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REVIEW

The Role of Mitochondrial Regulation in Macrophage Polarization: Implications for the Pathogenesis of Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is an autoimmune arthropathy closely associated with chronic inflammation, whose pathogenesis involves macrophages, particularly M1 macrophage-induced inflammatory responses. Mitochondria, as key organelles governing macrophage metabolism and function, regulate M1/M2 macrophage polarization through multiple pathways and signaling molecules, thereby inducing immune and inflammatory responses that contribute to RA development. Therefore, this paper delves into the intricate mechanisms by which mitochondria regulate macrophage-specific polarization. These pathways encompass metabolic processes, signaling molecules, mitochondrial dynamics, mitochondrial-associated molecules, mitochondrial autophagy, ion homeostasis, and mitochondrial translocation. The study underscores the pivotal role of mitochondria in macrophage-specific polarization and highlights the potential for basic research to intervene in RA by modulating Mitochondrial metabolism, mitochondrial dynamics, mitochondrial autophagy, and mitochondrial translocation to promote M1-to-M2 macrophage conversion and suppress RA inflammatory responses. This holds significant implications for repairing RA-induced bone destruction and advancing clinical treatment.

Keywords: rheumatoid arthritis, macrophages, M1/M2 polarization, inflammatory response, pathogenesis

Introduction

Rheumatoid arthritis (RA) is an autoimmune joint disorder strongly linked to chronic inflammation. Its pathological features are primarily driven by immune cell infiltration (ICI) and synovial lesions, which can result in joint destruction, deformity, and ultimately functional impairment.[1,2] The underlying mechanisms of bone destruction in RA are mainly attributed to persistent inflammation, immune cell dysfunction, and excessive release of inflammatory mediators. Macrophages play a central role in bone immunity. Depending on both in vivo and in vitro conditions, they can differentiate into classically activated M1 macrophages or alternatively activated M2 macrophages. These polarized subtypes regulate osteocyte activity and contribute to maintaining bone homeostasis.[3]

In RA, the aberrant immune microenvironment disrupts the balance between M1 and M2 macrophages, favoring M1 polarization. This shift results in an increased release of inflammatory cytokines, thereby promoting the progression of inflammatory bone disease.[4,5] Consequently, modulating macrophage polarization represents a promising therapeutic approach for RA-related bone destruction. Further research into the mechanisms of inflammatory macrophage polarization is therefore warranted.

Mitochondria, commonly referred to as the "powerhouse" of the cell, are essential organelles responsible for critical functions including energy metabolism, substance synthesis, and signal transduction. The functional state of mitochondria is closely linked to macrophage polarization, with mechanisms involving alterations in metabolic pathways, regulation of signaling molecules, mitochondrial dynamics, mitochondrial-associated molecules, mitochondrial autophagy, as well as ion

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homeostasis and mitochondrial translocation. Basic research indicates that biological materials can promote the conversion of M1 macrophages to M2 macrophages by intervening in mitochondrial metabolism, mitochondrial ion homeostasis, and mitochondrial translocation.[6] For RA treatment, targeting the suppression of M1 macrophages and upregulating the number and activity of M2 macrophages can modulate the immune response in RA, suppress inflammatory reactions, and hold significant implications for repairing RA-induced bone destruction and clinical management.

Macrophage Polarization

Macrophages are a highly plastic and dynamic cell population capable of altering their phenotype and function in response to various environmental stimuli. This adaptive process is known as macrophage polarization.[7] Typically, macrophages polarize into either classical (M1) or alternative (M2) phenotypes, both of which play roles in the development of RA. A non-polarized state, referred to as M0, also exists.

Studies have shown that M0 macrophages undergo polarization upon exposure to cytokines and other factors in the microenvironment. The M1 phenotype, which is pro-inflammatory, can be induced by Th1 cytokines, such as interferon-γ (IFN-γ). Upon activation, M1 macrophages release large quantities of IL-1, IL-6, IL-12, TNF-α, nitric oxide (NO), and reactive oxygen species (ROS), along with other pro-inflammatory and immunostimulatory cytokines.[8] Chronic activation of M1 macrophages can trigger excessive immune responses, contributing to persistent inflammation and the onset of inflammatory diseases.[9]

Cytokines IL-4 and IL-13 bind to the IL-4Rα receptor, promoting M2 macrophage polarization. M2 macrophages are further classified into four subtypes: M2a, M2b, M2c, and M2d.[10] M2a macrophages, induced by IL-4 or IL-13, are also known as wound-healing macrophages. M2b macrophages, stimulated by immune complexes, TLR ligands, or IL-1β, are referred to as regulatory macrophages. M2c macrophages are elicited by glucocorticoids, IL-10, or TGF-β, while M2d macrophages, induced by TLR antagonists, are termed tumor-associated macrophages (TAM).[11] M2-type macrophages produce anti-inflammatory cytokines, including IL-10, IL-4, transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), and platelet-derived growth factor (PDGF). These cytokines suppress T-cell activation and proliferation, participate in Th2-type immune responses, and contribute to tissue repair and angiogenesis (Figure 1). [12,13]

Macrophage Polarization and RA

Macrophage-Induced Inflammation in RA

Research on the role of macrophages in inflammatory responses is progressing rapidly. Infiltrating macrophages contribute to various inflammatory cell states in RA and synovitis by orchestrating cytokine networks (Figure 2).[14]

(1) In RA, an aberrant immune environment causes abnormal macrophage activation, impaired phagocytosis, decreased clearance of apoptotic cells, and increased apoptotic cell accumulation. These changes promote the generation of autoantigens and autoantibodies, thereby aggravating inflammation.[15]
(2) Macrophages facilitate T-cell migration and abnormal activation. They promote Th17 differentiation, decrease the Th1/Th17 ratio, and inhibit Treg differentiation. Moreover, they stimulate osteoclastogenesis by secreting cytokines such as IL-17 and IL-26. This leads to abnormal B-cell activation and the production of specific antibodies targeting macrophage-presented antigens, further amplifying inflammatory responses.[16]
(3) An imbalance in the M1/M2 macrophage ratio is strongly linked to RA pathogenesis. Hyperactivation of M1 macrophages enhances the release of pro-inflammatory cytokines, including IL-6, iNOS, TNF-α, and IL-1β, intensifying local inflammation. Conversely, impaired M2 polarization diminishes anti-inflammatory cytokine production and immune tolerance.[8]
(4) Macrophages in synovial tissue and bodily fluids induce chemotaxis and endothelial cell proliferation, promote vascular endothelium formation, and recruit inflammatory cells. By producing vascular endothelial growth factor (VEGF), they further exacerbate RA-associated inflammation.[17]

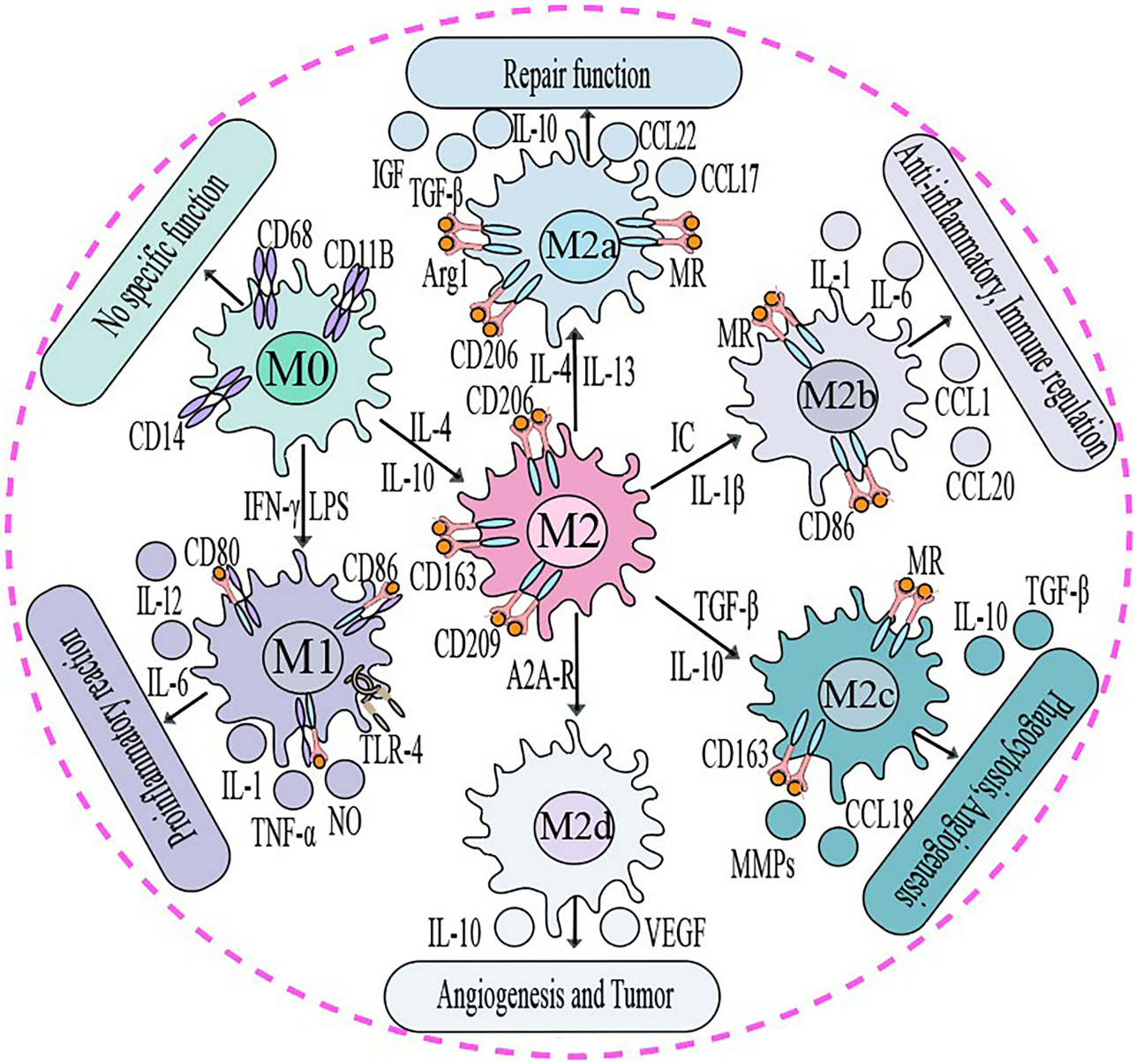

Figure 1 Macrophage Phenotypic Conversion and Surface Active Substance Expression.

Notes: When M0 macrophages are exposed to stimuli, they undergo polarization. M1 macrophages can trigger immune responses and chronic inflammation; M2 macrophages are further subdivided into M2a, M2b, M2c, and M2d, each with distinct functions primarily associated with suppressing inflammation and promoting tissue repair.

Abbreviations: IFN-γ, interferon γ; LPS, lipopolysaccharide; IGF, insulin like growth factor; TGF-β, transforming growth factor β; CCL, C C motif ligand; Arg1, arginase-1; IC, immune complex; A2A-R, A2Aadenosine receptor; IL, Interleukins; TNF-α, Tumor necrosis factor α; VEGF, vascular endothelial growth factor.

Macrophage Polarization and RA Bone Cells

Bone metabolism is maintained by the dynamic balance between osteoclasts (OCs) and osteoblasts (OBs). OCs resorb bone by migrating to and degrading the bone surface, while OBs regenerate bone tissue. Disruption of this balance, such as excessive OC activity surpassing OB function, leads to bone destruction in RA.

M1 macrophages serve as precursors to OCs and promote their differentiation. They also release pro-inflammatory cytokines like TNF-α and IL-1 that stimulate bone resorption. TNF-α is the most potent inducer of OC formation secreted by M1 macrophages. It directly enhances the generation of OC precursors and upregulates RANKL expression, further driving osteoclastogenesis.[18]

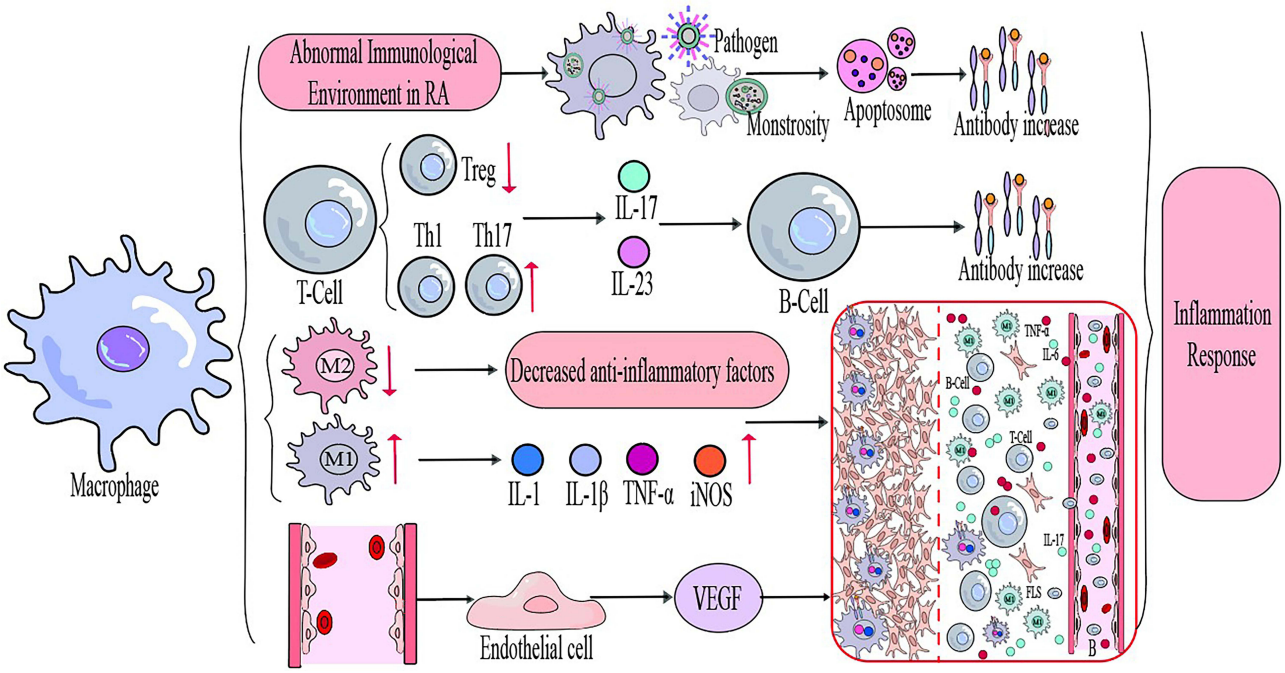

Figure 2 Macrophages in the Inflammatory Response and Related Mechanisms in RA Patients.
Notes: Macrophages induce autoantibodies, inflammatory mediators, and vascular endothelium in RA through different pathways.
Abbreviations: VEGF, vascular endothelial growth factor; iNOS, inducible nitric oxide synthase; IL, Interleukins.

IL-1, the most prominent pro-inflammatory cytokine in the interleukin family, also promotes OC formation and bone resorption. It induces the release of TNF-α and IL-6, compounding inflammatory damage.[19] In contrast, anti-inflammatory M2 macrophages secrete IL-4 and IL-10, which inhibit OC precursor differentiation and suppress OC formation by downregulating pro-inflammatory cytokines such as TNF-α, IL-1, and IL-6.[20]

Macrophages are also essential for OB maintenance. Timely transition from the M1 to M2 phenotype enhances OB proliferation, adhesion, and mineralization, and increases the expression of osteogenic genes including RUNX2, ALP, COL1A1, OPN, and OCN. Thus, M2 macrophages are key regulators of OB differentiation and osteogenesis.[21] In contrast, M1 macrophages negatively regulate OBs. For instance, TNF-α secreted by M1 macrophages suppresses RUNX2 expression through Smurf1 and Smurf2-mediated protein degradation, thereby inhibiting OB activation. Additionally, TNF-α downregulates OB differentiation by inhibiting IGF-1 signaling (Table 1). [22]

Table 1 Macrophage Polarization and RA Bone Cells

Macrophage	Bone Cells	
	Direct Effect	**Indirect Effect**
M1 macrophages	As OCPs, differentiate into OC	A. Secretes TNF-α, IL-1, and IL-6, upregulating the RANKL/OPG signaling pathway to promote both OCP formation and osteoblast differentiation. B. Secretes TNF-α, which inhibits osteoblast activation by regulating Smurf1 and Smurf2 (degrading RUNX2 protein).
M2 macrophages	Promote OB differentiation and activity	A. Promotes expression of osteogenic genes Runx2, ALP, OPN, COL1A, and OCN, thereby facilitating osteoblast differentiation; B. Secretes IL-4 and IL-10 to inhibit osteoblast precursor cell (OPC) differentiation into osteocytes, while suppressing pro-inflammatory factors such as TNF-α, IL-1, and IL-6 to reduce osteocyte numbers.

Abbreviations: OC, osteoclasts; OB, osteoblasts; IL, Interleukins; TNF-α, Tumor necrosis factor α; ALP, Alkaline Phosphatase; OPN, Osteopontin; COL1A, Collagen Type I Alpha Chain; OCN, Osteocalcin.

M1-Type Macrophages Exacerbate RA, While M2-Type Macrophages Alleviate It

Studies have shown that the abundance of M1-type macrophages correlates positively with synovial hyperplasia, DAS28 scores, and joint erosion in RA patients.[23] Notably, M1 macrophages are predominantly observed in individuals with active RA[24] and are considered major producers of inflammatory mediators such as TNF-α, IL-1, and IL-6. These cytokines promote Th17 cell differentiation, stimulate osteoclastogenesis, and thereby accelerate RA progression.[25,26] In addition, M1-type macrophages in synovial tissue and fluid mediate endothelial cell chemotaxis and proliferation, facilitate neurofibril formation and immune cell infiltration (ICI), and further intensify the RA inflammatory response through VEGF production.[27,28]

An increase in anti-inflammatory M2 macrophages is a key indicator of RA remission, highlighting the importance of shifting M1 macrophages toward the M2 phenotype in RA therapy. M2 macrophages suppress OC formation and support the function of osteoblasts and bone marrow-derived stem cells, which are essential for bone synthesis, mineralization, and repair.[29]

Mitochondrial Function in RA and Macrophage Polarization

Mitochondrial Metabolism

Mitochondrial Glycolysis Promotes M1 Macrophage Polarization and Induces RA Inflammation

Macrophages undergo profound metabolic reprogramming during polarization. M1-type (classically activated) macrophages exhibit enhanced glycolytic metabolism, characterized by increased glucose uptake, lactate production, and decreased oxygen consumption, which supports their proinflammatory activity.[30] During the transition from M0 to M1 macrophages, glycolysis is upregulated, with elevated activity and expression of key glycolytic enzymes, including hexokinase (HK) and glucose-6-phosphate dehydrogenase (G-6-PD). This upregulation increases NO and ROS, which in turn activate the NF-κB signaling pathway, driving RA-related inflammation.[31,32]

Therefore, targeting mitochondrial glycolysis may offer a novel strategy for treating macrophage polarization-related diseases such as RA. IFN-γ or LPS has been shown to induce M1 macrophage polarization by enhancing glycolysis via the UDPG/P2Y14/STAT1 signaling pathway. Inhibition of this pathway can suppress inflammation.[33–35] HIF-1α is a key regulator of glycolysis in M1 polarization and is significantly upregulated in inflammatory conditions; its inhibition can reduce M1 polarization and impair bactericidal function.[36,37] Furthermore, the AMPK pathway—implicated in RA pathogenesis—has been found to reprogram glucose metabolism during M1 polarization, promoting cell proliferation and glycolytic activity.[38] In summary, HIF-1α and AMPK are central regulators of mitochondrial glycolysis, and represent promising therapeutic targets for diseases involving macrophage polarization.

Mitochondrial Oxidative Phosphorylation Promotes M2 Macrophage Polarization to Suppress RA Inflammation

M2-type macrophages (alternatively activated macrophages) primarily rely on enhanced oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO)—energy-efficient metabolic pathways that support their anti-inflammatory and tissue-repair functions.[39] IL-4 and IL-10 are the main inducers of M2 polarization. IL-4 activates STAT6, which enhances mitochondrial OXPHOS, further activating PGC1β, thereby promoting M2 polarization.[40] IL-10 indirectly facilitates M2 polarization by inhibiting glucose uptake and glycolysis in M1 macrophages, while enhancing OXPHOS. This shift reduces the M1/M2 ratio and suppresses RA-related inflammation.[41] Notably, inhibition of M2-associated OXPHOS can promote M1 macrophage polarization and pro-inflammatory activity.[42] In addition, activation of the AMPK signaling pathway enhances mitochondrial enzyme activity to support OXPHOS,[38] which may favor M2 polarization. However, whether AMPK activation selectively promotes M1 or M2 polarization remains to be fully clarified.

FAO also modulates M2 macrophage polarization. It not only supplies energy but is also directly linked to the M2 anti-inflammatory phenotype.[43] Moreover, FAO is essential for plasmacytoid dendritic cell (pDC) function. Activation of pDCs increases FAO and OXPHOS, which are crucial for initiating antiviral responses.[44]

Mitochondrial Signaling Molecules Participate in Macrophage Polarization in RA

ROS Mitochondria are the primary source of ROS in cells. ROS participate in immune regulation, including signal transduction, redox balance, and autophagy. They are closely linked to the activation and function of M1 macrophages

and are involved in inflammatory signaling pathways such as NF-κB, MAPK, and Nrf2.[45,46] For example, M1 macrophages produce large amounts of ROS in response to lipopolysaccharide (LPS) stimulation. These ROS not only exert direct antibacterial effects but also act as signaling molecules to promote the secretion of inflammatory cytokines.[47]

In RA patients, the NF-κB/HIF-1α signaling cascade is significantly activated, resulting in increased ROS levels and enhanced M1 polarization, which further exacerbates disease progression.[48] Inhibiting this signaling axis may promote the transition from M1 to M2 macrophages, which is crucial for RA treatment. Additionally, the ROS–ATM–Chk2 pathway has also been identified as a contributor to M1 polarization.[49] Therefore, the ROS-ATM-Chk2 axis and HIF-1α/NF-κB axis are implicated in abnormal macrophage polarization, directly contributing to the pathogenesis and progression of RA. Consequently, future basic research may consider targeting these pathways to reduce the proportion of M1 macrophages, thereby exerting therapeutic effects on RA.

The role of ROS in M2 polarization remains controversial. Some studies suggest that the Th2 cytokine IL-25 can induce ROS production, enhance the activity of mitochondrial respiratory chain complexes, activate AMPK, and trigger mitochondrial autophagy, thereby promoting M2 polarization in monocytes.[50] Others report that Astragalus polysaccharides increase ROS through the Nrf2/HO-1 pathway, inhibit the release of pro-inflammatory cytokines (TNF-α, IL-6, IL-12), and promote M2 macrophage polarization.[51]

In contrast, some researchers have found that reducing ROS levels can also induce M2 polarization and suppress inflammation.[52,53] It is noteworthy that the role of mitochondrial reactive oxygen species (mtROS) in macrophage polarization is dual-sided. Moderate levels of mtROS can promote macrophage polarization and function. From the perspective of RA pathogenesis, mtROS can promote both M1 and M2 macrophage polarization, but overall, the effect of promoting M1 macrophage polarization is stronger than that of promoting M2 polarization. On the other hand, excessive mtROS may lead to oxidative stress and cellular damage, causing macrophage apoptosis.

Metabolite regulation Pro-inflammatory M1 macrophages acquire energy mainly through glycolysis. During this process, the tricarboxylic acid (TCA) cycle is disrupted, leading to the abnormal accumulation of metabolites such as citrate, succinate, and itaconate.[54] Mitochondrial metabolites like succinate and citrate act as signaling molecules in macrophage polarization.

For instance, succinate, released at sites of tissue damage or in pro-inflammatory microenvironments, functions as a pro-inflammatory factor.[55] It enhances macrophage migration, promotes their activation, and stabilizes HIF-1α, thereby inducing the transcription of glycolytic genes and sustaining M1 metabolism.[56] Succinate also binds to its receptor SUCNR-1 on the macrophage surface, triggering downstream signaling that leads to the production of pro-inflammatory cytokines and chemokines.[57] Macrophages act as both producers and targets of succinate. In inflammatory diseases such as RA, succinate secreted by macrophages upregulates SUCNR-1 expression on M1 macrophages and promotes IL-1β secretion, worsening arthritis.[58]

When citrate accumulates abnormally and enters the cytoplasm, it contributes to lipid synthesis, gluconeogenesis, and the production of NADPH and acetyl-CoA. Acetyl-CoA is especially important for protein acetylation.[59] During M1 polarization, acetyl-CoA modulates the expression of proteins such as NF-κB, IL-6, and IL-10 through acetylation.[59] Studies suggest that citrate accumulation drives M1 polarization by upregulating the mitochondrial citrate carrier (CIC) and reducing isocitrate dehydrogenase activity, thereby impairing the TCA cycle.[60]

Itaconic acid is primarily known for its antimicrobial effects. In macrophages, overexpression of ACOD1 (which encodes cis-aconitate decarboxylase) converts cis-aconitate into itaconate. Itaconate inhibits succinate dehydrogenase, causing succinate accumulation and indirectly promoting M1 macrophage polarization.[61]

Mitochondrial Dynamics are Associated with Macrophage Polarization in RA

Mitochondrial Fission Abnormalities Contribute to M1 Macrophage Polarization

The size, shape, and number of mitochondria dynamically change in response to cellular energy demands and mitochondrial health. These changes are governed by mitochondrial dynamics, which include tightly regulated fission and fusion processes.[62] Mitochondrial fusion maintains normal mitochondrial function, while fission is activated in response to damage or stress to remove dysfunctional mitochondria. Mitochondrial fission is a complex event involving multiple pathways, with the endoplasmic reticulum (ER)–mitochondria signaling axis playing a central role.[63] This interaction

occurs at mitochondria-associated membranes (MAMs), where tubular ER structures encircle mitochondria, initiating early fission events.[64] These sites subsequently recruit fission machinery and support the process in an actin-dependent manner.

Proper mitochondrial function is critical for the physiological activity of various cells, particularly immune cells like macrophages. During RA-related inflammation, macrophages undergo metabolic reprogramming, and mitochondrial dynamics appear to contribute to these changes. Studies have shown that lipopolysaccharide (LPS), a primary M1 polarization stimulus, induces mitochondrial fragmentation at 0.5 μg/mL, resulting in small fragmented mitochondria and increased Drp1 dephosphorylation. In contrast, IL-4, which promotes M2 polarization, induces mitochondrial fusion and upregulates fusion-related proteins such as Mfn1, Mfn2, Fam73a, and Fam73b.[65]

DRP1 is a well-established regulator of mitochondrial fission.[66] Hyperactivation of DRP1 during fission leads to mitochondrial dysfunction, characterized by increased outer membrane permeability, decreased ATP production, elevated ROS and cytochrome c release, and enhanced glycolysis in macrophages.[67] These changes are closely linked to M1 polarization. DRP1 has also been implicated in OC differentiation.[68] During this process, M1 macrophages promote OC formation through inflammatory mediators and mitochondrial metabolic reprogramming (Figure 3).[69] Therefore, Drp1 signaling has been identified as a key factor promoting macrophage polarization toward a proinflammatory state and metabolic reprogramming, closely associated with RA pathogenesis, positioning it as a potential therapeutic target for RA.

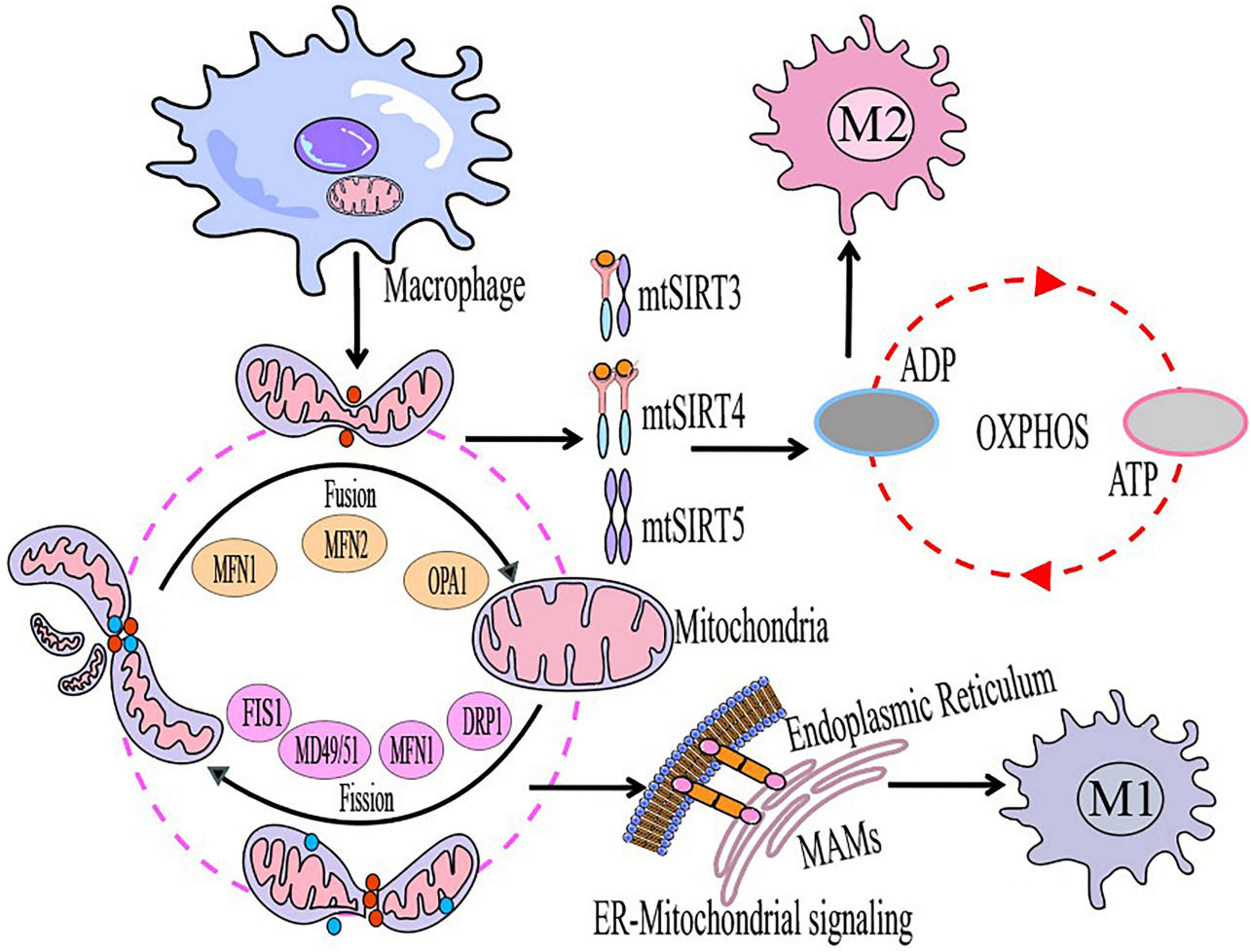

Figure 3 Mitochondrial dynamics and macrophage polarization in RA.
Notes: Abnormal mitochondrial fission and increased glycolysis in macrophages promote M1 macrophage polarization; mitochondrial fusion facilitates OXPHOS in M2 macrophages and is closely associated with mitochondrial SIRT (mtSIRT).
Abbreviations: MAMs, Mitochondria-associated membranes; mtSIRT, Mitochondrial SIRT; OXPHOS, Oxidative phosphorylation; ATP, adenosine triphosphate; ADP, adenosine diphosphate.

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Mitochondrial Fusion Promotes OXPHOS in M2 Macrophages

Mitochondrial fusion is a multi-step process involving the outer and inner membranes. Fusion of the outer membrane is mediated by mitofusins (Mfn1/2), while inner membrane fusion is regulated by OPA1.[70,71] Although Mfn1 and Mfn2 share structural similarity, Mfn1 exhibits stronger GTPase activity and is more effective in promoting membrane fusion. OPA1 activity is also closely associated with Mfn1.[72]

Mitochondrial fusion results in elongated, interconnected mitochondria that enhance ATP production.[73] Fusion-related processes also help preserve mitochondrial function and prevent the accumulation of defective mitochondrial DNA.[74] Mitochondrial sirtuins (mtSIRTs) serve as crucial regulators linking metabolism and mitochondrial dynamics.[75] Specifically, SIRT3/4/5 influence OPA1 and/or MFN2 to promote fusion and regulate cellular metabolism. SIRT3 enhances mitochondrial respiration, whereas SIRT4 and SIRT5 suppress it in certain cell types, such as fibroblasts, MDA-MB-231, and C2C12 cells. In macrophages, however, SIRT3/4/5 collectively enhance OXPHOS and glycolysis to support macrophage function.[76] Notably, SIRT5 has been reported to regulate the degradation of GLUD1 in IL-4–polarized bone marrow–derived macrophages (BMDMs), thereby increasing GLUD1 activity and promoting α-ketoglutarate (αKG) production. This, in turn, facilitates M2-like macrophage polarization.[77]

Mitochondria-Related Molecules and Macrophage Polarization

NDUFS4

Mitochondria are the primary site of oxidative phosphorylation (OXPHOS), producing cellular energy in the form of adenosine triphosphate (ATP). They are also involved in ROS generation, fatty acid oxidation, heme biosynthesis, apoptosis, thermogenesis, and calcium (Ca^{2+}) homeostasis.[78] During OXPHOS, the nuclear-encoded NDUFS4 gene produces the NADH: ubiquinone oxidoreductase subunit S4 (Ndufs4) of complex I. Phosphorylation of Ndufs4 affects mitochondrial import, mitochondrial targeting sequence (MTS) cleavage, and its subsequent incorporation into complex I.[79,80] Thus, Ndufs4 is critically involved in mitochondrial function.

Studies indicate that the complex I–associated protein Ndufs4 plays a pivotal role in macrophage polarization.[81] Mutations or deletions in Ndufs4 have been shown to alter mitochondrial membrane potential, ROS levels, and NADPH homeostasis. These alterations enhance pro-inflammatory gene expression in macrophages and can also trigger macrophage apoptosis, ultimately impairing tissue repair.[82] This highlights the important role of Ndufs4 in promoting M1 macrophage polarization.

In the context of RA-related bone destruction, reduced or absent Ndufs4 expression correlates with decreased OC number and function, thereby inhibiting bone resorption.[82] These findings suggest that Ndufs4 levels are positively associated with OC activity. Moreover, liver-specific deletion of Ndufs4 induces a metabolic shift from fatty acid oxidation (FAO) to glycolysis, leading to fatty acid and lactate accumulation. This, in turn, activates Ndufs4-deficient macrophages via ROS and reduces OC numbers.[83] Further investigation reveals that TLR4 deficiency in Ndufs4-knockout mice alleviates inflammation and bone destruction, indicating that TLR4 acts as a key mediator of systemic inflammation in the absence of Ndufs4.[84] In summary, Ndufs4 plays a vital role in both macrophage polarization and OC activation.

HtrA2

HtrA2 is a member of the highly conserved high-temperature requirement A (HtrA) serine protease family and is implicated in the development of neurodegenerative diseases, prostate cancer, and hepatocellular carcinoma.[85] Recent studies also link HtrA2/Omi to the pathogenesis of RA.[86] Located in the mitochondrial intermembrane space, HtrA2/Omi is a key regulator of mitochondrial protein quality control. It primarily functions in the degradation of misfolded proteins via the mitochondrial unfolded protein response (UPRmt), thereby preserving mitochondrial function and structure.[87]

HtrA2/Omi deficiency promotes the accumulation of mitochondrial ROS, which leads to the generation of oxidatively damaged mitochondrial DNA (Ox-mtDNA). Elevated ROS levels disrupt mitochondrial membrane potential and induce the opening of the mitochondrial permeability transition pore (MPTP), resulting in the release of Ox-mtDNA into the cytoplasm.[88,89] There, it is recognized by cytoplasmic damage-associated molecular pattern (DAMP) receptors. DAMPs activate the NF-κB pathway via TLR9, driving the production of pro-inflammatory cytokines such as IL-1β, IL-12, and type I interferons (IFNs), and promoting M1-type macrophage polarization (Figure 4). [90]

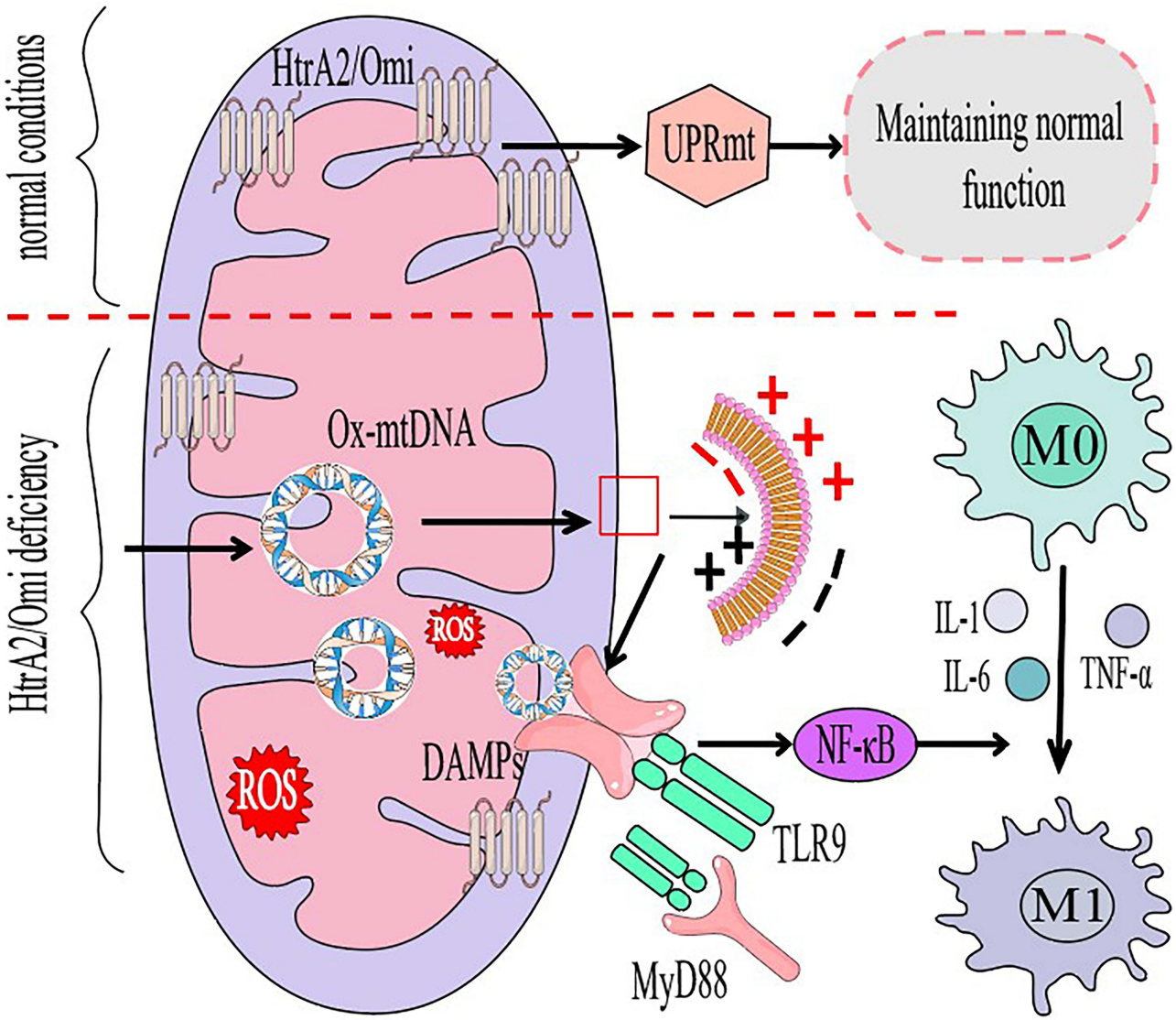

Figure 4 HtrA2 and macrophage polarization.
Notes: Normal levels of HtrA2/Omi maintain mitochondrial function; HtrA2/Omi deficiency promotes M1 macrophage polarization through ROS, NF-κB pathway, and other pathways.
Abbreviations: Ox-mtDNA, Oxidative damage to mitochondrial DNA; MPTP, Mitochondrial permeability transition pore.

TFAM

Mitochondrial transcription factor A (TFAM), encoded by nuclear DNA, is essential for maintaining mitochondrial DNA (mtDNA) function and is a key component of the mitochondrial electron transport chain. This makes TFAM a critical regulator of energy production through oxidative phosphorylation.[91,92] Studies have shown that TFAM wraps tightly around mtDNA, forming a nucleoid structure that protects it from ROS-induced damage.[93] Additionally, TFAM regulates mtDNA copy number, which is closely linked to mitochondrial metabolic activity. Even slight changes in the TFAM-to-mtDNA ratio can significantly affect mtDNA transcription and replication,[94] indicating that subtle alterations in TFAM levels may disrupt normal mitochondrial function.

Mitochondrial dysfunction reduces TFAM expression and increases ROS levels, leading to structural abnormalities in the mitochondrial nucleoid. This causes direct mtDNA damage, activates the cGAS–STING pathway, and induces type I interferon production, a process implicated in RA pathogenesis.[95] Furthermore, TFAM plays a role in regulating macrophage polarization. For instance, TFAM deficiency impairs mitochondrial morphology and function in T cells, weakening immune responses and negatively impacting macrophage differentiation.[96] Other studies have reported that TFAM promotes dendritic cell (DC)

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maturation both in vivo and in vitro, enhances T cell proliferation, and increases the secretion of proinflammatory cytokines, thereby promoting M1 macrophage differentiation and contributing to RA progression.[97]

Mitochondrial Autophagy Can Suppress RA Inflammatory Responses

Mitochondrial Autophagy Inhibits M1 Macrophage Polarization in RA

Mitochondrial dynamics are critical for the removal of damaged mitochondria and for maintaining mitochondrial structure and function.[98] When fusion and fission are insufficient to address cellular stress, mitochondrial autophagy is initiated to eliminate dysfunctional mitochondria. This process preserves mitochondrial quality, reduces ROS generation and mtDNA release, and suppresses inflammation.[99] Conversely, impaired mitochondrial autophagy results in ROS accumulation, enhanced immune responses, systemic inflammation, and may contribute to RA onset.[100]

Recent studies have demonstrated that mitochondrial autophagy regulates macrophage polarization in RA by influencing mitochondrial function.[101] For example, acrylamide induces mitochondrial autophagy through the PINK1 pathway, promoting M2 macrophage polarization and reducing inflammation in RA.[102] In contrast, taurine inhibits PINK1-mediated mitophagy, increasing inflammatory markers and the proportion of M1 macrophages, while reducing M2 macrophages, thus exacerbating RA inflammation.[103] These findings suggest that mitochondrial autophagy suppresses M1 polarization and alleviates inflammatory responses in RA. Given the strong association between macrophage polarization and mitophagy, targeting this process may provide a novel strategy for RA-specific therapy.

From a Metabolic Perspective, Mitochondrial Autophagy Promotes M1 Macrophage Polarization

The role of mitochondrial autophagy in macrophage polarization is complex. From a metabolic standpoint, enhanced mitochondrial autophagy, mediated by receptors such as BNIP3L/NIX and FUNDC1, removes functional mitochondria, shifting macrophage metabolism toward glycolysis. This metabolic reprogramming supports the rapid energy and biosynthetic demands required for M1 polarization.[104,105] In addition, mitochondrial autophagy functions as a quality control mechanism that preserves mitochondrial integrity and supports oxidative phosphorylation, which is essential for M2 macrophage metabolism.[106] However, excessive mitophagy may disrupt energy supply and impair the polarization of both M1 and M2 macrophages.

Macrophage Autophagy Can Inhibit M1 Macrophage Polarization

Macrophage autophagy is a critical process by which damaged cellular components or pathogens are degraded and recycled via the autophagic machinery. This process is essential for immune defense, inflammation regulation, and cellular homeostasis.[107] Major forms of macrophage autophagy include: (1) Macroautophagy: Formation of double-membrane autophagosomes that encapsulate cytoplasmic materials, which then fuse with lysosomes to degrade the contents. (2) Microautophagy: Direct invagination of the lysosomal membrane to engulf cytoplasmic components. (3) Chaperone-mediated autophagy (CMA): Selective degradation of specific proteins marked by KFERQ-like motifs, guided by chaperones such as HSPA8/HSC70, which transport them into lysosomes. (4) Selective forms of autophagy: Including mitophagy, ER-phagy, heterophagy (following pathogen phagocytosis), and lipophagy (Figure 5). [108]

Autophagy plays a crucial role in regulating macrophage polarization.[109] Impaired macrophage autophagy has been shown to promote M1 polarization and exacerbate inflammatory responses.[110] Conversely, enhancing autophagy, such as through ubiquitin-specific protease 19 (USP19), can promote M2 polarization.[111] Experimental studies also support this: spermine, an autophagy-inducing compound, was found to suppress M1 polarization and promote M2 polarization in liver-resident macrophages (Kupffer cells) in TAA-treated mouse models.[112] In conclusion, mitochondrial autophagy, as a subset of macrophage autophagy, plays a significant role in inhibiting M1 polarization and alleviating chronic inflammation and immune responses.

Mitochondrial Ion Homeostasis Abnormalities Promote M1 Macrophage Polarization in RA

Mitochondrial Iron Overload

Iron, a highly reactive metal, is essential in numerous biological processes, including apoptosis, host defense, and mitochondrial respiration. It catalyzes free radical production through the Fenton reaction and regulates cell proliferation.[113,114] Thus, maintaining iron homeostasis is vital for physiological function (Figure 6). In pathological conditions, excessive iron

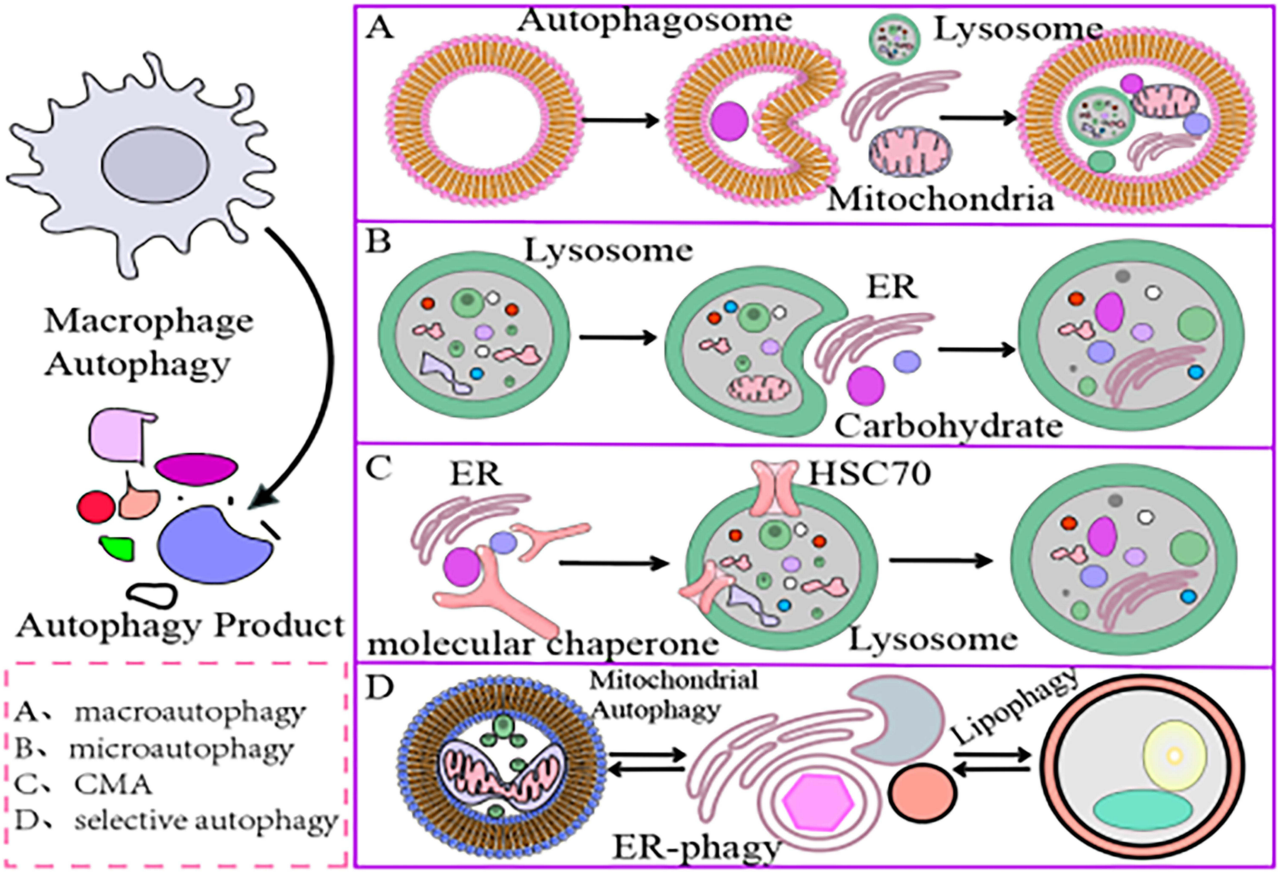

Figure 5 Macrophage Autophagy Processes and Classification.
Abbreviations: CMA, Chaperone-mediated autophagy; ER-phagy, endoplasmic reticulum autophagy; ER, endoplasmic reticulum.

accumulation, known as iron overload, can occur.[115] This state is recognized as a risk factor for infections, cancer, endocrine disorders, neurodegenerative diseases, and autoimmune conditions.[116,117]

In RA-related studies, Fe^{2+} has been identified as a key element for oxidative phosphorylation and the TCA cycle in macrophages, with iron-sulfur (Fe-S) clusters and mitochondrial ferritin (FtMt) playing crucial roles in polarization.[85] Evidence shows that M1 macrophages display iron overload, while Fe^{2+} levels in M2 macrophages remain stable.[86] Additional findings indicate that iron overload in macrophages activates the NF-κB signaling pathway, promoting M1 polarization and exacerbating RA inflammation.[87] Furthermore, mitochondrial iron overload increases ROS production and glycolysis, further facilitating M1 macrophage polarization.[88,89]

Mitochondrial iron overload promotes the differentiation of M1 macrophages into OCs Intracellular iron overload primarily contributes to OC differentiation (Figure 7). Studies[118] have shown that ferritin-induced iron accumulation significantly enhances the differentiation of RAW264.7 mouse macrophages into OCs. Moreover, iron overload increases systemic IL-6 production by elevating ROS levels in mouse models, thereby activating the STAT3 pathway and promoting RANKL production by osteoblasts.[119] This facilitates OC formation via the RANKL/RANK/OPG signaling axis, further contributing to bone resorption in RA. Additionally, iron overload induces ROS production in OCs through the Fenton reaction[120] or indirectly by enhancing mitochondrial function and respiration.[121] ROS, in turn, activate cAMP response element-binding protein (CREB) via phosphorylation, which upregulates transcription of peroxisome proliferator-activated receptor-γ coactivator 1β (PGC-1β), forming a positive feedback loop that further increases ROS levels.[122] These elevated ROS levels disrupt OC activity and impair bone homeostasis.

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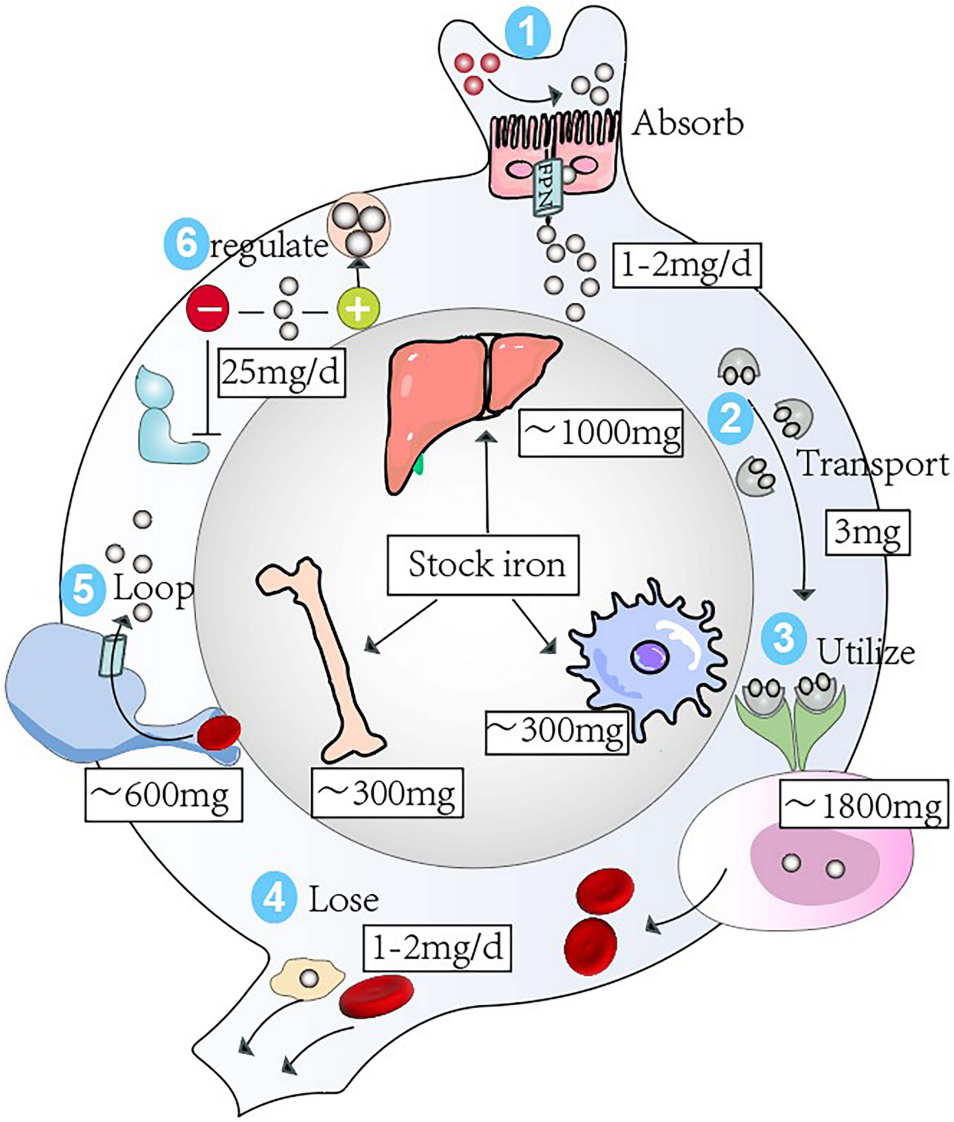

Figure 6 Iron metabolism.
Abbreviations: CMA, Chaperone-mediated autophagy; ERAG, endoplasmic reticulum autophagy.

Increased Mitochondrial Copper Ions Promote M1 Macrophage Polarization

Copper homeostasis involves copper absorption, distribution, utilization, and excretion, regulated by copper complexes, chaperone proteins, and transporters.[123] Once inside cells, copper ions can catalyze redox reactions and, together with glutathione, exert antioxidant effects that protect against oxidative stress. Additionally, copper is essential for cytochrome c oxidase (CCO) activity, which plays a key role in energy metabolism and ATP production.[124]

Copper homeostasis significantly influences inflammation and macrophage differentiation. Excess copper leads to elevated intracellular copper ion levels, promoting free radical generation, particularly ROS, and inducing oxidative stress.[125] In RA, copper overload increases ROS production, which activates NF-κB, a critical regulator of inflammation.[126] This amplifies immune and inflammatory responses while also promoting M1 macrophage polarization, thereby aggravating RA pathology. Experimental studies confirm that high concentrations of copper ions exert cytotoxic effects and stimulate inflammatory responses.[127] In macrophages, mitochondrial copper ion levels rise significantly, supporting M1-related metabolic reprogramming and epigenetic modifications.[128] In contrast, copper deficiency enhances M2 polarization, marked by increased expression of anti-inflammatory markers and reduced expression of M1 surface proteins and pro-inflammatory cytokines.[126]

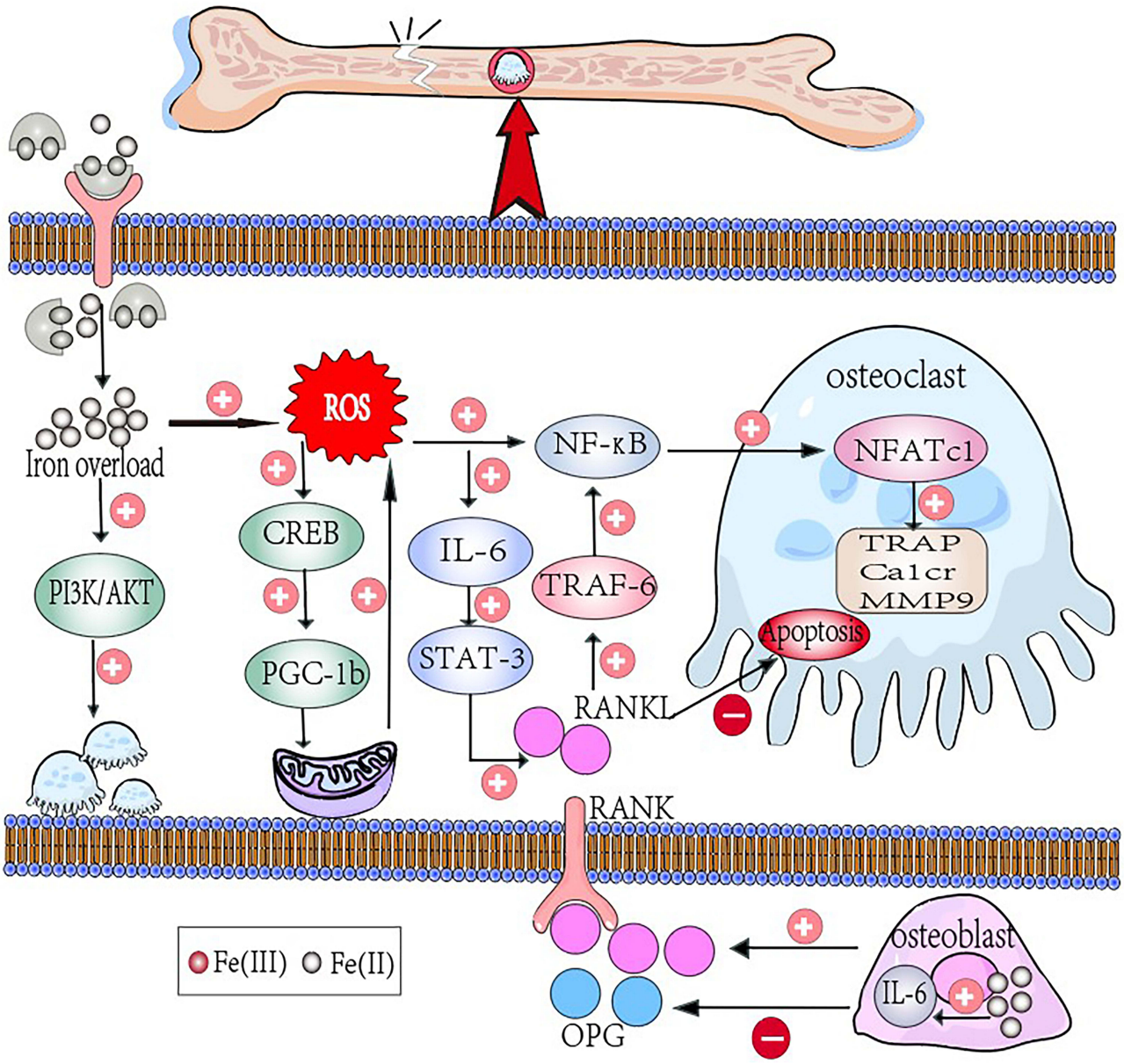

Figure 7 Mitochondrial iron overload and OC.
Notes: Iron overload induces ROS production in osteoclasts via the Fenton reaction or indirectly through activation of mitochondrial function and respiration. ROS can mediate osteoclast generation through the RANKL/NF-κB signaling pathway.
Abbreviation: CREB, cAMP response element-binding protein.

Mitochondrial Calcium Overload Promotes M1 Macrophage Polarization

Mitochondria play critical roles in calcium signaling, energy metabolism, and oxidative stress regulation.[129] Mitochondrial calcium levels directly influence macrophage polarization. Oxidative phosphorylation rate, regulated by calcium, affects ATP production and overall macrophage metabolic activity. The TCA cycle, a core component of this process, is modulated by calcium through activation of key enzymes and regulation of the mitochondrial permeability transition pore (mPTP), thereby increasing metabolic rates and inflammatory signaling.[130,131] Moderate increases in mitochondrial calcium enhance mitochondrial function. However, calcium overload disrupts membrane potential, induces excessive ROS production, and triggers mitochondrial DNA release. These events activate inflammatory pathways and drive M1 macrophage polarization.[132]

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Modulating Mitochondrial Ion Homeostasis Can Intervene in Macrophage Polarization in RA

Clinical translational research increasingly focuses on modulating macrophage phenotypic conversion by regulating mitochondrial iron homeostasis, thereby intervening in macrophage-driven inflammatory diseases such as RA. Cui et al reported on biomaterials that modulate macrophage polarization by regulating mitochondrial ion homeostasis. CQP hydrogel, an iron chelator, helps prevent Fe^2+ accumulation, restores mitochondrial function, and facilitates the shift of M1 macrophages toward the M2 phenotype. This transformation contributes to improved immune status and reduced inflammatory responses in vivo.[6] Solier et al developed LCC-12, a metformin dimer that inactivates Cu^2+ within mitochondria, thereby suppressing M1 macrophage activation. This compound effectively alleviated acute inflammatory responses and improved survival rates in mice.[133] Feng et al[134] employed a macrophage-targeted delivery system using polyethyleneimine (PEI) and β-aminoaniline (PBAA) to deliver siERN1, which modulates macrophage Ca^2+ levels and facilitates the M1-to-M2 transformation to maintain immune homeostasis. These studies provide significant insights for RA treatment, suggesting that ion chelators or related biomaterials may achieve M1-to-M2 macrophage conversion to restore immune dysregulation in RA.

Mitochondrial Transfer and RA

Mitochondrial Transfer Promotes M2 Macrophage Polarization

With growing understanding of mitochondrial roles in disease, mitochondrial transfer, the movement of mitochondria between cells, has gained attention.[135] This process occurs via several mechanisms: A. Cell fusion-induced mitochondrial transfer: Fusion between cells, either heterotypic or homotypic, leads to the exchange of organelles, including mitochondria.[136] While spontaneous under basal conditions, mitochondrial transfer is enhanced by stimuli such as viral infections or chemical exposure.[137] Though mechanisms remain unclear, membrane fusion may involve interactions between surface proteins and cytoskeletal reorganization.

B. Exosome- or tunneling nanotube-mediated mitochondrial transfer:[138] Exosomes are vesicles secreted by cells, enclosed by a membrane composed of components similar to the plasma membrane. They contain cellular materials such as DNA, proteins, and intact, functional mitochondria.[139] Exosomes can be directly taken up by recipient cells or internalized through endocytosis, subsequently fusing with the plasma membrane. Once internalized, they release their contents, including mitochondria, which may integrate into the recipient cell's metabolic system.[140] This mechanism is most commonly observed in mesenchymal stem cells and neuronal cells. Exosome-mediated mitochondrial transfer provides a protective environment that shields mitochondria from external stressors.[141]

Tunneling nanotubes are long, membrane-bound structures that facilitate direct intercellular communication and the exchange of cellular components, including mitochondria. This form of transfer is particularly prevalent among immune and cancer cells.[142] However, mitochondrial transfer via tunneling nanotubes has limitations. External mechanical stress during transfer may damage mitochondria or impair their function.[143]

The onset of RA is closely linked to inflammatory responses and macrophage phenotypes. Mitochondrial transfer plays a regulatory role in shaping macrophage behavior. Research has shown that mesenchymal stem cells (MSCs) regulate mitochondrial fusion and autophagy through the PGC-1α/TFEB signaling pathway, facilitating mitochondrial transfer, enhancing mitochondrial function, reducing ROS production, and promoting M2 macrophage polarization. At the same time, this process inhibits M1 polarization, thereby alleviating inflammation.[144] In addition, MSCs can also promote M2 polarization via exosome-mediated mitochondrial transfer (Figure 8). [145]

Mitochondrial Transplantation as a New Approach for Treating RA

Macrophages are key effector cells in RA pathogenesis, while mitochondria, critical for energy metabolism, ion balance, apoptosis, and phenotypic differentiation, serve as their central regulators. Mitochondrial transfer, a non-invasive technique, has shown potential for treating various diseases due to its minimal side effects and low complication rates.[136] Studies have demonstrated that transferring mitochondria from healthy to damaged cells enhances energy metabolism, promotes proliferation and differentiation, and facilitates tissue repair and regeneration.[146]

Evidence suggests that mitochondrial transfer promotes M2 macrophage polarization and inhibits M1 polarization, thus alleviating inflammation in RA and providing therapeutic benefits. Currently, mitochondrial delivery methods include injection, cell fusion, and phagocytosis of isolated mitochondria or mitochondria-containing particles.[147] However, these approaches face

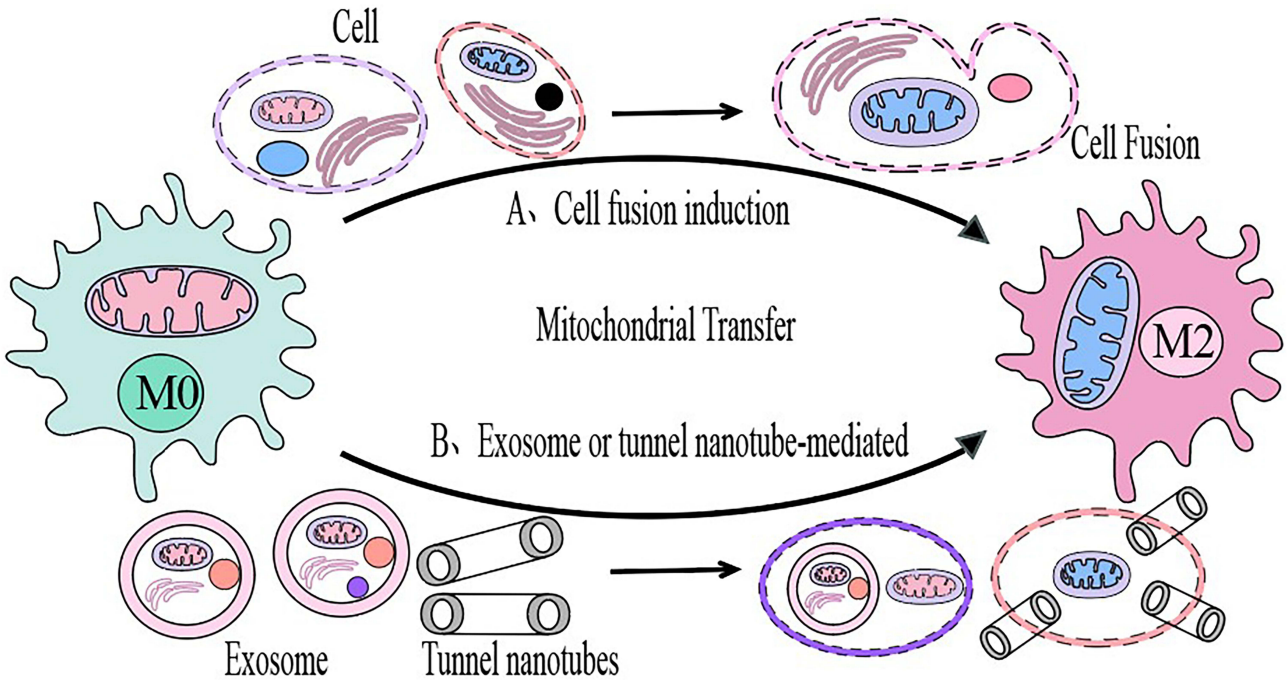

Figure 8 Mitochondrial transfer.
Notes: The mitochondrial transfer process primarily involves cell fusion-induced mitochondrial transfer and mitochondrial transfer mediated by exosomes or nanotubes. Mitochondrial transfer contributes to M2 macrophage polarization.

limitations regarding efficiency, specificity, and safety. Extracellular vesicles (EVs) or exosomes have emerged as promising alternatives due to their high uptake efficiency and precise mitochondrial delivery.[148] Future research may focus on enhancing mitochondrial function in RA patients by transferring healthy mitochondria, reducing the M1/M2 macrophage ratio, and suppressing inflammation. This strategy could potentially slow or even halt RA progression, offering a novel therapeutic avenue.

Summary and Outlook

Macrophages play a crucial role in the pathogenesis of RA), particularly through the inflammatory responses driven by M1 macrophages, which contribute to the development of inflammatory bone disease. Therefore, promoting the conversion of M1 macrophages into M2 macrophages represents a promising therapeutic strategy for RA. As central organelles regulating macrophage metabolism and function, mitochondria influence M1/M2 polarization through various mechanisms, including metabolic pathways, signaling molecules, mitochondrial dynamics, mitochondria-associated proteins, mitophagy, ion homeostasis, and mitochondrial transfer. These pathways collectively modulate immune and inflammatory responses, thereby contributing to RA progression. Elucidating these mechanisms, promoting M1-to-M2 transition, and suppressing inflammation are of great significance for the treatment and repair of inflammatory bone diseases.

However, mitochondrial regulation of macrophage polarization remains complex and poses several challenges: (1) Current research is primarily limited to theoretical frameworks and animal models, with limited support from human studies; (2) Mitochondrial glycolysis promotes M1 polarization, while oxidative phosphorylation promotes M2 polarization. The precise switch or balance point between these metabolic states remains unclear, and strategies to modulate these processes require further investigation. (3) Moderate increases in ROS, calcium, iron, and copper ions have been shown to promote M1 polarization, but excessive accumulation may lead to macrophage apoptosis. The specific concentration thresholds for these effects have not yet been defined.

Future research into RA, mitochondria, and macrophages may focus on the following directions: (1) Precise regulation of macrophage function: Targeting specific signaling pathways or chemokines through mitochondrial regulation to modulate macrophage activation states and enable immune intervention in RA. (2) Mitochondrial transfer: Transferring healthy mitochondria to RA patients to restore mitochondrial function, reduce the M1/M2

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ratio, and alleviate inflammation, offering a potential therapeutic approach. (3) Clinical research and translation: Bridging basic and clinical research to assess the therapeutic potential of targeting mitochondrial regulation of macrophage polarization in RA patients.

Data Sharing Statement

Data sharing is not applicable as no data was generated or analysed in this paper.

Author Contributions

Pingshun Li: Conceptualization, Original draft
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Lihuan Zhang: Data curation, Original draft
Fang Yang: Data curation, Review & Editing
Yong Wei: Data curation, Original draft
Meihan Pan: validation, Review & Editing
Haohao Zang: validation, Review & Editing
Mengru Zhou: Conceptualization, Review & Editing

All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest.

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