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REVIEW

Targeting Macrophage-Mediated Mechanisms in Sepsis-Induced Cardiomyopathy: From Pathophysiology to Therapeutic Strategies

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Abstract: Sepsis-induced cardiomyopathy (SICM) is a life-threatening complication of sepsis, characterized by dysregulated inflammation, metabolic disturbances, and complex cellular crosstalk. As central innate immune cells, macrophages exert a dual role in this pathology. This review focuses on the key mechanisms by which macrophages contribute to SICM. We discuss macrophage-driven pathogenesis across three interconnected themes. First, inflammatory activation. Macrophages amplify the inflammatory storm through dynamic M1/M2 polarization and activation of Toll-like receptor 4 (TLR4) / nuclear factor κB (NF-κB), as well as multiple inflammasome pathways such as NLR family pyrin domain containing 3 (NLRP3). Second, myocardial injury mechanisms. Activated macrophages promote cardiomyocyte damage via oxidative stress, suppression of mitophagy, direct cytotoxic effects, and indirect networks (such as MMP-9-mediated endothelial disruption). Third, regulatory layers. Immunometabolic reprogramming (enhanced glycolysis and succinate accumulation in M1 macrophages versus fatty acid oxidation in M2 macrophages) serves as an intrinsic driver linking immune activation to cardiomyocyte dysfunction. Additionally, macrophages engage in complex intercellular communication with neutrophils (NETs), T cells (PD-L1/PD-1), and via complement C5a/C5aR1 signaling, all of which amplify cardiac injury. Finally, based on these mechanisms, we discuss therapeutic strategies targeting macrophage polarization, metabolism, specific subsets (e.g. TREM2hi macrophages), and intercellular communication, aiming to offer a theoretical framework for developing precision immunotherapies for SICM.

Keywords: sepsis-induced cardiomyopathy, macrophage, immunometabolism, inflammasome, pyroptosis, therapeutic target

Introduction

Sepsis-induced cardiomyopathy (SICM) is clinically defined as an acute, reversible myocardial dysfunction occurring in a septic patient, characterized by left ventricular dilation, reduced ejection fraction (typically <50%), and impaired contractile response to volume infusion or catecholamines, in the absence of coronary artery disease or other known cardiac pathologies.[1] Despite its reversibility, SICM doubles or triples mortality risk, yet no specific pharmacotherapy exists beyond supportive care and infection control. Macrophages are among the first cells to recognize pathogen-associated molecular patterns (PAMPs, eg, lipopolysaccharide (LPS)) and damage-associated molecular patterns (DAMPs, eg, high mobility group box 1 (HMGB1)). Through their phenotypic plasticity, secretory activity, and high degree of microenvironment interaction, macrophages critically shape the initiation, progression, and outcome of SICM.[2]

The need for this review arises from three critical gaps: First, while macrophages are recognized as central orchestrators of sepsis, their specific contribution to cardiomyocyte dysfunction—distinct from systemic inflammation—remains incompletely

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integrated. Second, recent breakthroughs in immunometabolism, single-cell omics, and intercellular communication (eg, NETosis, exosomal miRNAs) have generated a surge of mechanistic data that require synthesis into a coherent, SICM-focused framework. Third, and most importantly, the field lacks a critical appraisal of how much of our current knowledge derives from non-SICM models (eg, ischemia-reperfusion, atherosclerosis) versus genuine SICM-specific studies, leading to potential overgeneralization. Therefore, this review systematically examines macrophage-driven mechanisms in SICM with emphasis on (i) distinguishing direct evidence from indirect inference, (ii) integrating novel layers of regulation (metabolic, neuro-immune, complement), and (iii) identifying translatable therapeutic targets with acknowledgment of current limitations.

Macrophage Heterogeneity and Dynamic Evolution in SICM

Macrophages are not a homogeneous population. In the heart, they can be categorized based on origin into embryo-derived tissue-resident macrophages (eg, C-C chemokine receptor type 2 (CCR2)- subsets) and bone marrow-derived monocyte-derived macrophages (CCR2+) that are continuously replenished in adulthood.[1,2] Under homeostasis, resident macrophages act as "guardians" of cardiac health by clearing apoptotic debris, promoting tissue repair, and even indirectly influencing cardiomyocyte electrophysiology through electrotonic coupling.[3–5]

Sepsis disrupts this equilibrium. Potent inflammatory signals (eg, LPS, interferon gamma (IFN-γ)) drive macrophage polarization towards the classically activated M1 phenotype. M1 macrophages are primary effectors of pro-inflammatory responses, producing high levels of tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), inducible nitric oxide synthase (iNOS)-derived nitric oxide (NO), and reactive oxygen species (ROS) via pathways like TLR4/NF-κB and NLRP3 inflammasome activation.[6–8] TNF-α and IL-1β directly impair cardiomyocyte contractility by disrupting calcium handling, while ROS and NO inhibit mitochondrial respiratory chain complexes, leading to ATP synthesis failure and a cellular "energy crisis".[6,7,9] Additionally, activated M1 macrophages release exosomes carrying miR-155-5p into the circulation. These exosomes are subsequently internalized by cardiomyocytes. MiR-155-5p may target MSK1 in cardiomyocytes, thereby activating the p38-MAPK signaling pathway. This activation triggers intrinsic inflammatory responses in cardiomyocytes, characterized by the production of pro-inflammatory cytokines such as IL-6 and TNF-α. Furthermore, it may promote the assembly of inflammasomes (eg, NLRP3), ultimately leading to pyroptosis of cardiomyocytes.[6]

As the disease progresses, microenvironmental cues shift. Cytokines like interleukin-4 (IL-4) and interleukin-13 (IL-13), signaling through the signal transducer and activator of transcription 6 (STAT6) pathway, promote alternative activation towards the M2 phenotype. M2 macrophages secrete anti-inflammatory cytokines (eg, interleukin-10 (IL-10), transforming growth factor beta (TGF-β)) and pro-repair factors (eg, vascular endothelial growth factor (VEGF), arginase-1 (Arg-1)), facilitating inflammation resolution and tissue healing.[10–12] In the early phase of SICM, appropriate M2 polarization can be protective by clearing apoptotic cells and limiting excessive inflammation.[13] However, persistent M2 polarization later in the course may drive excessive cardiac fibroblast activation via the TGF-β/Smad3 pathway, leading to aberrant collagen deposition, myocardial fibrosis, and subsequent diastolic dysfunction.[14,15] Excessive M2 polarization might also suppress antimicrobial immunity, increasing the risk of secondary infections.[16]

Therefore, the progression and outcome of SICM hinge on the precise spatiotemporal balance between M1 and M2 macrophages. Therapeutic strategies should aim not simply to suppress or activate one pole, but to achieve precise spatiotemporal modulation of macrophage polarization according to the disease stage.

Core Mechanisms of Macrophage-Driven Myocardial Injury

Amplification of Key Inflammatory Signaling Pathways

The central role of macrophages in SICM begins with the recognition of danger signals. The TLR4 / Myeloid differentiation primary response 88 (MyD88) / NF-κB axis is a quintessential inflammatory pathway. LPS binding to TLR4 triggers a signaling cascade via the adaptor protein MyD88, culminating in the nuclear translocation of NF-κB, which initiates the transcription of a plethora of pro-inflammatory cytokines and chemokines, creating an "inflammatory storm".[17] These factors directly impair cardiomyocyte function and recruit more neutrophils and monocytes to the heart, amplifying local inflammation. Concurrently, NF-κB-induced iNOS generates excessive NO, suppressing mitochondrial function and reducing vascular

reactivity.[17] Cross-talk exists between the NF-κB pathway and NLRP3 inflammasome activation, with the former providing a priming signal for the latter (eg, upregulating NLRP3 and pro-IL-1β expression).[18]

Emerging optogenetics approaches offer precise control. For instance, blue light activation of transfected photoactivated adenylyl cyclase (bPAC) specifically elevates intracellular cyclic adenosine monophosphate (cAMP) levels in macrophages. cAMP activates protein kinase A (PKA), which suppresses pro-inflammatory signaling like NF-κB, reducing TNF-α and IL-1β secretion while promoting anti-inflammatory mediators like IL-10 and Arg-1,[19] as illustrated in Figure 1.

Inflammasome Activation

Macrophages in sepsis can be activated via multiple, often interconnected, inflammasome pathways. The NLRP3 inflammasome acts as a classic "danger signal integrator," responding to various intracellular disturbances like K+ efflux, ROS burst, and lysosomal disruption. Its activation underpins macrophage pyroptosis and IL-1β release.[20] The NLR family apoptosis inhibitory protein (NAIP) / NLR family CARD domain containing 4 (NLRC4) inflammasome specifically detects cytosolic bacterial components (eg, flagellin, type III secretion system proteins),[21,22] inducing robust inflammation and, via caspase-1-mediated poly (ADP-ribose) polymerase 1 (PARP1) cleavage, epigenetically upregulating iNOS expression, leading to excessive NO production that directly inhibits cardiomyocyte mitochondrial respiration.[23] The absent in melanoma 2 (AIM2) inflammasome serves as a cytosolic double-stranded DNA (dsDNA) "sensor." In contexts like clonal hematopoiesis, metabolically hyperactive macrophages produce abundant ROS, causing DNA damage and replication stress, leading to activation by self or pathogen-derived cytosolic dsDNA, which exacerbates inflammation.[24] The Pyrin inflammasome uniquely acts as an "indirect monitor" of bacterial toxin activity by sensing Rho GTPase inactivation. Notably, neutrophil extracellular traps (NETs) have been identified as a novel upstream activator of Pyrin in macrophages, amplifying inflammation.[25,26] Despite distinct triggers, these inflammasomes converge on caspase-1 activation, which cleaves gasdermin D (GSDMD) to execute pyroptosis and processes pro-IL-1β and pro-interleukin-18 (pro-IL-18) into their active forms, forming a potent "inflammatory cell death" network that fuels the myocardial inflammatory storm.[22,23,25–27] IL-1β and NO promote cardiomyocyte apoptosis and metabolic dysfunction, while IL-18 enhances IFN-γ secretion, increasing immune cell infiltration, as illustrated in Figure 2. Pyroptotic release of inflammatory mediators also damages coronary endothelium, promoting microthrombosis and worsening perfusion. The inflammasome adapter protein Caspase recruitment domain family member 8 (CARD8) acts as a critical "endogenous brake," whose expression is finely tuned by the circular RNA (circRNA)-CARD8/miR-580-3p axis.[28] In sepsis, dysregulation of this axis reduces CARD8 protein levels, lifting the restraint on pyroptosis and rendering macrophages more susceptible, thereby amplifying myocardial inflammation. NLR family pyrin domain containing 6 (NLRP6), conversely, is a negative regulator of type 2 immunity, and its deficiency enhances type 2 innate lymphoid cells (ILC2) and T helper 2 cells (Th2) activity, elevating type 2 cytokines (eg, IL-4, interleukin-5 (IL-5), IL-13) and skewing the type1/type2 balance, which may indirectly affect myocardial repair.[29]

Oxidative Stress Injury

Activated macrophages generate excessive ROS and reactive nitrogen species (RNS) via nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NADPH oxidase 2 (NOX2)) and mitochondrial electron leak, directly damaging

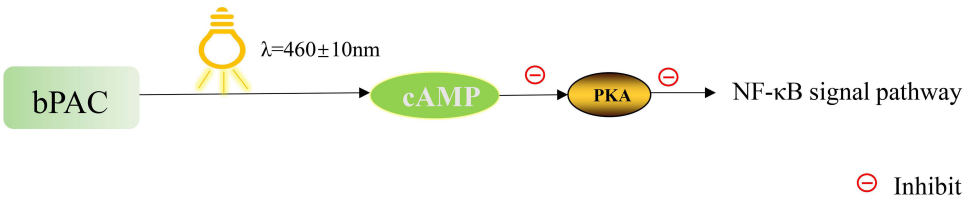

Figure 1 Optogenetic regulation of macrophage inflammatory response via the cAMP-PKA signaling pathway. Blue light (λ = 460 ± 10 nm) activates photoactivated adenylyl cyclase (bPAC) transfected into macrophages, leading to an increase in intracellular cyclic adenosine monophosphate (cAMP). Elevated cAMP activates protein kinase A (PKA), which subsequently suppresses the NF-κB signaling pathway, thereby reducing the expression of pro-inflammatory cytokines such as TNF-α and IL-1β. This optogenetic approach offers a precise spatiotemporal strategy to modulate macrophage-mediated inflammation in sepsis-induced cardiomyopathy (SICM).

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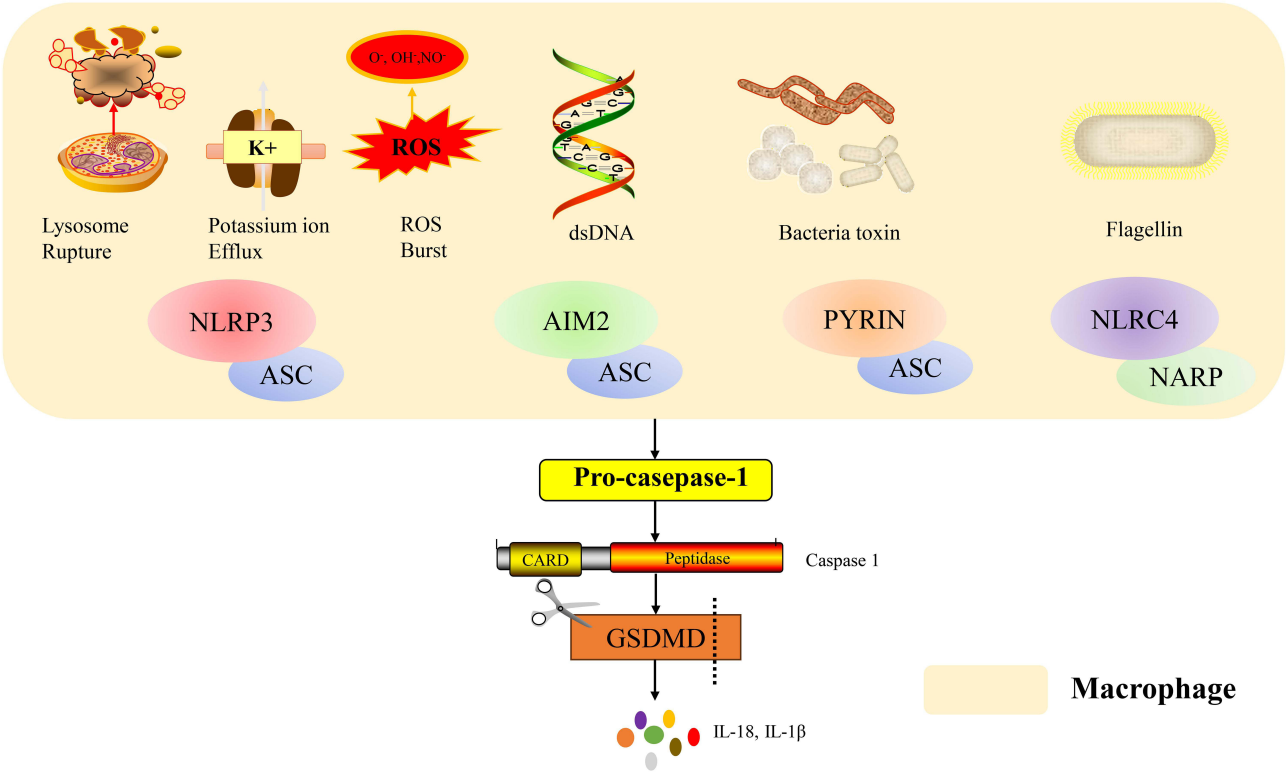

Figure 2 Mechanisms of inflammasome activation in macrophages. Different pathogen-associated molecular patterns (PAMPs) and danger signals activate specific inflammasome sensors. Lysosomal rupture, potassium ion efflux and ROS burst triggers the NLRP3 inflammasome. Cytosolic dsDNA is sensed by AIM2. Bacterial toxins activate the PYRIN inflammasome, while flagellin is recognized by NLRC4. NLRP3. AIM2 and PYRIN sensors recruit the adaptor protein ASC, while NLRC4 sensors recruit the adaptor protein NARP, leading to caspase-1 activation. Caspase-1 cleaves Gasdermin D (GSDMD), inducing pore formation and macrophage pyroptosis, accompanied by the release of IL-18 and IL-1β. The domain structure of pro-caspase-1 and its active form (Caspase-1, p20/p10) is shown.

cardiomyocytes through lipid peroxidation, protein denaturation, and DNA damage, leading to structural disruption, contractile dysfunction, and apoptosis.[30,31] In sepsis accompanied by hemolysis, macrophage phagocytosis of damaged erythrocytes causes iron overload, precipitating ferroptosis. Ferroptotic macrophages release oxidized lipids, inflammatory cytokines, and iron-loaded vesicles, which not only directly injure cardiomyocytes but also transmit ferroptotic signals via extracellular vesicles (EVs), inducing cardiomyocyte ferroptosis.[30,31]

Oxidative stress also alters the cargo of macrophage-derived small extracellular vesicles (sEVs), enriching them with pro-inflammatory miRNAs (eg, miR-155), oxidized lipids, and iron. Upon uptake by cardiomyocytes, these sEVs provoke intracellular inflammation, oxidative stress, and ferroptosis. Specifically, exosomes from IL-1β-stimulated macrophages (M-IL-exo) exhibit elevated miR-146a, which suppresses mitogen-activated protein kinase 4 (MAPK4) expression, affecting dynamin-related protein 1 (Drp-1) phosphorylation (Ser616), leading to excessive mitochondrial fission, loss of membrane potential, ROS burst, and reduced ATP synthesis, culminating in cardiomyocyte apoptosis or necrosis.[32] Macrophage-derived EVs, rich in transferrin receptor (TfR) on their surface, can chelate protein-bound iron. TfR knockdown ablates the iron-chelating capacity and cardioprotective effects of EVs, underscoring their role in mitigating iron overload and oxidative stress.[33] In myocardial infarction models, EV administration reduced cardiac iron content and oxidative markers (malondialdehyde (MDA), dihydroethidium (DHE)), enhanced antioxidant enzyme activity (glutathione (GSH), glutathione peroxidase 4 (GPX4)), limited infarct size, and improved cardiac function (left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS)).[33]

Collectively, these processes cause severe mitochondrial dysfunction, manifesting as fission/fusion imbalance (Drp1↑, mitofusin 2 (Mfn2)/optic atrophy 1 (OPA1)↓), impaired autophagy, and decreased respiratory chain complex activity, contributing to the release of cardiac enzymes and functional deterioration. Oxidatively stressed macrophages also secrete DAMPs like HMGB1 and S100 calcium-binding protein A8/A9 (S100A8/A9), which disrupt mitochondrial

quality control in cardiomyocytes via TLR4/receptor for advanced glycation end products (RAGE) receptors, leading to insufficient ATP synthesis and myocardial stunning.

Suppression of Mitophagy

Impaired macrophage autophagy contributes to SICM. Oxidized low-density lipoprotein (ox-LDL)-treated macrophages exhibit reduced autophagosome formation, decreased microtubule-associated protein 1A/1B-light chain 3 (LC3)-II/I ratio, and downregulated Beclin1, alongside cellular senescence (elevated senescence-associated beta-galactosidase (SA-β-gal) activity, increased P16/P21 expression).[34] These senescent macrophages exacerbate myocardial inflammation and injury via the senescence-associated secretory phenotype (SASP). Mechanistically, Notch1 signaling activation upregulates macrophage stimulating 1 (MST1), which phosphorylates Beclin1 (Thr108), enhancing its binding to B-cell lymphoma 2 (Bcl-2) and inhibiting the assembly of the autophagy initiation complex (autophagy-related 14-like protein (Atg14L)–Beclin1–vacuolar protein sorting 34 (Vps34)), thereby obstructing mitophagy.[34] Autophagy inhibition leads to mitochondrial dysfunction (swelling, cristae disruption, elevated ROS), accelerates senescence, and activates the NLRP3 inflammasome, ultimately depressing cardiac function. Notch1 deficiency improves mitochondrial morphology and function, attenuating cardiac injury.[34] Quercetin mitigates these effects by downregulating MST1, relieving autophagy inhibition, increasing the LC3-II/I ratio and Beclin1 expression, and restoring autophagic flux, thereby improving mitochondrial function, reducing ROS, and delaying senescence. This suggests that pharmacological (eg, rapamycin) or genetic strategies to enhance macrophage autophagy may be effective against SICM.[34]

Direct Cardiomyocyte Injury

Activated M1 macrophages highly express Fas ligand (FasL), which engages the death receptor Fas on cardiomyocytes, initiating caspase-8/caspase-3-mediated apoptosis and contributing to cardiomyocyte loss.[35] Furthermore, macrophage-derived TNF-α and IL-1β can activate the N-methyl-D-aspartate receptor (NMDAR) on cardiomyocytes, causing calcium influx and intracellular calcium overload. Calcium overload triggers mitochondrial permeability transition pore (mPTP) opening, disrupts mitochondrial function, and activates Bcl-2-like protein 11 (Bim)/caspase-3-mediated apoptosis, ultimately leading to contractile dysfunction.[36–38]

Indirect Regulatory Networks

Endothelial Barrier Disruption and Microcirculatory Dysfunction

In sepsis, activated M1 macrophages secrete high levels of matrix metalloproteinase-9 (MMP-9). MMP-9 degrades key components of the myocardial capillary basement membrane (eg, collagen IV, laminin) and tight junction proteins (eg, zonula occludens-1 (ZO-1)), directly disrupting microvascular barrier integrity. This increases vascular permeability, leading to plasma leakage, myocardial edema (which increases oxygen diffusion distance and exacerbates hypoxia), and exposure of pro-coagulant subendothelial matrix, activating coagulation and promoting microthrombosis. Together, these events cause severe microcirculatory impairment.[39]

MMP-9 also degrades structural proteins within cardiomyocytes (eg, myosin light chain) and the extracellular matrix, directly impairing contractility; degrades connexin-43, disrupting electrical coupling and promoting arrhythmias; and disrupts the interstitial collagen network (types I and III), contributing to adverse ventricular remodeling.[30] Moreover, MMP-9 cleaves latent pro-inflammatory factors and matrix-bound bioactive fragments from the extracellular matrix (ECM), recruiting more immune cells and creating a self-amplifying cycle of inflammation, as illustrated in Figure 3.

In addition to MMP-9-mediated proteolytic injury, emerging evidence identifies macrophage extracellular traps (METs) as a critical contributor to microvascular compromise in SICM.[40] METs are web-like structures composed of DNA, histones, and granule proteins released by activated macrophages in response to LPS, IL-1β, or complement C5a stimulation.[41,42] Structurally analogous to neutrophil extracellular traps (NETs), METs exert multifaceted deleterious effects on the myocardial microenvironment. First, METs directly compromise endothelial integrity by degrading adherens junction proteins (eg, vascular endothelial cadherin) and tight junction components (eg, ZO-1, occludin) via histone-driven cytotoxicity and associated proteases, thereby exacerbating vascular leakage and interstitial edema.[43] Second, METs serve as a scaffold for platelet adhesion and fibrin deposition, promoting microthrombosis and regional

ischemia.[44] Third, METs function as potent danger signals: their DNA backbone activates the AIM2 inflammasome in neighboring macrophages and cardiomyocytes, while associated HMGB1 and IL-1β sustain TLR4/NF-κB signaling, creating a self-amplifying inflammatory loop.[45] Notably, pyroptotic macrophage-derived microvesicles can induce NET formation in neutrophils, establishing a bidirectional MET-NET axis that further amplifies cardiac injury (Figure 3).[44,46] The convergence of MMP-9-mediated matrix degradation and MET-driven endothelial disruption underscores the central role of macrophage-derived extracellular effectors in SICM-associated microcirculatory failure.

Autonomic Nervous System Dysregulation

Macrophage-derived IL-1β and other inflammatory mediators act on central nervous system regions like the subfornical organ (SFO) and paraventricular nucleus (PVN), triggering intense sympathetic nervous system (SNS) activation.[47] Locally in the heart, macrophages exposed to high norepinephrine (NE) levels may see their beta-2 adrenergic receptor (ADRB2) signaling shift towards pro-inflammatory non-canonical pathways like MAPK. Parasympathetic vagal activity is often suppressed in sepsis, impairing the endogenous "cholinergic anti-inflammatory pathway (CAIP)".[47] Consequently, alpha-7 nicotinic acetylcholine receptor (α7nAChR) on macrophages receive insufficient acetylcholine signals, leading to disinhibition of NF-κB and uncontrolled release of TNF-α and IL-1β, as illustrated in Figure 4. Excessive inflammation suppresses myocardial contraction via iNOS/NO overproduction, inhibition of β-adrenergic receptor signaling, and disruption of calcium homeostasis. SNS activation also mobilizes monocytes/macrophages from bone marrow and spleen. Systemic inflammatory signals can access the brain via circumventricular organs, activating microglia and releasing mediators like prostaglandin E2 (PGE2) that further drive sympathetic excitation, creating a vicious cycle of "peripheral inflammation → central activation → enhanced sympathetic output → worsened peripheral inflammation," significantly increasing the risk of malignant ventricular arrhythmias.[47]

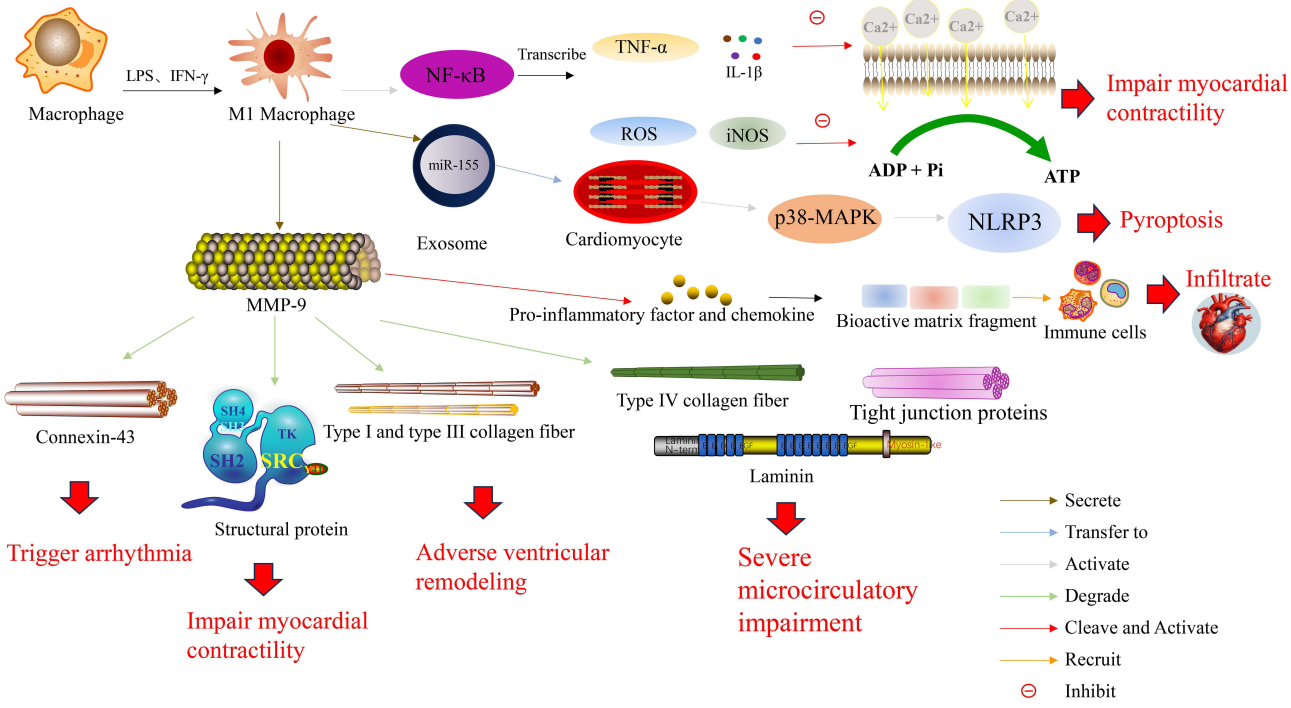

Figure 3 Pro-inflammatory role of M1 macrophages in cardiac injury and remodeling. Upon stimulation with LPS and IFN-γ, macrophages polarize into the M1 phenotype, leading to NF-κB activation. Activated NF-κB drives the production of TNF-α and IL-1β, which impair myocardial contractility by suppressing calcium (Ca^{2+}) influx. Concurrently, NF-κB activation promotes ROS generation and iNOS expression, which attenuate myocardial contractility through inhibition of ADP/ATP metabolism. M1 macrophages also secrete exosomes containing miR-155, which are transferred into cardiomyocytes to activate the p38-MAPK–NLRP3 axis and promote pyroptosis. In parallel, M1 macrophage-derived MMP-9 exerts multifaceted detrimental effects: it cleaves and activates pro-inflammatory factors and chemokines into bioactive matrix fragments, thereby recruiting immune cells and promoting infiltration; it degrades connexin-43 expression, triggering arrhythmia; it degrades type I and III collagen fibers, leading to adverse ventricular remodeling; it decreases structural proteins, resulting in impaired myocardial contractility; and it degrades type IV collagen fibers, tight junction proteins, and laminin, causing severe microcirculatory impairment.

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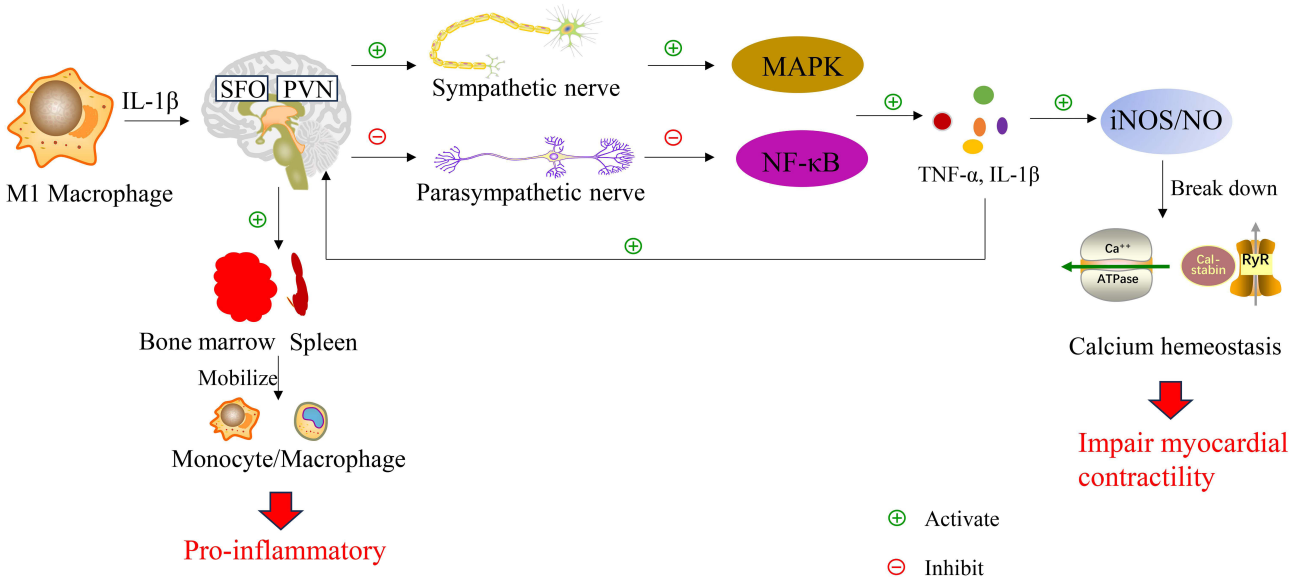

Figure 4 Neuro-immune crosstalk in cardiac inflammation. Pro-inflammatory cytokines such as IL-1 act on central nervous system regions including the subfornical organ (SFO) and paraventricular nucleus (PVN), modulating autonomic outflow. Sympathetic activation promotes MAPK and NF-κB pathways, enhancing TNF-α and IL-1 production. Excessive inflammation leads to overproduction of iNOS/NO, which disrupts calcium homeostasis and suppresses cardiac contractility. Parasympathetic activity may exert anti-inflammatory effects, highlighting bidirectional neuro-immune interactions in cardiovascular pathology.

Regulation of Repair and Pathological Fibrosis

During the intermediate phase, Smad3 activation promotes beneficial polarization, enhances phagocytic capacity (eg, via milk fat globule-EGF factor 8 protein (Mfge8)), and stimulates anti-inflammatory cytokine (IL-10, TGF-β1) secretion to curb excessive inflammation; indeed, Smad3 deficiency increases cardiomyocyte apoptosis.[48] However, persistent transforming growth factor beta 1 (TGF-β1) signaling, via Smad2/3 activation, potently drives cardiac fibroblast-to-myofibroblast transition (expressing α-smooth muscle actin (α-SMA)) and stimulates synthesis and deposition of collagen types I and III, promoting fibrosis.[49] Notably, macrophages (particularly M2) can themselves undergo TGF-β/Smad3-driven transdifferentiation into myofibroblasts (see Figure 5), directly contributing to excessive ECM accumulation.[50,51] Thus, uncontrolled M2-driven repair can shift from adaptive healing to pathological fibrosis, severely compromising long-term cardiac function.

Metabolic Reprogramming: Bridging Immune Activation and Cardiac Dysfunction

Recent research highlights the tight coupling of macrophage immune function with their intrinsic metabolic state. In sepsis, activated M1 macrophages exhibit a pronounced increase in glycolysis, akin to the "Warburg effect".[52] This process, largely driven by hypoxia-inducible factor-1 alpha (HIF-1α), upregulates glucose transporter 1 (GLUT1) and key glycolytic enzymes to rapidly generate ATP and biosynthetic precursors supporting massive cytokine production.[31,53] Critically, the glycolytic intermediate succinate accumulates. Oxidation of succinate drives mitochondrial ROS (mtROS) production, which stabilizes HIF-1α and activates the NLRP3 inflammasome, creating a positive feedback loop.[54,55] Circulating succinate can also act directly on cardiomyocytes via its receptor G protein-coupled receptor 91 (GPR91), inducing ROS and inhibiting oxidative phosphorylation.[56]

M2 macrophages rely more on fatty acid oxidation (FAO) for energy. Activation of the peroxisome proliferator-activated receptor gamma (PPARγ) pathway promotes fatty acid uptake and mitochondrial β-oxidation, supporting the long-term survival and repair functions of M2 cells.[57–59] However, excessive FAO can lead to lipid accumulation and excess acetyl-coenzyme A (acetyl-CoA), potentially activating the NLRP3 inflammasome under certain conditions, illustrating the complexity of metabolic regulation.[57] Therefore, targeting macrophage metabolic reprogramming, eg, using glycolytic inhibitors (2-deoxyglucose (2-DG)) or succinate dehydrogenase (SDH) modulators, represents a promising therapeutic avenue.

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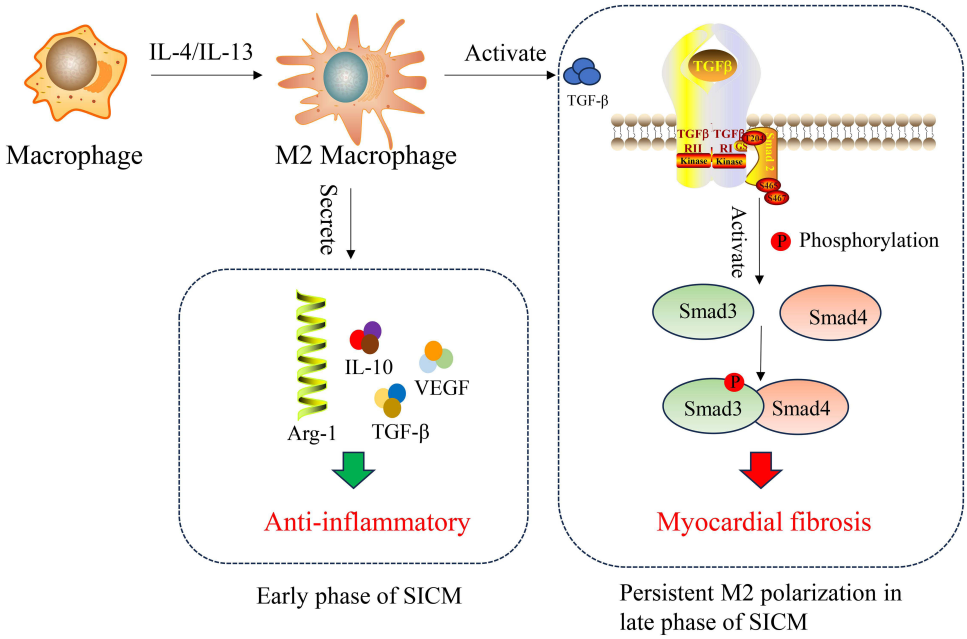

Figure 5 Protective and fibrotic roles of M2 macrophages in myocardial repair. In the early stage after injury, M2 macrophages exhibit anti-inflammatory properties and promote tissue repair. However, persistent M2 activation, driven by IL-4/IL-13, can lead to excessive collagen deposition (type I and III fibers), resulting in myocardial fibrosis and adverse structural remodeling.

Complex Intercellular Communication Network

Macrophages do not act in isolation but engage in complex crosstalk with other cardiac cells.

Synergy with Other Immune Cells: Microvesicles from pyroptotic macrophages can be engulfed by neutrophils, inducing mitochondrial dysfunction and mtROS burst in the latter, which activates GSDMD and promotes NET formation.[44] NETs directly damage cardiomyocytes and endothelial cells and promote microthrombosis, contributing to organ dysfunction.[60] During sepsis, cardiac endothelial cells, cardiomyocytes, and fibroblasts secrete chemokines like C-C motif chemokine ligand 2 (CCL2), which recruits CCR2-expressing monocytes from the circulation into the heart, where they differentiate into pro-inflammatory M1 macrophages, amplifying local injury.[61,62] Combined CCR2/C-C chemokine receptor type 5 (CCR5) inhibition appears more effective than single targeting, suggesting potential for multi-target intervention in SICM.[61] Furthermore, macrophage-expressed programmed death-ligand 1 (PD-L1) binding to programmed cell death protein 1 (PD-1) on T cells delivers inhibitory signals, causing T cell exhaustion and potentially enhancing regulatory T cell (Treg)-mediated immunosuppression, shaping an immune microenvironment unfavorable for myocardial repair.[63–65] The cyclooxygenase-2 (COX2)/PGE2 pathway may contribute to this suppression by upregulating PD-L1 and promoting Treg function.[63]

Complement System Interaction: The complement fragment complement component 5a (C5a), binding to C5a receptor 1 (C5aR1) on macrophages, enhances their inflammatory response via G protein-coupled receptor (GPCR) signaling, MAPK/extracellular signal-regulated kinase (ERK), NF-κB, and phosphoinositide 3-kinase / protein kinase B (PI3K/Akt) pathways, driving M1 polarization, cytokine release, and ROS production. C5a is also a potent neutrophil chemoattractant, promoting NETosis. Additionally, C5a acting on cardiomyocyte C5a receptor (C5aR) can cause calcium overload and apoptosis. Thus, C5a exerts a dual "immune-cardiomyocyte" hit, amplifying inflammation, oxidative stress, apoptosis, and dysfunction in SICM.[66] However, simply blocking C5aR1 may be detrimental in specific contexts (eg, transfusion-related acute lung injury (TRALI) models[67]), suggesting that direct C5 targeting might be a safer strategy.

Macrophage Migration Inhibitory Factor (MIF): MIF plays a complex role. It enhances immune recognition by upregulating TLR4 expression but exacerbates myocardial depression when overproduced.[68] MIF promotes monocyte migration/infiltration via receptors like CCR2, C-X-C motif chemokine receptor 4 (CXCR4), and angiotensin II type 1 receptor (AT-1R), amplifies systemic and local inflammation (IL-6, monocyte chemoattractant protein-1 (MCP-1)), directly activates the NLRP3

inflammasome, modulates MMP activity, promotes ROS generation, and antagonizes glucocorticoid actions.[61–63] MIF deficiency attenuates endoplasmic reticulum (ER) stress and calcium handling abnormalities, improving contractile function.[68–70] MIF's effects are cell source-dependent, with cardiac-derived MIF potentially being protective and immune-cell-derived MIF being predominantly pro-inflammatory.[68] MIF also influences cell survival/apoptosis via NF-κB and c-Jun N-terminal kinase (JNK)/mitochondrial pathways.[70–72] Thus, MIF is a multi-faceted player and a potential therapeutic target.

Novel Therapeutic Strategies Targeting Macrophages

Regarding the novel therapeutic strategies targeting macrophages in SICM, we have organized and summarized the relevant information in this section, and presented some treatment options along with their mechanism, evidence level, safety risks and other indicators in Table 1.

Table 1 Therapeutic Strategies Targeting Macrophages Across Different Time Windows of SICM

Time Window and Main Macrophage Phenotype	Therapeutic Goal	Specific Strategy/ Drug	Mechanism of Action	Evidence Level	Main Safety Risks
Acute Phase (Early) (hours to 1–2 days) M1-dominant (TLR4/NF-κB↑, NLRP3↑, iNOS↑, ROS↑, miR-155↑)	Inhibit/neutralize M1-mediated injury	TLR4 inhibitor (TAK-242)	Blocks LPS/PAMP recognition, reduces NF-κB-driven pro-inflammatory cytokines (TNF-α, IL-1β, IL-6)	Preclinical	Increased infection risk; may interfere with early immune defense
		Anti-TNF-α antibody	Neutralizes TNF-α, improves myocardial contractility, reduces calcium handling defects	Clinical (failed sepsis trials; limited SICM evidence)	Increased mortality (early sepsis trials); immunosuppression
		NLRP3 inhibitor (MCC950)	Blocks inflammasome activation, reduces IL-1β and GSDMD-mediated pyroptosis	Preclinical	Hepatotoxicity; infection risk
		IL-1 receptor antagonist (Anakinra)	Competitively blocks IL-1 signaling, reduces cardiomyocyte apoptosis and metabolic dysfunction	Clinical (approved for other inflammatory diseases; small SICM studies)	Injection site reactions; infection
		GSDMD inhibitor (disulfiram)	Directly inhibits pyroptosis pore formation, blocks IL-1β/IL-18 release	Preclinical	Hepatotoxicity; neurological side effects
		AntagomiR-155	Neutralizes M1 exosomal miR-155, prevents cardiomyocyte NLRP3 activation and pyroptosis	Preclinical	Delivery difficulties; off-target effects
		α7nAChR agonist (GTS-21)	Activates cholinergic anti-inflammatory pathway, inhibits NF-κB, reduces TNF-α/IL-1β	Preclinical / Early clinical	Bradycardia; hypotension
		Optogenetics (bPAC)	Blue light increases cAMP → PKA → inhibits NF-κB, precise anti-inflammation	Preclinical (mouse pericardial implantation)	Long-term safety of gene delivery; implant biocompatibility
Subacute/Repair Phase (Intermediate) (approx. 2–7 days) M2 begins to dominate (STAT6↑, IL-10↑, TGF-β↑, Arg-1↑)	Promote/enhance M2 repair functions while avoiding excessive fibrosis	PPARγ agonist (rosiglitazone)	Promotes fatty acid oxidation (FAO), supports M2 energy metabolism, enhances anti-inflammatory and repair functions	Clinical (for diabetes); Preclinical for SICM	Fluid retention; prior cardiovascular concerns

(*Continued*)

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Table 1 (Continued).

Time Window and Main Macrophage Phenotype	Therapeutic Goal	Specific Strategy/ Drug	Mechanism of Action	Evidence Level	Main Safety Risks
		TREM2hi macrophage transfer/agonist (AL002c)	Enhances resident macrophage mitophagy, maintains cardiomyocyte homeostasis, promotes repair	Preclinical (pericardial transfer)	Immune rejection; tumorigenic risk
		Autophagy enhancer (rapamycin)	Restores macrophage mitophagy (MST1/Beclin1 axis), reduces senescence-associated secretory phenotype (SASP)	Preclinical	Immunosuppression; metabolic disorders
Chronic/Fibrotic Phase (Late) (>7 days) Persistent M2 polarization (TGF-β/Smad3↑, collagen deposition↑)	Limit M2-driven pathological fibrosis	TGF-β/Smad3 inhibitor (pirfenidone, SB-431542)	Blocks TGF-β signaling, inhibits fibroblast activation and collagen synthesis, prevents myocardial stiffness	Clinical (for idiopathic pulmonary fibrosis); Not validated in SICM	Impaired wound healing; immunosuppression; increased tumor risk
		CCR2/CCR5 antagonist (maraviroc)	Prevents monocyte recruitment to the heart, reduces sustained supply of M2 precursors, indirectly limits fibrosis	Preclinical	Infection risk (JC virus)

Notes: This table summarizes the macrophage-targeted therapeutic strategies according to different post-injury time windows. It is organized into three phases: acute phase (hours to 1–2 days, M1-dominant), subacute/repair phase (approximately 2–7 days, M2 begins to dominate), and chronic/fibrotic phase (>7 days, persistent M2 polarization with fibrosis). For each phase, the table lists the therapeutic goal, specific strategy/drug, mechanism of action (based on Macrophage Heterogeneity and Dynamic Evolution in SICM and Core Mechanisms of Macrophage-Driven Myocardial Injury), evidence level, and main safety risks. The mechanisms of action are based on Macrophage Heterogeneity and Dynamic Evolution in SICM and Core Mechanisms of Macrophage-Driven Myocardial Injury of the main text in manuscript. References[6–8,10–15,19,47,49–51,61,73–79] support the information shown in this table.

Polarization

miR-133a Pathway

The miR-133a pathway exerts its protective effect by directly targeting and suppressing suppressor of cytokine signaling 3 (SOCS3), thereby blocking the activation of the JAK/STAT3 signaling cascade. Inhibition of this pathway reduces the polarization of pro-inflammatory M1 macrophages while promoting a shift toward the reparative M2 phenotype.[80] The evidence supporting this pathway is the most complete among the five, including dual-luciferase reporter assays, macrophage-cardiomyocyte co-culture, a cecal ligation and puncture (CLP) rat model, and validation using a nanoparticle-based delivery system. Regarding safety, nanoparticle delivery systems carry a moderate risk of off-target effects, and long-term miR-133a overexpression may affect other SOCS family members, potentially disrupting immune homeostasis.

PARP1/NLRP3 Pathway

Activation of PARP1 promotes the assembly and activation of the NLRP3 inflammasome, which in turn induces M1 polarization of macrophages and the release of pro-inflammatory cytokines such as IL-1β. Inhibition of PARP1 (eg, by atractylenolide I) blocks NLRP3 inflammasome signaling and suppresses M1 polarization.[81] However, the evidence supporting this pathway remains preliminary, as it is derived exclusively from LPS-stimulated RAW 264.7 macrophage and H9c2 cardiomyocyte co-culture systems, without validation in established in vivo sepsis models such as cecal ligation and puncture (CLP) or LPS-challenged rodents. Consequently, the safety profile of this approach remains unknown, although broad-spectrum PARP inhibitors are known to interfere with DNA repair and may carry potential genotoxicity with long-term use.

DANCR/IGF2BP2/HK2 Pathway

The long non-coding RNA DANCR interacts with the RNA-binding protein IGF2BP2 to stabilize HK2 (hexokinase 2) mRNA, thereby promoting glycolytic metabolic reprogramming in macrophages and providing energy and substrates for M1 polarization. Knockdown of DANCR disrupts the DANCR/IGF2BP2/HK2 axis and suppresses aerobic glycolysis required for M1 polarization.[82] Mechanistically, this pathway is well characterized (including RIP and RNA stability

assays) and has been validated in a CLP mouse model, but it lacks macrophage-specific knockout studies and has received limited citations to date. From a safety perspective, antisense oligonucleotides targeting lncRNAs pose moderate risks of liver accumulation and immunogenicity, and inhibiting HK2 may interfere with normal glucose metabolism in other cell types such as neurons and immune cells.

Piezo1/PI3K/AKT Pathway

Piezo1 is a mechanosensitive ion channel that, when overexpressed in septic cardiomyopathy, suppresses the activity of the PI3K/AKT signaling pathway. Knockdown or inhibition of Piezo1 restores PI3K/AKT signaling, thereby driving macrophage polarization toward the anti-inflammatory, reparative M2 phenotype while suppressing M1 polarization.[83] Strong support for this pathway comes from myeloid-specific Piezo1 knockout mice and an LPS-induced model, although it lacks validation using the CLP model and direct molecular binding data. In terms of safety, because Piezo1 is widely expressed in vascular endothelium and erythrocytes, systemic inhibition may affect blood pressure regulation and red blood cell volume; however, myeloid-specific targeting as used in the knockout models could mitigate such risks.

STAT3/FoxO3a/Sirt1 Pathway

This pathway involves the transcription factors STAT3 and FoxO3a together with the deacetylase Sirt1. Under septic conditions, activation of the STAT3/FoxO3a axis promotes M1 polarization of macrophages and suppresses Sirt1 expression. Therapeutic intervention (eg, with ginsenoside Rc) inhibits STAT3/FoxO3a signaling while upregulating Sirt1, which not only suppresses M1 polarization but also directly improves mitochondrial function in cardiomyocytes.[84] The evidence is based on network pharmacology, in vitro reverse validation (using a STAT3 agonist), and a CLP model, but it lacks independent genetic confirmation such as macrophage-specific knockout. Regarding safety, ginsenoside Rc is a natural product with relatively low toxicity, although long-term high-dose use may cause estrogen-like effects or drug interactions, and excessive Sirt1 activation has been linked to potential tumor promotion.

Enhancing the Function of Protective Macrophage Subsets

Activation of TREM2 enhances mitophagy and maintains cardiomyocyte homeostasis, improving cardiac function in septic mice;[73] direct delivery of TREM2hi macrophages to the pericardial space also reduces inflammation and increases survival, representing a promising cell-based therapy. Currently, these strategies are supported only by preclinical evidence in septic mouse models, and their safety concerns include potential immune rejection and tumorigenic risk associated with cell transplantation, as well as possible off-target effects of TREM2 agonists that remain to be evaluated.

Inflammatory Signaling Pathways

The TLR4 inhibitor TAK-242 blocks LPS binding to TLR4, thereby inhibiting the MyD88/NF-κB axis and reducing production of pro-inflammatory cytokines such as TNF-α and IL-1β;[74] however, evidence is limited to preclinical models, and broad suppression of innate immunity may increase infection risk and interfere with early host defense.

The anti-TNF-α antibody infliximab neutralizes TNF-α, improving cardiomyocyte contractility and calcium handling;[75] although it has reached clinical use for autoimmune diseases, sepsis trials have shown no survival benefit and even potential harm, with safety concerns including increased mortality, immunosuppression, and tuberculosis reactivation.

Inflammasome Activation

The NLRP3 inhibitor MCC950 reduces caspase-1-mediated pyroptosis and production of IL-1β and IL-18;[76] available data derive from preclinical inflammatory models, and safety concerns include hepatotoxicity (which led to termination of clinical trials for other indications) and potentially increased susceptibility to bacterial infection.

The GSDMD inhibitor disulfiram blocks gasdermin D pore formation, preventing pyroptosis and release of IL-1β/IL-18 from macrophages;[77] this strategy is still preclinical, and its safety is challenged by hepatotoxicity, neurological side effects (eg, peripheral neuropathy), and drug–drug interactions.

Oxidative Stress Injury

AntagomiR-155 neutralizes miR-155 derived from M1 macrophage exosomes, thereby preventing cardiomyocyte NLRP3 inflammasome activation and subsequent pyroptosis;[6] this approach remains at the preclinical stage in cardiovascular disease models, with safety concerns such as difficulties in oligonucleotide delivery, off-target effects, and possible hepatotoxicity.

M-IL-exo (IL-1β-stimulated macrophage-derived exosomes) carry elevated miR-146a, which suppresses MAPK4 and leads to excessive mitochondrial fission, ROS burst, and cardiomyocyte apoptosis;[32] although mechanistically promising, this strategy is still preclinical, and its safety risks include heterogeneity of exosome preparations, potential pro-tumorigenic effects of miR-146a, and the lack of standardized production protocols.

Suppression of Mitophagy

Autophagy enhancers (eg, rapamycin and quercetin) have been shown to restore autophagic flux by suppressing MST1-mediated Beclin1 inhibition, leading to improved mitochondrial function, reduced ROS levels, and delayed macrophage senescence. Specifically, rapamycin was tested in an LPS-induced septic rat model,[78] while quercetin was assessed using clinical serum samples from 20 SIC patients compared with 20 healthy controls, together with a CLP-induced septic rat model.[85]

Direct Cardiomyocyte Injury

IL-1 receptor antagonist (Anakinra) competitively blocks IL-1 signaling, reducing cardiomyocyte apoptosis, calcium overload, and metabolic dysfunction induced by macrophage-derived IL-1β.[6,7] Among septic patients with concurrent liver dysfunction and disseminated intravascular coagulation (DIC) (a pattern indicative of macrophage activation syndrome), the IL-1 receptor antagonist Anakinra improved 28-day survival, but showed no significant effect in other septic patients.[79]

Indirect Regulatory Networks

The α7nAChR agonist (GTS-21) activates the cholinergic anti-inflammatory pathway, thereby inhibiting NF-κB in macrophages and reducing TNF-α/IL-1β release;[47] accordingly, it has demonstrated anti-inflammatory effects in preclinical and early clinical studies using sepsis and inflammation models.[86,87]

MMP-9 inhibitors (eg, doxycycline, SB-3CT) have been shown to prevent degradation of tight junction proteins (eg, ZO-1) and basement membrane components, thereby preserving microvascular barrier integrity and reducing myocardial edema in myocarditis and aneurysm models.[39] However, evidence from SICM models is lacking.

Clopidogrel[51] and pioglitazone[49,50] have clinical evidence supporting their anti-fibrotic effects; however, these data are derived from fibrotic models, and only mechanistic inferences are available for SICM.

Metabolic Reprogramming

The PPARγ agonist rosiglitazone promotes fatty acid oxidation (FAO) and supports M2 polarization, thereby enhancing anti-inflammatory and repair functions;[12] although this mechanism is well established in metabolic research, direct evidence in SICM remains preclinical, and safety concerns include fluid retention and prior controversies over cardiovascular risks.

The SGLT2 inhibitor downregulates PFKFB3, suppresses glycolysis, and shifts macrophage polarization away from the pro-inflammatory M1 phenotype;[53] this class of drugs has already entered clinical use for diabetes and heart failure, but their application in SICM is still mechanistic, with known safety issues such as ketoacidosis and genitourinary infections.

The glycolysis inhibitor 2-DG inhibits the Warburg effect in activated M1 macrophages, reducing HIF-1α stabilization and pro-inflammatory cytokine production;[53] evidence is limited to preclinical models, and its safety is challenged by hyperglycemia, neurotoxicity, and QT interval prolongation.

The SDH modulator dimethyl malonate (DMM) blocks succinate oxidation, thereby reducing mitochondrial ROS and NLRP3 inflammasome activation in macrophages;[54,55] this strategy is at a preclinical stage, and potential risks include interference with the tricarboxylic acid cycle and general cellular energy metabolism.

Intercellular Communication Network

The CCR2/CCR5 antagonist maraviroc blocks monocyte recruitment to the heart by inhibiting CCL2-CCR2/CCR5 signaling, thereby reducing local M1 macrophage accumulation;[61] this approach has been tested in preclinical models of pulmonary hypertension and myocardial infarction, but direct evidence in SICM is lacking, and safety concerns include increased risk of infection (eg, JC virus reactivation) and potential hepatotoxicity.

By dismantling the DNA scaffold of both NETs and METs, DNase I not only attenuates direct cytotoxicity but also disrupts the platelet-activating and inflammasome-amplifying functions of these extracellular traps;[44,62] available data are preclinical, and safety risks include possible impairment of local NET-mediated antimicrobial defense and bleeding tendency.[88]

The C5aR1 antagonist avacopan blocks complement C5a receptor 1 on macrophages, reducing M1 polarization, cytokine release, and ROS production;[44,60] this drug has reached clinical approval for other immune-mediated diseases, but its efficacy in SICM has not been validated, and safety concerns include an increased risk of encapsulated bacterial infections.

MIF inhibitor ISO-1 inhibits macrophage migration inhibitory factor (MIF), thereby reducing TLR4 expression, NLRP3 inflammasome activation, and myocardial depression;[68–72,89] evidence remains preclinical, and potential risks include disruption of normal immune regulation and altered glucocorticoid sensitivity.

Limitations and Perspectives

While the above sections delineate plausible mechanistic pathways linking macrophage dysfunction to myocardial injury, it is imperative to critically assess the translational relevance of the cited evidence. A substantial portion of the mechanistic insights—particularly regarding ferroptosis,[30,44] exosomal miR-146a,[32] and metabolic reprogramming[31,53–55]—derives from in vitro studies or animal models of non-septic conditions such as myocardial infarction, atherosclerosis, or osteoarthritis. Although these models provide valuable mechanistic hypotheses, they may not fully recapitulate the unique, poly-microbial, and dynamically evolving inflammatory milieu of human sepsis-induced cardiomyopathy (SICM). Direct evidence from SICM-specific models, especially large animal or human tissue studies, remains sparse. For instance, the role of succinate accumulation as a key inflammatory driver has been elegantly demonstrated in LPS-stimulated macrophages,[53,55] but circulating succinate levels and their direct cardiodepressant effects in septic patients have yet to be validated. Furthermore, macrophage-targeted interventions showing promise in murine endotoxemia models (eg, optogenetics[19]) face significant hurdles in clinical translation, including species differences in immune signaling and the complexity of human sepsis with variable co-morbidities. Therefore, while these mechanistic pathways represent promising therapeutic frontiers, their direct causative role in human SICM requires confirmation through dedicated translational studies, including analysis of patient myocardial samples and longitudinal biomarker validation.

Deeper insights into the functions of specific macrophage subsets, particularly resident populations like TREM2hi macrophages, are revealing novel therapeutic targets. Future research should leverage single-cell multi-omics and spatial transcriptomics to map the dynamic landscape of macrophage subsets throughout SICM progression. However, several critical limitations must be explicitly acknowledged.

First, the overwhelming majority of mechanistic evidence—including polarization dynamics, inflammasome activation, and metabolic reprogramming—derives from murine models (eg, cecal ligation and puncture or LPS injection) or in vitro systems using immortalized macrophage cell lines. Human data are strikingly sparse: only a handful of studies have characterized cardiac macrophages from septic patients, and no prospective clinical trial has specifically targeted macrophages in SICM. Second, significant species differences exist in macrophage subset markers (eg, TREM2, CCR2), Toll-like receptor signaling thresholds, and inflammasome regulation, which profoundly impact translational predictability.[90] Third, current experimental interventions (eg, optogenetics, TREM2 agonists, GSDMD inhibitors) face formidable clinical hurdles, including delivery specificity to cardiac macrophages, off-target immunosuppression (eg, increased secondary infection risk).[91] There is no clear solution for patients with pre-existing immunosuppression.[92]

Finally, most studies focus on early hyperinflammation, whereas the prolonged immunosuppressive phase—where macrophages also contribute to chronic cardiac dysfunction and fibrosis—remains understudied. Therefore, while

macrophage-targeted strategies hold promise, future efforts must prioritize (i) validation in human samples (post-mortem cardiac tissue, circulating exosomes/monocytes from septic patients), (ii) large animal models with clinically relevant endpoints, and (iii) safety-focused trial designs addressing infection risk. Without such rigorous translational scrutiny, the leap from bench to bedside for macrophage-directed therapies in SICM will remain perilously wide.

Developing tools for spatiotemporally precise targeting of specific subsets or functions (eg, inhibiting pro-inflammatory output without compromising phagocytosis) is crucial for efficacy and safety. Identifying reliable biomarkers reflecting macrophage activation status (eg, specific EV miRNAs, metabolites like succinate) will aid in early diagnosis, risk stratification, and treatment monitoring. Ultimately, integrating macrophage-targeted strategies with antimicrobial therapy, hemodynamic support, and direct cardiomyocyte protection into a multi-targeted, personalized treatment framework holds the key to overcoming the challenge of SICM.

Abbreviations

SICM, Sepsis-Induced Cardiomyopathy; PAMPs, Pathogen-Associated Molecular Patterns; DAMPs, Damage-Associated Molecular Patterns; LPS, Lipopolysaccharide; HMGB1, High Mobility Group Box 1; CCR2, C-C Chemokine Receptor Type 2; IFN-γ, Interferon Gamma; TNF-α, Tumor Necrosis Factor Alpha; IL-1β, Interleukin-1 Beta; IL-6, Interleukin-6; iNOS, Inducible Nitric Oxide Synthase; NO, Nitric Oxide; ROS, Reactive Oxygen Species; VEGF, Vascular Endothelial Growth Factor; Arg-1, Arginase-1; TGF-β, Transforming Growth Factor Beta; TLR4, Toll-Like Receptor 4; NF-κB, Nuclear Factor Kappa B; NLRP3, NLR Family Pyrin Domain Containing 3; MyD88, Myeloid Differentiation Primary Response 88; bPAC, Blue Light-Activated Adenylyl Cyclase; cAMP, Cyclic Adenosine Monophosphate; PKA, Protein Kinase A; NAIP, NLR Family Apoptosis Inhibitory Protein; NLRC4, NLR Family CARD Domain Containing 4; PARP1, Poly (ADP-Ribose) Polymerase 1; AIM2, Absent in Melanoma 2; dsDNA, Double-Stranded DNA; NETs, Neutrophil Extracellular Traps; GSDMD, Gasdermin D; CARD8, Caspase Recruitment Domain Family Member 8; circRNA, Circular RNA; miRNA, MicroRNA; NLRP6, NLR Family Pyrin Domain Containing 6; ILC2, Type 2 Innate Lymphoid Cells; Th2, T Helper 2 Cells; NADPH, Nicotinamide Adenine Dinucleotide Phosphate; NOX2, NADPH Oxidase 2; RNS, Reactive Nitrogen Species; EVs, Extracellular Vesicles; sEVs, Small Extracellular Vesicles; M-IL-exo, Interleukin-1β-Stimulated Macrophage-Derived Exosomes; MAPK, Mitogen-Activated Protein Kinase; Drp1, Dynamin-Related Protein 1; TfR, Transferrin Receptor; MDA, Malondialdehyde; DHE, Dihydroethidium; GSH, Glutathione; GPX4, Glutathione Peroxidase 4; LVEF, Left Ventricular Ejection Fraction; LVFS, Left Ventricular Fractional Shortening; Mfn2, Mitofusin 2; OPA1, Optic Atrophy 1; ox-LDL, Oxidized Low-Density Lipoprotein; LC3, Microtubule-Associated Protein 1A/1B-Light Chain 3; SA-β-gal, Senescence-Associated Beta-Galactosidase; MST1, Macrophage Stimulating 1; SASP, Senescence-Associated Secretory Phenotype; FasL, Fas Ligand; NMDAR, N-Methyl -D-Aspartate Receptor; mPTP, Mitochondrial Permeability Transition Pore; MMP-9, Matrix Metalloproteinase-9; ZO-1, Zonula Occludens-1; SFO, Subfornical Organ; PVN, Paraventricular Nucleus; SNS, Sympathetic Nervous System; NE, Norepinephrine; ADRB2, Beta-2 Adrenergic Receptor; CAIP, Cholinergic Anti-Inflammatory Pathway; α7nAChR, Alpha-7 Nicotinic Acetylcholine Receptor; PGE2, Prostaglandin E2; FAO, Fatty Acid Oxidation; PPARγ, Peroxisome Proliferator-Activated Receptor Gamma; HIF-1α, Hypoxia-Inducible Factor-1 Alpha; GLUT1, Glucose Transporter 1; GPR91, G Protein-Coupled Receptor 91; CCL2, C-C Motif Chemokine Ligand 2; PD-L1, Programmed Death-Ligand 1; PD-1, Programmed Cell Death Protein 1; Treg, Regulatory T Cell; COX2, Cyclooxygenase-2; C5a, Complement Component 5a; C5aR1, C5a Receptor 1; GPCR, G Protein-Coupled Receptor; PI3K/Akt, Phosphoinositide 3-Kinase / Protein Kinase B; TRALI, Transfusion-Related Acute Lung Injury; MIF, Macrophage Migration Inhibitory Factor; AT-1R, Angiotensin II Type 1 Receptor; ER, Endoplasmic Reticulum; JNK, c-Jun N-Terminal Kinase; SGLT2is, Sodium-Glucose Cotransporter-2 Inhibitors; PFKFB3, 6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 3; SDH, Succinate Dehydrogenase; TREM2, Triggering Receptor Expressed on Myeloid Cells 2; METs, Macrophage Extracellular Traps; 2-DG, 2-Deoxyglucose; SOCS3, Suppressor of cytokine signaling 3; DIC, Disseminated intravascular coagulation.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

Author Contributions

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All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and to be accountable for all aspects of the work.

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