

The organelle interactome in osteoarthritis: from subcellular dysfunction to joint degeneration

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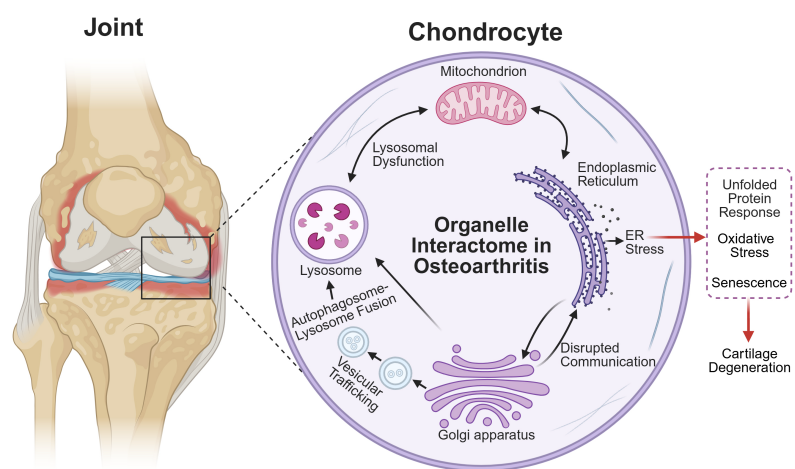


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ABSTRACT: Osteoarthritis (OA) has long been described as a “wear and tear” degenerative joint disorder, yet this definition fails to capture the complexity of the disease. Emerging evidence suggests that OA is more accurately characterized as a whole-joint disorder involving coordinated changes in cartilage, synovium, subchondral bone, and the local microenvironment. At the subcellular level, OA progression appears to involve not a single failing organelle, but disrupted communication among mitochondria, the endoplasmic reticulum, the Golgi apparatus, lysosomes, and intracellular trafficking systems in joint cells. In chondrocytes, disrupted organelle crosstalk promotes oxidative stress, unfolded protein response, lysosomal dysfunction and senescence, thereby amplifying cartilage degeneration. This review reexamines OA pathogenesis from the perspective of inter-organelle communication. We summarize major forms of organelle interaction in chondrocytes, including membrane contact sites (MCSs), vesicular trafficking, and autophagosome-lysosome fusion. We further discuss mitochondria-related crosstalk, endoplasmic reticulum stress regulation, and the lysosome-mTOR-autophagy network in OA progression. Furthermore, we address the preliminary evidence for migrasomes as an emerging research direction and compare the heterogeneous patterns of organelle crosstalk across chondrocytes, synovial cells, macrophages, and subchondral bone-related cells. By bridging subcellular dysfunction with whole-joint pathological changes, this review offers fresh insights and provides a new entry point for developing therapeutic strategies.



KEYWORDS: osteoarthritis, organelle crosstalk, chondrocytes, mitochondria, endoplasmic reticulum, membrane contact sites

1 Introduction

1.1 Pathological features and global disease burden of OA

Osteoarthritis (OA) is among the most prevalent joint disorders

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globally and remains a primary driver of chronic pain, impaired mobility, and long-term disability^[1]. Recent epidemiological studies and burden-of-disease reviews indicate that OA can no longer be characterized simply as “cartilage wear”; instead, it is recognized as a complex whole-joint disorder that compromises the joint as a cohesive functional unit^[2]. OA is now regarded as a heterogeneous disease involving the entire joint structure. Its hallmark pathological features include the progressive degradation of the articular cartilage extracellular matrix (ECM), sclerosis of the subchondral bone, meniscal calcification, osteophyte formation, and chronic inflammation of the surrounding synovium^[1,2].



With a progressively aging population and rising obesity rates, the global burden of OA has increased markedly in recent years. A systematic analysis from the Global Burden of Disease 2021 study estimated that approximately 595 million people were living with OA in 2020, representing 7.6% of the global population and a 132.2% increase in total cases since 1990^[3]. More recent GBD 2021-based analyses further estimated that the number of people living with OA reached approximately 607 million in 2021, accompanied by a marked increase in years lived with disability (YLDs)^[4-6]. Alarming, predictive models indicate a continued upward trajectory, fueled by demographic aging and high body mass index, with the global number of people affected projected to approach one billion by 2050^[3,4,6]. This persistent growth in patient numbers will exert an increasingly heavy long-term burden on healthcare systems and global economies^[6]. However, current clinical management of OA remains largely reactive, primarily limited to symptomatic relief through non-steroidal anti-inflammatory drugs or joint replacement surgery at end-stage disease^[7, 8]. To date, no disease-modifying osteoarthritis drugs (DMOADs) capable of effectively slowing or reversing structural joint damage have reached clinical practice. Given that chondrocyte metabolism is central to articular cartilage homeostasis, a more comprehensive understanding of organelle interaction networks within chondrocytes may offer a critical new entry point for DMOAD development and the identification of novel therapeutic targets^[9].

Previous reviews and original studies on OA have mainly focused on isolated subcellular pathologies, such as mitochondrial dysfunction, endoplasmic reticulum (ER) stress, impaired autophagy, and lysosomal decline^[10-14]. However, during the progression of the disease, these abnormalities rarely occur in isolation. Rather, the disruption of homeostasis in a single organelle often triggers a sequential failure of others, suggesting that a disturbance at any individual node within the subcellular network can drive a persistent and systemic imbalance^[15-18]. In OA, the extent and sequence of such inter-organelle propagation remain to be fully established. A review published in *Nature Reviews Rheumatology* in 2022 provided an in-depth discussion of the interactions among synovial cells, their activation during OA progression, and their interplay with other joint structures^[19]. More recently, Collins et al. framed OA as a systemic disease involving broader whole-body metabolic and inflammatory alterations^[20]. While that article primarily addressed communication at the tissue and cellular levels rather than at the organelle level, it offered a pivotal perspective: OA pathogenesis should no longer be understood simply as degeneration of a single structure, but must be viewed within a broader framework of disrupted homeostasis.

Rather than discussing individual organelles in isolation, this review situates OA pathogenesis within a comprehensive network of subcellular interactions. Focusing primarily on chondrocytes, we examine how mitochondria, the ER, the Golgi apparatus, and lysosomes collectively orchestrate cellular fate and drive OA progression. Furthermore, we explore the potential therapeutic benefits of targeted interventions aimed at modulating these organelle interactions. At present, experimental evidence linking OA to organelle crosstalk remains predominantly focused on mitochondria-ER and mitochondria-lysosome communication. While findings involving other organelle pairs are steadily emerging, their specific roles in joint degeneration warrant further investigation.

1.2 The role of organelle interactions in the development and progression of OA

Mature articular cartilage is a highly specialized connective tissue that is characterized by the absence of vasculature, nerves, and lymphatic vessels. As the sole resident cell type, chondrocytes are distributed sparsely within the ECM, comprising merely 2% of the total cartilage volume^[21]. Embedded within the cartilage matrix, chondrocytes persist for long periods in a hypoxic, poorly perfused microenvironment where nutrient supply and metabolism are both restricted. Consequently, chondrocytes must rely heavily on their intrinsic metabolic and regulatory machinery to sustain the synthesis and secretion of the dense ECM that surrounds them^[22, 23]. To preserve long-term homeostasis under these challenging conditions, chondrocytes must integrate energy production, protein folding and secretion, and the recycling and clearance of damaged macromolecules into a highly coordinated system. Organelle interactions are therefore essential, enabling these cells to optimize limited energy while maintaining cellular responses within a manageable physiological range.

Current research on OA-related cartilage degeneration frequently reports the characteristics of subcellular pathologies, including decreased mitochondrial membrane potential, ER stress activation, impaired autophagic flux, insufficient lysosomal acidification, and the accumulation of senescence markers^[24-27]. However, characterizing OA pathogenesis through isolated organelle defects is limited; the causal relationships and cascade-amplification effects among damaged subcellular structures need further investigation. For instance, when calcium homeostasis in the ER is disturbed, excessive Ca^{2+} transfer into the mitochondrial matrix can trigger calcium overload, resulting in mitochondrial depolarization and reactive oxygen species (ROS) accumulation. This, in turn, exacerbates the burden on the protein-folding and secretion machinery, driving sustained activation of the unfolded protein response (UPR), and ultimately committing the cell to a C/EBP homologous protein (CHOP)-mediated pro-apoptotic state^[24]. Furthermore, as mitochondrial dysfunction progresses, misfolded proteins rapidly accumulate in chondrocytes, overwhelming the downstream lysosomal clearance systems. When the generation of toxic macromolecules outpaces lysosomal hydrolysis, lysosomes become dysfunctional, leading to inflammasome activation and the initiation of chondrocyte senescence and apoptosis^[12,13,27].

In addition, articular cartilage is subjected to frequent and intense mechanical loading throughout life. Abnormal mechanical stress reduces the levels of superoxide dismutase 2, a key enzyme responsible for scavenging ROS in chondrocytes, thereby worsening mitochondrial dysfunction and subsequent cartilage injury^[28,29]. Consequently, these findings underscore that pathological changes at the organelle level are intrinsically coupled with the biomechanical environment of the joint.

2 Major forms of organelle interactions

To maintain cellular homeostasis, chondrocytes rely heavily on coordinated crosstalk among organelles to complete a series of metabolic reactions efficiently. At the subcellular level, these interactions are mainly achieved through three modes: membrane contact sites (MCSs), vesicular trafficking and membrane fusion,

and autophagosome-lysosome coupling. Together, they support short-range exchange, cargo transfer, and terminal quality control, and thereby help maintain subcellular homeostasis in chondrocytes. During OA progression, disruption of these interactions may contribute to cellular dysfunction (Fig. 1).

2.1 Organelle cascades amplified by membrane contact sites

MCSs bring the membranes of different organelles into close proximity without membrane fusion and provide the structural basis for non-vesicular transport of intracellular Ca^{2+} , lipids, and other molecules^[30]. Typical examples include mitochondria-associated membranes (MAMs), mitochondria-lysosome contacts (MLCs), and ER-lysosome contacts^[15]. In OA, abnormal mechanical loading and inflammatory stimulation can promote the accumulation of misfolded proteins in chondrocytes, triggering ER stress and apoptotic signaling, while changes in mitochondrial metabolism and ROS production may exert a feedback effect to further intensify ER stress through the MAMs pathway, creating an amplifying loop that drives chondrocyte senescence and death^[24,31,32]. At the same time, reduced lysosomal acidification in OA leads to the accumulation of damaged mitochondria, higher oxidative stress, and eventually more chondrocyte apoptosis. Lysosomal network dynamics are not static, but are actively regulated by proteins such as mitochondrial fission 1 protein (Fis1), which has been implicated in lysosomal untethering and mitochondrial network remodeling^[33]. However, it should be noted that current evidence linking this mechanism specifically to OA remains indirect, and whether similar regulatory processes operate in chondrocytes under

pathological conditions is still unclear. In an OA-specific context, the work by Kim et al. provides a somewhat different perspective. Rather than demonstrating a direct structural role for MLCs, their study showed that depletion of Fis1 in OA chondrocytes leads to a broad disruption of mitochondrial, peroxisomal, and lysosomal function, accompanied by impaired autophagy through miRNA-dependent mechanisms^[34]. Taken together, these observations imply that organelle crosstalk in OA may not rely solely on physically defined MCSs, but could also emerge from more diffuse, multi-layered regulatory interactions across organelle networks.

2.2 Vesicular trafficking and membrane fusion

In addition to direct membrane apposition, organelle communication also depends heavily on vesicular trafficking and membrane fusion. This dynamic network includes not only the classical route by which proteins synthesized in the ER are processed in the Golgi and transported to the plasma membrane, but also endocytosis, exocytosis, autophagosome formation, and fusion between autophagosomes and lysosomes^[35–38]. As the primary cells responsible for producing large amounts of ECM, chondrocytes depend heavily on an intact vesicle-based secretory system. Ohtsuki et al. demonstrated that extracellular vesicles (EVs) can be incorporated into chondrocytes and synoviocytes via a pathway partly dependent on dynamin-mediated endocytosis^[37]. These findings support the involvement of EV-mediated vesicular trafficking in communication between cartilage and adjacent synovial tissues. However, the cellular origins and cargo composition of OA-associated EVs at different stages of the disease remain to be further clarified. This form of vesicle trafficking serves

Major Forms of Organelle interactions in OA Chondrocytes

Three modes supporting subcellular homeostasis during OA progression

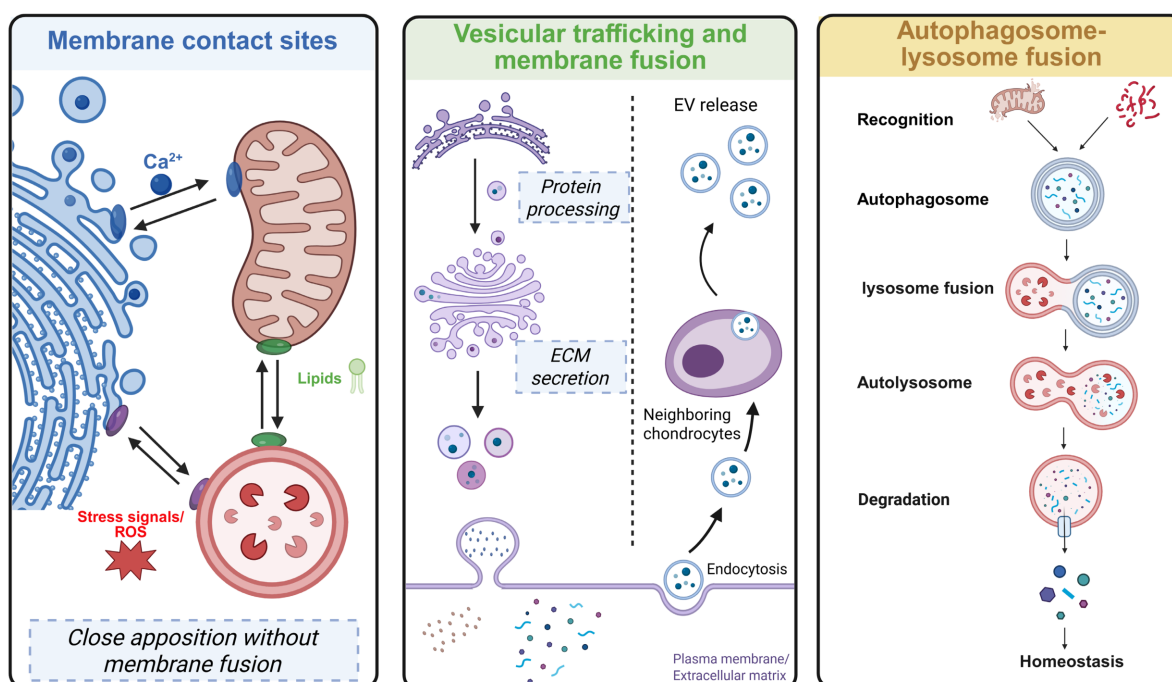


Figure 1 Major modes of organelle communication in osteoarthritic chondrocytes. This figure summarizes three principal forms of organelle interaction in chondrocytes during osteoarthritis progression: membrane contact sites, vesicular trafficking and membrane fusion, and autophagosome-lysosome fusion (Created with BioRender.com).

as a pivotal mode of cell-cell communication between the cartilage and its adjacent joint tissues. Abnormal mechanical stress has been found to induce osteocytes within the subchondral bone to secrete EVs. These osteocyte-derived EVs are enriched in miR-23b-3p, which targets and suppresses the expression of the OTU deubiquitinase 4 (OTUD4) in chondrocytes^[39]. Suppression of OTUD4 impairs mitophagy and disrupts mitochondrial homeostasis in chondrocytes. The expression of key chondrocyte markers, such as ACAN and COL2A1, is significantly reduced, while the levels of catabolic enzymes that degrade cartilage matrix, such as MMP13 and ADAMTS5, are increased, thereby accelerating OA progression^[39].

2.3 Autophagosome-lysosome fusion and terminal degradation

MCSs and vesicular trafficking determine the transport of intracellular materials and the exchange of information within and between cells, whereas autophagosome-lysosome coupling determines whether these molecular burdens can ultimately be cleared effectively. In chondrocytes, this process serves as the critical checkpoint for protein quality control and organelle turnover. In the late stage of OA, impaired lysosomal acidification and reduced degradative capacity can compromise autophagic flux^[13,38]. Once degradation is impaired, the accumulation of damaged mitochondria, misfolded proteins, and other uncleared substrates eventually drives the cell from a compensatory state toward senescence and apoptosis. Studies have shown that the transcription factor EB (TFEB) serves as a master regulator of autophagic flux by inducing lysosome biogenesis and promoting autophagosome formation and fusion with lysosomes. In both human and mouse degenerative cartilage, TFEB expression and its nuclear translocation are reduced, accompanied by severe impairment of autophagic flux in OA chondrocytes. Under oxidative stress, overexpression of TFEB protects chondrocytes from premature senescence and apoptosis by upregulating the autophagosome marker LC3 and the lysosome markers CTSB, LAMP1, and LAMP2, thereby rescuing damaged autophagic flux and restoring lysosomal function^[40].

Consistent with the disruption of the TFEB regulatory network, the study by Ansari et al. provides additional evidence highlighting the role of lysosomal dysfunction. In both OA and aged cartilage, the expression of lysosome-associated membrane proteins LAMP1 and LAMP2 is reduced, and lysosomal acidification is weakened. Either siRNA-mediated knockdown of LAMP2 or pharmacological disruption of lysosomal acidification leads to abnormal accumulation of dysfunctional mitochondria, loss of mitochondrial membrane potential, and fragmentation of the mitochondrial network^[13,38,41]. Mechanistically, lysosomal dysfunction-induced apoptosis was not prevented by the antioxidants used in that study, whereas inhibition of BAX markedly reduced apoptosis. Instead, it involves selective upregulation of the pro-apoptotic protein BAX and its translocation to the outer mitochondrial membrane. This triggers mitochondrial membrane permeabilization and the release of cytochrome c into the cytosol^[13]. Collectively, these findings suggest that restoring TFEB transcriptional activity or directly repairing lysosomal degradative capacity to maintain lysosomal function may represent a promising strategy for alleviating OA-related cartilage degeneration^[13,40].

3 Mitochondria-centered organelle interactions in OA

Among the various forms of organelle crosstalk documented in OA research, mitochondria-centered interactions warrant particular attention. This stems not only from the fact that mitochondrial dysfunction represents one of the most consistent hallmarks of degenerative cartilage, but also from the fact that these organelles seldom malfunction in isolation. Indeed, disruption of mitochondrial homeostasis can influence the function of the ER, lysosomes, and other metabolic compartments. Therefore, rather than viewing mitochondria as autonomous entities, it is increasingly imperative to analyze them within the context of their functional coupling with neighboring organelles^[10,11,42].

3.1 Mitochondria-ER interactions: calcium transfer and stress coupling

The ER and mitochondria are physically and functionally tethered through MAMs, which provide a structural basis for calcium exchange, lipid trafficking, and stress adaptation. In chondrocytes, the mitochondria-ER interface is particularly relevant because both mitochondrial ATP production and ER protein-folding capacity are altered in the OA microenvironment. Once MAM homeostasis is disrupted, the functions of both mitochondria and the ER may be affected. For instance, ageing-related downregulation of Lon peptidase 1 (LONP1) has been associated with mitochondrial dysfunction and increased ER stress in chondrocytes^[43]. More recent work has further suggested that restoring ER-mitochondrial communication can alleviate cartilage degeneration, highlighting the important role of this axis in OA pathophysiology^[44,45].

The physiological significance of the ER-mitochondrial interface lies not merely in its structural existence, but also in its functional remodeling under prolonged proteotoxic and inflammatory stress. In the OA microenvironment, excessive Ca^{2+} transfer from the ER to mitochondria may contribute to mitochondrial depolarization and ROS accumulation (Fig. 2a). In return, mitochondrial dysfunction feeds back onto the ER, exacerbating the burden of stress signaling, and rendering adaptive responses, such as the UPR unsustainable^[10,11,44,45]. Although the exact mechanisms in OA chondrocytes remain incompletely understood, available evidence suggests that disruption of this two-organelle axis may weaken cellular stress adaptation and promote senescence or apoptosis^[42,44,45].

3.2 Mitochondria-lysosome interactions: mitophagy and terminal quality control

Compared with several other organelle interactions discussed in OA, mitochondria-lysosome crosstalk is supported by relatively substantial evidence, particularly from studies of mitophagy and lysosomal dysfunction. Damaged mitochondria must be identified, sequestered, and degraded via mitophagy; however, when lysosomal function declines, this pathway stalls, causing mitochondrial defects to accumulate. In both osteoarthritic and aged cartilage, the downregulation of LAMP1 and LAMP2, impaired lysosomal acidification, and the persistence of dysfunctional mitochondria are consistently observed as co-occurring phenomena^[13]. Furthermore, when lysosomal activity is inhibited, chondrocytes exhibit a loss of mitochondrial membrane potential, elevated oxidative stress, and increased apoptosis. These findings suggest that lysosomal failure is a primary driver of

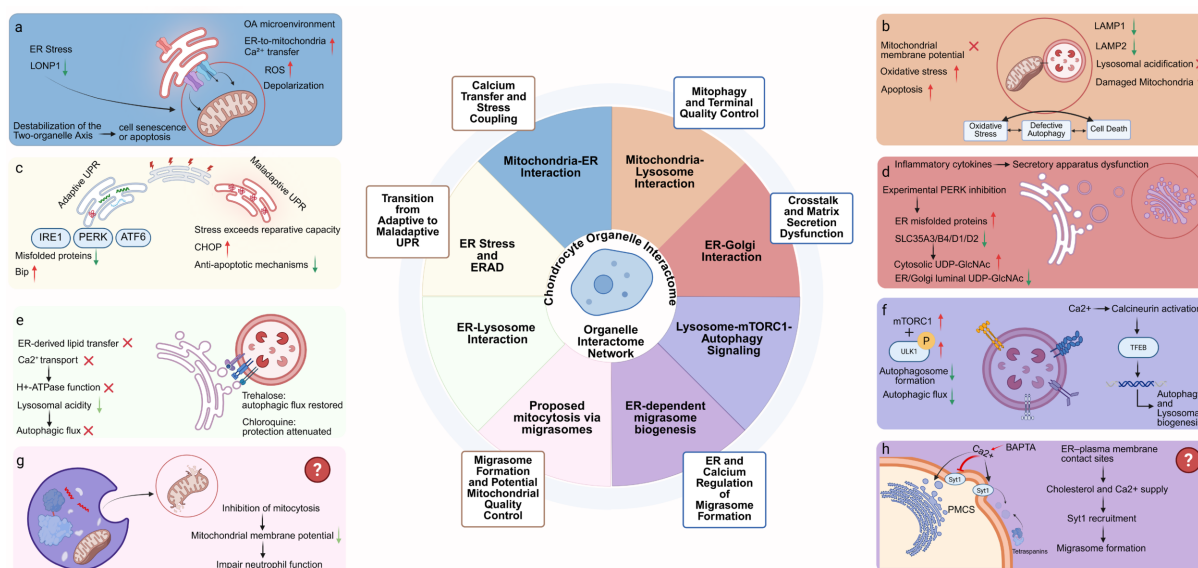


Figure 2 Organelle crosstalk and emerging migrasome-related mechanisms in osteoarthritis. **a**, Mitochondria-ER interaction involving Ca^{2+} transfer and oxidative stress. **b**, Mitochondria-lysosome crosstalk. Impaired lysosomal function disrupts mitophagy, leading to damaged mitochondria, oxidative stress, and apoptosis. **c**, Transition from adaptive to maladaptive unfolded protein response (UPR) during persistent ER stress. **d**, ER-Golgi dysfunction affecting protein processing, glycosylation and matrix secretion. **e**, ER-lysosome interaction contributing to lysosomal acidification and autophagic flux. **f**, Lysosome-mTORC1 signaling in OA suppresses autophagy and TFEB-dependent lysosomal biogenesis. **g**, Proposed mitophagy-mediated mitocytosis may help remove damaged mitochondria and maintain mitochondrial homeostasis. **h**, ER-plasma membrane contacts may support migrasome formation through cholesterol and Ca^{2+} supply. Question marks in **g** and **h** indicate mechanisms whose direct relevance to OA remains to be experimentally established (Created with BioRender.com).

pathology rather than a secondary bystander effect (Fig. 2b)^[13].

Mitophagy represents the most prominent intersection of mitochondria-lysosome crosstalk. Parkin-dependent clearance of dysfunctional mitochondria is essential for maintaining redox homeostasis and chondrocyte survival^[46]. Conversely, pharmacological interventions such as urolithin A have been shown to improve mitochondrial health and attenuate cartilage degeneration, largely by enhancing mitophagic flux^[47]. Similarly, SIRT3-based modulation of mitochondrial apoptosis and mitophagy, as well as the transfer of functional mitochondria to OA chondrocytes, has been shown to improve mitochondrial homeostasis and reduce cartilage damage^[48,49]. This axis is the final quality control checkpoint for the cell. If this last step fails, oxidative stress and defective autophagy trap the chondrocyte in a cycle of damage and death typical of OA^[13,41,46].

3.3 Mitochondria-peroxisome interactions: redox buffering and lipid metabolic coordination

The relationship between mitochondria and peroxisomes remains a relatively emerging chapter in OA pathophysiology. While the current body of evidence is less extensive and requires cautious interpretation, the functional synergy between these two organelles is undeniable. Both are integral to chondrocyte homeostasis, particularly through their shared roles in lipid metabolism and redox regulation. Peroxisomes are essential for the β -oxidation of very-long-chain fatty acids and the decomposition of ROS via catalase, while mitochondria provide the primary energy supply and broader metabolic control. Given these overlapping roles, it is plausible that pathological stress in one compartment necessitates a compensatory shift in the metabolic burden onto the other.

Despite these insights, the OA literature has yet to provide the same level of direct mechanistic evidence for this axis as it has for the mitochondria-ER or mitochondria-lysosome interfaces.

Nevertheless, several indirect clues support its potential relevance. Alterations in mitochondrial dynamics, involving key regulators such as OPA1, DRP1, and FIS1, have been linked to systemic organelle remodeling rather than being confined to mitochondrial morphology^[50]. Furthermore, emerging evidence suggests that master regulators like PGC-1 α may bridge mitochondrial biogenesis with lipid-processing programs integral to peroxisomal function^[11,42]. Even so, further investigations are needed in this emerging research frontier.

4 Endoplasmic reticulum-related interactions: protein synthesis and secretion

4.1 ER stress and impaired ER-associated degradation

As highly secretory cells exposed to heavy functional demands within the joint, chondrocytes must continuously synthesize and secrete large amounts of ECM components, including Col2a1 and aggrecan. These molecules are produced, folded, and modified in the ER, where ER homeostasis is closely tied to organelle crosstalk. The accumulation of misfolded or unfolded proteins in the ER lumen triggers ER stress, thereby activating the UPR^[14,51]. In the early phase of ER stress, the adaptive UPR serves a cytoprotective role mainly through three canonical signaling branches, IRE1, PERK, and ATF6^[52]. By attenuating global protein synthesis, upregulating molecular chaperones such as BiP, and enhancing ER-associated degradation, this response reduces the protein-folding burden and supports cellular proteostasis and ECM production^[24,51-53]. However, under the persistent pressure of inflammatory cytokines, abnormal mechanical loading, and oxidative stress, the ER stress level may exceed the reparative capacity of the UPR. At this juncture, the cell transitions into a maladaptive UPR phase^[54]. This phase is characterized by the upregulation of the pro-apoptotic factor

CHOP together with suppression of anti-apoptotic mechanisms, eventually leading to chondrocyte apoptosis, reduced cartilage matrix synthesis, and increased secretion of matrix-degrading enzymes (Fig. 2c)^[58].

Uehara et al. demonstrated that CHOP expression is markedly elevated in cartilage from patients with OA and animal models, whereas CHOP-deficient mice show less chondrocyte apoptosis and milder cartilage degeneration, confirming that maladaptive UPR aggravates OA progression^[56]. The transition from an adaptive to a maladaptive UPR can be influenced by inter-organelle stress signaling. In the OA microenvironment, persistent ER stress alters the MCSs between the ER and mitochondria, establishing a vicious feedback loop that disrupts organelle homeostasis and accelerates joint tissue degradation^[16,24,44,45].

4.2 The ER-Golgi axis and secretory homeostasis

Chondrocytes are embedded in the exceptionally dense extracellular matrix. Newly synthesized matrix macromolecules must undergo initial folding and quality control in the ER. Subsequently, these proteins are packaged into coat protein complex II (COPII)-coated vesicles and transported to the Golgi apparatus for complex glycosylation and final sorting^[56]. For chondrocytes, efficient trafficking between the ER and Golgi is essential for maintaining cellular function. In the pathological microenvironment of OA, inflammatory cytokines such as IL-1 β , oxidative stress, and abnormal mechanical loading may perturb the secretory apparatus of chondrocytes. Because Golgi integrity is essential for post-ER processing, sorting, and delivery of matrix proteins, stress-induced Golgi dysfunction may contribute to impaired secretory homeostasis^[57]. It remains unclear whether mechanical stress causes Golgi fragmentation in OA chondrocytes by remodeling Golgi matrix proteins. At present, stronger support for secretory dysfunction in chondrocytes comes from studies on ER-to-Golgi trafficking and glycosylation-related substrate transport. Hisanaga et al. demonstrated that protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK)-mediated translational control is required for collagen secretion in chondrocytes. When PERK is inhibited, misfolded proteins rapidly accumulate in the ER, transport of Col2a1 from the ER to the Golgi stalls and collagen macromolecules in cartilage are markedly reduced^[58]. A second pathological dimension of ER-Golgi dysfunction in OA was described by Kang et al., who identified a downregulation of the specific transporters responsible for delivering UDP-GlcNAc to the ER and Golgi, including members of the solute carrier (SLC) family: SLC35A3, SLC35B4, SLC35D1, and SLC35D2. In the damaged chondrocytes, this deficiency leads to an aberrant accumulation of UDP-GlcNAc in the cytoplasm, while its levels in the ER and Golgi lumen are reduced (Fig. 2d). This shift compromises the synthesis of glycosaminoglycan-rich proteoglycans, while increasing cytoplasmic O-GlcNAcylation, stabilizing GATA4, and driving the formation of a senescence-associated secretory phenotype^[59]. These findings have reshaped how we view the pathological significance of ER-Golgi crosstalk in OA. The senescent and inflammatory phenotype of OA chondrocytes is not only due to insufficient matrix replenishment; it also reflects a redirection of intracellular secretory flux, in which substrates that would normally enter the ER-Golgi pathway for matrix synthesis are instead diverted into programs that promote senescence and inflammation.

4.3 ER-lysosome interactions in maintaining degradative pathways

The interaction between the ER and lysosomes also depends on MCSs. Due to the unique anatomy of cartilage, chondrocytes cannot rely on exogenous immune cells to clear metabolic waste. When toxic macromolecules such as misfolded proteins and damaged mitochondria accumulate inside chondrocytes, these cells must depend on their own ER-lysosome system to degrade and remove endogenous toxic substrates in order to maintain homeostasis and cellular viability^[16,18,60].

In this process, the ER not only senses disturbances in unfolded proteins and calcium homeostasis, but may also influence lysosomal positioning and degradative function through ER-lysosome contact sites. Under normal physiological conditions, ER-resident vesicle-associated membrane protein-associated proteins (VAPs) can interact with the lysosomal cholesterol sensor oxysterol-binding protein-related protein 1L (ORP1L), thereby regulating late endosome positioning and autophagosome transport and fusion^[61,62]. Newly synthesized cholesterol and phospholipids in the ER are delivered through this route to the lysosomal membrane, helping to maintain both membrane fluidity and the acidic luminal environment. Additionally, the ER can release Ca²⁺ to lysosomes through this interface. Calcium homeostasis regulates lysosomal positioning along microtubules and is also closely linked to autophagy^[16,61].

During OA progression, abnormal mechanical loading and inflammatory factors in the microenvironment may destabilize subcellular structures in chondrocytes. When MCSs become disrupted under pathological conditions, ER-derived lipid transfer and Ca²⁺ transport are both impaired. This directly deprives lysosomes of part of their structural basis, leading to changes in membrane composition, and subsequently compromises the function of the vacuolar H⁺-ATPase (V-ATPase) on the lysosomal membrane. Once proton-pump activity is lost, the lysosomal lumen is no longer sufficiently acidic, and cathepsin activity drops sharply^[38]. Autophagosomes formed to clear toxic macromolecules in chondrocytes can no longer be efficiently degraded in deacidified lysosomes, leading to stagnation and blockade of autophagic flux^[27,38]. Using an inducible ER-stress mouse model, Hecht et al. showed that persistent ER stress restricted to adult articular cartilage is enough to induce early OA-like changes, including loss of proteoglycans, enhanced inflammation, increased cell death, and blocked autophagy^[63]. Likewise, work by Tang et al. on trehalose showed that in chondrocytes treated with the exogenous oxidative stress inducer tert-butyl hydroperoxide (TBHP) and in the destabilization of the medial meniscus (DMM)-induced OA model, the protective effect of trehalose is closely related to the restoration of autophagic flux. When autophagic flux was blocked again by chloroquine, this protective effect was markedly attenuated (Fig. 2e)^[64].

5 Lysosome-mTOR-autophagy signaling in OA

After examining the bidirectional interactions among the ER, mitochondria, and Golgi apparatus, a consistent organizational principle emerges: lysosomes function as the final node of the organelle interaction network. Whether clearing the unfolded proteins from the ER or degrading damaged mitochondria through

autophagy, the fate of upstream organelle crosstalk ultimately converges on the lysosome, where hydrolytic activity closes the final metabolic cycle.

Lysosomes were once viewed primarily as the endpoint for waste degradation. However, recent studies have shown that lysosomes are also involved in nutrient and metabolic sensing, determining whether cells proceed toward anabolism or degradation. In many cell types, mTORC1 is anchored on the lysosomal membrane through a series of scaffold proteins, including Rag GTPases and the V-ATPase complex^[65,66]. Under nutrient-dense conditions, the V-type proton pump senses amino acid signals within the lysosomal lumen and transmits these signals to Rag GTPases, thereby keeping mTORC1 active. Active mTORC1 promotes anabolic pathways while strongly suppressing autophagosome formation by phosphorylating core autophagy proteins such as Unc-51 like autophagy activating kinase 1 (ULK1)^[67]. In contrast, under stress conditions, lysosome-derived Ca^{2+} signals can activate calcineurin, triggering the dephosphorylation and nuclear translocation of TFEB, which initiates transcriptional programs associated with autophagy and lysosomal biogenesis (Fig. 2f)^[68-70]. Although these mechanisms have been defined largely in general cell-biological contexts, they provide an important framework for understanding lysosome-centered autophagy regulation in chondrocytes.

Yet in the pathological environment of OA, a striking paradox emerges. Despite the abundance of inflammatory signals and the accumulation of misfolded proteins, which are stimuli that would typically trigger stress-adaptive autophagy, mTORC1 remains abnormally active on the lysosomal surface, where it continues to suppress autophagic flux in chondrocytes.

Zhang et al. provided a mechanistic explanation for this phenomenon, demonstrating that mTOR is upregulated in human, mouse and canine OA cartilage. Crucially, the cartilage-specific deletion of mTOR leads to the upregulation of autophagy-related genes and significantly attenuates cartilage erosion in the DMM model^[71]. This conclusion is further reinforced by the findings showing that chondrocyte-specific knockout of autophagy-related 5 exacerbates age-related OA phenotypes in mice^[72]. Taken together, these findings indicate that proper activation of autophagy is essential for maintaining cartilage homeostasis.

The pathological influence of mTOR-autophagy signaling is not limited to chondrocytes. Lin et al. showed that mTORC1 is also abnormally activated in the subchondral preosteoblasts of both OA patients and mouse models. The activation of this pathway in subchondral preosteoblasts promotes abnormal bone formation and aggravates cartilage degeneration through increased secretion of C-X-C motif chemokine ligand 12 (CXCL12), whereas inhibition of this pathway reduces subchondral bone sclerosis and attenuates articular cartilage injury^[73].

6 Emerging migrasome-related interactions in OA

Migrasomes represent recently identified organelle-like structures that challenge the traditional definition of fixed intracellular organelles. These large vesicular bodies manifest as localized swellings at the distal tips or intersections of retraction fibers during cell migration^[74]. While direct evidence of migrasome function in OA is currently limited, a study in temporomandibular joint osteoarthritis (TMJ-OA) detected migrasomes in the synovial tissue

and synovial fluid^[75]. Utilizing single-cell transcriptomics and *in vitro* assays, the authors proposed that these synovial migrasomes originate primarily from infiltrating M1 macrophages. Using a biomimetic synovium-cartilage organoid co-culture system, they demonstrated that inhibiting the transfer of migrasomes from the synovium to the cartilage suppressed autophagic activity within the cartilage organoids. Conversely, the exogenous supplementation of M1-derived migrasomes restored autophagic flux^[75]. In a TNF- α -induced chondrocyte injury model, migrasome treatment improved cellular viability and stimulated proteoglycan synthesis while downregulating the catabolic enzymes MMP-13 and ADAMTS-5. Furthermore, in a rat temporomandibular joint-OA model, the intra-articular injection of migrasomes attenuated condylar cartilage erosion and subchondral bone remodeling^[75]. Whether similar migrasome-mediated protective mechanisms operate in knee or hip OA remains unknown.

Jiao et al. introduced the landmark concept of “mitocytosis.” This biological process involves the sequestration and subsequent disposal of damaged mitochondria via migrasomes in cells undergoing mild migratory stress. Their findings demonstrated that the activation of this pathway is essential for maintaining mitochondrial membrane potential. Conversely, inhibiting migrasome-mediated mitochondrial clearance leads to a significant decline in mitochondrial membrane potential and can even impair the systemic functions of neutrophils *in vivo* (Fig. 2g)^[76]. Given that OA progression is characterized by mitochondrial depolarization, elevated oxidative stress, and disturbed mitochondrial homeostasis, it is plausible that migrasomes within the joint microenvironment may facilitate the removal of dysfunctional mitochondria from chondrocytes. Thus, migrasomes could represent a previously unrecognized branch of the mitochondrial quality control network. However, direct experimental evidence validating this mechanism in the context of OA remains to be established.

Only in recent years has the relationship between migrasomes and the ER begun to be described in more mechanistic detail. Current evidence suggests that the ER contributes to migrasome biogenesis primarily by supplying key components, including cholesterol and Ca^{2+} , through contact sites associated with the plasma membrane, thereby supporting membrane expansion, structural stability, and the eventual release of migrasomes^[77]. Experimental studies have shown that Ca^{2+} is a limiting factor in migrasome formation. In this process, the Ca^{2+} -binding protein Synaptotagmin 1 (Sytl) is recruited to sites of migrasome initiation, where it facilitates the transition from local membrane swelling to the formation of unstable precursors. These structures are subsequently stabilized through the sequential assembly of tetraspanins. In addition, chelation of Ca^{2+} with 1,2-bis(2-aminophenoxy) ethane-N,N,N',N'-tetraacetic acid (BAPTA) markedly inhibits migrasome formation^[78] (Fig. 2h).

These findings raise the possibility that migrasome formation may be sensitive to changes in the ER- Ca^{2+} axis. Given that ER homeostasis and intracellular Ca^{2+} signaling are frequently disrupted in osteoarthritic chondrocytes, it is plausible that the efficiency of migrasome formation and release may also be altered under these conditions. However, this hypothesis remains speculative at present, as direct experimental evidence is still lacking, and the potential link warrants further investigation. The major organelle pairs, regulatory pathways, and pathological consequences in OA discussed above are summarized in Table 1.

Table 1 Organelle crosstalk and pathological alterations in osteoarthritis.

Organelle Pairs	Key Regulatory Molecules/Pathways	Pathological Alterations in OA	Cellular Fate & Matrix Effects
ER - Mitochondria	MAMs, LONP1, BiP	Abnormal mechanical loading and inflammatory stimulation trigger persistent ER stress; aging-related downregulation of LONP1 impairs mitochondrial homeostasis; excessive Ca^{2+} transfer from the ER into the mitochondrial matrix drives calcium overload, mitochondrial depolarization, and robust ROS accumulation.	Disrupts the cytoprotective unfolded protein response (UPR), establishes a vicious feedback loop at the ER-mitochondria interface, and ultimately commits chondrocytes to senescence or apoptosis.
Mitochondria - Lysosome	Mitophagy, Parkin, Fis1	Insufficient lysosomal acidification and aging-related downregulation of LAMP1/LAMP2 directly block downstream autophagic and mitophagic flux; depletion of Fis1 triggers a broad disruption of mitochondrial, peroxisomal, and lysosomal networks.	Causes the aberrant accumulation of dysfunctional mitochondria and elevated oxidative stress, triggering selective upregulation and translocation of BAX to the outer mitochondrial membrane to induce apoptosis.
ER - Golgi	Coat protein complex II-coated vesicles, PERK, SLC35 family (SLC35A3/B4/D1/D2)	Inflammatory cytokines and altered cellular microenvironment perturb the secretory apparatus; PERK-mediated translational control is impaired; downregulation of SLC35 family transporters reduces UDP-GlcNAc levels within the ER and Golgi lumens.	Stalls the transport of Col2a1, leading to matrix synthesis deficiency; cytosolic retention of UDP-GlcNAc increases O-GlcNAcylation and stabilizes GATA4, driving a senescence-associated secretory phenotype (SASP).
ER - Lysosome	MCSs, VAP proteins, ORPIL, V-ATPase	Pathological microenvironments disrupt ER-lysosome membrane contact sites (MCSs), impairing ER-derived lipid transfer and Ca^{2+} transport; this deprives lysosomes of structural integrity and compromises membrane V-ATPase proton pump activity.	Causes lysosomal deacidification and sharply reduces cathepsin activity, leading to the stagnation and blockade of autophagic flux, which induces early OA-like changes, inflammation, and cell death.
Lysosome - mTOR - Autophagy	mTORC1, V-ATPase, Rag GTPases, ULK1, TFEB	In OA cartilage, mTOR signaling is upregulated and protective autophagy is insufficiently activated despite persistent inflammatory and proteotoxic stress. Canonical Rag GTPase and V-ATPase-dependent lysosomal recruitment of mTORC1 provides a mechanistic framework, but its OA-specific regulation in chondrocytes remains to be fully defined.	Hyperactivated mTORC1 phosphorylates ULK1 and suppresses TFEB nuclear translocation, severely blocking protective autophagy; in subchondral bone, it promotes sclerosis and CXCL12 secretion, aggravating cartilage erosion.
Migrasome - ER/Mitochondria	Mitocytosis, Syt1, Tetraspanins	Synovial migrasomes originate primarily from infiltrating M1 macrophages; migrasome biogenesis requires ER-plasma membrane contact sites (PMCS) for cholesterol and Ca^{2+} supply, which may be altered by the dysregulated ER- Ca^{2+} axis in OA.	M1 macrophage-derived migrasomes restore autophagic flux and stimulate proteoglycan synthesis while downregulating MMP-13/ADAMTS-5.

7 Heterogeneity of organelle crosstalk across joint cell types

With the expansion of OA research, it has become increasingly clear that abnormal organelle crosstalk is not confined to chondrocytes. Pathological alterations have been described in synoviocytes, macrophages, and various subchondral bone-resident cells as well^[79-83] (Fig. 3).

7.1 Chondrocytes: breakdown of mitochondrial quality control

Chondrocytes remain the most studied cell type in this domain. As the sole cellular component of articular cartilage, chondrocytes are profoundly dependent on stable mitochondrial bioenergetics, robust autophagic flux, and the efficient management of proteotoxic stress. Once this delicate equilibrium is disrupted, mitochondrial impairment, oxidative stress, and cellular senescence typically manifest as a synchronized pathological cascade rather than isolated events^[79-81]. Mechanistically, Bu et al. demonstrated that circular RNA PAFAH1B2 (circPAFAH1B2) is significantly upregulated in OA chondrocytes, where it exacerbates mitochondrial dysfunction by interfering with caseinolytic peptidase B protein homolog (CLPB)-mediated protein homeostasis^[79]. Complementary studies further suggest that biomaterial-based or pharmacological interventions that improve mitochondrial function or enhance mitophagy can restore aspects of metabolic homeostasis in chondrocytes^[80, 81]. In this cell type, abnormal organelle crosstalk is recognized as a failure of

mitochondrial quality control, which subsequently drives chondrocyte apoptosis and dysregulated matrix metabolism^[80].

7.2 Synovial cells: inflammatory amplification and paracrine relay

In fibroblast-like synoviocytes (FLS), the emphasis shifts from cell-autonomous defects toward intercellular propagation of inflammatory and metabolic signals within the joint. Current evidence underscores that exosome-mediated intercellular communication is a pivotal driver of this process. Liu et al. reported that exosomes released from inflammatory FLS can effectively enhance glycolysis in macrophages, promoting M1-type polarization. This shift indirectly aggravates OA-like changes in the chondrocytes^[83]. Furthermore, Miron et al. also emphasized that exosomes have become central to regenerative medicine, as they modulate not only cargo transfer, but also inflammation and tissue repair^[84]. Therefore, synovial cells in the OA context act less as isolated injured cells and more as biological amplifiers that sustain and exacerbate the disturbed joint microenvironment.

7.3 Subchondral bone-related cells: remodeling bias in the deep joint compartment

The heterogeneity observed in subchondral bone-resident cells is fundamentally linked to aberrant remodeling rather than conventional cartilaginous degeneration alone. Zuo et al. demonstrated that mitochondria-targeted, selenium-doped carbon quantum dots can effectively penetrate the dense cartilage barrier to

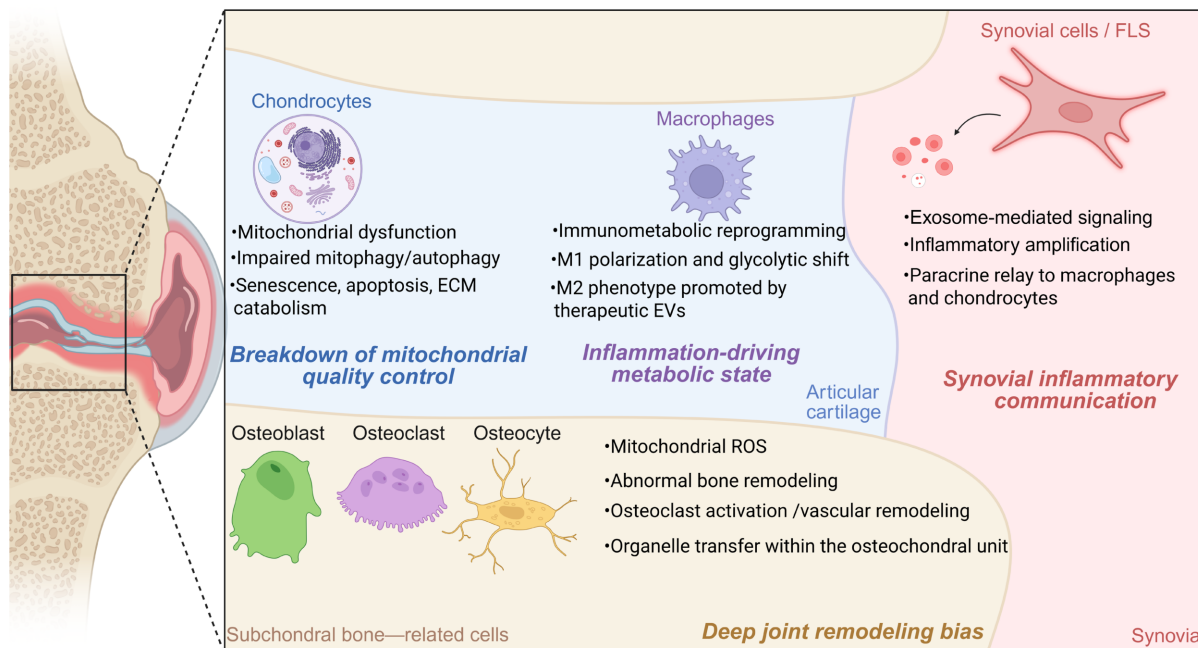


Figure 3 Cell-type heterogeneity of organelle crosstalk in the osteoarthritic joint. This figure summarizes distinct patterns of organelle dysfunction and intercellular communication across major joint cell types during osteoarthritis progression (Created with BioRender.com).

reach the subchondral compartment. After reaching the subchondral compartment, these mitochondria-targeted particles scavenged ROS in macrophage-lineage cells, inhibited osteoclast differentiation and function, and reduced H-type vessel invasion in vivo^[82]. These findings suggest that within the deep osteochondral compartment, mitochondrial abnormalities are not merely markers of cellular injury; they are active drivers of bone resorption, pathological vascular remodeling, and the broader structural imbalance across the cartilage-bone interface. Consequently, whereas mitochondrial dysfunction in chondrocytes commonly contributes to senescence or apoptosis, mitochondrial oxidative stress in subchondral bone-related cells can promote disordered bone remodeling^[82].

7.4 Macrophages: immunometabolic reprogramming

Macrophages illustrate another facet of organelle heterogeneity in OA. In these cells, the central pathological issue is not merely a localized energy deficiency, but the complex manner in which metabolic reprogramming dictates the inflammatory phenotype. Specifically, FLS-derived exosomes have been shown to drive M1-type polarization by upregulating glycolytic flux^[83]. Conversely, EVs harvested from preconditioned mesenchymal stem cells possess the capacity to pivot macrophage metabolism toward a more oxidative state, thereby fostering a pro-resolving M2 phenotype and improving the joint's overall inflammatory milieu^[85]. These findings suggest that mitochondrial immunometabolism and EV-mediated intercellular signaling are closely linked to macrophage phenotypic reprogramming in OA. Its primary significance lies in its role as a persistent driver of chronic inflammation, rather than as a direct mediator of isolated cell loss.

7.5 Osteocytes, osteoblasts, and osteoclasts: crosstalk within the osteochondral unit

While direct evidence remains more limited for osteocytes,

osteoblasts, and osteoclasts, accumulating studies suggest that these cell types are active participants in OA pathogenesis. Ma et al. reported that cholesterol enhances osteocyte-to-chondrocyte mitochondrial transfer through intercellular nanotubes. Transferred osteocyte mitochondria, which include a Nudt8-enriched subpopulation, increase cytosolic mtDNA in recipient chondrocytes and activate cGAS-STING signaling^[86]. That finding is particularly significant as it identifies organelle transfer as a novel mechanism for inflammatory activation that transcends traditional tissue boundaries. In comparison, current research on osteoclasts has primarily focused on the nexus between mitochondrial ROS and pathological bone resorption^[82], while evidence in osteoblasts remains quite limited. Taken together, these data suggest that the osteochondral unit should be viewed not simply as a collection of adjacent tissues, but as a metabolically integrated system in which organelle dysfunction is dynamically transmitted across diverse cell types.

8 Discussion and perspectives

Collectively, it is increasingly evident that organelle dysfunction in OA does not occur in isolation. Mitochondrial impairment, ER stress, lysosomal insufficiency, aberrant secretory trafficking, and impaired autophagic flux are intrinsically linked, forming a complex pathological network rather than a series of separate events. Often, a localized disturbance in one organelle propagates to others, culminating in a systemic intracellular homeostatic collapse. This explains why, in early-stage OA, chondrocyte injury may appear as a discrete organelle defect; however, as the disease progresses, such explanations become insufficient. In chondrocytes, the critical determinant of cellular fate is not the failure of a single organelle, but the functional integrity of the entire organelle interactome. Once this collective equilibrium is broken, cells are inexorably driven toward senescence, apoptosis, and catabolic matrix remodeling. Consequently, organelle crosstalk is not merely

a peripheral mechanistic detail, but the fundamental architecture through which subcellular stress translates into macroscopic cartilage degeneration. Despite these insights, current evidence remains disproportionate. While the mitochondria-ER and mitochondria-lysosome axes have been extensively characterized, research regarding the Golgi apparatus, peroxisomes, migrasomes, and intercellular organelle transfer remains limited.

A significant challenge lies in the prevailing reliance on endpoint markers, such as ROS accumulation, mitochondrial depolarization, or lysosomal deacidification. While informative, these metrics capture the resultant state of dysfunction rather than the dynamic spatiotemporal process of organelle crosstalk. Although we have established that organelle interactions are pivotal in OA, we lack a granular understanding of the "tipping points" where these interactions shift from adaptive/protective to maladaptive/pathogenic. Future investigations must move beyond static observations toward dynamic imaging, time-course flux analysis, and *in situ* models that more faithfully recapitulate the multifaceted joint microenvironment.

From a translational perspective, targeting organelle crosstalk has significant therapeutic potential, yet still remains complex. Preclinical models have shown that interventions aimed at restoring autophagic flux, acidifying lysosomes, or modulating ER stress signaling are promising. However, given the heterogeneity and chronicity of OA, it is unlikely that targeting a single pathway with a "silver bullet" will suffice to restore joint homeostasis. Response patterns vary significantly across different cell types and disease stages. Therefore, future therapeutic strategies should shift toward precision interventions that prioritize optimal timing, targeted local delivery, and stage-specific molecular matching. Ultimately, studying organelle crosstalk redefines OA as not merely a disease of "wear and tear", but as a continuous, maladaptive dialogue between intracellular compartments, diverse cell populations and distinct joint tissues. Understanding this dialogue will be crucial for developing the next generation of disease-modifying osteoarthritis drugs.

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Data available statement

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Author contribution

K.Z. designed the work. H.G. and X.L. wrote the initial draft of this paper. H.G. and X.L. organized the figures. K.Z. and X.Q. reviewed and edited the manuscript. All the authors revised the manuscript and approved the final version.

Ethics approval and consent

N/A

Consent for publication

All authors agree to publish.

Conflicts of interest

The authors have no competing interests to declare that are relevant to the content of this article.

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