

Exosomes in Sepsis Diagnosis and Treatment

Min Huang^{1*}, Huan Deng^{1*}, Jiang Li², Xingyu Tao¹, Baohui Jia^{3#}

¹The Third Affiliated Hospital of Nanchang University, Nanchang, China

²Zhengzhou Railway Vocational and Technical College/Henan Provincial Engineering Research Center of Natural Drug Extraction and Medical Technology Application, Zhengzhou, China

³The Fourth Affiliated Hospital of Nanchang University, Nanchang, China

Email: ¹bhjia@126.com

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Abstract

Sepsis has been redefined as a disorder of host response to infection, systemic circulation and cell/metabolic abnormalities. Exosomes are small (30 - 150 nm) vesicles produced by all cells under physiological and pathological conditions, with the potential to transfer proteins, lipids, small RNAs, messenger RNAs, or DNA between cells. Exosomes are natural cargoes for proteins, carbohydrates, nucleic acids and lipids. Exosomes play a central role in cellular communication and contribute to many pathophysiological processes, including immune responses and tumor progression. Exosomes have made great progress in many subject areas, and their potential role in sepsis is now being explored. In this review, several topics are mentioned. Firstly, we discuss the biological characteristics and functions of exosomes. Next, we focus on the diagnostic and therapeutic potential of exosomes in sepsis. Finally, we discuss some of the problems encountered by the current exosomes research institute. Therefore, the exosomes with combined diagnostic and therapeutic functions play a huge clinical application for the future research in sepsis.

Keywords

Exosomes, Sepsis, Biological Function, Targeted Vector, Inflammation

1. Introduction

Exosomes are natural carriers of many signaling molecules, including lipids, proteins, DNA, mRNA, miRNA, and siRNA. They can smoothly pass through the circulation without degradation by enzymes and thus transmit important mediators between cells [1]. Multi-functional circulating exosomes with various subtypes have been identified in many lesions such as cardiovascular, infectious

*Co-first author.

and autoimmune diseases. In addition, exosomes are also involved in adaptive immune response through the regulation of antigen presentation [2]. Sepsis remains a global medical problem, early diagnosis of which can inhibit its progression and improve outcomes [3]. However, the initiation or suspension of clinical interventions is still suffering from the lack of markers with high sensitivity and specificity. Accumulating evidence suggests that exosomes can be served as an attractive candidate for the treatment of sepsis. This review summarizes the biological behavior and application of exosomes [4].

2. Formation and Composition of Exosomes

2.1. Formation of Exosomes

Exosomes are small vesicles covered by plasma membrane [5]. The formation process of exosomes is complex and orderly. The intravesicular membrane is firstly inwardly depressed to form luminal vesicles, then multivesicular bodies are formed. When these polyvesicles are fused with lysosomes, they are degraded or recirculated and fused to the membrane, and then induced by endosomal sorting complex required for transport (ESCRT). The internal buds form granular vesicles, which are released into the extracellular environment and called exosomes [6].

2.2. Composition of Exosomes

Exosomes are mainly composed of lipids, proteins, mRNA, miRNAs, and long non-coding RNAs (lncRNAs) [7]. These components are essential for the unique biological functions of exosomes. The hydrophilic and lipophilic outer shell of exosomes is valuable in shuttling through hydrophilic and hydrophobic structures in the body fluid circulation [8]. Nucleic acids, including mRNA, microRNA, and lncRNA, can be absorbed by the recipient cells through fusion with the target cell membrane, thereby activating the signaling pathway and controlling the protein expression [9]. A variety of protein components on the surface of exosomes such as (CD9, CD63, CD81), Alix, HSP70, HSP90 and GTPase have a labeling effect.

2.3. Biological Roles in Exocytosis and Sepsis

The content function of the exosomes and the mechanical properties of the membrane are being unveiled [10]. The exosomal function of different subpopulations varies between different donor/recipient cells and the tissue microenvironment. Under the influence of pathophysiological factors, donor cells load specific cargoes such as functional RNAs (miRNAs and mRNAs) and proteins into exosomes. Exosomes transport these cargoes to the recipient cells, causing subsequent genetic and phenotype changes [11]. The intercellular communication mediated by exosomes in sepsis is mainly through activation of target cell surface receptors, which induces cells to cope with changes in the external environment. After fusion with the recipient cells, the contents of the vesicles, such

as microRNAs (miRNAs) or mRNAs and proteins, are transported to the cytoplasm [12]. **Table 1** identifies the current exosomes with diagnostic value for sepsis in the study of exosomes.

As long as the donor cells are free of apoptosis and necrosis in the body, the exosomes secreted by it can persist in body fluids and maintain a stable concentration.

As donor cells, whatever conditions, can secrete exosomes, the concentration of which remains steady. These unique features of exosomes make them ideal carriers for anti-sepsis drugs [13].

3. Exosomes and Sepsis

3.1. Exosomes Participate in the Onset Process of Sepsis

Sepsis is defined as a life-threatening organ dysfunction caused by the host's dysregulation of immune response. However, our current understanding of its process, including early diagnosis, treatment, and prognosis evaluation, is still

Table 1. Exosome in body fluids as biomarkers of sepsis.

Associated Protein, mRNAs or miR	Findings	Effects
miR-15a	Differentially expressed in adult a neonatal sepsis	Inhibits angiogenesis through direct targeting of VEGF and FGF [33]
miR-16a	in mice exposed to lipopolysaccharides	expression was shown to be up-regulated Following CLP [34]
miR-17	in the whole blood of mice after CLP	were significantly up-regulated in the microarray analysis in mice subcutaneously [35]
miR-20a/b	in the whole blood of mice after CLP	were significantly up-regulated in the microarray analysis in mice subcutaneously [35]
miR-21	in late sepsis of mice	with higher mortality in LPS-peritonitis model [36]
miR-146a	patients with severe sepsi	Predicted mortality and treatment outcomes induced by severe sepsis and sepsis.
miR-150	in septic patients	associated with survival rate in patients with sepsis [37]
miR-195	mice with CLP	only significantly expressed in the CLP model
miR-223	patients with mild sepsis severe sepsis and septic shock	as novel diagnostic biomarkers of sepsis [38]
ATF3	mice	an interesting sepsis-AKI biomarker [39]
SPTLC3	sepsis patient	potential classifier to monitor clinical progression of sepsis [40]

miR = microRNA, ATF3 = Activating transcription factor 3 RNA, SPTLC3 = Serine Palmitoyltransferase, Long Chain Base Subunit 3.

unclear. Almost all cells secrete exosomes, which are present throughout the body fluid circulation and mediate many aspects of disease development and progression by mediating cell-to-cell signaling [14] The currently evolving biotechnology of nanotechnology and genomics and proteomics provide the directions to target therapeutic agents in septic patients (Table 2).

In the setting of activation and apoptosis, exosomes are released and express specific membrane epitopes as their parental cells. The prospect for exosomes use in septic patients is bright, ranging from rapid and precise diagnostics [15]. Platelet-derived exosomes are isolated from patients with sepsis. These exosomes can produce oxidative enzymes in vascular endothelial cells and smooth muscle cells, induce apoptosis of vascular cells, suggesting a process of sepsis and septic shock. Platelet-derived exosomes may mediate vascular dysfunction through redox signaling pathways. During sepsis, platelets exposed to NO (nitric oxide) donors and LPS (lipopolysaccharide) secrete exosomes that activate caspase-3 and produce superoxide, NO and peroxynitrite. The base anion induces apoptosis, suggesting that platelet-derived exosomes can mediate vascular injury in a pathological, rather than physiological, environment. The anti-apoptotic effect

Table 2. Exosomes as therapeutic drug carriers and delivery vehicle.

Associated Protein, mRNAs or miR	Findings	Effects
miR-26b	mice with CLP	affected the antiviral response of the host
miR-27a	in the lungs of septic mice	up regulated in the progression to shock
miR-34a	in murine sepsis	Regulate vascular endothelial cell senescence
miR-106a/b	in whole blood of mice	Promote phagocytosis of macrophages by targeting SIRPa [41]
miR-126	in murine sepsis	Attenuates the increase in plasma levels of cytokines and chemokines induced by sepsis
NADPH oxidase	patients with diagnosis of septic shock	Improve dysfunction of heart and papillary muscles in patients with sepsis [42]
miR-223	in CLP mice	play an important role in MSC-induced cardioprotection in sepsis [43]
MFG-E8	rats by CLP	Reduce the level of inflammatory cytokines and increase the survival rate of experimental animals [44]
ADMSC	patients with diagnosis of septic shock	Improve dysfunction of heart and papillary muscles in patients with sepsis [45]

miR = microRNA, NADPH oxidase = Nicotinamide-adenine dinucleotide-phosphate hydrogen oxidase, MFG-E8 = Milk-fat-globule epidermal-growth factor-factor VIII, ADMSC = Adipose-derived mesenchymal stem cell.

of plasma-derived circulating exosomes on T lymphocytes in patients with sepsis can down-regulate the mRNA and protein levels of pro-apoptotic genes, and up-regulate the mRNA and protein levels of anti-apoptotic genes. Finally, it inhibits apoptosis of septic cells. These findings suggest that tissue vascular injury, apoptosis, and inflammatory responses in sepsis/septic shock are closely related to exosomes released by various effector cells *in vivo* [16].

3.2. Exosomes Can Be Used as Biomarkers for the Diagnosis of Sepsis

The high mortality rate of sepsis is closely related to complications, and sepsis cardiomyopathy is the main complication. In sepsis, the vascular endothelial physiology changes due to damage to the cardiovascular system, such as decreased Ca^{2+} response, mitochondrial dysfunction, and decreased β -adrenergic receptor response. Exosomes play an important role in the pathophysiology of the disease. When platelets are activated in sepsis, exosomes containing high concentrations of NADPH are released into the blood vessels of the heart, leading to cardiac function damage and failure.

Exosomes are released from the cells into the blood circulation. By detecting the content of some exosomes-including proteins and RNA in the body fluids, some diseases can be predicted before onset of clinical symptoms [17]. There was a highly significant correlation between the transit of exosomes-derived miRNAs and inflammatory responses, oxidative stress, and cell cycle regulation in patients with septic shock [18]. Exosomes can be detected in the setting of trauma and stress and maintain a certain concentration level even in lethal illness. From organ dysfunction to failure, exosomes are likely to play a monitoring and regulatory role, and also play an important role in predicting the outcome of the disease. Exosomal expression can be detected in sepsis. When animals are exposed to Gram-negative or Gram-positive infections, miRNA-16, miRNA-17, miRNA-20a, miRNA-20b, miRNA-26a and miRNA-26b can be abnormally elevated [19]. The plasma expression levels of miR-15a, miR-27a and miR-34a in exosomes are also closely related to the severity of sepsis development. These expressions of miRNA can be consistent with the changes of patients with sepsis. The level of miRNA in the plasma of patients with severe sepsis complicated with shock may change, which may provide more value for further study of the pathogenesis of sepsis endothelial dysfunction.

To this end, if the expression of miRNA is quantified, foreign miRNA expression can be used as a good biomarker for evaluating, monitoring and optimizing intensive treatment of sepsis in future critically ill patients.

3.3. Exosomes Are Expected to Be a New Treatment for Sepsis

Exosomes have the biological activity of substance transfer between cells, with the great potential of becoming therapeutic drug carriers. Exosomes can act as a mediator between cells and organs, regulating the biological activities of various substances involved in communication and signaling between cells. By upregu-

lating miR-21 to increase its expression, it can reduce apoptosis and reduce the production of pro-inflammatory factors. Protecting organ damage in local and distal areas of sepsis may be a potential treatment for sepsis [20]. As an important inclusion in exosomes, miRNA is involved in the regulation of each cellular process. Their expression changes are related to the occurrence, development and repair of many diseases and are important regulators in physiological and pathological processes. MiR-21 may act as a protective molecular medium between damaged tissues and organs. It is expected to be a targeted treatment for sepsis.

MiR-146a enhances the effect of IL-1 β on macrophage anti-sepsis infection. MiR-146a is a relatively important anti-inflammatory miRNA, and this exosome MiR-146a is greatly up-regulated due to inflammatory irritation. MiR-146a improves sexual performance and improves survival in mice with sepsis [21]. Although the mechanism for this study has not yet been fully elucidated, it can provide a new treatment for inflammatory disorders. MiR-145 can ameliorate sepsis-induced lung injury by inhibiting TGFBR2 signaling, and attenuate LPS-induced inflammation in mice by down-regulating IL-2 and TNF- α secretion, The overall survival rate of sepsis mice with lung injury was prolonged [22].

The circulating exosomes are rich in various types of biomolecules, affecting myocardial cell function, reducing the degree of myocardial infarction, reducing myocardial ischemia-reperfusion injury, and promoting myocardial regeneration and repair. And it is expected to be a specific biomarker for cardiovascular disease diagnosis, risk stratification and prognosis [23].

The use of proteins and nucleic acid components in exosomes as drug carriers and targeting tools for the treatment of sepsis is still being studied and discovered. The above studies suggest that it is effective to increase the content of some protective exosomes, thus avoiding the occurrence of multiple organ failure in sepsis.

3.4. Exosomes Play a Role in Important Organ Damage in Patients with Sepsis

Recently, sepsis has been redefined as a disorder of host response to infection, systemic circulation and cell/metabolic abnormalities, and its severity and clinical treatment depend largely on the organ dysfunction state of the patient. Every time an organ failure occurs, the probability of death will increase significantly [24]. Exosomes are released at different concentrations in healthy subjects and diseased populations, and the concentrations released into the circulation in different diseases are also different. Intratracheal instillation of extracellular vesicles derived from bone marrow mesenchymal stem cells can alleviate lung inflammation and edema caused by acute lung injury by inducing expression of keratinocyte growth factor [25]. The plasma concentrations of N-terminal B-type natriuretic peptide (NT-proBNP) and hypersensitive troponin T (hs-cTnT) in circulating blood in patients with severe sepsis or septic shock can follow the occur-

rence of acute myocardial infarction, therefore, exosomes can be used as a multifunctional clinical indicator of early ischemic myocardial injury in intensive care [26].

Zhou found in the experiment that exosomes miR-126-5p and 3p can inhibit LPS-induced human microvascular endothelial cells (HMVECs) high mobility group protein b1 (HMGB1) and vascular cell adhesion molecule 1 (VCAM1) levels. It was confirmed that the use of EPR exosomes to deliver miR-126 can prevent microvascular dysfunction, attenuate the increase in plasma cytokine and chemokine levels induced by sepsis, inhibit lung and renal vascular leakage in vital organs, and improve the survival rate of mice with sepsis [27]. In the mouse kidney ischemia/reperfusion injury model, the level of urinary extracellular ATF3 (activating transcription factor 3) was detected to be higher than normal before serum creatinine concentration had increased [28]. This finding suggests that extracellular ATF3 is more sensitive as a biomarker in early acute kidney injury than traditional clinical biomarkers, suggesting that exosomes are expected to be an effective tool for the diagnosis/treatment of early acute kidney injury in further studies.

4. Current Problems

However, there are many problems and challenges in the study of exosomes. How to separate pure exosomes from various body fluids is a key issue. Presently, exosome extraction methods are mainly in five categories, namely, ultracentrifugation, precipitation, immunoabsorption, ultrafiltration, and microfluidic separation techniques [29]. Although differential centrifugation and ultracentrifugation are the most commonly used techniques in clinical laboratories. However, this method has certain limitations due to its protein contamination and yield problems [30]. New methods such as density gradient centrifugation, while overcoming the above limitations, are complicated in steps, and the experimental process takes a long time and cannot be applied to the clinic. There are many reports on the relationship between extracellular vesicle biomarkers and various diseases. However, the results of individual studies vary widely, probably due to the differences of exosome in extraction and purification methods [31]. Due to the complex structure, variable composition and versatility of exosomes, exosomes in these natural states are difficult to be used as targeting targets for drugs. At the same time, most of these studies are preliminary, only in animal models, and further research is needed to translate into clinical applications.

5. Conclusion and Outlook

Although the pathogenesis and clinical treatment of sepsis have made great progress, the mortality rate of sepsis has not decreased [32]. So far, some indicators of sepsis have been used only to determine the presence of organ failure and to assess the patient's clinical outcome. Exosomes can play a huge potential as a disease-specific biomarker and a carrier for the treatment of sepsis/septic shock.

It is a hot research topic to make full use of the unique biological function of exosomes and to study and elucidate the mechanism of sepsis from different levels such as cells and molecules. It will provide new help for targeted specific treatment of sepsis/infectious shock.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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