Dynamic regulation of the 'mitochondria-immune axis' in myocardial infarction: Molecular mechanisms driving macrophage polarization through energy metabolism disorders (Review)

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Received July 17, 2025; Accepted March 27, 2026

DOI: 10.3892/mmr.2026.13907

Abstract. The pathological process of myocardial infarction (MI), an acute cardiovascular event that has a high global death and disability rate, includes not only widespread cardiomyocyte necrosis but also intricate reactions like immune system activation and problems with mitochondrial energy metabolism. An increasing body of evidence in recent years has shown that mitochondria are essential for maintaining metabolic homeostasis in cardiomyocytes and for regulating the immune system. After MI, ATP production is impaired, and metabolites such as reactive oxygen species and mitochondrial DNA are released in excess due to mitochondrial structural damage, kinetic imbalance [such as overactivation of dynamin-related protein 1 (Drp1)], and disruption of the sirtuin (SIRT)3 - AMP-activated protein kinase - peroxisome proliferative activated receptor γ (PPARγ) coactivator 1α (PGC-1α) pathway. These factors drive macrophage polarization toward the M1 proinflammatory phenotype via signaling pathways such as Toll-like receptor 9/NLR family pyrin domain containing 3, thereby aggravating secondary injury to myocardial tissue. However, repair-phase macrophages can remodel mitochondrial oxidative phosphorylation via the PPARγ/PGC-1α axis, shifting to an M2-type phenotype to promote tissue repair, thereby forming a closed loop of 'metabolic-immune' regulation. To improve energy metabolism and the immune microenvironment simultaneously, targeted regulation of the 'mitochondria-immunity axis' (e.g., inhibition of Drp1 hypersegmentation and activation of the SIRT3 antioxidant pathway) may offer a fresh perspective on the accurate treatment of MI. In this review, the key mechanism underlying mitochondrial energy metabolism disorder in cardiomyocytes after MI is described, and the signaling roles and functional shifts of metabolites in macrophage polarization are examined, thereby providing a theoretical basis and targeted new ideas for the precise treatment of MI.

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Key words: myocardial infarction, mitochondrial energy metabolism, macrophage polarization, mitochondrial-immune axis

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1. Introduction

As a frequent and dangerous acute circulatory condition, myocardial infarction (MI) is a significant burden globally (1).

The incidence of MI is increasing worldwide, with certain high-income countries reporting 50-100 cases per 100,000 individuals per year, whereas low- and middle-income countries report 10-50 cases per 100,000 individuals per year (2). In China, statistics show that the incidence of MI is increasing annually, with an average growth rate of >20% in the last 10 years, and the mortality rate, which remains high despite a decrease due to advancements in medical technology, even if a patient survives an MI, the quality of life post-survival is negatively affected (3,4). MI is now a major contributor to heart failure and sudden cardiac death (5). Therefore, improving patient outcomes requires a thorough examination of the pathophysiological mechanisms underlying MI and novel therapeutic targets.

Impaired mitochondrial energy metabolism in cardiomyocytes is hypothesized to be a key cause of the complex pathological cascade that follows widespread cardiomyocyte mortality after MI, in addition to directly resulting in loss of cardiac function (6). The functional integrity of mitochondria, as the 'energy factories' of cardiomyocytes, is crucial for maintaining efficient cardiac pumping (7). Increasingly, studies have shown that, after MI, mitochondrial function in cardiomyocytes is significantly impaired by persistent ischemia-hypoxia and reperfusion injury, resulting in reduced energy production, dysregulation of the redox balance and altered cell fate (8). For example, the tricarboxylic acid (TCA) cycle and the oxidative phosphorylation (OXPHOS) process can be disrupted by imbalances in mitochondrial dynamics (such as Drp1-mediated hypersegmentation), abnormal opening of the mitochondrial membrane permeability transition pore (mPTP) and dysregulation of the sirtuin (SIRT)3 - AMP-activated protein kinase (AMPK) - peroxisome proliferative activated receptor γ (PPARγ) coactivator 1α (PGC-1α) metabolic axis. These disruptions can lead to a notable reduction in ATP synthesis efficiency (9). In addition, there is a compensatory shift in substrate utilization patterns from fatty acid oxidation (FAO) to glycolysis, exacerbating the energy crisis of cardiomyocytes; these metabolic disorders are also accompanied by the release of a large quantities of reactive oxygen species (ROS), mitochondrial DNA (mtDNA) and metabolites such as succinic acid, which further amplifies impairment of mitochondrial function, resulting in the widespread death of normal myocardium (9,10).

Mitochondria-derived metabolites can serve as indicators of an energy imbalance and are crucial signals in the control of innate immune responses (11). In a myocardial ischemic environment, the accumulation of succinate activates hypoxia-inducible factor-1α (HIF-1α) and enhances the expression of pro-inflammatory factors (such as IL-1β and IL-6). Additionally, ROS and mtDNA function as damage-associated molecular patterns (DAMPs), activating the macrophage Toll-like receptor (TLR9)/NLR family pyrin domain containing 3 (NLRP3) pathway, which subsequently induces NLRP3 inflammasome activation and a surge in the production and release of inflammatory factors (12). Subsequently, macrophages following an MI are polarized towards an M1 or M2 phenotype by metabolic reprogramming: M1-type macrophages primarily utilize glycolysis, resulting in the secretion of numerous pro-inflammatory factors, while M2-type macrophages depend on increased OXPHOS and FAO, releasing reparative factors, such as IL-10, to facilitate tissue healing and fibrotic remodeling, thereby establishing a closely interconnected network of 'metabolism-immunity-repair' (13).

Consequently, following MI, compromised mitochondrial energy metabolism is not only a pivotal factor in cardiomyocyte damage but also a significant catalyst for alterations in the immunological microenvironment. An increasing body of evidence indicates that the 'mitochondrial-immune axis' plays bidirectional roles in regulating macrophage inflammatory polarization and myocardial injury repair, offering novel avenues for exploring metabolism-immunity-linked myocardial protection strategies (14,15).

The present review examined mitochondrial energy metabolism imbalance in cardiomyocytes, systematically elucidating key molecular mechanisms and the role of metabolites in regulating macrophage immune polarization. Additionally, the 'mitochondria-immune axis' is defined, highlighting the bidirectional regulatory network that involves: i) Paracrine metabolic signals released from damaged cardiomyocytes (such as mtDNA, succinate and excessive ATP) that activate macrophage inflammatory pathways, and ii) intrinsic mitochondrial metabolic reprogramming within macrophages that determines their M1/M2 polarization phenotype. This review focuses on the bidirectional interplay between metabolism and immunity in post-infarction repair and injury, with the objective of providing a novel theoretical foundation and potential targets for MI treatment, with a focus on mitochondrial function and immune modulation.

The following sections describe the mechanisms of mitochondrial metabolic impairment after MI, the regulation of macrophage polarization by mitochondrial-derived metabolites and the influence of metabolic-immune interactions on myocardial injury and repair.

2. Molecular mechanisms of impaired mitochondrial energy metabolism in cardiomyocytes

Mitochondrial kinetic dysregulation and structural impairment. In typical physiological settings, the stable preservation of mitochondrial morphology in cardiomyocytes relies on a precise equilibrium between fusion and fission processes, which is collaboratively controlled by fusion proteins [mitofusin (Mfn)1/2 and OPA1 mitochondrial dynamin like GTPase (OPA1)] and fission proteins [Drp1 and fission, mitochondrial 1 (Fis1)]. Mfn1 and Mfn2, dynamin-associated GTPases situated on the outer mitochondrial membrane, facilitate the fusing of this membrane, and when they form a trans-complex, they may approximate adjacent mitochondria. OPA1 primarily facilitates mitochondrial inner membrane fusion and cristae restructuring, with its long and short isoforms working in concert to promote efficient inner membrane fusion (16,17). Drp1 plays a central role in mitochondrial division. Typically, Drp1 resides in the cytoplasm, and several post-translational modifications are initiated upon receipt of mitochondrial division signals (18). During mitosis, the B1/cyclin-dependent kinase (Cdk)1 complex of the cell cycle phosphorylates the Ser-585 site of Drp1, inducing its aggregation in the outer mitochondrial membrane. Conversely, under healthy conditions, CDK19/Cdk8 phosphorylates Drp1

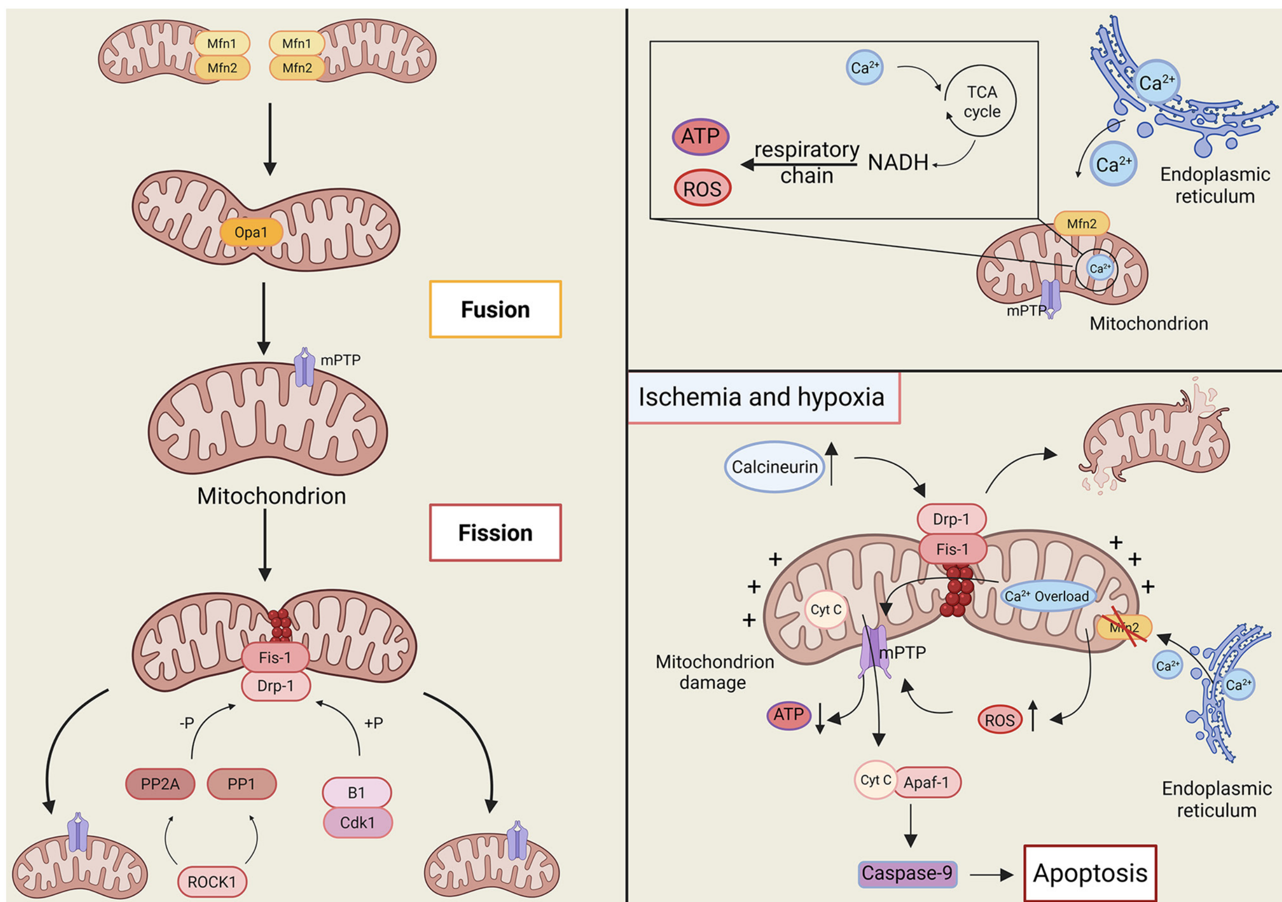

Figure 1. Mechanisms regulating mitochondrial morphologic stability in cardiomyocytes and the process of imbalance under pathological conditions. Physiological circumstances maintain a balance between mitochondrial fusion (Mfn1/2 for outer membrane fusion, Opa1 for inner membrane and cristae remodeling) and division (Drp1 in conjunction with Fis1, regulated by Cdk1, ROCK1, etc.). Ischemia and hypoxia induce the activation of calmodulin phosphatase, resulting in the overactivation of Drp1 and excessive mitochondrial fragmentation. Mfn2 aberrantly disrupts calcium signaling coupling, while Ca^{2+} overload and ROS provoke the opening of the mPTP, leading to the release of cytochrome C. This process activates apoptosis mediated by caspase-9 through Apaf-1, thereby exacerbating the injury. Mfn1, mitofusin 1; Opa1, optic atrophy 1; Drp1, dynamin-related protein 1; Fis1, fission 1; Cdk1, cyclin-dependent kinase 1; ROCK1, Rho-associated coiled-coil containing protein kinase 1; mPTP, mitochondrial permeability transition pore; Apaf-1, apoptotic protease activating factor 1; Caspase-9, cysteinyl aspartate specific proteinase-9; ROS, reactive oxygen species; Mfn2, mitofusin 2; PP1, protein phosphatase 1; TCA cycle, tricarboxylic acid cycle; NADH, nicotinamide adenine dinucleotide (reduced form); ATP, adenosine triphosphate; Cyt C, cytochrome C.

at Ser616, facilitating proper mitochondrial division (19). Furthermore, Rho-associated coiled-coil protein kinase 1 can dephosphorylate the Ser637 site of Drp1 by enhancing the activities of protein phosphatase 1 (PP1) and protein phosphatase 2A(PP2A), therefore activating Drp1 and facilitating its translocation to the mitochondria, where it assembles into a helical shape (20). Fis1, an auxiliary protein involved in mitochondrial division, interacts with Drp1 to recruit it to the site of division. Subsequently, GTP hydrolysis by GTP-bound Drp1 induces a conformational change, generating a mechanical force that facilitates mitochondrial membrane constriction and rupture, thereby completing the division process (21).

However, in pathological situations like ischemia and hypoxia, the balance of mitochondrial dynamics is disturbed in the case of Drp1, ischemia and hypoxia can augment the activity of calcium-modulated phosphatase (Calcineurin), which dephosphorylates the Ser637 site of Drp1, thereby increasing its affinity for the mitochondrial membrane and expediting its translocation to the mitochondria (22). Du *et al* (23) found that in the cardiac ischemia-reperfusion model, Drp1-Ser616 phosphorylation was markedly increased, accompanied by extensive Drp1 translocation to the mitochondrial surface, resulting in excessive mitochondrial division and fragmentation. In Sirt3-knockout mice, Sirt3 deficiency impaired deacetylation, thereby reducing activation of downstream proteins, including kinases that regulate Drp1 phosphorylation. This resulted in reduced Drp1 phosphorylation levels and heightened mitochondrial hypersegmentation, ultimately causing a marked deterioration in cardiac function. The absence of Mfn2 directly impaired mitochondrial fusion and disrupted calcium signaling coupling between mitochondria and the endoplasmic reticulum, owing to the role of Mfn2 in their linkage. Under physiological conditions, calcium ions released from the endoplasmic reticulum can be transported to mitochondria via Mfn2-mediated channels, and moderate calcium signaling can activate dehydrogenases and ATP synthase in the TCA cycle, thereby enhancing ATP production (24) (Fig. 1).

Following Mfn2 loss, mitochondrial calcium uptake becomes disordered and susceptible to calcium excess. Excessive calcium ions can activate calcium-dependent proteases and phospholipases within the mitochondria,

compromising mitochondrial membrane integrity and inducing substantial ROS production, which further impairs mitochondrial function. Mitochondrial morphological impairment is closely associated with aberrant mPTP opening (25). In compromised cardiomyocytes, disrupted energy metabolism and diminished ATP synthesis lead to impaired ion pump activity, which is essential for maintaining intracellular ionic homeostasis. This leads to excessive Ca^{2+} influx and intracellular accumulation, while the mitochondrial respiratory chain is concurrently dysregulated, hindering electron transfer and causing a significant rise in ROS production (26). Elevated Ca^{2+} and ROS levels can serve as cues to initiate mPTP opening. mPTP is a protein complex situated between the inner and outer mitochondrial membranes, which is typically in a closed state. Upon opening of the mPTP, the mitochondrial membrane potential rapidly dissipates; the proton electrochemical gradient across the inner membrane is reduced; OXPHOS coupling is disrupted; and ATP production decreases significantly. Concurrently, mPTP opening facilitates the release of cytochrome c from the mitochondrial intermembrane space into the cytosol, where it associates with apoptotic protease-activating factor 1, thereby recruiting and activating caspase-9, which subsequently initiates the downstream caspase cascade and induces apoptosis (27). Drp1 activation has been shown to promote excessive mitochondrial fission and to enhance mPTP opening via interactions with mPTP-associated proteins, thereby exacerbating mitochondrial injury. Conversely, the small molecule mitochondrial division inhibitor 1 (Mdivi-1), functioning as a Drp1 inhibitor, selectively binds to Drp1, impedes its GTPase activity and obstructs Drp1 from forming a helical shape with fission activity on the mitochondrial membrane, hence postponing mPTP opening (28). In the MI-reperfusion injury model, Mdivi-1 treatment reduced mitochondrial fragmentation, delayed mPTP opening and markedly decreased the myocardial infarct area, suggesting that modulating mitochondrial dynamics-related proteins may be an effective intervention for myocardial ischemic injury (29).

Disorders of essential energy metabolism pathways. The onset of MI involves the disruption of essential mitochondrial energy metabolism pathways, significantly impairing cardiomyocyte function, with the dysregulation of the SIRT3-AMPK-PGC-1α axis being pivotal (30). SIRT3, a mitochondrial deacetylase, is primarily localized in the mitochondrial matrix and modulates the acetylation status of several mitochondrial proteins. Under physiological conditions, SIRT3 preserves the proper function of mitochondrial proteins through deacetylating action (31). Superoxide dismutase 2 (SOD2) is a crucial mitochondrial antioxidant enzyme and its activity is modulated by acetylation. Physiological expression of SIRT3 deacetylates Lys-68 and other residues of SOD2, thereby activating SOD2, augmenting mitochondrial ROS scavenging capacity and preserving mitochondrial redox homeostasis (32). Additionally, SIRT3 deacetylates α-ketoglutarate dehydrogenase (OGDH), a pivotal enzyme in the TCA cycle that catalyzes the conversion of α-ketoglutarate to succinyl coenzyme A. Following deacetylation by SIRT3, OGDH activity is increased to facilitate the uninterrupted progression of the TCA cycle, allowing for the continuous supply of reducing equivalents (NADH, $FADH_2$) for OXPHOS (33). In MI, SIRT3 expression is markedly downregulated by stressors such as ischemia and hypoxia. Research indicates that in a mouse model of myocardial ischemia-reperfusion, SIRT3 protein levels in cardiac tissues decreased by ~50% following 20 min of ischemia and 24 h of reperfusion. The absence of SIRT3 reduced mitochondrial protein deacetylation, resulting in hyperacetylation (34). Excessive acetylation of SOD2 markedly diminished its activity and impaired its ability to scavenge ROS, leading to substantial ROS accumulation within the cell. Excessive ROS not only directly impaired the structural integrity of the mitochondrial membrane but also altered critical enzymes in the TCA cycle, thereby inhibiting their function (35). Simultaneously, the catalytic activity of OGDH was significantly diminished following hyperacetylation, thereby disrupting the TCA cycle. Obstruction of the TCA cycle reduced NADH and $FADH_2$ generation, thereby impairing OXPHOS and significantly reducing ATP synthesis efficiency, and resulting in a failure to meet the energy requirements of cardiomyocytes (36).

Conversion of substrate utilization. Under typical circumstances, cardiomyocytes primarily obtain energy by FAO, with ~70% of ATP generated by fatty acid β-oxidation, whereas glucose metabolism contributes considerably less to energy production. The pivotal rate-limiting step in the ingress of fatty acids into mitochondria for β-oxidation is facilitated by carnitine palmitoyltransferase 1 (CPT-1), which is located in the outer mitochondrial membrane, and catalyzes the conversion of lipoacyl-coenzyme A of long-chain fatty acids to lipoacylcarnitine, thereby permitting their entry into the mitochondrial matrix to ensure oxidation (37). At the onset of MI, the intracellular environment undergoes considerable alterations, resulting in inhibition of FAO and a gradual metabolic shift toward glycolysis. During ischemia and hypoxia, intracellular ATP concentrations decrease rapidly, whereas ADP and AMP levels rise, thereby activating AMPK. Activated AMPK phosphorylates and inhibits acetyl coenzyme A carboxylase, a crucial enzyme in fatty acid synthesis, leading to decreased generation of malonyl coenzyme A (38). Malonyl coenzyme A serves as an endogenous inhibitor of CPT-1; thus, reduced malonyl coenzyme A levels increase CPT-1 activity, presumably facilitating FAO. Of note, poor mitochondrial function resulting from ischemia, diminished activity of FAO-related enzymes and malfunction of fatty acid transporters collectively limit FAO, despite elevated CPT-1 activity (39). Concurrently, the cell redirects its metabolic flux toward glycolysis to meet its fundamental energy requirements. On the one hand, HIF-1α expression is upregulated and stabilized under ischemic hypoxic conditions. HIF-1α binds to the promoter regions of key glycolytic genes, such as glucose transporter 1 and hexokinase 2, thereby promoting their transcription and enhancing glucose uptake and glycolytic initiation. On the other hand, the activity of phosphofructokinase-1 (PFK-1), a key rate-limiting enzyme in glycolysis, was also increased (40,41). Elevated intracellular AMP concentrations can allosterically activate PFK-1 while concurrently increasing fructose-2,6-bisphosphate levels, the most effective allosteric activator of PFK-1. This interaction further enhances PFK-1 activity and accelerates glycolysis (42). The energy supply efficiency of glycolysis is significantly lower than that of FAO in conjunction with

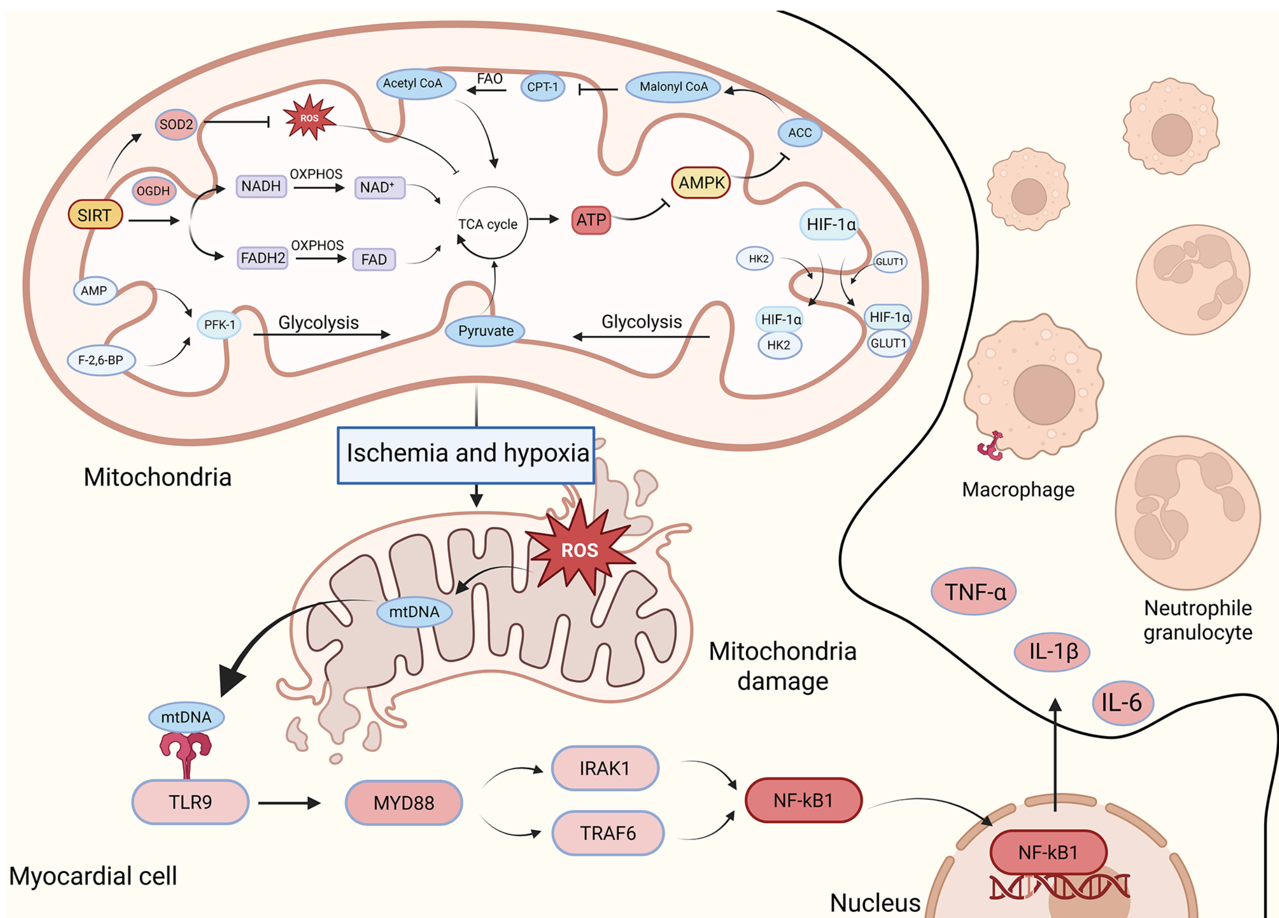

Figure 2. Disturbed energy metabolism and metabolic-immune cross-regulatory mechanisms in myocardial infarction. Under physiological settings, SIRT3 activates SOD2 and OGDH to sustain ROS scavenging and OXPHOS energy production, whereas FAO is regulated by CPT-1 and ACC. In the context of ischemia and hypoxia, the downregulation of SIRT3 results in the accumulation of ROS and damage to the TCA cycle and OXPHOS. Concurrently, AMPK and HIF-1α promote a metabolic shift towards glycolysis. The release of ROS and mtDNA from mitochondria activates the macrophage TLR9 pathway, leading to the release of pro-inflammatory factors and establishing a cycle of injury. SIRT3, sirtuin 3; SOD2, superoxide dismutase 2; OGDH, oxoglutarate dehydrogenase; ROS, reactive oxygen species; OXPHOS, oxidative phosphorylation; FAO, fatty acid oxidation; CPT-1, carnitine palmitoyltransferase 1; ACC, acetyl-CoA carboxylase; AMPK, adenosine 5'-monophosphate-activated protein kinase; HIF-1α, hypoxia-inducible factor 1α; mtDNA, mitochondrial DNA; TLR9, toll-like receptor 9; acetyl CoA, acetyl coenzyme A; NADH, nicotinamide adenine dinucleotide (reduced form); NAD^+, nicotinamide adenine dinucleotide (oxidized form); $FADH_2$, flavin adenine dinucleotide (reduced form); FAD, flavin adenine dinucleotide (oxidized form); ATP, adenosine triphosphate; AMP, adenosine monophosphate; TCA cycle, tricarboxylic acid cycle; PFK-1, phosphofructokinase-1; F-2,6-BP, fructose-2,6-bisphosphate; HK2, hexokinase 2; GLUT1, glucose transporter 1; MYD88, myeloid differentiation primary response 88; IRAK1, interleukin-1 receptor-associated kinase 1; TRAF6, TNF receptor-associated factor 6; NF-κB1, nuclear factor kappa-light-chain-enhancer of activated B cells 1; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β.

OXPHOS. One molecule of glucose can yield 30-32 molecules of ATP via complete decomposition through aerobic oxidation, while glycolysis results in the production of only 2 molecules of ATP. This substrate utilization conversion serves as an emergency strategy; however, prolonged dependence on glycolysis for energy does not meet the substantial energy requirements of cardiomyocytes. Additionally, the excessive lactate produced by glycolysis further impairs cardiomyocyte function. This results in a reduction of intracellular pH, subsequently compromising cardiomyocyte function (43,44) (Fig. 2).

Metabolite release induces an inflammatory response. Impaired mitochondrial energy metabolism affects energy supply and leads to the abnormal release of various metabolites. Notably, overproduction of ROS and mtDNA spillover are significant factors that trigger aseptic inflammation (45). In the standard mitochondrial respiratory chain, electrons are sent to oxygen through complexes I, II, III and IV, while ADP is phosphorylated to generate ATP. In MI, mitochondrial structural damage and respiratory chain dysfunction impede electron transfer, leading to significant electron leakage that reacts with oxygen to generate the superoxide anion ($O_2^{\cdot-}$). This ROS can subsequently generate hydrogen peroxide (H_2O_2), hydroxyl radicals (·OH) and other more reactive ROS (46). Excess ROS are potent oxidants that can directly damage lipids, proteins and mtDNA within the mitochondrial membrane. ROS in the mitochondrial membrane can induce lipid peroxidation, thereby diminishing membrane fluidity, increasing permeability and compromising the structural integrity of the mitochondrial membrane. For example, ROS can oxidize cardiolipin, a phospholipid unique to the inner mitochondrial membrane, crucial for the stability and functionality of the respiratory chain complex. The oxidation of cardiolipin impairs the function of respiratory chain complexes, thereby exacerbating ROS generation (47). Conversely, ROS can affect

mitochondrial proteins, hence changing their structure and function. For example, ROS can induce oxidative alterations of Drp1, thereby facilitating excessive mitochondrial division and fragmentation (48). Concurrently, ROS can also cause mtDNA damage, encompassing base mutations, deletions and double-strand breaks (49).

In conclusion, impaired mitochondrial energy metabolism in cardiomyocytes following MI leads to an injury network characterized by kinetic imbalances, disruption of metabolic pathways, alterations in substrate use and the release of inflammatory signals. An imbalance in mitochondrial fusion and fission disturbs energy production, dysregulation of the SIRT3 axis impedes OXPHOS, a metabolic shift to glycolysis intensifies the energy crisis and the activation of inflammation by ROS and mtDNA deteriorates the microenvironment. Therefore, targeting the mitochondrial metabolic network is a potential direction for prevention and treatment; modulation of Drp1/Mfn2, activation of the SIRT3 axis, optimization of substrate utilization and blockade of the inflammatory cascade improve energy supply and promote macrophage polarization toward the M2 phenotype by intervening in the mitochondrial-immune axis, providing a novel direction for clinical translation.

3. Dysfunctional mitochondrial metabolism promotes immunological responses by macrophages

Metabolites as immunological signals

Accumulation of succinate and activation of inflammation. Under physiological conditions, the TCA cycle operates in a coordinated manner, maintaining the equilibrium of cellular energy metabolism. Nonetheless, during MI, mitochondrial activity is compromised and the TCA cycle is disrupted (50). Succinate dehydrogenase activity is suppressed, leading to intracellular accumulation of succinate due to impaired conversion. Succinate, a crucial metabolic intermediate, activates HIF-1α upon its buildup. HIF-1α is a crucial transcription factor that is significant in hypoxic or metabolic stress circumstances. In general, HIF-1α is expressed at low levels in cells and undergoes hydroxylation by prolyl hydroxylase (PHD) domains before being degraded by the ubiquitin-proteasome system. Nonetheless, as succinate accumulates, it inhibits PHD activity, thereby stabilizing HIF-1α, which permits its substantial accumulation within the cell and subsequent translocation to the nucleus. HIF-1α translocates to the nucleus, attaches to the hypoxia response element in the promoter region of the target gene and activates the transcription of numerous genes, including the pro-inflammatory cytokines IL-1β and IL-6. IL-1β and IL-6, significant inflammatory mediators, are released in substantial amounts into the extracellular space, attracting immune cells, such as neutrophils and lymphocytes, to the MI site and initiating an inflammatory response. The inflammatory response facilitates the removal of necrotic tissue in the early phases; nevertheless, excessive or prolonged inflammation may cause further damage to cardiomyocytes (51).

Activation of NLRP3 inflammasomes by ATP/ROS. MI, resulting in mitochondrial impairment, leads to succinate accumulation and the release of ATP and ROS into the extracellular milieu, which function as DAMPs and can activate NLRP3 inflammatory vesicles. Compromised mtDNA is less stable and may be extruded from the mitochondria into the cytoplasm. mtDNA functions as a DAMP detectable by TLR9 in the cytoplasm. TLR9 is predominantly expressed on the surface of various cell types, including immune cells (for example, macrophages and dendritic cells) and cardiomyocytes. mtDNA binding to TLR9 initiates a downstream signaling cascade dependent on myeloid differentiation factor 88 (MyD88). MyD88 recruits IL-1 receptor-associated kinase (IRAK) family members, which activate tumor necrosis factor receptor-associated factor 6 (TRAF6), thereby activating nuclear factor-κB (NF-κB). Activated NF-κB translocates to the nucleus and associates with the promoter regions of pro-inflammatory cytokine genes (for example, TNF-α, IL-1β and IL-6), thereby enhancing their transcription and expression (52,53). These pro-inflammatory cytokines are secreted extracellularly to attract and activate immune cells, initiating a sterile inflammatory response. While the inflammatory response serves as a defensive mechanism, excessive inflammation can exacerbate cardiomyocyte damage and worsen MI, creating a detrimental cycle (54). The NLRP3 inflammasome is a multiprotein complex that primarily comprises NLRP3, apoptosis-associated speck-like protein (ASC) and caspase-1 (55). The construction and activation of NLRP3 inflammatory vesicles are triggered by ATP binding to the P2X7 receptor on the cell membrane or by ROS stimulating redox-sensitive signaling pathways within the cell (56). Specifically, ATP binding to the P2X7 receptor induces channel opening, resulting in intracellular potassium efflux that activates NLRP3. Conversely, ROS can activate NLRP3 by oxidizing cysteine residues, thereby inducing a conformational change. Activated NLRP3 inflammatory vesicles assemble multimeric complexes by attracting ASC, which then attracts and activates caspase-1 precursors, resulting in their cleavage into active caspase-1. Activated caspase-1 preferentially cleaves pro-IL-1β, converting it into physiologically active IL-1β, thereby facilitating the initiation and progression of inflammatory responses (57). Additionally, caspase-1 cleaves the Gasdermin D protein, releasing its N-terminal domain, which inserts into the plasma membrane to form a pore. This process induces cell death and the rapid release of inflammatory mediators, thereby intensifying the inflammatory cascade. It causes osmotic imbalance in cardiomyocytes, disrupts membrane integrity and impairs organelle function, ultimately exacerbating structural damage and functional loss in myocytes, while facilitating the pathological progression of MI toward a reversible state and eventually intensifying the structural impairment and functional decline of cardiomyocytes, hence advancing the pathological progression of MI irreversibly (58).

Metabolic reprogramming and polarization of macrophages. In the context of MI, macrophage metabolic reprogramming modulates inflammatory processes and tissue healing through bidirectional polarization patterns (59). Pro-inflammatory M1 polarization is induced by ischemia and a hypoxic milieu, in which increased HIF-1α stability promotes macrophage polarization toward the pro-inflammatory (M1) phenotype (60,61). HIF-1α can modulate the glycolytic pathway by transcriptionally activating pyruvate kinase M2 (PKM2),

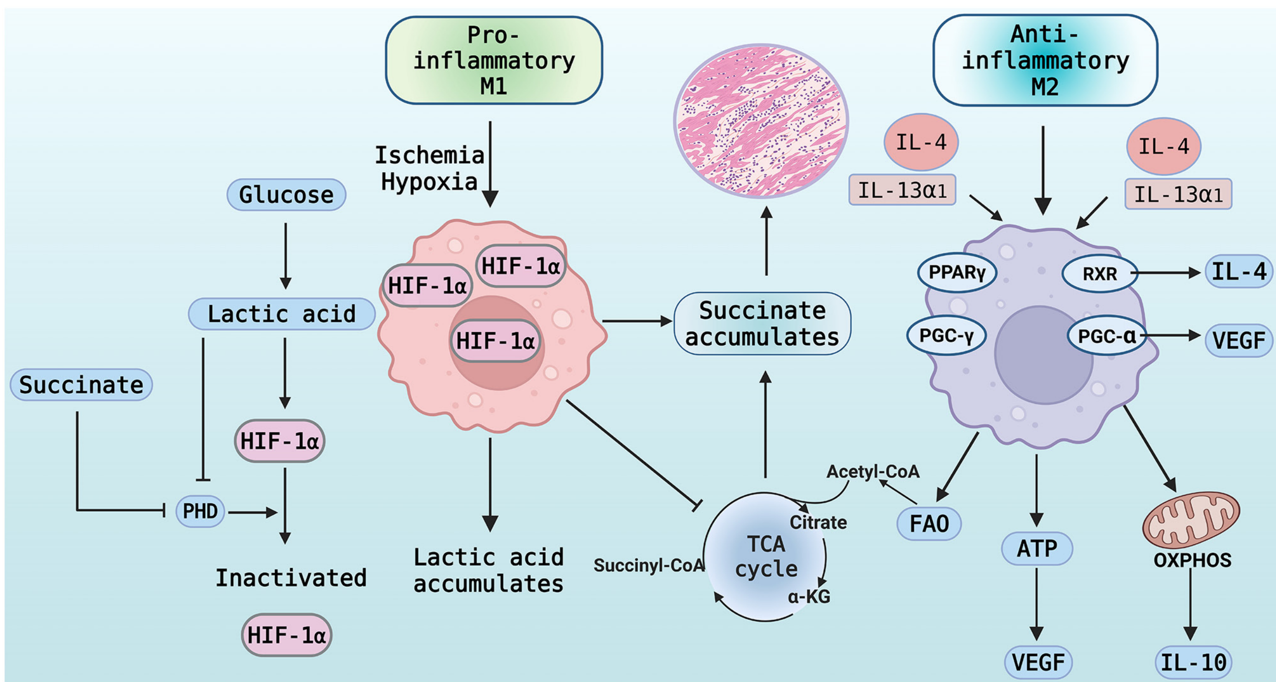

Figure 3. Dynamic mechanisms by which metabolites and cytokines synergistically regulate macrophage polarization in the microenvironment of MI. In the microenvironment of MI during the pro-inflammatory phase, mitochondrial dysfunction disrupts the TCA cycle, resulting in Succinate accumulation that inhibits PHD, stabilizes HIF-1α, activates the glycolytic pathway and facilitates macrophage polarization towards the M1 pro-inflammatory phenotype, thereby establishing a 'Succinate - HIF-1α' positive feedback loop. The repair phase involves IL-4 stimulating PPAR-γ to form a complex with RXR and PGC-1α, thereby enhancing mitochondrial metabolism to inactivate HIF-1α. Acetyl coenzyme A generated by the TCA cycle supports the anti-inflammatory phenotype, induces the secretion of IL-10 and VEGF, and promotes tissue repair, while lactate plays a regulatory role, illustrating the interplay between metabolism and immunity. MI, myocardial infarction; TCA, tricarboxylic acid cycle; HIF, hypoxia-inducible factor; PHD, prolyl hydroxylase; IL-4, interleukin-4; PPAR-γ, peroxisome proliferator-activated receptor γ; RXR, retinoid X receptor; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1α; VEGF, vascular endothelial growth factor; IL-13α1, IL-13 receptor α1; PGC-γ, peroxisome proliferator-activated receptor gamma coactivator γ; FAO, fatty acid oxidation; OXPHOS, oxidative phosphorylation; IL-10, interleukin-10; α-KG, α-ketoglutarate; acetyl-CoA, acetyl coenzyme A; succinyl-CoA, succinyl coenzyme A.

thereby steering glucose metabolism toward the lactic acid and pentose phosphate pathways, resulting in the accumulation of metabolic intermediates such as succinate. Succinate not only establishes positive feedback by stabilizing HIF-1α but also facilitates the maturation and release of IL-1β via the mitochondrial ROS-NLRP3 inflammatory vesicle pathway. In contrast, the glycolytic byproduct, lactic acid, inhibits histone deacetylase (HDAC) activity, thereby alleviating the transcriptional repression of NF-κB-mediated pro-inflammatory genes, thereby enhancing the 'metabolism-epigenetic' cascade. In a murine model of MI, PKM2 inhibition reduced the expression of the M1 macrophage marker inducible nitric oxide synthase, significantly decreased IL-1β levels and reduced infarct size (62).

Conversely, reparative M2 polarization is induced by IL-4/IL-13 activation of the JAK1-STAT6 signaling pathway through the IL-4Rα/IL-13Rα1 receptor (63). The phosphorylation of STAT6 within the nucleus promotes the expression of PPAR-γ, which assembles a transcriptional complex with retinoic acid X receptor (RXR) and coactivator PGC-1α to collaboratively modulate mitochondrial biosynthesis (for example, transcription factor A, mitochondrial and nuclear respiratory factor 1 and essential enzymes of FAO (e.g., CPT-1A and acyl-coa oxidase 1). PGC-1α facilitates repair via two metabolic mechanisms: i) Promoting FAO of long-chain fatty acids into β-oxidation, supplying acetyl coenzyme A for the TCA cycle; and ii) upregulation of electron transport chain complex expression to enhance OXPHOS efficiency. ATP generated by OXPHOS facilitates the ubiquitin-mediated clearance of HIF-1α via the AMPK/mTORC1 signaling pathway, thereby suppressing the glycolysis-dependent pro-inflammatory response. Significantly, the PPAR-γ agonist rosiglitazone augmented the percentage of CD206+ M2-type macrophages by 35% in the MI model and expedited neovascularization by enhancing vascular endothelial growth factor (VEGF) secretion. Conversely, PGC-1α knockdown led to a 40% reduction in macrophage FAO, accompanied by a decrease in the secretion of the anti-inflammatory factor IL-10, thereby supporting the role of mitochondrial metabolism in promoting M2-type polarization (64). This confirms that mitochondrial metabolism facilitates M2-type polarization (Fig. 3).

In summary, compromised mitochondrial metabolism during MI initiates a proinflammatory response through the release of metabolites such as succinate and ATP/ROS, which activate the HIF-1α/NF-κB and NLRP3 inflammatory vesicle pathways, thereby promoting macrophage polarization toward the glycolysis-dominant M1 phenotype. Simultaneously, IL-4/IL-13 modifies mitochondrial OXPHOS/FAO metabolism through the STAT6-PPARγ-PGC-1α pathway, facilitating M2-type polarization to promote repair. Therefore, focusing on the metabolism-immunity-linked interaction axis (for example, modulating the SIRT3-AMPK pathway or targeting

the HIF-1α-PDK1 axis) may reshape macrophage polarization phenotype and offer a novel approach for anti-inflammatory-restorative combination therapy in MI. Future research should focus on the spatial and temporal dynamics of transcellular metabolic signaling.

4. Bidirectional influence of metabolic-immune interactions in myocardial repair and damage

Initial injury phase. The immediate pathological response to MI is characterized by a temporal sequence of metabolic homeostasis disruption and inflammatory activation, which underlies early damage (65). Within minutes to hours following MI, the ischemia and hypoxic milieu swiftly induce an imbalance in mitochondrial dynamics and metabolic signaling, establishing a 'metabolic-inflammatory' positive feedback loop (52). Specifically, enhanced calcium-modulated phosphatase (Calcineurin) activity facilitates dephosphorylation of Ser637 on Drp1, markedly increasing its affinity for the mitochondrial membrane and leading to excessive mitochondrial fragmentation. When the damaged inner mitochondrial membrane ruptures during mitochondrial fission, mtDNA is released into the cytoplasm. Macrophage TLR9 recognizes these molecules as DAMPs. Through MyD88, TLR9 recruits IRAK, which, in turn, activates TRAF6, thereby inducing NF-κB nuclear translocation and increasing levels of pro-inflammatory cytokines such as IL-1β, TNF-α and IL-6 (66,67). These proinflammatory factors worsen secondary myocardial injury through two mechanisms: TNF-α causes cardiomyocytes to undergo apoptosis via the death receptor pathway, increases vascular permeability and encourages neutrophil infiltration; and IL-1β binds to IL-1R1 on cardiomyocytes, activates the MAPK/p38 pathway, inhibits mitochondrial complex II activity and further encourages succinate accumulation and ROS generation. The key involvement of the mtDNA-TLR9 axis in early inflammatory storms was confirmed by TLR9 silencing, which reduced infarct size by 35% and IL-1β levels by 40% in a mouse model of myocardial ischemia-reperfusion (68).

Repair stage. When the initial inflammatory surge reaches its peak, the body activates a reparative process facilitated by metabolic reprogramming, in which macrophage phenotypic switching is pivotal (69). Between 24 and 72 h post-MI, macrophages commence phagocytosis by identifying phosphatidylserine on the membranes of apoptotic cardiomyocytes, a mechanism that activates metabolic reprogramming in macrophages. Following phagocytosis of apoptotic cells, AMPK activity in macrophages increases markedly, leading to phosphorylation and activation of CPT-1, thereby facilitating FAO. Acetyl coenzyme A generated by FAO enters the TCA cycle and increases OXPHOS capability, supplying the energy required to sustain an anti-inflammatory phenotype (70). Concurrently, FAO intermediates, such as acetylcarnitine, stimulate SIRT1, which deacetylates PPARγ and enhances its capacity to heterodimerize with RXR. The PPARγ-RXR complex, in conjunction with PGC-1α, stimulates transcription of the anti-inflammatory genes IL-10, TGF-β and VEGF. IL-10 inhibits the release of pro-inflammatory factors by binding to IL-10R1/IL-10R2 receptors on macrophages, increasing JAK1/STAT3 signaling and suppressing NF-κB activity (71,72). In a rat model of MI, PPARγ overexpression led to a 2.3-fold increase in IL-10+ macrophages within the infarcted region and a 40% decrease in myocardial fibrosis area. Additionally, TGF-β facilitated organized type I collagen deposition rather than disorganized fibrosis by inducing fibroblast transformation into myofibroblasts, thereby preserving cardiac structural integrity (73). Furthermore, Willenborg *et al* (74) discovered that the metabolic phenotype of repair-phase macrophages is dynamically influenced by the oxygen partial pressure within the microenvironment: In the initial hypoxic region (oxygen partial pressure <10 mmHg), HIF-1α remained activated at a low level, facilitating energy for phagocytosis by transiently sustaining glycolysis through the induction of PDK1 expression; as neovascularization occurred, the oxygen partial pressure increased to 20-30 mmHg, leading to the dominance of the PPARγ/PGC-1α axis in the metabolic transition. Neovascularization resulted in oxygen partial pressure returning to 20-30 mmHg, leading to the ubiquitination and degradation of HIF-1α, while the PPARγ/PGC-1α axis governed the metabolic transition. This spatiotemporal regulatory mechanism of metabolism-immunity-linked interaction facilitated the timely transition of macrophages to a reparative phenotype following the removal of necrotic tissues, thereby preventing excessive inflammatory damage (74,75).

Molecular targeting methodologies for metabolic therapies to promote repair. Based on the aforementioned regulatory mechanisms of metabolism-immunity-linked interaction, targeted intervention in the metabolic signaling axis has emerged as a novel paradigm for enhancing cardiac healing. SIRT3-mediated modification of the mitochondrial-immunological axis has considerable therapeutic promise owing to its dual role in metabolic control and the inhibition of inflammation (76). Overexpression of SIRT3 ameliorated metabolic-immune disorders via a dual mechanism: First, SIRT3 deacetylation activated liver kinase B1, an upstream kinase of Drp1, thereby enhancing AMPK Thr172 phosphorylation, inhibiting Drp1 Ser637 dephosphorylation and reducing mitochondrial fragmentation. In SIRT3 transgenic mice, MI led to increased production of the mitochondrial fusion protein Mfn2 and increased the recovery of the mitochondrial membrane potential (77). Second, SIRT3 activated SOD2 via deacetylation, diminishing mitochondrial ROS levels, mitigating mtDNA damage and release, and inhibiting the TLR9/NF-κB inflammatory pathway (76,78). Following the restoration of mitochondrial function, ATP synthesis in cardiomyocytes increases, thereby influencing macrophage phenotype via paracrine signaling. ATP is released by the Connexin 43 hemichannel, activating macrophage P2Y purinoceptor 12, inhibiting adenylate cyclase via Gi proteins, reducing cyclic AMP levels and facilitating PPARγ phosphorylation. Lactate dehydrogenase A produced by cardiomyocytes can be taken up by macrophages, facilitating PPARγ binding to DNA and augmenting M2-type gene transcription via HDAC inhibition (79,80) (Fig. 4).

Therefore, metabolic-immune interactions during MI play a bidirectional regulatory function in both damage and healing.

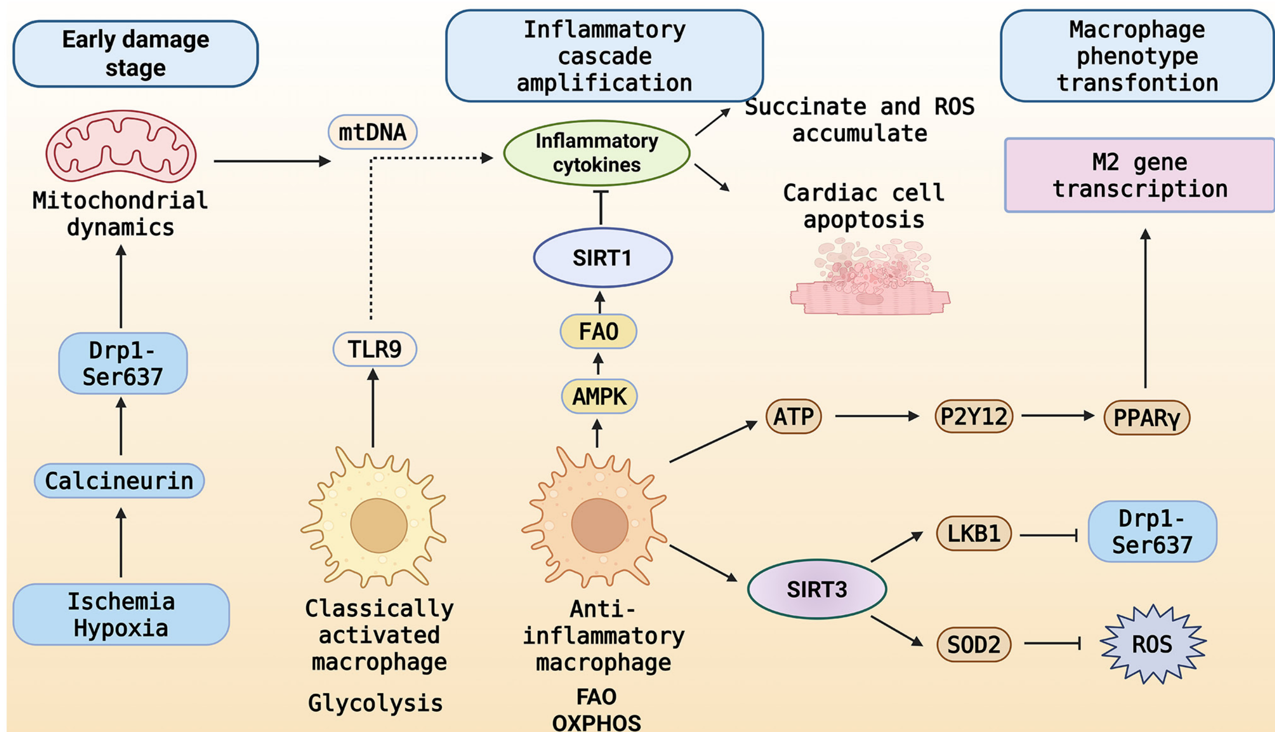

Figure 4. Bidirectional mechanism of metabolic-immune axis regulation of myocardial injury and repair after myocardial infarction. During the initial phase of injury, Ischemia and hypoxia stimulate calmodulin phosphatase, leading to the dephosphorylation of Drp1 Ser637, resulting in excessive mitochondrial fragmentation, the release of mtDNA, Succinate and ROS, and the activation of the macrophage proinflammatory pathway through TLR9, thereby polarizing it towards a proinflammatory phenotype and intensifying myocardial apoptosis. During the repair phase, SIRT3 enhances mitochondrial dynamics and diminishes ROS; ATP and other factors propel macrophage metabolism towards FAO and OXPHOS, facilitating a transition to an anti-inflammatory phenotype, commencing M2 transformation and fostering repair. Drp1, dynamin-related protein 1; mtDNA, mitochondrial DNA; ROS, reactive oxygen species; TLR9, Toll-like receptor 9; SIRT3, Sirtuin 3; ATP, adenosine triphosphate; FAO, fatty acid oxidation; OXPHOS, oxidative phosphorylation; Ser637, serine 637; AMPK, adenosine 5'-monophosphate-activated protein kinase; P2Y12, purinergic receptor P2Y12; PPAR-γ, peroxisome proliferator-activated receptor γ; LKB1, liver kinase B1; SOD2, superoxide dismutase 2.

During the initial injury phase, mitochondrial dysfunction releases mtDNA, which activates the TLR9/NF-κB pathway, thereby triggering a positive inflammatory feedback loop and exacerbating myocardial injury. During the repair phase, macrophages initiate the AMPK-CPT1-FAO axis via phagocytosis of apoptotic cells, activate the PPARγ/PGC-1α pathway, shift to an anti-inflammatory M2 phenotype, and suppress inflammation and promote myocardial repair through factors such as IL-10 and TGF-β. SIRT3 functions as a metabolic-immune nexus that activates AMPK and SOD2, diminishes ROS and mtDNA release and mitigates inflammation, while further promoting macrophage reprogramming via ATP- and lactate-mediated paracrine signaling. This mechanism reflects the coupled regulation of metabolism and immunity across spatial and temporal scales, providing theoretical support and potential targets for interventions in myocardial injury.

5. Discussion

In recent years, the focus in myocardial healing and injury research has been the metabolic-immune crossover between mitochondrial failure and the macrophage immunological response following MI (13). The molecular mechanisms underlying impaired mitochondrial energy metabolism in cardiomyocytes following MI are systematically reviewed in the present article, with a focus on the critical roles of aberrant substrate metabolism, imbalanced mitochondrial dynamics and disruption of key signaling pathways in immunological activation and cardiomyocyte death. Further investigation into functional alterations in inflammatory polarization and the reprogramming of macrophages in response to metabolites ultimately demonstrated the reciprocal regulatory functions of immunity and metabolism in myocardial damage and healing. Based on the above, this review summarizes and provides an overview of the research focus and challenges in this field across three in-depth aspects.

First, the inflammatory cascade reaction begins with decreased mitochondrial metabolism in cardiomyocytes following MI. Mitochondrial structural integrity and energy metabolism function are severely compromised by imbalances in mitochondrial dynamics, including Drp1-mediated hyper-fission and downregulation of Mfn2/OPA1 expression. When mitochondrial morphology is disrupted, the mPTP opens abnormally and the membrane potential collapses, triggering the mitochondrial-mediated apoptotic cascade. Concurrently, the energy crisis in cardiomyocytes is exacerbated by the buildup of metabolic intermediates like succinate in the TCA cycle, SIRT3 deficiency-induced defective deacetylation of important enzymes and the shift in substrate use from FAO to glycolysis. In this context, a closed-loop disease known as 'metabolic imbalance-immune activation' is initiated

when DAMPs, including ROS and mtDNA, are released in significant amounts, thereby triggering a sterile inflammatory response (18,21).

Second, mitochondrial metabolites play a major role in regulating macrophage reprogramming and phenotypic change, which are important effector cells in the immune response. While substances such as ROS and ATP exacerbate secondary damage to myocardial tissue by activating the NLRP3 inflammasome and promoting caspase-1-dependent IL-1β maturation and cellular pyroptosis, succinic acid is released from injured cells, activating HIF-1α and driving pro-inflammatory polarization of M1-type macrophages in the MI environment (57). M1-type macrophages' rapid inflammatory response is supported by their glycolytic metabolic advantage, whereas during the repair phase, FAO and OXPHOS-dominated metabolism polarizes macrophages towards an M2 phenotype, which secretes VEGF and IL-10 to promote fibrosis and neovascularization and finish tissue remodeling. Important signaling axes, such as SIRT3, PGC-1α and PPARγ, control this process, offering a biological foundation for the return of metabolic-immune balance (64).

Third, the metabolic-immune crossover is a key factor in the quality of myocardial repair and in the magnitude and duration of the inflammatory response. In the initial stages of MI, mtDNA leakage and mitochondrial damage induce Drp1 activation, creating an inflammatory 'signaling source' that initiates the macrophage TLR9-NF-κB pathway. This leads to the release of numerous inflammatory factors, including TNF-α, IL-6 and IL-1β, resulting in 'secondary cell death' and the development of MI (68). Conversely, M2-type macrophages regulate tissue healing throughout the repair phase by, among other functions, eliminating apoptotic cells and promoting collagen deposition and angiogenesis (75). Restoring mitochondrial fusion, improving energy metabolism efficiency and lowering ROS load, all of which promote the M2 polarization transition, by activating the SIRT3 axis, may slow cardiac remodeling following MI (76).

In addition, it is important to acknowledge that several regulatory mechanisms discussed above may exhibit context-dependent or even contradictory effects. Although SIRT3 is generally regarded as a protective metabolic regulator, recent evidence suggests that its actions are not uniformly beneficial. Excessive SIRT3-driven enhancement of FAO may increase metabolic stress during acute ischemia, and its anti-inflammatory effects may suppress the early M1-mediated clearance of damaged tissue, which is essential for clearing necrotic cardiomyocytes. Similarly, while prolonged M1 activation contributes to secondary injury, a timely and transient M1 response is indispensable for proper removal of debris and for establishing a microenvironment permissive to subsequent M2-driven repair. Recognizing these complexities highlights the need for stage-specific evaluation of metabolic and immune interventions in MI, rather than assuming uniform therapeutic benefits across all phases of injury and healing.

Several important questions remain unresolved, despite research that has provided a clearer picture of the molecular chain linking compromised mitochondrial metabolism, immunological polarization and cardiac healing. For example, i) whether mitochondrial structural alterations and metabolite release are linked in a 'lead event' or feedback mechanism; ii) whether macrophage phenotypes display more dynamic intermediate states; and iii) the distinct functions of various cardiomyocyte subpopulations in metabolic-immune crossover. Furthermore, current studies on regulatory nodes, such as SIRT3 and PGC-1α, focus on cellular models and animal experiments; comprehensive clinical translational research is still required to confirm their expression profiles in human cardiac tissues, to elucidate their dynamic patterns of change and to assess their potential for pharmacological regulation.

Taken together, these knowledge gaps highlight several future perspectives and unresolved questions that warrant further investigation. First, it remains unclear whether mitochondrial fission and structural disruption serve as initiating triggers that precede metabolite leakage, or whether they arise secondarily as a consequence of sustained oxidative stress and DAMP release. Time-resolved *in vivo* imaging and conditional manipulation of Drp1/Mfn2 in cardiomyocytes will be essential to disentangle causality along this axis. Second, the traditional dichotomy of M1 vs. M2 macrophages is likely an oversimplification in the evolving infarct microenvironment. Single-cell and spatial multi-omics analyses suggest the presence of hybrid or transitional states with mixed inflammatory and reparative signatures, yet their temporal distribution, plasticity and functional contribution to scar formation and ventricular remodeling remain poorly defined. Third, cardiomyocytes are not a homogeneous population: Subendocardial, subepicardial and conduction-system myocytes may differ in mitochondrial density, substrate preference and susceptibility to immune-mediated injury. How these distinct cardiomyocyte subpopulations participate in, or shape, the mitochondrial-immune crosstalk is largely unknown. Finally, although SIRT3, PGC-1α and related metabolic checkpoints are promising targets in preclinical models, their expression patterns, pharmacodynamic responsiveness and safety profiles in human myocardial tissue have not been systematically characterized. Addressing these questions will be crucial for rationally designing metabolism-based immunomodulatory therapies and for selecting the right patients, timing and endpoints in future clinical trials. From a therapeutic standpoint, targeting mitochondrial metabolic remodeling has considerable potential. In animal studies, Drp1-based inhibitors such as Mdivi-1, SIRT3 agonists such as Honokiol, and AMPK-PGC-1α pathway activators have demonstrated encouraging effects, improving energy metabolism and markedly reducing myocardial infarct size and left ventricular remodeling. In addition, immunometabolic modulators that have been shown to enhance M2-type polarization and promote myocardial healing include IL-10 carriers and FAO promoters. Future studies should investigate the combined metabolic-immune intervention method in greater detail, establish a more accurate treatment plan and timeline, and recognize the shift from 'symptomatic anti-inflammatory' to 'source metabolic intervention'.

6. Conclusion

Myocardial infarction profoundly disrupts mitochondrial energy metabolism, which not only compromises

cardiomyocyte survival but also shapes the inflammatory and reparative responses by affecting macrophage activation and polarization. Current evidence indicates that metabolic-immune interactions, including mitochondrial dynamics, SIRT3-mediated metabolic regulation, inflammasome activity and M1/M2 phenotypic switching, collectively determine the balance between tissue injury and healing.

These insights identify the mitochondria-immune axis as a promising therapeutic target for coordinating both inflammation control and myocardial repair. Future research should focus on clarifying the temporal sequence of metabolic and immune events, defining intermediate macrophage phenotypes and validating metabolic regulators such as SIRT3 and Drp1 in human myocardial tissue. Advancing this knowledge will facilitate the translation of metabolism-based immunomodulatory strategies into clinically applicable interventions for precise myocardial protection.

Acknowledgements

The figures were created with BioRender (https://app.biorender.com).

Funding

The present study was supported in part by research grants from the 'Project for Supporting Innovative Teams and Talents in Traditional Chinese Medicine' organized and implemented by the National Administration of Traditional Chinese Medicine (grant no. ZYYCXTD-C-202207) and Major and Key research Projects of Traditional Chinese Medicine of Sichuan Provincial Administration of Traditional Chinese Medicine in 2024 (grant no. 2024zd008).

Availability of data and materials

Not applicable.

Authors' contributions

YZ edited the manuscript. HF, QW and SY were involved in writing - original draft. YJ and HX were involved in the conception and design. LD and XL revised the manuscript. HC and GL were responsible for conceptualization and supervised the study. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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