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THE ROLES OF EXTRACELLULAR VESICLES IN SEPSIS AND SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

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ABSTRACT—Sepsis is a life-threatening organ dysfunction, caused by dysregulation of the host response to infection. To understand the underlying mechanisms of sepsis, the vast spectrum of extracellular vesicles (EVs) is gaining importance in this research field. A connection between EVs and sepsis was shown in 1998 in an endotoxemia pig model. Since then, the number of studies describing EVs as markers and mediators of sepsis increased steadily. Extracellular vesicles in sepsis could be friends and foes at the same time depending on their origin and cargo. On the one hand, transfer of EVs or outer membrane vesicles can induce sepsis or systemic inflammatory response syndrome with comparable efficiency as well-established methods, such as cecal ligation puncture or lipopolysaccharide injection. On the other hand, EVs could provide certain therapeutic effects, mediated *via* reduction of reactive oxygen species, inflammatory cytokines and chemokines, influence on macrophage polarization and apoptosis, as well as increase of anti-inflammatory cytokines. Moreover, EVs could be helpful in the diagnosis of sepsis. Extracellular vesicles of different cellular origin, such as leucocytes, macrophages, platelets, and granulocytes, have been suggested as potential sepsis biomarkers. They ensure the diagnosis of sepsis earlier than classical clinical inflammation markers, such as C-reactive protein, leucocytes, or IL-6.
This review summarizes the three roles of EVs in sepsis—mediator/inducer, biomarker, and therapeutic tool.

KEYWORDS—Extracellular vesicles, microparticles, microvesicles, sepsis, SIRS, septic cardiomyopathy, septic AKI, septic ARDS, DIC, MSCs

INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction, which is induced by dysregulation of the host response to infection. In clinical settings, sepsis can be represented by an increase in the Sequential Organ Failure Assessment (SOFA) score of ≥2 points, which strongly correlates with an increase in mortality >10% (1,2). Moreover, sepsis is a major public health concern, responsible for costs of more than $20 billion of the total US hospital costs (3). The vast spectrum of extracellular vesicles (EVs) is gaining importance in research studies focused on understanding the underlying mechanism of sepsis. Sepsis is caused by a systemic immune response in which EVs originating from different types of cells play diverse and crucial roles. The term "extracellular vesicles" is defined as small particles, released from cells, which are coated by a lipid bilayer and cannot replicate (4). Historically, EVs were subdivided in the following three main groups: exosomes (Exos), microvesicles (MVs), and apoptotic bodies (5,6). Exos and MVs are both released from healthy, intact cells, while apoptotic bodies are caused by cell apoptosis. Exosomes are the smallest EV population with a size between 30 and 150 nm. Because of their endocytic origin, Exos are commonly rich in endosome-associated proteins, such as Rab GTPases, SNAREs, annexins, and flotillin. Tetraspanins, a family of membrane proteins (CD9, CD63, and CD81), are also abundantly present in Exos and are considered as usable Exos markers (5,7,8). Microvesicles are shed from the budding plasma membrane, vary in size between 100 and 800 nm, and are rich in CD63, CD81, and annexin V proteins. The biggest in size population of EVs are the apoptotic bodies, ranging in size from 200 to 5,000 nm and expressing annexin V (5,7,8). Exos and MVs are described as important factors of the intercellular communication between cells in close neighborhood but can also act far away from the parenteral cell. Extracellular vesicles are loaded with proteins, such as chemokines and cytokines, heat shock proteins, MHC proteins, mRNA or micro RNA (miRNA), but also DNA. After active release from parental cells, the EVs could be responsible for changes on cell metabolism, function, and life span of the targeting cells (6,9,10). Extracellular vesicles are found in most body fluids, such as blood, urine, salvia, etc. Furthermore, the surface receptors of the EVs are providing the information from which cells the EVs are released (6,11,12).

A connection between EVs and sepsis was first shown in 1998 in an endotoxemia pig model (13). Since then, the number of studies focused on EVs as markers and mediators in sepsis increased steadily. Noteworthy, most studies (71%) that focused on this topic have been published in the last 5 years (PubMed April 2022). "EVs in sepsis" is a trendy issue that has seen a significant surge in research findings in recent years. This review summarizes the existing literature on sepsis/systemic inflammatory response syndrome (SIRS) and the role of EVs in it. The review specifically highlights the potential of EVs as markers, mediators, and therapeutic tool in sepsis and SIRS. To provide a systemic review of the existing literature, a "PubMed" research with the key words "extracellular vesicles sepsis" and "extracellular vesicles SIRS" was conducted. All in all, 351 articles were

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found, whereas 125 provided relevant information about EVs in sepsis or SIRS.

Extracellular vesicles as inducers of sepsis

The observations that EVs could induce sepsis originate from experimental studies. Recently, the list of classical inductors of experimental sepsis—LPS injection (i.v. or i.p) or cecal ligation and puncture (CLP)—was extended with a new one of EV origin. A new sepsis model based on the injection of a special type of EVs—outer membrane vesicles (OMVs)—has been described in the literature in the last few years. The OMVs are EVs, which are released from gram-negative bacteria, for example, *Escherichia coli*, and have spherical membrane-enclosed entities of endocytic origin (14). It was shown that injection of 5 to 25 μg of OMVs i.p. led to the clinical picture of sepsis in mice (15). In vitro stimulation of macrophages with OMV led to IL-6 and TNF production. Outer membrane vesicle–treated endothelial cells were shown to release high amounts of IL-8 in vitro (16). The transfer of OMVs was described to play an important role in the endothelial activation, because it significantly increased expression of tissue factor, P-selectin and E-selectin, and decreased thrombomodulin expression (17).

The role of EVs as sepsis inductors was also shown in experiments with septic-EV transfer. The transfer in healthy mice led to the induction of a sepsis-like condition indicated by leukopenia, intrahepatic inflammation, and bone marrow hyperplasia (18). The transfer of MVs from septic rats in healthy animals led to a decrease in the MAP and induced superoxide ion production, Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation, and stimulated NO synthesis (19). Similarly, i.p. injection of fecal EVs was shown to lead to both, local and systemic inflammation, including the lung tissue. However, this fecal EV–mediated sepsis was attenuated in mice lacking toll-like receptor (TLR) 2 or 4 (20).

The specificity of sepsis-EV function was shown in experiments with transfer of brain EVs. It was shown that transfer of brain-derived EVs isolated from CLP-sepsis model rats, but not from sham rats, led to the activation of coagulation and induced lung, liver, and kidney inflammation, as well as apoptosis (21). Microvesicles from septic patients were able to induce apoptosis in lymphocytes (22) and further influence the differentiation of T cells (23). Moreover, EVs were shown to be able to worsen the immune dysfunction in sepsis. The application of neutrophil-derived EVs from septic mice increased bacterial load, decreased neutrophil recruitment, increased expression of IL-10, and worsened mortality after sepsis (24). Platelet-derived Exos, obtained from septic patients and carrying nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity, seem to induce vascular dysfunction in sepsis *via* vascular cell apoptosis (25).

Extracellular vesicles as markers of sepsis

The early diagnosis of sepsis is of crucially important in clinical setting because it could help significantly improve patients' outcomes. In the last few years, EVs gained attention as potential early and stable markers of sepsis. The prevalence of cell type–specific EVs in sepsis conditions was described in several studies. In septic shock patients, leucocyte- and platelet-derived microparticles were significantly increased in patients requiring longer vasoactive support and mechanical ventilation (26). The presence of leukocyte-derived EVs and low level of endothelial cell–released EVs were correlated with a poor prognosis and development of septic coagulopathy in septic patients (27).

Similarly, monocyte-derived microparticles were shown to be significantly increased in patients with trauma and severe sepsis. In septic patients, this increase correlates with the acute physiology and chronic health evaluation score (APACHE II) and the International Society of Thrombosis and Homeostasis overt disseminated intravascular coagulation (DIC) diagnostic criteria (28,29). Endothelial cell–derived EVs are increased at 12 and 24 hours after sepsis and correlate negatively with the microvessel density in the cerebral cortex of septic rats. Therefore, EVs could be a possible marker of septic organ perfusion injuries (30).

In addition, EVs were shown to have specific protein expression signatures in case of sepsis. For example, it was shown that EVs from septic patients have differences in protein expression in 18 cases, whereas in LPS-stimulated monocyte-derived EVs, a difference in 15 proteins was observed (31). Kawamoto et al. (2019) described a correlation between B2 integrin expression in EVs from septic patients with hypotension and reduced kidney function (32). Cluster of differentiation (CD) 63^+ EVs were shown to be associated with more severe organ failure (SOFA score) and higher CD63 exosomal level was associated with higher 28-day and in-hospital mortality (33). $CD36^+$ microparticles (leucocyte-derived) as well as platelet-derived microparticles were increased in patients requiring longer vasoactive support and mechanical ventilation. The increase of E-selectin+ microparticles was associated with the development of acute kidney injury (AKI) in the same patients (26). In addition, Xe et al. (2018) described exosomal proteome as a sepsis-monitoring tool, based on the observation that exosomal SPTLC3 negatively correlates with the disease progression, indicated by body temperature and C-reactive protein (CRP) level (34).

Next to the diagnostic potential in sepsis, EVs were also shown to depict the development of SIRS. In patients who died with SIRS after acute liver failure, higher concentrations of procoagulant microparticles at days 1 and 3 were measured. The total microparticle concentration was 19 fold higher in acute liver failure patients compared with healthy controls (35). In septic patients in particular, the exosomal HMGB-1 concentration was associated with clinical liver damage (36,37). Patients developing SIRS after transcatheter aortic valve implantation showed higher amounts of $CD144^+$ endothelial microparticles directly after the procedure compared with patients without complications. Importantly, this observation was made 4 hours after transcatheter aortic valve implantation, while the classical inflammatory markers, such as procalcitonin, IL-6, and IL-8, increased only after 24 hours and the CRP only after 48 hours (38). Therefore, EVs could provide a diagnosis much earlier and then established inflammatory biomarkers. In severe burn injury patients, higher levels of leucocyte- and granulocyte-derived EVs were measured in nonsurvivors compared with survivors (39). Septic shock patients demonstrated 3-fold higher levels of $CD31^+$/CD41 MVs, which correlated with leucocyte count, whereas $CD41^+$-derived MVs were elevated in septic shock patients who died (40). In addition, macrophage-derived EVs were associated with sepsis development, mediated by the recruitment and activation of neutrophils *via* CXR/PKC/NOX4 pathway activation (41).

Extracellular vesicles from macrophages resulted in lower bacterial load and alleviated organ damage in a murine sepsis model by exosomal CD14 (42).

In addition, classical markers of immune reaction, such as CRP, were shown to be transported by EVs. In septic patients, Fendl et al. (2021) described elevated levels of total EV counts and CRP+ EVs counts when compared with healthy controls (43). Interestingly, in patients with septic shock, EV concentrations were extremely high at admission and decreased with time, while EVs concentration in infectious patients was relatively constant over a 7-day period (44).

Moreover, the origin of inflammation, for example, pneumonia or urinary tract infection, affects the EVs production during sepsis. Patients with pneumonia-induced sepsis showed higher levels of MVs compared with fecal peritonitis and healthy controls. Microvesicles were shown to be associated with survival in pneumonia, but not in patients with fecal peritonitis (45). Mixed fungal septic patients showed significantly elevated annexin V and CD41-positive microparticles on day 1 compared with nonfungal septic patients (46). Furthermore, $CD3^+$/T cells and CD41+/platelets EVs were qualified to discriminate trauma patients from the septic ones (47).

Next to the surface protein expression, the cargo content of EVs can be used as diagnostic markers. hsa_circRNA_104484 and hsa_circ RNA_104670 circular RNAs were upregulated in EVs from serum after sepsis (48). The following miRNAs in EVs cargo were associated with sepsis: 126-3p, 122-5p, 146a-5p, 145-5p, 26-5p, 150-5p, 222-3p, and 181-5p. These EVs promoted production of IL-6, TNF, IL-1β, and MIP-2, depending on TLR-7 presence. Moreover, there were some miRNAs packed in EVs, such as miR-34a, miR-122, and miR-146a, which induce the opposite effect (34). Qui et al. (2022) measured the exosomal miR-483-3p and let7d-3p as new biomarkers of sepsis (49).

In summary, the cellular origin of EVs seems to play an important role in the mediation of sepsis, and EVs from different type of cells—leucocytes, macrophages, platelets, and granulocytes—were described as potential sepsis biomarkers. In part, EVs can provide an earlier diagnosis of sepsis than standard clinical inflammation markers as CRP, leucocyte count, or IL-6. In particular, the exosomal miRNAs might be a reliable diagnostic tool of inflammatory processes.

Roles of EVs in septic organ injuries

Sepsis-induced AKI

Sepsis-associated AKI is a common complication in intensive care unit patients. Kidney injury can increase the risk of chronic comorbidities development and is associated with extremely high mortality (50). Acute kidney injury–specific EVs are detectable in urine of sepsis patients. Urine exosomal activating transcriptional factor 3 was shown to be increased in patients with septic AKI, which qualifies urinal EVs as potential biomarkers (51). Septic patients with renal dysfunction not only showed an increase in total amount of systemic microparticles but also displayed increase in $CD41^+$ platelet-derived and $CD13^+$ myeloid cell line released particles at hospital admission. In the same patients, $CD42a^+$ particles (platelet-relieved) correlated negatively with serum urea nitrogen and creatinine concentrations (52).

Sepsis and resulting AKI have a complex and unique pathophysiology, in which EVs could play multiple roles. Extracellular vesicles could play an important role in the development of endothelial barrier dysfunction. Endothelial cell–derived MVs induced a cytoskeleton junction response (myosin light chain phosphorylation, contractile fiber reorganization, VE-cadherin phosphorylation, and adherens junction dissociation), which led to increased albumin transendothelial flux and decreased barrier resistance. Responsible for these effects seems to be the cSrc-kinase in EVs (53). miR-93-5p from macrophage-derived Exos regulated thioredoxin-interacting proteins and therefore influenced pyroptosis in renal epithelial cells (54).

Another view on the possible role of EVs in sepsis-induced AKI could be gained from studies using EVs as therapeutics. He et al. (2020) described that endothelial progenitor cell–released EVs carry miR-93-5p, which protected the endothelium in sepsis-induced AKI by regulation of TNF-α (55). Exosomes from human umbilical cord mesenchymal stem cells could be a therapeutic option in septic AKI. The treatment with these Exos decreased serum creatinine and serum urea nitrogen levels, inhibited morphological damage and renal tubular cells apoptosis, and increased survival rate in mice undergoing CLP sepsis. The therapeutic effect was based on a decrease of IL-1 receptor–associated kinase expression due to an increase of miR-146b in kidney tissue and resulting inhibition of NF-κB activity (56). Significant reduction of mortality in AKI mice was reached after transfers of Exos from adipose tissue–derived mesenchymal stem cells (MSCs). The effect was mediated *via* SIRT activation, which reversed renal function and significantly alleviated inflammation, apoptosis, and microcirculation disorder in the kidney (57,58). In addition, therapeutic potential of Exos could be enhanced by cell-treatment approaches. Cao et al. (2022) pretreated adipose-derived mesenchymal stem cells with hypoxia and showed that Exo from these cells enhanced survival in septic mice *via* delivery of circular RNA mmu_circ_0001295, suppression of renal vascular leakage, inflammation, and kidney dysfunction (59). Overall, less is known about the role of EVs in the development of septic AKI. The first encouraging therapeutic outcomes call for greater research to fully comprehend the therapeutic potential of therapeutic EVs in the case of septic AKI.

Sepsis-induced acute lung injury

The lung is highly vulnerable and is the most frequent organ to fail during sepsis. Therefore, the development of acute lung injury (ALI) is one of the most critical mortality—prognostic factors in septic patients (60). Because of the high clinical relevance, understanding the mechanisms leading to ALI is of high scientific interest. Extracellular vesicles as markers and mediators of sepsis/SIRS-induced lung injury are broadly discussed in the scientific literature.

Extracellular vesicles from monocytes were found in the bronchoalveolar lavage (BAL) of septic patients and were shown to be significantly associated with ARDS and the mortality of patients (61). A significant release of Exos was observed in an experimental *in vitro* setting of LPS-treated alveolar macrophages, which induces lung inflammation and was significantly ameliorated *via* Exo downregulation due to hydrochloride hydrate treatment (62). Takei et al. (2019) described the promising prognostic

potential of endothelial cell–derived microparticles (EMPs). In particular, the angiotensin converting enzyme (ACE)+-EMPs and the ratio of ACE+EMPs/EMPs were shown to be significantly increased in septic patients who developed ARDS as compared with septic patients who did not (63).

Interestingly, EVs not only play a role in sepsis-induced ALI but also play a role in lung injury after SIRS. Exosomes from hemorrhagic shock patients activated alveolar macrophages and induced nicotinamide adenine dinucleotide phosphate oxidase–derived reactive oxygen species (ROS) production in neutrophils, which led to necroptosis and therefore posthemorrhagic shock lung injury (64). Exosomes from plasma of septic patients or CLP rats showed an increased exosomal expression of miR-1-3p, which resulted in the inhibition of cell proliferation, apoptosis, and increased monolayer endothelial cell permeability. The resulting weakness of the barrier function led to the development of ALI (65). Other microRNAs also participate in the mechanisms leading to lung injury. Exosomal miRNA-1298-5p was found to be elevated in patients with septic lung injury, and treatment of bronchial epithelial cell with these Exos was found to inhibit cell proliferation and induce cell permeability and inflammation (66). miR-155 stimulates lung inflammation through NF-κB activation in macrophages resulting in TNF and IL-6 production (67). Activation of NF-κB pathway after uptake of Exos from alveolar epithelial cells by alveolar macrophages was further associated with miR-92a-3p exosomal transfer. Thus, the crucial step of alveolar macrophages activation can be induced *via* different exosomal stimuli and different miRNAs (68). Next to the activation/polarization of macrophages *via* EVs, macrophage-derived EVs also contribute to the lung tissue injury after sepsis. Exosomes released from *in vitro* stimulated macrophages disrupt the expression of tight junction proteins in bronchial barrier and disrupted the structural barrier in lung (69). Moreover, the macrophage-derived Exos were internalized by other macrophages inducing TNF production. In consequence, macrophage Exo release was reduced and the inflammatory response was alleviated (70). Other coculture experiments showed that monocyte-derived Exos containing caspase-1 induce apoptosis in pulmonary vascular endothelial cells (71).

In addition to their harmful effects, EVs may have therapeutic effects in septic ALI. MSC-derived EVs are a promising tool in the treatment of experimental sepsis. MSC-derived EVs were shown to improve pulmonary microvascular permeability and inhibited histopathological changes and infiltration of the lung tissue with polymorphonuclear leukocytes in a CLP-sepsis model. This effect was associated with an increase in antioxidant enzymes and inhibition of NF-κB activation (72). Even macrophage polarization, an important step in the development of inflammatory lung injury, can be influenced by Exos released from bone marrow mesenchymal stem cells (BMSCs). Their Exos inhibited M1 polarization and promote M2 polarization in murine alveolar macrophages *via* inhibition of hypoxia-inducible factor 1α (HIF-1α) and downregulation of glycolysis (73). The LPS-induced inflammatory response in macrophages *in vitro* can be completely antagonized by BMSC-derived EVs through the inhibition of death-associated protein kinase 1 (74). Deng et al. (2022) investigated the therapeutic potential of Exos from different sources of human MSCs (adipose tissue, bone marrow, and umbilical cord) and observed in all groups an effective downregulation of sepsis-induced glycolysis and inflammatory response in macrophages, amelioration of pathological damage in the lung tissue, and improved survival rates in septic mice (75). The therapeutic effect of EVs is also strongly associated with the miRNA content of EVs. An increase of exosomal miR-125b-5p promoted VEGF expression, restrained lung water content, and reduced inflammatory protein content in BALF, as well as apoptosis in lung tissue by inhibiting the topoisomerase II α (67). The therapeutic miRNAs can also influence the macrophage polarization. For example, exosomal miRNA 16-5p from MSCs promoted anti-inflammatory macrophage polarization in mice through the suppression of TLR-4 (TLR) (76). Not only miRNAs but also exosomal long noncoding RNA-p21 were found in EVs derived from MSCs stimulated with LPS. These EVs led to an increase of Sirtuin-1 in epithelial cells and therefore protect them from apoptosis (77). Next to the noncoding RNA-p21, other long noncoding RNAs were associated with the development of multiple organ dysfunction for example after trauma (78). In addition, Shen et al. (2022) observed that delivery of circular circ-fryl RNA in Exos relieved from adipose-derived stem cells attenuated sepsis-induced lung injury through regulation of miR-490-3p/SIRT3 pathway (79). In conclusion, EVs are important mediators in the process of ALI development after sepsis. Especially macrophages polarization and inflammatory cytokines release are affected by EV cargo. While the damaging effects of EVs in septic lung injury seem to be crucial, the potential of EVs as a therapeutic tool is also enormous. More specifically, miRNAs (miR-16-5p, 125b-5p; miR-490-3p) from mesenchymal stem cells Exos could be a promising tool in future.

Septic cardiomyopathy

Severe sepsis is associated with a high mortality rate and cardiac dysfunction in patients and rodents (80,81). Myocardial dysfunction in sepsis is described as a global systolic and diastolic dysfunction, including right ventricular and left ventricular malfunction, and is characterized by increased morbidity and mortality (82,83). The literature about septic cardiomyopathies mainly focuses on systemic/local inflammation, complement activation, and structural changes. In the last few years, the role of EVs in septic cardiomyopathy has been addressed by *in vivo* and *in vitro* studies. An increase of small- and medium EVs, containing troponin I and muscle-associated glycogen phosphorylase, was detected in the LPS-injected mice (84). These EVs could be a useful tool to diagnose septic cardiomyopathy, although the advantages over the clinical criterion standards (troponin I/T) are not investigated yet. In addition to the role of EVs' as biomarkers of sepsis or septic cardiomyopathy, the transfer of EVs induced life-threatening cardiac dysfunction. Outer membrane vesicles were shown to induce irregular calcium oscillation with decreased frequency in cardiomyocytes *in vitro*. Outer membrane vesicle i.p. injection in mice resulted in a systemic and local increase of inflammatory cytokines and in elevated troponin T levels (85). In addition, the transfer of serum Exos from septic patients on AC16 myocardial cells inhibited glycolysis and promoted apoptosis in these cells through exosomal hsa-miR-1262 and its target SLC2A1 (86). Moreover, the transfer of septic ROS-enriched Exos on endothelial cells led to the generation of podosome cluster, thereby causing zonula occludens relocation, vascular leakage, and

cardiac dysfunction *in vitro* (87). Monocytes-derived $CD63^+$ Exos led to cardiovascular inflammation due to the overexpression of TXNIP-NLRP3, which cleave inactive IL-1β and IL-18 in macrophages and induce cardiovascular inflammation (88). The therapy of septic cardiomyopathy with EVs is also in the focus of modern research because of the lack of alternative therapeutic tools and high mortality rate in critically ill patients. Hong *et al.* transferred endothelial progenitor cell–derived EVs in septic rats and observed an improvement in cardiac function, suppression of inflammation, oxidative stress, and apoptosis. This therapeutic effect was linked to an upregulation of miR-375-3p in EVs, targeting the BRD4-mediated PI3K/AKT signaling pathway (89). Furthermore, EVs from MSCs were used as a new therapeutic tool in the case of septic cardiomyopathy. Human MSCs-Exos, carrying PTEN-induced putative kinase 1, when transferred to cardiomyocytes, prevented calcium efflux disorder in mitochondria and supported cardiomyocyte dysfunction recovery (90). Bone marrow mesenchymal stem cell–derived Exos also alleviated the CLP-induced myocardial depression, production of CK-MB, LDH, inflammatory infiltration, and cell apoptosis in a septic mice model. These effects were associated with an increase of miRNA-141 in myocardial tissue after Exo treatment, which regulate the PTEN/ß-catenin axis (91). Furthermore, MSC-derived exosomal miR-233 was associated with cardioprotection in sepsis (92). Cardioprotection was also mediated *via* miR-24-3–containing Exos released from M2 macrophages through the formation of Tnfsf10. This improved cardiac function and reduced cardiomyocyte apoptosis and systemic inflammation (93). Moreover, endothelial-derived Exos, carrying HSPA12B, significantly increased anti-inflammatory cytokine IL-10, decreased TNF-α and IL-1β expression in LPS-stimulated macrophages, and alleviated cardiac dysfunction in septic mice (94).

In conclusion, septic cardiomyopathy could be induced through transfer of septic EVs or OMVs. Apart from the damaging abilities, EVs (especially MSCs-derived EVs) were shown to have therapeutic potential. To make use of this potential, the microRNA profile of EVs requires more detailed investigation.

Disseminated intravascular coagulation

Disseminated intravascular coagulation is a common life-threatening complication in sepsis, which is defined by the coexistence of both, thrombosis and bleeding. In general, DIC is recognized as a systemic activation of coagulation with suppressed fibrinolysis resulting in organ dysfunction and intravascular inflammation (95,96). In the last few years, the role of EVs in the development of such complex sepsis complications gained attention. Matsumoto et al. (2017) described a correlation between the number of EVs and the development of DIC. The amount of monocyte-derived EVs was increased in trauma as well as sepsis patients and in case of sepsis correlated with the APACHE II and the development of DIC measured by the International Society on Thrombosis and Hemostasis score (28). The quantity of circulating microparticles negatively correlated with the amount of coagulation factors, caused by consumption, but did not correlate with clotting factor and tissue factor pathway inhibitors levels (97). Furthermore, the number of tissue factor and endothelin protein C receptor-positive MVs from endothelial cells correlated significantly with the SOFA score and the acute physiology and chronic health evaluation II score (98). A combination of prothrombin time, endothelial cell–derived CD105 microparcticles, and platelet count at admission predicted the absence of DIC in septic shock patients (99). Higher endothelial microparticles amounts were found in elderly patients who died as a consequence of sepsis as compared with survivors (100). These results reflect the importance of specific EVs as diagnostic tools in sepsis-induced DIC. Besides monocyte- and endothelial-derived EVs, EVs originating from the platelets also play an important role in the development of septic DIC. The release of platelet-derived microparticles was regulated by increased RAC-1 activity in platelets during sepsis and is further accompanied by thrombin formation (101). In addition to the role of platelet-derived microparticles as potent inducer of thrombin generation *via* phosphatidyl, microparticles activated both the intrinsic and extrinsic pathways of coagulation (102). Phosphatidylserine-containing microparticles were released from platelets, leucocytes (including neutrophils, monocytes, and lymphocytes), erythrocytes, and endothelial cells and augment coagulation in sepsis (27,103,104). Platelet-derived microparticles showed increased tissue factor activity, which led to the promotion of coagulation as observed by decreased clotting time with shortening of the lag time and the time to peak thrombin (105). Induction of coagulation disorders in sepsis mediated *via E. coli*–derived OMVs furthermore depended on the presence of TLR4 (106). *In vivo* and *in vitro* studies have shown the importance of caspase-11 and gasdermin in the development of septic DIC. In absence of caspase-11 or gasdermin, the OMV-mediated coagulopathy, organ injury, and mortality were attenuated (107).

The complex interaction of coagulation factors, different cells, and inflammation factors in the pathophysiology of DIC is supported by the fact that stimulation of immunomodulatory cells, such as macrophages with OMVs, could lead to reduction of tissue factor activity (107). Surprisingly, so far, there is no study investigating the therapeutic potential of EVs for DIC in sepsis. In summary, endothelial cell–, monocyte-, and platelet-derived EVs showed a high potential as diagnostic markers for DIC. Furthermore, EVs from different cell origins influence thrombin formation, consumption of coagulation factors, and tissue factor activation and are therefore important players in the complex pathophysiology of septic DIC.

Extracellular vesicles as a therapeutic tool in sepsis

This part of the review provides a summary of therapeutic options mediated/provided by EVs and their cargo in sepsis. The present literature describing the therapeutic aspects of EV treatments in sepsis is summarized in Table 1. As visualized in the Figure 1, EVs originating from different type of cells contain different cargo that distinguishes their therapeutic effects in sepsis.

One of the most promising cell sources of therapeutic EVs is MSCs. These EVs exerted effects on inflammation, macrophage viability, M1/M2 macrophage ratio, and cytokine expression. Bone marrow mesenchymal stem cell–derived EVs were described to inhibit LPS-induced macrophage-mediated inflammation *via* miR-17 and to influence the BRD4/EZH2/Trail axis. The exosomal miR-17 was shown to be associated with decreased apoptosis and improved macrophage viability *in vitro* (108). The therapeutic effect of BMSC-derived Exos was analyzed in the development of septic ARDS, and it was described that these Exos

TABLE 1. **Sepsis promotion and sepsis inhibition due to EVs**

Origin	Cargo	Effect	Ref
Sepsis inhibition			
Stem/progenitor cells—EVs			
Bone marrow MSC	miR-17	Apoptosis reduction; Macrophage viability improvement	(108)
	NA	Inhibition of M1-/promotion of M2-macrophage polarization *via* HIF1-α; Downregulation of glycolysis	(73)
	miR-141	Reduction of inflammation and apoptosis *via* PTEN/ß-catenin axis	(91)
	miR-27b	JMJD upregulation; NF-κB pathway inactivation	(109)
Adipose tissue MSC	miR-148a-3p	Inhibition of M1 macrophages; IL-1ß, IL-6, and TNF-α production	(110)
	miRNA-16-5p circ-fryl RNA	Attenuate macrophage polarization, TLR-4 suppression, miR-490-3p/sirtuin pathway downregulation	(76,79)
	NA	Reduction of ROS production	(111)
	NA	SIRT activation ➔ reduction of inflammation, apoptosis, and microcirculation disorders	(57,58)
Umbilical cord MSC	NA	Inhibition of NF-κB activation and increase of antioxidant enzymes	(72)
	miR-146-b	NF-κB activity reduction	(56)
MSC	NA	Increased of IL-10 mRNA	(112)
	PTEN-induced putative kinase 1	Prevention of calcium efflux in mitochondria; cardiomyocyte dysfunction recovery	(90)
IL-1ß–pretreated MSC	miR-21	M2 polarization	(104)
LPS-pretreated MSC	Let-7b	Improvement of macrophage polarization; reduction of cytokine production and chronic inflammation	(113,114)
Hypoxia-pretreated MSC	mmu_circ_0001295	Inflammation reduction	(59)
EPCs	NA	Cytokine/chemokine reduction, increase of anti-inflammatory macrophages	(115,116)
	miR-375-3p	Reduction of inflammation, oxidative stress and apoptosis *via* PI3K/AKT signaling pathway	(89)
	miR-93-5p	TNF-α reduction	(55)
Other cell types, serum, plasma—EVs			
Endothelial cell	HSPA12B	Stimulation of IL-10 and suppression of TNF/IL-1ß production in LPS-stimulated macrophages	(94)
M2 macrophage	miR-24-3	Tnfsf 10 formation	(93)
Serum	miR-125b-5p	Reduction of inflammation and apoptosis in lung tissue; increase in VEGF expression, lung water content restrainment	(67)
Sepsis promotion			
Blood cells—EVs			
Platelet	NA	Thrombin formation and activation of intrinsic and extrinsic coagulation pathways	(102)
	Tissue factors	Coagulation	(105)
	NADPH oxidase	Vascular dysfunction *via* vascular cell apoptosis	(25)
Monocytes	Caspase-1	Apoptosis in pulmonary vascular endothelial cells	(71)
	NA	Increase of IL-1ß and IL-18 production in macrophages *via* TXNIP-NLRP3 axis	(88)
Neutrophils	NA	Reduction of neutrophil recruitment and increase of IL-10	(24)
Other cell types, serum, plasma—EVs			
Endothelial cells	cSrc-kinase	Barrier dysfunction due to myosin light chain phosphorylation, contractile fiber reorganization, VE-cadherin phosphorylation, and adherens junction dissociation	(53)
Macrophages	miR-1298-5p	Inhibition of bronchial epithelial cell proliferation and increase of cell permeability and inflammation	(66)
Serum	Has-miR-1262	Inhibition of glycolysis; promotion of myocardial cells apoptosis	(86)
Sepsis serum	miR-93-5p	Pyroptosis in renal epithelial cells	(54)
Plasma	miR-155 miR-92a-3p	NF-κB activation ➔ production of TNF/IL-6	(67,68)
	Phosphatidylserine	Coagulation	(104)
Brain	NA	Activation of coagulation, organ inflammation, and apoptosis	(21)
Bacteria—MVs			
OMV	NA	Increase of IL-6, TNF, and IL-8 production	(16)
	NA	Increase of tissue factor, P- and E-selectin production; decrease of thrombomodulin	(17)
	NA	Decrease of calcium oscillation frequency in cardiomyocytes; local inflammation increase	(85)

EPC, endothelial progenitor cells; EV, extracellular vesicle; HIF1-α, hypoxia-inducible factor 1α; MV, microvesicle; MSC, mesenchymal stem cell; NA, not available; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor 'kappa-light-chain-enhancer' of activated B-cells; PTEN, Phosphatase and Tensin Homolog; OMV, outer membrane vesicle; PTEN, Phosphatase And Tensin Homolog; ROS, reactive oxygen species.

inhibit M1 macrophages and promote M2 macrophages polarization (73). In addition, BMSC-derived EVs decreased systemic inflammation and increased survival of septic mice (108).

adipose derived stem cells (ADSCs)-derived EVs also decreased IL-1β, IL-6, and TNF-α production *via* inhibition of M1 macrophages, although miR-148a-3p was described as

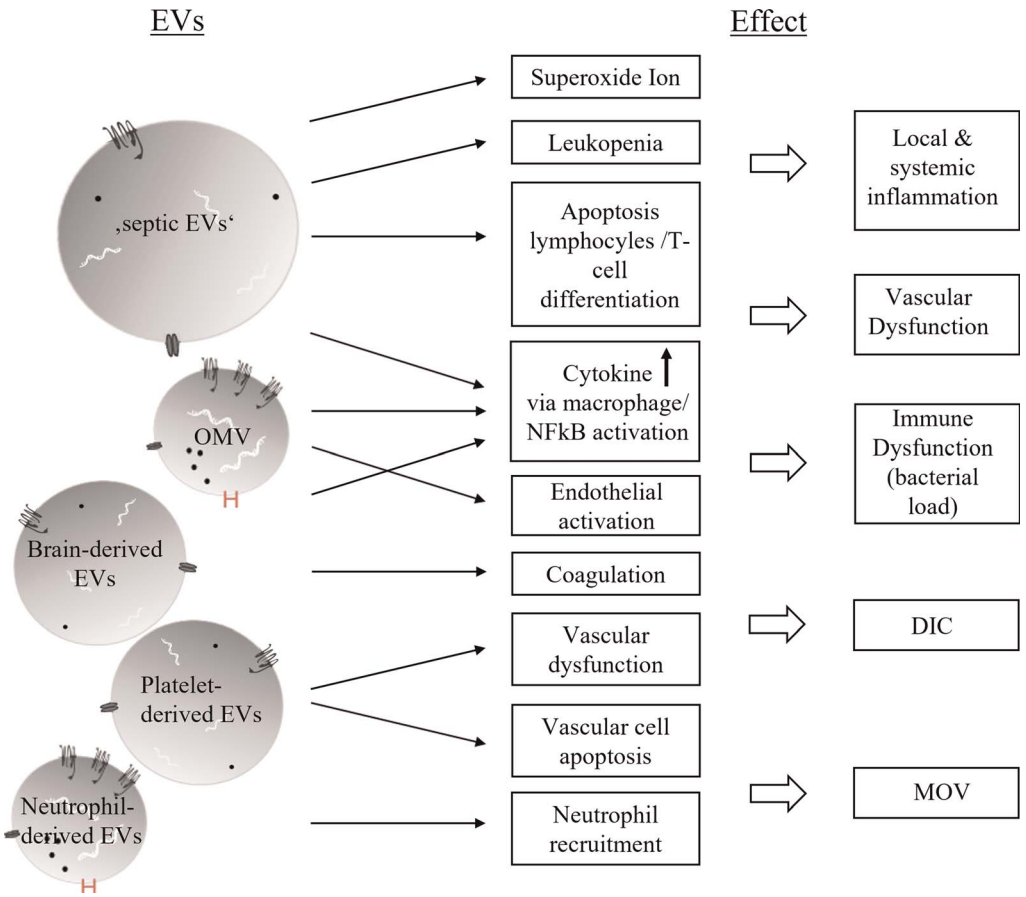

FIG. 1. **Extracellular vesicles as mediator of sepsis/SIRS.** DIC, disseminated intravascular coagulation; EV, extracellular vesicles; MOV, multiorgan failure; OMV, outer membrane vesicles; SIRS, systemic inflammatory response syndrome.

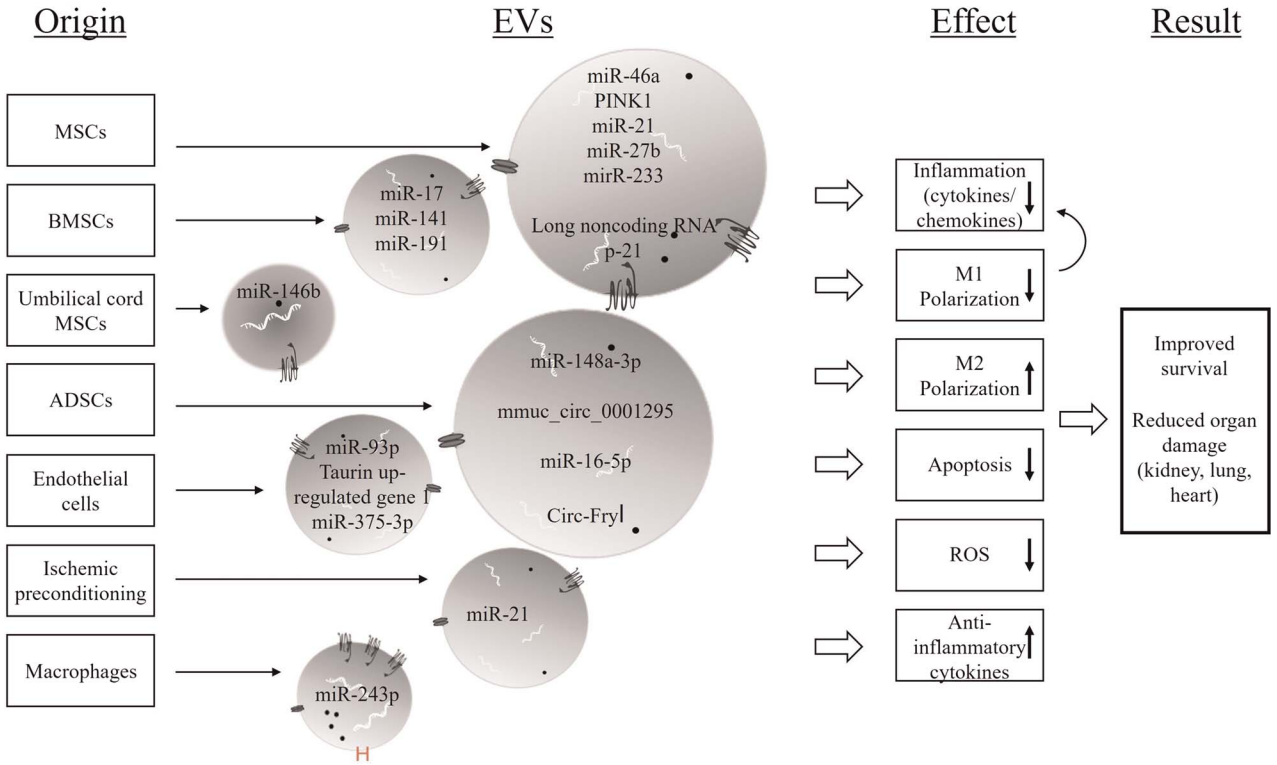

FIG. 2. **Extracellular vesicles, derived from different type of cells, have therapeutic potential in sepsis.** ADSC, adipose tissue mesenchymal stem cell; BMSC, bone marrow mesenchymal stem cells; circ, circular RNA; miR, microRNA; MSC, mesenchymal stem cell; ROS, reactive oxygen species.

TABLE 2. **The study on therapeutic potential of EVs**

EVs origin	Isolation method	Findings
LPS-induced sepsis model		
BMSCs	NA	miR-17 regulates BRD4-mediated EZH2/TRAIL axis and inhibits macrophages inflammation (108)
	UC	Inhibit M1 and promote M2 polarization in murine alveolar macrophages through downregulation of glycolysis; *in vivo* ameliorate inflammation and lung tissue damage (73)
	NA	Inflammation in macrophage-like cells due to inhibition of death-associated protein kinase 1 *via* miR-191 (74)
BMSCs-, ADSCs-, UC-, and MSCs-derived Exos	UC	Downregulate sepsis-induced glycolysis and inflammatory macrophages, ameliorate lung damage, and improve the survival rate (75)
Endothelial progenitor cells	UC	miR-93-5p protects endothelium in sepsis-induced AKI and regulates KDM68H/3K27me3/TNF alpha axis (55)
M2 macrophages	UC	miR-24-3p improves cardiac function and reduces cardiomyocyte apoptosis and serum inflammation (93)
Piceatannol-loaded neutrophil-derived EVs	UC	Alleviate ALI and LPS-induced sepsis (119)
Super repressor IkB-loaded Exos	TFF and SEC	EV attenuates mortality and systemic inflammation (120)
CLP-induced sepsis model		
BMSCs	UC	Alleviate myocardial impairment, production of CK-MB LDH, inflammatory infiltration, and apoptosis. miRNA-141 regulates PTEN/ß-catenin axis (91) PINK1 (PTEN-induced putative kinase 1) mRNA prevents $Ca2^{+}$ efflux disorder in mitochondria and leads to cardiomyocytes recover (90) Cardioprotection (reduced apoptosis and inflammation) through exosomal miR-233 (92) miR-27b inhibits development of sepsis by JMJD3—downregulation and NF-κB signaling pathway inactivation (109)
Human MSCs	UC	Improve pulmonary microvascular permeability and inhibit histopathological changes infiltration of PMNs; mediated *via* increase of antioxidant enzymes and inhibition of MAPK/NF-κB (72)
IL-1ß–pretreated MSC	DC	M2-like polarization of macrophages *in vitro* and *in vivo;* attenuation of symptoms and increased survival rate in septic mice; miR-21 as a key mediator (121)
	UC	IL-1β pretreatment effectively enhances immunomodulatory properties of MSCs partially through Exo-mediated transfer of miR-146a (118)
ADSCs	UC	mi-RNA-16-5p promotes macrophage polarization and attenuates septic lung injury *via* TLR4 suppression (76) Attenuate sepsis-induced lung injury through delivery of cric-fryl (circular RNA) and regulation of miR-490-3p/SIRT3 pathway (79) The mortality is reduced because of SIRT activation (57)
	NA	Alleviate LPS-induced ROS and IL-1ß, TNF, and IL-6 expression *in vitro*; M1 reduction and M2 macrophages enhancement; relief of inflammatory cytokine storm and organ injury *in vivo* (111)
hUC-MSCs–derived Exos	UC	Decrease serum creatinine and serum urea nitrogen levels and inhibit morphological damage and renal tubular cell apoptosis through increase of miR-146b and inhibition of the NF-κB activity (56)
Endothelial progenitor cells	NA	EVs taurine upregulates gene 1 that leads to anti-inflammatory (M2) macrophage polarization; amelioration of sepsis-induced organ damage (115)
	Kit	EVs improve survival, suppress lung/renal vascular leakage, reduce liver/kidney dysfunction, and attenuate systemic cytokines and chemokines (116)
	NA	Improve cardiac function and suppress inflammation, oxidative stress and apoptosis *via* mi375-3p targeting BRD4-mediated PI3K/AKT signaling pathway (89)
LL-37 stimulated neutrophils-derived MVs	UC	LL-37 induces ectosome, which lead to reduction of bacterial load and improved survival (122)
Neutrophil-derived EVs (NDTRs and NDMVs)	UC	NDTRs contain proinflammatory miR-1260, miR-1285, miR-4454, miR-7975; enhance M1 macrophage polarization, protect against lethality, NDMVs contain anti-inflammatory miR-126, miR-150, and miR-451a; induce anti-M2 macrophage polarization (123)
Exosomes from mice with remote ischemic preconditioning	UC	Protect from multiple organ dysfunction; induce systemic accumulation of inflammatory cytokines and cell apoptosis through upregulation of miR-21 (124)
Nutrient-deprived fibroblast CDNPs	UC	Enhance immune response at the site of infection and promote bacterial clearance, through direct bacterial killing and phagocyte activation increase (125)
Hypoxia-pretreated ADSCs-derived EVs	UC	EVs lead to enhanced survival, suppressed renal vascular leakage and decreased kidney dysfunction through delivering mmu_circ_0001295 (circRNA) (59)

ALI, acute lung injury; ADSCs, adipose derived stem cells; BMSC, bone marrow mesenchymal stem cell; CDNP, cell line derived nanoparticle; DC, differential centrifugation; DG-UC, density gradient ultracentrifugation; EV, extracellular vesicle; Exo, exosome; MSCs, mesenchymal stem cell; NA, not available; NF-κB, nuclear factor 'kappa-light-chain-enhancer' of activated B-cells; PMNs, polymorphonuclear leukocytes; PTEN, Phosphatase and Tensin Homolog; SE, serial extrusions; TFF, tangential flow filtration; UC, ultracentrifugation.

proinflammatory exosomal mediator (110). In treatment of septic ARDS, exosomal miRNA-16-5p and circular circ-fryl RNA were described to attenuate macrophage polarization and to release inflammation *via* TLR4 suppression (76) or downregulation of miR-490-3p/sirtuin pathway (79). Sirtuin activation due to ADSC-derived EVs reduced the sepsis severity in a septic animal model of AKI (57). Furthermore, Exos from ADSCs alleviate LPS-induced ROS production and therefore alleviate organ injury and systemic cytokine storm in septic animals *in vivo* (111).

Next to the reduction of inflammatory cytokines, MSC-derived EVs were also capable to increase the systemic IL-10 concentrations. In mice, this observation was associated with the inhibition of eye exudates, hypothermia, and clinical signs of a systemic cytokine storm (117). Moreover, different studies described the NF-κB activation as target point of MSC-derived EVs therapy. For example, miR-27b inhibited the development of sepsis by downregulating JMJD3 and inactivating the NF-κB signaling pathway (109), while the suppression of MAPK/NF-κB also inhibited pulmonary microvascular permeability, histopathological changes, and infiltration of polymorphonuclear leukocytes in septic ALI (72). In addition, functional recovery of cardiomyocytes was achieved with treatment of life-threatening complication of cardiac dysfunction with MSC-derived EVs (90).

Some pretreatment strategies have been used to improve the therapeutic effects of MSC EVs in sepsis models. Administration of Exos, derived from IL-1β pretreated MSCs, more effectively attenuated symptoms in septic mice and increased their survival rate as compared with Exos released by naive MSCs. miR-21, presented in these Exos, was shown to be responsible for M2 polarization *in vitro* and *in vivo* (100). Pretreatment of MSC with IL-1β was also shown to increase production of miR-146a–enriched Exos that led to an increase of septic mice survival (118). Exosomes derived from LPS-pretreated MSC were suggested to have improved regulatory abilities for macrophage polarization and resolution of chronic inflammation due to distributing let-7b miRNA (113). Exosomal Let-7b modulated inflammatory responses and suppressed LPS-induced cytokine production in mouse MSCs, dendritic, microglial, and human monocytes cells (114). A systematic analysis of different pretreatment strategies for optimizing the therapeutic potential of EVs is lacking in the recent literature (Fig. 2, Table 2).

Another source of therapeutic EVs is endothelial progenitor cells. Different studies describe that these EVs improved survival of septic mice, reduced cytokine and chemokine concentrations, increased the number of anti-inflammatory macrophages, and attenuated lung and renal vascular leakage (115,116). An improved cardiac function, suppressed inflammation, reduced oxidative stress, and apoptosis were attributed to endothelial progenitor cell–derived EVs transporting miR-375-3p and influencing the PI3K/AKT signaling pathway (89).

There are a few reports describing therapeutic effects of EVs, derived from naive- or pretreated neutrophils (119,122), macrophages (86,126), fibroblasts (125), and monocytes (16), although this field of research is very scarce and requires further development.

In conclusion, therapeutic EVs are primarily EVs derived from mesenchymal stem cells. Being applied in septic models, they alleviate the organ injuries (kidney, lung, and heart) and improve survival. To date, this therapeutic effect is mostly explained by the activity of miRNAs, but it is clear that other cargo components are also involved in it. As summarized in Figure 1, the therapeutic effects of EVs treatment are as follows: reduction of inflammatory cytokines and chemokines expression, apoptosis, and ROS production; influence on macrophage polarization; and increase of anti-inflammatory cytokines expression.

Our review of the literature on the role of EVs in sepsis identified the same complexities that are generally specific to the field of EV research. These are inconsistent nomenclature of EVs and absence of information regarding the isolation procedure or cellular origin. All this, unfortunately, slows down the development of this area of research. Future studies, consequently following the "Minimal Information for Studies of Extracellular Vesicles" criteria, should help clarify the role of EVs in sepsis and unlock their potential as therapeutic tool and/or specific and sensitive sepsis biomarkers.

CONCLUSIONS

To summarize, EVs in sepsis could be friends and foes at the same time depending on their origin and cargo. On the one hand, transfer of EVs or OMVs can induce sepsis or SIRS with comparable efficiency as well-established methods, such as CLP or LPS injection. On the other hand, EVs could provide certain therapeutic effects, mediated *via* reduction of ROS, inflammatory cytokines and chemokines, influence on macrophage polarization and apoptosis, and increase of anti-inflammatory cytokines. These effects were mainly observed in EVs from mesenchymal stem cells. In the future, EVs from mesenchymal stem cell could be a therapeutic tool, which might mitigate sepsis, SIRS, and sepsis-associated diseases. Furthermore, the understanding of the cell-cell communication *via* EVs could help develop further therapeutic approaches to improve the outcome of this life-threatening entity. Moreover, EVs could be helpful in the diagnosis of sepsis. Extracellular vesicles of different cellular origin, such as leucocytes, macrophages, platelets, and granulocytes, were suggested as potential sepsis biomarkers. They ensure the diagnosis of sepsis earlier than classical clinical inflammation markers, such as CRP, leucocyte count, or IL-6.

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