Review

Functional significance of exosomes applied in sepsis: A novel approach to therapy

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The nanoparticles referred as exosomes play an active role in intercellular communication. Their potential positive therapeutic effect in bacterial inflammation and sepsis has been the subject of several studies that have examined the feasibility of exosomes as drug-delivery vehicles. The underlying mechanism of interest involves the selective transport of cellular cargo. Most attention has been focused on the exosome-mediated transport of microRNA and protein. Thus, exosomes are expected to be an important tool in the treatment of inflammatory disease. This review covers the relevant literature, focusing on the relationship between exosomes and sepsis and therapeutic use of exosomes in bacterially mediated inflammation or sepsis. We evaluate exosomes as drug vehicles, including their therapeutic cargo, potential mechanisms of action, choice of donor cells, and routes of administration.

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1. Introduction

Sepsis remains to be a growing problem even international efforts have been taken to decrease the morbidity and mortality. Appropriate antibiotic therapy, hemodynamic support, and adequate source control are the most important parts in the management of life-threatening sepsis [1]; however, they are usually of limited effect in significantly improving the survival of septic patients. With the increase in multi-drug-resistant bacterial strains, most antimicrobials are ineffective for diminishing the survival of septic patients. With the increase in multi-drug-resistant bacterial strains, most antimicrobials are ineffective for diminishing the inflammatory response. Organ support such as ventilators and dialysis, is extensively available in intensive care units, but the morbidity and mortality related to severe inflammatory disease remains significant [2]. Other therapies like TNF-α antagonists though having encouraging findings in animal models are failed to be translated into clinical use. Apparently, more effective treatments in sepsis are in urgent need as before.

An approach that is receiving increasing interest is to inhibit excess pro-inflammatory responses by taking advantage of the properties of stem cells, in particular mesenchymal stem cells (MSCs). MSCs, whether from autologous or allogeneic sources, have suppressive and regulatory effects on both adaptive and innate immune responses [3]. Mounting evidence indicates that MSCs create an optimal microenvironment for the development of sepsis, primarily through their interaction with host macrophages, both in the circulation and in tissues, resulting in a reduction in the secretion of pro-inflammatory cytokines, such as IL-1, IL-6, high mobility group box 1 (HMGB1) protein, and TNF-α [4–6]. However, the therapeutic use of MSCs requires cell transplantation and is limited by the fact that large amounts of stem cells are not easy to obtain or to expand from low-density cultures. Thus, before their potential utility for the treatment of sepsis can be evaluated, MSCs, whether from patients or donors, require further study, including the potential carcinogenicity of these cells and their ability to differentiate into undesired cell types, such as osteocytes and chondrocytes. Moreover, stem cell transplantation does not simply result in cell replacement or direct cell–cell contact, because only ~1% of transplanted MSCs ultimately reach the target tissue, as most are trapped in the liver, spleen, and lungs [7].

Recent work has demonstrated that membrane vesicles such as exosomes transmit information to target cells and thus are essential components of intercellular communication. By activating surface receptors on target cells, exosomes induce changes in a cell’s response to its environment. After fusion with a recipient cell, the vesicles transport their contents, such as microRNA (miRNA) or mRNA, into the cytoplasm [8]. Sophisticated intercellular communication is also achieved via the proteins expressed on the surfaces of their membranes. The advantages of exosomes over stem cells include less toxicity, a minimal immune response, their relative stability in the circulation, and their ease of handling. Exosomes can be stored at −80 °C for nearly 2 years without a loss of biological activity [9] and may therefore be of value as an alternative to cell-based therapies. Based on our interest in the potential roles of exosomes in controlling bacterially mediated inflammation and perhaps also sepsis, and the mechanism underlying the therapeutic effects of exosomes, we carried out an online search for studies in which exosomes were investigated either for these purposes or as drug vehicles.
1.1. Exosome characteristics

Exosomes are nanosized vesicles (diameter 30–120 nm) that derive from inward budding of the inner endosomal membrane followed by fusion of multivesicular bodies (MVBs) with the plasma membrane. They are secreted by most cell types and existing ubiquitously in cell culture supernatants and body fluids [10]. Membrane receptors, soluble proteins, lipids, RNAs, and even organelles can be packaged in exosomes or expressed on their membrane surfaces for secretion into the above mentioned body fluids or into the environment [11]. More detailed information can be searched in the database ExoCarta (http://www.exocarta.org), which catalogs the proteins, lipids, and RNA identified in extracellular vesicles from different sources to date [12]. Depending on the cell type and the physiological or pathological state of the cell, the composition of its exosomes will vary accordingly [12]. It is now established that exosomes play significant roles in coagulation, cancer, inflammation, and stem cell renewal and expansion, all of which are reflected in the nature of their cargo [13]. Therefore, in their function as mediators of intercellular communication, exosomes act both locally and at a distance.

1.2. Exosome extraction and identification

Exosomes can be isolated from cell culture media or body fluids based on their size, density and biochemical properties. Current exosome extraction methods mainly depend on ultracentrifugation or gradient centrifugation, both of which separate exosomes from large particles and cell debris. For ultracentrifugation or gradient centrifugation, culture supernatants or fluids are collected and subjected to a series of centrifugations. Gradient centrifugation yields a purified exosome preparation in which the biological activity of the exosomes is preserved. However, as is also the case with ultracentrifugation, there are several drawbacks to the method, including the fact that it is time-consuming, the risks of vesicle rupture and thus maybe contaminate with protein aggregates and cell debris. Alternative methods include immunofinity and the use of commercially available kits. Immunoaffinity is a scalable and specific technique that uses magnetic beads conjugated with monoclonal antibody to extract exosomes expressing specific markers [14,15]. Commercially available kits, such as ExoQuick and ExoSpin Exosome Purification Kit, precipitate exosomes from serum, conditioned cell media, or urine, which greatly simplifies their isolation. However, it can be difficult to distinguish between extracellular vesicles of different sizes and membrane-free macromolecular aggregates [12]. Moreover, precipitation of the subcellular particles may disrupt the membrane components of the exosome.

Generally, exosomes can be characterized based on their size, protein content, and lipid content. Exosomes are sphere-shaped structures with sizes between 30 and 120 nm and are much smaller compared to other systems, such as a microvesicle, which has a size range from 100 to 500 nm. They share a common set of lipids, proteins, and nucleic acids that provide the basis for their identification. Proteins that common to most exosomes involved in membrane transport and fusion proteins (Rab, GTPases, flotillins, annexins), tetraspanins (CD9, CD63, CD81), major histocompatibility complexes (MHC I, MHC II), heat shock proteins (Hsp70, Hsp84, Hsp90), and proteins of the endosomal sorting complex required for transport (ESCRT) complex (Alix, TSG101, Gag) [9]. Among these proteins, heat shock proteins, tetraspanins, annexins, integrins, and proteins of the Rab family are abundantly detected in the exosomes and have been used as positive markers to identify the presence of exosomes. However, despite the characteristic expression of these proteins on exosomes, there is wide-ranging variation across exosomes from different cell types and a marker exclusive to exosomes has yet to be identified (Fig. 1).

1.3. Choice of donor cells for isolating exosome

1.3.1. MSCs

Most of the exosomes used for therapeutic purposes, as described in the literature, were isolated from MSCs, probably because the release of exosomes is increased in proliferative cells and MSCs produce the highest amount of exosomes among the cell types known to secrete exosomes [16]. In addition, MSC-derived exosomes are of low immunogenicity and therefore are well tolerated. And some studies indicate that MSCs derived exosomes appeared to home selectively to the sites of acute injury and inflammation, making them actively used in sepsis. In one study, exosomes were isolated from MSCs pre-conditioned with lipopolysaccharide (LPS). These cells exhibited increased paracrine effects and stimulated the regenerative and reparative properties of the target cells [17]. As an integral cellular component conferring these effects, exosomes isolated from pre-conditioned MSCs retain the properties of their parent cells.

1.3.2. Immune cells

Immune cells like monocytes, macrophages, lymphocytes and dendritic cells (DC) all actively participate in the progress of inflammation. These cells are known to secrete exosomes with source-specific immunoregulatory functions, an anti-inflammatory role for exosomes that has recently been demonstrated [18]. Also exosomes secreted by immune cell are posited to avoid entrapment in mononuclear phagocytes as they are part of the host immune system. Exosomes derived from antigen presenting cells have the ability to express major histocompatibility complex (MHC) class I and II molecules on the cell surface, which helps in activating CD8+ and CD4+ T-cells to induce specific immune responses. DCs are the master regulators of immune signaling, orchestrating responses to external signals and instructing T cells in the type of inflammatory responses to be exerted, sensing both live microbial cells and other microbial antigen [19]. Immature dendritic cells (IDC) are supposed to be more qualified with respect to immunogenicity due to their special surface protein composition, which make them relevant exosome donor cells [20]. In the study made by Fatemeh Momenn-Heravi et al. [21], they have proved that exosomes isolated from B cells can be a perfect vehicle for target drug in modulating pro-inflammatory activation of macrophages. One reason is that exosomes from B cells can efficiently deliver therapeutic cargo to macrophages to modulate the inflammation because exosomes inherit traits from B cells like. Another reason is that the number of exosomes increase more than 200 fold when stimulated with CD40 and IL-4 and maintain their B cell associated phenotypic traits [21].

1.3.3. Malignant cells

One study, by Teng et al. [22], showed that exosomes produced by H22 hepatic tumor cells protect mice from severe LPS-induced tissue damage. Because exosomes are involved in immune system suppression during the development and evolution of cancer cells, exosomes from malignant cells may also be capable of suppressing the inflammation induced by over-activation of the immune system [22]. They may also be exploitable as drug delivery systems, for example to target CNS inflammation. In the two published studies on exosome-based drug delivery as an anti-inflammatory strategy, a mouse lymphoma cell line (EL-4) served as the donor cell source. However, exosomes derived from cancer cells contain biomolecules that reflect their endosomal origin as well as oncogenic drivers [23]. The transfer of oncogenes between cells may contribute to cancer formation. In this sense, the potential tumorigenicity should be taken into carefully consideration when using cancer-released exosomes.

1.4. Experimental models, routes of administration and the distribution of injected exosomes in vivo

In most exosome studies, sepsis is induced in an animal model by cecal ligation and puncture (CLP) or LPS (LPS is a major component of the outer membrane of Gram-negative bacteria) stimulation. CLP has been considered as a gold-standard model for experimental sepsis. Perforation of the cecum, an endogenous source of bacterial contamination, results in bacterial peritonitis, which is followed by bacteremia. Septic
shock and multi-organ failure also can be triggered by CLP. Despite its heated use in experiments, several shortcomings still need to be taken seriously, like the varying severity of sepsis and abscess formation occurs randomly. CLP have some difficulties to get reliable and reproducible results. LPS-provoked experimental models are extensively used to shift valid anti-inflammatory drugs. Though LPS injection seems the simplest model for the study of sepsis and have good reproducibility, it differs from that induced by CLP model and of sepsis patient in the profiles of cytokine release.

Then the exosomes are administered via an intravenous, intraperitoneal, intranasal oral, intraventricular, subcutaneous, or intratumoral route, depending on the clinical issue of interest. Fluorescence labeling is widely used in imaging and tracking strategy for exosomes. The limit of Fluorescence labeling is that Fluorescence dyes may persistently exist in tissue even exosomes degraded [24]. Radionuclide and magnetic resonance imaging are supposed to be optical. Exosomes have been injected intravenously into the heart, kidney, lung, liver, and brain [25–28]. Due to their endogenous origin, exosomes administered via this route are not removed by immune cells or avoid hepatic clearance to the same extent as exogenous nanoparticles, which ensures enough time and a sufficiently high tissue dose to ensure uptake by recipient cells. Studies of the intraperitoneal administration of exosomes have shown that this route increases the stability of the polyphenol curcumin, as cargo, in the circulation. Significant amounts of exosomes initially accumulated in the intestine but not in other organs [29]. One hour later, they were predominantly detected in liver, lung, kidney, and splenic tissues [30]. So exosomes mainly accumulated in the liver, spleen, and lungs and cellular origin have a minor effect to change the gross accumulation and clearance patterns of exosomes from the target tissues. In a model of CNS inflammation, the intranasal administration of exosomes enabled the direct, noninvasive delivery of curcumin to the CNS and ensured target specificity. In the brain, exosomes target microglial cells, which are the brain-resident macrophages [29]. Intranasal administration of exosomes resulted in a rapid delivery of the encapsulated drug to the brain. If intravenously administered, exosomes can hardly across the blood-brain barrier.

1.5. Therapeutic function of exosomes in sepsis

It is well accepted that functional significance of exosomes are decided by the exosomal contents. Influenced by the physiological and pathological factors, parent cells load a specific set of cargo including functional RNAs (miRNAs and mRNAs) and proteins into the exosomes and then these exosomes are delivered to recipient cells, resulting in genetic and phenotypic modifications of the recipient cells. Three possible mechanisms accounting for exosome-mediated transfer have been reported [16]. Firstly, exosomes fuse with the plasma membrane of the recipient cell, and subsequently release exosomal cargos into the

**Fig. 1.** Exosomes are nanosized vesicles (diameter 30–120 nm) with lipid bilayer. Membrane receptors, soluble proteins, lipids, RNAs, and even organelles can be packaged in exosomes or expressed on their membrane surfaces. Multivesicular body.
cytoplasm. Secondly, exosomes interact with target cells through receptor–ligand interactions or lipids such as phosphatidylserine. Thirdly, exosomes are internalized into the recipient cells via endocytosis or transcytosis. Whatever the mechanism is, membrane proteins are key components for the cellular uptake via direct interactions with receptors on the target cell. This leads to a higher uptake efficiency and target cell selectivity [31].

1.5.1. MicroRNA

MicroRNAs are small (~22 nt long) regulatory RNA molecules which are important modulators of gene expression that target mRNA for degradation and prevent translation [32]. Exosomal miRNAs are selectively loaded into exosomes through a variety of pathways. The role for sumoylated heterogeneous nuclear ribonucleoprotein A2B1 (hnRNP2A2B1) has been widely suggested. By means of the recognition of hnRNP2A2B1 of precise motifs in the miRNA, the specific miRNAs are effectively sorted into exosomes [33] and then delivered from the parent cells to the recipient cells.

Emerging evidence has suggested that exosomal miRNAs modulate inflammation by regulating target proteins in inflammatory signaling pathways. Currently, it is well recognized that exosomal miRNAs like let-7b [34] and miR-181c [35] released by Human Umbilical Cord Mesenchymal Stem Cells (hUCMSCs) can specifically bind to the 3’ UTRs of target cellular miRNAs leading to inhibit the expression of TLR4 (Toll-like receptor 4) and further suppress the downstream NF-κB activity. TLR4 is one of the pattern recognition receptors which can recognize LPS. Once stimulated, the expression of TLR4 is activated and then through adaptor proteins of the myeloid differentiation factor 88 (MyD88) family to activate several downstream signal transduction pathways, such as NF-κB. While, the Nuclear Factor kappa-B (NF-κB) network is one of the earliest immune signal transduction networks that modulates the expression of genes about activating immune function such as the release of cytokines. In physiology conditions, NF-κB binds to the inhibitory kappa B (IκB) to take the shape of the fallow complex, IκB-NF-κB, existing only in the cytoplasm. Upon stimulation, IκB is phosphorylated by the kinase complex IKK and the IκB proteins are rapidly degraded, which activate the translocation of NF-κB from cytoplasm to the nucleus to regulate the transcription of multiple gene [36]. A significant down-regulation of miR-223 can be observed in CLP animal models. The underlying mechanism is that miR-223 directly targets signal transducer and activator of transcription 3 (STAT3) to regulate the pro-inflammatory cytokines. In turn, IL-6 which is triggered by TLR/NF-κB stimulation can down regulate miR-223, thus forming a positive regulatory loop for pro-inflammatory cytokine production, suggesting a deep integration of this miRNA in innate immune response which are non-immunogenic and able to home to target tissue by virtue of its potent upregulation in multiple immune cell lineages by TLR/innflamatory cytokines, specific antigen [38]. There are several possible reasons for even exosomes containing pro-inflammatory miRNAs they still exert an anti-inflammatory function in sepsis. Firstly, exosomes transfer both pro- and anti-inflammatory miRNAs together to buffer inflammatory response by recipient cells, aimed to achieve an optimal response. Immune cells locate more pro-inflammatory miRNAs in the exosomes when sensing a pathogen and initially transit to more anti-inflammatory miRNAs in the progression of inflammation. Secondly, pro- and anti-inflammatory miRNAs are located in the separated exosomes and are delivered to different recipient cells [32].

1.5.2. Protein

In terms of protein composition, exosomes contain a population of membrane proteins and cytosolic proteins. The mechanisms by which proteins in exosomes are sorted can be roughly divided into mechanisms that are dependent on or independent of endosomal sorting complexes required for transport (ESCRT). ESCRT 0, I, II and III proteins and the Alix accessory protein control the sorting of ubiquitinated proteins into the intraluminal vesicles (ILVs) of multivesicular bodies (MVBs) [39]. MVBs can fuse with the plasma membrane of the cell, releasing ILVs into extracellular space and these released ILVs are exosomes. Experiments in which integral ESCRT components were silenced have shown no influence in exosome formation, indication the existence of ESCRT-independent mechanisms [39]. The ESCRT-independent pathway maybe mediated by tetraspanins (CD81, CD9, CD63) or lipids. For example, tetraspanin CD81 defines the protein content of the exosome by influencing the physical organization of the membranes into micromdomains, but also through the interaction of the protein’s cytoplasmic domain [40]. Other lipids associated with the formation of exosomes through ESCRT independent mechanisms are cholesterol and phosphophatidic acid [41].

Milk fat globule-EGF8 (MFG-E8) is a glycoprotein that was originally identified as a component of milk fat globules budding from the mammary epithelia during lactation, but it has since been detected in various tissues as well as in macrophages and DCs [42]. MFG-E8 stimulates the engulfment of apoptotic cells by phagocytes through the C-terminal of MFG-E8 that contains a coagulation factor VIII homologous domain (C1 and C2, discoidin domain), and the N-terminal with an EGF like domain. They like a bridge connecting the phosphatidylserine expressed on apoptotic cells and a specific integrin (αvβ3 or αvβ5, vitronectin receptor) expressed on phagocytes [43]. In vivo, LPS directly inhibits MFG-E8 expression in murine macrophages, by targeting the Sp1 and AP-1-like motifs in the 5′-flanking region of the gene [44]. Exosomally engulfed exosomes containing MFG-E8 that are derived from DCs or IDCs is found to accelerate the clearance of accumulating apoptotic cells like B cells, CD4 T cells, DCs, vascular endothelial cells, and enteric epithelial cells in sepsis [20,45]. And avoid these cells undergoing secondarily necrotic, which leads to a surge of pro-inflammatory cytokines that further promote the progression of sepsis and the deterioration of the organism (Fig. 2).

1.6. Exosomes as drug-delivery vehicles

Given the shortcoming of clinical drugs in modulating severe inflammation, and because of the particular physical barriers (such as blood-brain barrier), their low degree of efficacy in penetrating underlying tissue, exosomes are gaining increasing interest as drug-delivery vehicles. Exosomes are made up of natural lipid bilayers into which an abundance of adhesive proteins that readily interact with cellular membranes are incorporated. Moreover, biological materials, including miRNAs and proteins, can be artificially loaded into exosomes [46]. As drug vehicles, they are less immunogenic and more compatible with the complex in vivo environment than artificial nanoparticles for their originating from the internal membranes of cells [47]. Especially, exosomes can be isolated from recipient’s own body fluids or cell culture which are non-immunogenic and able to home to target tissue more efficiently [21]. In addition, because they bypass both complement activation and interactions with coagulation factors, they have a long circulating half-life in the blood [14], while their membrane bilayer shields their cargo from degradation after their systematic injection. Above all, They provide a novel, noninvasive mode of endogenous delivery, and both their biological function and their specific cellular interactions have been characterized [48]. Curcumin is a hydrophobic polyphenol with anti-inflammatory, antineoplastic, antioxidiant, and chemopreventive activities. However, because it is hydrophobic and thus preferentially interacts with lipid membranes, its clinical use has been limited. Based on prior evaluations
of the stability and anti-inflammatory effects of Curcumin, curcumin was physically encapsulated in exosomes. As noted above, the incorporation of curcumin into exosomes increases its solubility, stability, and bioavailability. And the anti-inflammatory activity of exosomal curcumin have been assessed both in vitro and in vivo. In vitro, macrophages that treated with exosomal curcumin secrete less pro-inflammatory cytokines. In vivo, the injection of curcumin-containing exosomes reduces the inflammatory response and increases the survival rate without adversely affecting mice with LPS-induced septic shock [30]. Zhuang et al. [29] showed that intranasally administered curcumin-loaded exosomes are effective for protecting mice from LPS-induced brain inflammation. In this study, exosomes are proved to successfully across the blood-brain barrier thus improving drug transport to the brain.

Meanwhile, recent advances have broadened the scope of therapeutic options to RNA-based therapeutics ranging from using specific RNA, RNA interfaces (RNAi) such as siRNA to silent gene expression, or to introduce miRNA inhibitors and miRNA mimics [49,50]. Small interfering RNAs (siRNA) have long been used as molecular tools to allow any target genes of interest to be suppressed specifically. miRNA inhibitors are synthetic miRNA analogs, which are fully complementary, chemically modified oligonucleotides, and are capable of inhibiting target miRNA functions. On the contrary, miRNA mimics increase target miRNA levels. Yet, most of the RNAs mentioned above are unstable in the circulation, quickly cleared by renal, and have difficulties of intercellular delivery. Exosomes have the potential to shield RNA from the intravascular degradation and enhance the therapeutic effects. Likely, regarding the prominent role of miRNA-155 in the signaling pathways of monocytes and macrophages in the inflammation, miRNA-inhibitors which are synthetic miRNA target analogs are identified to be capable of inhibiting miRNAs function and decreasing the secretion of TNF-α in macrophages when artificially loaded in the exosomes from B cells [21]. However, miRNA-155 mimic loaded exosomes significantly increased miRNA-155 levels, getting a pro-inflammatory response. In summary, evidence show that exosome-based delivery of RNA-based therapeutics are effective in vitro and in vivo.

An important consideration is the methods for loading exosomes with therapeutic cargo. Exosomes have an aqueous core and a lipophilic shell formed by a lipid bilayer. Their amphiphilic character makes it possible to compartmentalize and solubilize both hydrophilic and hydrophobic materials. So for the hydrophobic drugs such as polyphenol curcumin, drugs can embedded within the inner fatty acid layers through incubation. While for hydrophilic molecules like siRNA and miRNA, loading could be achieved by creating pores on the exosome membrane through electroporation or commercial transfection reagents. The former works in an electrical field to a suspension of exosomes and the therapeutic cargo, and induces pores formation on the exosome membrane, which facilitating numerous molecules that would never passively diffuse across the hydrophobic bilayer. This methods will have a better encapsulation efficiency if optimized by adjusting the siRNA concentration, exosome density, pulse duration and applied voltage. The latter was less applied in the studies as the efficiency of siRNA loading into exosomes was lower when compared to electroporation. Both electroporation and commercial transfection reagents have their inherent limits including aggregation of exosomes and cargo RNA, the integrity of exosomes and cargo and the lower efficiency (Table 1).

2. Conclusion

Sepsis is a complicated clinical syndrome that remains poorly understood despite intensive investigation. The feasibility of exosomes for preventing the excess inflammation that leads to severe morbidity and high mortality has been demonstrated. As most of these studies are preliminary and have been carried out in animal models, further research is needed to translate the results into clinical applications. Exosomes derived from plasma, saliva, cerebrospinal fluid, and urine can serve as diagnostic and prognostic biomarkers in cancer.

Table 1

<table>
<thead>
<tr>
<th>Reference</th>
<th>Source</th>
<th>Cell</th>
<th>Animal model/cell model</th>
<th>Cargo/drug</th>
<th>Administration route</th>
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<td>MSCs</td>
<td>CLP</td>
<td>miR-223</td>
<td>i.v.</td>
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<td>LPS induced inflammation in mice and BMDCs</td>
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<td>i.v.</td>
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<td>hUCMSCs</td>
<td>Human Umbilical Cord Mesenchymal Stem Cells.</td>
<td>MFG-E8</td>
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</table>

MSC, mesenchymal stem cells; CLP, cecal ligation and puncture; LPS, lipopolysaccharide; MFG-E8, milk fat globule-EGF8, miR, microRNA; i.v., intravenous, i.p., intraperitoneal; IDCs, immature dendritic cells; BMDC, bone marrow dendritic cells; EL-4, mouse lymphoma cell line; hUCMSC, Human Umbilical Cord Mesenchymal Stem Cells.

Fig. 2. During sepsis, various cells undergo apoptosis and if not timely cleared by the phagocytes, they can induce a surge of pro-inflammatory cytokines, such as TNF-HMG1 and IL-1MFG-E8 act like a bridge between apoptotic cells and phagocytes which facilitate the clearance of apoptotic cells. However, the mount of MFG-E8 have been affected in sepsis. Therefore, administration of exosomes encapsulated with MFG-E8 maybe an effective therapeutic approach in sepsis.
neurodegenerative diseases, kidney disease, and liver injury [51]. Studies of the clinical applications of exosomes, including as drug-delivery vehicles, have shown promising results. Yet, any treatment that interacts with basic biological signaling pathways carries a significant risk of unwanted side effects. Therefore, in the development of drugs that interact with exosomes for use in a therapeutic setting, strict and comprehensive risk and safety analyses are needed before these agents can be tested in humans.

Transparency document

The Transparency document associated with this article can be found, in the online version.

References
