International Journal of Nanomedicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

How Extracellular Nano-Vesicles Can Play a Role in Sepsis? An Evidence-Based Review of the Literature

Xiaolin Jin[1], Haiyan Sun[2], Lina Yang[1,3]

[1]Department of International Physical Examination Center, The First Hospital of China Medical University, Shengyang, People's Republic of China; [2]Department of Endodontics, School of Stomatology, China Medical University, Shenyang, People's Republic of China; [3]Department of Geriatrics, The First Hospital of China Medical University, Shenyang, People's Republic of China

Correspondence: Haiyan Sun; Lina Yang, Email 13066784163@163.com; yanglina1984@163.com

International Journal of Nanomedicine downloaded from https://www.dovepress.com/
For personal use only.

Abstract: Sepsis is a systemic inflammatory reaction caused by infection. Severe sepsis can lead to multiple organ dysfunction, with a high incidence rate and mortality. The molecular pathogenesis of sepsis is complex and diverse. In recent years, with further study of the role of extracellular vesicles (EVs) in inflammatory diseases, it has been found that EVs play a dual role in the imbalance of inflammatory response in sepsis. Due to the great advantages such as lower toxicity, lower immunogenicity compared with stem cells and better circulation stability, EVs are increasingly used for the diagnosis and treatment of sepsis. The roles of EVs in the pathogenesis, diagnosis and treatment of sepsis were summarized to guide further clinical studies.

Keywords: extracellular vesicles, sepsis, inflammatory response, exosome, microvesicle

Introduction

Sepsis is a life-threatening disease, usually caused by the dysregulating host response to infection, resulting in multiple organ dysfunction or even death.[1–3] Although the mortality of sepsis has decreased to a certain extent with the strengthening of hemodynamic monitoring methods, the upgrading of intensive care measures and the early treatment of infection sources, it is still the leading cause of death around the world.[4,5] There were about 48.9 million new cases of sepsis and 11 million people died of sepsis in 2017 according to the latest study.[6] Thus, it seems that sepsis warrants more effective early diagnosis and treatment.

At present, a growing body of studies shows that the immune system plays a key role in sepsis.[7,8] Invading pathogens cause a pathological syndrome characterized by persistent excessive inflammatory activation and immunosuppression.[9] Therefore, stem cells, especially mesenchymal stem cells (MSCs), could regulate adaptive immune response and innate immune response.[10] The excessive inflammatory response can be inhibited by reducing pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α).[11–13] However, the clinical application of stem cells has many restrictions: on the one hand, they are difficult to cultivate in large quantities; on the other, the side effect of stem cells needs further research, including investigation of potential carcinogenicity and multi-differentiation. In addition, stem cell transplantation is not simply cell replacement, stem cells can be cleared by liver, spleen and lung, only about 1% of transplanted stem cells reach the target organization.[14,15] Of note, studies have shown that extracellular vesicles (EVs) are the key effectors of stem cell function.[16] Low immunogenicity and selective aggregate in acute injury and inflammation sites make EVs a promising therapy for sepsis.[17]

EVs are lipid bilayer-enclosed vesicles and secreted by various mammalian cells under physiological conditions and various disease states.[18] EVs can be divided into three main subtypes according to their biogenesis and size, including exosomes (Exos), microvesicles (MVs), and apoptotic bodies.[19] Various bioactive substances are contained in EVs, such as intracellular proteins, nucleic acids (DNA and RNA), lipids and metabolites, which can mediate intercellular communication and affect the biological functions of receptor cells.[20]

EVs have advantages such as low toxicity, low immunogenicity and more stable in blood circulation.[21] Therefore, as a choice of cell therapy, EVs have been proven to play an important role in many diseases, including malignant tumors, sepsis, cardiovascular diseases, and autoimmune diseases.[22–25] The influence of EVs on the immune system, including antigen

Received: 22 June 2023
Accepted: 8 October 2023
Published: 16 October 2023

© 2023 Jin et al. This work is published and licensed by Dove Medical Press Limited. The full terms of this license are available at https://www.dovepress.com/terms.php and incorporate the Creative Commons Attribution – Non Commercial (unported, v3.0) License (http://creativecommons.org/licenses/by-nc/3.0/). By accessing the work you hereby accept the Terms. Non-commercial uses of the work are permitted without any further permission from Dove Medical Press Limited, provided the work is properly attributed. For permission for commercial use of this work, please see paragraphs 4.2 and 5 of our Terms (https://www.dovepress.com/terms.php).

presentation, maturation and differentiation of immune cells, and the application as a drug carrier for immunotherapy have been extensively studied.[26,27] EVs may have promising clinical value as an important target and approach for the treatment of sepsis. Therefore, we reviewed the potential role of EVs in the pathogenesis of sepsis and summarized the diagnosis and efficacy in the treatment of sepsis.

What is the Role of Extracellular Vesicles in Sepsis?

The pathogenesis of sepsis is both complicated and dynamic and mainly includes imbalance of inflammatory response, immune dysfunction, abnormal coagulation, mitochondrial damage and autophagy. The imbalance of inflammatory response is the most predominant pathogenesis of sepsis, and an increasing number of studies have demonstrated that EVs play dual roles, both pro-inflammatory and anti-inflammatory, during the inflammatory response to sepsis. Thus, we concluded the important studies regarding inflammatory response in sepsis of EVs from various cell sources, such as tissue cells, immune cells, and others (Table 1).

The possible pro-inflammatory effect of tissue cell-derived EVs in multiple sepsis models has been reported by numerous studies. In sepsis-associated encephalopathy (SAE) rat model induced by cecal ligation and puncture (CLP), Xi et al found that intestinal epithelial cell (IEC)-derived Exos could induce M1 polarization in mesenteric lymph nodes (MLNs) and increase the level of circulating IL-1β, thus aggravating the damage to hippocampal neurons.[28] Balusu et al also suggested that miR-146a and miR-155 in EVs derived from choroid plexus epithelium (CPE) enhanced the transcription of the inflammatory gene, such as IL-1β, TNF, IL-6, NOS2, and NF-kB, which positively promoted the secretion of IL-6, IL-1β, and TNF in cerebrospinal fluid (CSF).[29] Lin et al concluded that brain-derived EVs also increased the production of pro-inflammatory mediators and induced lung, liver and kidney injury.[30] Another research by Liu et al showed that miR-92a-3p contained within alveolar epithelial cell (AEC)-derived Exos could activate alveolar macrophages (AMs) and activate the nuclear transcription factor-kB (NF-kB) signaling pathway in AMs by inhibiting the expression of PTEN.[31] This process increased the expression of pro-inflammatory cytokines and exacerbated lung injury. In addition, the Exos derived from hepatocytes contained much high-mobility group box-1 (HMGB1), which is considered to be an important late inflammatory mediator.[32,44]

EVs derived from immune cells also play an important role in the pathogenesis of sepsis inflammation. As a kind of immune cells, mononuclear-macrophage cells can kill and phagocytize a variety of pathogens in a non-specific manner, present antigens, and produce cytokines; the effect of EVs derived from mononuclear-macrophage cells in sepsis inflammation has been found in several studies. Li et al proved that the Exos released from macrophages could be internalized by neighboring macrophages and promote the release of TNF-α.[33] A recent study also showed that macrophage-derived EVs highly expressed CXCL2, which contributed to the recruitment of neutrophils in the liver and the EVs also activated neutrophils through CXCR2/PKC/NOX4 pathway, thereby promoting inflammatory action.[34] Sui et al proposed that Exos from macrophages promoted the release of pro-inflammatory factors such as TNF-α, IL-1β, and IL-6 in a sepsis-induced acute lung injury mouse model.[35] Dendritic cells derived Exos with the brain targeting peptide decoration can help access the blood–brain barrier, whereas these modified Exos increase the immune response of the target brain endothelium.[45,46] In addition, the pro-inflammatory effect of monocyte-derived Exos in sepsis-induced myocardial dysfunction has been reported by Wang et al.[36] They found monocyte-derived Exos delivered the TXNIP-NLRP3 complex to local macrophages, which could cleave the precursors of IL-1β and IL-18 and produce functional IL-1β and IL-18.[36]

Furthermore, the pro-inflammatory effect of EVs derived from plasma, serum or other body fluids has been confirmed by previous studies. Xu et al found the miR-126-3p, miR-122-5p, miR-146a-5p, miR-145-5p, miR-26a-5p, miR-150-5p, miR-222-3p, and miR-181a-5p in plasma derived EVs induced inflammation by promoting IL-6, TNF-α, IL-1β, and monocyte inflammatory protein-2 (MIP-2) released and neutrophil migration.[37] Li et al proposed that plasma EVs enriched with miR-210-3p promoted THP-1 macrophage inflammation and BEAS-2B cell apoptosis and inhibited autophagy by downregulating ATG7 targeted gene expression.[38] MiR-1-3p in plasma-derived Exos was confirmed to increase IL-1β and inducible nitric oxide synthase (iNOS) pro-inflammatory factor level by reducing the expression of the target gene stress-associated endoplasmic reticulum protein 1 (SERP1).[39] Jiang et al found miR-155 could promote inflammation by activating macrophages in the sepsis-related acute lung injury (ALI) mouse model.[40] In vitro, they found M1 macrophages proliferated significantly by targeting SHIP1, and the amount of pro-inflammatory cytokines, such as IL-6 and TNF-α, increased by targeting SOCS1.[40] In addition, Murao et al proved that the Exos from sepsis serum

Table 1 The Role of EVs in Sepsis Pathogenesis

Effect	Involved Organ	Model	Animal	Source of EVs/Exos/MVs	Cargo	Mechanisms	Refs.
Pro-inflammatory	Brain	CLP	Wistar rats	Intestinal epithelial cell-Exos		M1 polarization, circulating IL-1β↑	[28]
Pro-inflammatory	Brain	LPS	C57BL/6 mice	Choroid plexus-EVs	miR-146a, miR-155	IL-6, IL-1β, TNF↑	[29]
Pro-inflammatory	Lung, liver and kidney	CLP	SD rats	Brain-EVs		IL-1β, IL-6 and TNF-α↑	[30]
Pro-inflammatory	Lung	LPS	SD rats	Alveolar epithelial cell-Exos	miR-92a-3p	PTEN↓, alveolar macrophages and the NF-κB pathway↑	[31]
Pro-inflammatory		LPS	C57BL/6J mice	Hepatocyte-Exos		HMGB1↑	[32]
Pro-inflammatory	Lung	LPS	C57BL/6 mice	Macrophage-Exos		TNF-α↑	[33]
Pro-inflammatory		CLP	C57BL/6 mice	Macrophage-EVs		Recruit neutrophils, activate the CXCR2/PKC/NOX4 pathway↑	[34]
Pro-inflammatory	Lung	LPS	C57BL/6 mice	Macrophage-Exos		TNF-α, IL-1β, and IL-6↑	[35]
Pro-inflammatory	Heart	LPS	C57BL/6 mice	Monocyte-Exos	TXNIP-NLRP3 complex	Cleavage of inactive IL-1β and IL-18 in the macrophages↑	[36]
Pro-inflammatory		LPS	C57BL/6J mice	Plasma-EVs	miR-126-3p, miR-122-5p, miR-146a-5p, miR-145-5p, miR-26a-5p, miR-150-5p, miR-222-3p, and miR-181a-5p	IL-6, TNF-α, IL-1β, MIP-2↑, peritoneal neutrophil migration↑	[37]
Pro-inflammatory	Lung	CLP	mice	Plasma-EVs	miR-210-3p	IL-1β, IL-6 and TNF-α↑	[38]
Pro-inflammatory	Lung	CLP	SD rats	Plasma-Exos	miR-1-3p	SERP1↓, IL-1β and iNOS↑	[39]
Pro-inflammatory	Lung	LPS	BALB/c mice	Serum-Exos	miR-155	IL-6 and TNF-α↑	[40]
Pro-inflammatory		CLP	C57BL/6 mice	Serum-Exos		TNF-α, IL-6↑	[41]
Anti-inflammatory	Lung and liver	LPS	C57BL/6 mice	Serum-Exos		Differentiation of Th1/Th2 cells, lymphocyte cells proliferation and migration↑, TNF-α and IL-10↓	[42]
Anti-inflammatory	Intestines	CLP	BALB/c mice	Gut epithelial cell-EVs		TNF-α and IL-17A↓	[43]

Notes: ↑ Represents an increase or promotion; ↓ Represents a decrease or inhibition.
Abbreviations: EVs, extracellular vesicles; Exos, exosomes; MVs, microvesicles; CLP, cecal ligation and puncture; LPS, lipopolysaccharide; HMGB1, high-mobility group box-1.

https://doi.org/10.2147/IJN.S427116 DovePress

express a large amount of extracellular cold-inducible RNA-binding protein (eCIRP), which could induce the production of IL-6 and TNF-α and the migration of neutrophils.[41]

EVs not only have pro-inflammatory effects in the pathogenesis of sepsis but also have anti-inflammatory effects confirmed by some studies in recent years. Gao et al found that the Exos derived from sepsis mice serum can not only promote Th1/Th2 cell differentiation but also promote the proliferation and migration of lymphocytes. After the pretreatment of Exos from sepsis serum, both TNF-α and IL-10 declined, but TNF-α declined more significantly, which may be responsible for the anti-inflammatory effect of the Exos.[42] Appiah et al concluded that the EVs derived from gut epithelial cell in septic mice reduced intestinal mucositis by inhibiting TNF-α and IL-17A expression.[43] So far, the studies on the anti-inflammatory mechanism of EVs in the pathogenesis of sepsis are not clear enough, and both pro-inflammatory and anti-inflammatory effects in the inflammatory process of sepsis warrant further exploration.

How Local Extracellular Vesicles Can Treat Sepsis?

EVs are involved in intercellular communication and have the advantages of low toxicity, low immunogenicity and circulation stability. Therefore, EVs are increasingly becoming the focus of sepsis treatment. Here, we summarized the therapeutic effect of EVs on different organ injuries induced by sepsis (Table 2 and Figure 1).

How Local Extracellular Vesicles Can Treat Sepsis-Induced Lung Injury?

Lung injury is one of the common complications of sepsis, which can develop into acute respiratory distress syndrome (ARDS) with severe clinical symptoms, leading to a mortality rate of 40%.[66,67] The therapeutic role of EVs has been verified by several studies on sepsis-induced lung injury in mouse or rat models.

MSCs are the most common source of EVs in sepsis treatment. Exos derived from bone marrow mesenchymal stem cells (BMMSCs) inhibit the expression of hypoxia-inducible factor 1α (HIF-1α), which is anti-inflammation by suppressing M1 polarization while promoting M2 polarization.[47] Similarly, Liu et al found miR-191 in BMMSC-EVs attenuated macrophage inflammatory response by suppressing death-associated protein kinase 1 (DAPK1) translation.[48] In addition, Chen et al proposed that small EVs derived from human umbilical cord mesenchymal stromal cells (huMSCs) upregulated antioxidant enzymes IκB and inhibited mitogen-activated protein kinase/nuclear factor kappa B (MAPK/NF-κB) pathway, thus reducing microvascular permeability and suppressing neutrophil infiltration in lung tissue.[49] Deng et al reported that Exos derived from adipose tissue-derived mesenchymal stem cells (ADMSCs), BMMSCs, and huMSCs can all inhibit macrophage glycolysis, attenuate pro-inflammatory factor synthesis, and ameliorate lung injury. They further compared the Exos from different MSCs and ADMSC-Exos showed greater protection efficacy than the other two.[50] Zhou et al verified that Exos derived from endothelial progenitor cells (EPC) reduced cytokine and chemokine levels in plasma by promoting miR-126-3p and miR-126-5p release in CLP sepsis model,[51] and they further found miR-126-3p and miR-126-5p inhibited the delivery of HMGB1 and vascular cell adhesion molecule 1 (VCAM1) to ameliorate inflammatory and attenuate vascular permeability in the lung.[51]

Apoptosis of alveolar epithelial cells has been suggested as a crucial pathogenesis of ALI, inhibiting alveolar epithelial cell apoptosis is conducive to recovery of lung function.[68] Jiang et al found miR-125b-5p in cerebral microvascular endothelial cell-derived Exos suppressed the expression of topoisomerase II alpha (TOP2A) to inhibit inflammatory factor infiltration and alleviate apoptosis in the lung.[52] Mizuta et al found that the Exos derived from ADMSC activated PI3K/Akt pathway by transferring miR-126, thus reducing the apoptosis of vascular endothelial cells.[53] Similarly, lncRNA-p21 in BMMSC-Exos inhibited apoptosis of pulmonary epithelial cells by promoting sirtuin 1 (SIRT1) expression and downregulating miR-181.[54] Shen et al reported that circular RNA (circ)-Fryl in ADMSC-Exos inhibited the expression of inflammatory factors and apoptosis of alveolar epithelial cells by regulating miR-490-3p/SIRT3 pathway.[55]

Coagulopathies also influence the development and prognosis of sepsis to a significant extent.[69] Cointe et al certificated that granulocyte derived MVs with high plasmin generation capacity (PGC) reduced clot formation in lung and kidney by expressing a higher level of uPA receptor (uPAR) on the surface of MVs.[56]

Table 2 Therapeutic Effects of Native EVs in Sepsis Induced Organ Injury

Involved Organ/ Disease	Model	Animal	In vitro Model	Injection	Dosage	Source of EVs/Exos/ MVs	Cargo in EVs	Mechanism	Effect	Refs.
Lung injury	LPS	C57BL/6 mice	MH-S cells	Intraperitoneal	50mg Exos	BMMSC-Exos		HIF-1α↑	Reduce the inflammatory response	[47]
Lung injury			THP-1 cells			BMMSC-EVs	miR-191	DAPK1↓	Attenuate macrophages inflammatory response	[48]
Lung injury	CLP	C57BL/6 mice		Tail vein	30μL MSC sEVs	huMSC-EVs		Anti-oxidative enzymes↑, MAPK/NF-κB pathway↓	Improve pulmonary microvascular permeability, inhibit neutrophil infiltration in lung tissue	[49]
Lung injury	LPS	C57BL/6 mice	RAW264.7 cells	Intravenous	100μg Exos	ADMSC-Exos, BMMSC-Exos, huMSC-Exos			Inhibit glycolysis of macrophages and reduce the synthesis of pro-inflammatory factors	[50]
Lung injury	CLP	CD-1 mice	HMVECs	Intravenous	2 mg protein/kg	EPC-Exos	miR-126-3p, miR-126-5p	IL-6, IFNγ, TNF-α, HMGB1 and VCAM1↓	Reduce the inflammatory response, attenuate vascular permeability	[51]
Lung injury	CLP	BABL/c mice		Tracheal instillation	80 μg Exos	Cerebral microvascular endothelial cell-Exos	miR-125b-5p	Topoisomerase II alpha↓	Inhibit inflammatory factors infiltration and alleviate apoptosis	[52]
Lung injury	Histone infusion model	C57BL/6 N mice	HUVECs	Intravenous	3×10^5 cells ADMSC	ADMSC-Exos	miR-126	PI3K/Akt pathway	Suppress endothelial apoptosis	[53]
Lung injury	LPS	C57BL/6 mice	MLE-12 cells			BMMSC-Exos	lncRNA-p21	SIRT1↑, miR-181↓	Inhibit apoptosis of pulmonary epithelial cells	[54]
Lung injury	CLP	mice	AEC	Tail vein	200μg Exos	ADMSC-Exos	circ-Fryl	miR-490-3p/ SIRT3 pathway	Inhibit the expression of inflammatory factors and apoptosis of alveolar epithelial cells	[55]
Lung and kidney injury	CLP	CD-1 mice		Tail vein	10^7 MVs	Granulocyte-MVs		uPAR↑	Reduce clot formation	[56]
Myocardial injury	CLP	C57BL/6 mice	cardiomyocytes	Tail or jugular vein	2 μg/g body weight Exos	BMMSC-Exos	miR-223	Sema3A and Stat3↓	Reduce the inflammatory response and suppress cardiomyocyte apoptosis	[57]

(*Continued*)

https://doi.org/10.2147/IJN.S427116 DovePress

Table 2 (Continued).

Involved Organ/ Disease	Model	Animal	In vitro Model	Injection	Dosage	Source of EVs/Exos/ MVs	Cargo in EVs	Mechanism	Effect	Refs.
Myocardial injury	CLP	KM mice		Tail vein	2 μg Exo/g	BMMSC-Exos	miR-141	PTEN/β-catenin axis	Reduce the inflammatory response and cardiomyocyte apoptosis	[58]
Myocardial injury	LPS	C57BL/6 mice	cardiomyocyte HL-1	Tail vein		M2 macrophages-Exos	miR-24-3p	Tnfsf10↓	Reduce the inflammatory response and cardiomyocyte apoptosis	[59]
Myocardial injury	CLP	C57BL/6 mice	RAW264.7 cells			HUVEC-Exos	HSPA12B	NF-κB activation and nuclear translocation↓	Attenuate macrophages inflammatory response	[60]
Acute kidney injury	CLP	C57/BL6 mice		Tail vein	100 μg Exos	ADMSC-Exos		SIRT1 pathway	Inhibit inflammation, apoptosis and improve microcirculation in kidney	[61]
Acute kidney injury	CLP	C57BL/6 mice	BMDMs	Tail vein		BMMSC-Exos	miR-27b	JMJD3/NFκB/ p65 axis	Reduce pro-inflammatory cytokines	[62]
Acute kidney injury	CLP	C57Bl/6 mice		Tail vein	120 μg Exos	huMSC-Exos	miR-146b	IRAK1↓, NF-κB↓	Inhibit inflammation, renal tubular cells apoptosis, and improve kidney function	[63]
Acute kidney injury	LPS	SD rats			1×10^5 Exos and 5×10^5 Exos	ADMSC-Exos, BMMSC-Exos			Inhibit inflammation, oxidative stress and apoptosis	[64]
Acute kidney injury	CLP	C57/BL6 mice	HK2 cells	Intravenous	2 mg/kg EVs	EPC-EVs	miR-93-5p	KDM6B/ H3K27me3/ TNF-α axis	Inhibit inflammation, apoptosis, vascular leakage in kidney, and reduce organ damage	[65]

Notes: ↑ represents an increase or promotion; ↓ represents a decrease or inhibition.

Abbreviations: EVs, extracellular vesicles; Exos, exosomes; MVs, microvesicles; LPS, lipopolysaccharide; HIF-1α, hypoxia-inducible factor 1α; CLP, cecal ligation and puncture; sEVs, small extracellular vesicles; HMVECs, human microvascular endothelial cells; EPC, endothelial progenitor cells; HUVECs, human umbilical vein endothelial cells; SIRT1, sirtuin 1; AEC, alveolar epithelial cell; uPAR, urokinase plasminogen activator receptor; BMDMs, bone marrow-derived macrophages.

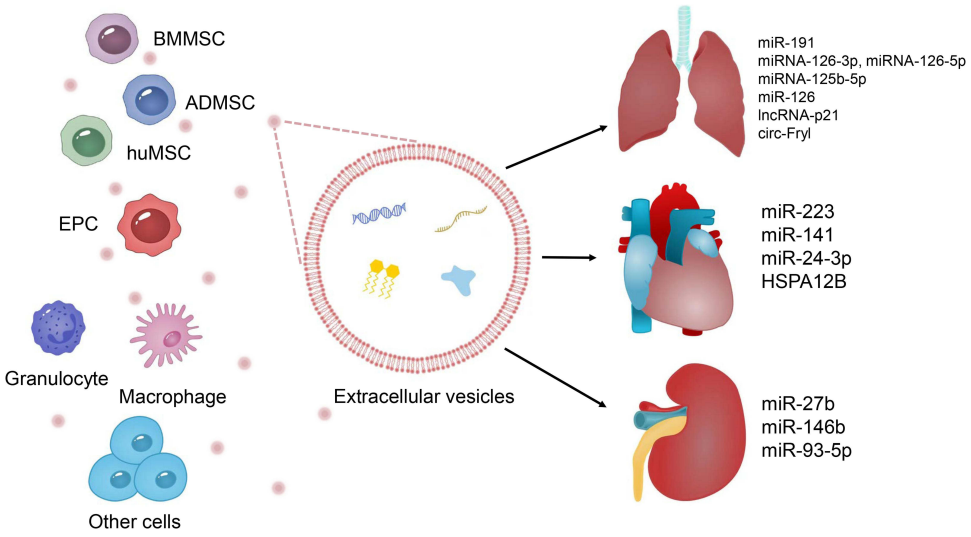

Figure 1 Therapeutic effects of native EVs in sepsis-induced organ injury.
Abbreviations: BMMSC, bone marrow mesenchymal stem cell; ADMSC, adipose tissue-derived mesenchymal stem cell; huMSC, human umbilical cord mesenchymal stromal cell; EPC, endothelial progenitor cell.

How Local Extracellular Vesicles Can Treat Sepsis-Induced Myocardial Injury?

Myocardial injury is one of the severe complications of sepsis and is linked to a poor outcome.[70,71] The mortality rate increased significantly when complicated with myocardial injury in patients with sepsis.[72] Therefore, reducing myocardial injury and promoting cardiac function recovery is helpful to reduce sepsis-associated mortality.

Wang et al suggested that BMMSC-Exos downregulated Sema3A and Stat3 by transferring miR-223 to cardiomyocytes, further reducing the inflammatory response and suppressing cardiomyocyte apoptosis.[57] Pei et al confirmed that miR-141 in BMMSC-Exos had the same myocardial protection effect by regulating PTEN/β-catenin axis.[58] A more recent study by Sun et al found the level of miR-24-3p was high in M2 macrophages-derived Exos, which played a protective role in myocardial cells and improved the cardiac function after sepsis injury by downregulating the expression of tumor necrosis factor superfamily member 10 (Tnfsf10).[59] Tu et al reported that the heat shock protein A12B mainly expressed in human umbilical vein endothelial cells (HUVEC)-Exos inhibited NF-κB activation and nuclear translocation in macrophages, thus attenuating the pro-inflammatory effect of macrophages.[60]

How Local Extracellular Vesicles Can Treat Sepsis-Induced Acute Kidney Injury?

About 60% of sepsis patients suffer from acute kidney injury,[73] which was considered as one of the common complications of sepsis.[74] The mortality and number of days of hospitalization of sepsis patients are closely related to acute kidney injury.[75]

Gao et al suggested that ADMSC-Exos inhibited inflammation, apoptosis and improved microcirculation in sepsis induced acute kidney injury model by activating the SIRT1 pathway.[61] Sun et al verified that miR-27b in BMMSC-Exos regulated the JMJD3/NFκB/p65 axis to suppress the expression of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6.[62] MiR-146b in huMSC-Exos also played an important role in relieving kidney injury and improving kidney function via downregulating interleukin-1 receptor-associated kinase (IRAK1) and inhibiting NF-κB activation.[63] A recent study by Zhang et al concluded that both ADMSC-Exos and BMMSC-Exos could attenuate inflammation, oxidative stress, and apoptosis in the sepsis rat model. In addition, they further compared the effect of these Exos and found that the protective effect of ADMSC-Exos was better than that of BMMSC-Exos.[64] In addition, He et al found that miRN-93-5p in EPC-EVs inhibited inflammation, apoptosis, and vascular leakage in kidney via the KDM6B/H3K27me3/TNF-α axis.[65] They further found that EPC-EVs alleviated the damage to kidney, liver and lung tissue caused by histological staining.[65]

How Engineered Extracellular Vesicles Can Treat Sepsis?

Although native EVs showed considerable efficacy in treating sepsis, engineered EVs received more attention in recent years due to their increased ability in sepsis target treatment. Here, we concluded several modification methods of EVs in sepsis treatment (Table 3).

How Genetic Modified Extracellular Vesicles Can Treat Sepsis?

Genetic modification of donor cells can be a promising approach for sepsis treatment. The genetic modified EVs presented anti-inflammatory, immunomodulatory and anti-apoptotic by overexpressing or knocking down specific genes or proteins.

Zhou et al transfected Pink1 siRNA into huMSC, which increased the expression of PTEN-induced putative kinase 1 (PINK1) in huMSC-Exos, and found that restoration of mitochondrial calcium efflux in cardiomyocytes provided a cardioprotective effect by modulating the PINK1-PKA-NCLX axis.[76] Li et al engineered MSC-Exos to overexpress CircRTN4, which can regulate miR-497-5p/MG53 axis to reduce inflammation and suppress apoptosis in cardiomyocytes.[77]

In addition, EVs with gene knockout or suppressed protein expression can also be used for sepsis treatment. Ding et al transferred siCCR2 to silence C–C receptor 2 (CCR2) in macrophage-derived EVs; these modified EVs eliminated the chemotaxis of mononuclear-macrophage cells to C–C ligand 2 (CCL2) and decreased the mobilization of monocytes in the spleen.[78]

How Extracellular Vesicles Can Serve as Delivery vehicles for the Treatment of Sepsis?

Proteins, genes, and drugs could be loaded selectively in EVs; the cargo was then delivered to target sites to exert therapeutic effects. Sun et al first used EVs as drug-delivery vehicles for the treatment of sepsis, and they found EL-4 derived Exos could specifically deliver curcumin to the inflamed tissues and exert anti-inflammatory effects in lung tissue by downregulating $CD11b^{+}Gr\text{-}1^{+}$ cell levels.[79] Gao et al took advantage of nitrogen cavitation for the rapid preparation of EVs and confirmed that these neutrophil-derived EVs subjected to nitrogen cavitation had the same function for drug delivery as native EVs, which inhibited neutrophil infiltration in the lung, liver and kidney tissues by loading piceatannol.[80] Choi et al used EXPLOR technology to load super-repressor IkB (srIkB) into human embryonic kidney 293T cell line-derived Exos, which were shown to inhibit the inflammatory response and inhibit tubular epithelial cell apoptosis in both LSP sepsis and CLP sepsis models.[81]

How Does Pretreatment of Extracellular Vesicles Treat Sepsis?

Precondition is a common EV-modification strategy that promotes EVs secretion, enhances circulatory stability, and regulates gene and protein expression in vesicles, thereby enhancing the treatment of disease. Multiple studies in recent years examined different pretreatments of EVs and found that EVs could exert antisepsis effects through multiple pathways.

For example, Kumagai et al pretreated neutrophils with LL-37 to promote EVs release and improve antimicrobial activity.[82] Song et al proved that the Exos isolated from huMSC stimulated by IL-1β could upregulate miR-146a, thus inducing M2 polarization and reducing the inflammatory response in the septic mouse model.[83] A recent study by Yao et al also pretreated MSC with IL-1β, they found miR-21 in Exos increased significantly and found the same result as Song et al.[84] Furthermore, Pan et al conducted limb remote ischemic preconditioning (rIPC) in C57BL/6 mice, they found miR-21 increased significantly in the Exos. MiR-21 as an anti-apoptotic miRNA could both suppress apoptosis in the kidney and reduce the production of pro-inflammation factors by regulating PDCD4/NF-κB and PTEN/AKT pathways.[85] They also verified the same effect of Exos derived from C2C12 cells after hypoxia and reoxygenation preconditioning.[85] Zhu et al used the same pretreatment strategy as Pan et al and found miR-142-5p reduced the level of pro-inflammatory factors and neutrophil infiltration, it also relieved pulmonary oedema via the PTEN/PI3K/Akt axis.[86] In addition, ADMSC subjected to hypoxic preconditioning promoted mmu_circ_0001295 expression in Exos, which attenuated renal vascular leakage and inflammation in kidney and improved kidney function.[87]

Table 3 Therapeutic Effects of Engineered EVs in Sepsis

Modifications	Involved Organ/ Disease	Sepsis Models	Source of EVs/Exos/MVs	Reengineering Routes	Target	Effect	ref.
Genetic modification	Myocardial injury	CLP	huMSC-Exos	Transfection to overexpress Pink1	PINK1-PKA-NCLX axis	Recover cardiomyocyte mitochondrial calcium efflux	[76]
Genetic modification	Myocardial injury	CLP	MSC-Exos	Transfection to overexpress CircRTN4	miR-497-5p/MG53 axis	Inhibit inflammation, suppress cardiomyocyte apoptosis and oxidative stress	[77]
Genetic modification	Lung	CLP	Macrophage-EVs	Transfect siCCR2 to silence CCR2		Inhibit the chemotaxis of mononuclear-macrophage cells to CCL2 and the mobilization of monocytes in the spleen	[78]
Delivery vehicles	Lung	LPS	EL-4-Exos	Deliver curcumin	$CD11b^{+}Gr\text{-}1^{+}$ cells↓	Inhibit inflammation	[79]
Delivery vehicles	Lung, liver, kidney	LPS	Neutrophil-EVs	Deliver piceatannol		Inhibit inflammation	[80]
Delivery vehicles	Kidney	CLP/LPS	HEK293T cells-Exos	Deliver srIκB		Reduce inflammatory response, inhibit renal tubular epithelial cells apoptosis	[81]
Precondition		CLP	Neutrophil-EVs	Pretreat neutrophil with LL-37		Promote EVs release, improve antimicrobial activity	[82]
Precondition	Liver, lung, kidney	CLP	huMSC-Exos	Pretreat huMSC with IL-1β	miR-146a↑	Inhibit inflammation	[83]
Precondition	Liver	CLP	MSC-Exos	Pretreat MSC with IL-1β	miR-21↑	Inhibit inflammation, attenuate liver injury	[84]
Precondition	Kidney	CLP	Serum-Exos	rIPC	miR-21↑	Inhibit inflammation, suppress apoptosis	[85]
Precondition	Lung	LPS	Serum-EVs	rIPC	miR-142-5p↑	Inhibit inflammation, reduce pulmonary edema	[86]
Precondition	Kidney	CLP	ADMSC-Exos	Pretreat ADMSC with hypoxia	mmu_circ_0001295↑	Attenuate renal vascular leakage and inflammation, improve kidney function	[87]

Notes: ↑ represents an increase or promotion; ↓ represents a decrease or inhibition.
Abbreviations: EVs, extracellular vesicles; Exos, exosomes; MVs, microvesicles; CLP, cecal ligation and puncture; LPS, lipopolysaccharide; rIPC, remote ischemic preconditioning.

https://doi.org/10.2147/IJN.S427116

How Extracellular Vesicles Can Help Diagnose Sepsis?

Early clinical intervention may improve outcomes and reduce the mortality of patients with sepsis.[88] Consequently, recent studies focus on the early diagnosis of sepsis. To date, conventional biomarkers for the diagnosis of sepsis were C-reactive protein, procalcitonin (PCT) and L-lactate.[89] Except these, novel biomarkers, such as heparin-binding protein,[90] presepsin,[91,92] iNOS[93] have been applied in the early diagnosis of sepsis, but their diagnostic value is controversial.[94,95] Of note, EVs might also play an important role in the early diagnosis, condition monitoring, and prognosis of sepsis.

Increased numbers of EVs have been suggested as an early marker for sepsis diagnosis in several studies.[96–98] In addition, elevated EVs in plasma are also strongly associated with mortality in patients with sepsis.[99,100]

EVs were actively secreted by a variety of cells, and the surface proteins were similar to donor cells. The association between membrane protein on the surface of EVs and the prognosis of sepsis has been certified by studies. For instance, higher CD63-positive Exos indicated severe organ failure and higher mortality in sepsis patients.[101] CD14-positive EVs derived from bronchoalveolar lavage fluid were correlated with the severity and mortality of sepsis-induced ARDS.[102] Annexin V-positive, CD45-positive, CD16-positive, CD14-positive, and CD41-positive EVs were increased significantly in case of death, which could be used as biomarkers for the prognosis of sepsis.[103]

In addition, bioactive substances contained in EVs, such as nucleic acids and protein, may be used as biomarkers for sepsis diagnosis and prognosis. MiR-483-3p and Let-7d-3p in plasma-derived EVs were related to the severity of sepsis and identified as biomarkers for early diagnosis.[104] In a recent clinical study, Ye et al found that the level of miR-150-5p from neutrophil-derived EVs in sepsis-induced cardiomyopathy patients was significantly lower than that in a healthy person and septic patients without septic cardiomyopathy; thus, miR-150-5p might be a predictor of septic cardiomyopathy.[105] The prognosis of sepsis could also be predicted by the presence and amount of miRNA in Exos, such as miR-125b-5p and miR-27b-3p.[106] Hermann et al regarded miR-1246 as the biomarker for the risk of community-acquired pneumonia complicated with sepsis.[107] DNA methyltransferase (DNMT) mRNA load in plasma EVs might be used to diagnose septic shock.[98] The levels of hsa_circRNA_104484 and hsa_circRNA_104670 in serum-derived Exos of sepsis patients were different from that of healthy people, which were considered as diagnostic biomarkers of sepsis.[108] Except for nucleic acids contained in EVs, proteins such as activating transcriptional factor 3 (ATF3), iNOS, were also helpful for early diagnosis.[109,110] Protein SPTLC3 was closely related to the development of sepsis, thus it might be useful to monitor the progression of sepsis.[111]

How Nano-Medicinal Materials Can Help Diagnose and Treat Sepsis?

There are still some deficiencies in EVs limiting the application in clinical practice: low production yield, presence of unwanted cargos, and rapid elimination.[112,113] To overcome these problems, nano-medicinal materials were widely used for the treatment of disease since the 1990s.[114,115] Nanoparticles (NPs) were synthesized from organic or inorganic particles, with a size of 1 to 100 nm.[116] In recent years, the importance of NPs in the diagnosis and treatment of sepsis has also received more attention. In this section, we classified NPs according to their structure and composition and summarized the therapeutic effects of different classification of NPs on sepsis (Figure 2).

Lipid NPs were the first nano-medicinal materials used as a durg-delivery system in clinical practice.[117] In recent years, Hou et al delivered the antimicrobial peptide and cathepsin B (AMP-CatB) mRNA to macrophages by using vitamin C lipid nanoparticles (V_CLNPs), which enhanced the bactericidal activity of macrophages and played a role in sepsis caused by multi-drug resistant (MDR) bacteria.[118] Schrijver et al loaded the fusion protein of apolipoprotein A1 and IL-4 into lipid NPs and found these lipid NPs could overcome immunoparalysis in septic mice.[119] As an early discovered lipid NPs, liposomes were proposed as an effective drug-delivery system. Chen et al suggested that lanosterol-containing liposomes (LAN-L) had anti-inflammatory effects in sepsis and reduced mortality in septic mice.[120]

Inorganic NPs are composed of a metal core and an organic layer covering the surface of the core. Due to their special structure, they are considered to be a good choice for sepsis diagnosis. NPs in electrochemical immunosensor can increase the detection sensitivity of sepsis biomarkers such as PCT.[121–123] NPs were also used in the biosensor for the detection of IL-6.[123–126] For MMP-9 detection, Alekhmimi et al used peptide-magnetic NP conjugates in the biosensor.[127] In addition, inorganic NPs also help for sepsis treatment. Gold nanoparticles (AuNP) that have anti-inflammatory and antioxidant effects were used to treat inflammatory diseases.[128] These effects were enhanced when the AuNP and n-acetylcysteine (NAC) association is present in

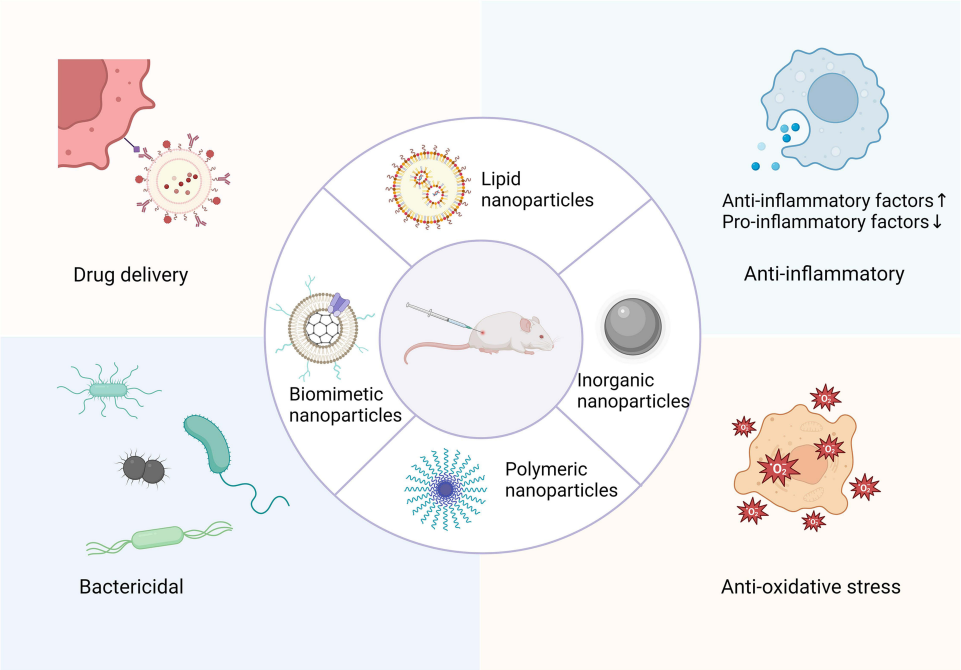

Figure 2 Therapeutic effects of nanoparticles in sepsis. Created with Biorender.com.

sepsis treatment.[129] Di Bella et al concluded that citrate-covered gold nanoparticles (cit-AuNP) had the same effect in the brain of septic mice.[130] In addition, Cu_2O-coated non-metallic core-shell selenium NPs were regarded as an effective therapeutic method for sepsis by consuming endogenous H_2S.[131] Wang et al found that zero-valent iron nanoparticles (nZVIs) could also alleviate sepsis induced myocardial injury through anti-inflammatory and antioxidant effects.[132] Wang et al concluded that sulfide-modified nZVIs had higher stability and more myocardial protective efficacy than nZVIs.[133] Inorganic NPs were also played a role in drug delivery. Silver NPs loaded with resveratrol conferred better protective effect in liver injury caused by sepsis.[134]

The therapeutic effect of polymeric NPs in sepsis has become a focus of much research. Poly(lactic-co-glycolic acid) (PLGA) and poly(lactic acid) (PLA) were often used as polymeric NPs for treatment of sepsis due to their good biocompatibility and biodegradability. Yang et al loaded γ3-PLGA NPs with Sparfloxacin (SFX) and Tacrolimus (TAC), which conferred a protective effect in lung injury by inhibiting inflammatory and immune responses.[135] Reddy et al encapsulated moxifloxacin (MOX) in transferrin decorated PLGA NPs to reduce complicated intra-abdominal infection.[136] Moreover, silymarin (SM) loaded PLGA NPs could reduce inflammatory response by promoting M2 polarization.[137] MiR-223 could promote macrophage polarization; thus, Ding et al loaded miR-223 on cyclodextrin-based NPs to target M1 macrophages; they found that these NPs reduced inflammation by targeting Pknox1 and inhibiting the NF-κB signaling pathway.[138] Furthermore, as a natural polymer, chitosan (CS) also be used as a drug-delivery carrier in sepsis treatment. Teng et al synthesized an octenylsuccinic anhydride (OSA)-functionalized CS nanoformulation to strengthen the treatment of sepsis-induced lung injury.[139] Polymeric NPs can also treat sepsis through immune regulation. For example, Lasola et al synthesized immunomodulatory nanoparticles (iNPs) by PLA with either poly(vinyl alcohol) (PVA) or poly(ethylene-alt-maleic acid) (PEMA), and found that iNPs exert anti-inflammatory effect through the inhibition of NF-κB p65 phosphorylation.[140] In addition, Koda et al synthesized amphiphilic block copolymers by poly(ethylene glycol) (PEG) and hydrophobic poly(cysteine) (PCys). These block copolymers were used to increase the half-survival time of septic mice.[141]

Biomimetic NPs have been suggested as a promising novel treatment of sepsis by several recent studies. For example, EV-mimetic ghost nanovesicles had a 200-fold greater production yield than EVs, and could inhibit the release of IL-8 by targeting the delivery of dexamethasone to endothelial cells.[142] Exosome biomimetic NPs loading specific miRNA ratio alleviated organ injury of sepsis by suppressing inflammation and diffuse coagulation, which showed a greater

therapeutic effect than native Exos.[143] Park et al prepared a large number of EV-mimetic nanovesicles (NVs) derived from MSCs by serial extrusions and floating in a density gradient.[144] The septic mice were then injected with these NVs intraperitoneally, and Park et al found that NVs play an anti-inflammatory role by increasing the level of IL-10.[144] Molinaro et al found that leukosomes, derived from macrophage biomimetic NPs, can suppress the inflammatory response of endothelial cells by decreasing pro-inflammatory factors and increasing anti-inflammatory factors, thus prolonging the life span of septic mice.[145] In addition, NPs derived from fibroblast cell have anti-inflammatory and bactericidal effects in the treatment of sepsis.[146]

Future Perspectives

Although EVs have been confirmed by multiple studies to play an important role in the inflammatory response and have significant potential in the early diagnosis and treatment of sepsis, the limitation of EVs still needs further study.

In the study of the pathophysiological role of EVs in sepsis, the imbalance of inflammatory response is still the focus, but the pathogenesis of sepsis is complex, immune dysregulation, abnormal coagulation, and autophagy are increasingly well accepted. Sepsis is a continuous process, so there might be significant pathophysiological differences between the different stages thereof. Excessive systemic inflammation and cytokine storms are the main cause in the early stage of sepsis; however, immunosuppression plays an important role in the late stage of sepsis.[147,148] It is therefore necessary to explore the effect of EVs in other mechanisms and different stages of sepsis.

For review of current preclinical studies, small animals, such as mice and rats, are mainly used in sepsis model construction, and the diagnostic and therapeutic role of EVs confirmed by small animal model may be different from that in humans. The administrative route and dosage of EVs in various organ injury models are inconsistent, necessitating exploration of the effect of EVs in large animal sepsis models to define the most effective mode of administration in different organ injuries induced by sepsis.

Although NPs showed the potential in promoting transmembrane transport, prolonging circulation times, with easy large-scale preparation, there remain some limitations of NPs, such as their simple types of cargo delivery and drug resistance. At present, the treatment of sepsis with EVs or NPs remains focused on preclinical research. Perhaps combining the knowledge of these two fields will accelerate the clinical application of sepsis treatment.

Abbreviations

MSCs, mesenchymal stem cells; IL-1, interleukin-1; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; EVs, extracellular vesicles; Exos, exosomes; MVs, microvesicles; SAE, sepsis-associated encephalopathy; CLP, cecal ligation and puncture; IEC, intestinal epithelial cell; MLNs, mesenteric lymph nodes; CPE, choroid plexus epithelium; CSF, cerebrospinal fluid; AEC, alveolar epithelial cell; AMs, alveolar macrophages; NF-κB, nuclear transcription factor-κB; HMGB1, high-mobility group box-1; MIP-2, monocyte inflammatory protein-2; iNOS, inducible nitric oxide synthase; SERP1, stress-associated endoplasmic reticulum protein 1; ALI, acute lung injury; eCIRP, extracellular cold-inducible RNA-binding protein; ARDS, acute respiratory distress syndrome; BMMSCs, bone marrow mesenchymal stem cells; HIF-1α, hypoxia-inducible factor 1α; DAPK1, death-associated protein kinase 1; huMSCs, human umbilical cord mesenchymal stromal cells; MAPK/NF-κB, mitogen-activated protein kinase/nuclear factor kappa B; ADMSCs, adipose tissue-derived mesenchymal stem cells; EPC, endothelial progenitor cells; VCAM1, vascular cell adhesion molecule 1; TOP2A, topoisomerase II alpha; SIRT1, sirtuin 1; PGC, plasmin generation capacity; uPAR, uPA receptor; Tnfsf10, tumor necrosis factor superfamily member 10; HUVEC, Human umbilical vein endothelial cells; IRAK1, interleukin-1 receptor-associated kinase; PINK1, putative kinase 1; CCR2, C–C receptor 2; CCL2, C–C ligand 2; srIκB, super-repressor IκB; rIPC, remote ischemic preconditioning; DNMTs, DNA methyltransferases; ATF3, activating transcriptional factor 3; NPs, nanoparticles; AMP-CatB, antimicrobial peptide and cathepsin B; V_CLNPs, vitamin C lipid nanoparticles; MDR, multi-drug resistant; LAN-L, lanosterol-containing liposomes; AuNP, Gold nanoparticles; NAC, n-acetylcysteine; cit-AuNP, citrate-covered gold nanoparticles; nZVIs, zero-valent iron nanoparticles; PLGA, Poly(lactic-co-glycolic acid); PLA, poly(lactic acid); SFX, sparfloxacin; TAC, tacrolimus; MOX, moxifloxacin; SM, silymarin; CS, chitosan; OSA, octenylsuccinic anhydride; iNPs, immunomodulatory nanoparticles; PVA, poly(vinyl alcohol), PEMA, poly(ethylene-alt-maleic acid); PEG, poly(ethylene glycol); PCys, poly(cysteine); NVs, nanovesicles.

Acknowledgments

This work was supported by the National Natural Science Foundation of China and Natural Science Foundation of Liaoning Province. Thanks for the help provided by Biorender.com for drawing Figure 2, the agreement number is SE25WFJTC1.

Funding

This work was funded by the National Natural Science Foundation of China (Grant No. 81970663) and Natural Science Foundation of Liaoning Province (2022-MS-07), and the funding body played no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7):1303–1310. doi:10.1097/00003246-200107000-00002
2. Vincent JL, Opal SM, Marshall JC, et al. Sepsis definitions: time for change. *Lancet*. 2013;381(9868):774–775. doi:10.1016/S0140-6736(12)61815-7
3. Singh S, Evans TW. Organ dysfunction during sepsis. *Intensive Care Med*. 2006;32(3):349–360. doi:10.1007/s00134-005-0038-9
4. Rhee C, Klompas M. Sepsis trends: increasing incidence and decreasing mortality, or changing denominator? *J Thorac Dis*. 2020;12(Suppl 1):S89–s100. doi:10.21037/jtd.2019.12.51
5. Dupuis C, Bouadma L, Ruckly S, et al. Sepsis and septic shock in France: incidences, outcomes and costs of care. *Ann Intensive Care*. 2020;10(1):145. doi:10.1186/s13613-020-00760-x
6. Rudd KE, Johnson SC, Agesa KM, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the global burden of disease study. *Lancet*. 2020;395(10219):200–211. doi:10.1016/S0140-6736(19)32989-7
7. Venet F, Monneret G. Advances in the understanding and treatment of sepsis-induced immunosuppression. *Nat Rev Nephrol*. 2018;14(2):121–137. doi:10.1038/nrneph.2017.165
8. Rubio I, Osuchowski MF, Shankar-Hari M, et al. Current gaps in sepsis immunology: new opportunities for translational research. *Lancet Infect Dis*. 2019;19(12):e422–e436. doi:10.1016/S1473-3099(19)30567-5
9. van der Poll T, van de Veerdonk FL, Scicluna BP, et al. The immunopathology of sepsis and potential therapeutic targets. *Nat Rev Immunol*. 2017;17(7):407–420. doi:10.1038/nri.2017.36
10. Marigo I, Dazzi F. The immunomodulatory properties of mesenchymal stem cells. *Semin Immunopathol*. 2011;33(6):593–602. doi:10.1007/s00281-011-0267-7
11. Németh K, Leelahavanichkul A, Yuen PS, et al. Bone marrow stromal cells attenuate sepsis via prostaglandin E(2)-dependent reprogramming of host macrophages to increase their interleukin-10 production. *Nat Med*. 2009;15(1):42–49. doi:10.1038/nm.1905
12. Anderson P, Souza-Moreira L, Morell M, et al. Adipose-derived mesenchymal stromal cells induce immunomodulatory macrophages which protect from experimental colitis and sepsis. *Gut*. 2013;62(8):1131–1141. doi:10.1136/gutjnl-2012-302152
13. Gonzalez-Rey E, Anderson P, González MA, et al. Human adult stem cells derived from adipose tissue protect against experimental colitis and sepsis. *Gut*. 2009;58(7):929–939. doi:10.1136/gut.2008.168534
14. Mei SH, Haitsma JJ, Dos Santos CC, et al. Mesenchymal stem cells reduce inflammation while enhancing bacterial clearance and improving survival in sepsis. *Am J Respir Crit Care Med*. 2010;182(8):1047–1057. doi:10.1164/rccm.201001-0010OC
15. Eiro N, Fraile M, González-Jubete A, et al. Mesenchymal (Stem) stromal cells based as new therapeutic alternative in inflammatory bowel disease: basic mechanisms, experimental and clinical evidence, and challenges. *Int J Mol Sci*. 2022;23(16):8905. doi:10.3390/ijms23168905
16. Li T, Yan Y, Wang B, et al. Exosomes derived from human umbilical cord mesenchymal stem cells alleviate liver fibrosis. *Stem Cells Dev*. 2013;22(6):845–854. doi:10.1089/scd.2012.0395
17. Wu J, Wang Y, Li L. Functional significance of exosomes applied in sepsis: a novel approach to therapy. *Biochim Biophys Acta Mol Basis Dis*. 2017;1863(1):292–297. doi:10.1016/j.bbadis.2016.10.024
18. Murao A, Brenner M, Aziz M, et al. Exosomes in Sepsis. *Front Immunol*. 2020;11:2140. doi:10.3389/fimmu.2020.02140
19. van Niel G, Carter DRF, Clayton A, et al. Challenges and directions in studying cell-cell communication by extracellular vesicles. *Nat Rev Mol Cell Biol*. 2022;23(5):369–382. doi:10.1038/s41580-022-00460-3
20. Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes. *Science*. 2020;367(6478). doi:10.1126/science.aau6977
21. Ohno S, Drummen GP, Kuroda M. Focus on extracellular vesicles: development of extracellular vesicle-based therapeutic systems. *Int J Mol Sci*. 2016;17(2):172. doi:10.3390/ijms17020172
22. Raeven P, Zipperle J, Drechsler S. Extracellular vesicles as markers and mediators in sepsis. *Theranostics*. 2018;8(12):3348–3365. doi:10.7150/thno.23453
23. Yáñez-Mó M, Siljander PR, Andreu Z, et al. Biological properties of extracellular vesicles and their physiological functions. *J Extracell Vesicles*. 2015;4:27066. doi:10.3402/jev.v4.27066
24. Lapitz A, Arbelaiz A, Olaizola P, et al. Extracellular vesicles in hepatobiliary malignancies. *Front Immunol*. 2018;9:2270. doi:10.3389/fimmu.2018.02270

25. Yang J, Zou X, Jose PA, et al. Extracellular vesicles: potential impact on cardiovascular diseases. *Adv Clin Chem*. 2021;105:49–100. doi:10.1016/bs.acc.2021.02.002
26. Robbins PD, Dorronsoro A, Booker CN. Regulation of chronic inflammatory and immune processes by extracellular vesicles. *J Clin Invest*. 2016;126(4):1173–1180. doi:10.1172/JCI81131
27. Robbins PD, Morelli AE. Regulation of immune responses by extracellular vesicles. *Nat Rev Immunol*. 2014;14(3):195–208. doi:10.1038/nri3622
28. Xi S, Wang Y, Wu C, et al. Intestinal epithelial cell exosome launches IL-1β-mediated neuron injury in sepsis-associated encephalopathy. *Front Cell Infect Microbiol*. 2021;11:783049. doi:10.3389/fcimb.2021.783049
29. Balusu S, Van Wonterghem E, De Rycke R, et al. Identification of a novel mechanism of blood-brain communication during peripheral inflammation via choroid plexus-derived extracellular vesicles. *EMBO Mol Med*. 2016;8(10):1162–1183. doi:10.15252/emmm.201606271
30. Lin H, Chen H, Qi B, et al. Brain-derived extracellular vesicles mediated coagulopathy, inflammation and apoptosis after sepsis. *Thromb Res*. 2021;207:85–95. doi:10.1016/j.thromres.2021.09.014
31. Liu F, Peng W, Chen J, et al. Exosomes derived from alveolar epithelial cells promote alveolar macrophage activation mediated by miR-92a-3p in sepsis-induced acute lung injury. *Front Cell Infect Microbiol*. 2021;11:646546. doi:10.3389/fcimb.2021.646546
32. Li W, Deng M, Loughran PA, et al. LPS induces active HMGB1 release from hepatocytes into exosomes through the coordinated activities of TLR4 and caspase-11/GSDMD Signaling. *Front Immunol*. 2020;11:229. doi:10.3389/fimmu.2020.00229
33. Li ZG, Scott MJ, Brzóska T, et al. Lung epithelial cell-derived IL-25 negatively regulates LPS-induced exosome release from macrophages. *Mil Med Res*. 2018;5(1):24. doi:10.1186/s40779-018-0173-6
34. Wang G, Huang W, Wang S, et al. Macrophagic extracellular vesicle CXCL2 recruits and activates the neutrophil CXCR2/PKC/NOX4 axis in sepsis. *J Immunol*. 2021;207(8):2118–2128. doi:10.4049/jimmunol.2100229
35. Sui X, Liu W, Liu Z. Exosomes derived from LPS-induced MHs cells prompted an inflammatory response in sepsis-induced acute lung injury. *Respir Physiol Neurobiol*. 2021;292:103711. doi:10.1016/j.resp.2021.103711
36. Wang L, Zhao H, Xu H, et al. Targeting the TXNIP-NLRP3 interaction with PSSM1443 to suppress inflammation in sepsis-induced myocardial dysfunction. *J Cell Physiol*. 2021;236(6):4625–4639. doi:10.1002/jcp.30186
37. Xu J, Feng Y, Jeyaram A, et al. Circulating plasma extracellular vesicles from septic mice induce inflammation via MicroRNA- and TLR7-dependent mechanisms. *J Immunol*. 2018;201(11):3392–3400. doi:10.4049/jimmunol.1801008
38. Li G, Wang B, Ding X, et al. Plasma extracellular vesicle delivery of miR-210-3p by targeting ATG7 to promote sepsis-induced acute lung injury by regulating autophagy and activating inflammation. *Exp Mol Med*. 2021;53(7):1180–1191. doi:10.1038/s12276-021-00651-6
39. Gao M, Yu T, Liu D, et al. Sepsis plasma-derived exosomal miR-1-3p induces endothelial cell dysfunction by targeting SERP1. *Clin Sci*. 2021;135(2):347–365. doi:10.1042/CS20200573
40. Jiang K, Yang J, Guo S, et al. Peripheral circulating exosome-mediated delivery of miR-155 as a novel mechanism for acute lung inflammation. *Mol Ther*. 2019;27(10):1758–1771. doi:10.1016/j.ymthe.2019.07.003
41. Murao A, Tan C, Jha A, et al. Exosome-mediated eCIRP release from macrophages to induce inflammation in sepsis. *Front Pharmacol*. 2021;12:791648. doi:10.3389/fphar.2021.791648
42. Gao K, Jin J, Huang C, et al. Exosomes derived from septic mouse serum modulate immune responses via exosome-associated cytokines. *Front Immunol*. 2019;10:1560. doi:10.3389/fimmu.2019.01560
43. Appiah MG, Park EJ, Darkwah S, et al. Intestinal epithelium-derived luminally released extracellular vesicles in sepsis exhibit the ability to suppress TNF-A and IL-17A expression in mucosal inflammation. *Int J Mol Sci*. 2020;21(22):8445. doi:10.3390/ijms21228445
44. Deng M, Tang Y, Li W, et al. The endotoxin delivery protein HMGB1 mediates caspase-11-dependent lethality in sepsis. *Immunity*. 2018;49(4):740–753.e747. doi:10.1016/j.immuni.2018.08.016
45. Yuan D, Zhao Y, Banks WA, et al. Macrophage exosomes as natural nanocarriers for protein delivery to inflamed brain. *Biomaterials*. 2017;142:1–12. doi:10.1016/j.biomaterials.2017.07.011
46. Alvarez-Erviti L, Seow Y, Yin H, et al. Delivery of siRNA to the mouse brain by systemic injection of targeted exosomes. *Nat Biotechnol*. 2011;29(4):341–345. doi:10.1038/nbt.1807
47. Deng H, Wu L, Liu M, et al. Bone marrow mesenchymal stem cell-derived exosomes attenuate LPS-Induced ARDS by modulating macrophage polarization through inhibiting glycolysis in macrophages. *Shock*. 2020;54(6):828–843. doi:10.1097/SHK.0000000000001549
48. Liu H, Zhang L, Li M, et al. Bone mesenchymal stem cell-derived extracellular vesicles inhibit DAPK1-mediated inflammation by delivering miR-191 to macrophages. *Biochem Biophys Res Commun*. 2022;598:32–39. doi:10.1016/j.bbrc.2022.02.009
49. Chen J, Li C, Liang Z, et al. Human mesenchymal stromal cells small extracellular vesicles attenuate sepsis-induced acute lung injury in a mouse model: the role of oxidative stress and the mitogen-activated protein kinase/nuclear factor kappa B pathway. *Cytotherapy*. 2021;23(10):918–930. doi:10.1016/j.jcyt.2021.05.009
50. Deng H, Zhu L, Zhang Y, et al. Differential lung protective capacity of exosomes derived from human adipose tissue, bone marrow, and umbilical cord mesenchymal stem cells in sepsis-induced acute lung injury. *Oxid Med Cell Longev*. 2022;2022:7837837. doi:10.1155/2022/7837837
51. Zhou Y, Li P, Goodwin AJ, et al. Exosomes from Endothelial Progenitor Cells Improve the Outcome of a Murine Model of Sepsis. *Mol Ther*. 2018;26(5):1375–1384. doi:10.1016/j.ymthe.2018.02.020
52. Jiang L, Ni J, Shen G, et al. Upregulation of endothelial cell-derived exosomal microRNA-125b-5p protects from sepsis-induced acute lung injury by inhibiting topoisomerase II alpha. *Inflamm Res*. 2021;70(2):205–216. doi:10.1007/s00011-020-01415-0
53. Mizuta Y, Akahoshi T, Guo J, et al. Exosomes from adipose tissue-derived mesenchymal stem cells ameliorate histone-induced acute lung injury by activating the PI3K/Akt pathway in endothelial cells. *Stem Cell Res Ther*. 2020;11(1):508. doi:10.1186/s13287-020-02015-9
54. Sui X, Liu W, Liu Z. Exosomal lncRNA-p21 derived from mesenchymal stem cells protects epithelial cells during LPS-induced acute lung injury by sponging miR-181. *Acta Biochim Biophys Sin*. 2021;53(6):748–757. doi:10.1093/abbs/gmab043
55. Shen W, Zhao X, Li S. Exosomes derived from ADSCs attenuate sepsis-induced lung injury by delivery of Circ-Fryl and Regulation of the miR-490-3p/SIRT3 Pathway. *Inflammation*. 2022;45(1):331–342. doi:10.1007/s10753-021-01548-2
56. Cointe S, Vallier L, Esnault P, et al. Granulocyte microvesicles with a high plasmin generation capacity promote clot lysis and improve outcome in septic shock. *Blood*. 2022;139(15):2377–2391. doi:10.1182/blood.2021013328

57. Wang X, Gu H, Qin D, et al. Exosomal miR-223 contributes to mesenchymal stem cell-elicited cardioprotection in polymicrobial sepsis. *Sci Rep*. 2015;5:13721. doi:10.1038/srep13721
58. Pei Y, Xie S, Li J, et al. Bone marrow-mesenchymal stem cell-derived exosomal microRNA-141 targets PTEN and activates β-catenin to alleviate myocardial injury in septic mice. *Immunopharmacol Immunotoxicol*. 2021;43(5):584–593. doi:10.1080/08923973.2021.1955920
59. Sun X, Liu Y, Wang J, et al. Cardioprotection of M2 macrophages-derived exosomal microRNA-24-3p/Tnfsf10 axis against myocardial injury after sepsis. *Mol Immunol*. 2022;141:309–317. doi:10.1016/j.molimm.2021.11.003
60. Tu F, Wang X, Zhang X, et al. Novel role of endothelial derived exosomal HSPA12B in regulating macrophage inflammatory responses in polymicrobial sepsis. *Front Immunol*. 2020;11:825. doi:10.3389/fimmu.2020.00825
61. Gao F, Zuo B, Wang Y, et al. Protective function of exosomes from adipose tissue-derived mesenchymal stem cells in acute kidney injury through SIRT1 pathway. *Life Sci*. 2020;255:117719. doi:10.1016/j.lfs.2020.117719
62. Sun J, Sun X, Chen J, et al. microRNA-27b shuttled by mesenchymal stem cell-derived exosomes prevents sepsis by targeting JMJD3 and downregulating NF-κB signaling pathway. *Stem Cell Res Ther*. 2021;12(1):14. doi:10.1186/s13287-020-02068-w
63. Zhang R, Zhu Y, Li Y, et al. Human umbilical cord mesenchymal stem cell exosomes alleviate sepsis-associated acute kidney injury via regulating microRNA-146b expression. *Biotechnol Lett*. 2020;42(4):669–679. doi:10.1007/s10529-020-02831-2
64. Zhang W, Zhang J, Huang H. Exosomes from adipose-derived stem cells inhibit inflammation and oxidative stress in LPS-acute kidney injury. *Exp Cell Res*. 2022;420(1):113332. doi:10.1016/j.yexcr.2022.113332
65. He Z, Wang H, Yue L. Endothelial progenitor cells-secreted extracellular vesicles containing microRNA-93-5p confer protection against sepsis-induced acute kidney injury via the KDM6B/H3K27me3/TNF-α axis. *Exp Cell Res*. 2020;395(2):112173. doi:10.1016/j.yexcr.2020.112173
66. Wu C, Li H, Zhang P, et al. Lymphatic flow: a potential target in sepsis-associated acute lung injury. *J Inflamm Res*. 2020;13:961–968. doi:10.2147/JIR.S284090
67. Matthay MA, Zemans RL, Zimmerman GA, et al. Acute respiratory distress syndrome. *Nat Rev Dis Primers*. 2019;5(1):18. doi:10.1038/s41572-019-0069-0
68. Liu Y, Xiang D, Zhang H, et al. Hypoxia-inducible factor-1: a potential target to treat acute lung injury. *Oxid Med Cell Longev*. 2020;2020:8871476. doi:10.1155/2020/8871476
69. He W, Xi Q, Cui H, et al. Forsythiaside B ameliorates coagulopathies in a rat model of sepsis through inhibition of the formation of PAD4-dependent neutrophil extracellular traps. *Front Pharmacol*. 2022;13:1022985. doi:10.3389/fphar.2022.1022985
70. Hollenberg SM, Singer M. Pathophysiology of sepsis-induced cardiomyopathy. *Nat Rev Cardiol*. 2021;18(6):424–434. doi:10.1038/s41569-020-00492-2
71. Stanzani G, Duchen MR, Singer M. The role of mitochondria in sepsis-induced cardiomyopathy. *Biochim Biophys Acta Mol Basis Dis*. 2019;1865(4):759–773. doi:10.1016/j.bbadis.2018.10.011
72. Ravikumar N, Sayed MA, Poonsuph CJ, et al. Septic cardiomyopathy: from basics to management choices. *Curr Probl Cardiol*. 2021;46(4):100767. doi:10.1016/j.cpcardiol.2020.100767
73. Poston JT, Koyner JL. Sepsis associated acute kidney injury. *BMJ*. 2019;364:k4891. doi:10.1136/bmj.k4891
74. Trof RJ, Di Maggio F, Leemreis J, et al. Biomarkers of acute renal injury and renal failure. *Shock*. 2006;26(3):245–253. doi:10.1097/01.shk.0000225415.5969694.ce
75. Bouchard J, Acharya A, Cerda J, et al. A prospective international multicenter study of AKI in the intensive care unit. *Clin J Am Soc Nephrol*. 2015;10(8):1324–1331. doi:10.2215/CJN.04360514
76. Zhou Q, Xie M, Zhu J, et al. PINK1 contained in huMSC-derived exosomes prevents cardiomyocyte mitochondrial calcium overload in sepsis via recovery of mitochondrial Ca(2+) efflux. *Stem Cell Res Ther*. 2021;12(1):269. doi:10.1186/s13287-021-02325-6
77. Li J, Jiang R, Hou Y, et al. Mesenchymal stem cells-derived exosomes prevent sepsis-induced myocardial injury by a CircRTN4/miR-497-5p/MG53 pathway. *Biochem Biophys Res Commun*. 2022;618:133–140. doi:10.1016/j.bbrc.2022.05.094
78. Ding L, Zhou W, Zhang J, et al. Calming egress of inflammatory monocytes and related septic shock by therapeutic CCR2 silencing using macrophage-derived extracellular vesicles. *Nanoscale*. 2022;14(13):4935–4945. doi:10.1039/D1NR06922E
79. Sun D, Zhuang X, Xiang X, et al. A novel nanoparticle drug delivery system: the anti-inflammatory activity of curcumin is enhanced when encapsulated in exosomes. *Mol Ther*. 2010;18(9):1606–1614. doi:10.1038/mt.2010.105
80. Gao J, Wang S, Wang Z. High yield, scalable and remotely drug-loaded neutrophil-derived extracellular vesicles (EVs) for anti-inflammation therapy. *Biomaterials*. 2017;135:62–73. doi:10.1016/j.biomaterials.2017.05.003
81. Choi H, Kim Y, Mirzaaghasi A, et al. Exosome-based delivery of super-repressor IκBα relieves sepsis-associated organ damage and mortality. *Sci Adv*. 2020;6(15):eaaz6980. doi:10.1126/sciadv.aaz6980
82. Kumagai Y, Murakami T, Kuwahara A, et al. Antimicrobial peptide LL-37 ameliorates a murine sepsis model via the induction of microvesicle release from neutrophils. *Innate Immun*. 2020;26(7):565–579. doi:10.1177/1753425920936754
83. Song Y, Dou H, Li X, et al. Exosomal miR-146a contributes to the enhanced therapeutic efficacy of interleukin-1β-primed mesenchymal stem cells against sepsis. *Stem Cells*. 2017;35(5):1208–1221. doi:10.1002/stem.2564
84. Yao M, Cui B, Zhang W, et al. Exosomal miR-21 secreted by IL-1β-primed-mesenchymal stem cells induces macrophage M2 polarization and ameliorates sepsis. *Life Sci*. 2021;264:118658. doi:10.1016/j.lfs.2020.118658
85. Pan T, Jia P, Chen N, et al. Delayed remote ischemic preconditioning confersrenoprotection against septic acute kidney injury via exosomal miR-21. *Theranostics*. 2019;9(2):405–423. doi:10.7150/thno.29832
86. Zhu W, Huang X, Qiu S, et al. miR-142-5p encapsulated by serum-derived extracellular vesicles protects against acute lung injury in septic rats following remote ischemic preconditioning via the PTEN/PI3K/Akt axis. *J Innate Immun*. 2022;14(5):532–542. doi:10.1159/000522231
87. Cao S, Huang Y, Dai Z, et al. Circular RNA mmu_circ_0001295 from hypoxia pretreated adipose-derived mesenchymal stem cells (ADSCs) exosomes improves outcomes and inhibits sepsis-induced renal injury in a mouse model of sepsis. *Bioengineered*. 2022;13(3):6323–6331. doi:10.1080/21655979.2022.2044720
88. Jones J, Allen S, Davies J, et al. Randomised feasibility study of prehospital recognition and antibiotics for emergency patients with sepsis (PhRASe). *Sci Rep*. 2021;11(1):18586. doi:10.1038/s41598-021-97979-w
89. Loots FJ, Smits M, Hopstaken RM, et al. New clinical prediction model for early recognition of sepsis in adult primary care patients: a prospective diagnostic cohort study of development and external validation. *Br J Gen Pract*. 2022;72(719):e437–e445. doi:10.3399/BJGP.2021.0520

90. Linder A, Christensson B, Herwald H, et al. Heparin-binding protein: an early marker of circulatory failure in sepsis. *Clin Infect Dis*. 2009;49(7):1044–1050. doi:10.1086/605563
91. Wu CC, Lan HM, Han ST, et al. Comparison of diagnostic accuracy in sepsis between presepsin, procalcitonin, and C-reactive protein: a systematic review and meta-analysis. *Ann Intensive Care*. 2017;7(1):91. doi:10.1186/s13613-017-0316-z
92. Masson S, Caironi P, Spanuth E, et al. Presepsin (soluble CD14 subtype) and procalcitonin levels for mortality prediction in sepsis: data from the Albumin Italian Outcome Sepsis trial. *Crit Care*. 2014;18(1):R6. doi:10.1186/cc13183
93. Webber RJ, Sweet RM, Webber DS. Circulating microvesicle-associated inducible nitric oxide synthase is a novel therapeutic target to treat sepsis: current status and future considerations. *Int J Mol Sci*. 2021;22(24):13371. doi:10.3390/ijms222413371
94. Ulla M, Pizzolato E, Lucchiari M, et al. Diagnostic and prognostic value of presepsin in the management of sepsis in the emergency department: a multicenter prospective study. *Crit Care*. 2013;17(4):R168. doi:10.1186/cc12847
95. Kweon OJ, Choi JH, Park SK, et al. Usefulness of presepsin (sCD14 subtype) measurements as a new marker for the diagnosis and prediction of disease severity of sepsis in the Korean population. *J Crit Care*. 2014;29(6):965–970. doi:10.1016/j.jcrc.2014.06.014
96. Monnamorn L, Seree-Aphinan C, Molika P, et al. The concentration of large extracellular vesicles differentiates early septic shock from infection. *Front Med*. 2021;8:724371. doi:10.3389/fmed.2021.724371
97. Youn YJ, Shrestha S, Lee YB, et al. Neutrophil-derived trail is a proinflammatory subtype of neutrophil-derived extracellular vesicles. *Theranostics*. 2021;11(6):2770–2787. doi:10.7150/thno.51756
98. Dakhlallah DA, Wisler J, Gencheva M, et al. Circulating extracellular vesicle content reveals de novo DNA methyltransferase expression as a molecular method to predict septic shock. *J Extracell Vesicles*. 2019;8(1):1669881. doi:10.1080/20013078.2019.1669881
99. Im Y, Yoo H, Lee JY, et al. Association of plasma exosomes with severity of organ failure and mortality in patients with sepsis. *J Cell Mol Med*. 2020;24(16):9439–9445. doi:10.1111/jcmm.15606
100. Baweja S, Bihari C, Negi P, et al. Circulating extracellular vesicles induce monocyte dysfunction and are associated with sepsis and high mortality in cirrhosis. *Liver Int*. 2021;41(7):1614–1628. doi:10.1111/liv.14875
101. Im Y, Yoo H, E KR, et al. Exosomal CD63 in critically ill patients with sepsis. *Sci Rep*. 2021;11(1):20300. doi:10.1038/s41598-021-99777-w
102. Mahida RY, Price J, Lugg ST, et al. CD14-positive extracellular vesicles in bronchoalveolar lavage fluid as a new biomarker of acute respiratory distress syndrome. *Am J Physiol Lung Cell Mol Physiol*. 2022;322(4):L617–l624. doi:10.1152/ajplung.00052.2022
103. Puga ML, Menegueti MG, Silvestrini MMA, et al. Performance of microvesicles as biomarkers of clinical outcome in sepsis and trauma: a pilot study. *Biomed Pharmacother*. 2022;146:112490. doi:10.1016/j.biopha.2021.112490
104. Qiu G, Fan J, Zheng G, et al. Diagnostic potential of plasma extracellular vesicle miR-483-3p and Let-7d-3p for sepsis. *Front Mol Biosci*. 2022;9:814240. doi:10.3389/fmolb.2022.814240
105. Ye R, Lin Q, Xiao W, et al. miR-150-5p in neutrophil-derived extracellular vesicles associated with sepsis-induced cardiomyopathy in septic patients. *Cell Death Discov*. 2023;9(1):19. doi:10.1038/s41420-023-01328-x
106. Reithmair M, Buschmann D, Märte M, et al. Cellular and extracellular miRNAs are blood-compartment-specific diagnostic targets in sepsis. *J Cell Mol Med*. 2017;21(10):2403–2411. doi:10.1111/jcmm.13162
107. Hermann S, Brandes F, Kirchner B, et al. Diagnostic potential of circulating cell-free microRNAs for community-acquired pneumonia and pneumonia-related sepsis. *J Cell Mol Med*. 2020;24(20):12054–12064. doi:10.1111/jcmm.15837
108. Tian C, Liu J, Di X, et al. Exosomal hsa_circRNA_104484 and hsa_circRNA_104670 may serve as potential novel biomarkers and therapeutic targets for sepsis. *Sci Rep*. 2021;11(1):14141. doi:10.1038/s41598-021-93246-0
109. Panich T, Chancharoenthana W, Somparn P, et al. Urinary exosomal activating transcriptional factor 3 as the early diagnostic biomarker for sepsis-induced acute kidney injury. *BMC Nephrol*. 2017;18(1):10. doi:10.1186/s12882-016-0415-3
110. Webber RJ, Sweet RM, Webber DS. Inducible nitric oxide synthase in circulating microvesicles: discovery, evolution, and evidence as a novel biomarker and the probable causative agent for sepsis. *J Appl Lab Med*. 2019;3(4):698–711. doi:10.1373/jalm.2018.026377
111. Xu Y, Ku X, Wu C, et al. Exosomal proteome analysis of human plasma to monitor sepsis progression. *Biochem Biophys Res Commun*. 2018;499(4):856–861. doi:10.1016/j.bbrc.2018.04.006
112. Witwer KW, Wolfram J. Extracellular vesicles versus synthetic nanoparticles for drug delivery. *Nat Rev Mater*. 2021;6(2):103–106. doi:10.1038/s41578-020-00277-6
113. Nasiri Kenari A, Cheng L, Hill AF. Methods for loading therapeutics into extracellular vesicles and generating extracellular vesicles mimetic-nanovesicles. *Methods*. 2020;177:103–113. doi:10.1016/j.ymeth.2020.01.001
114. Parr MJ, Ansell SM, Choi LS, et al. Factors influencing the retention and chemical stability of poly(ethylene glycol)-lipid conjugates incorporated into large unilamellar vesicles. *Biochim Biophys Acta*. 1994;1195(1):21–30. doi:10.1016/0005-2736(94)90004-3
115. Pelt J, Busatto S, Ferrari M, et al. Chloroquine and nanoparticle drug delivery: a promising combination. *Pharmacol Ther*. 2018;191:43–49. doi:10.1016/j.pharmthera.2018.06.007
116. Makabenta JMV, Nabawy A, Li CH, et al. Nanomaterial-based therapeutics for antibiotic-resistant bacterial infections. *Nat Rev Microbiol*. 2021;19(1):23–36. doi:10.1038/s41579-020-0420-1
117. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. *Adv Drug Deliv Rev*. 2013;65(1):36–48. doi:10.1016/j.addr.2012.09.037
118. Hou X, Zhang X, Zhao W, et al. Vitamin lipid nanoparticles enable adoptive macrophage transfer for the treatment of multidrug-resistant bacterial sepsis. *Nat Nanotechnol*. 2020;15(1):41–46. doi:10.1038/s41565-019-0600-1
119. Schrijver DP, Röring RJ, Deckers J, et al. Resolving sepsis-induced immunoparalysis via trained immunity by targeting interleukin-4 to myeloid cells. *Nat Biomed Eng*. 2023;7(9):1097–1112. doi:10.1038/s41551-023-01050-0
120. Chen W, Zhu CS, Qiang X, et al. Development of procathepsin L (pCTS-L)-inhibiting lanosterol-carrying liposome nanoparticles to treat lethal sepsis. *Int J Mol Sci*. 2023;24:10.
121. Ge XY, Zhang JX, Feng YG, et al. Label-free electrochemical biosensor for determination of procalcitonin based on graphene-wrapped Co nanoparticles encapsulated in carbon nanobrushes coupled with AuPtCu nanodendrites. *Mikrochim Acta*. 2022;189(3):110. doi:10.1007/s00604-022-05179-8

122. Wang XY, Feng YG, Wang AJ, et al. Facile construction of ratiometric electrochemical immunosensor using hierarchical PtCoIr nanowires and porous SiO(2)@Ag nanoparticles for accurate detection of septicemia biomarker. *Bioelectrochemistry*. 2021;140:107802. doi:10.1016/j.bioelechem.2021.107802
123. Wang Y, Guan M, Mi F, et al. Combining multisite functionalized magnetic nanomaterials with interference-free SERS nanotags for multi-target sepsis biomarker detection. *Anal Chim Acta*. 2023;1272:341523. doi:10.1016/j.aca.2023.341523
124. Wang Y, Guan M, Hu C, et al. High-sensitivity biosensor based on SERS integrated with dendrimer-assisted boronic acid-functionalized magnetic nanoparticles for IL-6 detection in human serum. *Nanotechnology*. 2023;34:35.
125. Bradley Z, Coleman PA, Courtney MA, et al. Effect of selenium nanoparticle size on IL-6 detection sensitivity in a lateral flow device. *ACS Omega*. 2023;8(9):8407–8414. doi:10.1021/acsomega.2c07297
126. Zhou X, Li P, Wu X, et al. Multifunctional biosensor constructed by Ag-coating magnetic-assisted unique urchin core porous shell structure for dual SERS enhancement, enrichment, and quantitative detection of multi-components inflammatory markers. *Biosens Bioelectron*. 2022;210:114257. doi:10.1016/j.bios.2022.114257
127. Alekhmimi NK, Raddadi Z, Alabdulwahed AA, et al. Paper-based biosensor for the detection of sepsis using MMP-9 biomarker in FIP mice model. *Biosensors*. 2023;13:8.
128. Hornos Carneiro MF, Barbosa F. Gold nanoparticles: a critical review of therapeutic applications and toxicological aspects. *J Toxicol Environ Health B Crit Rev*. 2016;19(3–4):129–148. doi:10.1080/10937404.2016.1168762
129. Petronilho F, Tenfen L, Della Giustina A, et al. Gold nanoparticles potentiates N-acetylcysteine effects on neurochemicals alterations in rats after polymicrobial sepsis. *J Drug Target*. 2020;28(4):428–436. doi:10.1080/1061186X.2019.1678168
130. Di Bella D, Ferreira JPS, Silva RNO, et al. Gold nanoparticles reduce inflammation in cerebral microvessels of mice with sepsis. *J Nanobiotechnology*. 2021;19(1):52. doi:10.1186/s12951-021-00796-6
131. Gao Y, Wang Z, Li Y, et al. A rational design of copper-selenium nanoclusters that cures sepsis by consuming endogenous H(2)S to trigger photothermal therapy and ROS burst. *Biomater Sci*. 2022;10(12):3137–3157. doi:10.1039/D2BM00172A
132. Wang D, Wang C, Liang Z, et al. Protection of zero-valent iron nanoparticles against sepsis and septic heart failure. *J Nanobiotechnology*. 2022;20(1):405. doi:10.1186/s12951-022-01589-1
133. Wang D, Zhao H, Deng C, et al. Sulfide-modified nanoscale zero-valent iron as a novel therapeutic remedy for septic myocardial injury. *J Adv Res*. 2023. doi:10.1016/j.jare.2023.02.008
134. Üstündağ H, Danişman Kalindemirtaş F, Doğanay S, et al. enhanced efficacy of resveratrol loaded silver nanoparticle in attenuating sepsis-induced acute liver injury: modulation of inflammation, oxidative stress, and SIRT1 activation. *Shock*. 2023. doi:10.1097/SHK.0000000000002218
135. Yang Y, Ding Y, Fan B, et al. Inflammation-targeting polymeric nanoparticles deliver sparfloxacin and tacrolimus for combating acute lung sepsis. *J Control Release*. 2020;321:463–474. doi:10.1016/j.jconrel.2020.02.030
136. Reddy GA, Handa M, Garabadu D, et al. Transferrin decorated PLGA encumbered moxifloxacin nanoparticles and in vitro cellular studies. *Drug Dev Ind Pharm*. 2023;49(1):129–138. doi:10.1080/03639045.2023.2185463
137. Azadpour M, Farajollahi MM, Dariushnejad H, et al. Effects of synthetic silymarin-PLGA nanoparticles on M2 polarization and inflammatory cytokines in LPS-treated murine peritoneal macrophages. *Iran J Basic Med Sci*. 2021;24(10):1446–1454. doi:10.22038/IJBMS.2021.59312.13161
138. Ding N, Luo G, Li H, et al. A cyclodextrin-based pH-responsive microRNA delivery platform targeting polarization of M1 to M2 macrophages for sepsis therapy. *Adv Healthc Mater*;2023. e2301243. doi:10.1002/adhm.202301243
139. Teng L, Zhang Y, Chen L, et al. Fabrication of a curcumin encapsulated bioengineered nano-cocktail formulation for stimuli-responsive targeted therapeutic delivery to enhance anti-inflammatory, anti-oxidant, and anti-bacterial properties in sepsis management. *J Biomater Sci Polym Ed*. 2023;34(12):1716–1740. doi:10.1080/09205063.2023.2181554
140. Lasola JJM, Cottingham AL, Scotland BL, et al. Immunomodulatory nanoparticles mitigate macrophage inflammation via inhibition of PAMP interactions and lactate-mediated functional reprogramming of NF-κB and p38 MAPK. *Pharmaceutics*. 2021;13(11):1841. doi:10.3390/pharmaceutics13111841
141. Koda Y, Nagasaki Y. Newly designed cysteine-based self-assembling prodrugs for sepsis treatment. *Pharmaceutics*. 2023;15(6):1775. doi:10.3390/pharmaceutics15061775
142. Go G, Lee J, Choi DS, et al. Extracellular vesicle-mimetic ghost nanovesicles for delivering anti-inflammatory drugs to mitigate gram-negative bacterial outer membrane vesicle-induced systemic inflammatory response syndrome. *Adv Healthc Mater*. 2019;8(4):e1801082. doi:10.1002/adhm.201801082
143. Li Y, Zhang H, Chen C, et al. Biomimetic immunosuppressive exosomes that inhibit cytokine storms contribute to the alleviation of sepsis. *Adv Mater*. 2022;34(19):e2108476. doi:10.1002/adma.202108476
144. Park KS, Svennerholm K, Shelke GV, et al. Mesenchymal stromal cell-derived nanovesicles ameliorate bacterial outer membrane vesicle-induced sepsis via IL-10. *Stem Cell Res Ther*. 2019;10(1):231. doi:10.1186/s13287-019-1352-4
145. Molinaro R, Pastò A, Corbo C, et al. Macrophage-derived nanovesicles exert intrinsic anti-inflammatory properties and prolong survival in sepsis through a direct interaction with macrophages. *Nanoscale*. 2019;11(28):13576–13586. doi:10.1039/C9NR04253A
146. Kunz N, Xia BT, Kalies KU, et al. Cell-derived nanoparticles are endogenous modulators of sepsis with therapeutic potential. *Shock*. 2017;48(3):346–354. doi:10.1097/SHK.0000000000000855
147. Hu S, Wang Y, Li H. The regulation effect of α7nAChRs and M1AChRs on inflammation and immunity in sepsis. *Mediators Inflamm*. 2021;2021:9059601. doi:10.1155/2021/9059601
148. Huang M, Cai S, Su J. The pathogenesis of sepsis and potential therapeutic targets. *Int J Mol Sci*. 2019;20(21):5376. doi:10.3390/ijms20215376

International Journal of Nanomedicine Dovepress

Publish your work in this journal

The International Journal of Nanomedicine is an international, peer-reviewed journal focusing on the application of nanotechnology in diagnostics, therapeutics, and drug delivery systems throughout the biomedical field. This journal is indexed on PubMed Central, MedLine, CAS, SciSearch®, Current Contents®/Clinical Medicine, Journal Citation Reports/Science Edition, EMBase, Scopus and the Elsevier Bibliographic databases. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: https://www.dovepress.com/international-journal-of-nanomedicine-journal