

# The Use of Exosomes as Biomarkers for Evaluating and Monitoring Critically Ill Polytrauma Patients with Sepsis

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**Abstract** Regarding genetic biomarkers for early assessment and monitoring the clinical course in polytrauma patients with sepsis, in recent years a remarkable evolution has been highlighted. One of the main representatives is the exosome miRNAs. In this paper, we would like to present in more details the various methods of using exosome miRNAs as a biomarker for monitoring polytrauma patients with sepsis, as well as establishing a belated outcome by aggregating the entire clinical aspects. The use of exosome miRNAs for late evaluating and monitoring the clinical evolution of polytrauma patients can bring significant improvements in current clinical practice through the optimization and modulation of intensive care according to the needs of each patient individually.

**Keywords** Sepsis · Exosomal miRNAs · Epigenetic biomarkers · Critically ill polytrauma patient

## Introduction

Sepsis remains to be one of the major pathophysiological aspects encountered in the critically ill patients. In addition to this, sepsis is also considered to be one of the principle causes of death in intensive care units (ICU), due to secondary

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pathophysiological effects induced by it (Ince 2005; Reinhart et al. 2012). Moreover, the diagnosis, evaluation, and further monitoring the evolution of sepsis by the ICU physician remains to be an important step in optimizing the appropriate intensive therapy options for these patients. Latest methods of evaluation and monitoring are not able to give satisfactory responses, as the selectivity and specificity of the existing biomarkers is very low. Similarly, the biomarkers which are used currently, do not satisfy the demands of the latest therapeutic management options available, as intensive therapies cannot be optimized based on the molecular response obtained for each patient separately. Regarding the biomarkers used in sepsis, they are represented by the quantification of epigenetic markers found in these patients. Similarly, many studies lately have evaluated the expression of exosomal miRNAs in sepsis (Adams 2011; Benz et al. 2016). In this scientific work, we not only wish to demonstrate the epigenetic modifications seen in sepsis, but also the direct correlations between the modifications seen in miRNAs expression and a series of physiopathologies associated with sepsis.

## Pathophysiological Aspects of Sepsis

Sepsis over the years remain to be the leading cause of patient admission in the ICU. From the pathophysiological point of view, sepsis results by the drastic fall in the immunity of the patient, due to interaction of the pathogens with the biological system of the body. Hence, large quantities of pro-oxidative and pro-inflammatory molecules are produced, which are further responsible for the augmentation of the inflammatory status, affecting the endovascular system and the coagulation cascade both. From the clinical point of view, this pathophysiological aspect is reflected by vasodilation, increase in capillary permeability, increased pro-coagulant status, tissue hypoxia, and not only this, even the microvascular system is affected (Jacobi 2002). Above all, the hemodynamic status of the body is affected.

From the molecular point of view, sepsis induces a series of disturbances in the biochemical and the genetic system of the body (Jacobi 2002). Lipopolysaccharide (LPS) is responsible for the activation of specific receptors, which augment the inflammatory status. Principle pathways are represented by the activation of the nuclear transcription factor kappa B (NF- $\kappa$ B), which further activates the nuclear system of biosynthesis and pro-inflammatory molecules. In addition to this, in the aggressive cycle of biosynthesis, a series of miRNAs are implicated by the pro-inflammatory molecules. Similarly, the modifications seen in the concentration of the miRNAs can be quantified, may be due to decrease in the concentration, due to the fact of synthesis or may it be due to the increased concentration because of excessive stimulation of the nuclear receptors. In addition to this, a series of specific miRNAs are involved in the activation process of NF- $\kappa$ B and of biosynthesis of pro-inflammatory cytokines (Böhler et al. 1997; Jacobi 2002; Comim et al. 2011). On this mechanism, the practical concepts of evaluation and monitoring the sepsis, are based on identifying the specific miRNAs. Further, through identifying the miRNAs expression, optimal intensive therapy options can be established, taking into

consideration the molecular and pathophysiological dysfunction attack in the case of critical patients (Ince 2005; Adams 2011).

## Structural and Functional Aspects of the Exosomes

From the structural view point, the exosomes are fragments of dimensions between 30 and 120 nm, derived from the cells. They et al. (2002) represented in one of his works, an update, the fact that the exosomes are regained into a series of biologic fluids, like blood, urine, amniotic fluid, bronchial aspirates, or from the hydro thoracic fluid. Important to note is the fact that the exosomes are integrated in the fragments of the cells, as seen in the proteins, lipids, and miRNAs.

Various studies have demonstrated that the composition of the protein markers of exosomes, either originates from the cytoplasm or from a part of the cellular plasma membrane. Blanchard et al. (2002) identified the proteins of the same surface area of CD28, CD45 and CD40L of the T cell-derived exosomes. Dimitris et al. in one of his studies evidenced that the composition of the mastocyte-derived exosomes, is identified by increase in the actin expression (Skokos et al. 2001). One of the similar studies performed by They et al. identified the tubulin in the exosomes derived from the dendritic cells. In a similar manner, thioredoxin peroxidase expression was identified on the exosomes derived from the dendritic cells (They et al. 2001). Van Niel et al. (2001) studied similar composition of the enterocyte-derived exosomes, by identifying the Enolase-1.

Mechanisms are still not clear regarding the free circulation of the exosomes, while few studies have demonstrated the fact that one of the principle mechanisms is represented by the fusion of endocytic compartments with the plasma membrane (They et al. 2002; Lin et al. 2015).

Several studies have shown the presence of a high number of integrin in the exosomes of different cellular origins like  $\alpha 4\beta 1$ ,  $\alpha M\beta 2$ ,  $\beta 2$  and  $\alpha L\beta 2$ . Rieu et al. (2000)  $\alpha 4\beta 1$  studied the integrin's expression on the exosomes of the reticulocyte origin, and demonstrated increased concentration of the . They et al. (2001) further in one of his similar studies, proved the presence of the integrin  $\alpha M\beta 2$  in exosomes derived from the dendritic cells. Lankar et al. reported the presence of integrin  $\beta 2$  in exosomes derived from the T-cells (Blanchard et al. 2002), while Skokos et al. (2001) evidenced the presence of the integrin  $\alpha L\beta 2$  in mastocyte-derived exosomes.

A number of studies performed, are based on the identification of tetraspanins in the exosomes. Heijnen et al. (2015) documented the presence of CD63 in exosomes derived from the platelets. Vincent-Schneider et al. (2002) performed a similar study, stating the increase in expression of CD63 in mastocytes. Escola et al. (1998) reported in his study, the expression of tetraspanins in exosomes, based on the presence of CD37, CD53, CD81, and CD82 of the B-cell-derived exosomes.

One of the most important functions of the exosomes is represented by their information transmitting capacity between the cells. Skokos et al. (2001) demonstrated the fact that the mast cells release the exosomes, which then intervene in the modulation of the immune response by transferring the information enclosed in the CD80, CD86, and CD40 cells. Moreover, exosomes are implicated

in obtaining a specific immune response by transferring the information to the T-cells (Thery et al. 2001; Blanchard et al. 2002; Thery et al. 2002).

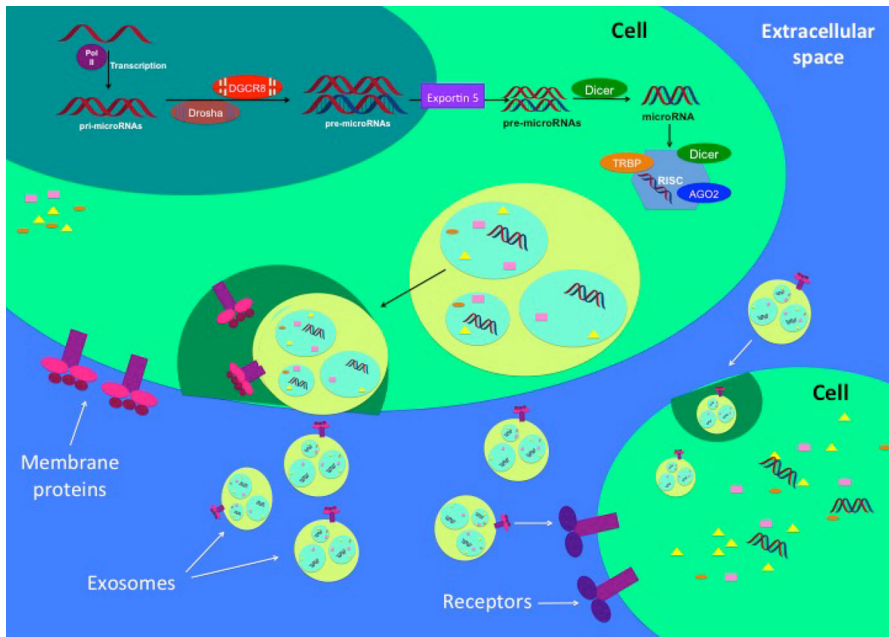
Interaction pathways between the exosomes and the cells are represented by two principle mechanisms. Either it is through, the exosomal transmembrane molecule interacting with the specific receptors on the surface of the cell, or through the exosomes embedded in the cytoplasm of the cell, by the fusion of the plasma membrane (Simons and Raposo 2009; Mathivanan et al. 2010; Montecalvo et al. 2012; Mulcahy et al. 2014; Zhang et al. 2015a).

One of the most important methods of evaluation and monitoring their physiopathology is identifying the miRNAs expression, found in the exosomal composition. From the biochemical point of view, miRNAs are non-coding single-stranded RNA, which are composed of an average of 15–23 nucleotides. The mechanism of biogenesis of the miRNA starts in the nucleus of the cells by the action of the RNA polymerase II on the specific genes. Further, the translation and transcription reactions take place, producing the pre-miRNAs, on which acts the RNase III endonuclease (Drosha) and cofactors on the DiGeorge Syndrome Critical Region 8 (DGCR8), forming the precursors of the pre-miRNAs. Pre-miRNAs then attach to the protein transporter Exportin-5, and are transferred from the nucleus into the cytoplasm. Reaching the cytoplasm, the second RNase III endonuclease (Dicer) acts on the pre-miRNAs, synergic with the transactivator RNA-binding protein (TRBP) and hence forming the mature miRNA (double-stranded). The last step is represented by the introducing the mature miRNA in RNA-induced silencing complex (RISC) (Fig. 1) (Pavic et al. 2006; Chen et al. 2015; Lenkala et al. 2015; Dumache et al. 2016; Hayashi et al. 2016; Zhang et al. 2016).

A series of modifications of the miRNAs exosomal expression were identified, which were able to be correlated to a series of physiopathologies. Sohn et al. (2015) analyzed the expression of the exosomal miRNAs in the hepatocellular carcinoma patients, and evidenced a significant increase in the concentration of the miRNA-18a, miRNA-221, miRNA-222, miRNA-224, and a decrease in the expression of miRNA-101, miRNA-106b, miRNA-122, and miRNA-195. A similar study, performed by Ogata-Kawata et al. (2014) aimed to study the exosomal expression of the miRNAs, and noted a rise in the concentration of the miRNA-1229, miRNA-1246, miRNA-150, miRNA-21, miRNA-223, miRNA-239, and let-7a. Perez-Hernandez et al. (2015) studied the exosomal expression of the miRNAs in urine of the patients suffering from systemic lupus erythematosus, and reported significant modifications in the miRNA-335, miRNA-302d, miRNA-200c, and miRNA-146a.

## Exosomes Expression in Sepsis

Alexander et al. (2015) studied the exosomes expression and their response in between the cells. Later on the study documented that miRNA-155 and miRNA-146a are both transferred through the intermediate exosomes derived from the dendritic cells, and are thus responsible for the modulation of the inflammatory response. Likewise, it was witnessed that the miRNAs are the factors that play a critical role in the differentiation of T lymphocytes and B lymphocytes through the



**Fig. 1** The biosynthesis of exosomal miRNAs

intermediary Dicer enzyme. Liu et al. performed a study aiming to find out the connection between the miRNA-155 expression and Tregs, as well as to find out the prognosis of the patients with sepsis. In the group of patients with severe sepsis, intensified expression of miRNA-155 was noticed. And above this, they are associated with an intense expression of miRNA-155 with a very high SOFA score. Similarly, later on, his study documented a strong and significant correlation from the statistical point of view, between the high levels of miRNA-155 and the CD39<sup>+</sup> Tregs expression (Liu et al. 2015). It was reported that the CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> regulatory T-cells play an important role in modulation of the immune response in sepsis. In addition to this, they reported a series of links between raised expression of CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> complex and the excessive production of pro-inflammatory molecules like interleukin 4 (IL-4), interleukin 10 (IL-10), and gamma interferon (IFN- $\gamma$ ).

It is well known that pathogens are present on the principle Toll-like receptors interleukin 1 receptors (TIRs). Many studies were performed confirming this fact, as well as to evaluate classifying the receptors, responsible for the modulation of the immune response, such as 11 family members of the Toll-like receptors (numbered from TLR-1 to TLR-11) and 10 members of the IL-1 family receptors. Recent studies evidenced a series of important bonding between the specific miRNA expression and activation of TIRs. Above this, through activation of NF- $\kappa$ B, everything enters into a vicious cycle of inflammation, due to the hyperstimulation in the chain of production of pro-inflammatory mediators. Pro-inflammatory interleukin 1 beta mediators (IL-1 $\beta$ ) and TNF-alpha (TNF- $\alpha$ ) lead to the activation

of NF- $\kappa$ B, and are further considered to be the factors that lead to activation of interleukin 6 (IL-6) and the augmentation of the inflammatory status. In a similar way, a rise was noted in the expression of the miRNA-146a, miRNA-9, and miRNA-155, in the case of NF- $\kappa$ B activation (Wang et al. 2014).

A high percentage of patients with sepsis are infected by gram-negative bacteria. LPS produced by these gram-negative bacteria possess a high anti-inflammatory capacity, which is responsible for the augmentation of pro-oxidative and pro-inflammatory processes. One of the principle mechanisms of intensification of the inflammatory status due to LPS is represented by the activation of TLR-4, which further leads to the activation of NF- $\kappa$ B and activators of protein 1 (AP-1). In a similar manner, new mechanisms are activated, which are responsible for excessive bioproduction of pro-inflammatory chemokines. Hsieh et al. (2013) noted a rise in the expression of let-7d, miRNA-15b, miRNA-16, miRNA-25, miRNA-92a, miRNA-103, miRNA-107, and miRNA-451 in these patients. Similarly, Moschos et al. (2007) observed intensification in the expression of miRNA-21, miRNA-25, miRNA-27b, miRNA-100, miRNA-140, miRNA-142-3p, miRNA-181c, miRNA-187, miRNA-194, miRNA-214, miRNA-223, and miRNA-224 in the lung tissue exposed to LPS. Huang et al. (2014) studied the expression of miRNA in the acute respiratory distress syndrome (ARDS), reporting a marked fall in the expression of miRNA-24, miRNA-26a, miRNA-126, let-7a, let-7b, let-7c, let-7f, while an increase in the expression of miRNA-344, miRNA-346, miRNA-99a, miRNA-127, miRNA-128b, miRNA-135b, miRNA-30a, and miRNA-30b was noted. In a similar study, How et al. (2015) evidenced a significant decrease in the expression of let-7a and miRNA-150 in the patients infected by gram-negative bacilli.

Gambim et al. documented the fact that the exosomes are responsible for the activation of the endothelial cells and aggressive production of superoxide and peroxynitrite. Moreover, a series of modifications are seen in the exosomal expression in sepsis patients (Gambim et al. 2007). A similar study was performed by Azevedo et al. which studied the exosomal expression in 55 patients with septic shock. Later on his study demonstrated that there exists a series of implications which are responsible for the endovascular disease and the accelerated production of the azot monoxide (Azevedo et al. 2007). Wu et al. (2013) studied the exosomal miRNAs expression in sepsis, and reported an excessive rise in concentration of miRNA-16, miRNA-17, miRNA-20a, miRNA-20b, miRNA-26a, and miRNA-26b in laboratory experimental animals, when exposed to gram-negative and gram-positive bacteria. Moore et al. (2012) demonstrated a rise in miRNA-182, miRNA-199a-5p, miRNA-203, miRNA-211, miRNA-222, miRNA-29b expression in sepsis. Wang et al. studied the miRNAs expression in the patients suffering from sepsis, and SIRS, respectively. Later on, his studies documented a significant increase in the expression of miRNA-146a and miRNA-223 in the sepsis cases, compared to that seen in the patients suffering from SIRS (Wang et al. 2010). Zhou et al. (2015) in one of the similar studies, analyzed the miRNAs expression in sepsis and evidenced a decrease in the expression of miRNA-182, miRNA-143, miRNA-145, miRNA-146a, miRNA-150, and miRNA-155. Yao et al. studied the miRNAs expression in sepsis, and noticed a decrease in miRNA-25 expression. Likewise,

there exists a significant correlation between decreased expression of miRNA-25 to the increased pro-oxidative and pro-inflammatory status (Yao et al. 2015).

## Conclusion

In critically ill patients with sepsis, the epigenetic expression is significantly affected because of a series of molecular damages, which appear secondary, due to the pathophysiologies associated with it. The miRNAs expression can be easily quantified leading to a series of responses with high specificity and selectivity. Similarly, we can conclude that using the expressions of the exosomes, the miRNAs can be considered as a good biomarker for evaluating, monitoring, and optimizing the intensive treatment of critically ill patients with sepsis in future.

## Compliance with Ethical Standards

**Conflict of Interest** The authors have declared no conflict of interest.

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