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REVIEW

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

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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

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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.

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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*)

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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.

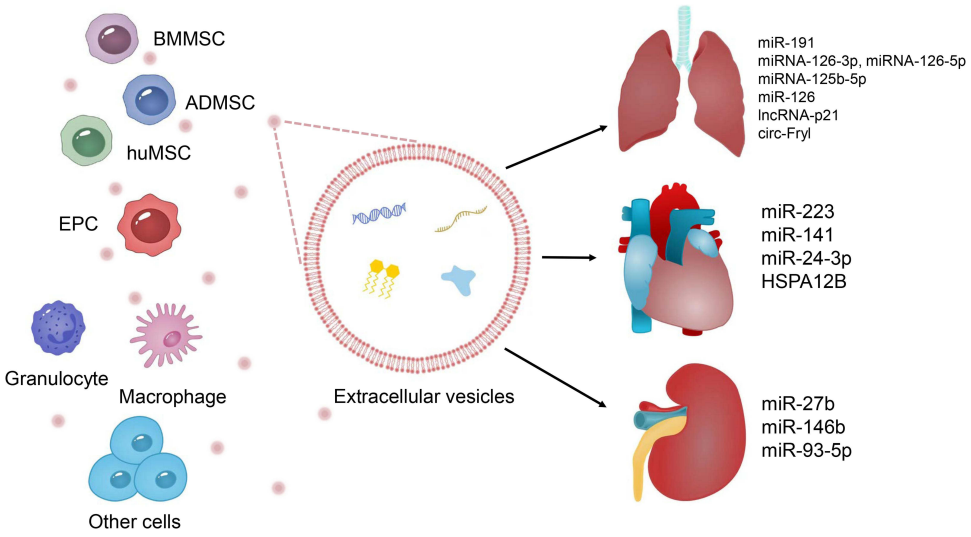

Figure 1 Therapeutic effects of native EVs in sepsis-induced organ injury.
Abbreviations: BMMSC, bone marrow mesenchymal stem cell; ADMSC, adipose tissue-derived mesenchymal stem cell; huMSC, human umbilical cord mesenchymal stromal cell; EPC, endothelial progenitor cell.

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.

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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

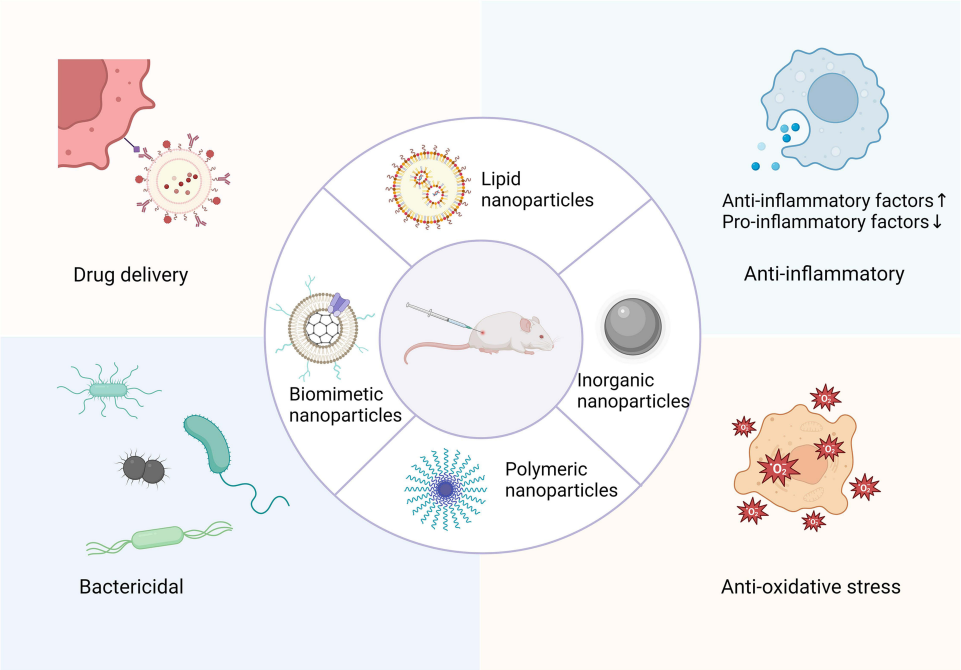

Figure 2 Therapeutic effects of nanoparticles in sepsis. Created with Biorender.com.

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.

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Disclosure

The authors report no conflicts of interest in this work.

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