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Progress in the role of exosomes in sepsis-induced cardiomyopathy

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Abstract: Sepsis is a life-threatening organ dysfunction triggered by a dysregulated host response to infection. Sepsis-induced cardiomyopathy(SICM)is an acute cardiac condition caused by sepsis, characterized by high incidence and extremely high mortality. Currently, there is a lack of specific treatment strategies, and its pathophysiological mechanisms are not fully understood. Exosomes, membrane-bound vesicles secreted by almost all living cells, can facilitate intercellular communication and influence physiological processes such as immune responses and inflammatory reactions. They are also involved in the progression of SICM, including inflammation, myocardial injury, and cardiac dysfunction. This review elaborates on the role of exosomes of different origins in SICM. In the future, in-depth research is needed to explore the molecular mechanisms by which exosomes affect the pathophysiology of SICM.

Keywords: Sepsis; Cardiomyopathy; Exosomes; Cardiac dysfunction; Macrophages; Endothelial Cells

Exosomes are membrane-bound vesicles with a diameter of 30-150 nm, secreted by nearly all viable cells. Their primary function is to facilitate intercellular communication by transferring various cargoes, such as proteins, nucleotides [DNA, mRNA, microRNA (miRNA), and long non-coding RNA (lncRNA)], and lipids, to target cells [5-6], thereby regulating physiological processes including immune response, inflammatory reaction, tissue repair, and cell apoptosis [7-8]. Recent studies have demonstrated that exosomes mediate communication among cardiomyocytes, endothelial cells, and macrophages in SICM, and are involved in inflammation, myocardial injury, and cardiac dysfunction during SICM progression.

1 Endothelial Cell-Derived Exosomes

Organ dysfunction induced by sepsis, such as myocardial injury and lung injury, is closely associated with endothelial dysfunction. Under physiological conditions, endothelial cells dynamically regulate vascular barrier function, coagulation, and vasomotor tone. However, pathogen-associated molecular patterns [e.g., lipopolysaccharide (LPS)] or endogenous ligands produced during sepsis stimulate endothelial cell activation. Activated endothelial cells upregulate the expression of chemokines and adhesion molecules, recruiting and promoting immune cell infiltration and inflammatory responses, which lead to damage of multiple organs including the heart [9-10]. Studies have shown that endothelial cell-derived exosomes influence cardiac function and remodeling during SICM progression. Heat shock protein (HSP) A12B secreted by endothelial cells has been confirmed to protect the myocardium against sepsis-induced cardiac dysfunction by upregulating the expression of miRNA (miR-126), which reduces immune cell infiltration in the myocardium and alleviates cardiac injury by inhibiting the expression of adhesion molecules [11].

A concurrent study verified that deficiency of HSPA12B in endothelial cells results in more severe cardiac dysfunction and adverse survival outcomes. HSPA12B plays a crucial role in limiting pro-inflammatory responses, protecting the host against SICM, and reducing mortality. Further investigation revealed that HSPA12B is released via exosomes during sepsis, and exosomal HSPA12B is taken up by macrophages. After endothelial cell-derived exosomal HSPA12B is internalized by LPS-stimulated macrophages, HSPA12B downregulates the activation and nuclear translocation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), reducing the production of tumor necrosis factor-α (TNF-α) and interleukin (IL)-1β while increasing IL-10 expression. This process attenuates macrophage-mediated pro-inflammatory responses, as well as sepsis-induced cardiac injury and mortality [12]. However, another study suggested that the cardioprotective effect of endothelial cell-derived exosomes may be restricted to the early stage of sepsis [13].

In that study, exosomes derived from endothelial cells stimulated with LPS (0.5 μg/mL) enhanced the viability and reduced apoptosis of neonatal rat cardiomyocytes, accompanied by decreased levels of lactate dehydrogenase (LDH) and reactive oxygen species (ROS), and increased superoxide dismutase (SOD) activity. These findings indicate the cardioprotective potential of endothelial cell-derived exosomes. Notably, under stimulation with a higher concentration of LPS (10 μg/mL), the microvesicles produced by endothelial cells are mainly apoptotic bodies, with a significant reduction in exosomes. Therefore, it is proposed that under high LPS concentrations, the cardioprotective effect of endothelial cell-derived exosomes on cardiomyocytes is attenuated or abolished due to endothelial cell apoptosis.

Endothelial cell-derived exosomes contain miRNAs

that are critical for cardiomyocyte protection. These miRNAs downregulate apoptosis-related proteins such as Bcl-2 antagonist/killer 1 (Bak1), tumor suppressor proteins, and phosphatase and tensin homolog (PTEN), thereby promoting cardiomyocyte survival and reducing sepsis-induced myocardial injury. Studies have shown that in LPS-induced endothelial injury, anisodamine improves inflammation, cardiomyocyte dysfunction, and myocardial injury through exosome-mediated regulation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) and NF-κB signaling pathways [14]. Thus, endothelial cell-derived exosomes hold promising cardioprotective potential during sepsis.

2 Macrophage-Derived Exosomes

Macrophage-derived exosome-mediated intercellular communication plays a vital role in SICM. Exosomes derived from different macrophage phenotypes regulate cardiomyocyte apoptosis, mitochondrial function, and inflammatory responses. Macrophages are classified into M1 and M2 phenotypes. Although M1 macrophages play a key role in cardiac immune responses, they can induce myocardial inflammation by producing pro-inflammatory cytokines such as TNF-α and IL-1β, and promote extracellular matrix degradation and cell death [15].

Previous studies have shown that M1 macrophage-derived exosomes deliver miR-155 to endothelial cells, targeting five molecular nodes to inhibit the silent information regulator 1/adenosine monophosphate-activated protein kinase (SIRT1/AMPK), endothelial nitric oxide synthase (eNOS), and ras-related C3 botulinum toxin substrate 1 (RAC1)/RAC1 activated kinase 2 (PAK2) signaling pathways. This leads to reduced angiogenic capacity of endothelial cells, aggravated myocardial injury, and inhibited cardiac repair [16]. In a mouse model of sepsis-induced cardiac dysfunction, oxidative stress increases the level of the thioredoxin-interacting protein (TXNIP)-NOD-like receptor pyrin domain-containing 3 (NLRP3) complex in monocyte-derived exosomes. This complex is transported to cardiac resident macrophages, where it activates caspase-1 and cleaves inactive IL-1β and IL-18 into their active forms, thereby exacerbating cardiovascular inflammation [17].

A study by Bi *et al*. [18] found that lncRNA Snhg14 is highly expressed in M1 macrophage-derived exosomes. By targeting and inhibiting miR-181a-5p, Snhg14 activates the high mobility group box 1 (HMGB1)/NF-κB pathway, aggravating sepsis-induced myocardial injury (apoptosis, oxidative stress, and inflammation). Knockdown of Snhg14 or overexpression of miR-181a-5p inhibits M1 macrophage polarization and alleviates cardiac injury in septic mice. In contrast, M2 macrophages exert a protective role in SICM by promoting the resolution of myocardial inflammation. Studies have shown that stimulating macrophage polarization toward the M2 phenotype increases the production of anti-inflammatory cytokines such as IL-10, which helps reduce myocardial injury [19].

Huang *et al*. [20] revealed the critical role of macrophages characterized by upregulated integrin subunit alpha M (ITGAM) in the cardiac tissue of SICM. First, single-cell sequencing analysis showed that macrophages are the most abundant immune cells in the cardiac microenvironment of SICM, with their numbers dynamically changing during disease progression (decreasing 3 days after cecal ligation and puncture, and recovering at 7 and 21 days), serving as core cells mediating cardiac inflammation and repair. Subsequently, in vitro experiments using LPS to simulate sepsis demonstrated that LPS significantly upregulates ITGAM expression in macrophages and induces high expression of intercellular adhesion molecule-1 (ICAM-1) in endothelial cells, suggesting that both play key roles in immune cell recruitment and intercellular communication. Finally, an LPS-induced SICM mouse model was established, and some mice were injected with ITGAM-neutralizing antibodies. After 24 hours, the ITGAM-neutralizing antibody-treated group showed reduced macrophage infiltration in the heart, decreased expression of heart failure marker B-type natriuretic peptide (BNP) and inflammatory genes (IL-6, IL-1β, etc.), and improved cardiac function (left ventricular ejection fraction and fractional shortening). Long-term observation (10 days) revealed increased mortality in the antibody-treated group in the later stage, indicating that ITGAM exerts a dual role in SICM: in the early stage, it exacerbates cardiac inflammation by promoting macrophage infiltration, and short-term inhibition of ITGAM can improve cardiac function; however, its mediated macrophage phenotypic transformation (e.g., differentiation into M2 subtype) is crucial for cardiac repair in the later stage, and excessive inhibition increases mortality.

3 Platelet-Derived Exosomes

Platelet-derived exosomes account for approximately 70% of total exosomes in plasma and can mediate various pathophysiological processes such as coagulation activation, pro-inflammatory responses, and vascular endothelial injury [21]. Under septic conditions, platelets are activated by interacting with pathogens, triggering microthrombus formation, which leads to cardiac ischemic injury and ultimately cardiac dysfunction [22]. In addition to participating in coagulation and thrombosis, platelets also exacerbate myocardial depression-related inflammatory responses and have been proven to be effective activators of neutrophil extracellular trap (NET) formation during sepsis [23].

Platelet-derived exosomes containing HMGB1 and/or miRNAs induce NET formation by regulating autophagy pathways associated with the protein kinase B/mammalian target of rapamycin (Akt/mTOR) pathway, which may induce vascular apoptosis and myocardial dysfunction during sepsis [24]. During sepsis, platelets exposed to LPS excessively produce exosomes, which trigger caspase-3 activation and apoptosis in endothelial cells by upregulating the expression of superoxide, nitric oxide, and peroxynitrite, leading to septic vascular dysfunction [25]. In an LPS-induced mouse model, platelet-derived exosomes promote inflammation by releasing nitric oxide synthase, NADPH

oxidase, and protein disulfide isomerase, thereby downregulating the anti-inflammatory miR-223 and further exacerbating vascular dysfunction. Currently, studies on the association between platelet-derived exosomes and SICM are scattered, and systematic analysis of their synergistic or antagonistic effects with exosomes from other cells is lacking, warranting further exploration in future research.

4 Mesenchymal Stem Cell (MSC)-Derived Exosomes

Stem cells are classified based on their differentiation potential into: (1) Totipotent stem cells, which can form complete organisms (e.g., zygotes); (2) Pluripotent stem cells, which can differentiate into all cell types of the ectoderm, mesoderm, and endoderm (e.g., embryonic stem cells); (3) Multipotent stem cells, which can differentiate into multiple cell types (e.g., MSCs, hematopoietic stem cells, bone marrow-derived stem cells, and adipose-derived stem cells); (4) Oligopotent stem cells, which have a narrower differentiation range than multipotent stem cells (e.g., myeloid stem cells); (5) Unipotent stem cells, which can only differentiate into one specific cell type (e.g., osteocytes).

MSCs are present in almost all tissues and can be easily isolated from bone marrow and adipose tissue. Under specific in vitro conditions, MSCs can differentiate into three cell types: ectoderm (neuronal cells), mesoderm (cardiomyocytes), and endoderm (alveolar epithelial cells). MSC-derived exosomes have been shown to improve the cardiac microenvironment by promoting neovascularization and inhibiting inflammatory responses [26]. MSC-derived exosomes overexpressing chemokine receptor 4 (CXCR4) exert a protective effect on cardiomyocytes by mediating Akt signaling [27]. miR-223 in bone marrow MSC-derived exosomes plays a cardioprotective role in polymicrobial sepsis by downregulating semaphorin 3A (Sema3A) and signal transducer and activator of transcription 3 (STAT3), reducing inflammation and cell death [28].

Exosomes from MSC-derived cardiac progenitor cells promote angiogenesis through extracellular regulated protein kinase/protein kinase B (ERK/Akt) signaling, facilitating endothelial cell migration and vascular formation. In SICM, miRNAs in MSC-derived exosomes exert anti-inflammatory effects to prevent disease progression [29]. For example, MSC-derived exosomal miR-223 has been confirmed to inhibit cardiomyocyte apoptosis, inflammatory responses, and cardiac dysfunction by downregulating the expression of Sema3A and STAT3 in septic mice. In addition, miR-146a-5p in MSC-derived exosomes can be delivered to LPS-induced cardiomyocytes, promoting cell proliferation and inhibiting apoptosis; furthermore, it suppresses inflammatory responses in the myocardial tissue of septic mice by reducing myeloblastosis-like protein 1 (MYBL1) expression [30].

Another study reported that MSC-derived exosomes loaded with miR-412-5p improve LPS-induced cardiomyocyte inflammation by inactivating the mitogen-activated protein kinase (MAPK) signaling pathway, which inhibits the expression of inflammatory mediators (including prostaglandin E2 and ROS) and the secretion of pro-inflammatory cytokines such as IL-1β and IL-6 [31]. Circular RNA RTN4 in MSC-derived exosomes has been shown to reduce the production of inflammatory factors (including ROS, IL-1β, IL-6, and TNF-α) and increase the activity of SOD and glutathione by inhibiting the miR-497-5p/trimethylguanosine synthase 53 (TGS53) axis in cardiomyocytes, thereby alleviating myocardial apoptosis and cardiac injury in LPS-treated cardiomyocytes and septic rats [32]. These studies highlight the great potential of MSC-derived exosomes in regulating cardiac inflammation and cardiomyocyte apoptosis in SICM.

5 Conclusion

This review summarizes the multifaceted roles of endothelial cell-, macrophage-, and platelet-derived exosomes in regulating inflammatory responses, oxidative stress, and cardiomyocyte apoptosis during SICM progression. Exosomes carry various bioactive molecules, including proteins, lipids, mRNA, and miRNAs, to facilitate signal transduction among these cell types, thereby influencing the progression of sepsis and its associated cardiac dysfunction. Although current studies have clarified the core role of exosomes in SICM, several issues remain to be addressed:

First, the "spatiotemporal-specific" regulatory mechanisms of exosomes from different sources in distinct pathological stages of SICM (early inflammation, middle-stage injury, and late-stage repair) have not been fully elucidated, making it difficult to precisely match intervention timing. Second, studies on the association between platelet-derived exosomes and SICM are scattered, and systematic analysis of their synergistic or antagonistic effects with exosomes from other cells is lacking. Third, the clinical translation of MSC-derived exosomes faces practical challenges such as carrier optimization, dosage standardization, and targeted delivery efficiency.

Future research should focus on the key signaling pathways and regulatory mechanisms of exosomes in SICM, further deciphering their functional rules. Meanwhile, preclinical validation and translational studies of MSC-derived exosomes should be promoted to provide new molecular targets and intervention strategies for the specific treatment of SICM.

Conflict of interest None

Reference

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·研究进展·

外泌体在脓毒症诱导的心肌病中的作用进展

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摘要：脓毒症是由宿主对感染的反应失调引发的危及生命的器官功能障碍，脓毒症诱导的心肌病（SICM）是其引发的急性心脏疾病，发病率高且死亡率极高，目前缺乏特异性治疗策略，病理生理机制也未完全明晰。外泌体作为几乎所有活细胞均可分泌的膜结合囊泡，能促进细胞间通信，影响免疫应答、炎症反应等生理过程，且参与SICM进展中的炎症、心肌损伤和心功能障碍等。本综述阐述不同来源外泌体在SICM中的作用，未来需深入研究外泌体影响SICM病理生理学的分子机制。

关键词：脓毒症；心肌病；外泌体；心功能障碍；巨噬细胞；内皮细胞
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Progress in the role of exosomes in sepsis-induced cardiomyopathy

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Abstract: Sepsis is a life-threatening organ dysfunction triggered by a dysregulated host response to infection. Sepsis-induced cardiomyopathy (SICM) is an acute cardiac condition caused by sepsis, characterized by high incidence and extremely high mortality. Currently, there is a lack of specific treatment strategies, and its pathophysiological mechanisms are not fully understood. Exosomes, membrane-bound vesicles secreted by almost all living cells, can facilitate intercellular communication and influence physiological processes such as immune responses and inflammatory reactions. They are also involved in the progression of SICM, including inflammation, myocardial injury, and cardiac dysfunction. This review elaborates on the role of exosomes of different origins in SICM. In the future, in-depth research is needed to explore the molecular mechanisms by which exosomes affect the pathophysiology of SICM.

Keywords: Sepsis; Cardiomyopathy; Exosomes; Cardiac dysfunction; Macrophages; Endothelial cells

脓毒症是一种危及生命的器官功能障碍，由宿主对感染的反应失调引起。2020年，全球疾病负担报告称，全球每年有近5 000万患者发生脓毒症[1]。脓毒症诱导的心肌病（sepsis-induced cardiomyopathy, SICM）是由脓毒症引起的一种急性心脏疾病，在脓毒症患者中的发生率高达50%~60%[2]，其特征为心肌收缩力受损、血流动力学改变甚至心源性休克，是脓毒症患者死亡率高的重要原因[3]。尽管SICM在脓毒症早期具有可逆性，存活患者可在7~10 d内完全康复，但有报道称其死亡率极高，70%~90%的患者会因此死亡[4]。目前尚无特异性治疗策略可减轻或逆转脓毒症导致的心功能障碍，且SICM的病理生理机制仍未完全阐明。

外泌体是直径30~150 nm的膜结合囊泡，几乎所有活细胞均可分泌，其主要功能是通过将其携带的各种物质，如蛋白质、核苷酸[DNA、mRNA、微小RNA（microRNA, miRNA）和长链非编码RNA（long non-coding RNA, lncRNA）]和脂质等转移到其他细胞来促进细胞间通信[5-6]，从而影响免疫应答、炎症反应、组织修复和细胞凋亡等生理过程[7-8]。近年研究表明，外泌体在SICM中参与介导心肌细胞、内皮细胞和巨噬细胞间的通信，参与SICM进展过程中的炎症、心肌损伤和心功能障碍等。

1 内皮细胞来源外泌体

脓毒症所致的器官功能障碍如心肌损伤、肺损伤等均与内皮细胞功能障碍有关。在生理状态下，内皮细胞可以动态调节血管屏障功能、凝血功能和血管舒缩张力，而脓毒症期间产生的病原体相关分子模式[例如脂多糖（lipopolysaccharide, LPS）或内源性配体]会刺激内皮细胞激活。活化的内皮细胞

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上调趋化因子和黏附分子的表达，吸引并促进免疫细胞浸润和炎症反应，导致包括心脏在内的多种器官损伤[9-10]。研究表明，内皮细胞来源的外泌体影响SICM进展过程中的心脏功能和重塑。内皮细胞分泌的热休克蛋白（heat shock protein，HSP）A12B被证实可通过上调miRNA（miR-126）的表达，保护心肌免受脓毒症诱导的心功能损伤，miR-126通过抑制黏附分子的表达减少心肌免疫细胞浸润并减轻心脏损伤[11]。同期有研究证实，内皮细胞中HSPA12B缺乏会导致更严重的心功能障碍以及不良的生存结局，在限制促炎反应和保护宿主免受SICM以及降低死亡率方面起着重要作用，并进一步阐明HSPA12B在脓毒症期间通过外泌体释放，然后外泌体HSPA12B被巨噬细胞吸收。当内皮细胞来源的外泌体HSPA12B被LPS刺激的巨噬细胞摄取后，HSPA12B通过下调活化B细胞核因子κ轻链增强子（nuclear factor kappa-light-chain-enhancer of activated B cells，NF-κB）的激活及其核转位，减少肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）和白细胞介素（interleukin，IL）-1β的产生，但同时增加IL-10表达水平，从而减轻巨噬细胞介导的促炎反应以及脓毒症诱导的心脏损伤，进而降低死亡率[12]。但是有研究认为内皮细胞来源的外泌体对心肌细胞的保护作用可能仅存在于脓毒症的早期[13]。该研究显示，LPS（0.5 μg/mL）刺激的内皮细胞来源外泌体增强了新生大鼠心肌细胞的活力并减少了细胞凋亡，与此同时，可导致乳酸脱氢酶和活性氧下降，超氧化物歧化酶上升。这些现象表明内皮细胞来源外泌体具有心脏保护作用。值得注意的是，在较高浓度（10 μg/mL）的LPS刺激下，内皮细胞产生的微泡主要是凋亡小体，而外泌体则显著减少。因此认为在高浓度的LPS下，由于内皮细胞凋亡，内皮细胞衍生的外泌体对心肌细胞的保护作用减弱或消失。

内皮细胞来源外泌体含有对保护心肌细胞至关重要的miRNA。这些miRNA下调B细胞淋巴瘤2-拮抗因子/杀伤因子1、肿瘤抑制蛋白及磷酸酶和张力蛋白等凋亡相关蛋白，从而促进心肌细胞存活，减少脓毒症所致的心肌损伤。研究显示，在LPS诱导的内皮损伤中，山莨菪碱通过外泌体介导的磷脂酰肌醇3激酶/蛋白激酶B和NF-κB信号通路调节改善炎症、心肌细胞功能障碍和心肌损伤[14]。因此，内皮细胞来源的外泌体在脓毒症期间对心肌细胞具有保护潜力。

2 巨噬细胞来源外泌体

巨噬细胞来源的外泌体介导的细胞间通信在SICM过程中起重要作用。源自不同巨噬细胞表型的外泌体影响心肌细胞凋亡、线粒体功能和炎症反应。巨噬细胞有M1和M2两种表型，尽管M1巨噬细胞在心脏免疫反应中起关键作用，但它们可通过产生TNF-α和IL-1β等炎症细胞因子导致心肌炎症状态，并促进细胞外基质降解和细胞死亡[15]。既往有研究表明，M1型巨噬细胞外泌体通过向内皮细胞递送miR-155，靶向作用于5个分子节点，从而抑制沉寂信息调节因子/腺苷酸活化蛋白激酶、内皮型一氧化氮合酶及大鼠肉瘤相关C3肉毒毒素底物1（ras-related C3 botulinum toxin substrate 1，RAC1）/RAC1激活激酶2（RAC1 activated kinase 2，PAK2）信号通路，降低内皮细胞的血管生成能力，加重心肌损伤并抑制心脏修复[16]。在脓毒症诱导的心肌功能障碍小鼠模型中，氧化应激增加了单核细胞来源的外泌体硫氧还蛋白相互作用蛋白（TXNIP）-NOD样受体热蛋白结构域相关蛋白3（NLRP3）复合物的水平，该复合物可被运输至心脏驻留巨噬细胞，在其中激活半胱天冬酶-1（caspase-1），并切割无活性的IL-1β和IL-18使其活化，从而加剧心血管炎症[17]。Bi等[18]的研究发现，M1型巨噬细胞来源的外泌体中高表达lncRNA Snhg14，通过靶向抑制miR-181a-5p，激活高迁移率族蛋白B1（HMGB1）/NF-κB通路，加剧脓毒症诱导的心肌损伤（凋亡、氧化应激、炎症）。敲低Snhg14或上调miR-181a-5p可抑制M1型巨噬细胞极化，减轻脓毒症小鼠的心脏损伤。而M2巨噬细胞在SICM中发挥保护作用，可促进心肌炎症消退。研究显示刺激巨噬细胞向M2表型极化，IL-10等抗炎细胞因子产生增加，有助于减轻心肌损伤[19]。Huang等[20]研究揭示了以整合素亚基alpha M（integrin subunit alpha M，ITGAM）上调为特征的巨噬细胞在SICM心脏组织中所发挥的关键作用。首先通过单细胞测序分析显示，巨噬细胞是SICM心脏环境中最丰富的免疫细胞，其数量随疾病进程动态变化（直肠结扎穿孔术后3 d减少，7 d和21 d回升），是介导心脏炎症与修复的核心细胞。然后用LPS模拟脓毒症状态进行体外实验，刺激小鼠单核巨噬细胞系、原代骨髓来源巨噬细胞及心脏微血管内皮细胞，发现LPS可显著上调巨噬细胞中ITGAM的表达，同时诱导内皮细胞中细胞间黏附因子-1的高表达，提示二者在免疫细胞募集和细胞间通信中起关键作用。最后构建LPS诱导的SICM小鼠模型，对部分小鼠注射ITGAM中和抗体，24 h后，ITGAM中和抗体处理组心脏中巨噬细胞浸润减少，心衰标志物B型脑钠肽及炎症基因（IL-6、IL-1β等）表达降低，心功能（左心室射血分数、短轴缩短率）改善；长期观察（10 d）发现，中和抗体处理组后期死亡率升高，提示ITGAM在SICM中具有双重作用——早期通过促进巨噬细胞浸润加剧心脏炎症，短期可通过抑制ITGAM改善心功能；但后期其介导的巨噬细胞表型转化（如向M2亚型分化）对心脏修复至关重要，过度抑制会增加死亡率。

3 血小板来源外泌体

血小板来源的外泌体约占血浆中外泌体总量的70%，可介导凝血激活、促炎反应及血管内皮损伤等多种病理生理过程[21]。在脓毒症状态下，血小板通过与病原体相互作用被激活，进而诱发微血栓形成，导致心脏缺血性损伤，最终引发心功能障碍[22]。除参与凝血与血栓形成外，血小板还可通过加剧心肌抑制相关的炎症反应发挥作用，已被证明是脓毒症期间中性粒细胞胞外陷阱（neutrophil extracellular trap，NET）形成的有效激活剂[23]。含有HMGB1和/或miRNAs的血小板来源外泌体通过调节蛋白激酶B/哺乳动物雷帕霉素靶蛋白通路相关的自噬途径诱导NET形成，可能在脓毒症期间诱导血管凋亡和心肌功能障碍[24]。在脓毒症期间，暴露于LPS的血小板过度产生外泌体可通过上调超氧化物、一氧化氮和过氧亚硝酸盐的表达触发内皮

细胞中的caspase-3激活和凋亡，从而导致脓毒性血管功能障碍[25]。在LPS诱导的小鼠模型中，血小板来源的外泌体通过释放一氧化氮合酶、还原型辅酶Ⅱ氧化酶和二硫键异构酶促进炎症，进而下调抗炎性miR-223，进而加剧血管功能障碍。目前关于血小板来源外泌体与SICM的相关机制研究较少，未来需要进一步探索。

4 间充质干细胞(mesenchymal stem cell，MSC)来源外泌体

干细胞根据其分化能力可以分为：(1) 全能干细胞，可形成完整的生物体(如受精卵)；(2) 多能干细胞，可分化为外胚层、中胚层和内胚层三个胚层的所有细胞类型(如胚胎干细胞)；(3) 多潜能干细胞，可分化为多种细胞类型(如MSC、造血干细胞、骨髓、脂肪来源的干细胞)；(4) 寡能干细胞，分化成的细胞类型范围比多潜能干细胞更窄(如髓系干细胞)；(5) 单能干细胞，只能分化为一种特定的细胞类型(如骨细胞)。MSC几乎存在于所有组织中，很容易从骨髓和脂肪组织中分离出来。且在特定的体外条件下，MSC可分化为内胚层(肺泡上皮细胞)、外胚层(神经细胞)和中胚层(心肌细胞)三种细胞类型。MSC来源的外泌体已被证明可通过促进新生血管形成、抑制炎症反应，改善心脏微环境[26]。过表达趋化因子受体4的MSC来源外泌体，通过介导蛋白激酶B信号传导，对心肌细胞产生保护作用[27]。骨髓MSC来源外泌体miR-223在多重微生物脓毒症中，通过下调信号素3A和信号转导及转录激活蛋白3，减少炎症和细胞死亡，发挥心脏保护作用[28]。来自MSC衍生的心脏祖细胞的外泌体，通过细胞外调节蛋白激酶/蛋白激酶B信号传导促进血管生成，促使内皮细胞迁移和血管形成。在SICM中，MSC来源的外泌体miRNA发挥抗炎作用以阻止疾病进展[29]。例如，MSC来源的外泌体miR-223已被证实可通过下调脓毒症小鼠中信号素3a和信号转导和转录激活因子3的表达，抑制心肌细胞凋亡、炎症反应和心功能障碍。此外，MSC来源外泌体中的miR-146a-5p可被递送至LPS诱导的心肌细胞，在其中促进细胞增殖并抑制凋亡；此外，它通过降低髓母细胞瘤样蛋白1表达抑制脓毒症小鼠心肌组织的炎症反应[30]。另外，有报道称，装载miR-412-5p的MSC外泌体通过灭活丝裂原活化蛋白激酶信号通路抑制炎症介质(包括一氧化碳、前列腺素E2和活性氧)的表达以及IL-1β和IL-6等促炎细胞因子的分泌，从而改善LPS诱导的心肌细胞炎症[31]。通过抑制心肌细胞中的miR-497-5p/三菱珠蛋白53轴，MSC来源外泌体中的环状RNA RTN4已被证实可减少炎症因子(包括活性氧、IL-1β、IL-6和TNF-α)的产生，并增加超氧化物歧化酶和谷胱甘肽的活性，从而减轻LPS处理的心肌细胞和脓毒症大鼠的心肌凋亡和心脏损伤[32]。这些研究突出了MSC来源外泌体在调节SICM中心脏炎症和心肌细胞凋亡方面的巨大潜力。

5 结 论

本综述总结了内皮细胞、巨噬细胞和血小板来源外泌体在SICM进展中调节炎症反应、氧化应激和心肌细胞凋亡的多方面作用。外泌体携带多种生物活性分子，包括蛋白质、脂质、mRNA和miRNA，促进这些细胞类型之间的信号传递，影响脓毒症及其相关心功能障碍的进展。当前研究虽明确了外泌体在SICM中的核心作用，但仍有部分问题亟待解决：一是不同来源外泌体在SICM不同病理阶段(早期炎症、中期损伤、后期修复)的“时空特异性”调控机制尚未厘清，难以精准匹配干预时机；二是血小板来源外泌体与SICM的关联研究较为零散，其与其他细胞外泌体的协同或拮抗作用缺乏系统分析；三是MSC来源外泌体的临床转化仍面临载体优化、剂量标准化、靶向递送效率等现实挑战。未来研究需聚焦外泌体调控SICM的关键信号通路机制，深入解析其作用规律，同时推进MSC来源外泌体的临床前验证与转化研究，为SICM的特异性治疗提供新的分子靶点与干预策略。

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