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REVIEW

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From powerhouse to modulator: regulating immune system responses through intracellular mitochondrial transfer

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Abstract

Mitochondria are traditionally known as the cells' powerhouses; however, their roles go far beyond energy suppliers. They are involved in intracellular signaling and thus play a crucial role in shaping cells' destiny and functionality, including immune cells. Mitochondria can be actively exchanged between immune and non-immune cells via mechanisms such as nanotubes and extracellular vesicles. The mitochondria transfer from immune cells to different cells is associated with physiological and pathological processes, including inflammatory disorders, cardiovascular diseases, diabetes, and cancer. On the other hand, mitochondrial transfer from mesenchymal stem cells, bone marrow-derived stem cells, and adipocytes to immune cells significantly affects their functions. Mitochondrial transfer can prevent exhaustion/senescence in immune cells through intracellular signaling pathways and metabolic reprogramming. Thus, it is emerging as a promising therapeutic strategy for immune system diseases, especially those involving inflammation and autoimmune components. Transferring healthy mitochondria into damaged or dysfunctional cells can restore mitochondrial function, which is crucial for cellular energy production, immune regulation, and inflammation control. Also, mitochondrial transfer may enhance the potential of current therapeutic immune cell-based therapies such as CAR-T cell therapy.

Keywords Mitochondria, Mitochondria Transfer, Immune system, Immunometabolism, Organelle therapy, Immunotherapy

Introduction

Mitochondria are double-membrane organelles found in the cytoplasm of almost every eukaryotic cell. They are bioenergetic powerhouses that generate ATP via oxidative phosphorylation (OXPHOS) and regulate anabolic processes. Mitochondria are dynamic structures that manage calcium balance and are involved in producing reactive oxygen species (ROS) [1]. Furthermore, they act as a signaling hub, regulating metabolism, cell fate, and immunological responses by releasing mitochondrial ROS (mtROS), mitochondrial DNA (mtDNA), and various metabolites [1, 2]. Mitochondrial activity influences the development and regulation of both innate and

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adaptive immunity. The correlation between mitochondria and immune response has been demonstrated in the activation of pattern recognition receptor (PRR) signaling pathways in innate immunity, as well as the development of multiple stages of T and B lymphocyte proliferation, activation, polarization, and memory formation in adaptive immunity [3, 4]. Notably, mitochondrial dysfunction has been associated with a variety of immunological disorders. For instance, the release of mitochondrial-derived nucleic acids has the potential to induce type 1 interferon (IFN) production in immunological disorders such as interferonopathies, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) [5–8]. Interestingly, there is a correlation between mitochondrial malfunction and aging. Due to immune system impairment, elderly individuals are more vulnerable to infectious illnesses and malignancies. In this context, aging-associated mitochondrial dysfunction may reduce immunological response [9, 10]. Recent investigation suggests that cells can exchange mitochondria with other cells; the procedure is known as intercellular mitochondrial transfer (MT). It has been shown that MT occurs in various cells and has key roles in normal physiology and disease progression [11]. There are two kinds of MT: horizontal and vertical transfer. During cell division, the mitochondria are transferred to the daughter cells, also known as mitochondrial inheritance. On the other hand, horizontal or intercellular transfer of mitochondria occurs when one cell as a donor delivers some of its mitochondria to another cell as a donor cell without cell division [12–14]. Several MT mechanisms have been described, including establishing tunneling nanotubes (TNTs), gap junction channels (GJCs), ejecting mitochondria into extracellular vesicles (EVs), mitochondrial extrusion, and cell-to-cell fusion [12]. Various new medicinal treatments suggest mitochondrial transplantation as a new therapeutic approach [15–17]. Recent studies highlighted the potential of MT in modulating immune functions, particularly in the context of inflammatory diseases, autoimmune disorders, and cancer [18, 19]. Mitochondria influence immune cell activation, differentiation, and survival by regulating reactive oxygen species (ROS) production, metabolic reprogramming, and controlling apoptosis [20]. In this regard, therapies targeting mitochondrial function, such as MT may offer novel strategies to restore immune homeostasis and improve the outcomes of immune-related disorders treatments. This review synthesizes findings from peer-reviewed articles (2015–2025) retrieved via PubMed, Scopus, and Google Scholar using keywords including "mitochondrial transfer", "mitochondria", and "immune system". Data were analyzed thematically, prioritizing high-quality studies and mechanistic insights. We emphasized the importance of mitochondrial activity in innate and adaptive immune responses. Then, we discussed how MT from immune cells to various cells contributes to biological implications. Finally, we described how MT from different cells to immune cells can regulate their functions.

Mitochondria orchestrating intracellular signaling

Mitochondria act as central hubs for intracellular communication and the regulation of immune responses. These organelles are not only responsible for generating ATP but also serve as critical platforms for immune system-related pathways, including RIG-I-like Receptors (RLRs), Toll-Like receptors (TLRs), and Nod-like receptors (NLRs). These receptors are expressed by both innate and adaptive immune cells, which are cytoplasmic sensors critical for appropriate immune responses [21–25]. Mitochondria can activate inflammatory factors to produce interferons and cytokines against viruses. mtROS boosts antibacterial responses and regulates inflammatory signaling. Mitochondria also support inflammasome assembly, enabling the production of inflammatory cytokines. Overall, mitochondria enhance immune reactions by integrating signaling and metabolic processes.

RLRs pathway

The RLR family members are cytosolic sensors for non-self RNAs. Retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated gene 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2) are the three members of this protein family [26]. All RLRs contain a central helicase/ATPase domain and a C-terminal domain (CTD), which work together to recognize foreign RNAs [27]. RIG-I and MDA5 also have two amino-terminal caspase activation and recruitment domains (CARDs) that mediate downstream oligomerization of mitochondrial antiviral-signaling protein (MAVS) [28]. MAVS is anchored to the outer mitochondrial membrane (OMM) and the mitochondria-associated membrane (MAM) through its C-terminal transmembrane domain [29, 30]. Sensing the viral RNA by RIG-I/MDA5 results in homotypic CARD–CARD interactions with MAVS and forming a "MAVS signalosome" on the mitochondria surface. This complex is necessary for recruiting the tumor necrosis factor receptor-associated factor (TRAF) proteins. TRAF proteins activate TANK-binding kinase 1 (TBK1) and IκB kinase-ε (IKKε) to phosphorylate the interferon regulatory factor 3 IRF3/IRF7 and nuclear factor-κB (NF-κB) transcription factors, which together induce the expression of type I/III interferons and other inflammatory cytokine genes [27, 30, 31].

TLRs pathway

They are crucial in recognizing pathogens and initiating immune responses, bridging innate and adaptive immunity. TLRs signaling, such as TLR1, TLR2, and TLR4 increase mtROS production in macrophages to promote their antibacterial killing [32]. Following TLRs activation, the TRAF6 binds to a complex I-assembly factor called evolutionarily conserved signaling intermediate in Toll (ECSIT) protein on the surface of mitochondria and ubiquitinates ECSIT, which results in the recruitment of mitochondria to phagosomes where they produce mtROS [33]. TLR4 activation also triggers NF-κB activation by assembling the TRAF6, ECSIT, and transforming growth factor-β- β (TGF- β) activated kinase 1 (TAK1) complex, which enhances TAK1 kinase activity [34]. Moreover, the mitochondrial protein membrane-associated ring-CH-type finger 5 (MARCH 5) regulates TLR7 signaling through the polyubiquitination and degradation of TRAF family member-associated NF-kappa-B activator (TANK) [35].

NLRs pathway

Activation of NLRP3 leads to the development of the inflammasome complex [36]. The NLRP3 protein has three domains: an N-terminal pyrin (PYD) domain that recruits proteins for the formation of inflammasome complexes, an ATPase-containing NACHT domain in the middle that facilitates oligomerization, and a C-terminal leucine-rich repeat (LRR) domain. Also, the NLRP3 inflammasome complex contains pro-caspase-1 and an adaptor called apoptosis-associated speck-like protein (ASC) [36]. Hence, caspase-1 can convert pro-IL (interleukin)−1β and pro-IL-18 into active forms during inflammasome activity, resulting in a broad inflammatory response. In this regard, mitochondria can provide a scaffold for inflammasome assembly via the interaction of activated NLRP3 and MAVS, thus enhancing inflammasome formation and activity (Fig. 1) [37].

Mitochondria impowering the functions of phagocyte cells

Mitochondria are crucial for the functioning of neutrophils and macrophages. In neutrophils, mtROS and mtDNA influence development, chemotaxis, degranulation, and NET formation. Macrophages depend on mitochondria as key regulators of metabolic processes and immune responses. They undergo metabolic reprogramming based on their activation state; M1 macrophages shift towards glycolysis to enhance bactericidal activity and produce pro-inflammatory cytokines, while M2 macrophages rely on OXPHOS and fatty acid oxidation for anti-inflammatory and tissue-repairing roles. Mitochondrial dynamics, signaling pathways, and metabolites further modulate macrophage function, highlighting the central role of mitochondria in controlling immune homeostasis and responses in both neutrophils and macrophages.

Neutrophils

The limited number and small size of mitochondria observed in neutrophil imaging, coupled with their restricted metabolic activity and neutrophils'reliance on glycolysis rather than OXPHOS for energy production, have historically led to the assumption that mitochondrial function in neutrophils is predominantly limited to apoptosis; hence, other potential roles remained largely unexplored. Recent studies increasingly demonstrate that neutrophil mitochondria have functions beyond apoptosis, including the dynamic regulation of neutrophil development, chemotaxis, ROS production, degranulation, and neutrophil extracellular trap (NET) formation [38]. mtROS plays a significant role in the formation of NET, particularly in pathways independent of the classical NADPH oxidase (NOX) system. While NOX-generated ROS are traditionally considered essential for NETosis, mtROS can act as an alternative or complementary source of ROS in certain contexts [39, 40]. Mitochondria-targeted antioxidants like SkQ1 and MitoTEMPO can inhibit NET formation by reducing mtROS production [41, 42]. mtDNA also plays key roles in NET formation, where neutrophils release web-like structures to trap pathogens and tumor cells. Viable neutrophils release mtDNA, combined with granule proteins, to form NETs, often without neutrophil death, enabling the continued functionality of neutrophils following NET formation. mtROS mediates this process, highlighting its importance in immune defense and inflammation regulation [39, 43–45].

Despite a partially dysfunctional mitochondrial network characterized by low respiration and ATP production rates, human neutrophils maintain their mitochondrial membrane potential (MMP) via the glycerol-3-phosphate shuttle, which transfers electrons from glycolysis to complex III of the electron transport chain [46, 47]. This process enables mitochondria to balance redox equivalents and facilitate glycolytic flux while preventing apoptosis. The interplay between these metabolic pathways is crucial for maintaining neutrophil viability during the release of mtDNA for NET formation [38]. Maintenance MMP has also been shown to play a significant role in the neutrophil chemotaxis chain [46]. Disruption of the *Polg* gene, which encodes the catalytic subunit of mitochondrial DNA polymerase, significantly impairs neutrophil interstitial migration. Additionally, inhibition of mitochondrial complexes I and III, key sites for ROS

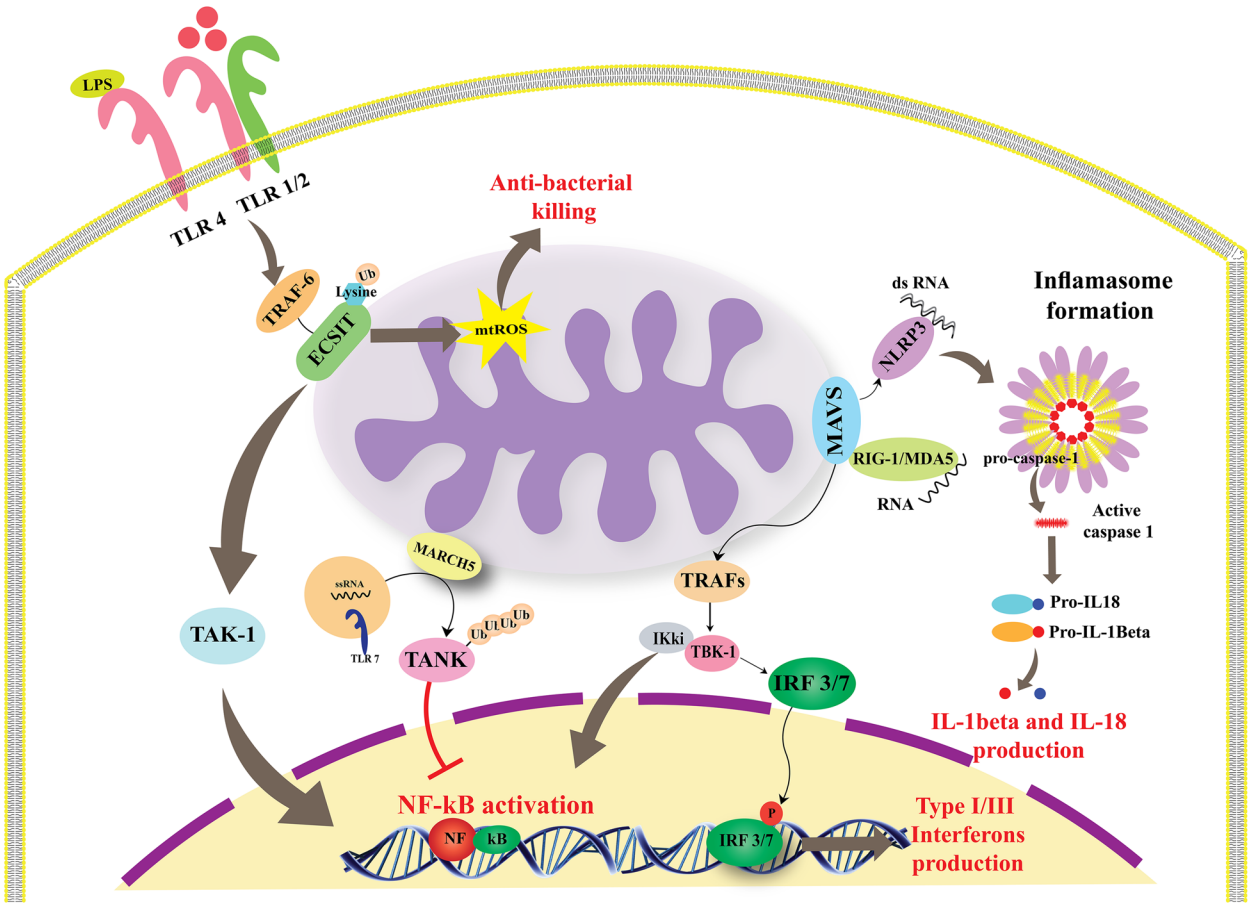

Fig. 1 The significance of mitochondria in intracellular signaling: RIG-I/MDA5 detection of viral RNA interacts with MAVS, resulting in the formation of MAVS signalosomes on the mitochondrial surface, which is necessary for recruiting TRAF proteins. TRAF proteins activate TBK1, IRF3/IRF7, and NF-κB, generating type I interferons. Additionally, mitochondria can provide a framework for inflammasome assembly through the interaction of activated NLRP3 with MAVS, hence increasing inflammasome formation and activity. Furthermore, MARCH 5 regulates TLR7 signaling by polyubiquitinating and degrading TANK. Following TLR activation, TRAF6 binds to and ubiquitinates ECSIT on the surface of mitochondria, causing mitochondrial migration to phagosomes and the production of mtROS. TLR4 activation activates NF-κB via assembling the TRAF6, ECSIT, and TAK1 complex, which leads to enhanced TAK1 kinase activity. TRAF; tumor necrosis factor receptor-associated factor, MARCH-5; mitochondrial protein membrane-associated ring-CH-type finger 5, TANK; TRAF family member-associated NF-kappa-B activator, ECSIT; evolutionarily conserved signaling intermediate in Toll

production, further reduces neutrophil motility [48]. Furthermore, the mitochondrial calcium uptake transporter (MCU) and the outer mitochondrial membrane protein MFN2 play critical roles in neutrophil polarization and chemotaxis by modulating mitochondrial dynamics and maintaining interactions with the endoplasmic reticulum (Fig. 2) [49, 50].

Macrophages

Mitochondria play crucial roles in macrophage biology, functioning as key regulators of both metabolic processes and immune responses. In response to various immune stimuli, such as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), macrophages undergo metabolic reprogramming that aligns with their activation state. For example, in classically activated macrophages (M1), the shift toward glycolysis (the Warburg effect) supports the production of pro-inflammatory cytokines and enhances the bactericidal activity of these cells [51, 52]. This metabolic shift is linked to the breakdown of the tricarboxylic acid (TCA) cycle, accumulating metabolites such as succinate and activating inflammatory pathways through mtROS [53, 54]. Glycolytic intermediates enter the PPP to produce NADPH, which is essential for NADPH oxidase activity and generates ROS to eradicate pathogens. Lactate dehydrogenase converts pyruvate to lactate to regenerate NAD^+, supporting glycolysis when oxidative

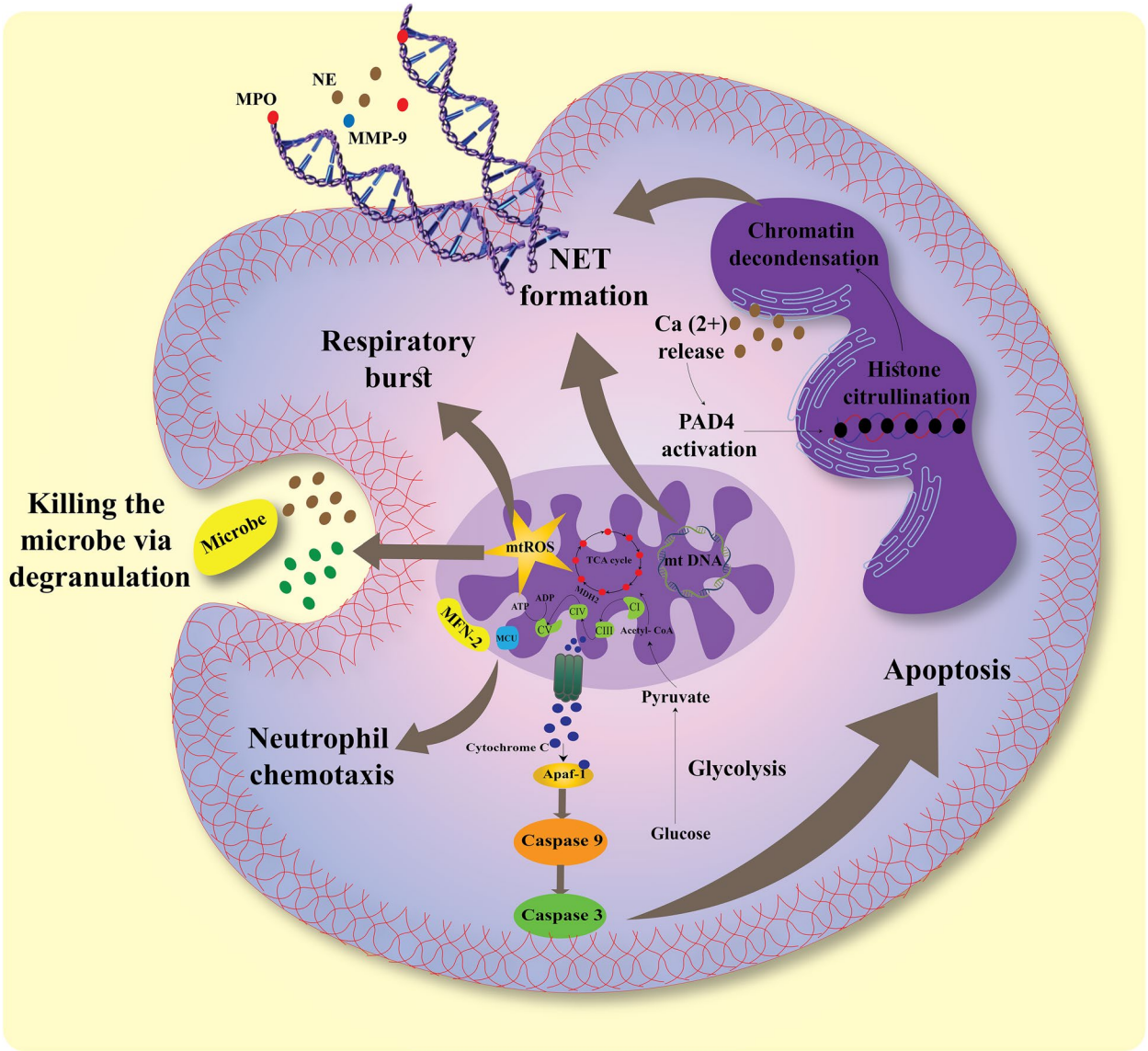

Fig. 2 Mitochondria enhance the phagocytic activity of neutrophils. Mitochondria in neutrophils contribute to various biological processes beyond apoptosis, including chemotaxis, ROS production, degranulation, and NET formation. As cytochrome c is released from the mitochondrial membrane, the apoptosome complex is formed, resulting in the subsequent activation of caspase 9 and caspase 3, consequently triggering apoptosis. MCU and the outer mitochondrial membrane protein MFN2 play key roles in neutrophil chemotaxis by regulating mitochondrial dynamics and maintaining interactions with the endoplasmic reticulum. Mitochondria can be an important source of intracellular ROS in neutrophils, and it is reported that mtROS is involved in the oxidative burst and the degranulation of neutrophils. Additionally, calcium release from the endoplasmic reticulum stimulates PAD4, enhancing histone citrullination and leading to chromatin decondensation (the starting point of NETosis). Both mtROS and mtDNA are important mediators of NET formation, assisting in releasing web-like structures consisting of chromatin and granule proteins like NE, MPO, and MMP-9, which trap pathogens. NETs serve an important role in pathogen capture and maintaining neutrophil performance. NET; neutrophil extracellular trap, MCU; mitochondrial calcium uptake transporter, PAD4, peptidyl arginine deiminase 4 NE; neutrophil elastase, MPO; myeloperoxidase, MMP-9; matrix metalloprotease 9

phosphorylation is limited. Glycolysis helps express iNOS for nitric oxide (NO) production, which is critical for macrophage function. Inhibiting glycolysis lowers iNOS levels and harms macrophages'ability to fight bacteria [55, 56]. HIF-1α enhances glycolytic enzyme expression and regulates pro-inflammatory cytokines and iNOS, connecting metabolism with immune functions. Blocking glycolysis or HIF-1α reduces M1 macrophage differentiation and their ability to manage infections like Listeria monocytogenes [57, 58].

Mitochondria play a crucial role in macrophage phagocytosis by regulating metabolic reprogramming and cellular dynamics essential for immune function. Mitochondrial fission, mediated by DRP1, enhances macrophage phagocytosis of tumor cells, while tumor-mediated metabolic competition impairs this process by disrupting mitochondrial dynamics [59]. Furthermore, mitochondrial transplantation has been shown to restore phagocytic capacity in foam cell macrophages and facilitate intercellular transfer of mitochondria, essential for immune regulation and metabolic homeostasis [60, 61]. Additionally, mitochondrial dynamics—particularly the balance between mitochondrial fission and fusion—further modulate macrophage function; fission promotes inflammation, and fusion protects against cell death under stress conditions [51]. In contrast, alternatively activated macrophages (M2) rely on OXPHOS and fatty acid oxidation (FAO) to support their anti-inflammatory and tissue-repairing roles [62]. These macrophages exhibit enhanced mitochondrial respiration, essential for their regulatory functions, such as the production of anti-inflammatory cytokines like IL-10 and TGF-β [53, 62]. Furthermore, mitochondrial signaling pathways, including the release of mtDNA and N-formyl peptides, play pivotal roles in initiating and sustaining inflammatory responses [61]. Mitochondrial-derived factors, such as itaconate, produced during immune responses, help modulate the macrophage's inflammatory activity by inhibiting specific TCA cycle enzymes, thus providing an additional layer of regulation [52, 53]. These molecular interactions underline the complex interplay between mitochondrial function and macrophage activation, emphasizing the organelle's central role in controlling immune homeostasis and responses (Fig. 3).

Monocytes

Monocytes are categorized into three main subtypes based on surface marker expression: classical (CD14 + CD16 −), intermediate (CD14 + CD16 +), and non-classical (CD14 +CD16 +). These subtypes differ in migratory behavior, cytokine production, and susceptibility to metabolic and inflammatory reprogramming [63]. Classical monocytes rely heavily on glycolysis for ATP production, even in normoxic conditions. This allows rapid energy generation to support inflammatory responses. They show limited OXPHOS and mitochondrial respiration compared to non-classical (CD14 +CD16 +) monocytes [64, 65]. In contrast, non-classical monocytes exhibit a distinct metabolic profile optimized for patrolling the vasculature, sensing damage, and maintaining immune surveillance. Their metabolism is characterized by higher OXPHOS, reliance on FAO, and lower glycolytic activity, aligning with their longevity and anti-inflammatory functions. Intermediate monocytes represent a transitional state between classical and non-classical monocytes, displaying a metabolic plasticity that combines glycolysis and oxidative metabolism elements. Their glycolytic activity is higher than that of non-classical monocytes but lower than that of classical monocytes. Also, the OXPHOS is active in intermediate monocytes but not dominant; thus, mitochondrial respiration is more engaged than classical monocytes but less than non-classical (Table 1). This dynamic metabolism in intermediate monocytes supports their role in immune surveillance, antigen presentation, and inflammatory modulation [66, 67]. These circulating innate immune cells rely on mitochondrial function to regulate inflammatory pathways and cell differentiation. Mitochondrial dysfunction in monocytes is related to chronic inflammatory and metabolic disorders, including obesity and atherosclerosis. mtDNA mutations and heteroplasmy in monocytes result in lipid dysregulation and inflammatory responses in coronary artery disease [68, 69]. Activated monocytes can release mitochondria-containing EVs or as free organelles, which induce proinflammatory effects on recipient cells. These mitochondria-enriched EVs have been shown to induce type I interferon and TNF responses in endothelial cells, a mechanism that may contribute to vascular inflammation and immune amplification in disease contexts [70].

Dendritic cells (DCs)

Mitochondria play a central role in DCs' development, function, and fate across physiological and pathological contexts. During differentiation from monocytes, DCs undergo substantial mitochondrial biogenesis, marked by increased mtDNA content and respiratory complex expression, under the control of key regulators such as PPARγ coactivator-1alpha (PGC-1α), nuclear respiratory factor-1 (NRF-1), and mitochondrial transcription factor A (TFAM) [71]. This expansion in mitochondrial content is paralleled by enhanced OXPHOS, ATP production, and antioxidant capacity [72]. Mitochondrial metabolism also shapes the functionality of DCs. Distinct DC subsets show differential reliance on fatty acid oxidation (FAO) and glycolysis (Table 1). For instance, $CD8\alpha^{+}$ cDC1 s exhibit elevated OXPHOS during early activation, facilitating robust T-cell priming [73]. However, in high-fat diet–induced obesity, enhanced FAO and mitochondrial respiration in splenic DCs disrupt antigen presentation due to ROS overproduction, impairing immune responses [74]. Mitochondria are also central in immune synapse formation. Upon T-cell interaction, mitochondria cluster at the DC–T cell interface, undergo partial depolarization, and engage mitophagy—a quality control mechanism critical for maintaining functional

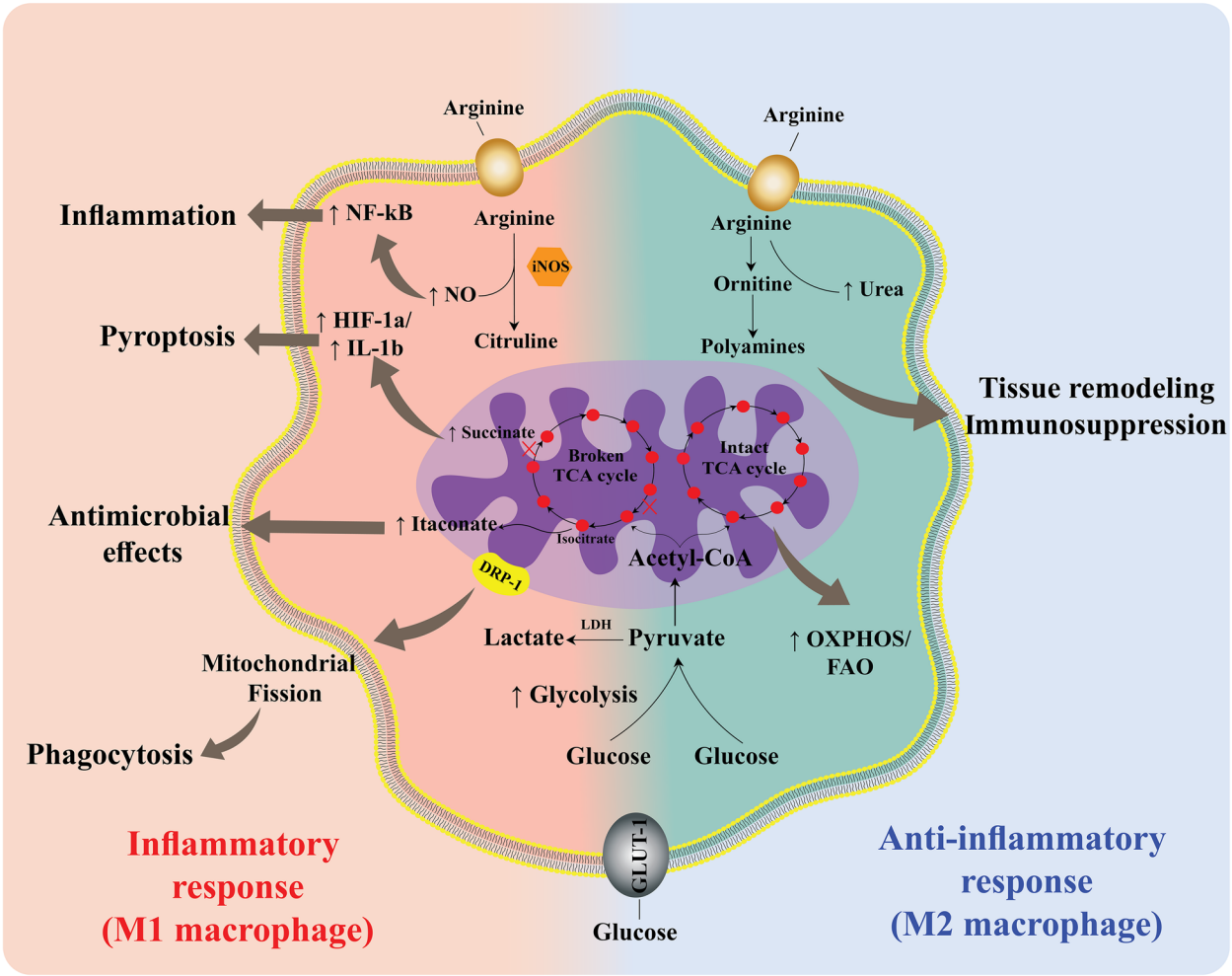

Fig. 3 Mitochondria play a crucial role in regulating both metabolic processes and immune responses in macrophages. Mitochondria play an important role in macrophage metabolism and immunological function, influencing their ability to respond to diverse immune stimuli via metabolic reprogramming. In M1 macrophages, glycolysis promotes pro-inflammatory cytokine production and increases bactericidal activity. This metabolic transition is connected with a disruption in the TCA cycle, resulting in the generation of metabolites such as citrate, which is then transformed into itaconate—a compound with direct antibacterial effects on intracellular and extracellular pathogens. Furthermore, mtROS contributes to the inflammatory response, whereas DRP1-mediated mitochondrial fission enhances tumor cell phagocytosis. Likewise, in M1 macrophages, L-arginine is metabolized by iNOS to produce nitric oxide, which has cytotoxic effects. On the other hand, M2 macrophages rely extensively on OXPHOS and FAO to perform their tissue-repairing and immunoregulatory functions. Unlike M1 macrophages, L-arginine metabolism in M2 macrophages is regulated by Arg-1, resulting in the generation of L-ornithine and polyamines, which stimulate tissue remodeling and repair. M1 and M2 macrophages'metabolic differences highlight the complex interplay between mitochondrial activity, metabolic pathways, and immune regulation. TCA; tricarboxylic acid, DRP-1; dynamin-related protein 1, iNOS; inducible nitric oxide synthase, OXPHOS; oxidative phosphorylation, FAO; fatty acid oxidation

mitochondrial pools. This localized mitophagy occurs even in the presence of active mTORC1, which normally inhibits autophagy, indicating the complexity of the structure and mechanism of immune synapse formation [75]. Pathological conditions such as aging and sepsis are marked by mitochondrial dysfunction in DCs, leading to impaired antigen uptake and cross-presentation. Aged DCs show reduced mitochondrial membrane potential, ATP production, and elevated mtROS, all contributing to diminished immune activation [76]. In sepsis, mtDNA accumulation in the cytoplasm activates the STING pathway, inducing immunoparalysis through decreased expression of co-stimulatory molecules and cytokine dysregulation [77]. Protective factors like PINK1 preserve DC function in sepsis by promoting mitophagy and mitigating mitochondrial fragmentation [78].These findings underscore the multifaceted influence of mitochondrial dynamics and signaling in shaping DC immunobiology,

Table 1 The metabolism profile of different subtypes of Monocytes and DCs

Cell Type	Metabolic Profile	Main Role
Monocytes		
Classical (CD14 + CD16 −)	Predominantly glycolytic metabolism	- Pro-inflammatory cytokine production (TNFα, IL-6, IL-1β) - Differentiation into moDCs and macrophages - Frontline response to infection and tissue damage
Intermediate (CD14 + CD16 +)	Intermediate between glycolytic and oxidative metabolism	- Bridge between classical and non-classical monocytes - Cytokine production - Antigen presentation - Differentiate into macrophages
Non-classical (CD14 + CD16 +)	More reliant on OXPHOS	- Patrolling the endothelium - Surveillance and clearance of apoptotic cells; - Type I IFN production in response to viruses
Dendritic cells		
cDC1 (Conventional DC Type 1)	High OXPHOS Fatty Acid Oxidation (FAO) Glycolysis upon activation	- Cross-presentation to CD8 +T cells - Anti-tumor immunity
cDC2 (Conventional DC Type 2)	Glycolysis-dominant Some OXPHOS Lipid synthesis	- Priming CD4 +T cells (Th2/Th17 responses)
pDC (Plasmacytoid DC)	High glycolysis Low OXPHOS (unless activated) Glutaminolysis	- Type I interferon (IFN-α/β) production in viral infections
moDC (Monocyte-Derived DC)	Glycolysis-heavy Decreased OXPHOS upon maturation PPP activation	- Inflammatory responses - Tissue damage repair

highlighting potential targets for immunotherapy and interventions in metabolic or inflammatory diseases.

Mitochondria determine the fate of T Cells and regulate cellular immunity

Mitochondria determine the fate of T cells through metabolism linked to their function. Mitochondrial activity plays a central role in proliferation, activation, polarization, and the development of memory or exhausted phenotypes. Proliferating T cells rely on glucose for survival, utilizing glycolysis and the TCA cycle for energy, biosynthesis, and signaling. In contrast, activated T cells undergo a metabolic shift towards glycolysis and glutaminolysis, producing mtROS crucial for activating key transcription factors and signaling molecules. T cell polarization is also influenced by mitochondrial metabolism, with glycolysis favoring pro-inflammatory subsets and OXPHOS supporting Treg differentiation, while memory T cells rely on FAO to fuel OXPHOS and maintain a high spare respiratory capacity. Conversely, exhausted T cells exhibit impaired mitochondrial metabolism and increased mtROS levels.

Proliferation

Proliferating T cells demand glucose to survive and undergo apoptosis without glucose [79]. Glycolytic intermediates enter the TCA cycle in mitochondria and regulate OXPHOS, biosynthesis, and intracellular signaling [80]. OXPHOS regulates the proliferation of T cells. Hence, alterations in the compartmentalization of the mitochondrial inner membrane or dysfunction of complex I, II, III, and IV reduce T cell proliferation [81, 82]. Moreover, mitochondria provide raw materials for protein synthesis. Upon mitochondrial oxidation, malate dehydrogenase-2 (MDH2) converts malate into oxaloacetate in a NAD-dependent manner and produces aspartate, which is a precursor of purines and pyrimidines [83, 84]. Furthermore, mitochondrial serine hydroxymethyltransferase 2 (SHMT2) feeds one-carbon units for purine and thymidine synthesis, thus promoting T cell proliferation [85]. T cell Proliferation is also accompanied by an increase in glutaminolysis pathways, and glutamine deprivation significantly reduces T cell proliferation [86, 87].

Activation

Naïve T cells have low rates of glycolysis, and they use the oxidation of glucose, glutamine, and fatty acids to fuel OXPHOS [87]. However, activated T cells shift their metabolism toward the pentose phosphate pathway (PPP) and glutaminolysis through the "Warburg effect" as the main source of ATP and anabolic materials [88, 89]. In addition to supplying energy, mtROS act as signaling messengers in T cell activation. mtROS is required to stimulate ROS-dependent transcription factors, including NF-B, AP-1, and NFAT, during the activation of antigen-specific T cells. In this regard, decreased mtROS

levels due to defective complex I or complex III disturb NFAT activation and cytokine production, such as IL-2 and IL-4, in TCR-activated T cells. Also, mitochondrial superoxide dismutase 2 (SOD2) controls NF-B and AP-1 by controlling mtROS levels [90, 91]. mtROS is also essential for activating mTOR and Myc, key regulators of lymphocyte metabolism and cell-cycle progression. It has been shown that eliminating mtROS results in the arrest of CD4 + T cells in the G0/G1 phase by increasing AMP-activated protein kinase (AMPK) phosphorylation, thereby suppressing mTOR and Myc activity [92]. Mitochondrial metabolism and signaling also participate in CD8 + cell activation. Resting naïve CD8 + T cells rely on OXPHOS; however, following antigen stimulation, their metabolism shifts toward aerobic glycolysis to support further proliferation and activation [93]. In this regard, mitochondria are essential for the activation of CD8 + T cells, and their dysfunctions negatively affect anti-tumor functions of these cells, also inducing exhaustion [94]. High levels of mtROS can damage cell structures, and disruptions in mitochondrial dynamics and signaling affect their numbers and lifespan [95–97]. Mitochondria also support CD8 + T cell 3D motility in tumor environments through the TCA cycle, fueled by glucose and glutamine. Pharmacological interventions that enhance mitochondrial activity improve CD8 + T cell intratumoral migration; however inhibiting glutaminolysis and ATP production significantly reduces their motility [98].

Polarization

Mitochondria has been considered a key factor that could affect the fate of T lymphocytes. The conditions that enhance aerobic glycolysis promote the polarization of proinflammatory T cell subsets, such as Th1 and Th17. These cells are more glycolytic and less contingent on mitochondrial respiration [89, 99]. In this respect, T cells with defects in mitochondria are more likely to differentiate into Th1 subsets and secrete greater amounts of IFN-γ [100]. Interestingly, excess levels of lactate due to the Warburg effect could convert into acetyl-CoA, which leads to histone acetylation and promotes IFN-γ transcription [101]. Forkhead box P3 (FOXP3) is the main regulatory T cells (Treg) transcription factor that enhances FAO through upregulating mitochondrial electron transport chain (ETC) components such as complex V [102]. On the other hand, Treg differentiation mostly depends on OXPHOS rather than glycolysis, whereas blocking the glycolysis pathway inhibits Th17 differentiation thus, mitochondria metabolism can regulate Th17/Treg plasticity through controlling OXPHOS/glycolysis pathways [103, 104].

Memory and exhaustion

Memory T cells enter into a quiescent state that mostly relies on FAO to fuel OXPHOS [105]. During the memory phase, mitochondria undergo fusion process to create a mitochondrion with greater mass. This remodeling depends on the fusing proteins such as mitofusin- 1, mitofusin-2, and OPA1 to increase OXPHOS and keep up spare respiratory capacity (SRC) [106]. Higher SRC allows memory T cells to produce extra energy under metabolic stress conditions and adapt to hypoxic situations [107]. Following re-exposure to an antigen, memory T cells preserve higher levels of ATP to support their quick proliferation and cytokines production [108]. Exhausted T cells show alleviated mitochondrial mass, impaired metabolism, and mitochondrial respiration [109]. Also, this metabolic exhaustion is accompanied by debilitated glucose uptake, glycolysis, and higher mtROS levels [109, 110]. It's been reported that T cell exhaustion marker programmed cell death protein 1 (PD-1) signaling represses mitochondrial biogenesis through suppressing the expression of peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC1α). Hence, PD-1 signaling blockade could enhance glucose uptake and improve mitochondrial metabolic function (Fig. 4) [111].

Mitochondria shape B Cell functions and antibody production

Mitochondria are essential for B cells' development, activation, and differentiation. During the maturation of B cells from pro-B to pre-B cells, their metabolism shifts from glycolysis to oxidative phosphorylation. Activated B cells have increased mitochondrial mass and mtROS production, while plasma cells have decreased mitochondrial activity. Memory B cells also depend on mitochondria for survival, and dysregulated mitochondrial function can harm memory B cells' survival, showing mitochondria's importance in B cell longevity and immune memory.

Development

Mitochondria guide the development of pro-B cells into pre-B cells through swiprosin-2 activation. Swiprosin-2 is a calcium-binding inner mitochondrial membrane protein that controls the metabolic switch during the development of pro-B cells into quiescent small pre-B cells. Swiprosin-2 knockout pro-B cells show increased glycolysis but decreased OXPHOS [112]. The pre-BCR and IL-7R signaling induce up-regulation of genes related to mitochondrial activity [113, 114]. Also, Large pre-B cells exhibit elevated levels of mtROS, enhanced glucose uptake, and increased MMP compared to small pre-B cells, aligning with their actively proliferative state [112].

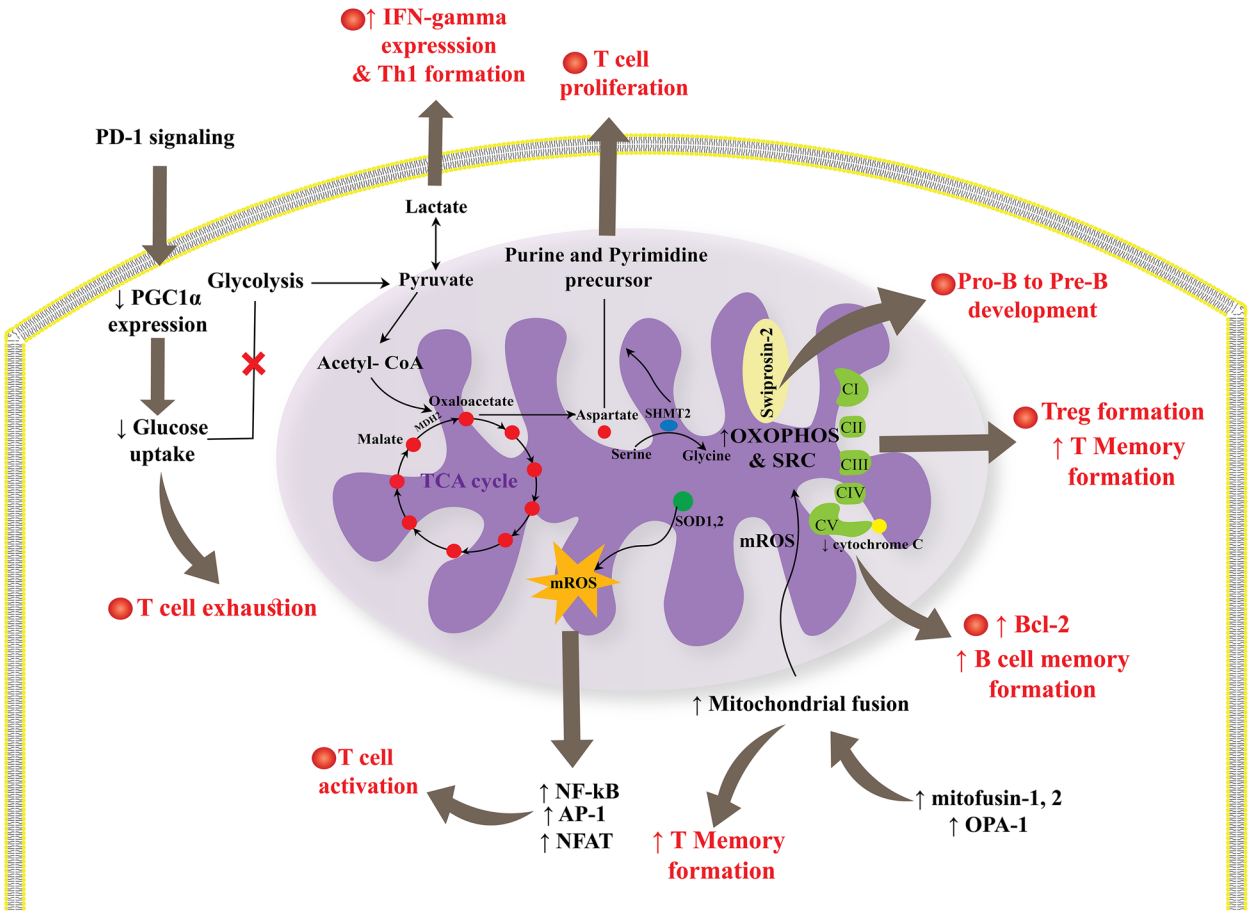

Fig. 4 Involvement of mitochondria in the adaptive immune response: Mitochondrial ROS leads to increased production of inflammatory genes such as NF-κB, AP-1, and NFAT. In addition, mitochondria provide the essential components for protein synthesis. For example, MDH2 converts malate to oxaloacetate, which yields aspartate, a purine and pyrimidine precursor. Furthermore, SHMT2 offers one-carbon units for purine and thymidine synthesis, aiding T-cell proliferation. Excess lactate from the Warburg effect can convert to acetyl-CoA, which promotes IFN-γ production through histone acetylation. On the other hand, Treg differentiation is mostly dependent on OXPHOS rather than glycolysis; thus, inhibiting the glycolysis pathway lowers Th17 differentiation. During the memory phase, mitochondria join together to generate larger mitochondria. This remodeling relies on the fusion of proteins, including mitofusin-1, mitofusin-2, and OPA1, to increase OXPHOS and maintain SRC. The T cell exhaustion marker PD-1 signaling suppresses mitochondrial biogenesis by inhibiting the expression of PGC1α. Thus, PD-1 signaling inhibition may accelerate glucose absorption and improve mitochondrial metabolic performance. Regarding B cell proliferation, mitochondria activate swiprosin-2, an inner mitochondrial membrane protein that regulates metabolic switching during the transition from pro-B cells to pre-B cells. Memory B cells rely significantly on mitochondria for long-term survival. For instance, memory B cells are more resistant to mitochondrial apoptosis due to increased expression of the Bcl-2 anti-apoptotic proteins. Bcl-2 proteins prevent the release of apoptosis-inducing chemicals, such as cytochrome c and AIF, from the intermembrane gap. On the other hand, M2 macrophages rely extensively on OXPHOS and FAO to perform their tissue-repairing and immunoregulatory functions. Unlike M1 macrophages, L-arginine metabolism in M2 macrophages is regulated by Arg-1, resulting in the generation of L-ornithine and polyamines, which stimulate tissue remodeling and repair. M1 and M2 macrophages'metabolic differences highlight the complex interplay between mitochondrial activity, metabolic pathways, and immune regulation. AP-1; activating protein 1, NFAT; nuclear factor of activated T cells, MDH2; malate dehydrogenase-2, SHMT2; mitochondrial serine hydroxymethyltransferase 2, FOXP3; Forkhead box P3, ETC; electron transport chain, SRC; spare respiratory capacity, AIF; apoptosis-inducing factor, PD1; programmed cell death protein 1, PGC-1α, peroxisome proliferator-activated receptor-γ coactivator 1-α

Activation

The destiny of B cells is tied to changes in mitochondrial function. Throughout B cell activation, mitochondrial mass as well as mtROS production are increased [115]. Different signals directly impact metabolic activity and mitochondrial status in B cells. TLR4 and BCR signaling activate the phosphoinositide 3 kinase (PI3 K) pathway, which enhances glucose uptake and glycolysis, but IL-4 upregulates glycolysis in a STAT6-dependent pathway [116–118]. PI3 K signaling also suppresses the expression of Forkhead box protein O1 (FOXO1) transcription factor. FOXO1 increases mitochondrial mass

by upregulating Mfn1 and Mfn2 fusion proteins. The balance between PI3 K and FOXO1 controls the development of B cells at different stages. In the quiescent centrocytes, PI3 K signaling is dominant, whereas proliferating centroblasts express higher levels of FOXO1 [119]. In addition, glycogen synthase kinase 3 (GSK3) plays an important role in mitochondrial reprogramming of germinal center (GC) B cells [120]. GSK3 could inhibit mitophagy through suppressing the mammalian target of rapamycin complex 1 (mTORC1). The Gsk3-deficient GC B cells show elevated metabolism and proliferation due to increased activity of c-Myc, which is well known for its role in mitochondrial biogenesis and cell proliferation [121, 122].

Plasma cells

The mitochondrial activity and content significantly decrease in plasma cells due to B-lymphocyte-induced maturation protein-1 (Blimp1) transcription factor activation. This reduces mitochondrial mass and mtROS production, which results in lower CSR and encourages commitment to the plasma cell lineage [123]. Long-lived plasma cells (LLPCs) and short-lived plasma cells (SLPCs) have similar amounts of mitochondria and basal oxidative phosphorylation activity. Still, the peak capacity for OXPHOS is significantly higher in long-lived plasma cells. Moreover, LLPCs have higher levels of Glut1 and the mitochondrial pyruvate carrier than SLPCs, indicating their need for more sustained energy production and survival mechanisms via glucose consumption and OXPHOS [123]. Long-lived plasma cells can also switch between several metabolic states and use different substrates to fuel mitochondrial energy production to survive when there are changes in the local microenvironment [124].

Memory

Mitochondria have a central role in the prolonged survival of memory B cells (MBCs) over a period of time. First, MBCS are more resistant to mitochondrial apoptosis principally due to up-regulation of the Bcl-2 anti-apoptotic proteins [125]. The Bcl-2 proteins inhibit the release of apoptosis-inducing molecules, such as cytochrome c, apoptosis-inducing factor (AIF), and endonuclease G (EndoG) from the intermembrane space [113, 126]. Another aspect through which mitochondria influence MBC survival and quiescence is autophagy. Compared to naive and GC B cells, MBCs demonstrate higher levels of mitophagy. This extends the survival of MBCs in the absence of antigen stimulation and cytokine-barren niches [127]. Mitophagy deficiency may reduce self-renewal capability and accelerate cell death in MBCs. Mouse, Atg7-/- B cell progenitors can normally develop into GC and memory cells, but MBCs'survival will be significantly compromised. In addition, Atg7-/- MBCs exhibit impaired mitochondrial membrane potential and elevated levels of mtROS. In this regard, mtROS neutralizing with antioxidant improves the survival of Atg7-/- MBCs, indicating that higher levels of mtROS result in impaired maintenance of memory B cells (Fig. 4) [128].

Mitochondrial transfer mechanisms and mitochondria tracking methods

Mitochondrial transfer mechanisms

Tunneling nanotubes

TNTs are membranous tubular structures that can connect two cells. They were first observed in rat pheochromocytoma PC12 cells, rat kidney cells, and human embryonic kidney (HEK) cells. The F-actin, myosin, and tubulin are necessary to form TNTs. Their diameters differ from 50 to 1500 nm and can be up to 100 μm long. This feature makes TNTs suitable for transferring cellular components or organelles such as mitochondria between cells [129, 130]. Accordingly, actin-binding toxins and cytochalasin B significantly inhibit the formation of TNTs and organelle transfer within cells. Mitochondria can be transported via TNTs by interacting with F-actin and the cytoskeleton. It's been suggested that mitochondria transferring through TNTs is a regulated process that can be unidirectional (from healthy to stressed cells) or bidirectional [131, 132]. In oxidative stress situations, damaged cells promote the formation of TNTs toward healthy cells through the activation of the AKT-PI3 K-mTOR pathway. However, the role of other intrinsic and extrinsic pathways such as CD38, M-Sec, exocyst complex, small GTPases (Rho1, Rho3, Cdc42, and RalA), as well as leukocyte-specific transcript 1 (LST1), has also been described in the formation of TNTs in different conditions [132].

Gap junction channels

GJCs are gigantic protein channels connecting the cytoplasm of nearby cells. Connexins are rod-shaped proteins that provide building blocks for the GJCs. Six Connexins are organized as a hexagonal structure called "connexon" to construct a hemichannel. The head-to-head connection of two hemichannels leads to the formation of a hydrophilic intercellular channel. The GJCs have a diameter of about 2–4 nm, allowing the exchange of chemicals, small molecules, ions, nutrients, and organelles between adjacent cells. There are 21 Connexin genes in the human genome; among them, Connexin-43 (Cx43) seems to participate in intercellular mitochondria transfer. Also, the Cx43 might indirectly facilitate the mitochondria transfer between donor and recipient cells via Ca2 + or ROS exchange. Intracellular signaling modulators such as Ca2

+could promote the formation of TNTs and support mitochondria transfer [133–135].

Extracellular vehicles

EVs, including exosomes and microvesicles (MVs), are 30–150 nm membranous vesicles that originate from the endosomal system or are released from the plasma membrane, respectively. They are involved in intercellular communication and allow cells to exchange small molecules such as proteins, lipids, nucleic acids, and organelles [136]. Under stress conditions, EVs can deliver mitochondria between different cells to reduce cellular damage. EV-mediated MT has been reported in astrocytes, myeloid-derived regulatory cells (MDRCs), retinal ganglion cells, and immune system cells [137–139]. The formation of mitochondria carrying EVs mostly depends on increased levels of extracellular NAD +. CD38 can catalyze extracellular NAD +to generate cADPR as a second messenger, leading to elevated intracellular Ca2 +concentration. Subsequently, increased levels of intracellular Ca2 +result in cytoskeleton remodeling and plasma membrane changes to generate EVs [140, 141].

Cell fusion

Through cell fusion, two or more distinct cells fuse their plasma membranes and share cytosolic substances and organelles while their nuclei remain intact. Cell fusion can occur spontaneously or artificially and can be used as a delivery method for mitochondria transfer between recipient and donor cells. Tissue injury, inflammation, or hypoxic stress may induce cell fusion; thus, this phenomenon contributes to tissue regeneration and cellular homeostasis, in which mitochondria transfer may play an important role [142].

Mitochondrial extrusion

Mitochondrial extrusion is a cellular process in which mitochondria are expelled from cells as naked organelles or encapsulated within vesicles, often as a response to stress or damage. This process requires intact actin and microtubule structures and plays a role in physiological maintenance and pathological conditions. It serves as a mitochondrial quality control system, potentially facilitating intercellular communication [143, 144] (Fig. 5A).

Mitochondrial tracking methods

Fluorescent-based labeling

Mitochondrial fluorescent dyes such as MitoTracker can enter live cells and label mitochondria, enabling real-time visualization via fluorescence microscopy or a flow cytometry instrument for quantification. Common MitoTracker dyes include MitoTracker Deep Red and MitoTracker Green. Deep Red accumulates in active mitochondria based on their membrane potential and preferentially stains active, respiring mitochondria. On the other hand, MitoTracker Green stains all mitochondria regardless of membrane potential, indicating total mitochondrial mass. As a limitation, photobleaching can degrade the detection signal. MitoTracker dyes are toxic at high concentrations, which may affect mitochondrial function. Also, these dyes can leak, leading to false-positive results [145].

Transgenic reporter systems

Green fluorescent protein (GFP) can be used for mitochondrial tracking by genetically fusing it to mitochondrial targeting sequences (e.g., for matrix localization) or via split-GFP systems to label specific mitochondrial proteins. These approaches enable detailed, live-cell visualization and quantification of mitochondrial morphology, dynamics, and localization with high specificity. Another transgenic reporter system is the Cre-lox models, which allow cell-type-specific labeling of mitochondria. For example, donor cells express a mitochondrially targeted fluorescent protein (DsRed) under a Cre-dependent promoter; thus, transfer of donor mitochondria to non-Cre-expressing recipient cells can be detected via fluorescence microscopy or flow cytometry [146, 147].

Analysis of mtDNA

Quantifying mtDNA using qPCR or sequencing methods is a strong approach for tracking species/strain-specific mitochondria in recipient cells. However, this method also comes with serious challenges. First, the mtDNA sequence between the donor and the recipient must differ. Furthermore, real-time tracking is not possible using this method, and lastly, it cannot distinguish between intact mitochondria and free mtDNA. Recently, a computational tool called MERCI (Mitochondrial-Enabled Single-Cell Deconvolution) has been introduced. This tool analyzes single-cell sequencing data to quantify and trace MT between cancer cells and T cells based on mtDNA composition [148–150] (Fig. 5B).

Mitochondrial transfer from immune cells alters biological implications

The transfer of mitochondria between immune cells and various recipient cells modulates cellular function and disease progression. M1 macrophages transfer mitochondria to cardiomyocytes, MSCs, and beta cells, often inducing ferroptosis and metabolic dysfunction. Conversely, MT from M2 macrophages facilitates tissue repair and cellular respiration in cardiac cells, neurons, and BMSCs. Monocytes, upon transferring mitochondria to target cells, generally activate inflammatory responses. In contrast, cancer cells can hijack T-cell mitochondria to

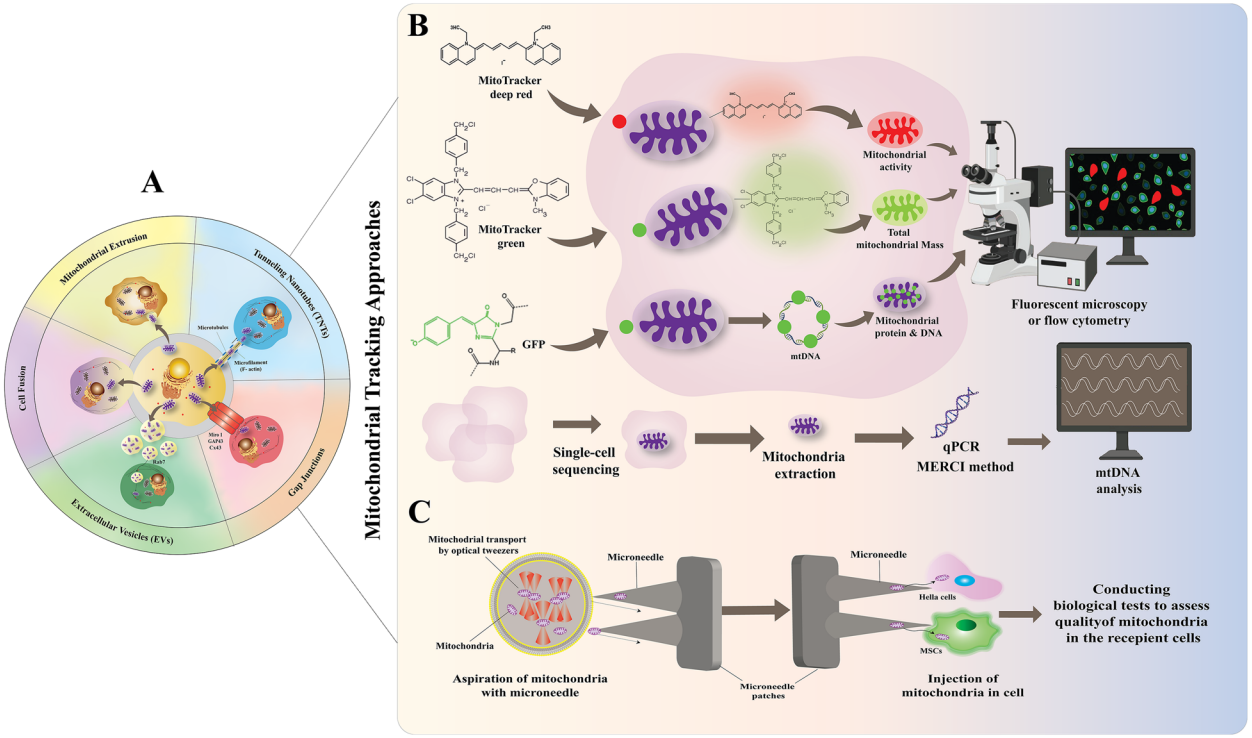

Fig. 5 Mitochondria transferring mechanisms and tracking methods: **A** Transferring mechanisms; TNTs, the tube-like structures that connect cells, are formed with the crucial involvement of F-actin, myosin, and tubulin. These components play a significant role in transferring cellular components such as RNAs, proteins, and mitochondria. Mitochondria, for instance, move through TNTs by interacting with F-actin and the cytoskeleton. GJCs, on the other hand, are large protein channels linked to the cytoplasm of adjacent cells and are made of connexins. Six connexins form a connexon, and two connexons create a channel, exchanging small molecules and nutrients. Cx43, a specific connexin, helps mitochondrial transfer through Ca2 + or ROS exchange. EVs, like exosomes and MVs, also facilitate intercellular communication. Mitochondrial extrusion occurs when cells expel mitochondria freely or in vesicles, usually due to stress or damage. This mechanism depends on intact actin filaments and microtubules, which are crucial in maintaining mitochondrial quality control. **B** Mitochondria tracking methods: Fluorescent-based labeling uses mitochondrial dyes such as MitoTracker deep red and green to observe mitochondria in live cells. Transgenic reporter systems use GFP to track mitochondria with targeting sequences. Quantifying mtDNA with qPCR or sequencing tracks specific mitochondria. A new tool, MERCI, analyzes single-cell sequencing data to trace mtDNA. **C** Mitochondrial transfer and quality control using a robot-aided micro-manipulation system; The innovative technique to control the quality and quantity of mitochondria injected into single live cells using a robotic microneedle and optical tweezers system. This method arranges Mitochondria and cells in a 1-D array within a microfluidic device. The robotic microneedle, aided by optical tweezers, collects a set number of functional mitochondria and injects them into live cells without causing damage. TNT; Tunneling nano tubes, GJC; Gap junction channel Cx43; Connexin-43, ROS; Reactive oxygen species, EV; Extracellular vesicle, MV; Micro vesicle, mtDNA; Mitochondrial DNA, GFP; Green fluorescent protein, qPCR; Quantitative polymerase chain reaction

promote tumor growth or sometimes trigger cancer cell apoptosis (Table 2).

M1 macrophages

Under conditions of stress or inflammation, peripheral macrophages can transfer their mitochondria to cardiomyocytes through clathrin-dependent endocytosis and lipid rafting. This phenomenon can disrupt fatty acid metabolism, the mitochondrial respiratory chain, and the antioxidant balance in cardiomyocytes. Specifically, MT from macrophages to cardiomyocytes increases the expression of ferroptosis-related genes, such as Ptgs2 and Acsl4, while suppressing anti-ferroptosis genes, such as Gpx4. In addition, these cardiomyocytes show increased Fe^{2+} levels, decreased GSH/GSSG ratio, and accumulation of peroxidized lipids, which are hallmarks of ferroptosis [151]. MT from M1 macrophages to MSCs results in increased mtROS and decreased MMP. This alters MSCs'metabolic state toward glycolysis, reduces oxygen consumption, and affects their osteogenic differentiation capacity. Recipient MSCs show decreased ATP levels, indicating impaired mitochondrial function. The MT between M1 macrophages and MSCs promotes the accumulation of succinate, a metabolite of the TCA cycle, leading to the activation of HIF-1α and inducing inflammatory changes in MSCs [152]. M1 macrophages MT to beta cells via EVs significantly impair beta cell health and function by increasing oxidative stress, ROS, and free Fe2

Table 2 Summary Of Mitochondrial Transfer from Different Immune Cells to Various Cells

Donor Cell	Recipient Cell	Mechanism	Main outcome	References
T cells	Tumor cells	TNTs/Cell fusion	- Impaired T cell antitumor functions - Tumor growth - Enhanced antitumor responses against lung cancer cells	[210, 211]
Activated monocytes	Endothelial cells	EVs	- Monocytes activation - Endothelial activation - Inflammation	[70]
M2 macrophages	Sensory neurons	Direct cell-to-cell contact	- Reduced inflammatory pain	[212]
M2 macrophages	MSCs	TNTs	- ROS burst - Metabolic remodeling - Osteogenic differentiation - Bone regeneration and repair	[213, 214]
M1 macrophages	Pancreatic beta cells	EVs	- Lipid peroxidation - Mitochondrial disruption - STING pathway activation - Ferroptosis	[215]
Macrophages	Cancer cells	Cell-contact	- Increased mtROS - Cancer cells proliferation and progression	[154]

+ levels in beta cells, which increases lipid peroxidation, initiates ferroptosis, and activates immune pathways such as STING, leading to cell death. This process ultimately leads to metabolic diseases, such as type 1 or type 2 diabetes and pancreatic dysfunction. Therefore, inhibiting EV-mediated MT from inflammatory macrophages may reduce beta cell damage, prevent metabolic disorders, and reduce treatment resistance in diseases such as diabetes and acute pancreatitis [153]. Macrophages MT to MDA-MB-231 breast cancer cells induce mtROS accumulation, increasing their proliferation through ERK signaling [154]. M1 macrophage metabolism is generally optimized for ROS production rather than ATP. To achieve this, M1 macrophages fragment their mitochondria and consume them as a source of ROS. When these fragments are released and absorbed by neighboring cells, they disturb normal cellular metabolism and ATP generation in the recipient cell. Low intracellular ATP, indicating metabolic stress, which can activate the NLRP3 inflammasome, promoting the cleavage of pro-IL-1β into active IL-1β. Low ATP also increases the AMP/ATP ratio, activating AMPK. While AMPK generally suppresses inflammation, chronic ATP depletion can lead to NF-κB activation and pro-inflammatory cytokine release. Normal cells often rely on low ROS levels for intracellular signaling; however, M1-derived mtROS overwhelms antioxidant defenses like glutathione, causing lipid, protein, and DNA damage and impairing cell functionality. In addition, M1 macrophages mitochondrial-related DAMPs such as mtDNA and cardiolipin can activate TLR9/NLRP3 inflammasomes, further suppressing metabolic genes and promoting cell death [155, 156].

M2 macrophages

In heart failure, transplanting M2 macrophages increases circulating IL-4 levels and stimulates Th2 responses. Activating type 2 immune responses improves mitochondrial health and reduces cardiac cell apoptosis and fibrosis. Transferring mitochondria from M2 macrophages to cardiac cells repairs the function of damaged mitochondria and positively affects cardiac cell survival under oxidative stress [157]. Additionally, M2 macrophages can help restore mitochondrial function in sensory neurons by transferring their mitochondria, increasing cellular respiration and oxygen consumption in these neurons, and ultimately ameliorating inflammatory pain. MT to neural cells requires expression of the CD200R receptor on M2 macrophages and the non-canonical CD200R ligand iSec1 on sensory neurons [158]. MT from M2 macrophages to adipocytes via EVs alters adipocyte metabolic status and function, associated with activating the TGF-β/PAI-1 pathway and adipocyte-myofibroblast transition (AMT). This process plays an important role in epidural fibrosis, which causes epidural scarring after spinal surgery [159]. MT from M2 macrophages to adipocytes via EVs alters adipocyte metabolic status and function, associated with activating the TGF-β/PAI-1 pathway and adipocyte-myofibroblast transition (AMT). This process plays an important role in epidural fibrosis, which causes epidural scarring after spinal surgery [160]. M2 macrophages are anti-inflammatory cells that promote tissue homeostasis and inflammation resolution. Unlike M1 macrophages, M2 macrophage metabolism is predominantly based on OXPHOS. When they donate mitochondria, it boosts OXPHOS in recipient cells, shifting their metabolism from glycolysis (common in pro-inflammatory states) to

a more anti-inflammatory metabolic profile. This metabolic reprogramming results in higher ATP production, which reduces AMPK/NF-κB-driven inflammation. Furthermore, MT from M2 macrophages can reduce HIF-1α stabilization (which stimulates glycolysis and pro-inflammatory cytokine production). M2-derived mitochondria scavenge ROS, decreasing oxidative stress and NLRP3 inflammasome activation in recipient cells. Finally, M2 mitochondria may upregulate NF-κB suppressors such as peroxisome proliferator-activated receptor (PPAR)-γ, SIRT1, and SIRT3 to facilitate anti-inflammatory responses [155, 161].

Monocytes and T cells

MT from monocytes to target cells activates inflammatory responses. During stress conditions, inflammatory monocytes release mitochondria containing MVs, and these Mito-MVs can be transported to endothelial cells and activate inflammatory signals, including TNFα and type I interferon signals, which increase the production of cell adhesion molecules and other inflammatory molecules [70]. Cancer cells can hijack CD8 + T cells'mitochondria by forming TNTs. This process is mediated by specific proteins, such as Sec3 and Sec5, to form nanotubes and mitochondrial GTPases, such as Miro1, to actively transport mitochondria into cancer cells. Inhibiting this process with nanotube-inhibiting drugs such as L-778123 reduces tumor growth and improves therapeutic efficacy. It has been suggested that combining drugs that target mitochondrial trafficking with immunotherapies, such as PD-1 inhibitors, may improve therapeutic outcomes in cancers that are resistant to single-agent therapies [162]. Cancer cells are notorious for hijacking mitochondria from surrounding cells, such as stromal cells, immune cells, or even neighboring tumor cells, to fuel their metabolic demands. This phenomenon provides tumors with metabolic advantages, stress resistance, and immune surveillance evasion. While cancer cells rely on the Warburg effect, hijacked mitochondria allow them to reactivate OXPHOS when needed. This hybrid metabolism helps tumors to survive in low-glucose or hypoxic conditions. Hijacked mitochondria support tumor proliferation by supplying extra ATP and essential intermediates such as citrate, NADH, and NADPH for lipid, protein, and nucleotide synthesis. Acquired mitochondria also buffer oxidative stress, preventing cancer cell death and helping tumor cells resist chemotherapy, which often targets mitochondrial apoptosis pathways [162, 163]. Interestingly, it has been reported that the hijacking of mitochondria from resting T cells by HCC1195 and HCC1438 cancer cells can indirectly cause cancer cell death through the release of cytochrome c from the hijacked mitochondria and the activation of apoptotic protein caspase-3 [164]. Naïve T cells naturally express anti-apoptotic proteins Bcl-2 and Bcl-xL, which prevent cytochrome C release. However, the hijacked mitochondria have relatively lower levels of these anti-apoptotic proteins, releasing cytochrome C and activating the apoptotic death of cancer cells.

Mitochondrial transfer to immune cells regulates their functions

MT regulates immune cells'function, metabolism, and immune responses. MT from MSCs to T cells suppresses Th1 and CD8 + T cell proliferation, promoting Treg differentiation and enhancing anti-inflammatory responses. MT to macrophages improves phagocytosis and oxidative phosphorylation, reduces inflammation, and promotes tissue repair. Neutrophils and NK cells also benefit from MT, with enhanced activation and tumor-killing capacity. This highlights potential therapeutic strategies for immune system-related diseases and cancers [165].

T cells

MSCs are well known for their immunomodulatory properties and are widely used in tissue engineering and regenerative medicine [166, 167]. The transfer of Mitochondria might represent a general mechanism of MSC-dependent immunomodulation. It is not fully clear how transferred mitochondria regulate T cell responses. Still, MT from MSCs to other cells enhances their function by replenishing damaged mitochondria, restoring energy production, improving cellular metabolism, and enhancing cell survival. This transfer also reduces oxidative stress and apoptosis in recipient cells by substituting dysfunctional mitochondria with healthy ones [10].

MSCs'mitochondria transfer to CD4 + T cells, suppressing Th1 proliferation and IFN-γ production by downregulating T-bet, the major Th1 transcription factor (Fig. 6A) [168]. Additionally, CD8 + T cells that acquire MSCs'mitochondria show decreased expansion, IFNγ production, and cytotoxic functions associated with downregulating T-bet and Eomes transcription factors [169]. It is unclear how MSC mitochondria modulate T cell function, but mitochondria transfer likely inhibits $CD8^+$ T and Th1 cell expansion through the IP3-AKT-mTOR pathway and glycolysis inhibition [170, 171]. MSC mitochondria may downregulate CD25, affecting IL-2 signaling and T-bet expression (Fig. 6A) [172].

MSCs transfer mitochondria to T cells, increasing gene expression associated with Treg differentiation and activation, including FOXP3, CTLA4, CD25, and TGF-β1. The artificial transplantation of MSC-derived mitochondria also promoted the differentiation of highly suppressive CD25 + FoxP3 + Tregs. In a mouse model of graft-versus-host disease (GVHD), the

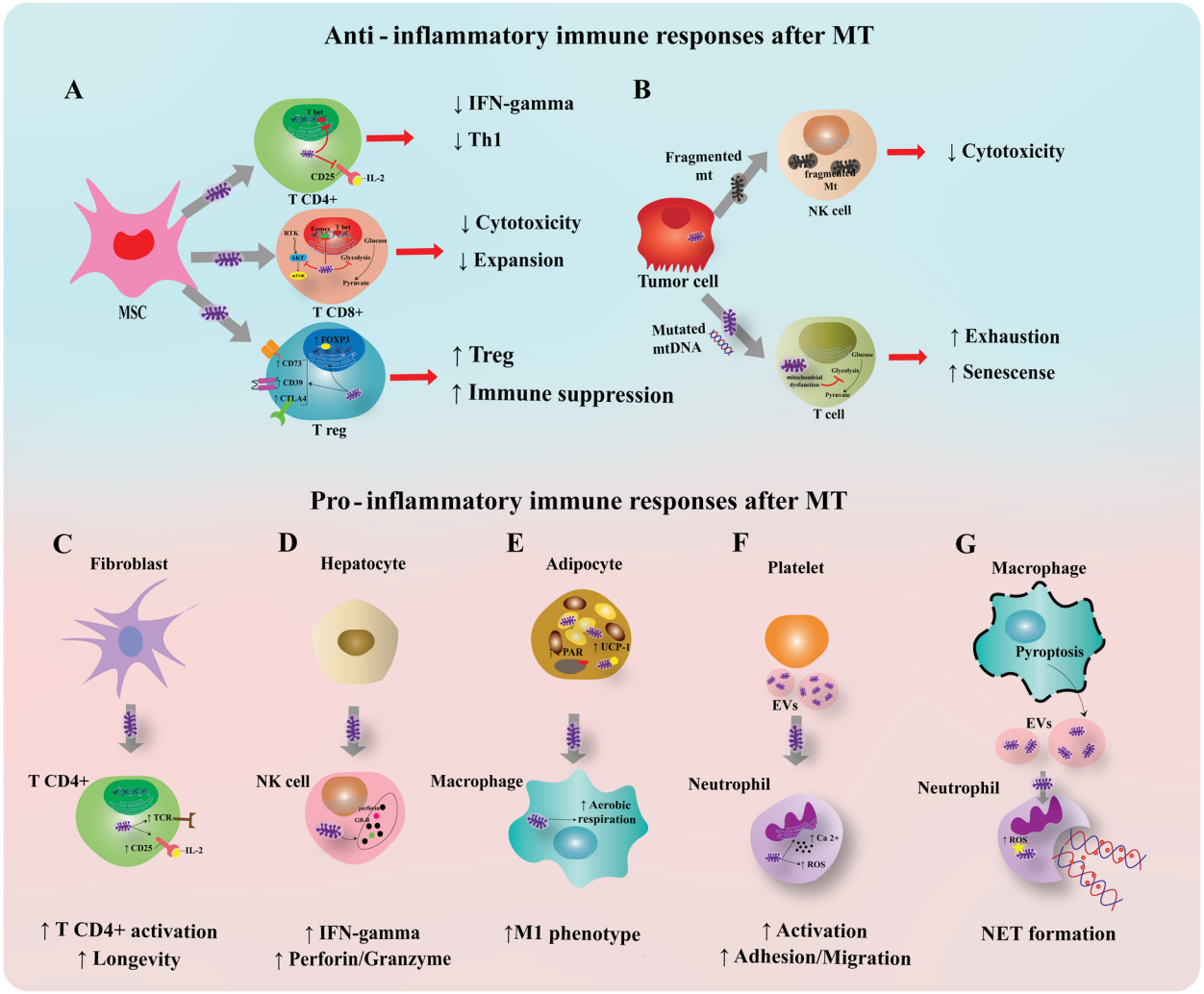

Fig. 6 Pro and anti-inflammatory effects of mitochondrial transfer. Transferring mitochondria has both pro- and anti-inflammatory effects. For instance, **A** transferring MSC mitochondria to CD4 +T cells can reduce Th1 proliferation and IFN-γ production by inhibiting T-bet. Also, CD8 +T cells that adopt MSCs'mitochondria exhibit lower growth, IFNγ production, and cytotoxic activities due to the downregulation of T-bet and Eomes transcription factors. This action is mostly performed by the IP3-AKT-mTOR pathway and glycolysis suppression. Furthermore, MSCs deliver mitochondria to T cells, enhancing the expression of genes associated with Treg development and activation, such as FOXP3, CTLA-4, CD39, and CD73. **B** Cancer cells share mutant mtDNA and fragmented mitochondria with T and NK cells in the tumor microenvironment, causing NK mitochondrial and cytotoxicity malfunction, T cell exhaustion, and senescence. Regarding the pro-inflammatory effects of Mito T, **C** it has been suggested that MT enhances the activation and longevity of elderly human CD4 +T cells, **D** transferring of mitochondria isolated from hepatocytes to NK cells, resulting in a significant increase in proliferation and elevated secretion of cytotoxic granules including granzyme B, perforin and IFN-γ, (**E**) it seems that under metabolically stressed conditions, adipose tissue MQs utilize exogenous mitochondria to support aerobic respiration and thermogenesis toward a pro-inflammatory phenotype, **F** platelets can transfer mitochondria to neutrophils via EVs to enhance activation, adhesion, and migration potential as well as elevating intracellular calcium and ROS levels in neutrophils, **G** the Mito T from MQs undergoing pyroptosis into neutrophils leads to increased mtROS production, lower MMP and activation of the Gasdermin D axis, ultimately triggering NETs formation. MT; mitochondrial transfer, MSC; mesenchymal stem cells, IP3; *inositol 1,4,5-trisphosphate, mTOR;* mammalian target of rapamycin

delivery of MT-induced human T cells improved survival and reduced tissue damage and organ infiltration by T CD4 +, CD8 +, and IFN-γ expressing cells [173] (Fig. 6A). Bone marrow-derived mesenchymal stem cells (BM-MSCs) transfer mitochondria to Th17 cells, leading to impaired IL-17 production and increased oxygen consumption in Th17 cells and promoting their plasticity into Tregs [174]. Allogeneic adipose-derived mesenchymal stem cells (ASCs) impact Tregs immunoregulatory function. Direct contact between Tregs and ASCs, which is HLA-dependent, involves the transfer of active mitochondria ASCs to Tregs. This direct communication

further promotes CD69 expression and FoxP3 preservation in Tregs. Notably, allogeneic ASCs MT enhances Tregs'ability to suppress conventional T cell proliferation and increase the accumulation of immunosuppressive adenosine by upregulating CD39 and CD73 [175]. BM-MSCs transfer mitochondria to iTregs, elevating the expression of FOXP3-stabilizing factors BACH2 and SENP3 via CD39/CD73 signaling, thus enhancing their immunosuppressive function even in inflammatory conditions (Fig. 6A). Blocking MT with Cytochalasin B, a TNT formation inhibitor, reduces FOXP3 expression in iTregs [176]. Bronchoalveolar lavage fluid from asthmatics contains more EVs with mitochondria and higher levels of mitochondrial DNA than healthy individuals. These mitochondria-containing exosomes are derived from pro-inflammatory myeloid-derived regulatory cells (MDRCs). They are transferred to T cells, which co-localize with the mitochondrial network and generate ROS [177].

Bone marrow stromal cells (BMSCs) can transfer mitochondria to T cells via a Talin 2 (TLN2) —dependent process. Transfer of mitochondria to $CD8^+$ T cells enhances basal respiration and spare respiratory capacity (SRC), which are essential for preventing $CD8^+$ T cells from exhaustion in challenging tumor microenvironments. $Mito^+CD8^+$ cells express lower levels of terminal exhausted (TEX) markers, including PD-1, LAG3, and TIGIT, compared to $Mito^-$ cells. $Mito^+CD8^+$ cells also express more Granzyme B (GzmB), indicating better cytotoxic function in the tumor microenvironment [178]. Umbilical cord MSCs (UC-MSCs) mitochondria transfer to CD3 + T cells, making them resistant to Staurosporine (STS)-induced apoptosis. MT prevents the collapse of mitochondrial membrane potential, increases the expression of BCL-2, and decreases caspase-3 cleavage. The protective effect of UC-MSCs MT mainly relates to more ATP production and less ROS [179].

The age-related decline in CD4 + T cell function increases susceptibility to age-related immune dysfunctions. The exogenous delivery of functional embryonic fibroblast mitochondria to CD4 + T cells from old mice can decrease mitoROS levels, increase antioxidant protein expression, and remodel the mitochondrial proteome toward improved aerobic respiration. This may promote CD4 + T cell survival and proliferation by inducing intracellular phosphorylation of key proteins involved in TCR signaling, increasing IL-2 production and CD25 expression after ex vivo activation [180].

Cancer cells can also transfer their mitochondria to immune cells, including T cells, macrophages, and DCs, which allows tumors to suppress anti-cancer immunity. Cancer-derived mitochondria are often damaged or depolarized, inducing an energy crisis in T cells by disturbing OXPHOS and forcing them to waste their ATP on maintaining these damaged mitochondria. ATP is crucial for TCR signaling activation and release of Granzyme B/perforin; thus, ATP depletion weakens T cell responses and cytotoxic effector functions. MT from cancer cells to T cells also elevates ROS, inhibiting proteasomal degradation of HIF-1α, causing its accumulation. HIF-1α drives a metabolic shift toward glycolysis and upregulates exhaustion-associated genes such as PD-1 and Tim-3 [82, 162, 181]. Cancer cells share mutated mtDNA mitochondria with T cells through tunneling nanotubes and EVs within the tumor microenvironment, thus leading to mitochondrial dysfunction, T cell exhaustion, and senescence (Fig. 6B). These mutations impair OXPHOS and increase glycolysis, disturbing T cell responses. These mtDNA mutations in tumor tissues correlate with poorer outcomes in PD-1 blockade therapies. Experiments using knockout mice and clinical data analysis suggest that mitochondrial dysfunction may reduce immune checkpoint inhibitor efficacy (Fig. 6B) [182].

It has been suggested that MT enhances the activation and longevity of elderly human CD4 + T cells. Embryonic fibroblast MT to elderly effector CD4 + T cells (E-CD4 +) and elderly effector memory CD4 + T cells (EM-CD4 +) improves their viability and proliferation compared to E-CD4 + T cells through increasing their mitochondrial mass and modulating cytokine production. These cells also express higher activation markers (CD69), lower exhaustion markers (PD1 +, TIM3 +, LAG3 +), and reduced senescence markers (β-gal, p16) [183] (Fig. 6C).

Macrophages

MSCs transfer mitochondria to MQs through (TNTs), enhancing their phagocytosis, oxidative phosphorylation, and antimicrobial activity [184, 185]. Transfer of mitochondria from MSCs to MQs has been shown to activate PGC-1α, which improves mitochondrial biogenesis and reduces inflammation, thereby alleviating kidney injury in diabetic nephropathy mice [186]. EV-mediated MT to MQs suppresses pro-inflammatory cytokine production and increases M2 macrophage expression in acute respiratory distress syndrome (ARDS) models [187]. MQs are also primary recipients of adipocyte-derived mitochondria, mainly mediated by heparan sulfate and CD36, a class B scavenger receptor (SR). It is unclear why fat cells transfer mitochondria to resident MQs. However, it seems that under metabolically stressed conditions, adipose tissue MQs capture and utilize exogenous mitochondria to support aerobic respiration. Long-chain fatty acids (LCFA) can directly inhibit MT to MQs. This may push the MQs metabolism into the glycolysis pathway and probably skew their function toward a pro-inflammatory phenotype (Fig. 6E) [188, 189]. Furthermore, MQs are crucial to managing mitochondrial quality in

brown adipose tissue (BAT). Stressed fat cells release EVs containing damaged mitochondria, which are absorbable by MQs. Hence, preventing mitochondria transfer to macrophages disturbs thermogenesis in BAT by inhibiting the expression of PPAR and key mitochondrial proteins such as uncoupling protein 1 (UCP1) [190].

Other immune cells

Platelets can transfer mitochondria to neutrophils via EVs. Internalizing these mitoEVs by neutrophils leads to changes in surface markers indicative of activation, enhanced adhesion, and migration potential. MitoEVs also elevate intracellular calcium and ROS levels in neutrophils. Interestingly, the internalization of platelet mitochondria impairs the neutrophils'ability to engulf bacteria, suggesting reduced phagocytic capacity. Conversely, mitoEV exposure enhances the formation of NETs both independently and in response to LPS and PMA stimulation (Fig. 6F) [191]. MQs undergoing pyroptosis release MVs containing mitochondria, which can be taken up by neutrophils during sepsis. This compromises neutrophil functionality, leads to increased mtROS production, lower MMP, and activation of the Gasdermin D (GSDMD) axis, ultimately triggering NET formation. The GSDMD inhibitor disulfiram partially mitigates these effects, indicating that GSDMD-N-expressing mitochondria (Fig. 6G) [192]. Mitochondria are essential for NK cell function, providing energy and metabolic support for NK cell activity. Dysfunctional mitochondria in NK cells can impair their antitumor capacity. Tumor-infiltrating NK (TINK) cells have fragmented mitochondria; this fragmentation correlates with reduced cytotoxicity and impaired NK cell function, contributing to tumor immune escape. Hypoxia in tumors causes this fragmentation via the mTOR-Drp1 pathway. Inhibiting Drp1 and reducing mitochondrial breaking enhances NK cell metabolism, survival, and ability to fight tumors [193]. In this context, the allogeneic transfer of healthy mitochondria to NK cells improves their metabolic function and enhances their tumor-killing capacity. Transferring of mitochondria isolated from WRL-68 hepatocytes to NK cells, resulting in a significant increase in proliferation and elevated secretion of cytotoxic granules including granzyme B, perforin and IFN-γ (Fig. 6D) [194].

Future prospectives and conclusion

The transfer of mitochondria holds significant promise for the future of immune-based cell therapy by enhancing the metabolic and functional capacities of immune cells. Replenishing damaged mitochondria or augmenting existing mitochondrial function can improve immune cells'proliferation, cytotoxicity, and longevity. Aging is correlated with mitochondrial dysfunction. It's been suggested that mitochondria contribute to low-grade chronic inflammation related to aging, which is known as "inflammaging." Mitochondrial-derived DAMPs, including N-formyl peptides, cardiolipin, mtROS, and mtDNA, could be recognized by formyl peptide receptor 1 (FPR1), TLR4, NLR3, and cGAS/STING pathways [195, 196]. Released ATP from damaged mitochondria promotes inflammation via P1 and P2 purinoceptors [197]. It has been reported that aged T cells have lower respiratory activity and mitochondrial membrane potential. As a result, their activation and proliferation are limited due to impaired OXPHOS and ATP generation. Aged T cells also show defective Ca2 + mitochondrial regulation of intracellular Ca2 +, which could lead to improper NFAT signaling and IL-2 production. Furthermore, aging-related mitochondrial dysfunction is associated with poor function of the memory T cells and lower counts of Tregs in elderly individuals. Thus, immune system compromise related to aging makes older individuals more susceptible to infectious diseases and malignancies [195, 198].

Adoptive transfer of mito-transferred naive CD4 + T cells from old mice into Rag1-KO mice protected these mice against influenza A virus (IAV) and Mycobacterium tuberculosis (M.tb) infections (Fig. 7A)[180]. MT from MSCs to Th17 reduces IL-17 production in rheumatoid arthritis (RA), thus suggesting a novel mechanism for regulating Th17 cells. This process is compromised in the inflammatory environment of RA (Fig. 7B) [174]. MT also enhances the function of elderly human T cells by increasing mitochondrial mass, modulating cytokine production, enhancing T cell activation, and reducing markers of exhaustion and senescence. These make MT a novel strategy to rejuvenate aged CD4 + T cells, potentially improving immune responses in elderly patients, with broader implications for diseases linked to mitochondrial dysfunction and T cell impairment (Fig. 7C) [183]. MT to T cells can supercharge their anti-tumor activity. MT from bone marrow stem cells (BM-SCs) to CD8 + T cells expressing pmel-1 transgenic TCR promotes their anti-tumor activity against melanoma cells. These Mit + CD8 + T cells show robust expansion and superior tumor infiltration (Fig. 7D).

Additionally, tumor-infiltrating lymphocytes (TILs) could acquire donor mitochondria and show enhanced cytotoxicity against target cancer cells. MT can also improve the effectiveness of chimeric antigen receptor (CAR)-T cells against tumors. In mouse models, Mito + CD19-CAR T reduced leukemia cells and improved survival rates (Fig. 7E) [178]. MSCs MT reduces early and late apoptosis following electroporation in CAR-T cells and shows a trend toward increased cytotoxic activity.

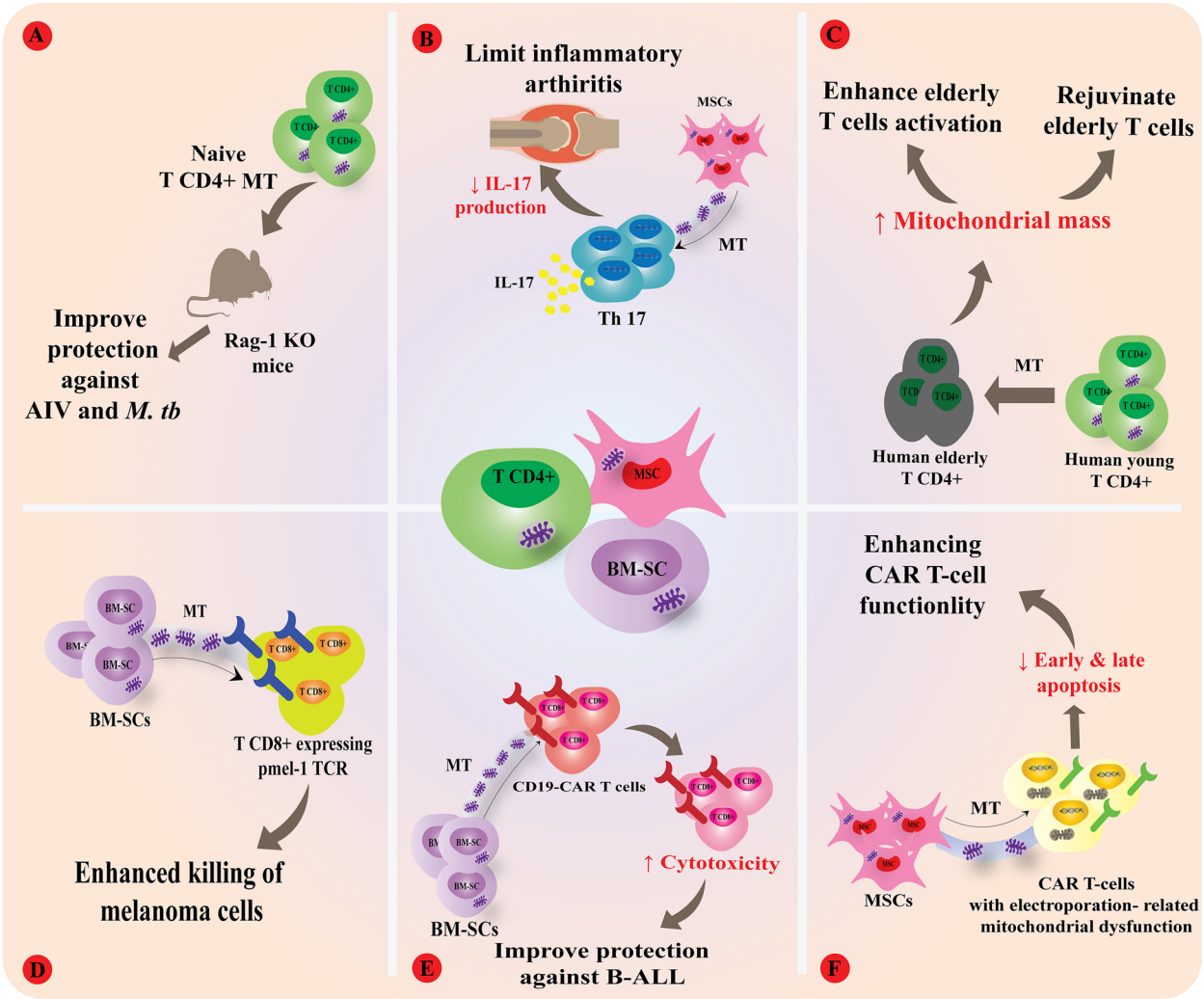

Fig. 7 Therapeutic effects of MT in pathological conditions. **A** Adaptive transfer of mito-transferred naive CD4 +T cells from old mice into Rag1-KO mice protected these mice against IAV and M. tb infections. **B** MSCs MT to Th17 reduce IL-17 production in RA, suggesting a novel mechanism for regulating Th17 cells in the inflammatory environment of RA. **C** MT enhances the function of elderly human T cells by increasing mitochondrial mass, modulating cytokine production, enhancing T cell activation, and reducing exhaustion markers to rejuvenate aged CD4 +T cells, potentially improving immune responses in elderly patients. **D** transfer of mitochondria from BM-SCs to CD8 +T cells expressing pmel-1 transgenic TCR to promote their antitumor activity against melanoma cells. **E** MSCs MT reduces early and late apoptosis following electroporation in CAR-T cells and shows an increased cytotoxic activity, potentially enhancing CAR-T treatment outcomes. **F** In mouse models, Mito +CD19-CAR T reduced leukemia cells and improved survival rates. MT; mitochondrial transfer, RA; rheumatoid arthritis, IAV; influenza A virus, M.tb; mycobacterium tuberculosis, BM-SCs; bone marrow stem cells

MT could improve CAR-T cells'metabolic fitness and stress resistance, potentially enhancing CAR-T treatment outcomes (Fig. 7F) [179]. Despite MT's promising potential to enhance immune cell abilities, several challenges must be addressed for successful future clinical translation. The transplanted mitochondria can undergo mitophagy, which degrades mitochondria through autophagy [199]. Mitophagy is a selective autophagic process that removes damaged or dysfunctional mitochondria to maintain mitochondrial quality and cellular health. It primarily involves the PINK1/Parkin pathway, where damaged mitochondria accumulate PINK1, recruit Parkin to ubiquitinate outer membrane proteins, and signal autophagy adaptors to engulf the mitochondria in an autophagosome for lysosomal degradation. Mitophagy prevents cellular damage by eliminating mitochondria with impaired membrane potential and excessive ROS and supports energy metabolism [200]. Exogenous mitochondria often undergo stress during isolation and transfer procedures, triggering depolarization or membrane

Table 3 Clinical trials and pre-clinical studies used mitochondrial transfer

Condition	Method	Result	NCT number	Year	Country	Reference
IVF failure	ICSI	Recruiting	NCT02586298	2017	Spain	-
LHON	Co-culturing LHON iPSC-derived NPCs with MSCs	Enhancing mitochondrial function in NPCs	Pre-clinical (in vitro)	2024	China	[216]
Stroke injury	Co-culturing cortical neurons with MSCs	Enhancing neuroprotective capacity	Pre-clinical (in vitro)	2015	Russia	[217]
Retinal ischemia	Co-culturing retinal pigmented epithelium with MSCs	Restoring mitochondrial respiration, morphology, and mitochondrial dynamics	Pre-clinical (in vivo)	2019	USA	[218]
RGC degeneration	Mitochondrial donation from iPSC-MSCs into mice with RGC degeneration	Improving retinal function	Pre-clinical (in vivo)	2019	China	[219]
Lung injury	MSC Mitochondrial transfer via TNTs and EVs into the epithelium	Reducing leukocyte numbers, normalized surfactant secretion, and improving ATP levels in alveolar epithelia	Pre-clinical (in vivo)	2012	USA	[133]
Asthma	MSC Mitochondrial transfer via TNTs into injured lung epithelial cells	Reversing mitochondrial dysfunction in bronchial epithelial cells	Pre-clinical (in vivo and in vitro)	2014	India	[220]
Allergy	iPSC- MSC mitochondrial transfer through Connexin43-dependent TNTs in damaged epithelial cells	Reducing airway inflammation and improving mitochondrial function	Pre-clinical (in vivo and in vitro)	2018	China	[221]
COPD	iPSC-MSC mitochondrial transfer into the epithelium	Reducing oxidative stress-induced mitochondrial dysfunction in the airways	Pre-clinical (in vivo and in vitro)	2018	China	[222]
Acute respiratory distress syndrome	MSC mitochondrial transfer via EV to macrophages	Repression of proinflammatory cytokine secretion and improving phagocytic capacity by promoting an M2 anti-inflammatory phenotype	Pre-clinical (in vitro and ex vivo)	2017	United Kingdom	[187]
Ischemic heart disease	Mitochondrial transfer via TNTs into cardiomyocytes	Elevating mitochondrial membrane potential and function in the cardiomyocytes, and reducing apoptosis	Pre-clinical ex vivo	2019	China	[223]

damage. These stress signals activate the PTEN-induced kinase 1 (PINK1)/Parkin pathway, marking mitochondria for mitophagy [201]. It has been suggested that blocking PINK1/Parkin signaling prevents mitophagy and improves mitochondrial engraftment. However, complete inhibition of PINK1/Parkin may increase the risk of accumulating dysfunctional mitochondria [202]. Also, transferred mitochondria are not always fully functional. They can be depolarized and dysfunctional, acting more as signaling sources (for instance, through ROS production) rather than supplying sustained bioenergetic benefits. This limitation constrains their ability to restore long-term mitochondrial function in recipient cells, which may, in turn, restrict the long-term therapeutic effects [203]. Thus, standard mitochondrial isolation and transfer techniques should be developed to ensure consistent quantity and functionality across different cell types and donors. Recently, a creative microfluidic method has been described to control the quality and quantity of mitochondria injection into single live cells using a robot-aided microneedle and optical tweezers (Fig. 5C) [204]. The potential for immune rejection of donor cells due to the transplantation of allogeneic mitochondria remains a concern [205]. Mitochondria contain allogeneic antigens that can be presented to the recipient's immune system through MHC class I and II molecules. mtDNA encodes 13 proteins involved in oxidative phosphorylation, including subunits of complexes I, III, IV, and ATP synthase. Due to genetic polymorphisms, these proteins can differ slightly between individuals, making them potential alloantigens. In addition, mtDNA and N-formyl peptides can act as DAMPs, triggering innate immune responses via TLR9 or inflammasomes [206–208]. In this regard, the precise mechanisms by which transferred mitochondria enhance immune cell function, including metabolic reprogramming and signaling pathways, are critical to optimizing this approach [209]. In the old view, mitochondria were only supposed to be an energy supplier for the cell. However, based on our new knowledge, mitochondria are not just the cell's powerhouse but one of the most influential organelles involved in various cellular processes, including metabolism and intracellular signaling, determining the cell's fate. Despite the challenges and technical limitations in MT therapy, this approach promises a new era of organelle-based treatments, particularly for treating immune system-related disorders like cancer, autoimmunity, and infectious diseases. Mitochondrial transplantation exhibits lower immunogenicity than whole-cell therapies, reducing the risk of immune rejection and making it a safer alternative for treating immune-related diseases. Mitochondrial dysfunction is linked to metabolic diseases that often have an inflammatory component, such as autoimmune disorders. Currently, limited pre-clinical and clinical data are available; therefore, further studies are needed in this field. However, pre-clinical has shown promising results for reducing inflammation and improving mitochondrial function, which may translate into therapeutic benefits for immune system diseases (Table 3).

Abbreviation

BMSCs	Bone marrow stromal cells
ROS	Reactive oxygen species
mt	Mitochondria
mtROS	Mitochondrial ROS
mtDNA	Mitochondrial DNA
MT	Mitochondrial transfer
Th	T helper cell
Treg	Regulatory T
CAR	Chimeric antigen receptor
TIL	Tumor-infiltrating lymphocyte
NKC	Natural killer cell
MQ	Macrophage
NO	Nitric oxide
iNOS	Inducible nitric oxide synthase
NF-κB	Nuclear factor kappa B
TNF-α	Tumor necrosis factor-α
IL	Interleukin
IFN	interferon
ARDS	Acute respiratory distress syndrome
LPS	Lipopolysaccharides
PMA	Phorbol 12-myristate 13-acetate
EV	Extracellular vesicle
MV	Micro vesicle
TNT	Tunneling nanotubes
GJC	Gap junction channel
OXPHOS	oxidative phosphorylation
Cyto D	Cytochalasin D
GSDMD	Gasdermin D
NET	Neutrophil extracellular trap
MMP	Mitochondrial membrane potential
SRC	Spare respiratory capacity
TCA	Tricarboxylic acid cycle
GFP	Green fluorescent protein

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Authors'contributions
M.Ch. Hypothesized the topic and wrote the manuscript. Z.A.T. and M.K. prepared the figures and table. S.A.K. and T.K.Ch. reviewed and revised the manuscript. S.S. and S.M.H. supervised the project and revised the manuscript. All authors reviewed the manuscript and approved the final version.

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Data Availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
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