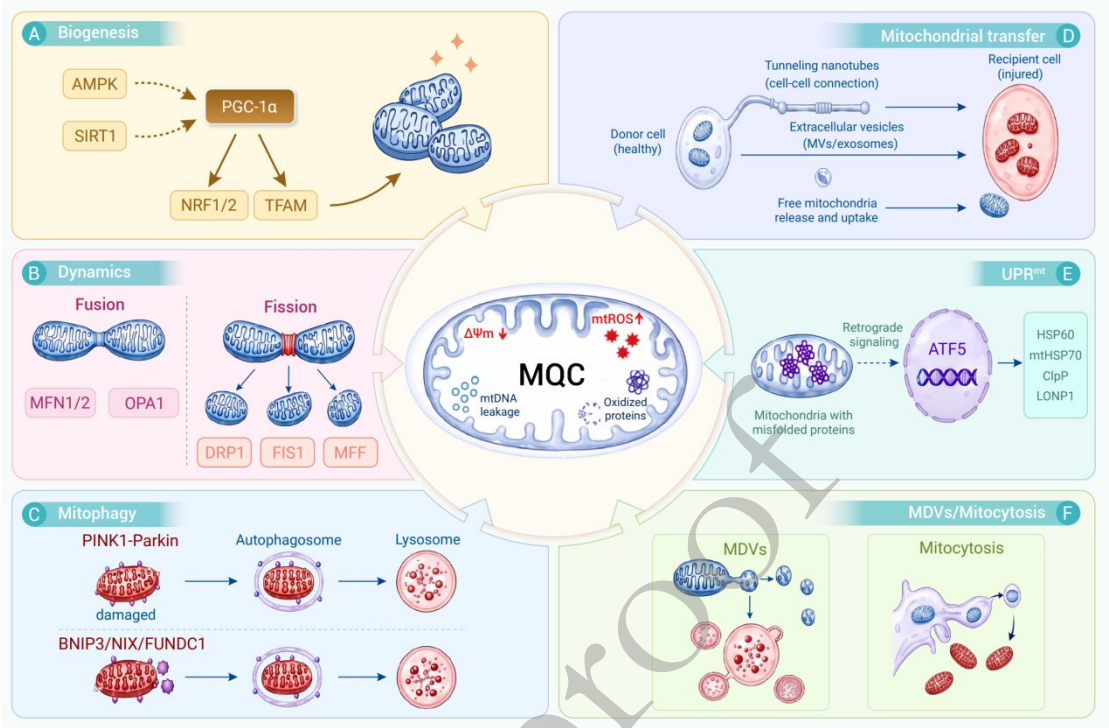


Figure 1. Molecular mechanisms of mitochondrial quality control (MQC) MQC functions as an integrated regulatory platform consisting of biogenesis, mitochondrial dynamics, mitophagy, intercellular mitochondrial transfer, mitochondrial unfolded protein response and ancillary pathways including mitochondrial-derived vesicles and mitocytosis. These coordinated processes act as a defense system to sense cellular stress and maintain a healthy mitochondrial pool.

Mitochondrial biogenesis

Mitochondrial biogenesis involves the synthesis of new mitochondria to replace damaged or senescent organelles, ensuring a healthy functional mitochondrial pool. This process is orchestrated by the peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), the master regulator that coordinates nuclear and mitochondrial genome expression.[36] PGC-1α activates transcription factors such as

nuclear respiratory factors 1 and 2 (NRF1/2) and estrogen-related receptors (ERRα/γ), which in turn drive the expression of genes encoding electron transport chain (ETC) components, mitochondrial transcription factor A (TFAM), and proteins involved in fatty acid oxidation and oxidative phosphorylation (OXPHOS).[37-39] The AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1) pathways critically regulate PGC-1α activity.[40-41] AMPK phosphorylates PGC-1α in response to energy stress, enhancing its stability and transcriptional activity.[42] SIRT1, an NAD^+-dependent deacetylase, deacetylates PGC-1α under conditions of metabolic stress, further potentiating its function.[43-44] Calcium signaling via calcium/calmodulin-dependent protein kinase (CaMK) and cyclic AMP-responsive element-binding protein (CREB) also activates PGC-1α.[45-46]

Mitochondrial dynamics: Balancing fission and fusion

Mitochondria undergo continuous cycles of fission and fusion to maintain a functional network, distribute components, and segregate damaged segments for removal. These dynamics adapt to cellular stress levels: fusion dominates under mild stress (e.g., nutrient scarcity) to promote content mixing and functional complementation, while fission is triggered by severe or prolonged stress (e.g., low glucose, ETC inhibition) to isolate damaged organelles.[47-48] Fusion promotes content mixing, diluting damaged proteins and mitochondrial DNA (mtDNA), and supports mitochondrial respiration, membrane potential, apoptosis regulation, and calcium signaling, while fission isolates dysfunctional portions for degradation and prevents oxidative damage.[49-51]

Mitochondrial fusion is mediated by dynamin-related GTPases: mitofusins 1/2 (MFN1/2) on the outer membrane and optic atrophy 1 (OPA1) on the inner membrane. MFN1/2 facilitate outer membrane tethering, while OPA1 coordinates inner membrane fusion and cristae maintenance.[52] Under mild stress, fusion prevails to enable content

mixing and functional complementation.[53] OPA1 orchestrates inner membrane fusion and cristae maintenance, existing as long (L-OPA1) and short (S-OPA1) isoforms whose balance is regulated by proteases such as OMA1 and YME1L. Stress-induced cleavage of L-OPA1 to S-OPA1 promotes fission, and mutations in OPA1 cause dominant optic atrophy and infantile-onset encephalopathy.[54-56] Post-translational modifications regulate these proteins; for example, SIRT3 deacetylates OPA1, enhancing its GTPase activity and promoting fusion.[57]

Mitochondrial fission is driven by DRP1, which oligomerizes at fission sites marked by receptors FIS1, MFF, MID49, and MID51.[58-59] Notably, human FIS1 (hFIS1) can induce fission independently of DRP1 by inhibiting fusion proteins (OPA1, MFN1/2), and DRP1 recruitment is modulated by phosphorylation: ERK1/2 and cyclin B-CDK1 phosphorylate Ser616 to activate fission, while PKA phosphorylates Ser637/S656 to inhibit it.[60-62] Fission is essential for segregating depolarized or ROS-generating mitochondria, facilitating their removal via mitophagy.[63-64] However, this process is not monolithic but involves distinct mechanistic pathways tailored for specific outcomes. Kleele et al. reveal that mitochondrial fission occurs through at least two specialized types: peripheral fission and midzone fission. Peripheral fission, occurring near the tips of mitochondria, is specifically dedicated to quality control. It is preceded by hallmarks of damage, such as decreased membrane potential, increased ROS, and elevated Ca^{2+} levels. This type of fission is regulated by the mitochondrial outer membrane protein FIS1, often involves lysosomal contact, and generates smaller, daughter mitochondria frequently lacking mtDNA, which are destined for engulfment by autophagosomes. Conversely, midzone fission, which divides the mitochondrial central region, is primarily associated with biogenesis and proliferation. It is mediated by endoplasmic reticulum (ER) contact, actin polymerization, and the adaptor protein MFF.[65] Beyond DRP1-dependent mechanisms, a novel fission machinery operating independently of the classic dynamin-related protein Dnm1/DRP1 has been identified. The protein Atg44, residing in the mitochondrial intermembrane space, drives fission by directly binding

to lipid membranes and inducing membrane fragility. This pathway is specifically essential for mitophagy, as its loss prevents the engulfment of mitochondria by the phagophore, despite correct cargo recognition.[66]

Mitophagy: Selective clearance of damaged organelles

Mitophagy, a selective form of autophagy, eliminates dysfunctional mitochondria to prevent ROS propagation and apoptosis. Two primary pathways exist: ubiquitin-dependent (PINK1-Parkin) and receptor-mediated (e.g., BNIP3, NIX, FUNDC1).[67]

PINK1-Parkin Pathway: Under depolarization (ΔΨm loss), PTEN-induced kinase 1 (PINK1) accumulates on the outer mitochondrial membrane (OMM) and recruits the E3 ubiquitin ligase Parkin.[68] PINK1 phosphorylates ubiquitin and Parkin, activating Parkin's ligase activity. Parkin then ubiquitinates OMM proteins (e.g., MFN1/2, VDAC), marking mitochondria for autophagosomal engulfment via adaptors like p62/SQSTM1 and optineurin.[69-70] PINK1 accumulation is antagonized by the intramembrane protease PARL, which cleaves PINK1 to promote its degradation. The scaffold protein prohibitin 2 promotes mitophagy by suppressing PARL activity, thus stabilizing PINK1.[71-73]

Receptor-mediated mitophagy: Hypoxia-inducible factors induce receptors like BNIP3 and NIX during hypoxia, while FUNDC1 responds to metabolic stress.[74] These receptors contain LC3-interacting regions that directly bind autophagosomal LC3, bypassing ubiquitination. FUNDC1 activity is regulated by dephosphorylation under stress, enhancing LC3 recruitment.[75-76] Additionally, BNIP3 and NIX expression is transcriptionally controlled by the circadian gene BMAL1, which binds to the E-box element in the BNIP3 promoter, and BMAL1 deficiency leads to reduced BNIP3 levels, impaired mitophagy, and dilated cardiomyopathy.[77] Conversely, the SCF-FBXL4 ubiquitin ligase complex ubiquitinates BNIP3/NIX, targeting them for degradation and thus limiting mitophagy. The scaffold protein PPTC7 bridges BNIP3/NIX to FBXL4,

facilitating this turnover.[78-79] As an additional layer of receptor regulation, BNIP3 can also be degraded through an autophagy-independent route that engages the ER membrane complex and secretory trafficking, delivering BNIP3 to lysosomes without autophagosome formation.[80] Additionally, nuclear mechanisms have emerged as key regulators of mitophagy. For instance, the WW domain-containing adaptor with coiled-coil forms biomolecular condensates in nuclear speckles via liquid-liquid phase separation, which recruits splicing factors like RBM12 to modulate alternative splicing of genes such as BECN1. This process promotes the expression of the BECN1-S splice variant, leading to hyperactivated mitophagy, thereby linking nuclear condensate dynamics to mitochondrial quality control.[81]

Mitochondrial transfer

Mitochondrial transfer between cells and organs represents a significant mechanism for regulating MQC in both donor and recipient cells. This process occurs through distinct mechanisms depending on cellular context and stress signals.[82-83] Intercellular mitochondrial transfer occurs through three distinct mechanistic pathways: transient cellular connections, extracellular vesicle-mediated transport, and release of free mitochondria.[84] Transient connections, primarily involving tunneling nanotubes (TNTs) and connexin-43-based gap junctions, enable direct cell-to-cell shuttle of mitochondria via actin-microtubule networks and Rho-GTPase Miro1.[85-87] Alternatively, mitochondria are packaged into extracellular vesicles, often marked by tetraspanins or LC3.[88] Lastly, free mitochondria are ejected independently of vesicles and captured by recipient cells in a heparan sulfate-dependent manner, with fission proteins like DRP1 facilitating their release.[89-90] These transmitophagy mechanisms constitute an externalized MQC pathway, thereby alleviating proteotoxic stress and mitochondrial dysfunction in the donor cell. For instance, cardiomyocytes or endothelial cells under oxidative stress transfer depolarized mitochondria to mesenchymal stem cells (MSCs)

via small extracellular vesicles, where they are degraded, preventing cytotoxic buildup in the stressed donor cell.[91] Conversely, functional mitochondrial transfer from healthy cells to stressed recipient cells enhances bioenergetics and activates intrinsic MQC pathways. For example, internalized healthy mitochondria can stimulate PINK1-Parkin-mediated mitophagy in recipient cells, thereby clearing endogenous dysfunctional mitochondria. This is evidenced by studies where artificial transplantation of exogenous mitochondria (even dysfunctional or mtDNA-free ones) into endothelial cells triggered Parkin recruitment, $LC3B^{+}$ autophagosome formation, and degradation of endogenous damaged mitochondria, leading to enhanced cell survival and engraftment.[92] Furthermore, mitochondrial transfer acts as a signaling cue; extracellular mitochondria or components released from damaged cells act as damage-associated molecular patterns (DAMPs), sensed by recipient cells via CD38 or HO-1 pathways, to upregulate mitochondrial biogenesis and antioxidant responses in MSCs, priming them for further mitochondrial donation.[93-94] This bidirectional regulation occurs in homeostasis and diseases such as ischemia-reperfusion injury, pulmonary fibrosis, and cancer.[95-99] In tumors, stromal cells transfer mitochondria to cancer cells, enhancing OXPHOS and chemoresistance, while conversely, cancer cells expel damaged mitochondria to stromal cells for degradation, highlighting the role of transfer in modulating cellular fitness within the tumor microenvironment.[100-101] Thus, mitochondrial transfer serves as a dynamic, intercellular MQC strategy, adapting to cellular stress states to maintain metabolic homeostasis.

Mitochondrial unfolded protein response

Mitochondrial unfolded protein response (UPRmt) addresses proteotoxic stress within mitochondria.[102] Upon accumulation of misfolded proteins, impaired mitochondrial import triggers nuclear translocation of ATF5 in mammals (or ATFS-1 in *C. elegans*), initiating transcriptional reprogramming that extends beyond HSP60 and mtHSP70 to

include HSP10 and ClpP. This retrograde signaling cascade alleviates proteotoxicity through coordinated refolding by chaperonin complexes and degradation of irreparably damaged proteins via LONP1 and ClpP proteases, with LONP1 additionally stabilizing the HSP60-mtHSP70 complex under oxidative stress. Crucially, UPRmt maintains ETC integrity by preserving OXPHOS complex assembly and function, thereby preventing a vicious cycle of mtROS overproduction and further protein damage.[103] Building upon this protective mechanism, UPRmt orchestrates a comprehensive quality control network that extends beyond proteostasis to safeguard mitochondrial function. By transcriptionally upregulating chaperones and proteases, UPRmt not only resolves immediate proteotoxic stress but also proactively regulates mitochondrial translation through degradation of MRPP3, thereby preventing accumulation of unprocessed RNA precursors and ensuring synchronized synthesis of OXPHOS subunits.[104-105]

Building upon the foundational mechanisms of UPRmt, emerging evidence highlights its critical role in maintaining the function and homeostasis of bone cells. In human bone marrow stromal cells (hBMSCs), UPRmt activation via melatonin-induced PDI-6 upregulation ameliorates age-related mitochondrial dysfunction and enhances osteogenic differentiation by stabilizing protein folding and reducing oxidative stress, thereby counteracting cellular senescence and OP progression.[106] Similarly, in chondrocytes, UPRmt activation through transcription factors like SPI1 regulates PERK-mediated signaling to mitigate OA-associated inflammation and senescence by suppressing mitochondrial ROS production and maintaining proteostasis via HSP60, LONP1, and ClpP.[107] The protective role of UPRmt in OA is further underscored by its induction in chondrocytes under pathological stress, where enhancement with nicotinamide riboside reduces cartilage degradation, apoptosis, and inflammatory markers through ATF5-dependent pathways, improving mitochondrial respiration and energy metabolism.[108] Notably, UPRmt intersects with mitophagy to coordinate mitochondrial quality control, as seen in septic cardiomyopathy models where UPRmt activation compensates for mitophagy deficiency to attenuate inflammation-driven

tissue injury by stabilizing mitochondrial membrane potential (ΔΨm) and reducing caspase-3 activation.[109] Recent studies have provided direct evidence that UPRmt dysfunction actively participates in the pathogenesis of inflammatory bone diseases. In OA, UPRmt activation via ATF5 in chondrocytes protects against cartilage degradation by improving mitochondrial function and promoting autophagy, and enhancing UPRmt with nicotinamide riboside or engineered exosomes alleviates OA progression in rodent models.[108,110] In OP, muscle-specific disruption of mitochondrial proteostasis triggers UPRmt and upregulates the myokine FGF21, which drives bone resorption and loss.[111] Thus, UPRmt is directly implicated in OA and OP, though its role in periodontitis and immune cells remains unexplored.

Ancillary mechanisms: Mitochondrial-derived vesicles and mitocytosis

Mitochondrial-derived vesicles (MDVs) are small vesicles budding from mitochondria that shuttle specific cargo directly to lysosomes or peroxisomes, independent of mitophagy.[112] MDV formation is regulated by proteins like DRP1 and Parkin and serves as a rapid response to localized damage.[59] Building on this, the biogenesis of MDVs involves a tightly coordinated, GTPase-driven mechanism beginning with MIRO1/2-dependent formation of thin membrane protrusions pulled along microtubule filaments, which facilitates the initial deformation of the mitochondrial outer membrane. Subsequently, phosphatidic acid enrichment at these protrusion sites recruits DRP1 via its receptors MID49, MID51, and MFF, enabling DRP1 to assemble into small foci that catalyze membrane scission, thereby generating discrete MDVs.[59] Following vesicle generation, Tollip recruits Parkin to facilitate MDV entry into the endolysosomal pathway via PI(3)P-enriched early endosomes. This process requires Tollip's ubiquitin-binding CUE domain and membrane association to mediate Rab7-dependent late endosomal maturation, ultimately delivering MDVs to lysosomes for degradation.[113] These processes selectively package fully assembled

protein complexes, such as the TOM import machinery and β-barrel proteins, into MDVs, which are then trafficked to lysosomes for degradation, providing a precise quality control mechanism that maintains mitochondrial integrity by removing dysfunctional or damaged components without requiring organelle-wide mitophagy.[59,114] Emerging evidence now directly links MDVs to bone pathophysiology. During osteogenic differentiation of bone marrow stromal cells, MDVs carrying mitochondrial DNA and other cargo promote osteogenic differentiation of recipient cells but simultaneously activate the cGAS-STING pathway, leading to increased reactive oxygen species and inflammatory cytokine expression, indicating a dual role in bone formation and inflammation.[115] Moreover, in osteoarthritic subchondral bone, mineralizing osteoblasts release extracellular vesicles enriched with mitochondrial components via a process involving Wnt-regulated mitophagy; these vesicles accelerate pathological subchondral bone sclerosis and cartilage degradation.[116] Collectively, these findings establish MDVs as functional mediators in inflammatory bone microenvironments, particularly in osteoarthritis and osteogenic inflammation.

Mitocytosis is a newly identified mitochondrial quality-control mechanism mediated by migrasomes, which facilitates the selective expulsion of damaged mitochondria from migrating cells. The core mechanism involves the peripheral translocation of mildly stressed mitochondria via KIF5B-mediated transport and Myo19-mediated tethering to cortical actin. These damaged mitochondria accumulate at TSPAN-enriched macrodomains (particularly TSPAN9) on the plasma membrane. Subsequently, migrasomes, organelles formed on retraction fibers during cell migration, encapsulate and expel the mitochondria extracellularly.[117-118] In glioblastoma, enzyme-activable polymer-drug conjugates (e.g., GBEPPT) exploit mitocytosis for deep tumor penetration. GBEPPT undergoes GGT-triggered charge reversal, enters cells, disturbs mitochondria, and induces mitocytosis. This enables intracellular-to-intercellular drug transfer, improving antitumor efficacy while reducing systemic toxicity.[119] Xu et al. fabricate gene-engineered aligned electrospun fibers loaded with TSPAN9-plasmid

liposomes to promote mitocytosis in fascia repair. The fibers mimic fascial topography, directing cell migration while releasing TSPAN9 to upregulate migrasome formation. This clears damaged mitochondria, reduces inflammation, and enhances collagen deposition, accelerating tissue regeneration.[118] In contrast to UPRmt and MDVs, direct evidence linking mitocytosis to the pathogenesis of periodontitis, osteoporosis, or osteoarthritis is currently absent, and its role in inflammatory bone diseases remains entirely speculative.

In summary, the coordinated actions of biogenesis, dynamics, mitophagy, transfer, and ancillary mechanisms constitute an integrated MQC system that is essential for cellular homeostasis. This system functions as a unifying regulatory platform by sensing various stresses and orchestrating adaptive responses to maintain mitochondrial fitness. Its dysregulation represents a pivotal convergence point in inflammatory diseases, leading to mitochondrial dysfunction, elevated ROS, and sustained inflammatory cascades. The subsequent sections will detail how the breakdown of this platform disrupts the functional state of key effector cells in inflammatory bone diseases.

IMPACT OF MQC ON THE HOMEOSTASIS AND FATE OF BONE-FORMING CELLS

Mitophagy, a core MQC mechanism, orchestrates bone regeneration by eliminating damaged mitochondria and maintaining homeostasis in osteoblasts, osteocytes, and chondrocytes (Figure 2). In glucocorticoid-induced OP, SIRT3 activates PINK1/Parkin-dependent mitophagy to inhibit ferroptosis and restore osteogenic capacity.[120] In contrast, in OA, Wnt signaling dynamically controls mitophagy in osteoblast subtypes, such as mineralizing osteoblasts, where mitophagy activation facilitates amorphous calcium phosphate release via extracellular vesicles, thereby promoting subchondral bone remodeling and cartilage degradation.[116] Osteocyte-

derived extracellular vesicles further mediate bone-cartilage crosstalk by transferring miR-23b-3p, which suppresses mitophagy in chondrocytes through OTUD4 targeting, leading to metabolic dysregulation and OA progression; inhibiting miR-23b-3p enhances mitophagy and reduces cartilage degeneration.[121] Moreover, PINK1 deficiency impairs osteoblast differentiation by disrupting mitochondrial quality control, as evidenced by reduced ΔΨm, increased ROS production, and aberrant calcium handling, exacerbating bone loss post-ovariectomy.[122] Conversely, PINK1/Parkin-mediated mitophagy serves as a protective mechanism against osteoblast apoptosis induced by advanced oxidation protein products, where rapamycin-enhanced mitophagy clears damaged mitochondria and ROS, thereby ameliorating bone microstructural destruction and mineral density loss.[123]

Beyond mitophagy, mitochondrial dynamics serve as another critical pillar of mitochondrial quality control, directly regulating the morphological and functional adaptations of bone regeneration-related cells. Specifically, mitochondrial dynamics modulate cellular energy metabolism and redox balance in osteoblasts and chondrocytes through fission-fusion cycles, with imbalances leading to pathological states such as diabetic OP or bacterial-induced bone loss.[124-125] Under diabetic conditions, hyperglycemia suppresses PINK1/DRP1 mitophagy, causing mitochondrial fragmentation, ΔΨm loss, and ROS elevation, thereby inhibiting late-stage osteoblast differentiation. This can be rescued by BMP9 via PINK1/DRP1 activation.[126] In physiological osteogenesis, mitochondrial fragmentation and donut formation enhance secretion of mitochondria and MDVs via CD38/cADPR signaling, promoting osteoprogenitor differentiation. Augmenting fission accelerates osteoblast maturation, whereas inhibiting fusion impairs it, indicating that controlled fission is adaptive for bone formation.[127] However, pathological disruptions, such as those induced by bacterial extracellular vesicles, can exacerbate OP; for instance, *P. gingivalis*-derived extracellular vesicles disrupt mitochondrial dynamics in osteoblasts by promoting fission (e.g., upregulating DRP1 and FIS1) and inhibiting fusion (e.g., downregulating

MFN1, MFN2, and OPA1), leading to mitochondrial fragmentation, impaired fatty acid oxidation due to reduced Cpt2 levels, and decreased ATP production, thereby suppressing osteogenic differentiation and aggravating bone loss.[128]

Alongside dynamics and mitophagy, mitochondrial biogenesis completes the MQC triad by generating new mitochondria to meet cellular demands during bone repair and adaptation. Mitochondrial biogenesis, driven by master regulators like PGC-1α, determines the metabolic fitness and differentiation fate of bone-regenerative cells, including skeletal stem cells and osteocytes, by modulating oxidative stress and energy production pathways. In hyperlipidemia-induced OP, PGC-1α expression is suppressed in bone marrow mesenchymal stem cells (BMSCs), leading to mitochondrial dysfunction and a shift toward adipogenic differentiation at the expense of osteogenesis; however, Coenzyme Q10 supplementation restores PGC-1α levels, enhances mitochondrial function, and promotes osteoblastic differentiation while inhibiting adipogenesis, thereby ameliorating bone loss.[129] Similarly, the mitochondrial-derived peptide MOTS-c mitigates osteolysis by activating the AMPK-PGC-1α axis, which reduces ROS production and suppresses NF-κB and STAT1 signaling pathways, resulting in decreased osteoclastogenesis and inflammation in osteocytes and macrophages.[130] Furthermore, PGC-1α serves as a critical determinant of skeletal stem cell lineage allocation, where its age-related decline promotes adipogenic differentiation and marrow adipose tissue accumulation while impairing osteogenesis, whereas PGC-1α induction upregulates TAZ expression to reinforce osteoblastic commitment and attenuate osteoporosis.[131] In cadmium-induced OP, oxidative stress inhibits SIRT1 and dysregulates the SIRT1/PGC-1α/p53 axis, increasing p53 acetylation at Lys382 and triggering caspase-dependent apoptosis in osteoblasts; this pathway is reversible through SIRT1 activation or antioxidant intervention, highlighting the role of PGC-1α in integrating mitochondrial stress with apoptotic signaling.[132]

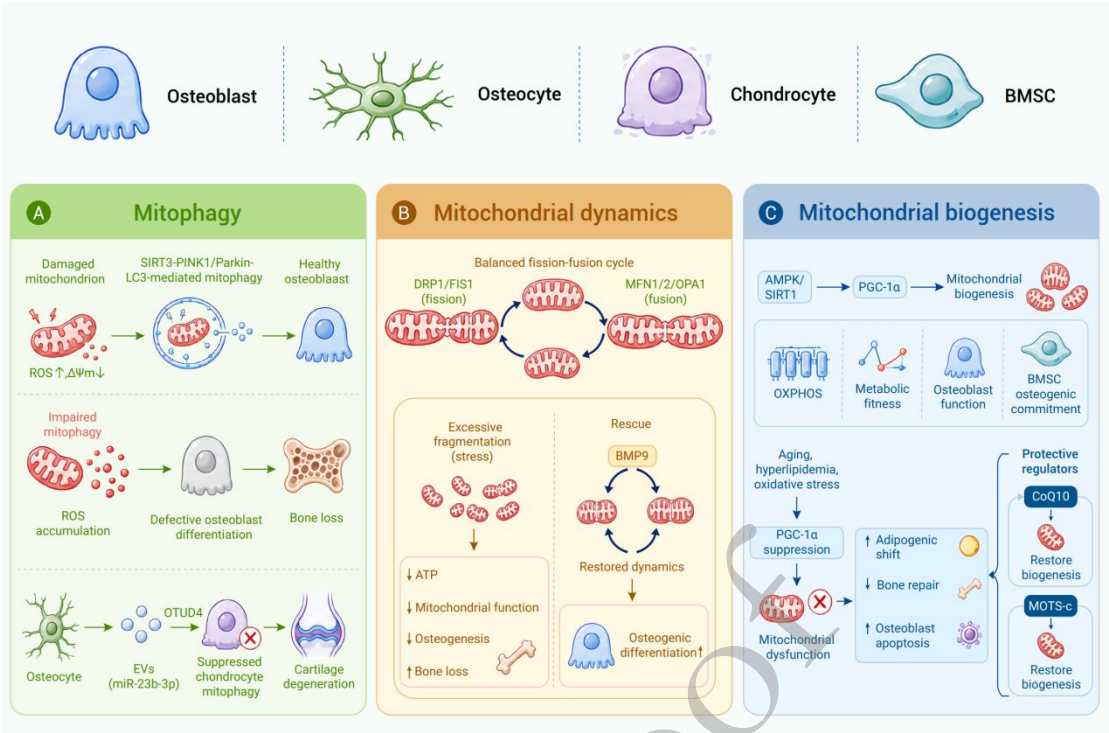


Figure 2. Regulation of bone cell fate and homeostasis by MQC mechanisms Mitophagy, mitochondrial dynamics, and biogenesis collectively orchestrate the metabolic fitness and differentiation commitment of osteoblasts, chondrocytes, and skeletal stem cells, whereas their impairment under pathological stresses drives bone loss and cartilage degeneration.

MQC-MEDIATED REGULATION OF OSTEOCLASTS AND IMMUNE CELLS IN INFLAMMATORY BONE DISEASES

Beyond bone-forming cells, MQC mechanisms critically regulate osteoclasts and immune cells, shaping the bone immune microenvironment in inflammatory diseases (Figure 2). In osteoclasts, multiple MQC pathways converge on the Ca^{2+}-NFATc1 axis. MFN2 controls osteoclast differentiation via ER-mitochondria tethering rather than canonical fusion or mitophagy. Conditional deletion of Mfn1 and Mfn2 in osteoclast precursors increases bone mass and abolishes osteoclastogenesis in vitro, an effect specifically rescued by MFN2. MFN2 deficiency blunts store-operated Ca^{2+} entry and reduces NFATc1, whereas tethering-competent MFN2 restores both, establishing

ER-mitochondrion tethering as essential for osteoclast formation.[133] In parallel, the fission machinery also drives osteoclastogenesis. RANKL induces DRP1 and its receptors Fis1, Mid49/51. Inhibiting DRP1 genetically or with Mdivi-1 suppresses c-Fos/NFATc1, blunting osteoclast formation and bone resorption.[134]

PINK1-dependent mitophagy restrains osteoclast activation; Pink1 knockout exacerbates periodontitis bone loss, with impaired mitophagy and ROS accumulation, rescued by spermidine or N-acetylcysteine (NAC).[135] Further, Sirt3 promotes osteoclast function by activating PINK1-BNIP3/NIX-dependent mitophagy; Sirt3 deletion attenuates age-related and ovariectomy-induced bone loss in females, reduces osteoclast respiratory capacity, and increases PINK1 acetylation while decreasing BNIP3/NIX.[136] Conversely, excessive mitophagy is detrimental: Brevilin A, a BNIP3 inhibitor, suppresses osteoclastogenesis by impairing BNIP3-mediated mitophagy and oxidative phosphorylation, reducing ROS and NFATc1, and preventing ovariectomy-induced bone loss.[137] Thus, balanced mitophagy in osteoclasts, integrating PINK1, Parkin, and alternative receptors, is critical for bone homeostasis, and therapeutic targeting must consider compensatory mechanisms.

In immune cells, MQC orchestrates macrophage polarization and inflammasome activation. In apical periodontitis, *P. gingivalis* LPS induces DRP1 phosphorylation in macrophages, causing fragmentation, $\Delta\Psi m$ loss, and ROS, thereby promoting NLRP3 activation and M1 polarization.[138] Similarly, hyperactivated STAT3 in macrophages from infectious and aseptic osteolytic lesions correlates with cleaved IL-1β. STAT3 inhibition triggers PINK1-dependent mitophagy, reverses membrane potential collapse, reduces mtROS, and restrains NLRP3 activation. Conditioned medium from STAT3-inhibited macrophages fails to promote RANKL-induced osteoclastogenesis via reduced IL-1β, and in vivo STAT3 inhibition protects against periapical and titanium particle-induced bone loss.[139] Apelin-13 activates APJ, enhancing BNIP3-PINK1-PARKIN mitophagy via AMPK, reducing mtROS, restraining NLRP3, and skewing macrophages toward an M2 phenotype, thereby attenuating inflammatory

bone loss.[140] Likewise, the fumaric acid ester dimethyl fumarate (DMF) elevates the mitochondrial translation factor TUFM by blocking its ubiquitin-proteasomal degradation. TUFM-dependent mitophagy preserves mitochondrial membrane potential, curbs ROS production, and promotes the transition from M1 to M2 polarization, effectively mitigating periodontal bone destruction.[141]

Beyond cell-intrinsic MQC, intercellular mitochondrial transfer acts as an externalized quality control mechanism. Mitochondria-loading erythrocytes deliver functional mitochondria and O_2 to macrophages in an ROS-responsive manner, reversing LPS-induced metabolic reprogramming from glycolysis to oxidative phosphorylation, suppressing HIF-1α signaling and osteoclast differentiation, and promoting M2 over M1 polarization, thereby reducing calvarial bone loss.[142] Additionally, macrophages transfer mitochondria to MSCs in the bone marrow. Under steady-state conditions, this supports MSC osteogenesis; under osteoporotic conditions, M1-polarized macrophages deliver oxidatively damaged mitochondria to MSCs, triggering a ROS burst, succinate accumulation, HIF-1α stabilization, and pro-inflammatory gene upregulation, impairing osteogenic differentiation. Healthy mitochondria rescue ovariectomy-induced bone loss, whereas M1-derived mitochondria recapitulate osteoporosis, showing that the functional status of transferred mitochondria determines beneficial or pathological outcomes.[143]

Together, MQC mechanisms function as an integrated regulatory hub within osteoclasts and immune cells, linking metabolic fitness, inflammatory signaling, and lineage commitment to drive pathological bone resorption or its resolution, thereby offering distinct and actionable therapeutic nodes for inflammatory bone diseases.

DISRUPTION OF MQC CONTRIBUTES TO THE PATHOGENESIS OF INFLAMMATORY BONE DISEASES

Periodontitis: Pathogen-induced MQC disruption and inflammatory bone loss

Periodontitis, a chronic inflammatory disease affecting the supporting structures of teeth, represents a significant global health burden due to its high prevalence and association with systemic conditions such as diabetes and cardiovascular diseases.[144-147] The pathogenesis of periodontitis involves a complex interplay between dysbiotic microbial communities and aberrant host immune responses, leading to progressive periodontal tissue destruction.[148-150] Emerging evidence underscores mitochondrial dysfunction as a central mechanism linking local damage to systemic comorbidities.[151-153] Cells critical to periodontal integrity, such as gingival epithelial cells (GECs), periodontal ligament fibroblasts (PDLFs), and periodontal ligament stem cells (PDLSCs), exhibit mitochondrial abnormalities in periodontitis.[154-157] These include fragmented mitochondrial networks, reduced ATP synthesis, and impaired mitophagy, which collectively diminish cellular resilience and reparative capacity. For example, DRP1-driven fission promotes ROS and apoptosis in PDLSCs, impairing osteogenesis, while fusion proteins are downregulated.[158]

P. gingivalis, a keystone pathogen in periodontitis, induces mitochondrial fragmentation and dysfunction in endothelial cells by promoting DRP1 phosphorylation at Ser616 and its translocation to mitochondria. This DRP1-dependent fission leads to excessive mitochondrial fragmentation, reduced $\Delta\Psi m$, elevated mitochondrial ROS, and decreased ATP production. Inhibition of DRP1 with Mdivi-1 reverses these defects, confirming DRP1's central role in *P. gingivalis*-induced mitochondrial pathology.[152] Mechanical force also triggers DRP1-mediated fission in PDLSCs, shifting them to anaerobic metabolism.[159] Furthermore, inflammatory macrophage-derived mitochondria-rich extracellular vesicles transfer damaged mitochondria and lipocalin 2 (LCN2) to bone marrow MSCs. LCN2 disrupts mitochondrial dynamics in MSCs by inducing OMA1 degradation and OPA1 accumulation, thereby blocking the formation of donut-shaped mitochondria required for osteogenic mineralization. This mechanism directly links macrophage MQC dysfunction to impaired osteogenesis and alveolar bone loss in periodontitis.[160]

In apical periodontitis, PINK1/Parkin-mediated mitophagy is upregulated in macrophages within periapical lesions, as evidenced by increased LC3-II/TOMM20 colocalization and mitochondrial ultrastructural changes (e.g., mitophagosomes). This adaptive response likely mitigates inflammation by removing dysfunctional mitochondria.[161] Conversely, in diabetic conditions, hyperglycemia suppresses PINK1/Parkin signaling in gingival epithelial cells (hGECs), leading to impaired mitophagy, accumulated mtROS, and exacerbated apoptosis.[162] Consistent with these findings, PINK1 expression is also downregulated in periodontal tissues during periodontitis progression. In osteoclast precursors, PINK1 deficiency impairs mitophagy and strengthens mitochondria-endoplasmic reticulum (MAM) coupling via enhanced Mfn2-IP3R-VDAC1 interaction, leading to mitochondrial Ca^{2+} overload and hyperactivation of the calcineurin-NFATc1 axis, which drives excessive osteoclast differentiation and exacerbates alveolar bone loss. This pathological MAM-mediated Ca^{2+} transfer can be reversed by the IP3R inhibitor Bcl-XL.[1] In aged PDLSCs, reduced mitophagy contributes to mitochondrial dysfunction and diminished osteogenic capacity, highlighting age as a risk factor for periodontitis progression.[163] In apical periodontitis, hyperactivated STAT3 signaling correlates with NLRP3 inflammasome activation. Mechanistically, STAT3 hyperactivation suppresses PINK1-dependent mitophagy, leading to NLRP3 inflammasome activation and IL-1β production, thereby promoting osteoclastogenesis and inflammatory bone loss.[139]

ER contact sites, regulated by proteins like MFN2, IP3R, and GRP75, facilitate calcium signaling and lipid transfer, influencing inflammatory responses.[164-166] *P. gingivalis* and *Fusobacterium nucleatum* infection in gingival fibroblasts dysregulates these contact proteins, altering calcium flux and promoting ROS production.[165] In endothelial cells, RhoA/ROCK1 activation by *P. gingivalis* enhances DRP1 phosphorylation (Ser616) and mitochondrial translocation, further driving fission and mPTP opening. RhoA/ROCK1 inhibitors reverse these effects, confirming this pathway's role in mitochondrial dysfunction.[167]

Oxidative stress is both a cause and consequence of mitochondrial dysfunction in periodontitis. In refractory apical periodontitis, impaired mitochondrial biogenesis, evidenced by reduced PGC-1α and Nrf2 expression, leads to diminished antioxidant defenses, mtDNA damage, and elevated markers of oxidative damage (3-NT, 4-HNE, 8-OHdG). This creates a vicious cycle where mtROS accumulation further damages mitochondria, exacerbating tissue destruction.[168] Similarly, in diabetic periodontitis, translocator protein (TSPO) overexpression amplifies mtROS and inhibits mitophagy, while *Tspo* knockdown or inhibition restores mitochondrial function and reduces inflammation.[169]

In summary, MQC disruptions, including aberrant fission, impaired mitophagy, and dysregulated mitochondrial-ER contacts, drive mitochondrial dysfunction, oxidative stress, and inflammation in periodontitis. These alterations compromise cellular bioenergetics, amplify ROS production, and promote apoptosis, ultimately contributing to periodontal tissue destruction and disease progression.[158,170] The fact that such diverse pathogens and stressors converge on disrupting the MQC platform underscores its role as a common pathological axis, which similarly underlies other inflammatory bone diseases like osteoporosis and osteoarthritis (Figure 3).

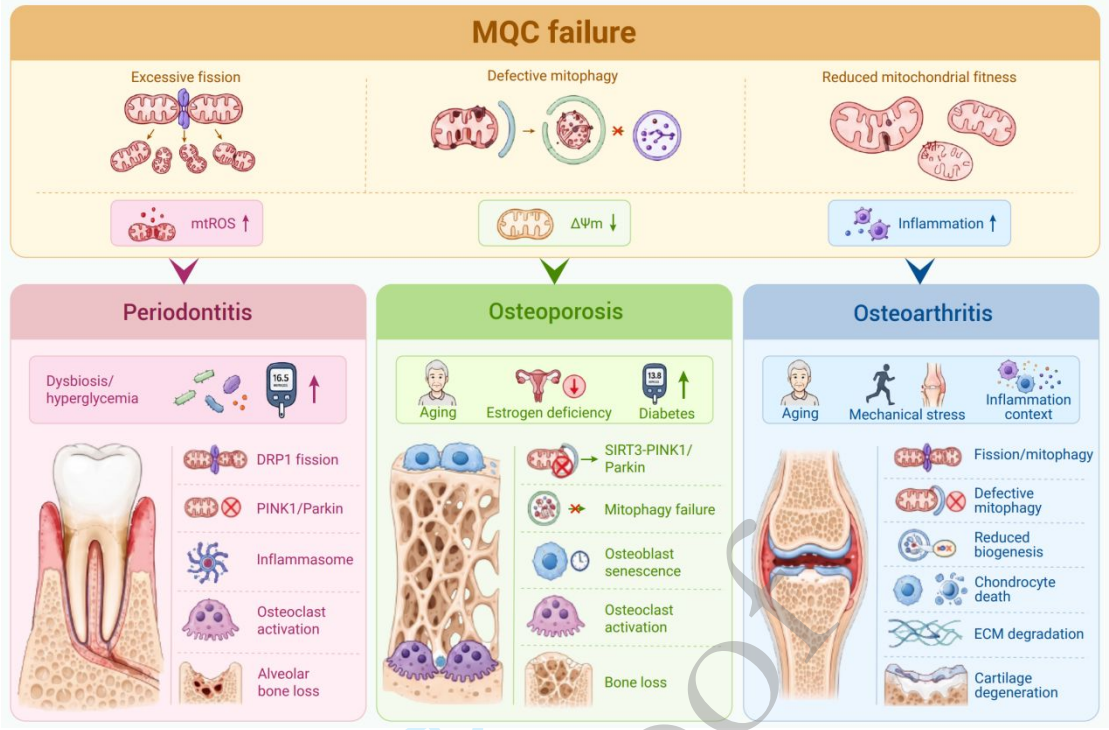


Figure 3. MQC failure as a common pathological axis in inflammatory bone diseases Dysregulated mitochondrial dynamics, impaired mitophagy, and reduced biogenesis converge to amplify oxidative stress and inflammatory signaling, thereby driving the characteristic tissue destruction and cellular dysfunction observed in periodontitis, osteoporosis, and osteoarthritis.

Osteoporosis: MQC failure in bone remodeling and cellular senescence

OP is a systemic skeletal disorder characterized by low bone mass and microarchitectural deterioration, leading to increased bone fragility and susceptibility to fracture.[171] The concept of immunoporosis recognizes chronic, low-grade inflammation as a central driver, not just a hormonal consequence.[172] In postmenopausal OP, estrogen deficiency promotes Th17 cells, TNF-α, M1 macrophages, and mast cells, increasing IL-6/IL-1β/TNF-α, which amplify osteoclastogenesis and suppress osteoblasts.[173-174] This chronic inflammation, together with age-related inflammaging, uncouples bone remodeling.[175-176] Clinical studies have

demonstrated an inverse correlation between systemic bone mineral density and alveolar bone loss, and OP therapies such as hormone replacement improve periodontal outcomes, supporting a bidirectional epidemiological link between osteoporosis and periodontitis.[6] Thus, beyond its metabolic and endocrine basis, OP also qualifies as an inflammatory bone disease driven by immune dysregulation and sustained cytokine signaling. Within this inflammatory milieu, disruption of MQC further impairs osteogenesis and enhances osteoclastogenesis, aggravating bone loss.[177] Dysregulated mitochondrial dynamics across multiple bone cell types drive various forms of programmed cell death in OP. In osteoblasts, excessive fission under stress promotes apoptosis, necroptosis, and ferroptosis, while in osteocytes, reduced MFN2 impairs ER-mediated mitochondrial transfer, leading to apoptosis and necroptosis. In osteoclasts, fission is essential for differentiation, and blocking mitophagy forces apoptosis, highlighting that the balance of fission/fusion and mitophagy is context-dependent.[2,178]

In OP, impaired mitophagy results in oxidative stress and apoptosis of osteoblasts, as seen in glucocorticoid-induced models where PINK1/Parkin activation mitigates osteoblast apoptosis by clearing damaged mitochondria.[123] Similarly, mitophagy deficiency exacerbates bone loss, as demonstrated in *Pink1*-knockout models that show reduced osteogenic differentiation and increased OP susceptibility.[122] Mechanistically, PINK1 loss in osteoblasts impairs mitophagy, reduces mitochondrial functional mass, disrupts dynamics, and increases ROS, thereby suppressing osteoblast differentiation. Clinically, PINK1 expression is downregulated in bone tissues of osteoporotic patients, confirming its relevance.[122] In the specific context of type 2 diabetes mellitus (T2DM)-associated OP, SIRT3 downregulation in osteoblasts leads to hyperacetylation of FOXO3, which fails to translocate to the nucleus, resulting in reduced transcription of the Prkn (Parkin) gene. Consequently, PINK1/PRKN-dependent mitophagy is impaired, leading to mitochondrial fragmentation, loss of membrane potential, increased ROS, and suppressed osteogenesis. SIRT3 activation restores this pathway and rescues bone mass in T2DM mice.[179] Sirtuins, particularly SIRT1 and SIRT3, regulate MQC by

enhancing mitophagy and reducing ROS. SIRT1 promotes mitophagy via deacetylation of FOXO3a and activation of BNIP3, while SIRT3 directly deacetylates SOD2 to scavenge ROS, thereby protecting osteoblasts from apoptosis and improving bone density.[180] Under diabetic conditions such as high glucose and palmitic acid exposure, SIRT3 downregulation leads to hyperacetylation of FOXO3, impairing its nuclear translocation and subsequent transcriptional activation of PINK1/Parkin-mediated mitophagy. This results in accumulated dysfunctional mitochondria, increased ROS production, and ultimately osteoblast dysfunction, contributing to bone loss in type 2 diabetes mellitus.[179] Similarly, maternal prednisone exposure increases OP risk in offspring by elevating m6A modification, which activates mitophagy and reduces FNDC5/irisin expression in skeletal muscle, leading to bone loss.[181] Additionally, NDR2 regulates osteoclastogenesis through ULK1-mediated mitophagy, where inhibition of ULK1 reduces mitophagy and ameliorates bone loss.[182] Notably, intercellular mitochondrial transfer acts as a novel MQC mechanism that regulates bone homeostasis. In the osteoporotic microenvironment, M1-polarized macrophages transfer oxidatively damaged mitochondria to MSCs. These damaged mitochondria trigger a ROS burst in recipient MSCs, shift their metabolism toward glycolysis, and impair osteogenic differentiation. In contrast, transplantation of healthy mitochondria ameliorates ovariectomy (OVX)-induced bone loss, revealing that the functional status of transferred mitochondria determines whether the outcome is beneficial or pathological.[143]

In conclusion, MQC is integral to OP by influencing oxidative stress, cell survival, and differentiation. Enhancing mitophagy and mitochondrial function through pathways like PINK1/Parkin, Sirtuins, and ULK1 offers potential therapeutic strategies, as evidenced by various studies. Understanding these mechanisms provides insights for developing treatments aimed at restoring MQC to prevent or reverse bone loss.

Osteoarthritis: Defective MQC as a pivotal mechanism in chondrocyte death and cartilage degradation

OA is an age-related inflammatory joint disease characterized by progressive cartilage degeneration and structural alterations across the entire joint, leading to functional impairment and pain.[183-184] As with periodontitis and osteoporosis, the integrity of the MQC platform is critical in OA, and its failure represents a unifying mechanism that connects aging, mechanical stress, and inflammation to disease progression. Impaired MQC disrupts chondrocyte function, leading to excessive ROS production, metabolic dysfunction, and apoptosis.[185] Key regulators such as AMPK, SIRT1, and PGC-1α are downregulated in OA cartilage, resulting in diminished mitochondrial biogenesis and accumulation of damaged mitochondria.[186-187] Pro-inflammatory cytokines activate ERK1/2, which phosphorylates DRP1 at Ser592 (equivalent to Ser616), driving excessive fission, ΔΨm loss, oxidative stress, and Bax-mediated cytochrome C release, leading to chondrocyte apoptosis.[188] Similarly, loss of OPA1 disrupts mitochondrial fusion by impairing inner membrane integrity and cristae remodeling, resulting in mitochondrial fragmentation with disorganized cristae morphology, which reduces LC3B-mediated autophagosome formation and mitophagy efficiency, leading to accumulation of dysfunctional mitochondria and chondrocyte apoptosis, thereby accelerating OA progression in aged mice.[189] Our group has identified hybrid extracellular vesicles (EVs) in OA joint fluid that drive irreversible mitochondrial fragmentation in chondrocytes by suppressing ΔΨm via ADT1, leading to persistent senescence. Mechanistically, hybrid EV-induced mitochondrial dysfunction depletes acetyl-CoA and α-KG, epigenetically locking chondrocytes in a catabolic state.[185]

Defective mitophagy also contributes to the development of OA. Mitophagy-related biomarkers such as GABARAPL2 and SNX7 are significantly dysregulated in OA. These biomarkers not only exhibit high diagnostic accuracy but also correlate strongly with immune cell infiltration.[190] Shao et al. reveal that mechanical overload induces

chondrocyte senescence primarily through mitochondrial dysfunction. Specifically, overload downregulates PDZK1, leading to impaired mitochondrial integrity via increased ROS production, reduced mtDNA content, and disrupted mitophagy, which is mediated by Hmgcs2 ubiquitination.[191] Fu et al. demonstrate that extracellular matrix (ECM) stiffening, another critical mechanical stress, promotes chondrocyte senescence by downregulating HDAC3, which enhances Parkin acetylation and hyperactivates PINK1/Parkin-mediated mitophagy, leading to mitochondrial dysfunction and cartilage degeneration.[192] Furthermore, the protein PARP12 is significantly upregulated in OA cartilage. PARP12 inhibits PINK1/Parkin-dependent mitophagy by promoting ISGylation of MFN1/2, which stabilizes these fusion proteins. Elevated MFN1/2 levels shift the balance toward fusion, but paradoxically this stabilization inhibits mitophagy, leading to mitochondrial dysfunction, NLRP3 inflammasome activation, and cartilage degradation. The PARP12 inhibitor XAV939 restores mitophagy and ameliorates OA in animal models, identifying PARP12 as a disease-specific therapeutic node.[193] These studies underscore how mechanical stress directly compromises mitochondrial homeostasis, accelerating cellular aging and OA progression. Conversely, SIRT3 deacetylates PINK1 to enhance mitophagy, promoting mitochondrial renewal and metabolic switching via PKM2, thereby protecting against OA.[194] Similarly, TBK1 phosphorylates DRP1 at Ser637 to inhibit mitochondrial fission and promote fusion, thereby facilitating the clearance of damaged mitochondria, which alleviates oxidative stress and chondrocyte apoptosis in OA pathogenesis.[195]

The interplay between ferroptosis and mitophagy further underscores the complexity of MQC in OA, where iron overload driven by dysregulated TFR/FPN expression and NCOA4-mediated ferritinophagy triggers ROS accumulation and lipid peroxidation. This oxidative stress inhibits mitophagy while concurrently engaging GPX4-dependent antioxidant defenses, thereby creating a vicious cycle that ultimately promotes chondrocyte death.[196]

MQC dysfunction across inflammatory bone diseases: commonalities and disease-specific features

While periodontitis, OP, and OA are distinct clinical entities, they converge on a shared core of MQC dysfunction. The common pathological axis includes:

(i) excessive mitochondrial fission driven by DRP1 hyperactivation, (ii) impaired PINK1/Parkin-mediated mitophagy leading to the accumulation of damaged organelles, (iii) suppressed mitochondrial biogenesis due to downregulation of the AMPK-SIRT-PGC-1α axis, and (iv) a resultant state of chronic oxidative stress and mitochondrial ROS production, which fuels inflammatory signaling and tissue destruction. In all three diseases, this MQC failure ultimately promotes the death of parenchymal cells (osteoblasts, chondrocytes, periodontal ligament cells) and enhances the activity or differentiation of bone-resorbing osteoclasts.

Despite these unifying principles, each disease exhibits distinct MQC features that reflect its unique cellular and etiological landscape. Table 1 summarizes these commonalities and specificities, highlighting how the same MQC platform is differentially perturbed across diseases. Recognizing these shared vulnerabilities and unique nodes is essential for developing tailored, stage-dependent therapeutic strategies that target MQC with precision.

TARGETING MQC: NOVEL THERAPEUTIC AVENUES FOR INFLAMMATORY BONE DISEASES

As mentioned above, MQC encompasses a suite of adaptive mechanisms that collectively maintain mitochondrial integrity and cellular homeostasis. Rather than a collection of isolated pathways, MQC represents a programmable therapeutic platform, because its modular processes—such as mitophagy, mitochondrial dynamics, and biogenesis—can be targeted individually. For instance, pharmacological activation of

mitophagy enhances mitochondrial turnover, improves neuronal survival, and attenuates neuroinflammation by suppressing NLRP3 inflammasome activation.[197] In heart failure and ischemic heart disease, disrupted mitochondrial dynamics (e.g., excessive fission via DRP1) contribute to cardiomyocyte apoptosis and contractile dysfunction. Inhibiting DRP1 with Mdivi-1 or enhancing fusion via MFN2 overexpression restores mitochondrial network integrity, improves ATP production, and reduces infarct size.[198] Building on this paradigm of MQC modulation as a therapeutic strategy across diverse systemic diseases, we summarize recent evidence underscoring its critical relevance within the specialized context of inflammatory bone diseases (Figure 4).

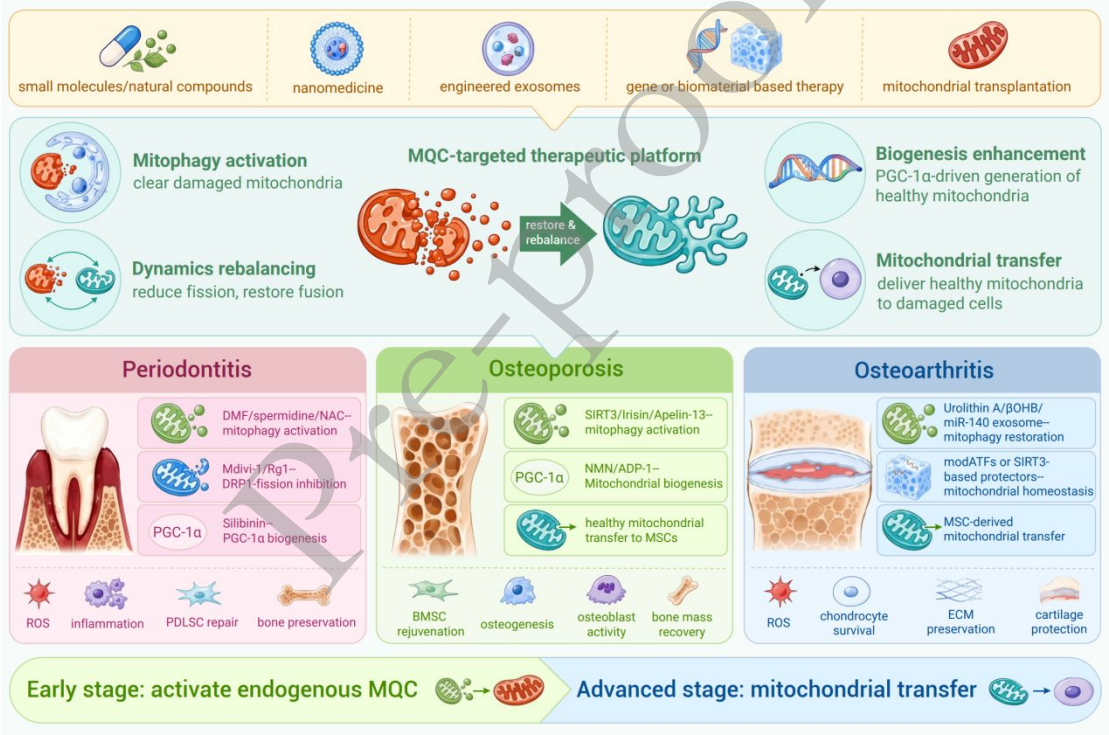


Figure 4. MQC-targeted therapeutic platform for inflammatory bone diseases Diverse interventions, ranging from small-molecule drugs to mitochondrial transplantation, precisely modulate MQC modules to restore bioenergetic homeostasis and promote tissue regeneration across various stages of periodontitis, osteoporosis, and osteoarthritis.

Restoring periodontal homeostasis: Therapeutic interventions via MQC modulation

Mitophagy, a selective autophagic process for eliminating dysfunctional mitochondria, has emerged as a critical therapeutic target in periodontitis. Chen et al. demonstrate that DMF alleviates periodontal destruction by activating TUFM-mediated mitophagy, which reduces oxidative stress and shifts macrophage polarization from pro-inflammatory M1 to anti-inflammatory M2 phenotypes. This shift is achieved through the ubiquitin-proteasome pathway, where DMF stabilizes TUFM to enhance mitochondrial clearance.[141] Similarly, PINK1 deficiency exacerbates ligature-induced periodontitis by impairing mitophagy, leading to mitochondrial dysfunction and osteoclast hyperactivation. Restoration of mitophagy via spermidine or NAC rescues mitochondrial homeostasis and suppresses osteoclastogenesis.[135] Another study further supports this strategy, showing that spermidine recruits $Gli1^+$ PDLSCs to damaged sites by inhibiting STING activation via PINK1-dependent mitophagy, thereby promoting tissue repair.[199] These findings underscore mitophagy enhancers as promising agents to mitigate mitochondrial damage and inflammation in periodontitis. Recently, nanoparticles engineered to modulate mitochondrial quality control offer precise interventions for periodontitis. Zhu et al. fabricate MnO_2 nanoparticles that scavenge ROS and induce mitophagy via the SIRT1-FOXO3-BNIP3 axis, reducing alveolar bone loss in ligature-induced periodontitis.[200] Li et al. develop ROS-responsive nanoparticles that release mitoquinone to activate PINK1/Parkin-mediated mitophagy, thereby reducing oxidative stress and promoting periodontal regeneration.[201] These nanoplatforms exemplify innovative approaches to target mitochondrial dysfunction with spatiotemporal precision.

Restoration of mitochondrial fission/fusion dynamics is also considered a promising therapeutic strategy in periodontitis.[202] Pharmacological inhibition of fission, for

instance, has shown protective effects across various disease models by promoting fusion, preserving mitochondrial function, and reducing cell death.[203-205] Extending this principle to periodontitis, Chu et al. demonstrate that ginsenoside Rg1 inhibits mitochondrial fission in human periodontal ligament cells (hPDLCs) by phosphorylating DRP1 at Ser637 via the AMPK pathway, thereby reducing ROS and pyroptosis under LPS stimulation.[206] Cui et al. extend this concept, showing that nicotine activates the JNK/DRP1 pathway, leading to mitochondrial fragmentation and apoptosis in hPDLCs. The DRP1 inhibitor Mdivi-1 reverses these effects by blocking mitochondrial fission, restoring membrane potential, and enhancing osteogenic differentiation.[207] Another study corroborates this by linking luteolin to suppressed JNK/STAT3 signaling, which normalizes mitochondrial dynamics and promotes M2 macrophage polarization.[208] These studies highlight fission inhibitors as key modulators of mitochondrial dynamics to counteract periodontitis progression.

Therapeutic strategies targeting PGC-1α exploit its role as a master regulator of mitochondrial biogenesis and cellular metabolism across diverse diseases. Pharmacological or genetic activation of PGC-1α enhances mitochondrial function, mitigates oxidative stress, and restores bioenergetic capacity in pathologies including neurodegenerative disorders, diabetic complications, cardiovascular diseases, and cancers.[209-212] These interventions improve tissue resilience by augmenting OXPHOS, ATP production, and antioxidant defenses through coactivation of downstream effectors like NRF1 and TFAM.[213-215] Building on this broad therapeutic potential of PGC-1α modulation in systemic diseases, its specific application in periodontitis offers promising avenues for mitigating mitochondrial dysfunction and promoting periodontal regeneration. Silibinin attenuates diabetic periodontitis by activating PGC-1α-dependent mitochondrial biogenesis, enhancing mitochondrial function, and promoting osteogenesis in hPDLCs. Crucially, knockdown of PGC-1α abolishes silibinin's protective effects.[216] Similarly, adenosine exerts anti-inflammatory effects in human gingival fibroblasts by activating the AMPK/SIRT1/PGC-1α axis, driving metabolic

reprogramming towards mitochondrial biogenesis and OXPHOS.[217] Wang et al. further reveal that PGC-1α overexpression rescues cementoblast mineralization under hypoxic conditions by reversing $CoCl_2$-induced mitochondrial dysfunction.[218] These findings position PGC-1α activators as vital for enhancing mitochondrial mass and function in periodontitis therapy.

Multifaceted MQC-targeting strategies for OP: From mitophagy activation to mitochondrial transfer

OP is a prevalent metabolic bone disorder characterized by an imbalance between bone resorption and formation, partly driven by mitochondrial dysfunction in bone cells.[219-220] As mentioned above, dysregulation of MQC contributes significantly to OP pathogenesis, making it a promising therapeutic target. Various interventions targeting MQC have been explored to restore bone health, as evidenced by numerous studies.

One key approach involves enhancing mitophagy to eliminate damaged mitochondria and reduce oxidative stress. For instance, SIRT3 activation through overexpression or pharmacological means restores mitophagy in BMSCs, alleviating senescence and improving osteogenic differentiation in age-related and diabetic OP models.[180] In this context, Guo et al. further demonstrate that advanced glycation end products inhibit SIRT3-mediated mitophagy, leading to BMSC senescence and senile osteoporosis; conversely, SIRT3 overexpression via rAAV9 activates PINK1/Parkin mitophagy and reverses bone loss in SAMP6 mice.[221] Similarly, genistein, a natural isoflavone, promotes mitophagy and mitochondrial biogenesis via ERRα signaling, rescuing BMSCs from senescence and enhancing bone formation in OVX rats.[222] Irisin, an exercise-induced myokine, induces osteocyte mitophagy through AMPK activation, reducing age-related bone loss by clearing dysfunctional mitochondria and promoting osteoblast function.[223] In line with this, Apelin-13, an endogenous adipokine, activates AMPK-mediated mitophagy in BMSCs, as demonstrated by increased LC3-II, Pink1,

and Parkin expression, and reduced p62 levels. This activation rescues osteogenic differentiation under H_2O_2-induced damage, while in OVX rats, Apelin-13 administration reinstates bone microarchitecture and reduces marrow adiposity.[224] Additionally, inhibition of leucine-rich repeat containing 17 (LRRc17) activates mitophagy via the mTOR/PI3K pathway, rejuvenating senescent BMSCs and improving bone microarchitecture in OP.[225] Conversely, protein tyrosine phosphatase 1B knockdown ameliorates BMSC senescence by enhancing AMPK-mediated mitophagy, promoting osteogenesis in senile OP.[226] L-arginine supplementation promotes mitophagy via the PINK1/Parkin and BNIP3 pathways, enhancing angio-osteogenesis and inhibiting adipogenesis in OVX-induced OP.[227] MK-4 (menaquinone-4), a form of vitamin K2, alleviates diabetic OP by activating PINK1/Parkin-mediated mitophagy in endothelial cells, thereby improving type H vessel formation and bone regeneration.[228] Antioxidant interventions reduce ROS and support MQC. NAC mitigates cadmium-induced OP by scavenging ROS, restoring SIRT1 expression, and inhibiting osteoblast apoptosis via the PGC-1α/p53 pathway.[132] Enhanced SIRT3 expression rescues mitochondrial function in type 2 diabetes mellitus-related OP by deacetylating FOXO3 and activating PINK1/Parkin-mediated mitophagy.[179] Nanomaterials, such as honeycomb bionic graphene oxide quantum dot/layered double hydroxide composites, also promote mitophagy activation, reversing osteoporotic bone loss by rescuing osteoblast apoptosis and enhancing mitochondrial function.[229] A DNA tetrahedron-based nanoparticle encapsulating curcumin has been developed to target the NRF2/GPX4 axis, effectively inhibiting ferroptosis, enhancing mitochondrial function, and promoting osteogenic differentiation of BMSCs in diabetic OP.[230] Similarly, a tFNA-based delivery system loaded with metformin demonstrates significant efficacy in diabetic periodontitis, highlighting the potential of tFNA nanomaterials for broader application in the treatment of inflammatory bone diseases.[231] Notably, the regulation of mitophagy is context-dependent, and its inhibition may also confer therapeutic benefits in certain pathological processes. For

example, Brevilin A, a sesquiterpene lactone, suppresses osteoclastogenesis by inhibiting BNIP3-mediated mitophagy and mitochondrial metabolism, thus preventing OVX-induced bone loss.[137] In a complementary anti-osteoclastogenic strategy, Sarkar et al. show that epigallocatechin-3-gallate inhibits RANKL-induced osteoclast differentiation by reducing mitochondrial ROS, restoring membrane potential, and suppressing PINK1/PARKIN/DRP1-mediated mitophagy, highlighting that pharmacological inhibition of mitophagy in osteoclasts can also prevent bone loss.[232]

Another strategy focuses on modulating mitochondrial biogenesis to boost energy production and osteogenesis. Nicotinamide mononucleotide (NMN) treatment enhances mitochondrial biogenesis and mitophagy in osteoblasts, reducing senescence and promoting bone healing in OP models by increasing NAD^+ levels and activating SIRT1/PGC-1α signaling.[233] The adiponectin-derived peptide ADP-1 stimulates mitochondrial biogenesis and OXPHOS via the Akt/GSK-3β/Wnt and PGC-1α pathways, rebalancing bone remodeling and increasing bone mass in OVX rats.[234] Locamidazole, an aminoindazole derivative, mimics exercise by inducing calcium signaling-dependent PGC-1α expression, augmenting both muscle and bone through enhanced mitochondrial biogenesis and function.[235] Gut microbiota modulation, specifically with Lactobacillus salivarius LI01, fosters mitochondrial biogenesis by increasing glutathione synthesis and reducing ROS, thereby preventing OVX-induced bone loss.[236]

Mitochondrial transfer emerges as a pivotal mechanism within MQC, facilitating the intercellular exchange of functional mitochondria to restore cellular bioenergetics and homeostasis in OP. Osteolineage cells transfer mitochondria to myeloid cells via MIRO1-dependent mechanisms, inhibiting osteoclastogenesis and bone resorption by altering glutathione metabolism and inducing ferroptosis. Impairment of this transfer, such as by MIRO1 deletion, exacerbates osteoclast activity and bone loss, whereas glutathione depletion alleviates glucocorticoid-induced osteoporosis.[237] In addition, macrophages can deliver mitochondria to MSCs to promote osteogenic differentiation;

however, under osteoporotic conditions, M1-like macrophages increasingly transfer oxidatively damaged mitochondria, triggering ROS accumulation and metabolic remodeling in MSCs and thereby impairing osteogenesis.[143] Zhang et al. further show that a cerium-based nanosystem activates autophagy and mitochondrial biogenesis in senescent macrophages, enabling efficient transfer of healthy mitochondria to MSCs, which rescues osteogenic function and reverses bone loss in senile OP, highlighting nanomaterials as tools to enhance MQC through mitochondrial transfer.[238] These studies collectively illustrate that mitochondrial transfer integrates with MQC pathways to ameliorate OP by restoring cellular energy dynamics and function.

Multimodal interventions for OA: Integrating molecular, cellular, and biophysical approaches

OA involves complex interactions among mechanical, metabolic, and inflammatory factors.[239] Within this setting, MQC is emerging as a pivotal therapeutic target (Figure 4). Gene editing approaches targeting MQC have shown promise, such as the use of nanoengineered cargo delivering CRISPR/Cas9-based Foxo3 gene editing tools, which activate mitophagy via the PINK1/Parkin pathway to alleviate OA progression by reducing apoptosis and ECM degradation in chondrocytes.[240] Similarly, pharmacological interventions include Urolithin A encapsulated in pH-responsive lipid nanoparticles, which target mitochondria to enhance mitophagy and inhibit ferroptosis, thereby reducing ROS and inflammation in OA chondrocytes.[241] β-Hydroxybutyrate (βOHB) alleviates OA by enhancing mitophagy through the HCAR2/AMPK/PINK1/Parkin pathway in chondrocytes. The mechanism was validated using HCAR2 knockdown and AMPK inhibition, which abolished βOHB's protective effects on mitochondrial quality control and chondrocyte homeostasis.[242] Tiopronin, a thiol antioxidant, activates BNIP3-mediated mitophagy through the Bnip3-Pink1-Parkin signaling axis, promoting ECM synthesis and reducing oxidative

stress in chondrocytes.[243] Physical therapies like focused low-intensity pulsed ultrasound have been demonstrated to restore impaired FUNDC1-mediated mitophagy by promoting PGAM5-dependent dephosphorylation of FUNDC1, which enhances mitophagic flux and reduces chondrocyte apoptosis in OA models.[244] Traditional Chinese medicine formulations, such as Gubi Zhitong formula, alleviate OA by upregulating BNIP3L-mediated mitophagy, which improves mitochondrial function and reduces cartilage degradation through RNA-seq-identified pathways.[245] MicroRNA-based strategies involve engineered exosomes overexpressing miR-140, which target CAPN1 to enhance mitophagy and mitochondrial function, reducing ROS and improving chondrocyte viability in OA.[246] Additionally, sdRNA-D43, derived from snoRNA, regulates mitophagy by dual-targeting NRF1 and WIPI2, inhibiting PINK1/Parkin-mediated mitophagy and exacerbating chondrocyte senescence, with inhibition of sdRNA-D43 showing therapeutic benefits.[247]

Natural compounds like Lentinan, a β-glucan, activate mitophagy through the mTOR/PINK1/Parkin pathway, promoting mitochondrial biogenesis and reducing ECM degradation and cellular senescence in IL-1β-induced chondrocytes.[248] Xia et al. demonstrate that activation of SIRT3 by the natural agonist dihydromyricetin rebalances mitochondrial apoptosis and mitophagy in chondrocytes, suppressing the BCL2/BAX-cytochrome c-apoptosome cascade and activating the PINK1-Parkin-LC3B axis.[249] Sestrin2 overexpression attenuates OA pain by inducing AMPK/PGC-1α-mediated mitochondrial biogenesis, which enhances energy production and suppresses neuroinflammation in the spinal cord of OA models.[250] PGC-1α activation alleviates prenatal prednisone exposure-induced OA susceptibility in female offspring by restoring mitochondrial glutamine metabolism, histone acetylation, and cartilage ECM synthesis.[251] BNIP3-dependent mitophagy, regulated by PGC-1α, plays a dual role in OA; while its activation can promote mitophagy, excessive BNIP3 may drive cartilage degradation, highlighting the need for balanced modulation.[252] β2-adrenergic receptor agonists like isoprenaline and salbutamol inhibit

pyroptosis and promote mitochondrial biogenesis by downregulating β-arrestin and GRK2, restoring metabolic homeostasis in chondrocytes.[253]

Beyond mitophagy, emerging therapies have also begun to harness the UPRmt to restore mitochondrial proteostasis and protect articular cartilage. Engineered exosomes delivering modAtf5 mRNA via injectable thermogels have been shown to persistently activate UPRmt, thereby enhancing chondrocyte viability, suppressing catabolic enzyme expression, and promoting extracellular matrix synthesis in OA models.[110] In addition, self-assembled hydrogels exploit UPRmt by targeting SIRT3 to orchestrate ROS scavenging and mitochondrial autophagy, effectively reducing synovial inflammation and subchondral bone sclerosis in OA joints through downstream regulation of the mTOR/Ulk1 pathway and metabolic reprogramming.[254] These findings suggest that UPRmt-based interventions may complement existing MQC-targeted strategies by restoring mitochondrial proteostasis and attenuating OA progression.

Similar to OP, mitochondrial transfer also shows therapeutic potential in OA as an MQC-based strategy. Mitochondrial transfer from mesenchymal stromal cells to fibroblast-like synoviocytes in synovitis models restores cellular plasticity, reduces inflammation, and promotes mitochondrial biogenesis, offering a promising approach for OA treatment.[255] In chondrocytes, MSC-derived mitochondria restore redox and metabolic homeostasis, reduce ROS, inhibit apoptosis, and increase extracellular matrix synthesis.[256] Fusogenic liposome-encapsulated healthy mitochondria directly enter chondrocytes via membrane fusion, enhancing delivery efficiency and suppressing inflammatory cytokine production and cartilage degradation.[257] Furthermore, extracellular vesicles from adipose-derived stromal cells deliver functional mitochondria to dendritic cells, reprogramming cellular metabolism via the MAPK/ERK/FoxO1/autophagy pathway and reversing pro-inflammatory states in temporomandibular joint OA.[258] Importantly, intra-articular transplantation of MSC-derived mitochondria improves joint histopathology and reduces subchondral bone

mineralization in murine OA models without provoking adverse immune responses.[259] These strategies highlight the potential of exogenous mitochondria to rescue dysfunctional cellular energetics and mitigate OA progression.

Building upon the promising potential of mitochondrial transfer in both OP and OA intervention, we speculate that a stratified therapeutic approach could be optimized based on disease severity. In early stages of OP and OA, where mitochondrial function remains relatively preserved and MQC mechanisms, such as mitophagy and biogenesis, are still operational, targeted pharmacological or genetic interventions, such as enhancers of mitophagy or biogenesis, may help restore cellular homeostasis and halt progression. Conversely, in advanced stages marked by significant mitochondrial dysfunction and MQC failure, where clearance of damaged mitochondria and de novo generation are impaired, direct mitochondrial transfer emerges as a viable strategy. By delivering healthy mitochondria to regenerative cells such as chondrocytes or osteoblasts, this approach could replenish metabolic capacity and participate in MQC processes, potentially enhancing mitophagic clearance of dysfunctional organelles.

Overall, MQC-based interventions for OA span genetic, pharmacological, physical, and cellular approaches, targeting mitophagy, biogenesis, and dynamics to restore chondrocyte health. These approaches sit within a broader regenerative landscape that includes progenitor-cell, gene, and tissue-engineering strategies for joint repair.[260-261] Mitochondrial transfer represents an emerging avenue with significant therapeutic potential, though further clinical validation is needed. It should be noted that the vast majority of the evidence discussed above comes from in vitro cellular studies and preclinical animal models; direct clinical strategies targeting MQC in inflammatory bone diseases have not yet been established.

CONTEXT-DEPENDENCE OF MQC MODULATION: CELL TYPE, PATHWAY, AND FLUX LEVEL DETERMINE THERAPEUTIC OUTCOMES

The preceding therapeutic section highlights the promising potential of targeting MQC, particularly mitophagy, in inflammatory bone diseases. However, as emerging evidence from both our review and other studies makes clear, MQC modulation is not uniformly beneficial. Rather, its net effect on tissue homeostasis and disease progression is highly context-dependent, varying fundamentally with cell type, the specific MQC pathway engaged, and the flux level of the process being modulated. Ignoring this complexity could lead to paradoxical or even deleterious outcomes, especially when therapeutic strategies are applied indiscriminately.

1. Cell type-dependent outcomes of MQC modulation

The same MQC pathway can exert opposing effects in different cell lineages within the same disease. For instance, PINK1/Parkin-mediated mitophagy plays a protective role in osteoblasts by clearing damaged mitochondria and suppressing apoptosis under oxidative stress; accordingly, PINK1 deficiency impairs osteoblast differentiation and exacerbates bone loss.[122-123] In contrast, in osteoclasts, PINK1-dependent mitophagy restrains pathological activation, and Pink1 knockout paradoxically enhances osteoclastogenesis.[135] However, within the same osteoclast lineage, excessive mitophagy driven by SIRT3 promotes bone resorption and age-related bone loss, whereas pharmacological inhibition of mitophagy preserves bone mass, demonstrating that even the same cell type can display opposite responses depending on metabolic state and regulatory context.[262]

A striking example of cell-type specificity is seen in intercellular mitochondrial transfer. Transfer of healthy mitochondria from macrophages to mesenchymal stem cells (MSCs) supports osteogenesis under steady-state conditions; however, under osteoporotic conditions, M1-polarized macrophages deliver oxidatively damaged mitochondria to

MSCs, triggering a ROS burst, metabolic reprogramming, and impaired osteogenesis.[143] Hence, the functional status of the transferred organelle, not merely the transfer event itself, determines outcome.

2. Pathway-specific divergence within the same cell type

In OA chondrocytes, different mitophagy receptors yield opposing consequences. Activation of PINK1/Parkin-dependent mitophagy (e.g., by lentinan, α-ketoglutarate, or urolithin A) promotes mitochondrial renewal, reduces ROS, and protects against cartilage degradation.[248,263-265] By contrast, hyperactivation of BNIP3-mediated mitophagy, which can occur upon PGC-1α loss, drives excessive mitochondrial clearance, energy collapse, and cartilage breakdown; this effect is mitigated by BNIP3 inhibition or PGC-1α restoration.[252] Similarly, in osteoclasts, BNIP3-mediated mitophagy supports differentiation and bone resorption, and its inhibition by Brevilin A suppresses ovariectomy-induced bone loss.[137] Therefore, therapeutic targeting must distinguish between receptor-specific mitophagy pathways rather than merely enhancing or inhibiting mitophagy as a unitary process.

3. Flux level: The U-shaped therapeutic window of MQC

The level of MQC activity is equally critical. In glucocorticoid-exposed osteoblasts, excessive PINK1/Parkin-mediated mitophagy triggers ferroptosis and impairs osteogenesis; both the fission inhibitor Mdivi-1 and SIRT3 activation (which restrains overactive mitophagy) are protective.[120,266] Conversely, in inflammatory macrophages from periodontitis lesions, insufficient mitophagy leads to accumulation of damaged mitochondria, NLRP3 inflammasome activation, and M1 polarization; here, enhancing mitophagy via DMF or Apelin-13 restores immune homeostasis and alleviates bone loss.[140-141] Thus, MQC operates within a U-shaped therapeutic window: too little permits pathogenic damage accumulation, while too much drives cell death or excessive resorption.

This principle extends to mitochondrial dynamics. In physiological osteogenesis,

controlled mitochondrial fission facilitates the secretion of mitochondria-containing vesicles and promotes bone formation.[127] However, in periodontitis, pathogen-induced DRP1 hyperactivation drives excessive fission, ROS overproduction, and apoptosis of periodontal ligament cells, which is reversed by DRP1 inhibition.[152,207] Hence, optimal flux, not maximal or minimal activity, defines the therapeutic goal.

4. Disease-stage dependence and the rationale for stratified intervention

The net effect of MQC modulation also shifts with disease stage. In early OA, where mitophagy is insufficient due to downregulated PINK1 or FUNDC1, pharmacological activation is beneficial.[244,248] In advanced OA with ECM stiffening and HDAC3 downregulation, PINK1/Parkin becomes hyperacetylated and overactive, driving excessive mitophagy and chondrocyte senescence; here, inhibition of excessive mitophagy (e.g., by targeting PARP12 or restoring HDAC3) is required.[192-193] Similarly, in postmenopausal osteoporosis, SIRT3-driven mitophagy in osteoclasts accelerates bone resorption, whereas in diabetic osteoporosis, osteoblasts exhibit insufficient mitophagy, demanding opposite interventions.

These observations compel a stratified intervention paradigm: In conditions with MQC insufficiency (e.g., inflamed macrophages, early OA, diabetic osteoblasts, PINK1-deficient periodontitis), MQC activators (mitophagy enhancers, biogenesis agonists, or fission correctors) are warranted. In conditions with MQC overactivation (e.g., aged osteoclasts, glucocorticoid-stressed osteoblasts, ECM-stiffened OA chondrocytes, BNIP3-driven cartilage degradation), MQC inhibitors (e.g., moderate fission inhibitors, BNIP3 antagonists, or upstream regulators like SIRT3 modulators that curb excessive flux) should be considered. Clinical translation requires quantitative biomarkers of MQC flux—circulating mtDNA, mitophagy reporters, or ΔΨm imaging—to guide patient stratification and monitor response.

CONCLUSIONS AND PERSPECTIVES

This review has synthesized evidence positioning MQC as a unifying regulatory platform in inflammatory bone diseases. The cumulative evidence underscores that impaired MQC mechanisms, including aberrant mitochondrial dynamics, deficient mitophagy, disrupted biogenesis, and compromised proteostasis, drive a vicious cycle of oxidative stress, metabolic insufficiency, and inflammatory amplification in the bone microenvironment. Critically, MQC failure not only accelerates local tissue damage but also bridges inflammatory bone diseases to systemic comorbidities. Emerging interventions targeting MQC, such as mitophagy enhancers and fission inhibitors, have shown efficacy in preclinical models by restoring mitochondrial homeostasis and promoting bone repair. These advances may represent a paradigm shift from symptom management toward mechanism-directed therapy.

However, key challenges must be addressed to translate MQC-targeted strategies into clinical practice. First, the cell type-specific heterogeneity of MQC across stem cells, osteocytes, osteoclasts, and immune cells remains poorly mapped. Single-cell multi-omics approaches could unravel distinct mitochondrial vulnerabilities and refine precision interventions. Second, the roles of ancillary MQC programs (UPRmt, MDVs) in periodontal disease and immune cells are largely unexplored, and whether mitocytosis operates in bone pathologies remains an open question. Future research elucidating alterations in these ancillary MQC mechanisms is essential for a comprehensive understanding of pathological mechanisms and the development of novel therapeutic strategies. Third, the bidirectional relationship between inflammatory bone diseases and systemic diseases necessitates comparative studies to identify shared versus unique MQC nodes across conditions. Finally, clinical translation demands robust biomarkers of mitochondrial health to stratify patients and monitor therapeutic efficacy. By addressing these gaps, future research may unlock combinatorial regimens that synergistically enhance MQC, supporting the development of treatment strategies for inflammatory bone diseases grounded in mitochondrial homeostasis.

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FIGURE TITLES AND LEGENDS

Figure 1. Molecular mechanisms of mitochondrial quality control (MQC) MQC functions as an integrated regulatory platform consisting of biogenesis, mitochondrial dynamics, mitophagy, intercellular mitochondrial transfer, mitochondrial unfolded protein response and ancillary pathways including mitochondrial-derived vesicles and mitocytosis. These coordinated processes act as a defense system to sense cellular stress and maintain a healthy mitochondrial pool.

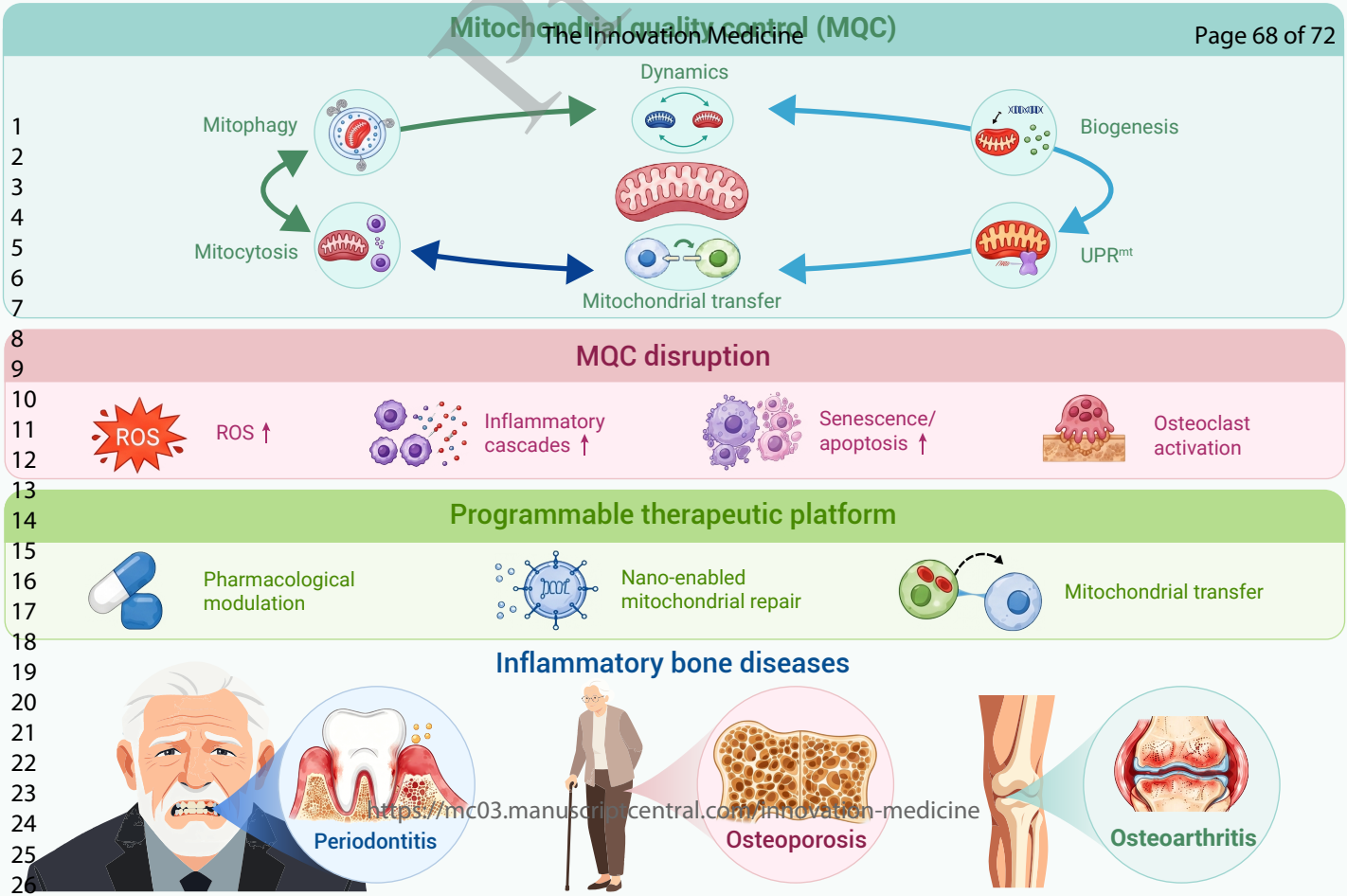
Figure 2. Regulation of bone cell fate and homeostasis by MQC mechanisms Mitophagy, mitochondrial dynamics, and biogenesis collectively orchestrate the metabolic fitness and differentiation commitment of osteoblasts, chondrocytes, and skeletal stem cells, whereas their impairment under pathological stresses drives bone loss and cartilage degeneration.

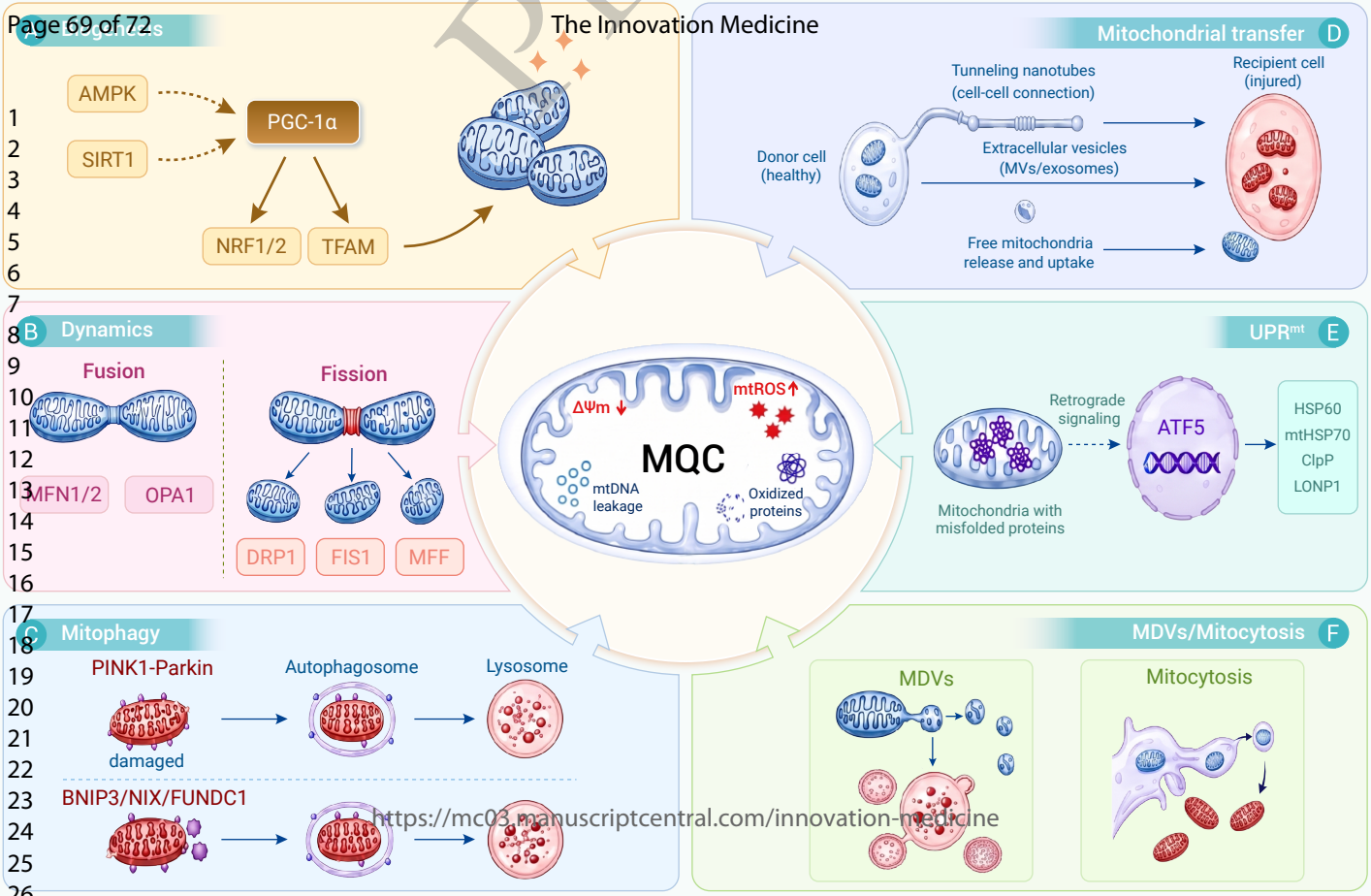
Figure 3. MQC failure as a common pathological axis in inflammatory bone diseases Dysregulated mitochondrial dynamics, impaired mitophagy, and reduced biogenesis converge to amplify oxidative stress and inflammatory signaling, thereby driving the characteristic tissue destruction and cellular dysfunction observed in periodontitis, osteoporosis, and osteoarthritis.

Figure 4. MQC-targeted therapeutic platform for inflammatory bone diseases Diverse interventions, ranging from small-molecule drugs to mitochondrial transplantation, precisely modulate MQC modules to restore bioenergetic homeostasis and promote tissue regeneration across various stages of periodontitis, osteoporosis, and osteoarthritis.

Table 1. Shared and disease-specific features of MQC dysfunction in inflammatory bone diseases.

MQC module	Periodontitis	Osteoporosis	Osteoarthritis
Mitochondrial dynamics	↑DRP1 (Ser616) by *P. gingivalis*; ↓ MFN2 in PDLSCs	↑DRP1 via RANKL/TNF-α; MFN2 degradation mediated by RIPK4	↑ DRP1 (Ser592) by ERK1/2; ↓ OPA1 in aged chondrocytes
Mitophagy	PINK1/Parkin impaired by hyperglycemia; TUFM-mediated mitophagy exerts protection (via DMF); STAT3 activation suppresses PINK1-dependent mitophagy	PINK1/Parkin repressed by SIRT3/FOXO3 dysregulation; BNIP3-mitophagy promotes osteoclastogenesis	PINK1/Parkin disrupted by HDAC3-mediated acetylation; FUNDC1 impaired by overload; BNIP3-mediated mitophagy plays dual roles
Mitochondrial biogenesis	↓PGC-1α in diabetic periodontitis (reversed by silibinin)	↓PGC-1α in aging/estrogen deficiency	↓ PGC-1α in OA cartilage
Mitochondrial transfer	Macrophage transfer of damaged mitochondria to BMSCs	Macrophages transfer damaged mitochondria to MSCs; Osteolineage-to-myeloid transfer regulates resorption	MSC-to-chondrocyte transfer restores cartilage homeostasis; Fusogenic liposomes deliver healthy mitochondria
Disease-specific trigger	Pathogen (*P. gingivalis*) LPS and outer membrane vesicles	Estrogen deficiency	Mechanical overload (PDZK1 loss) and matrix stiffening (HDAC3↓)
Unique molecular node	TSPO overexpression; STAT3/mitophagy axis; APJ-BNIP3-PINK1 pathway	SIRT3-FOXO3-PINK1 axis; NDR2-ULK1 pathway; MFN2-ER tethering	PARP12-ISG15-MFN1/2 axis; TBK1-DRP1 (Ser637) regulation; ferroptosis-mitophagy crosstalk



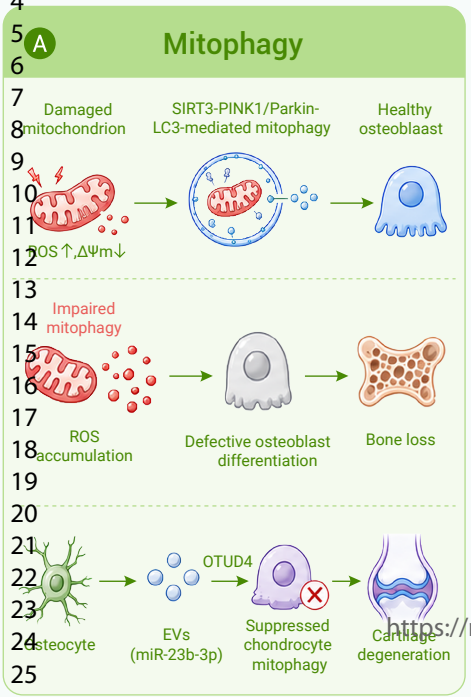


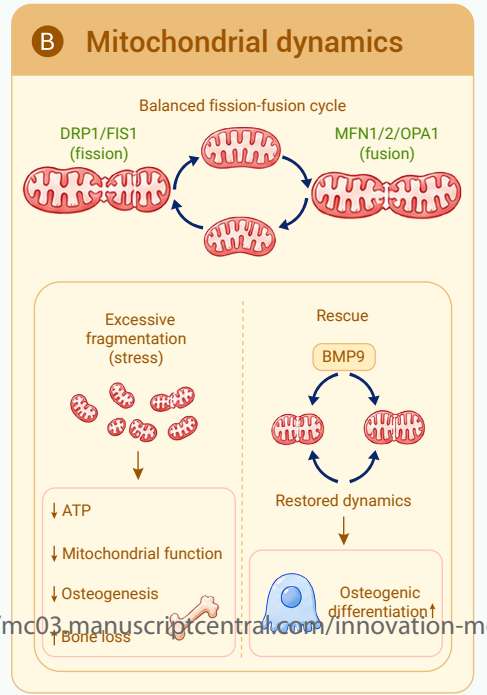

Osteoblast

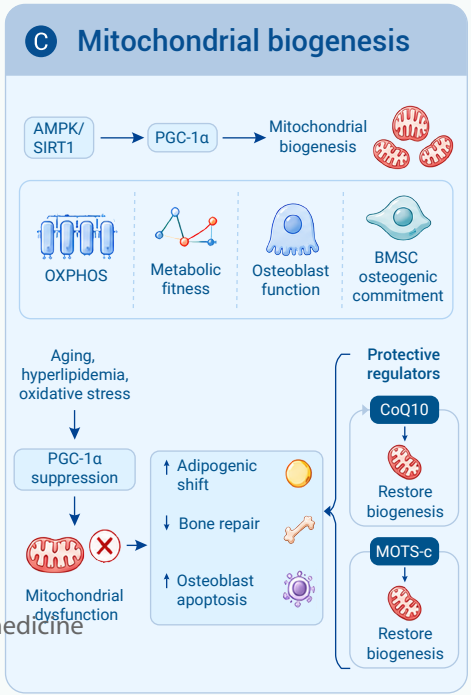

Osteocyte


Chondrocyte


BMSC

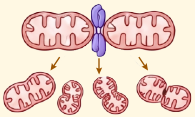




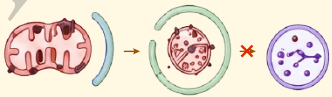


MQC failure

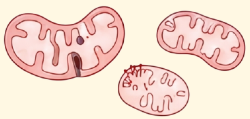
Excessive fission



Defective mitophagy



Reduced mitochondrial fitness



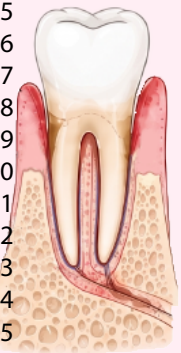
mtROS ↑

ΔΨm ↓

Inflammation ↑

Periodontitis

Dysbiosis/ hyperglycemia



DRP1 fission

PINK1/Parkin

Inflammasome

Osteoclast activation

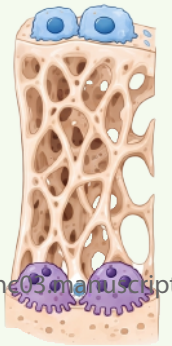
Alveolar bone loss

Osteoporosis


Aging


Estrogen deficiency

Diabetes



SIRT3-PINK1/ Parkin

Mitophagy failure

Osteoblast senescence

Osteoclast activation

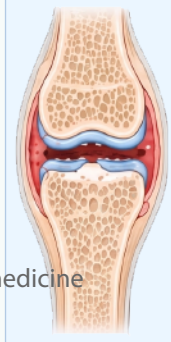

Bone loss

Osteoarthritis


Aging


Mechanical stress


Inflammation context



Fission/mitophagy

Defective mitophagy

Reduced biogenesis

Chondrocyte death

ECM degradation

Cartilage degeneration

small molecules/natural compounds | nanomedicine | engineered exosomes | gene or biomaterial based therapy | mitochondrial transplantation

MQC-targeted therapeutic platform

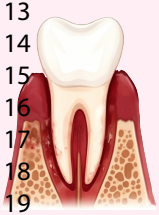
Mitophagy activation
clear damaged mitochondria

Dynamics rebalancing
reduce fission, restore fusion

Biogenesis enhancement
PGC-1α-driven generation of healthy mitochondria

Mitochondrial transfer
deliver healthy mitochondria to damaged cells

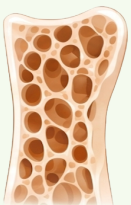
Periodontitis



- DMF/spermidine/NAC-- mitophagy activation
- Mdivi-1/Rg1-- DRP1-fission inhibition
- PGC-1α: Silibinin-- PGC-1α biogenesis

ROS | inflammation | PDLSC repair | bone preservation

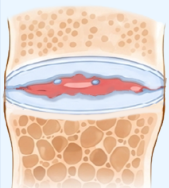
Osteoporosis



- SIRT3/Irisin/Apelin-13-- mitophagy activation
- PGC-1α: NMN/ADP-1-- Mitochondrial biogenesis
- healthy mitochondrial transfer to MSCs

BMSC rejuvenation | osteogenesis | osteoblast activity | bone mass recovery

Osteoarthritis



- Urolithin A/βOHB/ miR-140 exosome-- mitophagy restoration
- modATFs or SIRT3-based protectors-- mitochondrial homeostasis
- MSC-derived mitochondrial transfer

ROS | chondrocyte survival | ECM preservation | cartilage protection

Early stage: activate endogenous MQC → **Advanced stage: mitochondrial transfer**