DE GRUYTER OPEN

Review

DOI: 10.1515/rrlm-2016-0015

A novel evaluation of microvascular damage in critically ill polytrauma patients by using circulating microRNAs

Evaluarea modernă a disfuncțiilor microvasculare la pacientul critic politraumatizat prin utilizarea microRNAs circulant

Ovidiu Horea Bedreag[1], Alexandru Florin Rogobete[2*], Carmen Alina Cradigati[3], Mirela Sarandan[3], Radu Nartita[4], Florin George Horhat[1], Sonia Elena Popovici[1], Dorel Sandesc[1], Marius Papurica[1]

1. Faculty of Medicine, "Victor Babeș" University of Medicine and Pharmacy, Timișoara, Romania 2. Emergency County Hospital Timișoara, Romania, 3. Clinic of Anesthesia and Intensive Care "Casa Austria", Emergency County Hospital "Pius Brinzeu", Timișoara, Romania, 4. Faculty of Chemistry, Biology, Geography, West University of Timișoara, Timișoara, Romania

Abstract

The management of the critically ill polytrauma patient is complex due to the multiple complications and biochemical and physiopathological imbalances. This happened due to the direct traumatic injury, or due to the post-traumatic events. One of the most complex physiopathology associated to the multiple traumas is represented by microvascular damage, subsequently responsible for a series of complications induced through the imbalance of the redox status, severe molecular damage, reduction of the oxygen delivery to the cell and tissues, cell and mitochondrial dead, augmentation of the inflammatory response and finally the installation of multiple organ dysfunction syndrome in this type of patients. A gold goal in the intensive care units is represented by the evaluation and intense monitoring of the molecular and physiopathological dysfunctions of the critically ill patients. Recently, it was intensely researched the use of microRNAs as biomarkers for the specific physiopathological dysfunctions. In this paper we wish to present a series of microRNAs that can serve as biomarkers for the evaluation of microvascular damage, as well as for the evaluation of other specific physiopathology for the critically ill polytrauma patient.

Keywords*: microRNAs, microvascular disease, polytrauma patient, hypoxia, biomarkers*

Rezumat

Managementul pacientului critic politraumatizat este complex datorită complicațiilor multiple, dar și a dezechilibrelor biochimice și fiziopatologice pe care le dezvoltă. Acestea au loc atât datorită injuriilor directe traumatice, cât și celor secundare post-traumatice. Una dintre cele mai complexe disfuncții fiziopatologice asociată cu traumele multiple este reprezentată de disfuncțiile microvasculare, responsabile semnificativ de o

***Corresponding author**: Alexandru Florin Rogobete, Emergency County Hospital Timișoara, Timișoara, TM Romania, e-mail: alexandru.rogobete@umft.ro

serie de complicații ce induc ulterior dezechilibrul statusului redox, disfuncțiile moleculare severe, reducerea capacității de distribuție a oxigenului către celule și țesuturi, moartea mitocondrială și celulară, augmentarea răspunsului inflamator și în final instalarea sindromului de disfuncție multiplă de organ. Obiectivul principal în unitățile de terapie intensivă este reprezentat de evaluarea și monitorizarea intensivă a disfuncțiilor moleculare și fiziopatologice. Recent, s-a studiat intens utilizarea microRNAs ca biomarker pentru analiza dinfuncțiilor fiziopatologice la acest tip de pacienți. În această lucrare de acutalizare dorim să prezentăm o serie de microRNAs care pot servi ca biomarkeri pentru evaluarea disfuncției microvasculare, dar și utilizarea acestora pentru evaluarea fiziopatologiilor specifice pacientului critic politraumatizat.

***Cuvinte cheie**: microARN, boala microvasculară, pacient politraumatizat, hipoxia, biomarcheri*

Received: 13th December 2015; Accepted: 6th March 2016; Published: 14th March 2016

Introduction

A high percentage of polytrauma patients presents severe haemorrhagic shock (1). This is one of the most common causes of death in the intensive care unit (ICU). The increased mortality rate is due to both the primary traumatic injuries as well as by the secondary one to the haemorrhagic shock. Among the most common secondary physiopathological phenomenon for the haemorrhagic shock are tissue hypoperfusion, tissue hypoxia, lactic acidosis, endothelium vascular damage and the formation of microthrombi in small vessels (2). In the case of this type of patients the common therapeutic action is volemic resuscitation. The post-resuscitation physiopathological status is considerably aggravated especially by the ischemia-reperfusion syndrome.

Because of the traumatic injuries, ischemia-reperfusion syndrome, coagulophaty and of microvascular damage are being produced increased quantities of inflammatory molecules (3). Also in the critically ill patients, the microvascular system is compromised by severe sepsis. The intensification of the inflammatory status, severe infections, hypermetabolism and microvascular damage lead to multiple organ dysfunction syndrome (MODS), responsible of patient death.

Gold goals in the management of these patients consist in ”unblocking” the microvascular system and in assuring an adequate tissue perfusion. Evaluation and monitoring of the microvascular system is possible through some conventional biomarkers for inflammation, hypoperfusion and hypoxia (4,5). However, these do not present high selectivity and specificity, mostly bringing tardive answers. Thus, lately were intensely studied the circulating microRNA species as biomarkers (6).

Numerous studies have highlighted that microRNA presents high selectivity and specificity for some physiophatological dysfunctions, becoming so a new biomarkers era (7–9).

In this paper we wish to present the microvascular damage in the polytrauma patient with haemorrhagic shock, as well as the microRNA species as biomarker for this.

The physiophatology of microvascular damage and hypoxia

At the critically ill polytrauma patient, the microvascular system is affected by a complex series of causes such as SIRS, sepsis, imbalance of the redox status, coagulopathy and a series of other molecular dysfunctions. Also, the microvascular system dysfunction affects and augments a series of other biochemical and physiopathological systems, mainly due to decreasing the delivery of oxygen and nutrients to the tissues. Subsequently to oxygen privation of the cell take place mitochondrial dysfunctions and nuclear transcription dysfunction, which lead to cell death. Also along with the destruction of the

integrity and functionality of the cell are activated numerous pro-inflammatory systems, that are being responsible for worsening the inflammatory response and aggravation of the clinical patient status.

In the case of the critically ill polytrauma patient with haemorrhagic shock, in volemic resuscitation most often is administered red blood packet (RBP) in order to increase the oxygen delivery toward the tissues. However, a series of study reports numerous side effects such as the augmentation of the inflammatory status and imbalance of the redox status due to the inadequate tissue oxygenation. This phenomenon is due to cell degradation especially, by inhibiting the adenosine triphosphate system (ATP), to phospholipid membrane degradation through lipid peroxidation, as well as to the loss of the cell structure. Therefore, the microvascular system is significantly affected leading to the intensification of the ischemia-reperfusion syndrome. Moreover, are being produced increased quantities of interleukin 1beta (IL-1β), interleukin 6 (IL-6), interleukin 8 (IL-8) and tumour necrosis factor alpha (TNF-α) (10).

Through the endothelial injury are being bioproduced a series of pro-inflammatory cytokines, having place the lipid peroxidation of cellular membrane, destruction of the endothelial basal membrane as well ass the imbalance of the coagulation cascade.

Another biochemical system affected in endothelial injury is represented by the nitric oxide (NO) system through ischemia and hypoxia. Decreased expression of the NO system as well as the aggressive biosynthesis of vasoconstrictor substances lead to the impairment of the microvascular flow.

A high percentage of critically ill polytrauma patients present sepsis. Regarding the microvascular system at patients with sepsis, the vascular endothelium is severely affected due to direct adhesion of the pathogens, aggregation and activation of the inflammatory cells, release of pro-inflammatory cytokines, as well as activation of the complement system.

Bateman et al., have studied the microvascular system status at the laboratory animal with sepsis induced. Following their study they have highlighted a dramatic decrease of microvascular autoregulation, oxygen delivery capacity, as well as an increase of nitric oxide synthase in plasma (11). Another important cause of the microvascular system dysfunction at the patients with SIRS and sepsis is due to the structural modification of glycocalyx. Following the structural and functional degradation of glycocalyx are being produced a series of physiophatological dysfunctions reflected upon the microvascular flow. Among these the most common are represented by the exaggerated increase of the paracellular permeability, the loss of the electric charge, as well as the disturbance of the coagulation cascade with formation of numerous microthrombs at the microvascular level (12).

The incapacity of the organism to maintain the equilibrium between the free radicals (FR) and the substances with antioxidant activity leads to the installation of the phenomenon called oxidative stress (OS) (Figure 1).

The main pathway of attack of the OS on the vascular endothelium is represented by the interaction between the superoxide anion and the molecules of NO, for which presents a high affinity. Following this interaction the microvascular system is affected through two ways. One is represented by depriving the endothelium of NO, and the other one by the production of new FR species, derived from nitrogen. The new formed FR bring significant prejudices to the vascular endothelium by DNA, lipids and protein degradation.

Another important factor in microvascular damage is represented by the activation of the nuclear transcription factor kappa B (NF-kB). NF-kB is responsible for the generation of some

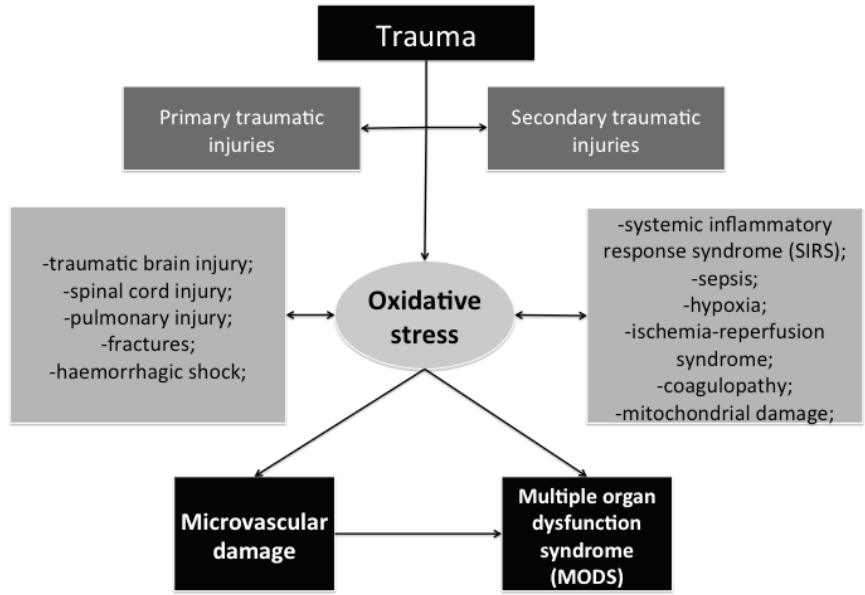

Figure 1. Schematic representation of the secondary pathophysiology associated with trauma. The implications on microvascular damage.

cellular stimuli that produce increased quantities of proinflammatory cytokines, FR and adhesion molecules by activating the transmembrane receptors (13).

microRNAs biogenesis

From the biochemical point of view, the microRNA species are single-stranded non-coding RNA. Regarding their constitution they are formed of 19-24 nucleotides. The microRNA synthesis begins in the nucleus by the action of RNA polymerase II on microRNA genes. Thus are obtained the primary species, called pri-microRNA. In what fallows on pri-microRNA acts RNase III endonuclease (Drosha), forming pre-microRNA. Drosha require the cofactor DiGeorge Syndrome Critical Region 8 (DGCR8) in order for the transformation reaction of pri-microRNA in pre-microRNA to take place. The next step in microRNAs biogenesis in constituted by the pre-microRNA transport from to nucleus in the cytoplasm. This is possible through the transport protein called Exprtin-5.

In cytoplasm, pre-microRNA is attacked by RNase III endonuclease (Dicer) together with the trans-activator RNA binding protein (TRBP). Following this reaction is forming mature microRNA (double – stranded) and microRNA* (passenger strand). The next biochemical step of microRNA biosynthesis is represented by introducing the mature species in the RNA induced silencing complex (RISC).

The use of microRNA as biomarkers is due to the fact that microRNAS are synthetized and released by the cell in differ physiophatological conditions. Regarding the release mechanisms of microRNAs two types are described, passive release and active release (Figure 2).

The use of microRNAs as biomarkers for microvascular damage

microRNA presents high stability in biological fluids and it can be analysed without modifying its structure or functionality. Circulating microRNA can be identified in a series of biological fluids, such as blood, urine and others.

microRNAs expression and endovascular disease

Dysfunctions of the microvascular system can be evaluated and monitored by using circulating microRNAs. Zhang et al., have studied the expression of microRNA-150 at the specific cell lines, highlighting a series of connections significant from a statistical point of view, between the expression of the microRNA species and the endothelial dysfunction (14). Following their study they have highlighted significant decrease of microRNA-122, microRNA-148a, microRNA-19a, let-7i, microRNA-320d and microRNA-4429. Also, they have reported important increases in the expression of microRNA-363 and microRNA- 487b (15). Another study regarding the microRNA expression in microvascular disease was effectuated by Scott et al. Following their study, they have identified modifications for microRNA-17-92, microRNA-221, microRNA-222 and microRNA-126 (16). A similar study was effectuated by Hulsmans et al., highlighting important increases in the expression of microRNA-146 in the patients with endovascular disease (17).

microRNAs expression and the hypoxia

The critically ill polytrauma patient in haemorrhagic shock, in respiratory dysfunctions, such as acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), as well as in sepsis is exposed to severe tissue hypoxia. Numerous studies have reported significant modification on the expression of microRNA-23, microRNA-24, microRNA-26, microRNA-27, microRNA-103, microRNA-107, microRNA-181, microRNA-210 and microRNA-213 in hypoxia. Agrawal et al., have also studied the microRNA expression in hypoxia. Following their study, they have reported increased expression of microRNA-210-3p, microRNA-1275, microRNA-376c-3p, microRNA-23b-3p, microRNA-193a-3p, microRNA-145-5p and decreased expression of microRNA-92b-3p, microRNA-20a-5p, microRNA-10b-5p, microRNA-181a-2-3p and microRNA-185-5p (18). More

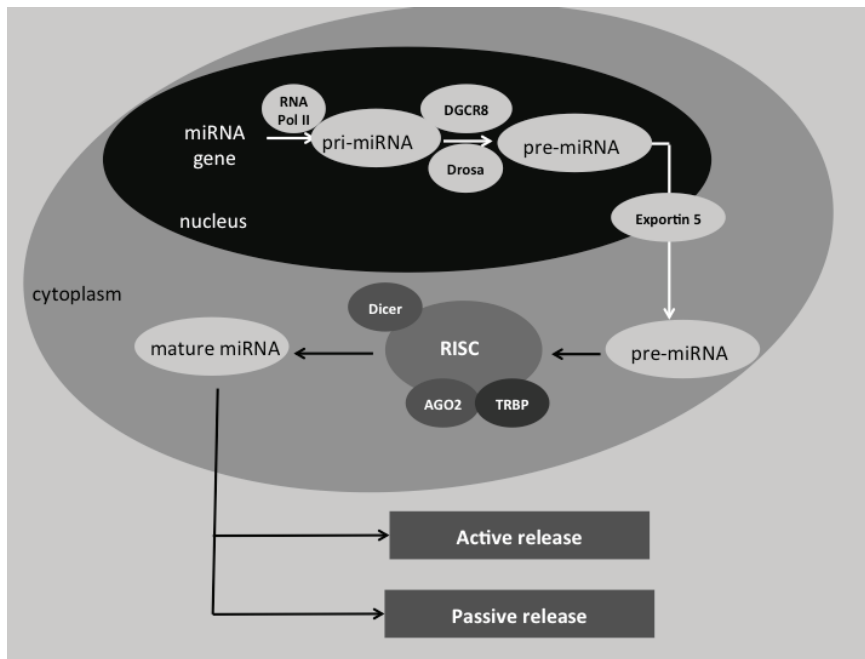

Figure 2. Biogenesis of microRNAs. For explanations see the text.

than that, Hung et al., have stuied the microRNAs profiles in the laboratory animals with ARDS induced. Following their study they have reported a decreased expression of miRNA-24, miRNA-126, miRNA-26a and let-7a. Also, following their study they have reported an increased expression of miRNA-346, miRNA-344, miRNA-127, miRNA-999, miRNA-128b, miRNA-30b and miRNA-30a (19).

microRNAs and the ischemia-reperfusion syndrome

In ischemia-reperfusion syndrome are produced a multitude of microvascular damages due to oxygen deprivation of the endothelium, mitochondrial dysfunction and to the excessive production of FR and proinflammatory molecules. Studies regarding the microRNAs expression in ischemia-reperfusion syndrome reports important increases in the expression of microRNA-290, microRNA-145 si microRNA-26, as well as decreases in the expression of microRNA-192, microRNA-187, microRNA-805 and microRNA-194 (20). Zhou et al., in a similar study on the microRNAs expression in in ischemia-reperfusion syndrome have highlighted important increases in the expression of microRNA-21, microRNA-193-3p and microRNA-210. In a similar study effectuated by Zhon et al., were highlighted increases in the expression of 20 microRNAs, as well as a decreases in the expression of 39 microRNAs (21).

microRNAs, adhesion molecules, inflammation and the coagulation cascade

Regarding the microRNAs expression given by the adhesion molecules from the vascular endothelium, mainly responsible for the microvascular damage, were realised a series of experimental studies. Harris et al., in a study on the adhesion molecules and endothelial inflammation have highlighted significant modifications in the expression of microRNA-126 (22). Another important dysfunction for the critically ill polytrauma patients is represented by the thromboembolic events. Salloum-Asfar et al., have studied microRNAs expression regarding the dysfunctions of the coagulation cascade. Following their study they have reported significant correlations between the expression of microRNA-181a-5p and the action of the coagulation factor XI (23).

microRNAs expression and the redox disease

The disruption of the microvascular system induces mainly the intensification of the redox imbalance. Regarding evaluation and monitoring of OS, have been realized a series of study on the microRNAs expression and its use as biomarker. Thus, a series of study regarding microRNAs expression in OS were effectuated, being highlighted significant correlations between the expression of miRNA-872, miRNA-155, miRNA-183 and the intensity of the oxidative dysfunctions (17). From a cellular point of view, OS affects and augments the functionality and integrity of mitochondria. Chen et al., have proved that the expression of microRNA-210 is significantly correlated with mitochondrial dysfunction induced by hypoxia and ischemia (24). In the hypoxic episodes mitochondria is responsible for producing increased quantities of FR through some essential biomechanisms such as growth factor adaptor Shc, transport complexes I and III, as well as NADPH oxidase-4 (NOX4). Along with the mitochondrial dysfunction appears a number of other pathophysiology that are implicated in the aggravation of the clinical status of this patients, especially due to the dysfunction of the energetic balance and to the programmed cell death by mitochondria (25). Recent studies have highlighted significant modifications in the expression of microRNA-25, microRNA-17*, microRNA-335, microRNA-34a and microRNA-181a in the case mitochondrial damage due to hypoxia (26–29).

Mitochondrial dysfunctionality involves also a series of disruptions of the biochemical mechanisms of nuclear transcription. More than this, the activation of the nuclear transcription factor kappa B (NF-kB) leads to the accelerated biosynthetis of proinflammatory molecules, thus augmenting the inflammatory response of the critically ill polytrauma patient. microRNAs can also be used in this case for the evaluation of the nuclear transcription imbalances (30). The studies have highlighted a significant correlation between the expression of microRNA-146, microRNA-155, microRNA-181b, microRNA21 and microRNA-301a (30). An important study was effectuated by Li et al. on the modifications of the microRNAs expression induced by the NF-kB imbalances. Following their study, they have highlighted an important decrease of microRNA-223, microRNA-15a and microRNA-16 (31). A similar study was effectuated by Zhang et al., that have noticed significant correlations between NF-kB damage and microRNA-143 (32). More than that, NF-kB dysfunctionality involves the intensification of the inflammatory response through excessive stimulation and bioproduction of inflammatory mediators. The increased concentration of proinflammatory molecules is also responsible for microvascular damage through harming the microvacular endothelium. The studies have highlighted a series of implications between the NF-kB dysfunctionality and the increased concentration of proinflammatory cytokine (33).

microRNAs expression in sepsis

Regarding to monitoring of sepsis by using epigenetic biomarkers were effectuated numerous studies being reported a series of microRNAs with high specificity and selectivity. et al (34), have studied the microRNAs expression in sepsis. Thus they have identified a series of microRNAs cu high specificity and selectivity such as, microRNA-15b, let-7b, microRNA-16, microRNA-324-3p, microRNA-210, microRNA-486-5p, microRNA-484, microRNA-340 and microRNA-324-3p (34). A similar study was effectuated by Wang et al (35). They have examined the expression of microRNAs on 232 patients highlighting modifications regarding the expression of microRNA-122 (35). Other studies have reported the utilization of microRNAs species from the microRNA-4772 family for the evaluation and monitoring of sepsis (36). In Table 1 are summarized a series of microRNAs species that can be used in the evaluation of the microvascular system status.

Conclusions

The complexity of the physiopathology in the critically ill polytrauma patient has imposed intense research regarding the specific biomarkers. Because of the importance of the microvascular damage in the evolution of the clinical status of the critically ill patient, lately have been studied numerous microRNAs capable of bringing answers regarding the direct injury, as well as the secondary one induced secondary by the microvascular disease. Even if the microRNAs can bring quick answers with high selectivity and specificity for the microvascular disease in the case of the critically ill patient, are required more studies in this regard.

Acknowledgements

The authors wish to thanks for the support to Association for Anaesthesia and Intensive Therapy „Aurel Mogoseanu" and to Emergency County Hospital "Pius Brinzeu" Timisoara, Romania.

Conflict of interests

The authors have no conflict of interest to declare regarding this article.

Table 1. The use of microRNAs as biomarker for the evaluation of microvascular disease

microRNAs	Observations	Reference
microRNA-17-92, microRNA-126, microRNA-222, microRNA-221	Signification modifications of the microRNAs expression in microvascular damage and endothelial dysfunctions;	(16)
microRNA-221, microRNA-222	The modifications of the expression of these microRNAs are associated with the intensification of the inflammatory status. Also, microRNAs modifications have been correlated with important increases of TNF-alpha	(17)
microRNA-769-3p	Modifications of these microRNAs expression is correlated with ischemia-reperfusion syndrome	(37)
microRNA-29b, microRNA-15a, microRNA-16, microRNA-199a-5p, microRNA-182, microRNA-203, microRNA-222, microRNA-211,	The expressions of this microRNAs species are significantly elevated in sepsis; An increased concentration of these microRNAs is also correlated with a significant increase of the concentrations of the pro-inflammatory molecules.	(34), (38)
microRNA-146a, microRNA-122, microRNA-574-5p, microRNA-223, microRNA-342-5p, microRNA-483-5p, microRNA-150, microRNA-499-5p, microRNA-193b, microRNA-150	The expression of this microRNAs species decreases drastically in sepsis; The reduced expression of these microRNAs is also correlated with a significant increase of the concentrations of the pro-inflammatory molecules.	(34) (39)

References

1. Kalla M, Herring N. Physiology of shock and volume resuscitation. Surg. 2013;31(11):545–51. DOI: 10.1016/j.mpsur.2013.08.012
2. White NJ, Martin EJ, Brophy DF, Ward KR. Coagulopathy and traumatic shock: Characterizing hemostatic function during the critical period prior to fluid resuscitation. Resuscitation. 2010;81:111–6. DOI: 10.1016/j.resuscitation.2009.09.017
3. Zampieri FG, Kellum J a, Park M, Ranzani OT, Barbeiro H V, de Souza HP, et al. Relationship between acid-base status and inflammation in the critically ill. Crit Care. 2014;18(4):R154. DOI: 10.1186/cc13993
4. Trancă SD, Laura C, Hagă N. Biomarkers in polytrauma induced systemic inflammatory response syndrome and sepsis – a narrative review. Rom J Anesth Int Care. 2014;21(2):118–22.
5. Maschirow L, Khalaf K, La-Aubaidy H, Jelinek HF. Inflammation, coagulation, endothelial dysfunction and oxidative stress in prediabetes — Biomarkers as a possible tool for early disease detection for rural screening. Clin Biochem. 2015;48(9):581-5. DOI: 10.1016/j.clinbiochem.2015.02.015
6. Gilad S, Meiri E, Yogev Y, Benjamin S, Lebanony D, Yerushalmi N, et al. Serum microRNAs are promising novel biomarkers. PLoS One. 2008;3(9):1–7. DOI: 10.1371/journal.pone.0003148
7. Weber J, Baxter DH, Zhang S, Huang DY, Huang KH, Lee MJ, et al. The microRNA spectrum in 12 body fluids. Clin Chem. 2010;56:1733–41. DOI: 10.1373/clinchem.2010.147405
8. Zhou J, Chaudhry H, Zhong Y, Ali MM, Perkins LA, Owens WB, et al. Dysregulation in microRNA expression in peripheral blood mononuclear cells of sepsis patients is associated with immunopathology. Cytokine. 2015;71(1):89–100. DOI: 10.1016/j.cyto.2014.09.003
9. Roderburg C, Luedde T. Circulating microRNAs as markers of liver inflammation , fibrosis and cancer. J Hepatol. 2014;61(6):1434–7. DOI: 10.1016/j.jhep.2014.07.017
10. Donati A, Damiani E, Luchetti M, Domizi R, Scorcella C, Carsetti A, et al. Microcirculatory effects of the transfusion of leukodepleted or non-leukodepleted red blood cells in patients with sepsis: a pilot study. Crit Care. 2014;18(2):R33. DOI: 10.1186/cc13730
11. Bateman RM, Sharpe MD, Jagger JE, Ellis CG. Sepsis impairs microvascular autoregulation and delays capillary response within hypoxic capillaries. Crit Care. 2015;19(1):389. DOI: 10.1186/s13054-015-1102-7
12. Chelazzi C, Villa G, Mancinelli P, De Gaudio a R, Adembri C. Glycocalyx and sepsis-induced alterations in vascular permeability. Crit Care. 2015;19(1):1–7. DOI: 10.1186/s13054-015-0741-z
13. Donato A, Pierce G, Lesniewski L, Seals D. Role of NFκB in age-related vascular endothelial dysfunction in humans. Aging. 2009;1(8):678–81. DOI: 10.18632/aging.100080
14. Zhang Y, Liu D, Chen X, Li J, Li L, Bian Z, et al. Secreted Monocytic miR-150 Enhances Targeted Endo-

thelial Cell Migration. Mol Cell. 2010;39(1):133–44. DOI: 10.1016/j.molcel.2010.06.010
15. Jickling GC, Ander BP, Zhan X, Noblett D, Stamova B, Liu D. MicroRNA expression in peripheral blood cells following acute ischemic stroke and their predicted gene targets. PLoS One. 2014;9(6). DOI: 10.1371/journal.pone.0099283
16. Scott E, Loya K, Mountford J, Milligan G, Baker AH. MicroRNA regulation of endothelial homeostasis and commitment - Implications for vascular regeneration strategies using stem cell therapies. Free Radic Biol Med. 2013;64:52–60. DOI: 10.1016/j.freeradbiomed.2013.04.037
17. Hulsmans M, De Keyzer D, Holvoet P. MicroRNAs regulating oxidative stress and inflammation in relation to obesity and atherosclerosis. FASEB J. 2011;25(8):2515–27. DOI: 10.1096/fj.11-181149
18. Agrawal R, Pandey P, Jha P, Dwivedi V, Sarkar C, Kulshreshtha R. Hypoxic signature of microRNAs in glioblastoma: insights from small RNA deep sequencing. BMC Genomics. 2014;15(1):686. DOI: 10.1186/1471-2164-15-686
19. Huang C, Xiao X, Chintagari NR, Breshears M, Wang Y, Liu L. MicroRNA and mRNA expression profiling in rat acute respiratory distress syndrome. BMC Med Genomics 2014;7(1):1–15. DOI: 10.1186/1755-8794-7-46
20. Weiss JB, Eisenhardt SU, Stark GB, Bode C, Moser M, Grundmann S. MicroRNAs in ischemia-reperfusion injury. Am J Cardiovasc Dis. 2012;2(3):237–47.
21. Zhou L, Zang G, Zhang G, Wang H, Zhang X, Johnston N, et al. MicroRNA and mRNA signatures in ischemia reperfusion injury in heart transplantation. PLoS One. 2013;8(11):e79805. DOI: 10.1371/journal.pone.0079805
22. Harris T a, Yamakuchi M, Ferlito M, Mendell JT, Lowenstein CJ. MicroRNA-126 regulates endothelial expression of vascular cell adhesion molecule 1. Pnas. 2008;105(5):1516–21. DOI: 10.1073/pnas.0707493105
23. Salloum-Asfar S, Teruel-Montoya R, Arroyo AB, García-Barberá N, Chaudhry A, Schuetz E, et al. Regulation of Coagulation Factor XI Expression by MicroRNAs in the Human Liver. PLoS One. 2014;9(11):e111713. DOI: 10.1371/journal.pone.0111713
24. Chen Z, Li Y, Zhang H, Huang P, Luthra R. Hypoxia-regulated microRNA-210 modulates mitochondrial function and decreases ISCU and COX10 expression. Oncogene. 2010;29(30):4362–8. DOI: 10.1038/onc.2010.193
25. Hu Y, Deng H, Xu S, Zhang J. MicroRNAs Regulate Mitochondrial Function in Cerebral Ischemia-Reperfusion Injury. Int J Mol Sci. 2015;16(10):24895–917. DOI: 10.3390/ijms161024895
26. Varga Z V, Kupai K, Szűcs G, Gáspár R, Pálóczi J, Faragó N, et al. MicroRNA-25-dependent up-regulation of NADPH oxidase 4 (NOX4) mediates hypercholesterolemia-induced oxidative/nitrative stress and subsequent dysfunction in the heart. J Mol Cell Cardiol. 2015;62:111–21. DOI: 10.1016/j.yjmcc.2013.05.009
27. Xu Y, Fang F, Zhang J, Josson S, St Clair WH, St Clair DK. miR-17* suppresses tumorigenicity of prostate cancer by inhibiting mitochondrial antioxidant enzymes. PLoS One. 2010;5(12):e14356. DOI: 10.1371/journal.pone.0014356
28. Bai X-Y, Ma Y, Ding R, Fu B, Shi S, Chen X-M. miR-335 and miR-34a Promote renal senescence by suppressing mitochondrial antioxidative enzymes. J Am Soc Nephrol. 2011;22(7):1252–1261. DOI: 10.1681/ASN.2010040367
29. Wang L, Huang H, Fan Y, Kong B, Hu H, Hu K, et al. Effects of Downregulation of MicroRNA-181a on H 2 O 2 -Induced H9c2 Cell Apoptosis via the Mitochondrial Apoptotic Pathway. Oxid Med Cell Longev. 2014;2014:960362. DOI: 10.1155/2014/960362
30. Ma X, Becker Buscaglia LE, Barker JR, Li Y. MicroRNAs in NF-kappaB signaling. J Mol Cell Biol. 2011;3(3):159–66. DOI: 10.1093/jmcb/mjr007
31. Li T, Morgan MJ, Choksi S, Zhang Y, Kim Y-S, Liu Z. MicroRNAs modulate the noncanonical transcription factor NF-κB pathway by regulating expression of the kinase IKKα during macrophage differentiation. Nat Immunol. 2010;11(9):799–805. DOI: 10.1038/ni.1918
32. Zhang X, Liu S, Hu T, Liu S, He Y, Sun S. Up-regulated microRNA-143 transcribed by nuclear factor kappa B enhances hepatocarcinoma metastasis by repressing fibronectin expression. Hepatology. 2009;50(2):490–9. DOI: 10.1002/hep.23008
33. Haddad JJ. Science review: Redox and oxygen-sensitive transcription factors in the regulation of oxidant-mediated lung injury: role for nuclear factor-κB. Crit Care. 2002;6:481–90. DOI: 10.1186/cc1839
34. Huang J, Sun Z, Yan W, Zhu Y, Lin Y, Chen J, et al. Identification of MicroRNA as sepsis biomarker based on miRNAs regulatory network analysis. Biomed Res Int. 2014;2014.
35. Wang H, Yu B, Deng J, Jin Y, Xie L. Serum miR-122 correlates with short-term mortality in sepsis patients. Crit Care. 2014;18(6):1–4. DOI: 10.1186/s13054-014-0704-9
36. Ma Y, Vilanova D, Atalar K, Delfour O, Edgeworth J, Ostermann M, et al. Genome-Wide Sequencing of Cellular microRNAs Identifies a Combinatorial Expression Signature Diagnostic of Sepsis. PLoS One. 2013;8(10). DOI: 10.1371/journal.pone.0075918
37. Magenta A, Greco S, Gaetano C, Martelli F. Oxidative stress and microRNAs in vascular diseases. Int J Mol Sci. 2013;14(9):17319–46. DOI: 10.3390/ijms140917319
38. Moore CC, McKillop IH, Huynh T. MicroRNA expression following activated protein C treatment

during septic shock. J Surg Res. 2012;182(1):116–26. DOI: 10.1016/j.jss.2012.07.063
39. Vasilescu C, Rossi S, Shimizu M, Tudor S, Veronese A, Ferracin M, et al. MicroRNA fingerprints identify miR-150 as a plasma prognostic marker in patients with sepsis. PLoS One. 2009;4(10). DOI: 10.1371/journal.pone.0007405
40. McClure C, Brudecki L, Ferguson D a., Yao ZQ, Moorman JP, McCall CE, et al. MicroRNA 21 (miR-21) and miR-181b couple with NFI-A to generate myeloid-derived suppressor cells and promote immunosuppression in late sepsis. Infect Immun. 2014;82(9):3816–25. DOI: 10.1128/IAI.01495-14
41. Vaporidi K, Iliopoulos D, Francis RC, Bloch KD, Zapol WM. MicroRNA Expression Profile In A Murine Model Of Ventilator-induced Lung Injury. Am J Physiol Lung Cell Mol Physiol. 2012;303(3):L199–L207. DOI: 10.1152/ajplung.00370.2011