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REVIEW

Important Role of Mitochondrial Dysfunction in Immune Triggering and Inflammatory Response in Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is an inflammatory autoimmune disease, primarily characterized by chronic symmetric synovial inflammation and erosive bone destruction.Mitochondria, the primary site of cellular energy production, play a crucial role in energy metabolism and possess homeostatic regulation capabilities. Mitochondrial function influences the differentiation, activation, and survival of both immune and non-immune cells involved in RA pathogenesis. If the organism experiences hypoxia, genetic predisposition, and oxidative stress, it leads to mitochondrial dysfunction, which further affects immune cell energy metabolism, synovial cell proliferation, apoptosis, and inflammatory signaling, causing the onset and progression of RA; and, mitochondrial regulation is becoming increasingly important in the treatment of RA.In this review, we examine the structure and function of mitochondria, analyze the potential causes of mitochondrial dysfunction in RA, and focus on the mechanisms by which mitochondrial dysfunction triggers chronic inflammation and immune disorders in RA. We also explore the effects of mitochondrial dysfunction on RA immune cells and osteoblasts, emphasizing its key role in the immune response and inflammatory processes in RA. Furthermore, we discuss potential biological processes that regulate mitochondrial homeostasis, which are of great importance for the prevention and treatment of RA.

Keywords: mitochondria, rheumatoid arthritis, immune triggers, inflammatory response, osteoblasts, synovial cells

Introduction

Mitochondria are intracellular organelles present in almost all eukaryotic organisms and are involved in various cellular processes, primarily playing a critical role in energy production. They also regulate calcium homeostasis, produce reactive oxygen species(ROS), and are involved in cellular proliferation and metabolism.[1,2] Mitochondria are particularly important for immune cells, eg, T cells, macrophages, and neutrophils, which serve as the sentinel cells of the immune response and require a large supply of energy for their rapid response and metabolic reprogramming processes.[3] Interest in these organelles has grown with recent findings linking mitochondria to various pathologies, including immune disorders, inflammation, cancer, aging, and neurodegenerative diseases.[4] Dysfunctional mitochondria are unable to meet the energy demands of high-energy tissues such as the heart, brain, and skeletal muscles, leading to a wide range of clinical manifestations.[5]

RA is a systemic autoimmune disease characterized by synovial inflammation and hyperplasia, the production of autoantibodies, including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), cartilage destruction, vascular opacification, and bone erosion.[6] In RA, autoimmune tissue destruction manifests as synovitis, a joint inflammation triggered and sustained by complex interactions among various dendritic cell (DC) subtypes, T cells, macrophages, B cells, neutrophils, fibroblasts, and osteoclasts.[7] Due to the persistent activation and incomplete clearance

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of specific autoantigens in RA patients, this ongoing immune cell activation and abnormal immune response result in recurrent chronic synovitis in the joints. This process leads to the formation of vascular opacities, which invade the cartilage-bone junction, causing bone erosion and cartilage degeneration.[8,9]

Studies have shown that mitochondrial dysfunction plays a significant role in the development of RA. Structurally and functionally intact mitochondria are essential for the normal survival of osteoblasts, synoviocytes, and immune cells. Once mitochondrial function is compromised, it affects the survival, activation, and differentiation of both immune and non-immune cells involved in RA pathogenesis, ultimately contributing to the development of RA.[10,11] In this review, we examine the structure and function of mitochondria, analyze the potential causes of mitochondrial dysfunction in RA, and focus on the mechanisms by which mitochondrial dysfunction triggers chronic inflammation and immune disorders in RA. We also review the effects of mitochondrial dysfunction on immune cells and osteoblasts in RA, highlighting the physiological functions and pathological roles of mitochondria in RA, to promote the understanding of mitochondrial mechanisms and emphasize their role in RA pathogenesis.

Mitochondrial Structure

Mitochondria are intracellular organelles primarily responsible for energy conversion and supply within the cell.[12] They function mainly through three key systems: the respiratory chain, the tricarboxylic acid cycle, and fatty acid oxidation. Additionally, mitochondria play critical roles in regulating apoptosis, cell signaling, and maintaining cellular metabolic homeostasis.[13,14]

Bilayer Membrane Structure

Mitochondria are enclosed by two phospholipid membranes: the outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM), which create two distinct spaces within the organelle, the matrix and the intermembrane space (IMS).[15] These membranes differ significantly in lipid composition, transmembrane protein characteristics, permeability, and shape, which reflect the organelle's symbiotic origin.

The OMM closely resembles eukaryotic membranes in lipid composition, while the IMM is similar to bisphosphatidylglycerol-rich bacterial membranes.[16] The IMM has a high protein-to-lipid ratio and forms densely stacked invaginations in the matrix called cristae.[17] These cristae increase the surface area and the capacity for ATP production, as the oxidative phosphorylation (OXPHOS) machinery is embedded within them, along with other essential proteins. Mitochondrial cristae morphology undergoes significant changes in the face of mitochondrial stress or energy demand, and optimizes mitochondrial function mainly by adjusting the number and structure of cristae to protect cells from damage. For example, cold stimulation promotes the transport of MICOS complex subunit MIC19 protein to mitochondria in brown adipose tissue, which in turn promotes the formation of mitochondrial cristae and improves mitochondrial function; the mechanism of this is mainly related to the activation of the unfolded protein response (UPR) pathway.[18] The portion of the IMM that does not extend into the matrix but runs parallel to the OMM is known as the inner boundary membrane (IBM). The cristae and IBM are connected by narrow tubular or slit-like structures called cristae junctions (CJ) (Figure 1).[19]

Additionally, the OMM and IMM differ significantly in permeability. The IMM is far less permeable than the OMM. The IMM is mainly characterized by the presence of voltage-dependent anion channels (VDAC) and α-helical transport proteins, such as protein translocases and various metabolite and ion carriers, which facilitate the passage of ions and small molecules.[20] In contrast, the OMM contains channel-forming proteins such as β-barrel transmembrane hydrophilic pores, which allow the passage of precursor proteins, small hydrophilic metabolites (eg, O2 and CO2), and ions. This selective permeability enables the formation of electrochemical gradients across the mitochondrial membrane, which are essential for ATP production. Additionally, it tightly regulates the concentration of other ions, such as calcium, which plays a crucial role in intracellular signaling.[21,22]

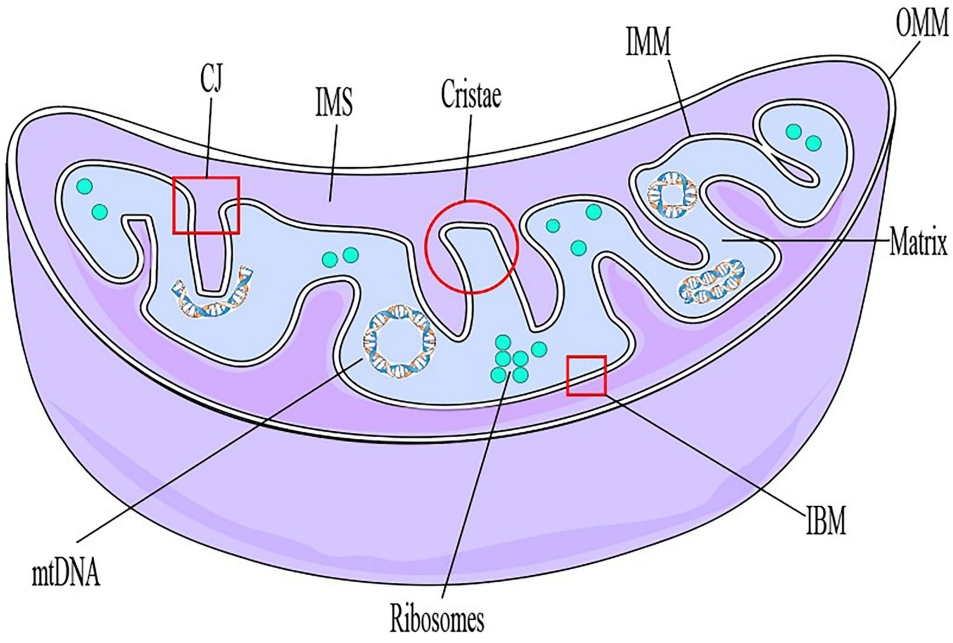

Figure 1 Schematic of mitochondrial structure.
Abbreviations: CJ, cristae junctions; IMS, intermembrane space; OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane; IBM, inner boundary membrane; mtDNA, mitochondrial DNA.

Matrix and Intermembrane Space

Mitochondrial function is not only closely related to its double-membrane structure, but the mitochondrial matrix also plays an important role

The interior of the mitochondrion consists of the matrix and the intermembrane space.[23] The matrix contains various soluble enzymes and mitochondrial DNA (mtDNA), while the intermembrane space lies between the inner and outer membranes. Mitochondrial DNA shares typical characteristics with bacterial DNA: it is a circular, double-stranded molecule containing 16,569 base pairs (bp) and lacks introns, primarily exhibiting cis-trans arrangements.[24] Structurally, each gene is adjacent to the next, except for substitution loops or non-coding regions in the D-loop, although some genes may overlap.

Unlike nuclear DNA, mtDNA exists in multiple copies within a cell, ranging from approximately 100 to 10,000 copies, depending on the energy demands of the tissue.[25] Additionally, mtDNA genetic codons differ slightly from nuclear DNA, using distinct codons for tryptophan and methionine, and it includes only two termination codons. Over the course of evolution, most mitochondrial genes were lost or transferred to nuclear DNA, leaving mtDNA with only 37 genes: 11 messenger RNAs (mRNAs) encoding 13 proteins, 2 ribosomal RNAs (rRNA, 12S and 16S), and 22 tRNAs.[26]

Mitochondrial Function

Energy Metabolism

Mitochondria serve as the intracellular "energy factories" and are the primary site of oxidative phosphorylation within the cell.[27] The mitochondrial respiratory chain forms the core structure of oxidative phosphorylation, consisting of four enzyme complexes: nicotinamide adenine dinucleotide ubiquinone reductase (NADH dehydrogenase) (Complex I, CI), succinate ubiquinone oxidoreductase (Complex II, CII), ubiquinone cytochrome oxidoreductase (Complex III, CIII), and cytochrome c oxidase (Complex IV, CIV). These complexes are accompanied by two mobile electron carriers, ubiquinone (CoQ) and cytochrome c (Cyt c), which are embedded in the inner mitochondrial membrane, creating a continuous reaction system.[28,29] Through this system, mitochondria oxidize and break down nutrients such as sugars, fats, and amino acids, releasing significant amounts of energy.[30] This process involves the electron transport chain and ATP synthase. The electron transport chain transfers electrons and protons from substrates to oxygen, creating a proton gradient that is

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harnessed by ATP synthase to generate ATP, ATP as a mediator of energy storage and energy conversion, which powers various cellular functions.[31] Therefore, mitochondria are the central site of oxidative metabolism in eukaryotes and are essential for maintaining normal cellular physiological functions (Figure 2).[32]

Apoptosis and Autophagy

Mitochondria play a crucial role in both apoptosis and autophagy.[33] When cells are severely damaged or exposed to specific signals, mitochondria promote the oligomerization of pro-apoptotic proteins BAX and BAK at the outer mitochondrial membrane (OMM) by regulating transmembrane potential and bioenergetic exhaustion.[34] This process induces the release of pro-apoptotic proteins, including cytochrome c, from the intermembrane space (IMS) into the cytosol.[35] In the cytosol, cytochrome c binds to and activates apoptotic protease-activating factor 1 (Apaf-1) and proteasome 9, forming a complex known as the "apoptosome". The apoptosome then cleaves and activates caspase-3, leading to DNA fragmentation, degradation of cytoskeletal and nuclear proteins, protein cross-linking, and the formation of apoptotic vesicles. This mechanism is essential for maintaining internal environmental stability by preventing excessive proliferation of abnormal cells and the development of malignant cells.[36] Mitochondria also participate in autophagy, a process that preserves cellular homeostasis by removing damaged or surplus organelles and proteins.[37]

Regulation of Calcium Ion Homeostasis

Mitochondria have the capacity to rapidly take up calcium ions, which pass through the OMM via VDAC, known for their high conductivity and low anion selectivity.[38] In contrast, calcium ion passage through the IMM is more tightly regulated. It involves the mitochondrial calcium uniporter (MCU), which translocates $Ca2^+$ into the matrix, and the Na^+/$Ca2^+$ exchanger, predominantly found in excitable cells such as muscle and brain tissue. In other cell types, the H^+/$Ca2^+$ exchanger releases calcium ions from the matrix into the IMS.[39] This process allows mitochondria to act as a buffer for intracellular calcium ion storage.

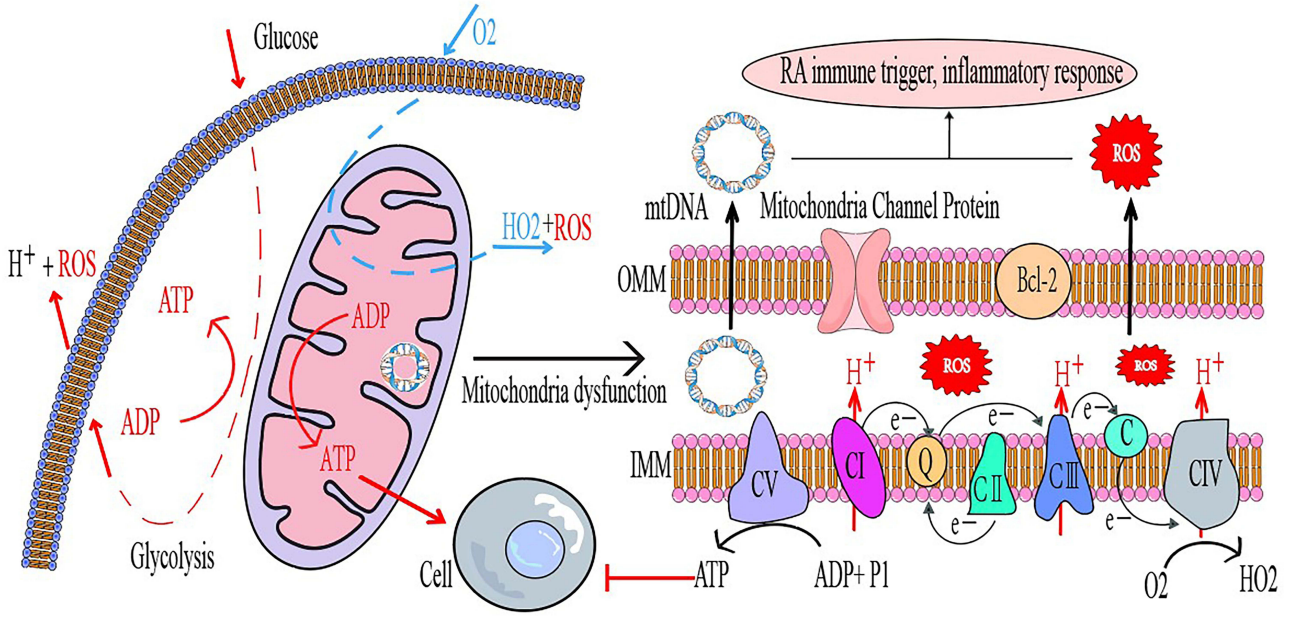

Figure 2 Energy metabolism and ROS Production.

Note: Under normal conditions, the mitochondrial respiratory chain provides ATP to the cell, and mitochondrial dysfunction promotes ROS production and mtDNA release, causing immune triggers and inflammatory responses.

Abbreviations: RA, Rheumatoid arthritis; ROS, Reactive oxygen species; CI, Complex I; CII, Complex II; CIII, Complex III; CIV, Complex IV; ATP, Adenosine triphosphate; ADP, Adenosine Diphosphate.

ROS Production and Scavenging

Mitochondria are a major source of intracellular ROS and also possess mechanisms for scavenging ROS.[40] ROS play a role in cellular signaling and immune responses, but excessive ROS can result in oxidative stress and cellular damage.[41]

Synthesizing Proteins and Nucleic Acids

Mitochondria are a key site for the synthesis of essential biomolecules, including proteins, nucleic acids, and lipids, which are critical for normal cellular function and metabolism.[42]

Immune and Inflammatory Regulation

Mitochondria play a crucial role in regulating immune responses and inflammatory processes by activating immune signaling pathways, serving as a platform for innate immune signaling, and participating in both apoptotic and necrotic pathways.[43] Mitochondrial dysfunction is closely linked to the development and progression of various immune and inflammation-related diseases.[44]

Other Functions

Mitochondria also participate in several other physiological processes, such as cholesterol and hormone synthesis in the liver, blood glucose homeostasis, iron-sulfur cluster synthesis, pyrimidine synthesis, regulation of the intracellular environment, and muscle metabolism (Figure 3).[45,46]

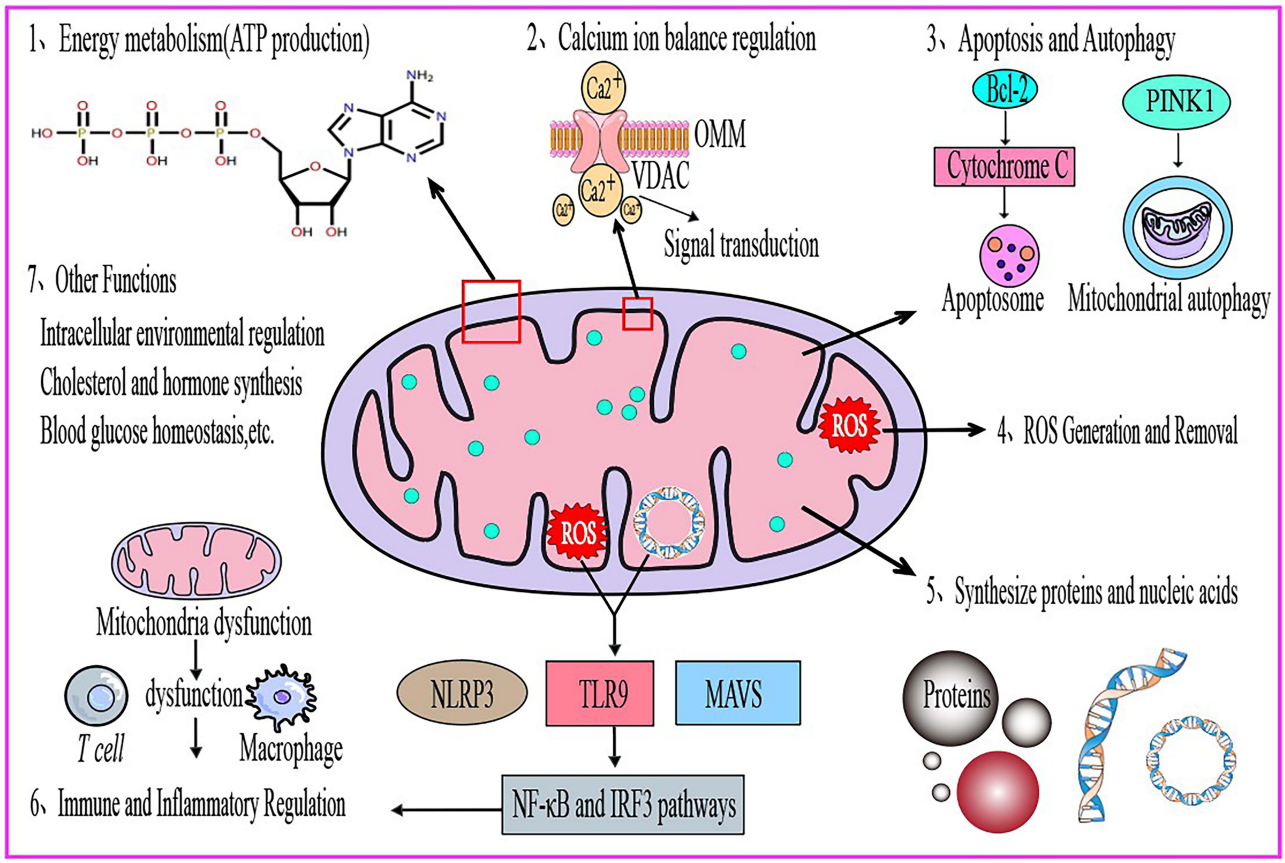

Figure 3 Mitochondrial function.

Abbreviations: ATP, Adenosine triphosphate; VDAC, Voltage-gated Anion Channel; Bcl-2, B-cell lymphoma-2; PINK1, PTEN induced putative kinase 1; ROS, Reactive oxygen species; TLR9, Toll-like receptors 9; MAVS, Mitochondrial antiviral signaling protein; NLRP3, NOD-like receptor protein 3.

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Causes of Mitochondrial Dysfunction in RA

Hypoxia

RA is primarily characterized by chronic synovitis, synovial cell proliferation, and the formation of vascular opacification. Under normal physiological conditions, a layer of endothelial cells lines the interior of synovial blood vessels, where leukocyte migration is minimal, the vasculature remains stable, and blood perfusion and oxygen supply are maintained at normal levels.[47] In chronic synovitis associated with RA, unstable vasculature interacts abnormally with endothelial cells and surrounding tissues. As vascular opacification forms, endothelial cells become activated, lose polarity, and detach, protruding into the vessel lumen. This leads to vascular dysfunction, severely impairing the transport of nutrients and oxygen through the synovial membrane, resulting in hypoxia.[48] The severity of synovitis correlates with the degree of oxygen deprivation in the synovial membrane.[49] Biniecka et al cultured primary rheumatoid arthritis synovial fibroblasts (RASF) under hypoxic conditions and observed mitochondrial function. The study demonstrated that hypoxia induced mitochondrial dysfunction, promoting glycolysis, pannus formation, and neovascularization.[50] Furthermore, hypoxia leads to significant alterations in mitochondrial structure, genome, and dynamics, reducing ATP synthesis, increasing ROS production, and accelerating the accumulation of mtDNA mutations.[51,52]

Mutations in Mitochondrial DNA (mtDNA)

The high mutation rate of mtDNA can be attributed to its lack of protection by histones and chromatin structures, making it more vulnerable to environmental damage. Additionally, the activity of DNA repair enzymes is less robust in mitochondria compared to the nucleus.[53] Mutations in genes encoding mitochondrial proteins often result in altered peptide sequences, leading to mitochondrial dysfunction.When the mutation occurs, it may affect the function of the mitochondrial respiratory chain complex, so that electron transport and oxidative phosphorylation processes are impaired, and ATP cannot be synthesized efficiently, thus affecting organismal function.This dysfunction can cause cellular damage, such as increased ROS production, immune cell activation, and autoantibody production, all of which can exacerbate the progression of RA.[54]

Inflammatory environments have been shown to promote mtDNA mutations. LC Harty et al discovered that higher levels of TNF-α or interferon gamma (IFN-γ) in the synovial membrane were associated with an increased frequency of mtDNA mutations. In in vitro experiments, treating RA FLS with TNF-α also resulted in a higher frequency of mtDNA mutations, indicating that inflammation can induce mtDNA mutations. This suggests a vicious cycle between mitochondrial dysfunction and inflammation.[55] Additionally, hypoxia is a key factor in inducing mtDNA mutations. M. Biniecka et al found a greater number of mtDNA mutations in RA fibroblasts cultured under hypoxic conditions in vitro.[56]

Oxidative Stress

Excessive ROS production in mitochondria increases the risk of mtDNA mutations, impairs ATP synthesis, and contributes to mitochondrial dysfunction.[57] In RA patients, ROS levels may significantly rise due to environmental stressors (eg, pathogenic factors). The accumulation of ROS leads to oxidative stress, which causes DNA damage. This damage results in the production of incorrect polypeptides encoded by mtDNA, further damaging the mitochondria and leading to cellular dysfunction and disease.[58]

Mechanisms Associated with Mitochondrial Dysfunction Triggering Chronic Inflammation and Immune Disorders in RA

In recent years, mitochondria have become a central focus in immunology for two key reasons. First, there is increasing evidence that metabolic reprogramming of immune cells is crucial for the proper regulation of immune activation. Regulating mitochondrial metabolic pathways, such as respiration, β-oxidation, and OXPHOS, can significantly alter immune cell properties and shape immune responses.[59] Second, mitochondria have been shown to play a direct role in activating the immune system, as the release of various mitochondrial products can directly trigger immune and inflammatory responses, ultimately contributing to the pathogenesis of RA.[60]

MtDNA Release

The innate immune system, as the first line of defense, protects against numerous injuries and microbial invasions. Pattern recognition receptors (PRRs) in cells detect specific pathogen-associated molecular patterns (PAMPs) to recognize pathogenic infections.[61] PRRs are broadly categorized into four types: NOD-like receptors (NLRs), Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), and C-type lectin receptors (CLRs).[62]

The nucleus of the cell contains all the DNA that makes up the human genome and is called "nuclear DNA". The mitochondria in a cell are encoded by "mitochondrial DNA", which makes up only 0.1% of nuclear DNA and is inherited exclusively from the mother's side of the family. However, in a recent study, researchers compared the mitochondrial and nuclear DNA of thousands of people and found that mitochondrial DNA can be transferred in trace amounts to the nucleus and that changes in mitochondrial DNA are determined by nuclear DNA. This finding tells us that there is a subtle relationship between the mitochondria and the nucleus in our cells that is critical to maintaining cellular health.[63]

mtDNA is located in the mitochondrial matrix near the electron transport chain, which is the primary source of ROS. Due to this proximity, mtDNA is particularly vulnerable to oxidative stress. When mitochondria experience damage or stress, they release danger-associated molecular patterns (DAMPs) such as mtDNA, succinate, N-formyl peptides, ROS, cardiolipin, and ATP, all of which activate multiple immune response pathways.[64] When mtDNA is present in the cytoplasm or extracellular environment, it acts as a potent agonist for PRRs, initiating a range of signaling pathways. These pathways lead to the upregulation of type I interferons, pro-inflammatory chemokines, and cytokines, contributing to chronic inflammation and immune dysregulation in RA (Figure 4).[65]

The cGAS-STING Pathway

The structure and signaling mechanisms of the cGAS-STING pathway have been extensively studied in recent years. Structurally, cGAS contains three dsDNA-binding sites and can recognize both self and non-self DNA in a sequence-independent manner.[66] cGAS monomers interact with mtDNA that is over 45 base pairs in length, forming a stable network of ladder-like dimers that activate cGAS.[67] Upon activation, cGAS catalyzes the conversion of GTP and ATP into 2′3′-cyclic GMP-AMP (cGAMP), a second messenger that binds to the endoplasmic reticulum (ER)-resident protein, stimulator of interferon genes (STING), causing a conformational change in its C-terminal tail.[68] This conformational shift recruits TANK-binding kina se 1 (TBK1) to STING, leading to the activation of the NF-κB and IRF3 pathways. This, in turn, triggers the transcription of hundreds of interferon-stimulated genes (ISGs), which exert potent antiviral effects.[69]

TLR9 Pathway

TLR9 is a type I integral membrane protein with an N-terminal ligand-recognizing domain, a single transmembrane helix, and a C-terminal cytoplasmic signaling domain. The N-terminal domain exhibits a characteristic horseshoe shape formed by leucine-rich repeat (LRR) motifs.[70] TLR9 is predominantly localized in plasma cell-like dendritic cells, monocytes, B-cells, and macrophages. It is situated in the ER and translocates to intracellular compartments upon stimulation by hypomethylated CpG DNA.[71] TLR9 was the first receptor identified to recognize unmethylated CpG DNA, a hallmark of both bacterial DNA and mtDNA, making mtDNA a potent agonist for TLR9.[72] When bound to mtDNA, TLR9 recruits myeloid differentiation factor 88 (MyD88), forming a signaling complex with interleukin-1 (IL-1) receptor-associated kinase (IRAK) and tumor necrosis factor receptor-associated factor 6 (TRAF6), as well as IRF7. This complex also includes transforming growth factor-β-activated kinase 1 (TAK1), which interacts with NF-κB inhibitor IκB (IκKBα) or TAK1-mitogen-activated protein kinase 1 (MAPK1). Together, these pathways promote the expression of pro-inflammatory genes by activating transcription factors such as IRF7, NF-κB, and activator protein-1 (AP-1).[73]

Inflammatory

Vesicles mtDNA plays a key role in activating inflammatory vesicles, such as NLRP3 and AIM2, both of which promote the secretion of pro-inflammatory cytokines.[74] NLRP3 is a PRR located on the cell membrane that responds to a variety

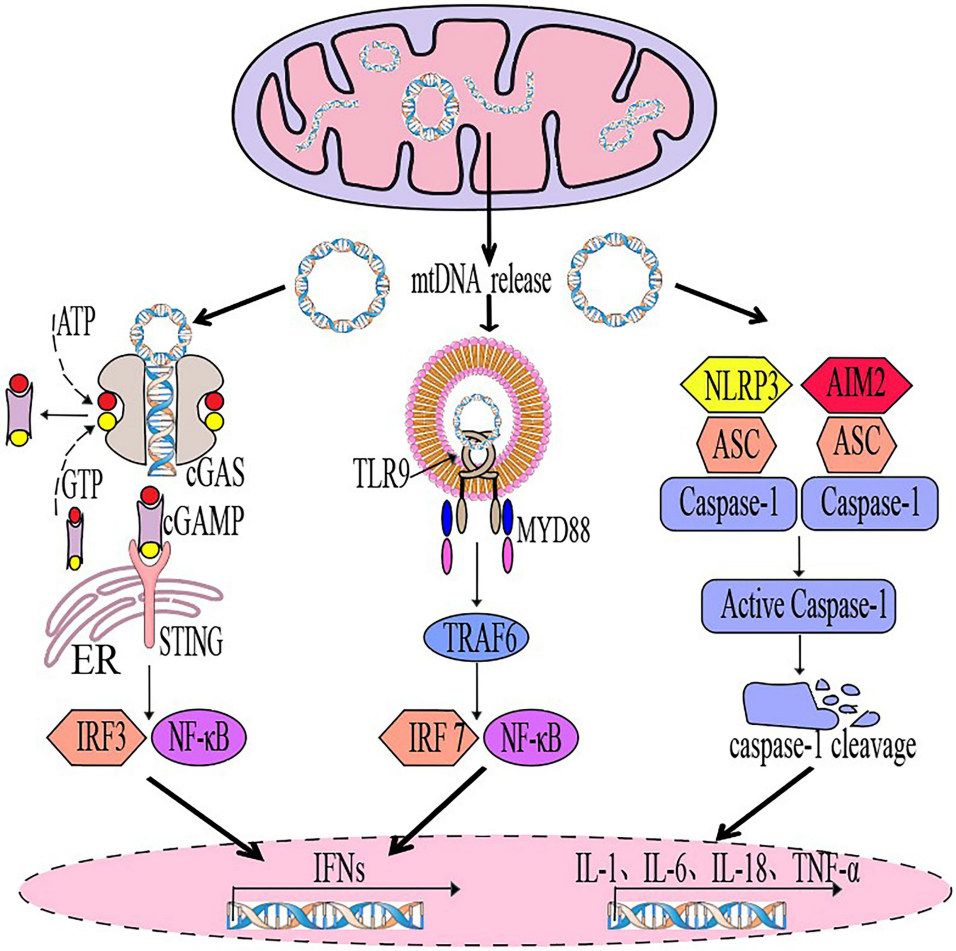

Figure 4 Mechanisms associated with immune triggering and inflammatory response induced by mtDNA release.
Abbreviations: cGAMP,2′3′-Cyclic GMP-AMP; cGAS, cyclic GMP-AMP synthase; STING, Stimulator of interferon genes; MyD88, Myeloid differentiation factor 88; ER, Endoplasmic reticulum; IRF3, Interferon regulatory factor 3; NF-κB, Nuclear factor-kappa B; ASC, Apoptosis-associated speck-like protein containing CARD; IL, Interleukins; IFNs, Interferons; TNF, Tumor necrosis factor.

of pathogen-derived and endogenous substances. Upon encountering DAMPs, NLRP3 undergoes a conformational change, exposing its central nucleotide-binding and oligomerization domains, which promotes its oligomerization and activation.[75] AIM2 is another cellular receptor that recognizes dsDNA and triggers an inflammatory vesicle cascade. Extracellular dsDNA released by necrotic cells is phagocytosed and recognized intracellularly by AIM2, which activates inflammatory vesicles and drives the secretion of cytokines such as IL-18 and IL-1β.[76] As a result, cytoplasmic mtDNA serves as an ideal endogenous agonist, triggering the activation of NLRP3 and AIM2 vesicles. This activation leads to caspase-1 cleavage, and the resulting active caspases promote the maturation and secretion of pro-inflammatory cytokines, including IL-1, IL-6, IL-18, and TNF-α.[77]

ROS Generation

ROS are by-products of cellular aerobic respiration, generated when electrons are transferred from highly reducing compounds to molecular oxygen. ROS encompass several types, including superoxide anion (O2-), hydrogen peroxide (H2O2), hydroxyl radical (HO-), and nitric oxide (NO), which also falls under the category of ROS.[78] Mitochondria are the primary site of ROS generation. Upon exposure to various stimuli such as pathogens, radiation, or photoactivation, electrons leak from the electron transport chain (ETC) complexes in the cytoplasm, cell membrane, or other cellular compartments like peroxisomes and the endoplasmic reticulum (ER). These leaked electrons interact with molecular

oxygen to form superoxide anions, which are subsequently converted to H2O2 through the action of mitochondria-specific superoxide dismutase (SOD).[79,80]

Mitochondrial ROS (mt-ROS) play a critical role in the formation and activation of the NLRP3 inflammasome,[81] a cytoplasmic multiprotein complex composed of NLRP3, ASC, and caspase-1, serving as a key mediator of innate immunity.[82]

mt-ROS promote NLRP3 activation through several mechanisms (Figure 5): (1) promoting NF-κB transcription, which increases the naturally low levels of NLRP3 sensors, (2) oxidizing mtDNA synthesized via the TLR pathway, which directly binds to and activates NLRP3, and (3) enhancing mt-ROS production due to impaired autophagy proteins (eg, beclin-1), further driving NLRP3 activation. NLRP3 is an intracellular sensor that, upon stimulation by mt-ROS, forms an inflammasome through interactions between a single NLRP3 pyrin domain unit and the ASC pyrin domain. ASC then interacts with pro-caspase-1 through its CARD domain, forming an activated inflammasome. This activation triggers caspase-1 and leads to the release of pro-inflammatory factors such as IL-1β and IL-18, thereby contributing to the inflammatory response.[40,83]

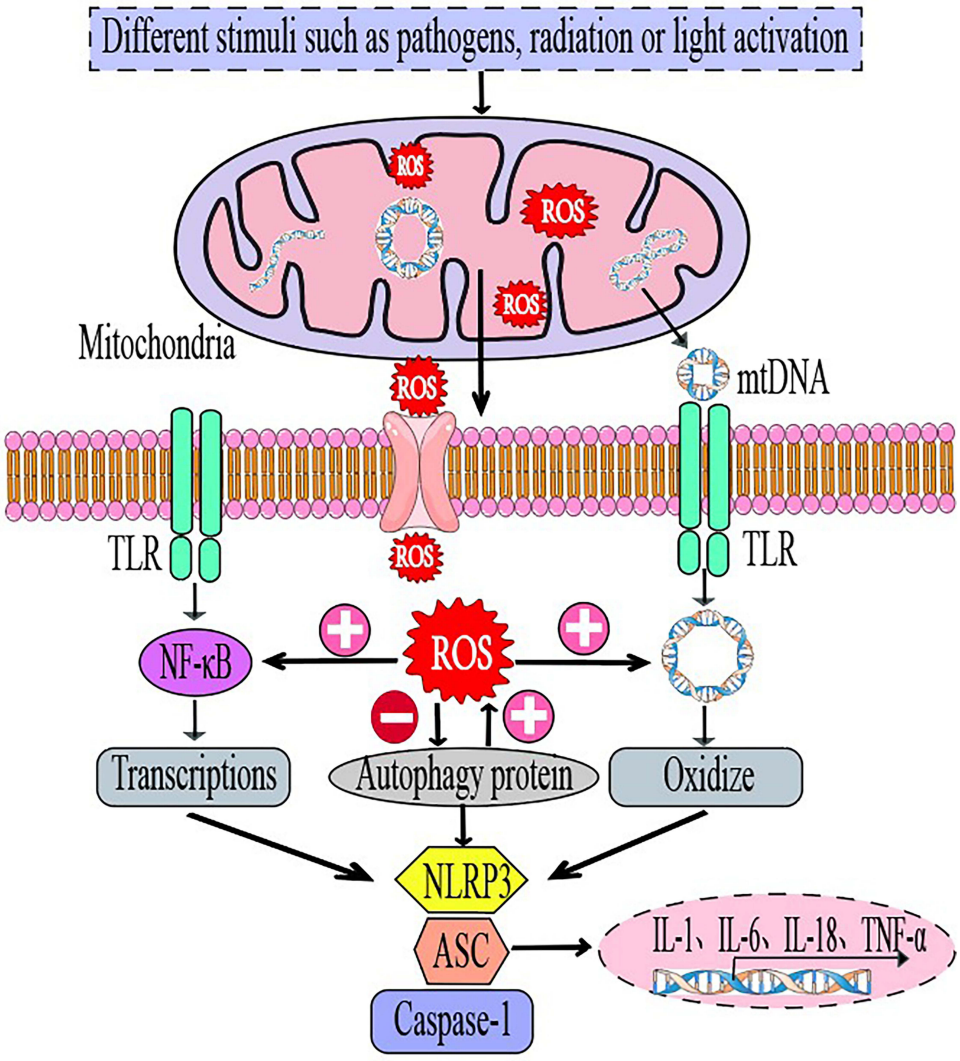

Figure 5 Mechanisms associated with ROS priming to promote NLRP3 activation.
Notes: +, Represents promotion, activation, etc; –, Represents inhibition, slowing, etc
Abbreviations: TLR, Toll-like receptors 9; NF-κB, Nuclear factor-kappa B; IL, Interleukins; IFNs, Interferons; TNF, Tumor necrosis factor.

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Mitochondrial Dynamics

Mitochondrial dynamics refer to the equilibrium state in which mitochondria continuously divide and fuse within the cell, maintaining their morphology, number, size, and structure.[84] Fusion allows for the mixing of mitochondrial contents, helping to preserve the functional integrity of mitochondria, while division enables mitochondria to adapt to changes in intracellular energy demands and to remove damaged mitochondria through autophagy in response to cellular injury.[85] This dynamic balance is crucial for the energy supply, metabolic regulation, and overall health of the cell. Changes in mitochondrial dynamics can manifest as varying morphological forms within the cytoplasm, such as dots, fragments, or elongated structures.[86]

Mitochondrial dynamics are closely tied to essential cellular functions, including cell proliferation, metabolism, and migration, and are regulated by various enzymes and proteins.[87] Mitochondrial fission is primarily controlled by dynamin-related protein 1 (Drp1), which is recruited to the outer mitochondrial membrane upon stimulation. Drp1 interacts with other proteins and hydrolyzes GTP, leading to the contraction of both the inner and outer mitochondrial membranes, ultimately triggering fission. Conversely, mitochondrial fusion is mediated by mitofusin 1 and 2 (Mfn1/2) for the outer membrane and optic atrophy 1 (Opa1) for the inner membrane, which are responsible for promoting membrane fusion.[88] These regulatory mechanisms ensure that mitochondria can quickly respond and maintain cellular homeostasis under various physiological and pathological conditions (Figure 6).

Normal mitochondrial dynamics are essential for maintaining proper cellular function, while dysregulation of these dynamics is closely linked to the development of various diseases, including cancer, autoimmune disorders, and neurodegenerative conditions.[89] In RA, dysregulated mitochondrial dynamics may contribute to disease progression by influencing processes such as mitochondrial ROS production, mtDNA release, and apoptosis, all of which play roles in regulating immune and inflammatory responses. For instance, total glucosides of Paeonia lactiflora (TGP), a commonly used drug for RA treatment, have been shown to reduce oxidative stress and inflammation caused by mt-ROS by correcting mitochondrial dynamics and improving mitochondrial function. This effect may be mediated by the AMPK pathway.[90]

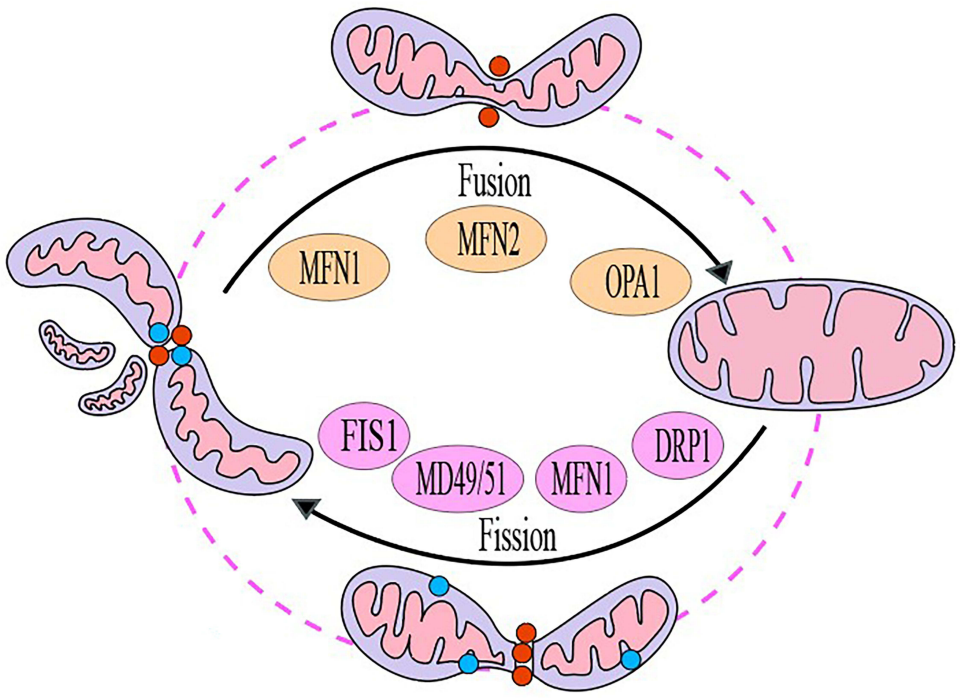

Figure 6 Mitochondrial dynamics.
Abbreviations: Opa1, outer membrane and optic atrophy; Mfn1/2, mitofusin 1 and 2; Drp, dynamin-related protein; FIS1, Fission 1 (mitochondrial outer membrane) Homolog.

Mitochondrial fission and fusion are critical for mitochondrial function, with dynamin-related protein 1 (DNM1L) serving as a key regulator of mitochondrial fission. Upregulation of DNM1L expression has been associated with shorter mitochondrial length and increased RA severity in the ST of RA patients. This is primarily because upregulated DNM1L expression and mitochondrial fission promote cell survival, LC3B-associated autophagy in FLS, and ROS production, all of which contribute to inflammation by regulating the AKT/IKK/NFKBIA/NF-κB signaling pathway. Inhibition of DNM1L in FLS leads to mitochondrial depolarization, mitochondrial elongation, decreased cell viability, reduced production of ROS, IL-8, and COX-2, and increased apoptosis.[91]

Mitochondrial Autophagy

Mitochondrial autophagy, or mitophagy, is a crucial quality control process that allows cells to selectively encapsulate and degrade damaged or excess mitochondria, helping to regulate mitochondrial numbers and maintain energy metabolism.[92] Mitophagy involves four main steps (Figure 7): (1) Mitochondrial damage, often indicated by membrane potential depolarization due to reactive oxygen species (ROS), nutrient deprivation, cellular senescence, or external stressors, which is a prerequisite for autophagy; (2) Encapsulation of mitochondria by autophagosomes: a double-membrane structure forms around the damaged mitochondrion and elongates, eventually enclosing it in an

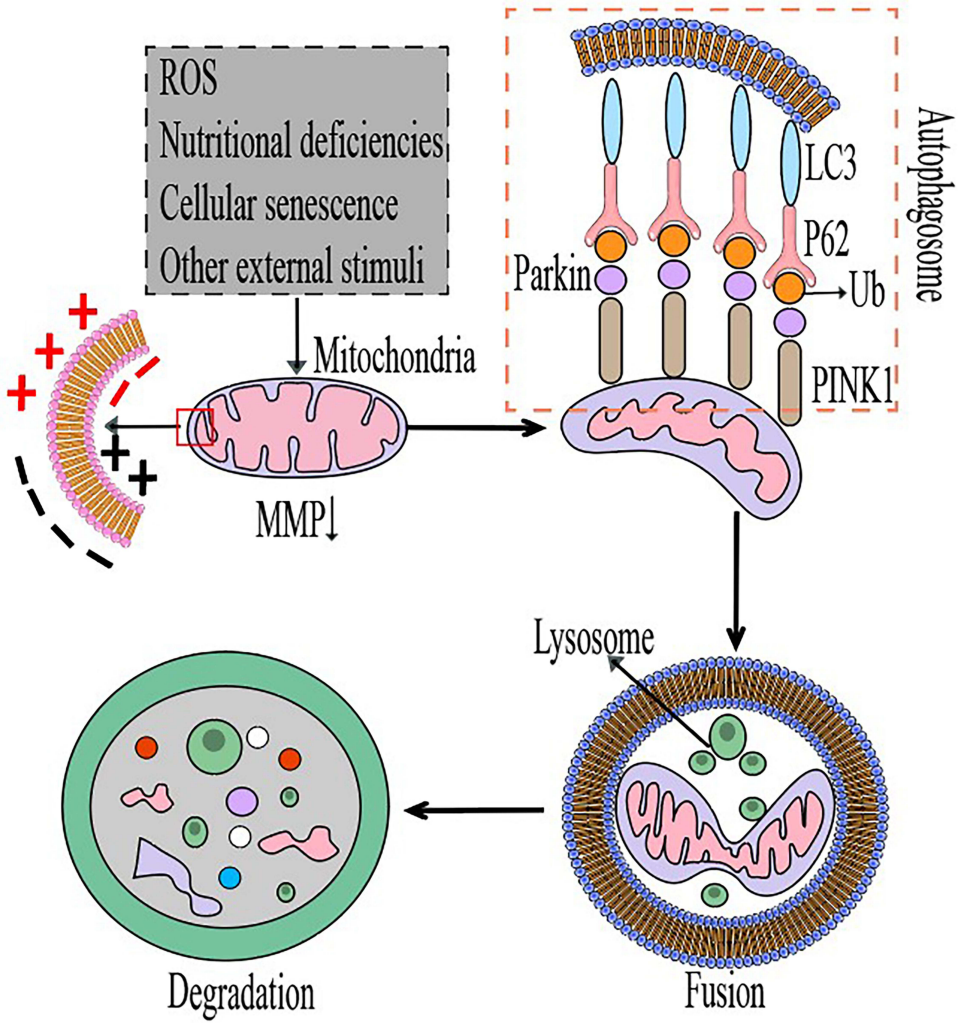

Figure 7 Mitochondrial autophagy process.
Abbreviations: MMP, mitochondrial membrane potential; LC3, Microtubule-associated protein 1 light chain 3; PINK1, PTEN induced putative kinase 1.

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autophagosome; (3) Fusion of the mitochondrial autophagosome with a lysosome; and (4) Degradation of mitochondria by lysosomal enzymes, where lysosomal hydrolases break down the encapsulated mitochondrion.[93]

The mechanisms underlying mitochondrial autophagy can be broadly categorized into two pathways: ubiquitin-dependent and non-ubiquitin-dependent pathways (Figure 8).[94] In the ubiquitin-dependent pathway, mitochondrial surface proteins undergo ubiquitination to induce autophagy. The most extensively studied pathway in this category is the PINK1/Parkin pathway, which plays a key role in clearing damaged mitochondria in mammals. In healthy mitochondria, PINK1 levels are kept low because PINK1 is continuously translocated to the inner mitochondrial membrane and degraded by proteases. However, when mitochondrial membrane potential (MMP, $\Delta\Psi m$) is compromised, the translocation of PINK1 is disrupted, leading to its accumulation on the outer mitochondrial membrane. This accumulation of PINK1 recruits Parkin, an E3 ubiquitin ligase, to the mitochondria. Upon mitochondrial damage, PINK1 phosphorylates Parkin, activating it to ubiquitinate outer mitochondrial membrane proteins, thereby recruiting downstream receptor proteins and initiating ubiquitin-dependent mitophagy.[95]

In addition to the PINK1/Parkin pathway, other ubiquitin-dependent pathways also promote mitochondrial autophagy without relying on Parkin. For instance, PINK1 can directly recruit autophagy receptors such as OPTN and NDP52 to promote autophagy through ubiquitin phosphorylation. Furthermore, several other E3 ubiquitin ligases, including SMURF1, MUL1, and Gp78, can also participate in the ubiquitination of mitochondrial proteins, thereby inducing mitochondrial autophagy.[96]

Unlike PINK1/Parkin-mediated pathways, certain proteins located on the outer mitochondrial membrane contain LIR (LC3-interacting region) motifs and serve as autophagy receptors. These proteins can directly bind to LC3 without the need for ubiquitination, initiating mitochondrial autophagy. In mammals, key receptors involved in this non-ubiquitin-dependent pathway include Nip3-like protein X (NIX)/BCL2-interacting protein 3-like (BNIP3L), BCL2-interacting protein 3 (BNIP3), and FUN14 domain-containing protein 1 (FUNDC1).[97,98]

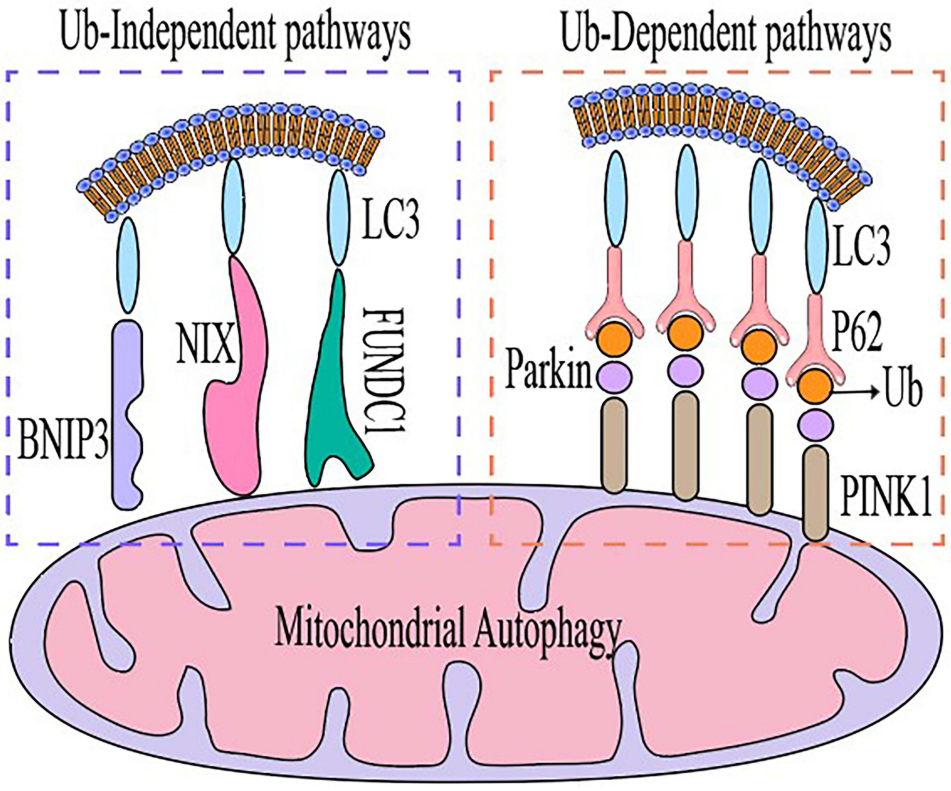

Figure 8 Ubiquitin-dependent and non-ubiquitin-dependent mitochondrial autophagy.
Abbreviations: LC3, Microtubule-associated protein 1 light chain 3; PINK1, PTEN induced putative kinase 1. BNIP3, BCL2-interacting protein 3; FUNDC1, FUN14 domain-containing protein 1.

Mitochondrial autophagy selectively removes damaged or dysfunctional mitochondria. By clearing these damaged mitochondria, the process helps maintain mitochondrial quality and function, reduces ROS production, and limits the release of mtDNA, thereby inhibiting inflammatory responses. When mitochondrial autophagy is impaired, mitochondrial dysfunction can occur, leading to excess ROS production and accumulation, which triggers immune responses and oxidative cellular damage, contributing to the onset of RA. For example, the traditional Chinese herbal formula Gui Zhi Shao Yao Zhi Mu Tang (GSZG), used to treat RA-associated bone destruction, has been shown to inhibit bone erosion by regulating the ROS/NF-κB axis through the PINK1/Parkin-mediated autophagy pathway, thus reducing osteoclast precursor production.[99] Additionally, various bioinformatics approaches have identified mitochondrial autophagy-related genes, such as ATG5, GSK3A, MFN1, NRAS, RELA, RRAS2, SLC25A46, and TSCA, as potential biomarkers for RA diagnosis and progression.[100]

Mitochondrial Biogenesis

Mitochondrial biogenesis is the process by which new mitochondria are generated through the growth and division of pre-existing mitochondria, producing large amounts of ATP. This process is coordinated by both mitochondrial DNA (mtDNA) and the nuclear genome.[101] The primary regulator of mitochondrial biogenesis is peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α).[102] PGC-1α activates nuclear respiratory factor 1 and 2 (Nrf1/2) and estrogen-related receptor-α, which, in turn, stimulate mitochondrial transcription factor A (TFAM), promoting mtDNA replication and transcription, thereby driving mitochondrial biogenesis.[103] PGC-1α itself is regulated by various pathways, including the AMP-dependent protein kinase (AMPK) and cAMP-response element-binding protein (CREB) pathways. The sirtuin 1 (SIRT1)/PGC-1α signaling pathway also plays a significant role in regulating mitochondrial biogenesis by acting on PGC-1α to promote mtDNA replication and transcription.[104]

Proper mitochondrial biogenesis can increase both the number and functionality of mitochondria, boosting cellular energy metabolism and enhancing immune and anti-inflammatory responses.[105] However, when mitochondrial biogenesis is abnormally activated, it can lead to a substantial increase in mitochondrial numbers and excessive mtDNA release, which may result in the overproduction and accumulation of ROS. This, in turn, can trigger immune responses and cause inflammatory damage.

Mitochondrial Antiviral Signaling Proteins

Mitochondrial antiviral signaling protein (MAVS) is a junction protein located on the outer mitochondrial membrane, playing a critical role in the innate immune system. MAVS is also known by other names, such as IFN-β promoter stimulator (IPS-1), caspase activation and recruitment domain (CARD)-containing adaptor inducing IFN-β (Cardif), and virus-induced signaling adapter (VISA).[106] In the resting state, MAVS remains inactive. However, during viral infections, the interferon gene stimulator protein (STING), also known as MITA, MPYS, or ERIS, acts as a crucial intermediary in the recognition of DNA viruses, with the MAVS-STING interaction being key to mitochondria-mediated antiviral innate immune responses.[107] When RNA viruses are detected, RIG-I recognizes viral double-stranded RNA, activating the RIG-I/MAVS antiviral pathway.[108]

Recent research on MAVS' downstream signaling pathways has shown that it mediates viral activation of NF-κB and IRF3(Figure 9):[109] (1) MAVS strongly activates IRF3 through the Toll-like receptor (TLR) and RIG-I-like receptor (RLR) families. During interferon (IFN) induction, MAVS recruits TANK-binding kinase 1 (TBK1) and IKKϵ, which phosphorylate interferon regulatory factors 3 and 7 (IRF3/IRF7). IRF3/IRF7 are essential for the production of IFN. (2) In the resting state, NF-κB is sequestered in the cytoplasm by members of the inhibitory κB (IκB) family. Upon MAVS activation, IκB kinases (IKKα, IKKβ, and IKKγ) are recruited. IKKγ, also known as the NF-κB essential modulator (NEMO), induces the phosphorylation of IκB. This phosphorylation causes IκB degradation, allowing NF-κB to translocate to the nucleus and bind to enhancers/promoters of target genes, thereby triggering a pro-inflammatory response.

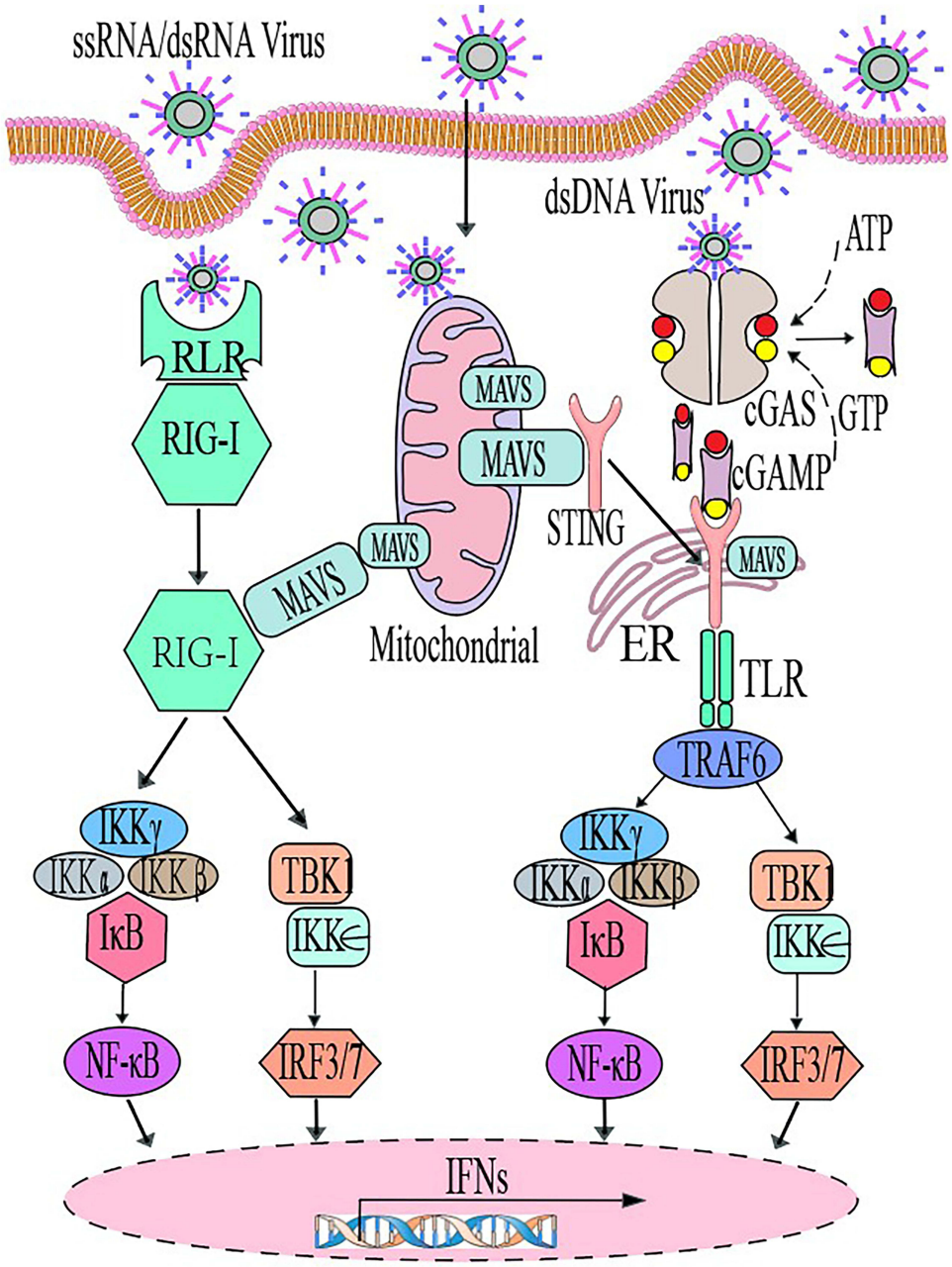

Figure 9 Schematic diagram of MAVS immune triggering and inflammatory response.
Note: ssRNA/dsRNA viruses activate RIG-I/MAVS via TLR; ssDNA viruses activate RIMAVS-STING via RLR, both of which ultimately activate the NF-κB and IRF3 pathways, eliciting immune-triggered and pro-inflammatory responses.
Abbreviations: MAVS, Mitochondrial antiviral signaling protein; RLR, RIG-I-like receptor; RIG-I, retinoic acid-inducible gene I; TBK1,TANK-binding kinase 1; TLR, Toll-like receptor; IKK, IκB kinases; IRF, Interferon regulatory factor; NF-κB, Nuclear factor-kappa B; IFN, Interferon

NLRP3 Inflammasome

The NLRP3 inflammasome is a multiprotein complex composed of NLRP3, ASC, and caspase-1. Mitochondrial dysfunction can activate the NLRP3 inflammasome, leading to the activation of caspase-1 and the subsequent release of inflammatory cytokines, such as IL-1β and IL-18, which are central to the inflammatory response (Figure 4).[110]

Ferulic Acid

Ferulic acid, also known as fumaric acid, is a significant modulator of innate immunity. Fumaric acid hydratase (FH) is a metabolic enzyme in the tricarboxylic acid (TCA) cycle that catalyzes the reversible conversion of fumarate to malate.

When mitochondrial dysfunction occurs, FH activity decreases, leading to the abnormal accumulation of fumaric acid. Studies have shown that increased intracellular levels of fumaric acid induce remodeling of the mitochondrial network and the formation of mitochondria-derived vesicles, which release mtDNA into the cytoplasm. This triggers the activation of the cGAS-STING-TBK1 pathway, initiating immune responses and inflammatory reactions.[111]

LKB1-AMPK Signaling Pathway

The LKB1-AMPK signaling pathway plays a crucial role in regulating cellular metabolism, proliferation, and survival in response to changing nutrient and energy demands. LKB1-AMPK signaling promotes ATP-generating catabolic pathways and allows for metabolic flexibility in T cells under energetic stress. Through metabolic reprogramming, LKB1 and AMPK influence T cell differentiation and function.[112]

Activation of LKB1 is linked to changes in mitochondrial metabolism and fitness, as well as increased mevalonate metabolism under specific conditions. By regulating various downstream targets, AMPK signaling inhibits glycolysis, glutaminolysis, and fatty acid synthesis while promoting catabolic processes like mitophagy and autophagy. AMPK also drives mitochondrial biogenesis by facilitating mitochondrial apoptosis and regulating mitochondrial dynamics, thereby impacting immune and inflammatory responses.[113]

Role of the Mitochondrial Bilayer Membrane Structure in the Regulation of Inflammation

The mitochondrial bilayer membrane structure provides dual-layered control over cellular processes. The OMM serves as a platform for signaling molecules, such as MAVS in the RIG-I pathway, and NLRP3 inflammasomes.[114] Mitochondrial stress and injury result in the release of mitochondrial damage-associated molecular patterns (mtDAMPs) from their respective PRRs into the cytoplasm or extracellular space. These mtDAMPs include mtDNA, ATP, formyl peptides, cardiolipin, cytochrome c, succinate, and mitochondrial transcription factor A (TFAM). Once released, mtDAMPs activate NLRP3 inflammasomes, upregulate MyD88 and NF-κB, and increase the production of cytokines like TNFα, IL-1, IL-6, and IL-10, playing a significant role in regulating cellular stress and inflammation.[115]

Other Mechanisms

Mitochondria also influence immune and inflammatory responses by regulating cellular metabolism, calcium homeostasis, endoplasmic reticulum stress, and other signaling pathways.[116]

Impact of Mitochondrial Dysfunction on RA Immune Cells

Innate immune cells, including T cells, macrophages, and dendritic cells (DCs), play a crucial role in regulating the immune-inflammatory response in RA. Abnormal activation of these cells can lead to the overproduction of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-17, exacerbating the disease.[117] The energy required for the survival and function of immune cells is primarily derived from glucose, fatty acids, and amino acids. These molecules fuel the tricarboxylic acid (TCA) cycle via glucose metabolism, gluconeogenesis, and glutaminolysis, respectively. Mitochondria are central to energy production in immune cells, with oxidative phosphorylation providing a stable ATP supply under normal conditions. Research has shown that disruptions in immune cell metabolism, particularly mitochondrial dysfunction, are key contributors to the pathogenesis of RA.

T Cells

Under normal physiological conditions, primary T cells transform into effector T cells after recognizing antigens presented by antigen-presenting cells (APCs), initiating proliferation. Different activation states of T cells require distinct metabolic patterns to meet their functional needs. Effector T cells, including pro-inflammatory T cells found in inflammatory tissue lesions, rely heavily on rapid glucose uptake and glycolysis to meet their energy demands.[118] In short, T cells require substantial energy to exert their effects (Figure 10).

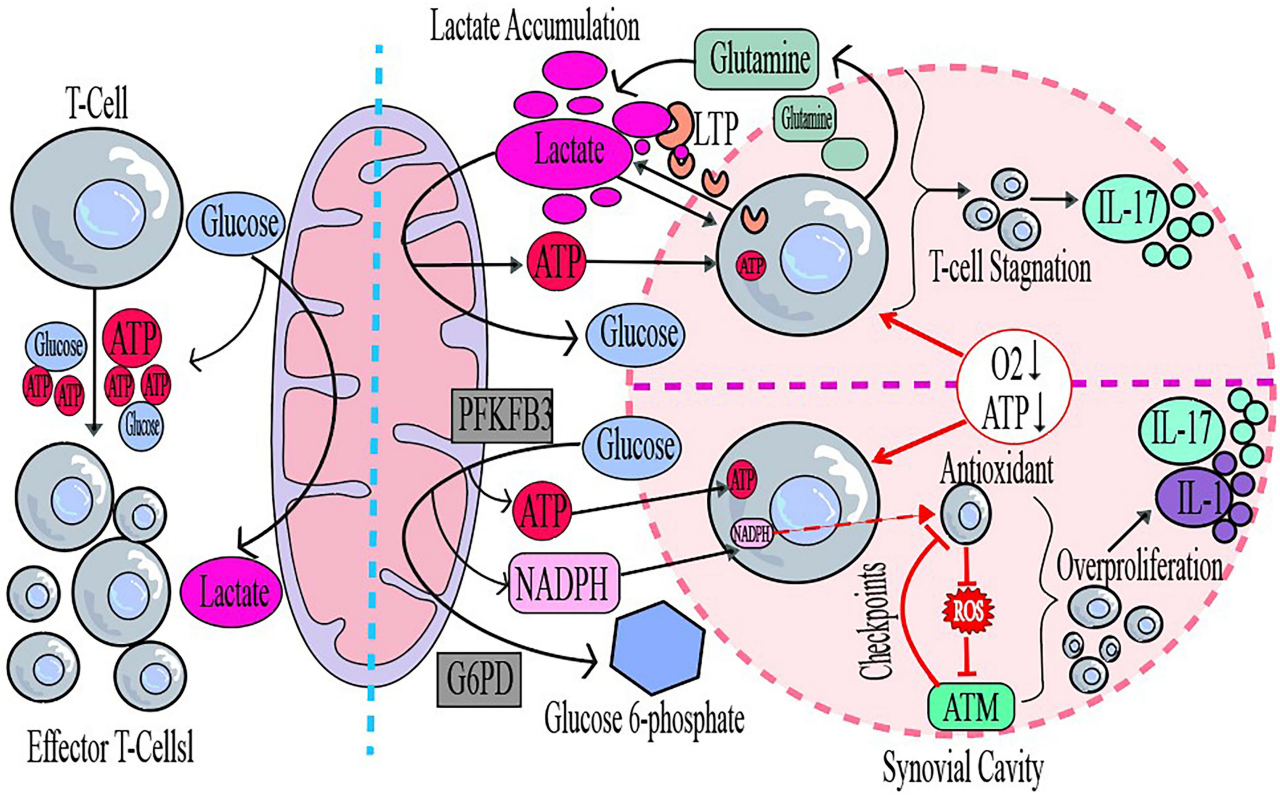

Figure 10 Effect of mitochondrial dysfunction on T cells in RA.
Abbreviations: ATP, Adenosine triphosphate; L, lactate transporter protein;PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase3; G6PD, glucose-6-phosphate dehydrogenase; NADPH, nicotinamide adenine dinucleotide phosphate; ATM, ataxia telangiectasia-mutated; IL, Interleukins.

In RA patients, the synovial cavity presents a relatively hypoxic microenvironment, with significantly reduced glucose concentrations. This forces tissue-resident cells to seek alternative energy sources, such as lactate.[119] Research has shown that under hypoxic and low-glucose conditions, $CD8^+$ T cells in RA convert glutamine to lactate to meet their energy needs.[120] Thus, both $CD4^+$ and $CD8^+$ T cells in RA patients may exhibit mitochondrial defects that compel them to rely on lactate for energy. Persistent hypoxia and low glucose levels can lead to lactate accumulation. Studies suggest that in RA synovitis, this accumulation upregulates lactate transporter protein(LTP) expression in $CD4^+$ and $CD8^+$ T cells, supporting the hypothesis that synovial T cells consume lactate. Lactate consumption has been linked to the persistence of T cells in inflamed tissues, with lactate-consuming T cells producing higher levels of IL-17, further exacerbating the inflammatory response.[121]

As RA progresses, T cells shift their energy metabolism beyond mitochondria and lactate utilization, diverting carbon into the pentose phosphate pathway (PPP) to produce NADPH and nucleotides. This process is regulated by two key rate-limiting enzymes: 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) and glucose-6-phosphate dehydrogenase (G6PD).[122] PFKFB3, a crucial rate-limiting enzyme in glycolysis, is suppressed in RA T cells, leading to decreased glycolysis and reduced T cell activation.[123] In contrast, G6PD is overexpressed in RA T cells, resulting in elevated NADPH levels and increased reduced glutathione (GSH). Glutathione's antioxidant properties impair the signaling functions of intracellular ROS, which, in turn, prevents activation of the ATM kinase, a cell cycle checkpoint regulator. This leads to the overproliferation of T cells, favoring inflammatory Th1 and Th17 differentiation, further worsening the inflammatory response.[124]

B Cells

A key feature of RA is the production of autoantibodies, including RF and ACPA, which are primarily produced by B cells. Studies on B cell biology show that naïve B cells are metabolically quiescent, primarily storing energy and

synthesizing precursors. This relatively inactive state is lifted when B cells are activated, allowing them to use stored energy for growth and proliferation.[125] While the role of mitochondria in B cell development and differentiation is well-established, there is limited data on how mitochondrial regulation of B cell function contributes to RA pathogenesis.

Experimental evidence provides indirect insights into this relationship. First, the effects of mitochondria on B cells may involve the peroxisome proliferator-activated receptor γ (PPARγ), a ligand-activated transcription factor involved in adipogenesis and lipid metabolism, which regulates B cell function and plays a critical role in antibody responses.[126] Second, B-cell activation factor (BAFF), also known as B lymphocyte stimulator (BLyS), plays a role in B cell activation, proliferation, and differentiation.[127] BAFF-induced signaling regulates B cell metabolism by regulating glucose metabolism and mitochondrial activity. Treatment with BAFF increases B cell size, cellular protein content, and mitochondrial membrane potential, making BAFF-treated B cells more prone to proliferation.[128]

Macrophages

Macrophages play a crucial role in the pathogenesis of RA and are key cells in bone immunity. These cells can be polarized into two types: pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages, depending on environmental signals. Macrophages interact with various cell types, including T cells, B cells, and fibroblast-like synoviocytes, leading to the production of numerous inflammatory cytokines, which contribute to bone and cartilage destruction.[129] In RA, M1 macrophages are characterized by increased mitochondrial activity, which increases their energy demands. To meet these needs, macrophages shift their glucose metabolism from oxidative phosphorylation to glycolysis, driving the production of large amounts of ROS and ATP.[130] This increased mitochondrial activity is associated with the formation of mitochondria-associated membranes (MAMs), structures that connect mitochondria with other organelles, such as the endoplasmic reticulum (ER).[131] The formation of MAMs allows mitochondria to exchange calcium with the ER, regulating various cellular signaling pathways. This interaction promotes the production of pro-inflammatory cytokines, including CCL18, TNFα, IL-6, and IL-1β, and histone modifications, which are closely linked to the progression of RA.[132]

Effects of Mitochondrial Dysfunction on RA Osteoblasts

Fibroblast-Like Synoviocytes (Figure 11)

Fibroblast-like synoviocytes (FLS) are the primary cell type in the synovial membrane, comprising a lining layer and a sublining layer. Their main function is to produce lubricin and hyaluronic acid, essential for joint lubrication.[133] During the progression of RA, mitochondrial dysfunction, primarily involving abnormalities in mitochondrial fission and autophagy, plays a critical role in FLS metabolism and apoptosis. FLS not only secrete inflammatory cytokines and chemokines that drive inflammation but also promote the production of matrix metalloproteinases, which degrade cartilage and stimulate osteoclast differentiation, leading to bone erosion.[134]

In RA, mitochondria in FLS exhibit stress-related phenotypes, such as fragmentation and elevated expression of the mitochondrial fission GTPase dynamin-related protein 1 (Drp1).[91] DNM1L, a key regulator of mitochondrial fission, is highly expressed in FLS. Silencing DNM1L expression increases mitochondrial length and induces mitochondrial depolarization. Inhibiting mitochondrial fission also decreases the ratio of LC3B-II to LC3B-I, promotes FLS apoptosis, and reduces inflammation in RA synoviocytes.[135]

The synovial environment in RA patients is characterized by hypoxia, which increases mitochondrial membrane potential by activating mitochondrial ATP-sensitive potassium channels. This leads to mitochondrial dysfunction in FLS and is associated with elevated ROS production from a dysfunctional electron transport chain. The increased ROS levels further upregulate key proteins in autophagy, such as ATG5 and LC3, promoting the formation of autophagic vesicles.[136] Moreover, hypoxia-induced mitochondrial dysfunction in RA FLS can cause mutations in the mitochondrial genome, resulting in increased secretion of pro-inflammatory cytokines, including IL-17 and TNF-α, and disruption of mitochondrial homeostasis.[137] TNF-α, in particular, acts as a mitochondrial stressor, reducing mitochondrial autophagy and leading to the release of mtDNA, which further drives the production of additional pro-inflammatory factors.[138] Mitochondria are key regulators of programmed cell death, with the balance between pro-apoptotic Bax and anti-

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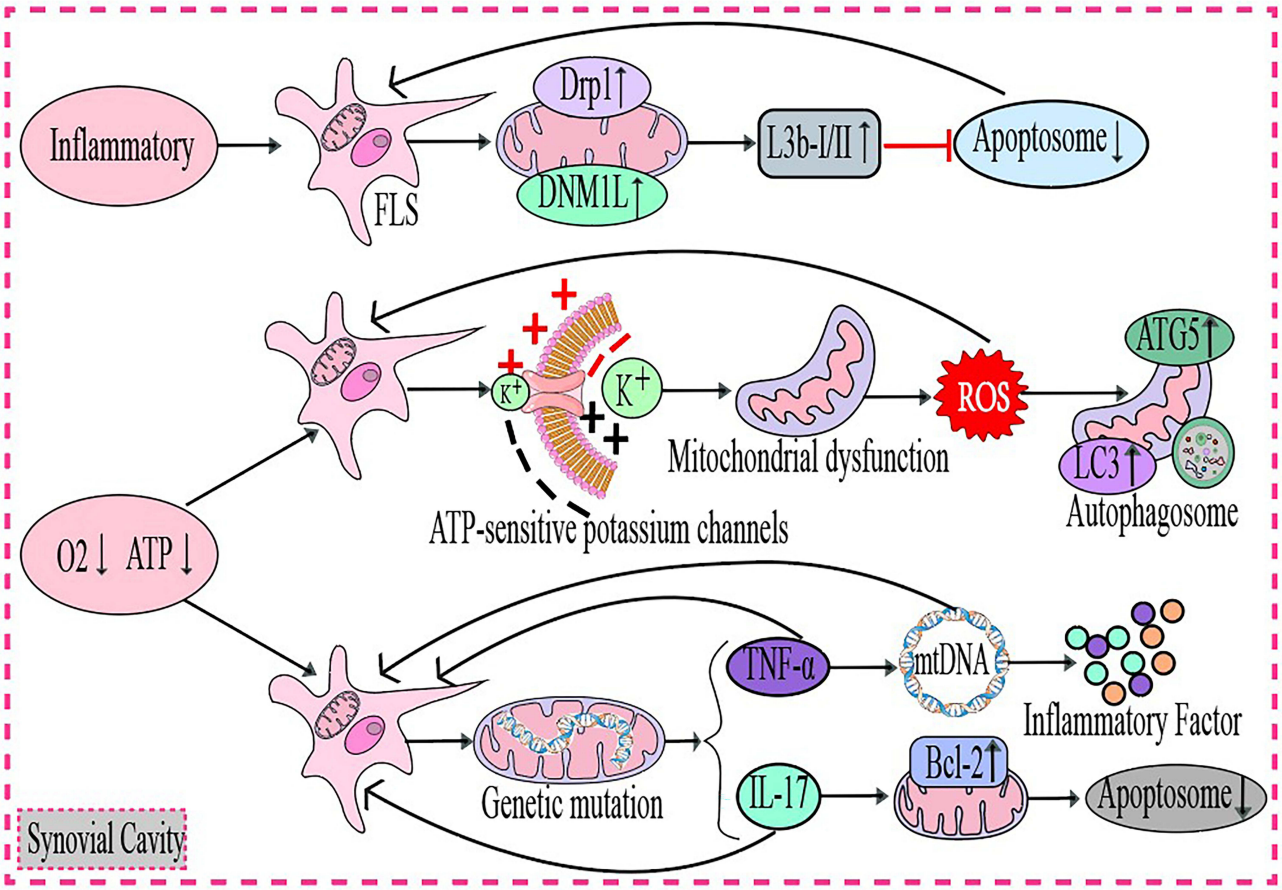

Figure 11 Effect of mitochondrial dysfunction on FLS in RA.
Abbreviations: FLS, Fibroblast-like synoviocytes; Drp1, Dynamin-related protein 1; IL, Interleukins; DNM1L, Dynamin-1-like Protein; LC3, Microtubule-associated protein 1 light chain 3; ATG5, Autophagy-related gene 5; IL-17, Interleukins 17; TNF-α, Tumor Necrosis Factorα; Bcl-2, B-cell lymphoma-2.

apoptotic Bcl-2 proteins playing a key role in FLS survival. IL-17 has been shown to increase the expression of the anti-apoptotic protein Bcl-2 in RA FLS, promoting their survival. Consequently, IL-17 is considered a significant factor in rescuing RA FLS from apoptosis, contributing to the persistence of inflammation.[139,140]

Osteoclasts

Osteoclasts are derived from osteoclast precursor cells, which originate from the hematopoietic lineage of monocytes and macrophages. Their primary role in bone homeostasis is to secrete substances that dissolve inorganic bone components and degrade bone matrix proteins, promoting bone resorption. In RA, osteoclasts are the key effector cells responsible for bone destruction.[141] The activity and function of osteoclasts are closely linked to mitochondrial health, as alterations in mitochondrial function can either inhibit or overactivate osteoclasts, disrupting bone tissue homeostasis. The influence of mitochondria on osteoclast activity can be understood through the following mechanisms (Table 1):

(1) Oxidative phosphorylation energy supply mode: Oxidative phosphorylation is the primary energy source for osteoclast proliferation and differentiation. Studies by Lemma et al[142] revealed that cellular oxygen consumption and the expression of respiratory chain-related proteins significantly increased during osteoclast proliferation and differentiation. Further, research by Kim et al[143] demonstrated that inhibiting the mitochondrial oxidative phosphorylation pathway suppressed osteoclast differentiation, highlighting the critical role of mitochondrial oxidative phosphorylation in supporting osteoclast development and function.

(2) ROS production-clearance: Mitochondria are the primary site for both the production and clearance of ROS. During oxidative phosphorylation, a large amount of ROS is generated as a byproduct of energy production.

Accumulation of ROS can lead to oxidative stress, causing severe damage to cell structures and functions. To counter this, mitochondria possess their own antioxidant system, which includes enzymatic components such as peroxidase, Mn-SOD, and non-enzymatic systems like cytochrome and reduced coenzyme Q10.[148] These systems maintain a dynamic balance between ROS production and scavenging, which plays a crucial role in regulating osteogenesis and osteoclast differentiation. Arai et al[153] found that elevated intracellular ROS levels inhibited osteoblast mineralization, while ROS also acted as signaling molecules promoting osteoclast differentiation. Studies by Fraser et al and Baek et al[144,145] showed that H2O2 promoted the proliferation and differentiation of osteoclasts. Evidence of H2O2 activity was found in the cranial bones of mice, in bone marrow cells, and in human bone marrow cells. Additionally, a study by Srinivasan et al[154] demonstrated that adding antioxidants to mouse cells significantly reduced the number of differentiated and mature osteoclasts. This suggests that intracellular ROS influences osteoclast differentiation through pathways such as RANK/RANKL signaling, as NF-κB activity was found to be elevated under hypoxic conditions. Ishii et al[155] discovered that ROS were involved in the transcription of PGC-1β, which positively regulates ROS production, thereby promoting osteoclastogenesis. Furthermore, Kim et al[156] found that knocking down the endoplasmic reticulum transmembrane protein 64 in mice reduced intracellular calcium oscillations, decreased ROS levels, and inhibited bone resorption, suggesting that calcium signaling may also be a pathway through which ROS regulate osteoclast differentiation.

(3) Mitochondrial dynamics pathway: Mitochondrial dynamics involve several key processes, including mitochondrial biogenesis, fusion, and autophagy. Mitochondrial biogenesis replenishes new mitochondria, while autophagy removes senescent and damaged mitochondria. Mitochondrial fusion and fission provide energy and support signaling pathways essential for cellular functions. Lemma et al[142] observed that osteoblast differentiation is associated with changes such as increased mitochondrial size, number, and elevated expression of electron transport chain complexes. This suggests a potential link between mitochondrial dynamics and osteoblast differentiation, possibly mediated by PGC-1β. PGC-1β, a member of the peroxisome proliferator-activated receptor gamma coactivator 1 family, plays a key role in regulating transcription during mitochondrial biogenesis.

(4) Mitochondrial calcium unidirectional transporter (MCU): The MCU is the primary calcium transporter within mitochondria and is crucial for maintaining mitochondrial structure and function.[157] Research by Yinbo Wang[146] demonstrated that MCU promotes osteoclast differentiation, playing distinct roles at different stages. During the early stage of osteoclast differentiation, MCU increases mitochondrial calcium levels, supporting ATP production needed for differentiation. In the later stages, MCU induces ROS production, which further promotes osteoclast differentiation.

(5) Mitochondrial Ferroptosis: Ferroptosis, or iron-dependent cell death, is a non-apoptotic form of necrotic cell death driven by the accumulation of intracellular iron and toxic lipid peroxides.[158] Iron overload is a critical factor in ferroptosis. Osteoclast differentiation is closely tied to the OPG/RANK/RANKL signaling pathway, with factors such as RANK, RANKL, TNF, and IL-6 driving macrophage-to-osteoclast differentiation.[159] Li et al[147] found that iron overload induces the expression of RANKL and IL-6, which, in turn, promotes osteoclast differentiation. This suggests that mitochondrial ferroptosis may be mediated by the OPG/RANK/RANKL pathway during the osteoclast differentiation process.

Osteoblasts

Osteoblasts are specialized cells responsible for bone formation during bone repair and reconstruction. They primarily differentiate from bone mesenchymal stem cells (BMSCs) in the bone marrow. Abnormalities in osteoblast differentiation and function play a key role in the development of bone metabolic diseases,[160] which manifest as decreased bone mass and sparse trabeculae, leading to increased bone fragility and a higher risk of fractures. Mitochondria serve as the energy source for cellular functions, producing large amounts of ATP through oxidative phosphorylation to support osteoblast metabolism. Additionally, mitochondria influence osteoclastogenesis by participating in osteogenesis-related signaling pathways. The regulation of osteoblast function by mitochondria is primarily mediated through the following mechanisms (Table 1):

(1) Regulation of oxidative phosphorylation: Osteoblast differentiation and mineralization require substantial energy to synthesize high levels of collagen and bone matrix proteins. Mitochondrial oxidative phosphorylation is crucial for maintaining osteoblast function and is also involved in regulating osteogenic signaling pathways that affect osteoblast proliferation and differentiation. β-catenin, a key component in this process, enters the nucleus and binds to transcription

Table 1 Effects of Mitochondrial Dysfunction on RA Osteoblasts

Bone Cell	Mitochondrial Involvement Approach	Relevant Mechanisms	References
Osteoclast	1.Oxidative	1.Energy supply	[142,143]
	2.ROS production-clearance	2.ROS↑	[144,145]
	3.Mitochondrial dynamics	3.PGC-1β↑	[142]
	4.MCU	4.MCU→Ca2+↑→ATP↑→ROS↑	[146]
	5.Mitochondrial iron death	5.Induces RANK, RANKL,TNF-α and IL-6 expression	[147]
Osteoblast	1.Oxidative phosphorylation	1.Energy supply, promoting β-catenin acetylation	[148]
	2.Mitochondrial biogenesis	2.AMPK, SIRT1,SIRT3↑→PGC-1α↑→ROS↓→OB	[149,150]
	3.Mitochondrial dynamics	3.Upregulation of Mnf2 levels	[151]
	4.Mitochondrial autophagy	4.ATP↓,ROS↓→BMSCs↓	[163]

Abbreviations: ROS, Reactive oxygen species; PGC-1β, Peroxisome proliferator-activated receptor gamma coactivator 1-β; MCU, Mitochondrial calcium unidirectional transporter; ATP, Adenosine triphosphate; TNF-α, Tumor necrosis factor-α; IL-6,Interferons-6; AMPK, Adenosine 5'-monophosphate (AMP)-activated protein kinase; SIRT, Sirtuin; PGC-1α,Proliferator-activated receptor gamma coactivator 1-alpha; OB, Osteoblast; BMSCs, bone mesenchymal stem cells.

factors such as LEF/TCF, regulating the expression of osteogenic genes like Runx2 and osteocalcin.[161] These genes are essential for osteogenesis. β-catenin maintains its activity through acetylation, a process dependent on the mitochondria-produced acetyl donor, acetyl-CoA. Acetyl-CoA is generated in the tricarboxylic acid cycle and exported from the mitochondria as citrate. Shares et al[148] found that stimulating mitochondrial oxidative phosphorylation with galactose increased acetyl-CoA levels, upregulating β-catenin acetylation and promoting osteogenic differentiation. Conversely, inhibiting ATP-citrate lyase (ACLY) with SB204990 reduced β-catenin acetylation levels, reversing the effects of galactose-stimulated mitochondrial oxidative phosphorylation on osteoblast differentiation. These findings suggest that mitochondrial oxidative phosphorylation supports osteoblast differentiation by promoting β-catenin acetylation.

(2) Mitochondrial biogenesis: Mitochondrial biogenesis is the process by which mature mitochondria generate new mitochondria, co-regulated by mtDNA and nuclear DNA (nDNA). This process is essential for repairing mitochondrial structures and maintaining their function. The key regulator of mitochondrial biogenesis is peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which acts as an intermediary regulator. PGC-1α is activated by upstream signaling molecules such as AMPK, SIRT1, and SIRT3. Once activated, PGC-1α influences downstream signaling molecules, including NRF-1 and NRF-2, which upregulate mitochondrial biogenesis, reduce ROS production, maintain mitochondrial quality, and promote the proliferation and differentiation of osteoclasts.[149,150]

(3) Mitochondrial dynamics: Mitochondrial dynamics, encompassing processes like fission and fusion, play a vital role in osteoblast activity by influencing energy production, ROS accumulation, and signal transduction. Forni et al[151] found that changes in mitochondrial dynamics are critical for the differentiation of MSCs into osteoblasts, adipocytes, and chondrocytes. Increased levels of Mnf2 and increased mitochondrial fusion were shown to promote osteogenic differentiation. Similarly, Wan et al[162] demonstrated that regulating mitochondrial dynamics, including accelerated mitochondrial production, helps maintain the energy balance required during osteoblast proliferation and differentiation.

(4) Mitochondrial autophagy: Dysregulated mitochondrial autophagy disrupts the functional integrity of mitochondria, leading to reduced ATP production and excessive oxidative stress due to ROS accumulation. This impairs the survival and bone-forming abilities of BMSCs, directly affecting osteoblast proliferation and differentiation.[163]

Conclusion

In recent years, significant progress has been made in understanding the role of mitochondria in immune cell function and the pathogenesis of autoimmune diseases like RA. Various factors, including hypoxia, oxidative stress, and mtDNA mutations, can lead to mitochondrial dysfunction, which in turn affects RA through multiple mechanisms: (1) Direct Effects: Mitochondrial dysfunction directly influences the differentiation and function of synoviocytes, osteoclasts, and osteoblasts, disrupting bone metabolic homeostasis and contributing to RA pathogenesis. (2) Indirect Effects: Mitochondrial components, such as mtDNA, ROS, and the processes of mitochondrial dynamics, autophagy, and biogenesis, play key roles in immune regulation. These dysfunctions can trigger the release of mitochondrial antiviral

signaling proteins (MAVS), NLRP3 inflammasomes, and signaling pathways such as LKB1-AMPK, leading to immune dysregulation, which promotes the development of RA and amplifies inflammatory responses.

However, the effects of mitochondrial dysfunction on other immune cells, such as neutrophils and B cells, require further exploration. Neutrophils, a source of self-antigens that drive inflammation and tissue damage.It has been found that mitochondrial stress induces the rapid release of mitochondrial protein-derived molecules (eg, N-formyl peptide (mtNFP) and N-formylmethionine (fMet)), both of which act through the Formyl Peptide Receptor-1 (FPR1), which is abundantly expressed on neutrophils, and which, in combination with homologous ligands, can trigger the release of antigens and activation processes in neutrophils and play a role in inducing inflammation in RA.[164,165] Consequently, Mitochondrial dysregulation in neutrophils significantly impacts the progression of RA.[166]

Currently, the regulatory mechanism of mitochondria on neutrophils and B cells is mainly related to metabolic reorganization; when mitochondria are dysfunctional, the metabolic mode of neutrophils and B cells tends to favor glycolysis rather than oxidative phosphorylation, leading to abnormal activation of neutrophils and B cells, and inducing inflammatory responses in RA.[152] However, other data on mitochondrial regulation of neutrophils and B cells to induce RA are limited and deserve further study.

In clinical settings, antirheumatic drugs that regulate mitochondrial homeostasis by regulating mitochondrial biosynthesis, dynamics, and autophagy have shown promising results in treating RA. For example, methotrexate (MTX) inhibits the mitochondrial folate pathway through competitive inhibition of dihydrofolate reductase (DHFR), affecting mitochondrial biogenesis and exerting antiproliferative effects.[167] Additionally, leflunomide inhibits mitochondrial dihydroorotate dehydrogenase (DHODH), reducing pyrimidine synthesis and increasing mitochondrial fusion by promoting Mfn1/2 expression.[168] This review examines mitochondrial structure and function in the context of RA, analyzes the potential causes and effects of mitochondrial dysfunction, and highlights how this dysfunction influences immune cells and osteoblasts, contributing to RA pathogenesis. Thus, identifying targeted biological processes (eg, mitochondrial biogenesis, dynamics and mitochondrial autophagy) to regulate mitochondrial homeostasis, holds great promise for improving RA prevention and treatment strategies.

Data Sharing Statement

The data are included in the article as table.

Author Contributions

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

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Disclosure

The authors declare that they have no conflicts of interest.

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