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REVIEW

Bidirectional Regulatory Roles in the Immune Modulation, Organ Dysfunction, and Therapy of Sepsis

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Abstract: Exosomes have emerged as central mediators in sepsis pathogenesis and therapy. Exosomes play an important role in cell communication by transferring functional proteins, metabolites, and nucleic acids to recipient cells. Recently, Low-immunogenic exosomes serve as novel biomarkers in sepsis, and they confer a 46% enhancement in survival benefit in animal models. However, exosomes drive the early inflammatory storm and late immune paralysis in sepsis. There are also limitations related to heterogeneity and translational barriers. Therefore, this review discusses the basic signaling pathways underlying the bidirectional effects of exosomes in the pathogenesis and treatment of sepsis, the interaction between organ dysfunction and exosomes in sepsis, the current progress in exosome therapy for sepsis, as well as the challenges and limitations faced in this field. In summary, exosomes have bright prospects in diagnosis and clinical translation, as well as the potential for standardized production.

Keywords: extracellular vesicles, biomarkers, immunomodulation, exosomes, sepsis, bidirectional regulatory roles

Introduction

Sepsis leads to over 11 million deaths globally each year from 1990 to 2017.[1] Its core pathological feature is biphasic immune dysregulation: the early stage manifests as Systemic Inflammatory Response Syndrome (SIRS) with a "cytokine storm", while the late stage progresses to immune paralysis marked by T-cell exhaustion and heightened secondary infection risk. However, traditional biomarkers such as procalcitonin[2] cannot capture stage-specific immune changes, and broad-spectrum anti-inflammatory drugs like glucocorticoids may even worsen late-stage immune suppression. Therefore, exosomes became candidates.

Exosomes—40–150 nm extracellular vesicles originating from intracellular multivesicular bodies and secreted by nearly all cell types (including immune and endothelial cells)—mediate precise intercellular communication via bioactive cargo (microRNAs). In sepsis, they exhibit dual roles: early on, exosomes from activated macrophages carry pro-inflammatory substances (HMGB1,[3] miR-155[4]), amplifying the cytokine storm by activating pathways like TLR4/NF-κB; in the late stage, those from apoptotic T cells or regulatory macrophages deliver immunosuppressive molecules (miR-146a,[5] TGF-β), inducing T-cell exhaustion. Notably, exosomes synergize with neutrophil extracellular traps (NETs)[6] for organ injury: early sepsis exosomal cargo activates neutrophils to form NETs (histones, NE, DNA). Histones induce renal tubular necrosis, NE degrades alveolar basement membranes, and this "exosome-NETs crosstalk" spreads damage.

Current research gaps include inconsistent exosome isolation methods[7] (ultracentrifugation vs commercial kits), patient heterogeneity[8] (divergent exosomal transcriptomes in elderly vs pediatric patients), overlooked crosstalk with metabolic pathways, and unresolved translational challenges of engineered exosomes. This review contextualizes

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exosome function within sepsis' biphasic immuno-metabolic pathology, emphasizes their inter-organ communication role, summarizes advances in natural (mesenchymal stem cell-derived) and engineered (folate-functionalized) exosome therapies, and highlights their "context-dependent" nature (pathogenic early, therapeutically promising late). It draws on evidence (LPS-induced exosomes protecting CLP-model mice[9]) to provide an integrated framework for exosomes as both pathological mediators and therapeutic tools in sepsis. In addition, we critically evaluate both pathogenic and therapeutic roles of exosomes in sepsis, highlight mechanistic pathways, and identify translational challenges. To lay the groundwork, we first clarify exosome biogenesis.

Biogenesis Process of Mammalian Exosomes

Exosomes are bio-nanoscale spherical lipid bilayer vesicles secreted by cells[10] and classified as extracellular vesicle (EVs).[11] A distinction exists between mammalian exosomes (MEs) and bacterial exosomes, such as outer membrane vesicles (OMVs). MEs are spherical with a diameter range of 40–150 nm,[12] and are derived from the endocytic compartment of cells, specifically multivesicular bodies (MVBs).[13] In contrast, OMVs are also spherical but have a diameter of 20–250 nm and originate from the envelope of gram-negative bacteria.[14] (Figure 1) Notably, these bacterial exosomes (OMVs) and exosomes from other pathogen types play distinct roles in different sepsis subtypes: Gram-negative sepsis exosomes (bacterial OMVs) carry LPS to activate TLR4/NF-κB, while Gram-positive ones deliver toxins (pneumolysin) to induce pyroptosis; viral sepsis exosomes shuttle viral RNA to evade host immunity.

Synthesis

The synthesis of exosomes begins with endocytosis of the cell membrane, where molecular substances are incorporated into early endosomes.[15] The cell membrane invaginates to form early endosomes,[16] and the invaginating membrane portion forms vesicles.[17] Some early endosomes enter the endosomal maturation pathway, where molecular substances are concentrated in the central vacuole region to form late endosomes,[18] accompanied by changes in the endosomal

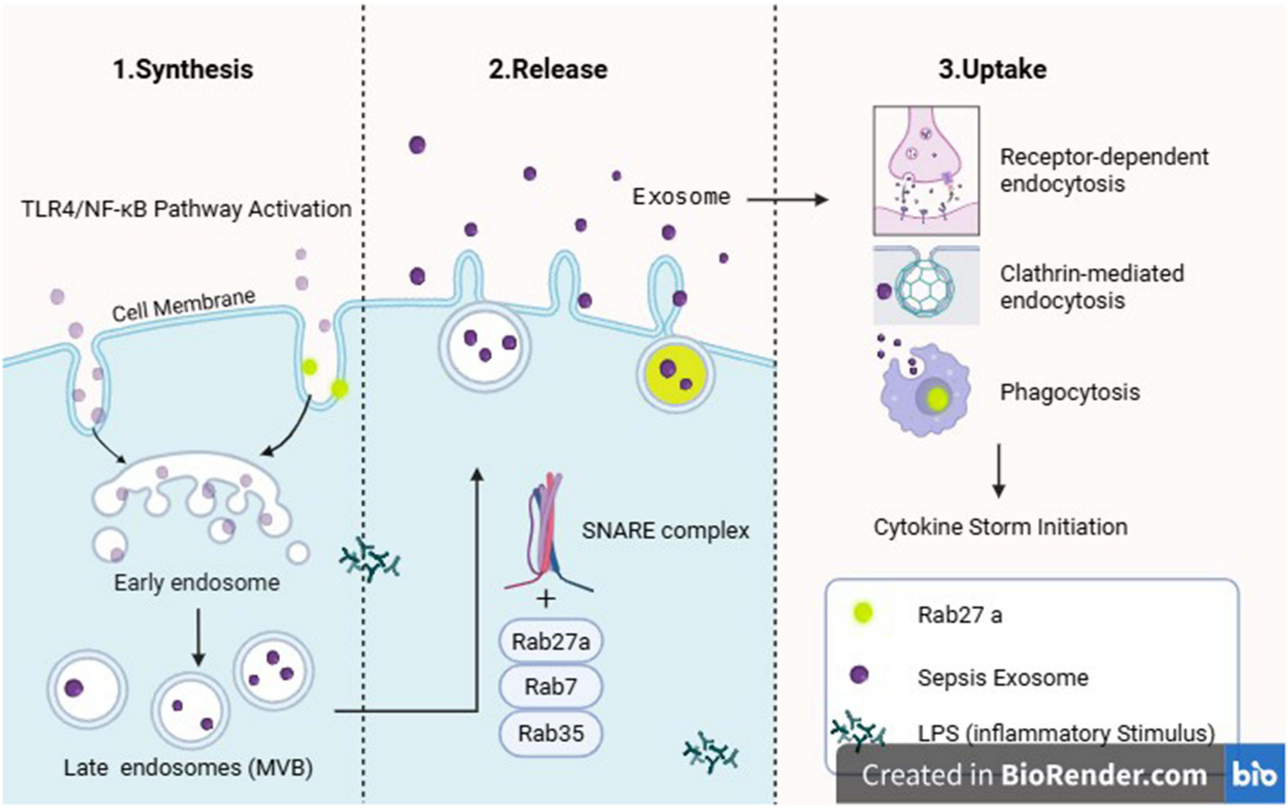

Figure 1 The process of synthesis, release, and uptake of mammalian exosome-associated sepsis.

membrane. Classical endosomal sorting complexes required for transport (ESCRT)-dependent or -independent mechanisms are involved in vesicle initiation and maturation,[19] enclosing molecular substances in intraluminal vesicles (ILVs), and generating MVBs.[20] Dynamic reorganization of the cytoskeleton transports MVBs near the plasma membrane in preparation for exosome release.[21]

Release

MVBs fuse with the plasma membrane to release ILVs (exosomes) via exocytosis.[22,23] Various cell types, including reticulocytes, platelets, macrophages, dendritic cells (DCs), B cells, and T cells, can release exosomes into intercellular spaces.[24,25] Rab and SNARE proteins synergistically regulate MVB trafficking, localization, and fusion to ensure proper exosome release.[21] Rab proteins, which belong to the small GTPase family, recruit effector proteins involved in membrane recognition, vesicle formation, and trafficking. Specific Rab proteins such as Rab7, Rab27a, and Rab35 regulate the localization of MVBs and their binding to plasma membranes.[26] Calcium (Ca^{2+}) regulates the activity of Rab proteins.[27] SNARE proteins are core components of membrane fusion,[21] with the SNARE complex, characterized by a "helix-shaped" structure consisting of v-SNARE and t-SNARE to drive membrane fusion.[28] The activity of SNARE proteins is regulated by various factors, including calcium ion concentration and cytoskeletal dynamics.[29] Rab proteins provide the necessary conditions for the assembly and membrane fusion of the SNARE complex by regulating the transport and localization of MVBs. The SNARE complex directly mediates the fusion of MVBs and the plasma membrane to complete the exosome release process.[21]

Uptake

The primary mechanisms by which exosomes are internalized include lipid raft-mediated endocytosis,[30] clathrin-mediated endocytosis,[31] phagocytosis,[32] receptor-dependent uptake,[33] direct membrane fusion,[34] and pinocytosis and vesicle fusion.[35] The uptake of exosomes is selective, specifically targeting recipient cells and participating in diverse cellular communication processes. With exosome basics clear, we turn to sepsis immunity.

Early and mid-to-late immune Responses in sepsis

Early stage (hours to days): The initial phase of sepsis is characterized by a predominance of innate immunity. Antigen-presenting cells (APCs) utilize the innate immune system (IIS) through specific pathogen recognition receptors (PRRs), such as Toll-like receptors (TLRs), which recognize pathogen-associated molecular patterns (PAMPs).[36,37] This interaction triggers downstream intracellular inflammatory signaling pathways, among which NF-κB acts as a key mediator.[38] This process is accompanied by the activation of inflammasomes, the complement system, an imbalance in macrophage pro-inflammatory and anti-inflammatory responses, and the formation of neutrophil extracellular traps (NETs).[39] These events lead to excessive release of inflammatory cytokines,[40] including TNF-α, IL-1β, and HMGB1. The massive release of inflammatory mediators further activates additional immune cells, creating an inflammatory cascade that can potentially result in cytokine release syndrome or "cytokine storm".[41]

Mid-to-late stage (days to weeks): As sepsis progresses, the adaptive immune system (AIS) becomes more prominent. AIS responds to specific receptors, such as TLRs, on the surface of APCs,[42] thereby activating T-cell responses.[43] Sepsis disrupts the balance between different T cell subsets, particularly the Th17/Treg ratio in CD4+T,[44,45] where over-activation leads to an inflammatory storm. Key features of the adaptive immune response in sepsis include: Th17 cell overactivation: Recruits neutrophils, exacerbating tissue inflammation and organ damage; Treg cell amplification: suppression of the immune response, potentially worsening immune paralysis and increasing the risk of secondary infection;[46] CD8+ T cell depletion: results from continuous antigenic stimulation,[47] leading to loss of cytotoxic function and metabolic disorders that accelerate apoptosis;[48] and T cell depletion, which is caused by sustained antigen load and extremely high levels of pro-inflammatory and anti-inflammatory cytokines.[49,50] The humoral immune response is also affected, characterized by a delayed antibody response involving B cells, inadequate specific IgM production, and decreased levels of IgG and IgA,[51] which are ineffective in neutralizing exotoxins.[52] This repeated circulation leads to B-cell depletion and expanded Breg secretion of IL-10, further aggravating the immunosuppressive state.[53] The

pathophysiology of sepsis is fundamentally driven by the immune imbalance[54] between the overactivation of innate immunity and profound suppression of adaptive immunity in sepsis.[55]

Early excessive inflammation and late-stage immune paralysis represent a bidirectional imbalance and synergistic damage in sepsis. Early excessive inflammation directly damages tissues through cytokines and metabolic products, while late-stage immune paralysis increases the risk of persistent infection. Long-term immune dysfunction and its consequences in sepsis survivors include: ① Persistent immune suppression and increased susceptibility to infection.[56] ② Chronic inflammation and metabolic disorders.[57] ③ Organ dysfunction and fibrosis.[58] ④ Neurocognitive and psychological disorders, etc.[59] Targeted immunomodulatory therapies are needed to improve outcomes for survivors. Building on sepsis immunity, we analyze exosome mechanisms.

Exosomes in Sepsis: Pathological Mechanism and Therapy

The lipid bilayer membrane of exosomes is rich in various components, including sphingomyelin, cholesterol, cytoskeletal proteins, ESCRT, adhesion molecules (quadruple transmembrane proteins, tetraspanins), transport/binding proteins, enzymes, and signaling molecules.[60,61] This composition facilitates fusion with target cells and encapsulation of pathogens, proteins, and nucleic acids.[62] Exosomes serve several critical functions: 1) Maintaining intercellular and inter-organ communication: exosomes facilitate the transfer of bioactive molecules between epithelial, endothelial, and immune cells.[63] By traveling through the circulatory system, exosomes can reach distant organs.[64] 2) Modulating immune responses: exosomes can either activate or suppress immune responses by delivering antigens, costimulatory molecules, or immunosuppressive factors.[65,66] 3) Preservation of cellular homeostasis and provision of metabolic support: exosomes contribute to tissue repair, cellular waste removal,[67] and energy support for target cells.[68] They also regulate lipid metabolism,[69,70] deliver miRNAs, and protect mitochondrial functions.[71] In the following sections, we summarize the specific regulatory mechanisms of exosomes in sepsis from four perspectives.

Pathogen-Derived Exosomes Trigger the Early Inflammatory Response

Exosomes play a crucial role in pathogen-host interactions and the regulation of inflammation. OMVs released by gram-negative bacteria contain endotoxins, specifically LPS,[72] which activate the host TLR4/NF-κB pathway and NLRP3 inflammasomes,[73] thereby amplifying the inflammatory cascade. In the serum exosomes of patients with sepsis, there is a significant increase in mRNA expression associated with redox metabolism and miRNA expression,[74] which enhances the inflammatory response. Viral RNA or fungal β-glucan can evade immune recognition via exosomes, facilitating the spread of infection and activating the Dectin-1/TLR pathway.[75] Furthermore, mesenchymal stem cell (MSC)-derived exosomes delivering miR-27b have the potential to downregulate JMJD3 and NF-κB/p65, thereby inhibiting inflammatory responses and mitigating sepsis.[76]

Immune Cell-Derived Exosomes Exacerbate the Cytokine Storm

Exosomes play a crucial role in modulating the immune response of various cell types, including macrophages, neutrophils, and T cells. Macrophages secrete high mobility group box 1 (HMGB1)-containing exosomes,[77] which activate the NF-κB pathway via receptor for advanced glycation end products (RAGE) receptors, thereby amplifying the inflammatory cascade.[78] Activation of the NLRP3 inflammasome[79] is facilitated by exosomes delivering apoptosis-associated speck-like protein containing a CARD (ASC) protein to macrophages,[80] inducing IL-1β release and pyroptosis, and consequently amplifying systemic inflammation.[81] Neutrophils release exosomes that carry NETs that promote thrombosis.[82] Exosomes mediate the release of the deleterious protein (HMGB1) via ESCRT-dependent sorting; they also induce NETs (via miR-223) and METs (via DAMPs like mtDNA), which trigger organ injury (renal necrosis, hepatic sinusoidal damage). Exosomal programmed death-ligand 1 (PD-L1) binds to programmed cell death protein 1 (PD-1) on T cells, promoting apoptosis and inhibiting effector function and T cell activity, leading to immune paralysis.[83] Exosomal TGF-β and IL-10 drive Treg amplification and inhibit excessive immune responses.[84] MSC-derived exosomes can deliver anti-inflammatory factors, such as IL-10 and TGF-β, inhibit macrophage polarization to pro-inflammatory phenotypes, and alleviate tissue damage.[85] Additionally, MSC exosomes regulate the macrophage high-mobility group AT-hook 2 (HMGA2)/NF-κB pathway by delivering miR-let7 to inhibit the inflammatory response in atherosclerosis[86] and miR-146a, targeting TRAF6 to inhibit the TLR4/NF-κB pathway, thereby alleviating inflammatory storms.[87]

Endothelial-Derived Exosomes Contribute to DIC

Exosomes are involved in regulating vascular function and coagulation. Hypoxic conditions result in endothelial cell damage, leading to the release of intercellular adhesion molecule (ICAM-1)-containing exosomes and recruitment of leukocytes in response to inflammatory stimuli.[88] LPS induces upregulation of ICAM-1.[89] Exosomal miR-1-3p contributes to endothelial cell dysfunction by targeting stress-associated endoplasmic reticulum protein 1 (SERP1), thereby increasing vascular permeability and resulting in pulmonary vascular leakage and interstitial edema.[90] Exosomal damage-associated molecular patterns (DAMPs) disrupt endothelial junctions, causing microvascular leakage and hypotension.[91] Tissue factor (TF) and phosphatidylserine (PS) exposed on the exosome surface activate the coagulation cascade, exacerbating disseminated intravascular coagulation (DIC).[92] Exosomes also deliver plasminogen activator inhibitor-1 (PAI-1), inhibiting fibrinolysis and leading to persistent thrombosis.[93] Pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF), present in exosomes may facilitate the repair of ischemic tissues and improve perfusion.[94] Exosomal miR-126 derived from endothelial progenitor cells (EPCs) inhibits endothelial activation and coagulation by downregulating adhesion molecules and pro-coagulation pathways, thereby preventing microvascular dysfunction and improving sepsis prognosis.[95]

Metabolic Disorders and Mitochondrial Damage

Exosomes carrying miR-34a inhibit the respiratory chain complex, increase lactate accumulation, and lead to mitochondrial dysfunction.[96] miR-34a promotes TLR6 expression and exacerbates infection-induced inflammation in ALI/ARDS.[97] Mitochondrial DNA (mtDNA) carried by exosomes activates the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway, exacerbating inflammation and apoptosis.[98] Exosomal miRNAs can affect immune cell metabolic reprogramming by regulating glycolysis and oxidative phosphorylation.[99] Exosome-carried miR-27a promotes macrophage pro-inflammatory polarization, enhancing the Warburg effect, which increases glycolysis.[100] Exosomes inhibit mTOR signaling by delivering miR-148a (an AMP-activated protein kinase [AMPK] activator) and coordinate glycolipid metabolism and mitochondrial biogenesis.[101] Engineered exosomes can target anti-inflammatory miRNAs such as miR-223 and miR-146a[102] or mitochondrial coenzymes (such as CoQ10), which restore metabolism and mitochondrial function[103] (Table 1).

The Interaction Between Organ Dysfunction and Exosomes in Sepsis

Exosomes in sepsis are a double-edged sword: they propagate organ dysfunction through inflammatory, coagulatory, and metabolic cascades. But exosomes also offer therapeutic potential through immune regulation and tissue repair. The interaction between sepsis-induced organ dysfunction and exosome-mediated signaling, with exosomes acting as key messengers in the systemic spread of injury. Dysfunctional organs release exosomes, which trigger or directly damage distant tissues, thereby generating a self-reinforcing cascade of inflammation and tissue damage.

Lung-kidney axis: Inflammatory mediators (such as IL-8 and CXCL10) induce chemotactic neutrophil infiltration into alveoli.[104] Neutrophil-derived proteases (such as elastases), reactive oxygen species (ROS), and inflammatory exosomes disrupt the alveolar epithelial and endothelial barriers,[109] leading to edema and atelectasis.[105] Inflammatory mediators such as IL-1β inhibit type II lung cells from producing surfactant, increasing alveolar surface tension and hypoxemia.[106] Both conditions lead to acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). Injured alveolar epithelial cells and pulmonary endothelial cells release exosomes containing miR-223 and TREM-1.[107,108] These exosomes are taken up by renal tubular cells, promoting neutrophil infiltration and tubular necrosis in acute kidney injury (AKI).[110] AKI releases exosomes containing HMGB1,[111] which exacerbate pulmonary inflammation by activating alveolar macrophages and enhancing neutrophil extravasation in ARDS.[112]

Gut-liver-brain axis: Ischemia and inflammation lead to apoptosis of intestinal epithelial cells, it causes intestinal epithelial barrier disruption and allows bacteria and endotoxins to translocate into the portal venous circulation,[113] activating hepatic Kupffer cells,[114] and it can release exosomes containing TNF-α and IL-6,[115] amplifying liver inflammation and fibrosis, leading to liver dysfunction.[116] Cytokines such as TNF-α and IL-6 increase the permeability of the blood-brain barrier,[117] allowing toxins to enter the brain and causing neurotoxicity and septic encephalopathy.[118]

Table 1 Bidirectional Regulatory Roles of Exosomes in Sepsis (Pathology vs Therapy)

Regulation Dimension	Pathological Role (Harmful)	Regulation Dimension (Protective)
Pathogen-Host Interaction & Inflammation	Gram-negative bacterial OMVs (LPS) → Activate TLR4/NF-κB and NLRP3 inflammasome → amplified inflammation;[79] Septic serum exosomes → Elevated redox-related mRNA/miRNA → enhanced inflammation.[80]	MSC-exosomes (miR-27b) → Downregulate JMJD3/NF-κB/p65 → inhibit inflammation and sepsis progression.[82]
Immune Cell Function	1. Macrophage-exosomes (HMGB1) → Activate NF-κB/NLRP3 → pyroptosis;[83,87] 2. Neutrophil-exosomes (NETs) → Promote thrombosis;[88] 3. Exosomal PD-L1 → Bind T-cell PD-1 → immune paralysis.[89]	1. Exosomes (TGF-β/IL-10) → Expand Tregs → suppress excessive immunity;[90] 2. MSC-exosomes (miR-146a) → Target TRAF6 → inhibit TLR4/NF-κB → reduce inflammation.[93]
Endothelial/ Vascular/ Coagulation	1. Exosomes (ICAM-1) → Recruit leukocytes → enhanced inflammation;[94] 2. Exosomal miR-1-3p (target SERP1) → Pulmonary leakage/edema;[96] 3. Exosomal TF/PS → Aggravate DIC;[98] 4. Exosomal PAI-1 → Sustained thrombosis.[99]	1. Exosomes (VEGF/FGF) → Repair ischemic tissue → improve perfusion;[100] 2. EPC-exosomes (miR-126) → Downregulate adhesion/pro-coagulant factors → improve prognosis.[101]
Metabolism & Mitochondria	1. Exosomal miR-34a → Inhibit respiratory complex → mitochondrial dysfunction and ALI/ARDS;[102,103] 2. Exosomal mtDNA → Activate cGAS-STING → inflammation/apoptosis;[104] 3. Exosomal miR-27a → Promote M1 polarization → enhanced glycolysis.[105]	1. Exosomes (miR-148a, AMPK activator) → Inhibit mTOR → regulate glycolipid metabolism/mitochondrial biogenesis;[106] 2. Engineered exosomes (miR-223/146a, CoQ10) → Restore metabolism/mitochondrial function.[107,108]

Heart-multiple organs: Exosomes carrying TNF-α and IL-1β inhibit β-adrenergic receptor signaling and sarcoplasmic reticulum calcium ATPase (SERCA2a),[119] it reduces calcium ion recycling, decreases myocardial contractility, and leads to impaired myocardial contraction and relaxation function and myocardial ischemia. It ultimately results in heart failure.[120] Therefore, this leads to ①insufficient portal vein perfusion, reduced microvascular blood flow in hepatic sinusoids, and impaired nutrient and oxygen delivery to hepatocytes, exacerbating hepatic cell injury.[121] ②Reduced renal blood flow and inadequate blood perfusion[122] cause renal vasoconstriction, decreased glomerular filtration rate, and AKI.[123] ③Reduced mesenteric blood flow leads to mucosal atrophy and ulcers,[124] gastrointestinal (GI) mucosal damage, and impaired intestinal barrier function.[125]

Immune cells-endothelial cells: Activated neutrophils and monocytes release NETs-coated exosomes,[39] promoting microthrombosis in the lungs, kidneys, and brain, leading to DIC and multi-organ ischemia.[92] Injured endothelial cells release exosomes carrying PD-L1, thereby suppressing T cell function,[83] leading to immune paralysis and increased susceptibility to secondary infections.[46]

In sepsis, exosomes act as systemic "signaling hubs" connecting organ dysfunction, enabling bidirectional flow of injury signals between tissues. This interplay transforms local infection into systemic infection. Therefore, targeting the exosome pathway by inhibiting harmful cargo transfer or enhancing protective signaling may disrupt the vicious cycle of sepsis and improve outcomes in critically ill patients. Shifting to therapy, we explore exosome sources.

The Source of Exosomes and Their Role in Sepsis Treatment

Self-Derived Exosomes

Exosomes derived from MSCs and adipose-derived stem cells (ADSCs) have extensive applications owing to their inherent anti-inflammatory properties and low immunogenicity (Figure 2).[126] (1) MSCs: Exosomes containing miR-140-3p ameliorate sepsis by modulating HMGB1 and S-lactyl glutathione metabolism, addressing cognitive dysfunction in encephalopathy.[127] Exosome-functionalized sweroside attenuates infection-induced myocardial injury by regulating oxidative stress and apoptosis in rats.[128] Exosomes reduce infection-associated acute liver injury by inhibiting MALAT1 through microRNA-26a-5p.[129] (2) ADSCs: Exosomes regulate hippocampal pyroptosis in sepsis and provide neuroprotection in encephalopathy.[130] Exosomal miR-125b-5p attenuates ferroptosis in non-invasive pulmonary microvascular endothelial cells through the Keap1/Nrf2/GPX4 axis.[131]

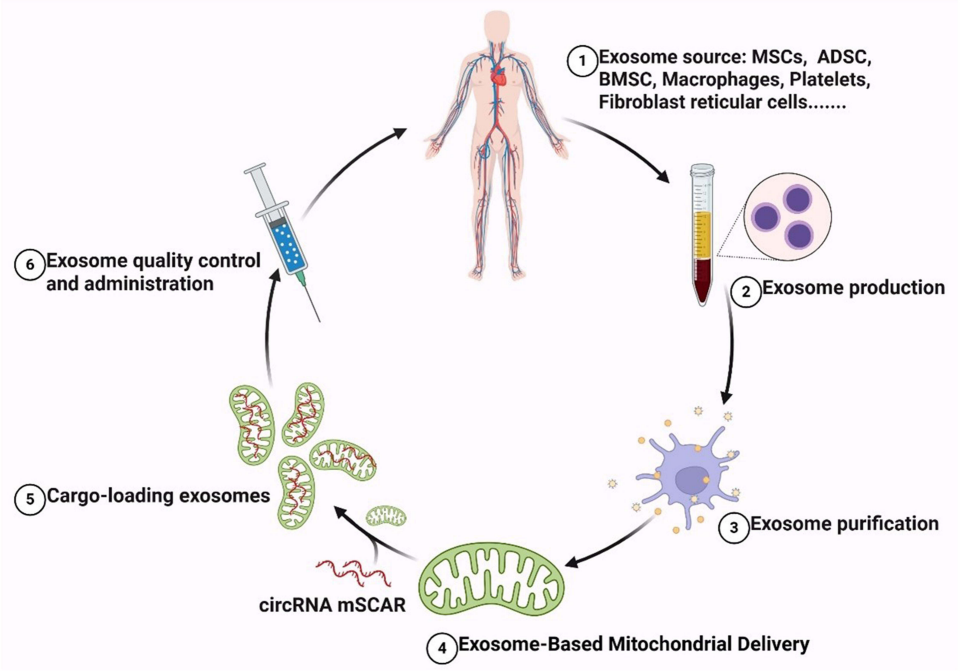

Figure 2 The entire process of sourcing, production, purification, mitochondrial delivery, cargo-loading, and quality control and management of self-derived exosomes.

Rat bone marrow mesenchymal stem cell (BMSC)-derived exosomes containing miR-125b-5p inhibit infection-induced ALI via STAT3-mediated macrophage pyroptosis.[132] Other sources of natural exosomes: Fibroblast reticulocyte-derived exosomes can impede NLRP3 inflammasome activation.[133] Platelet exosome-derived miR-223-3p mediates NLRP3 regulation of infection-induced pyroptosis in a cell model of AKI by targeting NLRP3,[134] thereby inhibiting cell pyroptosis and improving kidney function, which increases survival in infectious conditions. Exosome-based mitochondrial delivery of circular RNA mSCAR (circRNA mSCAR) coordinates macrophage activation to alleviate infectivity.[135] Exosome-shuttling miR-150-5p from LPS-pretreated MSCs is downregulated by Irs1 to enhance the PI3K/Akt/mTOR pathway and promote anti-inflammatory macrophage polarization.[136] Exosomal PGE2 from anti-inflammatory macrophages inhibits neutrophil recruitment and NET formation through infectious mesolipid mediator class switching,[137] thereby maintaining organ function.

Engineered Exosomes

A novel exosome-like nanovesicle derived from Catharanthus roseus elicits immunostimulatory effects via the TNF-α/NF-κB/PU.1 axis.[138] Folic acid-functionalized exosomes loaded with resveratrol and celastrol exhibit enhanced therapeutic efficacy against infectious diseases.[139] Milk-derived exosomes (mEx) serve as a promising vehicle for oral drug delivery; specifically, Oral TF-mEx@FGF21 alleviates infectious inflammation and multiorgan damage.[140] A nanosystem preparation involving tumor cell-derived exosome hybridization, loaded with rhein and tanshinone IIA, enhances macrophage internalization, reduces TNF-α expression, inhibits apoptosis, regulates intestinal flora, and mitigates immunosuppression.[141] MEP (HucMSCs-EXOs loaded with anti-PD-1 peptide) represent a novel therapeutic approach for PD-1 in septic ALI, reducing the expression of inflammasome-related genes and pro-inflammatory macrophage marker iNOS, thereby diminishing inflammation.[142] Neutrophil membrane-engineered ginseng root exosome-loaded miRNA182-5p targets the NOX4/Drp-1/NLRP3 signaling pathway to alleviate infectious ALI.[143] Mannose-modified exosomes loaded with MiR-23b-3p, targeting alveolar macrophages attenuate ALI in infectious diseases[144] (Tables 2 and 3).

Table 2 Therapeutic Modification of Exosomes & Significance in Sepsis

Modification Type	Specific Strategy	Core Role in Sepsis
Ligand Functionalization[139]	Folate-functionalized exosomes (resveratrol/celastrol-loaded)	Target inflamed tissues; boost anti-inflammatory efficacy
Peptide Loading[142]	HucMSCs-EXOs + anti-PD-1 peptide (MEP)	Block PD-L1/PD-1; ease septic acute lung injury (ALI)
miRNA Loading[144]	1. Neutrophil membrane-ginseng exosomes + miRNA182-5p 2. Mannose-exosomes + MiR-23b-3p	1. Inhibit NOX4/Drp-1/NLRP3; reduce ALI 2. Target alveolar macrophages; suppress inflammation
TCM Component Loading[141]	Tumor exosome hybrids + rhein/tanshinone IIA	Enhance macrophage uptake; reduce apoptosis/immunosuppression
Small Molecule Conjugation[128]	MSCs-exosomes + sweroside	Regulate oxidative stress; protect myocardium from sepsis injury
Membrane Camouflage[143]	Ginseng exosomes coated with neutrophil membrane	Mimic neutrophil chemotaxis; target ALI tissues

Table 3 Classification, Advantages, and Limitations of Exosomes Involved in the Treatment of Sepsis

Classify	Natural Exosomes	Engineered Exosomes
Source	MSCs,[127] ADSC,[131] BMSC.[132]	Plant,[138] Milk,[140] MEP.[142]
Advantages	Natural anti-inflammatory, low immunogenicity,[126] biocompatibility, natural targeting, barrier penetration, from a wide range of sources.	Enhanced targeting, optimized drug-loading capacity, controllable load, and multifunctional synergy.[143]
Limitations	Heterogeneity leads to unstable efficacy, insufficient targeting, low drug loading efficiency,[145] production and purification bottlenecks.	Safety and immunogenicity risks, mechanisms of action, and long-term effects are unknown[146] Production complexity and high cost, quality control is difficult.

Table 4 Exosome-Associated Biomarkers & Preclinical Progress in Sepsis

Biomarker Type	Specific Biomarker	Key Clinical Progress
mRNA	Redox metabolism-related[74]	Highly expressed in sepsis patients' serum exosomes; potential early diagnostic indicator.
Protein	HMGB1[3,77,111]	Correlates with sepsis severity (septic shock) and poor prognosis (MODS risk).
	PD-L1[83]	High in late sepsis; linked to immune paralysis and secondary infection risk.
	ICAM-1[88,89]	Correlates with endothelial injury; used to monitor vascular dysfunction progression.
miRNA	miR-126[95]	Preclinical efficacy confirmed; optimizing GMP production for Phase I trial.
	MSC-exosomal miRNAs[76,127]	Phase I trials ongoing to test safety/efficacy in moderate-severe sepsis.
Exosome Tools	miRNA panel (miR-155+miR-146a+miR-223)[4–6]	Sensitivity 89%, specificity 82% for distinguishing sepsis from non-infectious SIRS.
	MSC-Exosome[126,145]	Phase I/II trials (NCT04852314) ongoing; reduces inflammatory cytokines safely.

Discussion

Exosomes function as both pathological mediators and potential therapeutic agents in sepsis, but this review's key novelty—setting it apart from prior works—lies in its systemic framing: unlike most earlier studies that reduce exosomes to isolated players in inflammation or therapy and fail to connect them to sepsis' defining multi-organ failure cascade, this work positions exosomes as core regulators of the sepsis-associated multi-organ crosstalk axis. It directly links their molecular functions (miRNA shuttling to distant organs like the kidneys or lungs) to the progressive worsening of organ dysfunction, filling a longstanding literature gap that overlooked how exosomes drive inter-organ damage spread in sepsis.

The sharp take-home message is not a generic restatement of their dual role, but a targeted insight: exosomes are pivotal hubs governing inter-organ injury propagation in sepsis. This unique positioning means they can simultaneously disrupt harmful inter-organ signaling (pro-inflammatory cytokine transport) and deliver repair molecules to damaged tissues—an advantage no other sepsis therapy currently offers—moving far beyond descriptive claims to an actionable conclusion for researchers.

For future directions, we prioritize three urgent, innovative gaps over scattered, low-priority ideas (untested AI peptide designs or basic hydrogel concepts): 1) Leveraging single-cell sequencing to decode cell-type-specific exosomal miRNA signatures that drive metabolic reprogramming—a process now confirmed to underpin irreversible organ damage in sepsis, making this the field's most critical mechanism gap; 2) Integrate exosomes with organoid models (sepsis-induced lung or liver organoids) to optimize GMP-standardized production and targeted delivery, addressing scalability and safety flaws that have stalled clinical progress; 3) Develop exosome-based point-of-care testing (POCT) for early sepsis warning (rapid detection of exosomal miRNA biomarkers in emergency settings) and launch Phase I/II trials to validate both diagnostic markers and therapeutic efficacy in diverse patient groups (elderly or immunocompromised patients).

Clinically, the bench-to-bedside gap remains wide: most exosome research stays in preclinical models, with no consensus on GMP manufacturing protocols (a non-negotiable prerequisite for human use) and little progress toward regulatory approval (FDA/EMA guidelines for exosome therapeutics). Addressing these two barriers—alongside the prioritized research gaps—is essential to turn exosomes from promising lab tools into tangible, life-saving interventions for sepsis patients (Table 4).

Conclusion

Exosomes act as a pivotal link mediating sepsis pathogenesis, inter-organ crosstalk, and therapeutic intervention, with their roles—either harmful or beneficial—strictly dictated by the stage of sepsis and the exosomes' cellular source. Pathologically, exosomes exert harmful effects in a stage-dependent manner: in the early hyperinflammatory stage, activated macrophages release exosomes containing HMGB1/miR-155, activating pathways to amplify cytokine storms, which triggers SIRS. Mid-late, exosomes from apoptotic T/regulatory macrophages deliver PD-L1/miR-146a, inducing T-cell exhaustion, raising infection risk. As hubs, they spread organ injury, worsening dysfunction to form a cycle.

Therapeutically, exosomes become beneficial when targeted: Natural exosomes from MSCs or ADSCs leverage low immunogenicity and anti-inflammatory factors (TGF-β, IL-10) to ease inflammation without weakening the body's residual immunity. Engineered variants are modified to enhance targeted drug delivery to inflamed tissues, effectively bridging immunomodulation and the repair of damaged organs.

This review's unique contribution lies in systematically integrating exosomes' mechanisms across sepsis-related immune, organ, and metabolic processes—distinct from previous studies focusing on single aspects. It clarifies the "context-dependent" nature of exosomes' dual roles (pathogenic vs therapeutic) and organizes translational progress of different exosome sources, providing a comprehensive framework for understanding exosome-sepsis interactions. Notably, practical limitations persist: heterogeneous natural exosome composition causes unstable efficacy; large-scale standardized production (purification, quality control) remains a bottleneck; long-term safety/immunogenicity of engineered exosomes lacks clinical validation; and variability in isolation methods and patient heterogeneity further hinder translation. Future research should prioritize elucidating exosomal miRNA-metabolic reprogramming crosstalk and optimizing production/delivery technologies. Despite challenges, exosomes' unique dual properties position them as a promising tool to revolutionize sepsis care, paving the way for more effective, personalized strategies to mitigate this life-threatening syndrome's global burden.

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Disclosure

The authors declare that there is no conflict of interest in this work.

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