Cite as: Wang ZQ, Guo J, Xia YC, Sha YY, Hu GY, Fu YQ, Chu MY, Qian YM. Research progress of exosomal microRNA in sepsis-induced acute lung injury [J]. Chin J Clin Res, 2025, 38(8): 1150-1153.

DOI: 10.13429/j.cnki.cjcr.2025.08.003

Research progress of exosomal microRNA in sepsis-induced acute lung injury

WANG Zhuoqi, GUO Jian, XIA Yichun, SHA Yuanyuan, HU Guanyu, FU Yuqing, CHU Mengyao, QIAN Yiming

Department of Emergency，Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine，Shanghai 200437,China

Corresponding author: QIAN Yiming, E-mail：qianym2004@163.com

Abstract: Sepsis is one of the most common acute and critical cases in intensive care units with high morbidity and mortality. Acute lung injury is a serious complication of sepsis. At present, the pathogenesis of sepsis-induced lung injury is still unclear, and reliable biomarkers and specific therapeutic methods are lacking. Exosomes, as extracellular vesicles, carry microRNA and play an important role in intercellular communication in respiratory system and inflammation-related diseases. Therefore, this article mainly discusses the pathogenesis, diagnostic and therapeutic value of exosomal microRNA in sepsis-induced lung injury, as well as its prospect in traditional Chinese medicine, providing reference for clinical application.

Keywords: Sepsis; Acute lung injury; Exosome; MicroRNA; Traditional Chinese medicine

Fund Program: Natural Science Foundation of Shanghai Science and Technology Innovation Action Plan (23ZR1464200); University Science System Construction Fund (QY71.42.12)

Sepsis is one of the most common acute and critical diseases in intensive care units, often secondary to trauma, infection, shock, etc. It is characterized by difficult treatment and high mortality. In 2016, the concept of Sepsis 3.0 was officially proposed, defining it as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Acute lung injury (ALI) is one of the common complications of sepsis. In sepsis patients, inflammatory factors accumulate in the body, and pro-inflammatory factors are released in large quantities, causing damage to the alveolar-capillary barrier and diffuse injury to alveolar epithelial cells and microvascular endothelial cells, leading to lung injury characterized by hypoxemia, inflammation, and non-cardiogenic pulmonary edema [2]. Currently, there is a lack of specific drugs and specific treatment measures, and it can develop into acute respiratory distress syndrome (ARDS) in the advanced stage. At present, the pathogenesis of sepsis-induced ALI is not yet clear, and exosomes, as important mediators of intercellular communication and material transfer, are closely related to the pathogenesis of ALI. Based on exosomes and the holistic theory of traditional Chinese medicine (TCM), giving full play to the characteristic role of TCM in the diagnosis and treatment of sepsis-related ALI. Therefore, this study reviews the mechanism of action, diagnostic value, and progress in Chinese and Western medicine treatment of exosomal microRNA (miRNA) in sepsis-induced ALI, in order to provide a reference for the integrated Chinese and Western medicine diagnosis and treatment of sepsis-induced ALI.

1 Biological characteristics of exosomes

Exosomes are extracellular vesicles enclosed by a lipid bilayer, formed through the fusion of intracellular multivesicular bodies with the plasma membrane and subsequent exocytosis. With a diameter ranging from approximately 40 to 160 nm, they play crucial roles in intercellular communication, mammalian reproduction and development, immune responses and infections, metabolic and cardiovascular diseases, neurodegenerative diseases, and cancer [3]. Exosomes contain various bioactive molecules, including proteins, lipids, DNA, RNA, miRNAs, and long non-coding RNAs (lncRNAs), among which miRNAs have garnered the highest attention and most extensive research.

miRNAs are endogenous small RNA molecules that regulate gene expression at the post-transcriptional level, with a length of 18–25 nucleotides. They mediate post-transcriptional silencing by binding to and inhibiting target gene translation [4], and are widely involved in growth, development, and pathological processes such as cell proliferation, differentiation, apoptosis, cell communication, stem cell maintenance, and immune responses [3]. MiRNAs can be transported via exosomes to nearby or distant target cells, facilitating intercellular communication. As carriers, exosomes fuse with the plasma membrane of recipient cells, delivering miRNAs into the cytosol. Protected by this specialized membrane structure, miRNAs maintain their stability and avoid degradation [4]. Additionally, exosomes can traverse recipient cells via transcytosis and release internal miRNAs into adjacent cells to exert intercellular

communication functions [5]. Exosomal miRNAs not only regulate genetic information but also serve as biomarkers for disease diagnosis and prognosis. Abundant miRNAs have been identified in plasma and bronchoalveolar lavage fluid, which may participate in the pathogenesis of sepsis and aid in determining sepsis severity.

2 Mechanisms of exosomes in sepsis-induced ALI

The pathogenesis of sepsis-induced ALI remains unclear, but it is thought to be related with systemic inflammatory responses, oxidative stress, and immune responses. The most widely studied and accepted mechanism suggests that activated alveolar macrophages release large amounts of inflammatory mediators and reactive oxygen species (ROS), such as tumor necrosis factor-α (TNF-α), interleukin (IL) -1, IL-6, and IL-8. These mediators bind to surface receptors on target cells to phagocytose pathogens. Excessive inflammatory factors and ROS can attack pulmonary microvascular endothelial cells, leading to lung injury. During sepsis, plasma exosome levels increase significantly, possibly due to their role as communication vehicles disseminating to organs throughout the body. Exosomes are involved in regulating inflammatory responses and maintaining airway immune balance during these processes [6], but the specific mechanisms require further exploration.

2.1 Inflammatory response

The Sepsis 3.0 definition identifies dysregulated infection responses as a key contributor to sepsis-related mortality, characterized by uncontrolled inflammation leading to multiple organ failure and shock [7]. An imbalance between pro-inflammatory and anti-inflammatory factors influences infection severity. During sepsis, activation of inflammatory cells releases massive inflammatory mediators, disrupting the alveolar-capillary endothelial barrier, promoting neutrophil infiltration, and causing diffuse pulmonary edema [8].

Exosomes can deliver miRNAs to target sites, interfering with inflammatory mediator binding and altering lung injury severity. For example, in ARDS models [9], miRNA-466 family molecules are secreted into airways via extracellular vesicles, promoting NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome processing and pro-inflammatory cytokine (e.g., IL-1β) release through extracellular histones. Transfection of bone marrow-derived macrophages with miRNA-466g upregulates NLRP3 activation pathways, accelerating LPS-induced pro-IL-1β expression during sensitization. Inhibition of extracellular vesicle release reduces sepsis-induced inflammation. Similarly, circulating exosomes in peripheral blood deliver key mediators like miR-155 to macrophages, stimulating NF-κB activation. By targeting SHIP1 and SOCS1, miR-155 induces TNF-α and IL-6 production, exacerbating lung inflammation. However, pro-inflammatory and pro-proliferative activities of serum miR-155 are reversed after its knockdown [10]. Liu *et al.* demonstrated that demethylation of the miR-138-5p promoter restores miR-138-5p expression, directly targeting the NLRP3 inflammasome to protect alveolar macrophages, alleviate LPS-induced apoptosis, and reduce lung inflammation and injury. The results induced by mitochondrial autophagy inducers were consistent with the demethylation of the miR-138-5p promoter.

Exosomes were isolated from plasma for miRNA sequencing when using a cecal ligation and perforation (CLP) model to induce sepsis-induced lung injury in rats. Compared with the control group, the expression of miR-13p was significantly increased in CLP-derived exosomes. Gao *et al.* [12] showed that LPS-stimulated human umbilical vein endothelial cells (HUVECs) transfected with miR-1-3p mimics exhibited inhibited proliferation, increased apoptosis, and enhanced inflammation, while miR-1-3p inhibitors reversed these effects. miR-1-3p directly targets the 3'UTR of SERP1, suppressing its expression and increasing cell contraction, inflammation responses, endothelial monolayer permeability, and membrane damage.

2.2 Oxidative stress

Oxidative stress, resulting from an imbalance between oxidation and antioxidant defenses, is closely linked to physiological and pathological processes, participating in aerobic metabolism and inflammatory pathogenesis of various diseases. ROS, including superoxide anions, peroxides, hydroxyl radicals, and singlet oxygen, can overwhelm antioxidant systems (e.g., superoxide dismutase, catalase, glutathione peroxidase, and glutathione), disrupting redox balance and causing lipid, protein, and DNA damage. This induces free radical production and persistent cellular injury.

Exosomes can deliver miRNAs to alveolar macrophages, reducing ROS accumulation and pulmonary oxidative damage. Shen *et al.,* [13] demonstrated that adipose stem cell-derived exosomes specifically deliver miR-125b-5p, which protects mice from LPS-induced M1 macrophage activation via the Keap1/Nrf2/GPX4 axis, mitigating ROS accumulation and oxidative damage. Keap1 was identified as a target of miR-125b-5p; its downregulation upregulates Nrf2 and GPX4, alleviating ferroptosis in septic pulmonary microvascular endothelial cells. Zhang *et al.* [14] showed that circTDRD9 regulates RAB10 expression by competitively targeting miR-223-3p. Enrichment of miR-223-3p downregulates RAB10, reducing LPS-induced macrophage activation and ameliorating lung injury by alleviating inflammation, oxidative stress, and fibrosis. Jiao *et al.* [15] found that ROS production may promote leukocyte infiltration and neutrophil extracellular trap (NET) formation. M2 macrophage-derived exosomes (M2-Exos) inhibit polymorphonuclear neutrophil (PMN) migration and NET formation during sepsis. PGE2-enriched M2-Exos upregulate 15-LO expression in PMNs via EP4 receptors, increasing lipoxin A4 (LXA4) production to downregulate CXCR2 and ROS expression, thereby

reducing lung injury and mortality.

2.3 Immune response

Dysregulated immune responses during sepsis impair pathogen clearance and accelerate organ damage. As a key immune organ, the lung maintains immune homeostasis in sepsis-related ALI through macrophages, neutrophils, airway epithelial cells, and dendritic cells. Macrophages, critical components of innate immunity, polarize into M1 or M2 phenotypes in response to microenvironmental signals, exhibiting opposing functions throughout sepsis [16]. M1 macrophages release pro-inflammatory mediators, while M2 macrophages secrete quantities of anti-inflammatory factors.

Exosomes from different sources deliver miRNAs to macrophages, regulating polarization, apoptosis, inflammation, and lung injury. Exosomal miR-30d-5p from PMNs activates NF-κB signaling, inducing sepsis-related ALI. Macrophages cultured with exosomes from TNF-α-stimulated PMNs showed elevated miR-30d-5p levels, indicating TNF-α enhances miR-30d-5p transfer to recipient macrophages. miR-30d-5p targets SOCS-1 and SIRT1, inducing macrophage pyroptosis. miR-30d-5p inhibitors reduce M1 macrophage activation and pyroptosis, alleviating lung injury [17]. Bone marrow mesenchymal stromal cells (BMSCs)-derived exosomal miR-125b-5p reduces macrophage apoptosis, inflammation, and lung injury in septic mice by inhibiting signal transducer and activator of transcription 3 (STAT3). miR-125b-5p inhibitors restore STAT3 expression and attenuate suppression of inflammatory markers and apoptotic proteins under LPS stimulation [18]. Zheng *et al.* [19] demonstrated that MSC-derived exosomes transfer miR-150-5p to macrophages, protecting against LPS-induced inflammation. miR-150-5p targets Irs1, downregulating the PI3K/Akt/mTOR pathway to induce M2 polarization and reduce plasma IL-6 and TNF-α levels.

3 The diagnostic value of exosomes in sepsis-induced ALI

Sepsis-induced ALI is characterized by rapid onset, rapid progression, and critical condition. There is an urgent need for effective and stable early markers to predict its progression for early intervention. Exosomes are natural nanocarriers that can transport proteins, lipids, and nucleic acids across the blood-brain barrier to target cells, reflecting the pathological and physiological characteristics of donor cells [20-21]. miRNAs are key regulators of gene expression and are widely present in mammalian body fluids such as serum, plasma, tears, urine, and bronchoalveolar lavage fluid. Due to their minimally invasive nature, high safety, convenient sampling, and ease of implementation, they are important potential biomarkers for ALI. miR-15a, miR-16, miR-122, miR-143, miR-146a/b, miR-150, miR-155, and miR-223 are the most extensively studied miRNAs in the field of sepsis [22]. In a study on exosome expression profiles in septic ALI mice [23], miR-122-5p and miR-671-5p expressions were downregulated. Ma *et al.* [24] showed a positive correlation between serum miR-499a-5p and growth factor FGF9 in sepsis complicated with ALI. Moreover, serum levels of miR-499a-5p and FGF9 in patients with sepsis complicated with ALI showed a decreasing trend with the increase of disease severity. The combination of both had a higher area under the receiver operating characteristic curve (AUC) and sensitivity in predicting patient prognosis.

4 The therapeutic value of exosomes in sepsis-induced ALI

Exosomes exhibit a long circulatory half-life and good tolerability in the human body [25]. Utilizing exosomes themselves or as effective carriers for drug delivery represents the most commonly used therapeutic approach to date. As powerful genetic regulators, miRNAs can modulate entire cellular pathways through interactions with a broad spectrum of target genes, influence intracellular homeostasis, and alter disease outcomes. miRNA mimics, inhibitors, and gene knockout strategies have been demonstrated in numerous studies to modify the progression and prognosis of sepsis-induced ALI, emerging as promising novel therapeutic agents.

In experiments by Dang *et al.* [26], miR-223 overexpression stimulated by IL-4 in a sepsis model inhibited macrophage polarization toward the M1 phenotype by reducing the expression of hypoxia-inducible factor-1α (HIF-1α), phosphoinositide-dependent protein kinase-1 (PDK-1), and phosphofructokinase (PFK). This resulted in enhanced anti-inflammatory properties, decreased TNF-α levels, increased IL-10 expression, and reduced damage to the lungs, liver, and kidneys. Tao *et al.* [18] showed that treatment of LPS-induced mice with a miR-125b-5p inhibitor promoted the expression of pyroptosis-related proteins (STAT3, p-STAT3) and pyroptosis-associated proteins, significantly attenuated the inhibition of IL-6 and IL-18, induced pyroptosis of alveolar macrophages, and exacerbated lung tissue structural damage.

Wang *et al.* [27] found that BMSC-derived exosomes reversed the high expression of PTEN in LPS-induced pulmonary microvascular endothelial cells (PMVECs). Overexpression of miR-26a-3p reduced apoptosis and inflammation, and promoted autophagy by silencing PTEN. In animal experiments, miR-26a-3p overexpression in LPS-induced PMVECs effectively ameliorated LPS-induced lung injury in rats, reducing apoptosis, improving inflammation, and enhancing autophagy. A growing number of recent research confirms the potential therapeutic value of various miRNAs in sepsis-induced ALI.

5 The combination between exosomes and TCM

Due to the complexity and uncertainty of the pathogenesis of ALI, there is still no specific treatment

method so far. Currently, the treatment strategies for sepsis-induced ALI mainly focus on controlling the primary disease and symptomatic supportive therapy. TCM, a treasure of ancient Chinese science, has played a unique and effective role in the treatment of ALI and has become a current research hotspot.

Liangge San, derived from the *Taiping Huimin Heji Ju Fang* in the Song Dynasty, is effective in purging fire, promoting defecation, clearing heat from the upper jiao, and purging fire from the lower jiao. Its composition includes *Forsythia suspensa, Scutellaria baicalensis, Gardenia jasminoides, Mentha haplocalyx, Rheum palmatum, Natrii Sulfas,* and *Glycyrrhiza uralensis*. A study on ALI showed that Liangge San can assist in alleviating sepsis-induced ALI. Similarly, in cell experiments, exosomes pretreated with Liangge San exhibited upregulated expression of miRNA-21, reduced expression of inflammatory markers TNF-α and IL-6 in bronchoalveolar lavage fluid, and decreased total inflammatory protein content. It significantly alleviated inflammatory cell infiltration and pulmonary edema in mouse lung tissues, while reducing apoptosis of macrophages and alveolar epithelial cells through the PI3K/AKT pathway [28].

Paeonol is a component extracted from *Paeonia suffruticosa,* the roots of *Paeonia lactiflora,* and *Dioscorea opposita*. It possesses anti-inflammatory, anti-proliferative, and antioxidant properties, and is widely involved in various physiological processes. The research proposed by Jin *et al.* [29] demonstrated that paeonol can increase miR-126 levels in lung tissues, alleviate sepsis-induced ALI by inhibiting inflammatory responses, oxidative stress, and cell apoptosis, enhance the expression of antioxidant protein Nrf2, reduce the expression of inflammatory protein high mobility group box 1 (HMGB1), and inhibit apoptotic protein Bcl-2. These findings provide a theoretical basis for the clinical treatment of sepsis-induced ALI with TCM.

6 Conclusion

Exosomal miRNAs, as biomarkers for sepsis-related ALI, hold significant importance for early diagnosis, helping to improve patients' clinical prognosis and presenting promising application prospects in sepsis-related ALI. However, current challenges include strong exosomal heterogeneity, high purification difficulty, high cost, and long operation time. Refining and updating exosome extraction methods is a key direction in current research. Exploring miRNAs and exosomal carriers associated with sepsis-induced ALI, investigating their complex regulatory signal transduction pathways, and fully leveraging the unique advantages of TCM in this field are important directions for future research.

Conflict of interest None

Reference

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Submission Received: 2024-12-26

·研究进展·

外泌体微小RNA在脓毒症急性肺损伤中的研究进展

王卓琦，郭健，夏一春，沙媛媛，胡冠宇，傅育情，褚梦瑶，钱义明
上海中医药大学附属岳阳中西医结合医院急诊医学科，上海 200437

摘要：脓毒症是重症监护室中最常见的急危重症，具有发病率高、死亡率高的特点，而急性肺损伤是脓毒症严重的并发症。目前脓毒症急性肺损伤的发病机制尚不明确，缺少可靠的生物标志物及特效治疗方法。外泌体作为一种细胞外囊泡，携带微小RNA（miRNA），在呼吸道及炎症相关疾病的细胞间通信中发挥重要作用。因此，本文主要阐述目前外泌体miRNA在脓毒症急性肺损伤发病机制、诊断及治疗上的价值及在中医药研究中的前景，为临床应用提供参考。

关键词：脓毒症；急性肺损伤；外泌体；微小RNA；中医药
中图分类号：R563　R278　**文献标识码：**A　**文章编号：**1674-8182(2025)08-1150-04

Research progress of exosomal microRNA in sepsis-induced acute lung injury

WANG Zhuoqi, GUO Jian, XIA Yichun, SHA Yuanyuan, HU Guanyu, FU Yuqing, CHU Mengyao, QIAN Yiming
Department of Emergency, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai 200437, China
Corresponding author: QIAN Yiming, E-mail: qianym 2004@163.com

Abstract: Sepsis is the most common acute and critical diseases in intensive care units, with high morbidity and mortality. Acute lung injury is a serious complication of sepsis. At present, the pathogenesis of sepsis-induced lung injury is still unclear, and reliable biomarkers and specific therapeutic methods are lacking. Exosomes, as extracellular vesicles, carry microRNA and play an important role in intercellular communication in respiratory system and inflammation-related diseases. Therefore, this article mainly discusses the pathogenesis, diagnostic and therapeutic value of exosomal microRNA in sepsis-induced acute lung injury, as well as its prospect in traditional Chinese medicine, providing a reference for clinical application.

Keywords: Sepsis; Acute lung injury; Exosome; microRNA; Traditional Chinese medicine
Fund program: Natural Science Foundation of Shanghai Science and Technology Innovation Action Plan (23ZR1464200); University Science System Construction Fund (QY71.42.12)

脓毒症是重症监护室中最常见的急危重症之一，常继发于创伤、感染、休克等情况后，具有治疗难度大、死亡率高等特点。2016年脓毒症3.0的概念正式被提出，其被定义为宿主对感染的反应失调引起的危及生命的器官功能障碍[1]。急性肺损伤（acute lung injury，ALI）是脓毒症常见的并发症之一。脓毒症患者体内炎症因子聚集，促炎因子大量释放，引起肺泡-毛细血管屏障破坏，肺泡上皮细胞和微血管内皮细胞弥漫性损伤，导致以低氧血症、炎症和非心源性肺水肿为特征的肺损伤[2]，且缺乏特效药物和具体治疗措施，晚期可发展为急性呼吸窘迫综合征（acute respiratory distress syndrome，ARDS）。目前脓毒症ALI的发病机制尚未明确，而外泌体作为细胞间通信及物质传递的重要介质，与ALI的发病密切相关。基于外泌体及中医药整体理论，中医药在脓毒症相关ALI诊疗中发挥特色作用。本研究综述外泌体微小RNA（microRNA，miRNA）在脓毒症ALI中的作用机制、诊断价值及中西医治疗进展，以期为脓毒症ALI的中西医结合诊疗提供参考。

1　外泌体的生物学特点

外泌体是一种细胞内多囊泡体与质膜的融合和胞吐作用形成的由脂质双分子层包裹的细胞外囊泡，直径约为40~160 nm，在细胞间通信、哺乳动物的繁殖和发育、免疫反应与感染、代谢和心血管疾病、神经退行性疾病、癌症中发挥重要的作用[3]。外

DOI:10.13429/j.cnki.cjcr.2025.08.003
基金项目：上海市科技创新行动计划自然科学基金项目(23ZR1464200)；大学科制建设基金(QY71.42.12)
通信作者：钱义明，E-mail:qianym2004@163.com
出版日期：2025-08-20

QR code for English version

泌体中含有多种生物活性分子，包括蛋白质、脂质、DNA、RNA、miRNAs、长链非编码RNA（long non-coding RNAs，lncRNA）等，其中miRNA是关注度最高、研究最广的一种。

miRNA是一类在转录后调控基因表达的内源性小分子RNA，长度18～25个核苷酸，通过结合和抑制靶基因的翻译而实现转录后沉默[4]，广泛参与生长发育和病理过程，如细胞增殖、细胞分化、细胞凋亡、细胞通信、干细胞维持、免疫反应等[3]。miRNA可随外泌体循环传递至较近或远处的靶细胞中，发挥细胞间通信的作用。外泌体作为载体，与受体细胞的质膜融合，携带miRNA递送到胞质溶胶中，并在这一特殊膜结构的保护下维护自身的稳定性，从而避免miRNA的降解[4]。还通过转胞吞作用，使其穿过受体细胞并将其内部miRNA释放到相邻细胞中发挥细胞间的通信作用[5]。外泌体miRNA不仅是遗传信息的调控者，也可以作为疾病诊断及预后预测的生物标志物。在血浆和支气管肺泡灌洗液中发现了丰富的miRNA，且其可能参与了脓毒症的发病，并可用于脓毒症严重程度的判断。

2 外泌体在脓毒症ALI中的作用机制

目前对于脓毒症ALI的发病机制尚不明确，认为该病可能与机体炎症反应、氧化应激反应、免疫应答等有关。而目前研究最广、接受度最高的机制认为，肺泡巨噬细胞被激活后，释放大量的炎症介质和活性氧（ROS），例如肿瘤坏死因子-α（TNF-α）、白细胞介素（IL）-1、IL-6、IL-8等，与相应细胞表面受体相结合，吞噬病原体。过量的炎症因子和ROS易攻击肺微血管内皮细胞，从而导致肺损伤。脓毒症发病期间，血浆中外泌体含量显著上升，这可能与其作为通信工具播散至全身各器官相关。外泌体存在于以上反应的发生过程，参与调控炎症反应和维持气道免疫平衡[6]，但具体机制仍需进一步探索。

2.1 炎症反应 脓毒症3.0概念中提出，感染反应失调是导致脓毒症患者死亡的重要原因，脓毒症患者发生不可控制的炎症反应，导致多脏器衰竭和休克[7]。促炎因子与抗炎因子之间的不平衡是影响感染严重程度的重要因素。脓毒症期间，多种炎症细胞激活并释放大量炎症介质，导致肺泡-毛细血管内皮细胞屏障结构完整性被破坏，中性粒细胞浸润和弥漫性肺水肿[8]。

外泌体可以将miRNA传递至不同部位释放，干预其与炎性介质之间的结合，从而改变肺部损伤的程度。例如，在ARDS模型中[9]，miRNA-466家族分子通过细胞外囊泡分泌到气道中，经细胞外组蛋白促进NLR家族Pyrin域蛋白3（NLRP3）炎性小体加工和释放IL-1β等促炎因子，并且miRNA-466基因转染骨髓源性巨噬细胞后，靶向上调NLRP3的启动途径，加速脂多糖（LPS）诱导的致敏期pro-IL-1β表达，而细胞外囊泡释放受抑制时，脓毒症诱导的炎症因子水平有所降低。同样，分泌到外周血中的循环外泌体，递送miR-155等关键介质至巨噬细胞，刺激核因子-κB（NF-κB）活化，通过靶向选择性SH2结构域的肌醇-5-磷酸酶1（SHIP1）和细胞因子信号转导抑制因子1（SOCS1），诱导TNF-α和IL-6的产生，加重肺部炎症，然而，血清miR-155的促炎和促增殖活性在其敲低后逆转[10]。Liu等[11]研究发现，miR-138-5p启动子的去甲基化，可以恢复miR-138-5p表达，直接靶向NLRP3炎性小体，保护肺泡巨噬细胞，缓解LPS所致的肺泡巨噬细胞凋亡，有效减轻肺部炎症水平及损伤程度。使用线粒体自噬诱导剂所致结果与miR-138-5p启动子去甲基化一致。用盲肠结扎（CLP）诱导脓毒症肺损伤大鼠模型，从血浆中分离外泌体进行miRNA测序，与对照组相比，CLP衍生的外泌体中miR-1-3p的表达显著提高。Gao等[12]使用miR-1-3p模拟物或抑制剂转染的人脐静脉内皮细胞（human umbilical vein endothelial cell，HUVEC），接受LPS诱导，过表达的miR-1-3p显著抑制HUVECs增殖，并促进HUVECs凋亡和炎症反应，下调miR-1-3p表达可逆转上述作用，且miR-1-3p直接靶向应激相关内质网蛋白1（SERP1）的3'UTR并抑制其表达，引起细胞收缩、炎症反应、单层内皮细胞通透性和膜损伤增加。

2.2 氧化应激 氧化应激作为机体内氧化与抗氧化之间失衡的结果，与人体生理病理活动密切相关，参与生理有氧代谢和多种疾病发生发展的病理炎症过程。ROS包括超氧阴离子、过氧化物、羟基自由基和单线态氧等，过量ROS的产生会导致机体抗氧化系统的表达异常，例如超氧化物歧化酶、过氧化氢酶、谷胱甘肽过氧化物酶、谷胱甘肽等，从而引起氧化还原反应平衡的失调，最终导致脂质、蛋白质和DNA的损伤，诱导自由基的产生，对机体细胞造成持续性的伤害。

外泌体可以传递miRNA至肺泡巨噬细胞，减少ROS积累和肺部氧化损伤。Shen等[13]的研究表明，脂肪干细胞衍生的外泌体特异性递送miR-125b-5p，通过Keap1/Nrf2/GPX4轴，保护小鼠减轻LPS诱导的M1表型的巨噬细胞激活，减轻ROS积累和氧化损伤，并且证明了Keap1作为miR-125b-5p的靶标，减弱Keap1的表达，上调Nrf2和GPX4的表达，可缓解脓毒症肺微血管内皮细胞铁死亡。Zhang等[14]证明，环状含图多尔结构域蛋白9的RNA（circTDRD 9）通过竞争性靶向miR-223-3p调控RAB 10的表达，miR-223-3p的富集，靶向下调RAB 10的表达，减少LPS诱导的巨噬细胞活化的抑制程度，减轻炎症、氧化应激和纤维化来改善肺部损伤。Jiao等[15]研究表明，ROS的产生可能促进白细胞浸润和中性粒细胞胞外陷阱（neutrophil extracellular traps，NET）形成，而M2巨噬细胞来源的外泌体（M2-Exos）可以通过抑制脓毒症期间的多形核中性粒细胞（PMN）迁移和NET形成，富含M2-Exos的前列腺素E2（PGE2）通过作用于EP4受体来增加PMNs中15-脂氧合酶的表达，上调脂氧素A4（LXA4）的产生以下调趋化因子受体2（CXCR2）和ROS表达，减轻肺损伤并降低死亡率。

2.3 免疫应答 脓毒症期间，免疫应答失调可能会导致病原体清除效率低下，加重机体负担，增加不可控制的器官损伤。肺部作为人体重要的免疫器官，主要通过巨噬细胞、中性粒细胞、气道上皮细胞、树突状细胞等在脓毒症相关ALI中维持免疫稳态。巨噬细胞作为先天性免疫系统的重要组成部分，可以通过免疫微环境中的不同信号分子极化成M1和M2表型，

这些极化的巨噬细胞参与脓毒症的所有阶段，并表现出几乎相反的免疫功能[16]，其中，M1型巨噬细胞释放大量促炎介质，而M2型巨噬细胞释放大量抗炎介质。

不同来源的外泌体可以通过递送miRNA至巨噬细胞，调控不同表型巨噬细胞的活化与凋亡，影响炎症反应及肺损伤。PMNs中的外泌体miR-30d-5p通过激活NF-κB信号传导诱导脓毒症相关的ALI。巨噬细胞在与TNF-α离体刺激PMN后分离的外泌体培养后表现出更高水平的miR-30d-5p，表明TNF-α离体刺激PMN可以增强miR-30d-5p从外泌体转移到受体巨噬细胞，进一步靶向SOCS1和SIRT1诱导巨噬细胞极化，引发巨噬细胞焦亡，使用miR-30d-5p特异性抑制剂显著降低了肺中M1型巨噬细胞的活化和焦亡，缓解肺损伤进程[17]。骨髓间充质干细胞（bone marrow mesenchymal stem cells，BMSCs）来源的外泌体miR-125b-5p通过抑制信号转导子和转录激活子3（signal transducer and activator of transcription 3，STAT3）的表达来减轻脓毒症小鼠中的巨噬细胞凋亡，改善肺部炎症，缓解肺损伤。而使用miR-125b-5p抑制剂后，STAT3的表达水平有所恢复，小鼠暴露于LPS的刺激，对炎症标志物和凋亡蛋白表达的抑制减弱[18]。Zheng等[19]的动物实验表明，BMSCs来源的外泌体，将miR-150-5p转移到巨噬细胞中，保护小鼠对抗LPS诱导的炎症反应，并靶向Irs1下调PI3K/Akt/mTOR通路诱导其向M2型极化，降低血浆中IL-6和TNF-α的水平。

3 外泌体在脓毒症ALI中的诊断价值

脓毒症相关ALI具有发病快、进展迅速、病情危重的特点，亟需有效且稳定的早期标志物预测其进展，以求尽早干预。外泌体属于天然的纳米载体，可以通过血脑屏障将蛋白质、脂质、核酸转运到靶细胞，并反映供体细胞的病理及生理特征[20-21]。miRNA是基因表达的关键调节因子，广泛存在于哺乳动物的体液中，例如血清、血浆、泪液、尿液、支气管肺泡灌洗液等，由于其获取侵入性较小，安全性高，采样便利，易于实施，是目前ALI重要的潜在生物标志物。miR-15a、miR-16、miR-122、miR-143、miR-146a/B、miR-150、miR-155和miR-223是目前脓毒症领域相关研究最多的miRNA[22]。一项脓毒症ALI小鼠外泌体表达谱的研究显示，miR-122-5p和miR-671-5p的表达下调[23]。马静等[24]研究表明，在脓毒症并发ALI中，血清miR-499a-5p与成纤维细胞生长因子9（fibroblast growth factor 9，FGF9）之间具有正相关性，且脓毒症并发ALI组患者的血清miR-499a-5p、FGF9水平均随疾病的严重程度增高而呈递减趋势，两者联合预测患者预后的受试者工作特征曲线下面积（AUC）和灵敏度更高。

4 外泌体在脓毒症ALI中的治疗价值

外泌体具有较长的循环半衰期，对人体具有良好的耐受性[25]，通过外泌体自身或将其作为递送药物的有效载体是目前最常使用的治疗手段。而miRNA作为强大的遗传调节因子，可以通过其与广谱靶基因相互作用来指导整个细胞通路，影响细胞内环境的稳定，改变疾病的结局。miRNA模拟物、miRNA抑制剂、miRNA基因敲除在各大实验中已被证明，能够改变脓毒症ALI的结局及预后，是目前具有广泛前景的新型治疗剂。Dang等[26]实验显示，脓毒症模型中，给予IL-4刺激的miR-223过表达可以通过降低缺氧诱导因子-1α（hypoxia-inducible factor 1α，HIF-1α）、3-磷酸肌醇依赖性蛋白激酶-1（3-phosphoinositide-dependent protein kinase-1，PDK-1）和磷酸果糖激酶（phosphofructokinase，PFK）的表达，抑制巨噬细胞向M1型极化，抑炎特性更显著，TNF-α降低，IL-10表达增加，减少肺肝肾等器官的损伤。Tao等[18]通过miR-125b-5p抑制剂处理LPS诱导的小鼠促进了焦亡蛋白STAT3、p-STAT3和热解相关蛋白的表达，对IL-6和IL-18的抑制作用显著降低，诱导肺泡巨噬细胞焦亡，肺组织结构损伤加重。Wang等[27]发现，BMSCs来源的外泌体可逆转LPS诱导的肺微血管内皮细胞（pulmonary microvascular endothelial cells，PMVECs）中PTEN的高表达，miR-26a-3p过表达减少细胞凋亡和炎症，并通过沉默PTEN促进自噬。动物实验中，在LPS诱导的PMVEC中，miR-26a-3p过表达能有效改善LPS诱导的大鼠肺损伤，减少细胞凋亡、改善炎症和自噬。近期大量研究结果均可证实多种miRNA对脓毒症ALI具有潜在治疗价值。

5 外泌体与中医药结合

由于ALI发病机制的复杂性与不确定性，至今尚无特效治疗方法。目前针对脓毒症ALI的治疗策略主要以控制原发病及对症支持治疗为主。中医药学是中国古代科学的瑰宝，在ALI的治疗中发挥出了独特且有效的作用，是目前研究的热点。

凉膈散出自宋代《太平惠民合剂局方》，具有泻火通便、清上泻下的功效，组成包括连翘、黄芩、栀子、薄荷、大黄、芒硝、甘草等药物。一项关于ALI的研究中，凉膈散可以辅助缓解脓毒症引起的ALI，同样在细胞实验中，凉膈散预处理的外泌体内miRNA-21的表达上调，支气管肺泡灌洗液中炎性标志物TNF-α和IL-6的表达以及炎性总蛋白的水平降低，显著缓解小鼠肺部组织的炎性细胞浸润和肺水肿程度，同时，通过PI3K/AKT通路减少巨噬细胞和肺泡上皮细胞凋亡[28]。

芍药醇是从牡丹皮、白芍根和野山药中提取的一种成分，具有抗炎和抗细胞增殖、抗氧化等的特性，广泛参与各项生理过程。金焕治等[29]的研究显示，芍药醇可以提高肺组织中miR-126水平，抑制炎症反应、氧化应激和细胞凋亡来减轻脓毒症ALI，增加抗氧化蛋白Nrf2表达，减少炎症蛋白高迁移率族蛋白B1（HMGB1）的表达，抑制凋亡蛋白Bcl-2。为临床中医药治疗脓毒症ALI提供理论依据。

6 结 语

外泌体miRNA作为脓毒症相关ALI的生物标志物，对其早期诊断具有重要意义，有助于改善患者的临床预后，对于脓毒症相关ALI的治疗具有良好的应用前景，但目前仍面临外泌体异质性强、提纯难度大、价格昂贵、操作时间长等挑战。外泌体提取方式的更新精炼是目前科研的重要方向。探寻与脓毒症ALI有关的miRNA及外泌体载体，研究其调控的复杂

的信号传导途径，充分发挥中医药在其中的特色优势，是未来研究的重要方向。

利益冲突 无

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收稿日期:2024-12-26 **编辑**:王娜娜