Modes of action and diagnostic value of miRNAs in sepsis

Nikolaos Antonakos†, Charly Gilbert‡, Charlotte Théroude, Irene T. Schrijver and Thierry Roger*

Infectious Diseases Service, Department of Medicine, Lausanne University Hospital and University of Lausanne, Epalinges, Switzerland

Sepsis is a clinical syndrome defined as a dysregulated host response to infection resulting in life-threatening organ dysfunction. Sepsis is a major public health concern associated with one in five deaths worldwide. Sepsis is characterized by unbalanced inflammation and profound and sustained immunosuppression, increasing patient susceptibility to secondary infections and mortality. microRNAs (miRNAs) play a central role in the control of many biological processes, and deregulation of their expression has been linked to the development of oncological, cardiovascular, neurodegenerative and metabolic diseases. In this review, we discuss the role of miRNAs in sepsis pathophysiology. Overall, miRNAs are seen as promising biomarkers, and it has been proposed to develop miRNA-based therapies for sepsis. Yet, the picture is not so straightforward because of the versatile and dynamic features of miRNAs. Clearly, more research is needed to clarify the expression and role of miRNAs in sepsis, and to promote the use of miRNAs for sepsis management.

KEYWORDS
miRNA, sepsis, infection, innate immunity, biomarkers, critically ill

Abbreviations: AKI, acute kidney injury; ALI, acute lung injury; APACHE, acute physiology and chronic health evaluation; ARDS, acute respiratory distress syndrome; CCL, C-C motif chemokine ligand; CXCL, C-X-C motif chemokine ligand; DAMP, damage or danger-associated molecular pattern; DC, dendritic cell; HMGBl, high mobility group box-1; HSP, heat shock protein; ICU, intensive care unit; IFN, interferon; IL, interleukin; IRF, IFN response factor; IRAK, IL-1 receptor-associated kinase; lncRNA, long non-coding RNA; LPS, lipopolysaccharide; MAMP, microbial-associated molecular pattern; MAPK, mitogen-activated protein kinase; miRNA, microRNA; MyD88, myeloid differentiation primary response 88; NF-kB, nuclear factor-kB; PCT, procalcitonin; PRR, pattern-recognition receptor; SIRS, systemic inflammatory response syndrome; SOCS, suppressor of cytokine signaling; SOFA, sequential organ failure assessment; STAT, signal transducer and activator of transcription; TLR, Toll-like receptor; TNF, tumor necrosis factor.
1 Introduction

1.1 Innate immune sensing

Innate immune cells sense signals of microbial origin (microbial-associated molecular patterns or MAMPs, also known as pathogen-associated molecular patterns or PAMPs) or endogenous components released by injured or stressed cells (damage or danger-associated molecular patterns or DAMPs) through pattern-recognition receptors (PRRs). Lipopolysaccharide (LPS), peptidoglycan, flagellin, β-glucan, lipoproteins, glycoproteins, double-stranded and single-stranded RNA, and unmethylated CpG motif containing DNA from bacteria, mycoplasma, mycobacteria, fungi, parasites and viruses are MAMPs/PAMPs. The best described DAMPs are high mobility group box-1 (HMGB1), fibrinogen, fibronectin, nucleic acids, histones, heat shock proteins (HSPs), uric acid, ATP, cytochrome c, S100 molecules and serum amyloid A. The main families of PRRs comprise Toll-like receptors (TLRs), NOD-like receptors (NLRs), c-type lectin receptors, RIG-I-like receptors, cytosolic DNA sensors and scavenger receptors (1–4). The triggering of PRRs by MAMPs/DAMPs activates intracellular signal transduction pathways such as the nuclear factor-κB (NF-κB), interferon (IFN) response factor (IRF), mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) pathways regulating the expression of cytokines, acute phase proteins, and adhesion, co-stimulatory and major histocompatibility complex molecules as well as metabolism. A fine control of these pathways is essential to restore homeostasis following injury.

1.2 Sepsis

Sepsis-3 alliance redefined sepsis as “a life-threatening organ dysfunction caused by a dysregulated host response to infection” (5). Sepsis remains one of the leading causes of mortality worldwide. Recent estimations indicate that sepsis affects around 50 million people and is responsible of at least 11 million deaths annually worldwide (6). These numbers increased during the COVID-19 pandemic. Indeed, most patients dying from COVID-19 present respiratory failure (mostly acute respiratory distress syndrome, ARDS) and multi-organ failure, which are manifestations of sepsis (5). Despite progresses in basic, clinical and translational research, the pathophysiology of sepsis remains not fully understood. Sepsis-specific targeting strategies tested in clinical trials failed to show benefit for patients (7–19).

Sepsis is characterized by an exacerbation of antimicrobial defense mechanisms responsible for collateral tissue injury, organ dysfunctions and early mortality involved in around 10% of all fatal cases (Figure 1). The hyper-inflammatory response is associated with a concurrent shift towards inflammation resolution and tissue repair involved in immuno-paralysis or immunosuppression. The suppressive phase is related to the depletion of dendritic cells (DCs), T cells and B cells through apoptosis, a reduced expression of proinflammatory cytokines,
costimulatory and antigen-presenting molecules, and an increased expression of anti-inflammatory cytokines and inhibitory checkpoint molecules. Immunosuppression can persist for months to years (Figure 1). A subset of patients with prolonged stay in intensive care units (ICUs) suffer from persistent inflammation, immunosuppression and catabolism syndrome (PICS) (20). Dysregulated immune responses favor the development of secondary infections, viral reactivation and long-term immune disabilities accounting for late morbidity and mortality (7–13, 20). Delayed mortality associated with viral reactivation and nosocomial infections represent 20-40% and long-term mortality 50-70% of total fatal sepsis cases. Twenty percent of sepsis survivors develop secondary infections within 30 days, and nearly half of sepsis survivors are re-hospitalized within a year.

The identification of biomarkers and targets is one the most burning areas of research in the sepsis field. A biomarker is “any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease” (21). The identification of diagnostic, prognostic and theragnostic biomarkers to distinguish sepsis, identify patients who may benefit from host-targeted therapies, predict responsiveness and monitor the effectiveness of outcome or disease or predict the incidence from host-targeted therapies, predict responsiveness and monitor the effectiveness of treatment holds great promise for improving patient management (10, 12, 22–29). In the last years, microRNAs (miRNAs) have been suggested to be potential biomarkers and targets for sepsis.

In this review we aim to shed light on the role of miRNAs involved in the pathogenesis of severe infections and sepsis. We will start by briefly summarizing the biogenesis, modes of action, circulation and delivery of miRNAs, which are described comprehensively elsewhere (30–35).

2 miRNAs

2.1 Identification

Non-coding RNAs (ncRNAs) comprise a growing list of RNA species, including miRNAs, small interfering RNAs, long non-coding RNAs (IncRNA), Piwi-interacting RNAs, small nuclear RNAs, small nucleolar RNAs, extracellular RNAs and small Cajal body-specific RNAs. ncRNAs regulate numerous biological and pathological processes such as cancer and autoimmunity, cardiovascular and metabolic diseases.

In 1993, Lee et al. and Wightman et al. described a small RNA of 22 nucleotides, lin-4, with antisense complementarity to the heterochronic gene lin-14 in Caenorhabditis elegans (36, 37). In 2000, the description of let-7, a small RNA conserved in diverse species and with silencing abilities, highlighted the critical role of this category of RNA molecules (38–40). The following year, the term microRNA was coined by Tuschi et al. (41). Along with other groups, they paved the way for the discovery of numerous miRNAs. About 38’600 miRNAs have been identified in 271 species (http://www.mirbase.org). Around 2’600 human mature miRNAs are encoded in the human genome, with half annotated in miRBase V22 (42). The expression atlas of miRNAs generated by the Functional Annotation of the Mammalian Genome (FANTOM5) consortium revealed that the five most expressed miRNAs represent around 50% of the miRNA pool in a given human cell type (43). About half of miRNAs are cell type-enriched, a quarter are broadly expressed, and a quarter are expressed at small levels regardless the cell type.

2.2 Biogenesis

miRNAs can be encoded in non-coding (intergenic miRNAs) and intronic regions of genes. miRNAs are generated through canonical and non-canonical pathways (32, 44, 45) (Figure 2). In the canonical pathway, a long primary transcript (pri-miRNA) of hundreds to thousands nucleotides is generated by RNA polymerase II (Pol-II) or Pol-III and cleaved through the action of the RNA-binding protein DiGeorge syndrome critical region gene 8 (DGCGR8) and the nuclear RNase III enzyme Drosha into a precursor-miRNA (pre-miRNA) of approximately 70 nucleotides (46–49). Intronic pri-miRNAs are generated from host RNA transcripts (pre-mRNAs) by RNA splicing and excised into pre-miRNAs by spliceosomal components. Their expression relies on transcription factors and Pol-II (50). pre-miRNAs are exported into the cytoplasm in an exportin-5/RanGTP-dependent manner. Pre-miRNAs are converted into active miRNAs of approximately 22 nucleotides by a complex composed of the cytoplasmic RNase III Dicer and cofactors including transactivation response (TAR) RNA binding protein (TRBP) and the protein kinase RNA activator (PACT) (49, 51, 52). Of note, miRNAs (-5p and -3p) can be generated from the 5’ and 3’ arms of a pre-miRNA precursor, and co-expression of miRNA-5p and -3p species have been repeatedly reported. Non-canonical miRNA biogenesis pathways use different combinations of proteins, and are grouped into DGCGR8/Drosha-independent and Dicer-independent pathways (Figure 2). Small hairpin RNA (shRNA) are cleaved by the DGCGR8/Drosha complex and exported into the cytoplasm as in the canonical pathway, while pre-miRNA can be exported into the cytoplasm through exportin-1. A more detailed description of miRNA biogenesis pathways is beyond the scope of this review, but available in excellent reviews (32–35).

2.3 Modes of action

miRNAs interact with the 3′-untranslated region (3′-UTR) of mRNAs to induce mRNA degradation and translational...
repression. Additionally, miRNAs can interact with gene promoter, 5′-untranslated region (5′-UTR) and coding sequence, and can activate transcription in a phenomenon known as RNA activation (53). Finally, miRNA can interact with proteins to modify their activity.

Crosslinking and immunoprecipitation analyses revealed that most miRNA binding events have little functional consequences (54). miRNAs do not possess catalytic functions, but form effector ribonucleoprotein complexes known as RNA induced silencing complexes (RISCs) (55). Mature miRNA molecules bind with proteins of the Argonaute (AGO) family in an ATP-dependent manner. Four AGO proteins (AGO1-4) playing a key role in the formation of RISCs are expressed in humans (56). RISCs bind to target mRNA molecules based on complementarity of miRNA (Figure 2). The result can be translational inhibition by interfering with the eukaryotic initiation factor 4F (eIF4F) followed by the decay of the target mRNA. Moreover, AGO2 initiates mRNA deadenylation by poly (A)-deadenylases, uncapping and 5′-3′ degradation by an exoribonuclease (32, 55, 57). While full complementarity with the target mRNA triggers AGO2 and mRNA degradation, partial complementarity results in transient binding to RISC. It induces the unloading of miRNA from AGO2 (57, 58). AGO-free miRNA molecules and endogenous miRNA-mRNA duplexes have been studied during the past years (59, 60). Mature miRNAs may adopt secondary structures like hairpin and homoduplex that may increase their half-life, affinity and specificity for targets (61).

Free miRNAs interact with proteins, but the prevalence and outcome of such interactions are poorly described. For instance, miR-130b-3p binds to extracellular cold-inducible RNA binding protein (eCIRP) (62). miR-130b-3p and eCIRP are increased in the blood of septic mice and sepsis patients. eCIRP acts as a DAMP sensed through TLR4, promoting the release of inflammatory mediators. Upon binding to eCIRP, miR-130b-3p inhibits eCIRP/TLR4 interaction and cytokine release by immune cells. Injection of a miR-130b-3p mimic reduces cecal ligation and puncture (CLP)-induced inflammation and acute lung injury (ALI) in mice (62). Moreover, miR-130b-3p has been shown to inhibit M1 macrophage polarization (63). A single miRNA can thus interfere with immune responses through multiple ways.

2.4 Circulation and delivery

miRNA secretion and release are intrinsic to cell response to hypoxia, starvation, heat, triggering of PRRs and cytokine/growth factor receptors, and other environmental factors (32, 59, 64, 65). miRNAs are present in biological fluids like blood, plasma, serum, urine, tears, saliva, semen, cerebrospinal fluid, bronchial and peritoneal fluids, and breast milk (32, 59, 64). An
Important feature of extracellular miRNAs is their stability and resistance to RNaseA-mediated degradation (64, 66). miRNAs in fluids exert paracrine or endocrine effects as signal transducers of intracelluar communication (32, 65).

miRNAs are released passively accompanying apoptotic bodies or cell debris (from one to few μm) or secreted actively (59, 65). Secretion occurs through microvesicles of 100 to 1000 nm usually containing a RISC or a miRNA-AGO complex, and through exosomes (59). MAMPs or DAMPs trigger the release of exosomes containing miRNAs as well as DAMPs such as HMGB1, HSPs and histones, and cytokines, interleukins (ILs), chemokines and IFNγ. Early endosomes gradually turn to multivesicular bodies that integrate miRNAs and a RISC or similar complexes through mechanisms regulated by ceramide synthesis and neutral sphingomyelinase 2 (65, 67). Multivesicular bodies merge with lysosomes inducing the degradation of trapped material, or fuse with the cell membrane expelling exosomes containing miRNAs (59, 68). Exosomes can carry oncogetic miRNAs promoting tumor invasiveness (69), or anti-oncogenic and anti-angiogenic miRNAs inhibiting the growth of malignant cells (70). Similarly, exosomes can carry miRNAs that enhance or decrease cellular responses to MAMPs as reported for miR-155 and miR-146a in LPS-stimulated DCs (71). High-density lipoproteins (HDL) act as alternative carriers of miRNAs in the blood (Figure 2). This is an active and energy dependent procedure to differentiate from the passive release of miRNAs upon cell death (65).

The mechanisms of uptake of miRNAs by recipient cells is not fully deciphered (65). The uptake of microvesicles and exosomes occurs by endocytosis, phagocytosis or fusion with the plasma membrane. Endocytosis of microvesicles requires a docking step mediated by specific or non-specific molecules (72, 73). Because of their small size, microvesicles are also taken-up by micropinocytosis, which does not require a docking step (74). Exosomes and smaller extracellular vesicles are engulfed by phagocytosis mediated by TLRs and complement receptors. Exosomes released during sepsis impact on organs including lungs, kidneys, liver, heart and brain (75).

3 miRNAs in sepsis

Sepsis shows features of early immune hyper-activation and late immunosuppression. Accordingly, we may suggest that miRNAs having anti-inflammatory activities may be beneficial during early sepsis but detrimental during late sepsis. On the contrary, miRNAs having proinflammatory activities may be detrimental during early sepsis but beneficial during late sepsis (Figure 1).

Given that infection and stress modulate the expression of miRNAs, it is not surprising that miRNAs have been the focus of much interest. The stability, simple structure and expression of miRNAs in blood and other biological fluids represent an opportunity to stem new sepsis biomarkers (76). We will focus on promising miRNAs in sepsis. We will summarize observations about the modulation and the role of miRNAs in vitro and in vivo in models of sepsis (Table 1), and miRNAs as potential biomarkers in human sepsis (Table 2).

3.1 miRNAs and sepsis pathophysiology

3.1.1 miRNAs and innate immune cells

First, it should be recalled that miRNAs are not acting only as brakes, but also as promoters of inflammatory and innate immune responses. Cues to how miRNAs weight the inflammatory response have been obtained in studies using Dicer 1-deficient mouse macrophages depleted of miRNAs. Contrary to expectations, Dicer 1-deficient macrophages produce reduced levels of tumor necrosis factor (TNF), IL-6 and IL-12 in response to TLR1/2, TLR4, and TLR9 stimulation (84). It has been proposed that miRNAs expressed constitutively repress innate immune genes to preserve homeostasis, while stimulus-induced miRNAs fine-tune inflammatory responses and return to homeostasis (266).

miRNAs modulate immune signals by targeting positive or negative players of immune signaling pathways. This process is highly dynamic for several reasons. First, miRNAs are differentially expressed in innate and non-innate immune cell types. Second, miRNA expression is upregulated or downregulated in response to MAMPs/DAMPs/cytokines, and subjected to circadian rhythm (267). For example, miR-146a and miR-155 are upregulated while miR-27a and miR-532-5p are downregulated in macrophages exposed to LPS. Third, miRNAs regulate their own expression. The proinflammatory miR-375 inhibits the expression of the anti-inflammatory miR-21 by targeting the Janus kinase (JAK) 2-signal transducer and activator of transcription protein (STAT) 3 signaling pathway (185). Fourth, one miRNA targets many miRNAs, and one mRNA is regulated by various miRNAs. Consequently, miRNAs have additive or antagonistic effects on their targets. Fifth, one miRNA either inhibits or activates immune signaling, participating to feedback loop mechanisms controlling gene expression. Sixth, miRNAs circulate in fluids and act at a distance (268–272).

miRNAs target transcription factors, signaling proteins and growth factors to influence hematopoiesis and modulate the development of innate and adaptive immune cells. miRNAs regulate the functions of mature innate immune cells, including migration, phagocytosis, efferocytosis, production of cytokines, tolerance, tissue remodeling and promotion of tumor development (273–278). Macrophages display a continuum of functional states, ranging from proinflammatory M1 macrophages to pro-resolving/anti-inflammatory M2 macrophages. miR-155 is up-regulated in M1 macrophages. The knockout of mir155 and mir-155 antagonist
| miRNA   | Expression/model                                      | Target and effect                     | Observation/impact of miRNA                                                                 | Reference |
|---------|-------------------------------------------------------|---------------------------------------|-------------------------------------------------------------------------------------------|-----------|
| miR-15a/16 | Increased in BMDMs exposed to LPS                     | ↓ PU.1 & TLR4                         | Decreased phagocytic and bactericidal activities of BMDMs                               | (77)      |
|         |                                                      | ↓ TLR4 & IRAK1                        | Decreased inflammatory response                                                          |           |
|         |                                                      |                                 | Increased survival of miR-15a/16 knockout mice with sepsis (CLP and E. coli peritonitis) |           |
| miR-15a/16 | RAW 264.7 mouse macrophages exposed to LPS            | ↓ TLR4 & IRAK1                        | Increased expression of IL-1β, IL-6 and TNF                                              | (78)      |
| miR-15a-5p | Increased in RAW 264.7 mouse macrophages exposed to LPS | ↑ NF-κB pathway                      | miR-15a-5p inhibitor reduced cytokines and inflammation in mice challenged with LPS      | (79)      |
| miR-15-5p, miR378a-3p | Expressed in platelet-derived exosomes from sepsis patients | ↓ PDK1                               | Modulate Akt/mTOR-related autophagy pathway and induced NETs formation in organ injury   | (80)      |
| miR-16   | Increased in H69 human biliary epithelial cells and U-937 human monocytic cells exposed to LPS | ↑ NF-κB pathway by suppressing SMRT  | Increased expression of IL-1β, IL-6 and TNF                                              | (81)      |
| miR-17   | Decreased in RAW 264.7 macrophages exposed to LPS     | ↓ BRD4                                | Inhibition of BRD4 /EZH2/TRAIL pathway                                                   | (82)      |
| miR-19a  | Increased in B cells of sepsis patients               | CD22 ↑ 2 days after LPS stimulation  | Decreased inflammatory response of RAW 264.7 macrophages                                   | (83)      |
|         |                                                      | CD22 ↓ 4 days after LPS stimulation   | Positive feedback loop of B cell response                                                |           |
| miR19b   | HEK293T and HeLa cells, MEFs, human synovial fibroblasts | ↑ NF-κB pathway by suppressing A20/ Traf1p3, Rnf11, Bax11/ Kdm2a and Zbtb16             | Increased production of IL-6 and IL-8                                                     | (84)      |
| miR-21   | Increased in serum of pediatric sepsis patients (CLP) | ↑ NF-κB pathway & NLRP3 inflammasome  | Induction of pyroptosis in mouse macrophages, human THP-1 monocytic cells & primary PBMCs via activation of the NLRP3 inflammasome | (85)      |
| miR-21   | Increased in bone marrow of sepsis mice (CLP)         | ↑ NFI-A protein                       | Increased number of MDSCs by arresting myeloid progenitor differentiation and maturation  | (86)      |
| miR-21   | High levels in MDSCs from sepsis mice (CLP)           | –                                     | miR-21 antagonist improves late-sepsis survival                                          | (87)      |
| miR-23a  | Decreased in bone marrow mononuclear cells of sepsis mace | ↓ IncRNA MALAT1 & MCEMP1             | miR-21 up-regulated by STAT3 and C/EBPβ in MDSCs                                           | (88)      |
| miR-23a  | Decreased in RAW 264.7 mouse macrophages exposed to LPS | ↓ ATG12                               | Involved in the expansion of MDSCs                                                        |           |
| miR-23a-3p | Decreased in RAW 264.7 mouse macrophages exposed to LPS | ↑ PLK1                                | Decreased proliferation of monocytes                                                       | (89)      |
| miR-23a-3p |                                                      |                                       | Increased apoptosis of monocytes                                                          |           |
| miR-26a  | Decreased in serum and mononuclear of sepsis neonates | ↓ IL-6                                | Increased apoptosis of liver cells via inhibition of JAK/STAT pathway                      | (90)      |
| miR-26b  | Decreased in MEG-01 human megakaryocyte cells exposed to LPS or TNF | –                                     | Increased apoptosis of liver cells via inhibition of JAK/STAT pathway                      | (91)      |
| miR-27a  | Down-regulation by TUG1 (possible “sponge” action) in human cardiomyocyte cell line AC16 | ↓ TNF                                | LPS up-regulates miR-27a and down-regulates TUG1 overexpression inhibits TNF and apoptosis of AC16 cells | (92)      |
| miR-27a  | Increased in lung tissues of sepsis mice               | ↓ TNF, IL-6                           | miR-27a neutralization decreases pulmonary inflammation and increases survival of sepsis mice | (93)      |
| miR-27b  | Increased in MSCs-derived exosomes of sepsis mice      | ↓ JMDJ3 & JMDJ3/NF-κB/p65 axis         | Inhibition of pro-inflammatory response of BMDMs after LPS stimulation and in CLP-induced sepsis model | (94)      |
| miR-30a  | Increased in liver cells of sepsis rats                | ↓ SOCS-1                              | Increased apoptosis of liver cells via JAK/STAT pathway                                   | (95)      |
| miR-30e  | Decreased in liver cells and tissues of sepsis rats    | ↓ FOSL2                               | Decreased apoptosis of liver cells via inhibition of JAK/STAT pathway                      | (96)      |
| miRNA       | Expression/model                                      | Target and effect       | Observation/impact of miRNA                                                                 | Reference |
|-------------|-------------------------------------------------------|-------------------------|------------------------------------------------------------------------------------------------|-----------|
| miR-34a     | Increased in lung tissues of sepsis mice (CLP)        | ↓ SIRT1 & ATG4B         | Increased oxidative stress, inflammatory response and sepsis-induced ALI                          | (98)      |
| miR-34a     | Increased in macrophages of suckling rats after LPS stimulation | ↑ iNOS, phospho-STAT3/STAT3 | Increased sepsis-induced ALI I inhibition of miR-34a decreases sepsis-induced ALI | (99)      |
| miR-92a-3p  | Increased in the BALF of the sepsis rats              | ↓ PTEN                  | Increased activation of alveolar macrophages                                                   | (100)     |
| miR-98      | Decreased in myocardial tissues of sepsis mice (CLP)  | ↓ HMGA2, TNF, IL-6      | Decreased sepsis-induced cardiac dysfunction, liver and lung injury                             | (101)     |
| miR-103a-3p | Decreased in sepsis patients                          | ↓ HMGB1                 | Decreased HMGB1 expression, systemic inflammation and multi organ failure, and increased survival in mice with endotoxia | (102)     |
| miR-122     | HuH7 hepatocellular carcinoma cell line               | ↓ SOCS1                | Increased expression of IFN-α & IFN-β                                                         | (103)     |
| miR-122     | HuH7 cells                                            | ↓ SOCS3                | Increased expression of IFN-α & IFN-β                                                         | (104)     |
| miR-122     | HepG2, Huh7 and Huh7.5.1 hepatocellular carcinoma cell lines | ↓ FGFR1, IGFR1, MERTK  | Decreased STAT3 Tyr705 phosphorylation, increased IRF1 and IFN expression in response to HCV and poly (I: C) | (105)     |
| miR-122     | Huh7 and HepG2 cells                                  | ↓ HO-1                 | Inhibit HBV expression (HBsAg and HBeAg expression)                                            | (106)     |
| miR-122     | Increased in HepG2 and Huh7 cells                     | ↑ TLR4                 | Decreased the proliferation and the production of TNF and IL-16 by HepG2 and Huh7 cells        | (107)     |
| miR-122-5p  | Increased by LPS in the heart of rats and in H9c2 rat cardiomyocytes | –                      | Inhibition of miR-122-5p reduced myocardial injury through inhibiting inflammation, oxidative stress and apoptosis in endotoxin rats | (108)     |
| miR-124     | Decreased in organs of mice with LPS-induced acute lung injury (ALI) | ↓ MAPK14 (p38-α)       | Overexpression decreases IL-1β, IL-6, IL-10 and TNF in blood, and MAPK signaling and lung cell apoptosis and lung injury in ALI mice | (109)     |
| miR-125b    | Decreased in PBMCs exposed to LPS, and in PBMCs and serum of sepsis patients | ↓ STAT3                | Inhibition in peripheral blood monocytes increases STAT3 phosphorylation and the expression of PCT and NO Possibly acts downstream the NED25 gene intergenic lncRNA | (110)     |
| miR-125b    | Decreased in PBMCs exposed to LPS, and in PBMCs of sepsis patients | ↓ STAT3                | Decreased PCT                                                                                  | (111)     |
| miR-125-5p  | Decreased in mice with CLP and ALI                    | ↓ TOP2A                | Endothelial cell–derived exosomal miRNA–125b–5p & VEGF, protected from sepsis-induced ALI      | (112)     |
| miR-126-3p  | Increased in primary macrophages exposed to miR-126-3p-containing platelet microparticles | ↓ BCL2L2               | Overexpression inhibits anti-apoptotic function of BCL2L2 in AHI LncRNA-CRNDE binds miR-126-3p and restores BCL2L2 function | (113)     |
| miR-126-5p  | Increased in hepatic cells of mice with sepsis induced AHI | ↓ BCL2L2               | Overexpression inhibits anti-apoptotic function of BCL2L2 in AHI LncRNA-CRNDE binds miR-126-3p and restores BCL2L2 function | (114)     |
| miR-128     | Increased in kidneys of mice with sepsis induced AKI  | ↓ NRP1                 | NRP1 downregulates TNF, IL-6, and IL-1β                                                        | (115)     |
| miR-128-3p  | Decreased in HK2 cells exposed to LPS and serum of sepsis patients | ↓ TGFB2                | Decreased TGFB2 mediated apoptosis                                                              | (116)     |
| miR-129     | Decreased in lungs of mice with LPS-induced ALI       | ↓ TAK1                 | Inhibits TAK1/ NF-κB pathway Inhibits apoptosis and inflammation in sepsis-induced ALI          | (117)     |
| miR-129-5p  | Decreased in kidneys of mice with LPS-induced AKI      | ↓ HMGB1                | Inhibits HMGB1/TLR4/ NF-κB pathway Decreased apoptosis of kidney podocytes                      | (118)     |
| miR-129-5p  | Overexpression (use of agonists) in sepsis mice (CLP)  | ↓ HMGB1                | Decreased HMGB1, apoptosis and inflammation in sepsis-induced ALI                              | (119)     |
| miR-130a    | Decreased in sepsis patients with thrombocytopenia    | ↓ IL-18                | –                                                                                               | (120)     |
| miR-130b-3p | Increased in serum of sepsis mice (CLP) and in sepsis patients | Binds to and inhibit CIRP | Decreased CIRP-induced cytokine production by macrophages Delivery of miR-130b-3p in mice reduces CLP-induced inflammation and acute lung injury | (62)      |
TABLE 1 Continued

| miRNA    | Expression/model                                                                 | Target and effect | Observation/impact of miRNA                                                                 | Reference |
|----------|----------------------------------------------------------------------------------|-------------------|------------------------------------------------------------------------------------------|-----------|
| miR-130b-3p | Increased in RAW 264.7 mouse macrophages exposed to IFNγ+LPS                     | ↓ IRF1            | Inhibits M1 macrophage polarization and production of CCL5, CXCL-10, iNOS & TNF. Overexpression decreases lung inflammation in LPS-treated mice | (63)      |
| miR-132  | Increased in alveolar macrophages of sepsis rats                                | ↓ AChE            | Decreased ACh-mediated cholinergic anti-inflammatory reaction Inhibits NF-κB and STAT3 | (121)     |
| miR-133a | Decreased in TCMK-1 mouse kidney cell line exposed to LPS                       | ↓ BNIP3L          | Inhibits NF-κB pathway, apoptosis and TNF and IL-6 expression                             | (122)     |
| miR-133a | Increased in the blood of sepsis mice (CLP) and sepsis patients                 | ↓ SIRT1           | Inhibition of miR-133a decreased CLP-induced inflammation and lung, liver and kidney injuries | (123)     |
| miR-135a | Increased in serum of sepsis patients                                           | ↑ p38 MAPK        | Activation of p38 MAPK and NF-κB pathways Aggravation of sepsis-induced inflammation and myocardial dysfunction | (124)     |
| miR-139-5p | Decreased in lung tissues of sepsis mice (CLP)                                 | ↓ MrD88           | Decreased inflammation, oxidative stress and ALI                                         | (125)     |
| miR-141  | Decreased in serum of pediatric sepsis patients and in monocytes exposed to LPS | ↓ TLR4            | Decreased inflammatory response in neonatal sepsian                                         | (126)     |
| miR-142  | Decreased in blood of sepsis patients and in macrophages of sepsis mice         | ↓ PD-L1           | Decreased inflammation mediated by PD-L1                                                   | (127)     |
| miR-143  | Increased in the blood of healthy volunteers infused with LPS                   | –                 | Associated with strong reduction of BCL2 and silencing of inflammation related targets     | (128)     |
| miR-143  | Increased in mouse macrophages exposed to mycobacterial cell wall glycolipid and muramyl dipeptide | ↓ TAK1 (miR-143) | Negatively regulate the NOD2 pathway                                                        | (129)     |
| miR-150  | Decreased in blood of healthy volunteers exposed to LPS                         | ↓ RIP2 (miR-150)  | Suppress MDP-induced PI3K-PKC-MAPK-κ-catenin-mediated expression of COX-2, SOCS3 and MMP-9 | (129)     |
| miR-143  | Decreased in nasal mucosal tissues from patients with allergic rhinitis         | ↓ IL-13βR1        | Decreased expression of GM-CSF, eotaxin and mucin 5AC of cells exposed to IL-13             | (130)     |
| miR-143  | Decreased in HUVECs exposed to IL-1β                                             | ↓ ADAR1           | Promotes the activation of HUVECs by IL-1β                                                | (131)     |
| miR-143  | Increased in BEAS-2B human bronchial epithelium cells exposed to AngII and LPS  | ↓ ACE2            | miR-143-3p inhibitor increased ACE2 and decreased IL-1β, IL-6 and TNF and apoptosis in cells exposed to AngII and LPS | (132)     |
| miR-143  | Decreased in lung tissues of mice with mycoplasmal pneumonia                    | ↓ MyD88           | miR-145 increased IL-10 and decreased IL-2, TNF and alveolar epithelial cell apoptosis through Ilx and Bcl-2 | (133)     |
| miR-143  | Human umbilical cord MSCs exposed to poly (I:C)                                  | ↓ TAK1 and COX-2  | Infusion of TLR3-activated MSCs improved survival of sepsis mice (CLP), the co-infusion of miR-143 reduced survival benefit | (134)     |
| miR-145  | Decreased in blood samples of sepsis patients and in lung tissues of sepsis mice | ↓ TGFBR2          | Decreased LPS-induced inflammation and sepsis-induced ALI                                  | (135)     |
| miR-145  | Decreased in HUVECs exposed to LPS                                              | ↓ TGFBR2          | Decreased TGFBR2/SMAD2/DNMT1 pathway                                                          | (136)     |
| miR-146  | Decreased in EA.hy926 human vascular endothelial cells exposed to LPS           | ↓ NF-κB pathway   | Decreased LPS-induced expression of inflammatory cytokines                                 | (137)     |
| miR-146a | Increased uptake of miR-146a-expressing plasmid by splenic macrophages of sepsis mice | ↓ IRAK-1, TRAF6   | Decreased sepsis-induced inflammation and organ failure Splenectomy abolishes these effects | (138)     |
| miR-146a | Increased in peritoneal macrophages of sepsis mice after GSKJ4 treatment        | –                 | Decreased expression of pro-inflammatory cytokines by JMJ3 downregulation after GSKJ4 treatment | (139)     |
| miR-146a | Increased in heart-derived H9c2 cardiomyocytes exposed to LPS                   | ↑ ErbB4, ↓ IRAK1, TRAF6, caspase-3 | Decreased sepsis-induced inflammation and myocardial dysfunction                      | (140)     |
| miR-146a | Increased in mouse peritoneal macrophages exposed to LPS                        | ↓ Notch-1         | Decreased NF-κB signaling                                                                   | (141)     |
| miR-146a | Decreased in T cells of sepsis patients                                         | ↓ PRKCz           | Decreased STAT4 activation via PRKCz downregulation                                        | (142)     |
| miR-146a/b | Increased in human pulmonary microvascular endothelial cells exposed to TNF     | ↑ IL-6, IL-8      | Increased expression of HSP10                                                               | (143)     |

(Continued)
| miRNA          | Expression/model                                                                 | Target and effect | Observation/impact of miRNA                                                                                           | Reference |
|----------------|----------------------------------------------------------------------------------|-------------------|-----------------------------------------------------------------------------------------------------------------------|-----------|
| miR-146b       | Decreased in the blood on healthy volunteers infused with LPS                    | –                 | Associated with rapid transcriptional activation of IRAK2                                                            | (128)     |
| miR-146a-5p    | Increased in plasma of sepsis mice (CLP) and sepsis patients                     | ↓ IRAK1           | Interacts with TLR7 and activates proteasome<br>Knockout decreases inflammation, improves cardiac function, and survival of sepsis mice | (144)     |
| miR-146a-5p    | –                                                                                | –                 | Activates TLR7 to induce TNF release, pulmonary inflammation, endothelial barrier disruption and ARDS in sepsis mice  | (145)     |
| miR-150        | Decreased in MDSCs of sepsis mice (CLP) and in serum of sepsis patients          | ↓ ARG1            | Decreased proliferation and immunosuppressive functions of MDSCs from sepsis mice                                 | (146)     |
| miR-150        | Decreased in the blood on healthy volunteers infused with LPS                   | –                 | Associated with rapid transcriptional activation of IRAK2                                                            | (128)     |
| miR-150        | Increased in the serum of sepsis mice (CLP)                                    | –                 | –                                                                        | (147)     |
| miR-150-5p     | Increased in the serum of rats challenged with LPS                              | –                 | –                                                                        | (148)     |
| miR-150        | Increased during recovery from LPS-induced injury in mice                        | ↓ EGR2            | miR-150-/- mice show increased mortality from LPS and CLP<br>Rescuing miR-150 in lung endothelial cells decreased EGR2-dependent Ang2 expression, restored endothelial barrier function, and reduced mortality | (149)     |
| miR-150        | Decreased in the serum of mice challenged with LPS and in sepsis mice (CLP)     | ↓ NF-κB           | Protects HUVECs from LPS-induced apoptosis, decreased TNF and IL-6, ICAM-1, VCAM-1 and E-selectin expression          | (150)     |
| miR-150-5p     | Decreased in H9c2 cardiomyocytes exposed to LPS                                 | ↓ MALAT1          | Decreased IL-6 and TNF production                                                                                  | (151)     |
| miR-150-5p     | Decreased in the heart of rats challenged with LPS                               | –                 | Decreased myocardial apoptosis associated with a reduced expression of Akt2, cleaved caspase 3 and Bax, and increased expression of Bcl-2 in rat heart and H9c2 cardiomyocytes | (152)     |
| miR-150        | Decreased in HUVECs exposed to LPS                                              | ↓ MALAT1          | Decrease TNF and IL-6, ER stress-related proteins, cleaved caspase 3, Bax, apoptosis and increased IL-10 and Bcl-2 in LPS-stimulated HUVECs and PAECs from sepsis mice (CLP) | (153)     |
| miR-150-5p     | Decreased in RAW 264.7 macrophages exposed to LPS                               | ↓ Notch1          | Inhibits LPS-induced apoptosis and TNF, IL-1β, IL-6 production                                                      | (154)     |
| miR-150        | Decreased in THP-1 cells exposed to LPS                                         | ↓ STAT3           | Decreased IL-1β, IL-6 and TNF secretion                                                                            | (155)     |
| miR-150-5p     | Decreased in HK-2 human proximal renal tubular epithelial cells and in mice exposed to LPS | ↓ MEKK3           | Inhibits LPS-induced JNK pathway, apoptosis, inflammation (IL-1β, IL-6, TNF, BUN, Scr), and outcome of sepsis mice with AKI | (156)     |
| miR-150-5p     | Decreased in H9c2 cardiomyocytes and myocardial tissues of mice exposed to LPS   | ↓ XIST            | Decrease c-Fos axis, TXNIP-mediated pyroptosis and sepsis-induced myocardial injury                                 | (157)     |
| miR-155        | Comparison of miR-155-deficient and wild-type sepsis mice (CLP)                 | ↑ Neutrophil extracellular traps | Increased neutrophil recruitment<br>Increased sepsis-induced ALI                                                      | (158)     |
| miR-155        | Increased in pulmonary endothelial cells of sepsis mice and in HUVECs exposed to TNF | ↓ Claudin-1       | Increased vascular barrier breakdown and sepsis-related capillary leakage                                          | (159)     |
| miR-155        | Increased in intestinal tissue of sepsis mice (CLP)                             | ↑ NF-κB           | Increased intestinal barrier dysfunction                                                                         | (160)     |
| miR-155        | Increased in plasma and myocardial tissue of sepsis mice and patients           | ↑ NO, cGMP        | Increased sepsis-associated cardiovascular dysfunction                                                              | (161)     |
| miR-155        | Increased in HPMECs exposed to TNF                                              | ↑ IL-6, IL-8      | Increased HSP10                                                                                                      | (145)     |
| miR-155        | Increased in myocardial tissue of sepsis mice                                   | ↑ JNK phosphorylation, β-arrestin 2 | Decreased sepsis-induced myocardial dysfunction                                                                 | (162)     |
| miR-155        | Increased in liver tissue of sepsis mice                                        | ↑ JAK/STAT pathway ↓ SOCS1 | Increased sepsis-induced AHI                                                                                   | (163)     |
| miR-155        | Increased in myocardial tissue of mice exposed to LPS                           | ↑ Pea15a          | Increased sepsis-induced myocardial dysfunction                                                                 | (164)     |
| miR-181-5p     | Decreased in kidneys of sepsis mice (CLP)                                       | ↓ HMGB1           | Decreased inflammatory response<br>Decreased renal and hepatic dysfunction                                           | (165)     |

(Continued)
| miRNA          | Expression/model                                | Target and effect                  | Observation/impact of miRNA                                                                 | Reference |
|---------------|------------------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------------|-----------|
| miR-181a      | Increased in mouse DCs exposed to HMGB1        | ↓ TNF mRNA                        | Dual influence of HMGB1 on maturation and cytokine expression in DCs (↑ at low but ↓ at high concentrations) | (166)     |
|               | Increased in lung tissues of mice exposed to LPS | ↓ Bcl-2                           | Increased apoptosis on ALI by down-regulation of Bcl-2                                   | (167)     |
| miR-181b      | Decreased in myocardial tissue of sepsis rats (CLP) | ↓ HMGB1                           | Decreased apoptosis of myocardial cells                                                   | (168)     |
|               | Decreased in HUVECs exposed to TNF             | ↓ NF-κB pathway, VCAM-1, importin-α3 | Decreased sepsis-induced vascular inflammation and ALI                                    | (169)     |
| miR-181b      | Increased in bone marrow of sepsis mice (CLP)  | ↑ NFI-A                           | Increased number of MDSCs by arresting myeloid progenitor differentiation and maturation  | (86)      |
| miR-181b      | High levels in MDSCs from sepsis mice (CLP)    |                                   | miR-181b antagonimR improves late-sepsis survival                                         | (87)      |
| miR-181-5p    | Decreased in sepsis patients                  | ↓ NAMPT                           | miR-186-5p inhibited sepsis-induced coagulation disorders via targeting NAMPT and deactivating the NF-κB pathway | (171)     |
| miR-194       | Increased in rat H9c2 cardiomyocytes exposed to LPS | ↓ Slc7a5 gene                     | Increased sepsis related myocardial injury                                                  | (172)     |
| miR-194       | Increased in intestinal tissues of sepsis mice (abdominal sepsis) | ↓ Bcl-2, Sirt1, Pim-1             | Increased apoptosis                                                                      | (173)     |
| miR-195       | Increased in lung and liver tissues of sepsis mice (abdominal sepsis) | ↓ ATF6                            | Increased apoptosis on ALI by down-regulation of Bcl-2                                   | (174)     |
| miR-195-5p    | Increased in LPS-treated cardiomyocytes and sepsis mice (CLP) | ↓ Surfactant protein D           | Decreased inflammation, apoptosis, oxidative stress and endoplasmic reticulum stress in CLP mice | (175)     |
| miR-199a      | Increased in intestinal tissues of sepsis mice | ↓ NF-κB pathway                   | Increased apoptosis of intestinal tissues                                                   | (176)     |
| miR-200c-3p   | Increased in A549 cells infected with H1N1 or H5N1 influenza virus | ↓ ACE2 protein                    | Increased intestinal barrier dysfunction                                                   | (177)     |
| miR-212-3p    | Increased in RAW 264.7 macrophages exposed to LPS | ↓ HMGB1                           | Decreased TNF and IL-6 production                                                         | (178)     |
| miR-214-3p    | Increased in myocardic tissues of sepsis mice | ↓ p-AKT, p-mTOR                   | Decreased sepsis-induced myocardic dysfunction                                              | (179)     |
|               | Increased in RAW 264.7 mouse macrophages exposed to LPS Sepsis mice (CLP) | ↓ JNK2                            | Decreased autophagy via AKT/mTOR pathway                                                   | (180)     |
| miR-221       | Increased in RAW 264.7 mouse macrophages exposed to LPS Sepsis mice (CLP) | ↓ HDAC2                           | miR-223 levels negatively correlate with the HDAC2 expression in lungs from COPD patients Reduced HDAC2 increased fractalkine (CX3CL1) expression | (181)     |
| miR-223       | Increased in white blood cells of sepsis patients (especially survivors) | ↓ FOXO1                           | Decreased lymphocytes apoptosis                                                           | (182)     |
|               | Decreased in HCAECs exposed to TNF             |                                  | Negative correlation with SOFA score and clinical severity                                 | (183)     |
| miR-326       | Decreased in lung tissues and macrophages of mice exposed to LPS and sepsis mice (CLP) | ↓ TLR4                            | Decreased sepsis-induced ALI                                                              | (184)     |
| miR-375       | Decreased in whole blood of sepsis patients | ↓ miR-21, JAK2, STAT3              | Decreased MDSCs in sepsis mice (CLP)                                                       | (185)     |
| miR-376b      | Decreased in renal tubular cells in sepsis mice with AKI | ↓ NF-κB inhibitor ζ              | miR-375 agomir promotes survival of sepsis mice                                             | (186)     |
| miR-494       | Increased in human lung cancer cells           | ↓ NQO1, Nrf2                      | Increased sepsis-induced ALI                                                              | (187)     |
TABLE 1 Continued

| miRNA       | Expression/model | Target and effect | Observation/imact of miRNA | Reference |
|-------------|------------------|------------------|-----------------------------|-----------|
| miR-494-3p | Decreased in plasma of sepsis patients and in RAW 264.7 macrophages |  ↓ TLR6 | Decreased sepsis-induced inflammatory response | (188) |
| miR-499a   | Decreased in HUVECs exposed to LPS |  ↓ STAT1 | Decreased LPS-induced inflammatory injury and apoptosis | (189) |
| miR-574-5p | Increased in serum of mice with mastitis (especially survivors) |  ↓ TRADD | Increased viability of renal cell culture line (HK-2) | (190) |
| miR-1184   | Decreased in THP-1 cells exposed to LPS and serum of pediatric sepsis patients |  ↓ IL-16 | Decreased expression of TRADD, p65, IL-1β, IL-6 and TNF when overexpressed in THP-1 monocytes exposed to LPS | (191) |
| miR-1184   | Decreased in monocytes exposed to LPS and in pediatric sepsis patients |  ↓ IL-16 | Negatively correlates with IL-1β, IL-6, IL-16 and TNF in pediatric sepsis patients | (192) |
| miR-1298   | Increased in exosomes of sepsis patients |  ↓ SOCS6 | Increased bronchial epithelial cell injury via SOCS6/STAT3 pathway | (193) |
| miR-2055b  | Increased in serum and organ tissues (lung, liver, spleen, colon) of mice |  ↓ HMGBl | Reverse effects by miR-1298 inhibition | (194) |

ACE2, angiotensin-converting enzyme 2; ACHE, acetylcholinesterase; ADAR1, adenosine deaminase acting on RNA 1; AHI, acute hepatic injury; AJK, acute kidney injury; ALI, acute lung injury; Ang2, angiotensin-2; ARDS, acute respiratory distress syndrome; ARG1, arginase 1; ATG, autophagy related; BALF, bronchoalveolar lavage fluid; BCL2, B-cell lymphoma 2; BCL2L12, BCL-like 2; BMDM, bone marrow-derived macrophage; BNP31, BCL2 interacting protein 3 Like; BRD4, bromodomain containing 4; CCL, C-C motif chemokine ligand; BUN, blood urea nitrogen; CEA, carcinoembryonic antigen; CFTR, cystic fibrosis transmembrane conductance regulator; CIR, cyclic AMP responsive element binding protein; CIRBP, cold-inducible RNA binding proteins; CLP, cecal ligation and puncture; COPD, chronic obstructive pulmonary disease; COX, cyclooxygenase; CRNDE, colorectal neoplasia differentially expressed; CXL1, C-X-C motif chemokine ligand; DC, dendritic cell; DNMT1, DNA methyltransferase 1; EGR2, early growth response 2; ErbB4, Erb-B2 receptor tyrosine kinase 4; ERK, extracellular signal-regulated protein kinase; FGFR, fibroblast growth factor receptor; FOS, fos-like 2; FOXP1, forkhead box O1; GSK3, glycogen synthase kinase 3; GSK3, glycogen synthase kinase 3; HSP, heat shock protein; HUVEC, human umbilical endothelial cell; ICAM, intercellular adhesion molecule; IGF1R, insulin like growth factor 1 receptor; IL, interleukin; IL-13, IL-13 receptor α1; iNOS, inducible nitric oxide synthase; IRAK, IL-1 receptor-associated kinase; JAK, janus kinase; JHIC, human coronary artery endothelial cell; JNK, c-Jun N-terminal kinase; KLF4, Krueppel like factor 4; KDR, kinase insert domain-containing receptor; LPS, lipopolysaccharide; MALAT1, metastasis associated lung adenocarcinoma transcript 1; MAPK, mitogen-activated protein kinase; MCEM1, mast cell-expressed membrane protein 1; MDR, multidrug resistant; MEF, mouse embryonic fibroblast; MDS, myeloid-derived suppressor cell; MEK2, mitogen-activated protein kinase kinase; MERTK, myeloid-epithelial-reproductive tyrosine kinase; MIP, multiple organ failure; MSCT, mesenchymal stem cell; mTOR, mammalian target of rapamycin; MyD88, myeloid differentiation primary response 88; NAMPT, nicotinamide phosphoribosyltransferase; NFκB, nuclear factor kappa B; NFIL3, NOD-D3, NFκB- and pyrin domain-containing protein 3; NO, nitric oxide; NOX1, NADPH oxidase 1; Notch1, notch receptor 1; Nrf2, nuclear factor E2 p45-related factor 2; NRPI, neuropilin 1; PAEC, pulmonary arterial endothelial cell; PBMC, peripheral blood mononuclear cell; PCX, procarcinoin; PDK1, phosphoinositide-dependent protein kinase 1; PD-L1, programmed death-ligand 1; PKI3, phosphoinositide 3-kinase; PLK1, Polo-like kinase 1; PRCC, protein kinase C epsilon; PTEN, phosphatase and tensin homologous protein; RIP2, receptor-interacting protein 2; SIRTI1, silent information regulator T1; SMAD2, Smad-related protein 2; SMRT, silencing mediator for retinoid and thyroid hormone receptor; SOCS, suppressor of cytokine signaling; SOCS6, suppressor of cytokine signaling 6; STAT1, signal transducer and activator of transcription 1; TAK1, transforming growth factor activated kinase 1; TCMK-1, transformed C3H mouse kidney-1; TGFBR2, transforming growth factor receptor type II; TLR, Toll-like receptor; TNF, tumor necrosis factor; TNF, tumor necrosis factor; TNIP2, TNFAIP3 interacting protein 2; TOP2A, topoisomerase II alpha; TRADD, TNF receptor type 1; TRADD, TNF receptor-associated factor 2; TRAIL, TNF related apoptosis-inducing ligand; TUG1, taurine-upregulated gene 1; TXNIP, thioredoxin-factor beta receptor II; TLR, Toll-like receptor; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor; ZC3H13, zinc finger C3H type domain containing 3; ZNF113, zinc finger protein 113.

3.1.2 miRNAs and endothelium and coagulation activation in sepsis

DAMPs and MAMPs released during sepsis activate the complement and coagulation systems. Disseminated intravascular coagulation (DIC) affects around 35% of sepsis patients. Beside thrombosis, DIC is associated with bleeding due to the consumption of clotting factors, anticoagulant proteins, and platelets (9, 11). Thrombocytopenia develops in about 50% of sepsis patients. Signaling through PRRs and cytokine receptors triggers endothelial cells, increasing the expression of adhesion molecules, vascular permeability, transcellular...
| miRNA | Subjects (sepsis/controls [n] unless detailed) | Sample type | Observations | Reference |
|-------|-----------------------------------------------|-------------|--------------|-----------|
| miRNome (RNA-Seq) | Adults (117 sepsis survivors and 97 sepsis non-survivors based on 28-day mortality) | Serum | Less than 200 miRNAs detected by sequencing | (195) |
| miRNome (RNA-Seq) | Adults (21 severe & 8 non-severe sepsis, 23 severe & 21 non-severe non-infective SIRS, 16 no SIRS) | Plasma | 116 detectable blood miRNAs generally up-regulated in SIRS vs no-SIRS patients and higher in non-infective SIRS than sepsis. Inversely correlate with IL-1, IL-6, IL-8 and CRP levels | (196) |
| miRNome (RNA-seq) | Adults (22/23) | Cells, serum & serum exosomes | 77 miRNAs decreased & 103 miRNAs increased in patients (all compartments) | (197) |
| miRNome (microarray, 3’100 probes) | Adults (6 sepsis with AKI, 6 sepsis without AKI, 3 healthy controls) | Serum | 37 miRNAs differentially expressed among the groups | (198) |
| miRNome (microarray, 2’661 probes) | Adults (31 pneumonia, 34 sepsis secondary to pneumonia, 21 healthy controls) | Plasma | Decreased miR-940 & increased miR-765, miR-4800-5p, miR-6510-5p, miR-6740-5p, miR-7110-5p (microarray on 5 pneumonia & 5 sepsis) | (199) |
| miRNome (microarray, 2’578 miRNAs) | Neonates (36 NEC & 101 sepsis patients, 164 controls) | Plasma | 16 miRNAs decreased & 230 miRNAs increased and in NEC vs non-NEC (microarray) | (200) |
| miRNome (microarray) | Adults (60/30) | Blood | 11 differentially expressed miRNAs | (201) |
| miRNome (TaqMan Open Array, 754 miRNAs) | Adults (21/21) | Platelets | Decreased miR-150 & miR-342-5p and increased miR-15a, miR-16, miR-93, miR-143, miR-223 and miR-424 | (202) |
| miRNome (TaqMan Open Array, 754 miRNAs) | Adults (17/32) | PBMCs and plasma | 17 miRNAs differentiate sepsis from controls (microarray) | (203) |
| Microarray (n probes?) & RT-qPCR | Adults (31/34) | WBCs and T-cells | 35 miRNAs differentially expressed in sepsis vs controls (microarray, 7 patients/group) | (204) |
| miR-10a | Adults (62/20) | PBMCs | Decreased in patients | (205) |

(Continued)
| miRNA     | Subjects (sepsis/controls [n] unless detailed) | Sample type | Observations | Reference |
|-----------|---------------------------------------------|-------------|--------------|-----------|
| miR-15a   | Neonates (46/41) Serum                      | Increased   | miR-15a, miR-16 & decreased miR-378 and miR-451 in sepsis neonates | (78)      |
| miR-15b   |                                             |             |              |           |
| miR-16    |                                             |             |              |           |
| miR-206   |                                             |             |              |           |
| miR-223   |                                             |             |              |           |
| miR-378   |                                             |             |              |           |
| miR-451   |                                             |             |              |           |
| miR-15a   | Adults (166 sepsis, 32 SIRS, 24 healthy controls) Serum | Increased | in patients vs controls Higher levels of miR-15a in SIRS than in sepsis patients | (206)      |
| miR-15b   | Adults (166/24) Serum                       | Increased   | miR-223 & decreased miR-122, miR-193b*, miR-499-5p in patients | (207)      |
| miR-122   |                                             |             |              |           |
| miR-193b* |                                             |             |              |           |
| miR-223   |                                             |             |              |           |
| miR-483-5p|                                             |             |              |           |
| miR-499-5p|                                             |             |              |           |
| miR-15a   | Adults(123 on day of admission, and 45 on days 1, 3, 5, 7, 10 and 14 of ICU admission) Serum | Increased | miR-122 in patients with coagulation abnormalities at days 1, 3, 7 and 10 | (208)      |
| miR-16    |                                             |             |              |           |
| miR-122   |                                             |             |              |           |
| miR-193b* |                                             |             |              |           |
| miR-223   |                                             |             |              |           |
| miR-483-5p|                                             |             |              |           |
| miR-15a   | Neonates (32 sepsis/30 controls with respiratory infection/pneumonia) Serum | Increased | in sepsis neonates | (209)      |
| miR-16    |                                             |             |              |           |
| miR-15a-5p| Adult sepsis patients treated with gentamicin, vancomycin or non-nephrotoxic antibiotics (20/7/19) Serum | Increased | miR-122 in patients with coagulation abnormalities at days 1, 3, 7 and 10 | (208)      |
| miR-155-5p| Blood at day 1, 4 & 7                       | Increased   | miR-122 in patients with coagulation abnormalities at days 1, 3, 7 and 10 | (208)      |
| miR-192-5p|                                             | Increased   | miR-122 in patients with coagulation abnormalities at days 1, 3, 7 and 10 | (208)      |
| miR-423-5p|                                             | Increased   | miR-122 in patients with coagulation abnormalities at days 1, 3, 7 and 10 | (208)      |
| miR-15b   | Neonates (25/25) Serum                      | Increased   | miR-15b in sepsis neonates | (211)      |
| miR-378a  |                                             | Increased   | miR-378a in sepsis neonates | (211)      |
| miR-16a   | Neonates (25/25) Serum                      | Increased   | miR-378a in sepsis neonates | (211)      |
| miR-451   |                                             | Increased   | miR-378a in sepsis neonates | (211)      |
| miR-19b-3p| Adults (103/98) Serum                       | Decreased   | miR-122 in patients | (213)      |
| miR-21    | Adults (219/219) Plasma                     | Decreased   | miR-122 in patients | (214)      |
| miR-21    | Children (88/26) Blood                      | Increased   | miR-122 in patients | (213)      |
| miR-21    | Neonates (42/42) Plasma                     | Decreased   | miR-122 in patients | (213)      |
| miR-29a   |                                             | Decreased   | miR-122 in patients | (213)      |
| miR-31    |                                             | Decreased   | miR-122 in patients | (213)      |
| miR-146a  |                                             | Decreased   | miR-122 in patients | (213)      |
| miR-155   |                                             | Decreased   | miR-122 in patients | (213)      |
| miR-22-3p | Adults (69/89) Serum and urine              | Decreased   | miR-122 in patients | (213)      |
| miR-23a   | Adults (27 sepsis, 22 non-infectious SIRS)  | Decreased   | miR-122 in patients | (213)      |
| miR-23b   | Neonates (27 early onset & 21 late onset sepsis) Serum | Decreased | miR-122 in patients | (213)      |
| miR-25    | Adults (70/30) Serum                        | Decreased   | miR-122 in patients | (213)      |
| miR-26b   | Adults (68 AKI and 87 non-AKI sepsis patients and 57 patients with non-infectious SIRS) Urine | Increased | miR-122 in patients with coagulation abnormalities at days 1, 3, 7 and 10 | (208)      |
| miR-34a   | Neonates (90/90) Serum                      | Decreased   | miR-122 in patients with coagulation abnormalities at days 1, 3, 7 and 10 | (208)      |
| miR-199a-3p|                                             | Decreased   | miR-122 in patients with coagulation abnormalities at days 1, 3, 7 and 10 | (208)      |

(Continued)
| miRNA      | Subjects (sepsis/controls [n] unless detailed) | Sample type | Observations                                                                 | Reference |
|------------|-----------------------------------------------|-------------|------------------------------------------------------------------------------|-----------|
| miR-96     | Neonates (66/58*)                             | Serum       | Decreased in sepsis neonates Targets IL-16                                    | (221)     |
| miR-101-3p | Neonates                                     | Serum       | Increased in sepsis neonates Associated with PCT, CRP, IL-8 and TNF levels    | (222)     |
| miR-103    | Adults (108/89)                               | Serum       | Decreased in patients Negative correlation with IL-1β, IL-6 and TNF levels   | (223)     |
| miR-107    | Adults (196/196)                              | Plasma      | Decreased in patients                                                         | (224)     |
| miR-122    | Adults (25/25)                                | Serum       | Decreased in patients Limited predictive value for determination of outcome  | (225)     |
| miR-122    | Adults (108/20)                               | Serum       | Increased in patients Independent risk factor for 30-day mortality            | (226)     |
| miR-122    | Adults (232/24)                               | Serum       | Decreased in patients Negative correlation with 28-days mortality            | (227)     |
| miR-122    | Adults (204 ICU patients, among which 127 with sepsis) | Serum       | Increased miR-133a and decreased miR-143 & miR-223 in patients who did not survive the ICU stay | (228)     |
| miR-133a   | Serum                                         |             | A combination of 2 and 3 miRNAs predicts patients’ long-term prognosis and survival in ICUs |           |
| miR-143    | Serum                                         |             | Decreased in ARDS when compared to non-ARDS patients Negative correlation with 28-days mortality |           |
| miR-150    | Serum                                         |             | Decreased in ARDS when compared to non-ARDS patients Negative correlation with 28-days mortality |           |
| miR-155    | Serum                                         |             | Decreased in ARDS when compared to non-ARDS patients Negative correlation with 28-days mortality |           |
| miR-192    | Serum                                         |             | Decreased in ARDS when compared to non-ARDS patients Negative correlation with 28-days mortality |           |
| miR-124    | Adults (82/82)                                | Plasma      | Decreased in patients Negative correlation with IncRNA NEAT1 Negative correlation with 28-days mortality |           |
| miR-125a   | Adults (196/196)                              | Plasma      | Decreased in patients Negative correlation with IncRNA MALAT1                | (230)     |
| miR-125a/b | Adults (150/150)                              | Plasma      | Increased in patients Positive correlation of miR-125b with 28-days mortality | (231)     |
| miR-125b   | Adults (120/120)                              | Plasma      | Increased in patients Positive correlation with 28-days mortality            | (232)     |
| miR-125    | Adults (126/125)                              | Plasma      | Decreased in patients Negative correlation with Scr, CRP, APACHE II score, SOFA score, TNF, IL-6, IL-8, IL-17 | (233)     |
| miR-126    | Children (60/46)                              | Serum       | Decreased in patients Negative correlation with sepsis severity              | (234)     |
| miR-126    | Adults (208/210)                              | Plasma      | Increased in patients Positive correlation with 28-days mortality           | (235)     |
| miR-127    | Adults (200 ICU among whom 140 sepsis/100)    | Platelets   | Increased miR-320a/miR-127 ratio in sepsis patients                         | (236)     |
| miR-191    | Serum                                         |             | Decreased miR-132 & miR-223 in sepsis patients                              | (237)     |
| miR-320a   | Adults (15/7)                                 | Serum       | Increased in patients                                                        | (62)      |
| miR-132    | Neonates (25/25)                              | Plasma      | Decreased miR-132 & miR-223 in sepsis patients                              | (237)     |
| miR-145    | Serum                                         |             | Decreased miR-132 & miR-223 in sepsis patients                              | (237)     |
| miR-155    | Serum                                         |             | Decreased miR-132 & miR-223 in sepsis patients                              | (237)     |
| miR-223    | Serum                                         |             | Decreased miR-132 & miR-223 in sepsis patients                              | (237)     |
| miR-132    | Adults (80 sepsis-induced cardiomyopathy, 60 controls) | Serum       | Decreased in patients Negative correlation with CK, TNF & IL-6              | (238)     |
| miR-223    | Adults (223/76)                               | Serum       | Increased in patients Positive correlation with sepsis severity and 28-days mortality | (147)     |
| miR-133    | Adults (30/30)                                | Serum       | Increased in patients                                                         | (123)     |
| miR-143    | Adults (218 critically ill patients among which 135 sepsis/76 healthy controls) | Serum       | Trend for decreased levels in critically ill patients vs healthy controls No correlation with inflammatory markers Negative correlation with 28-days mortality | (239)     |

(Continued)
| miRNA | Subjects (sepsis/controls [n] unless detailed) | Sample type | Observations | Reference |
|-------|---------------------------------------------|-------------|--------------|-----------|
| miR-143 | Adults (103 sepsis, 95 SIRS, 40 healthy controls) | Serum | Increased in patients, higher in sepsis than in SIRS | (240) |
| miR-146a | Adults (146/19) | Plasma | Increased in severe patients | (241) |
| miR-155 | Adults (50 sepsis, 30 SIRS, 20 healthy controls) | Serum | Decreased in sepsis vs SIRS patients and healthy controls | (242) |
| miR-146a | Adults (14/14) | Plasma | Decreased in patients | (243) |
| miR-146a | Children (55/60) | Serum | Decreased in sepsis children | (244) |
| miR-146a-5p | Adults (11/12) | Plasma | Increased in patients | (245) |
| miR-146b | Adults (180/180) | Plasma | Increased in patients | (246) |
| miR-147b | Adults (130 bacterial sepsis, 69 dengue hemorrhagic fever and 82 healthy controls) | Plasma | Increased miR-146-3p, miR-147b, miR-155, miR-223 in sepsis compared to hemorrhagic fever and healthy controls | (247) |
| miR-150 | Adults (223/76) | Serum | No significant difference in critically ill patients with and without sepsis | (248) |
| miR-150 | Adults (22 SIRS, 23 sepsis, 21 healthy controls) | Blood | Decreased miR-150 in patients, more decreased in sepsis vs SIRS patients | (249) |
| miR-150 | Adults (120/50) | Serum | Decreased in patients | (250) |
| miR-150 | Adults (22/20), urosepsis | Serum | Decreased in patients | (251) |
| miR-150 | Adults (29 survivors and 12 non-survivors of sepsis) | Serum | Most strongly decreased miRNA in healthy subjects infused with endotoxin | (252) |
| miR-150 | Adults (30, with AKI/15) | Serum | Decreased in patients | (253) |
| miR-150 | Adults (78 sepsis/62 non-septic trauma patients/10 healthy controls) | Serum | Decreased in sepsis patients, increased in non-septic trauma patients | (254) |
| miR-150 | Adults (299 survivors and 138 non-survivors of sepsis) | Blood | Decreased miR-150 associated with 28-day mortality | (255) |
| miR-155 | Adults (73/83) | Plasma | Positive correlation with sepsis-induced ALI and ARDS | (256) |
| miR-155 | Adults (10/10) | BALF | Increased in patients (all with ARDS) | (257) |
| miR-181a | Neonates (102/50) | Serum | Decreased in sepsis neonates | (258) |
| miR-186-5p | Adults (34 sepsis and 34 respiratory infection/pneumonia) | Serum | Decreased in sepsis patients | (259) |
| miR-206 | Adults (93/28) | Serum | Decreased in patients | (260) |
| miR-218 | Adults (53/20) | PBMCs and Tregs | Increased according to severity | (261) |
| miR-223 | Adults (187/186) | Plasma | Increased in patients | (262) |

(Continued)
migration, microcirculation lesions, tissue ischemia and organ failure (287, 288). Many endogenous and microvesicles-derived miRNAs regulate endothelial cell functions acting on apoptosis, proliferation, migration and inflammation (289–292). For example, miR-155 is increased in pulmonary endothelial cells of sepsis mice, targets the tight junction protein Claudin-1 and induces capillary leakage during infection (159). In a model of ALI, endothelial cell-derived exosomal miRNA-125b-5p downregulates topoisomerase II α resulting in reduced lung injury and inflammatory cell infiltration in the pulmonary mesenchyme (112). Decreased exosomal miR-125b (and miR-30a-5p) is associated with mortality in sepsis patients (197).

Platelets play a role beyond thrombosis and hemostasis, regulating innate immune cells including PMNs, monocytes and macrophages (287, 293, 294). Platelets are an important sources of miRNAs that are released through microvesicles or exosomes and are taken up by endothelial cells and macrophages (113, 295). Reduced miR-26b in platelets is associated with increased P-selectin expression, and with severity and mortality in sepsis patients (92). In fact, miR-26b reduces platelet adhesion and aggregation in mice (296). An increased miR-320a/miR-127 ratio in platelets could help detecting sepsis (236). Platelet microvesicles containing miR-126-3p are taken up by macrophages, strongly affecting the transcriptome and decreasing the expression of cytokines/chemokines/growth factors in the cells (113). Additionally, miR-126-3p is associated with platelet activation (297). miR15b-5p and miR-378a-3p in platelet-derived exosomes obtained from sepsis patients induce the formation of neutrophil extracellular traps (NETs) involved in organ injury (80). On the contrary, platelet microparticles containing miR-223 reduce intercellular adhesion molecule 1 (ICAM-1) expression and binding to peripheral blood mononuclear cells by endothelial cells, providing a possible protective role against excessive sepsis-induced vascular inflammation (183).

**TABLE 2 Continued**

| miRNA   | Subjects (sepsis/controls [n] unless detailed) | Sample type | Observations                                                                 | Reference |
|---------|-----------------------------------------------|-------------|-------------------------------------------------------------------------------|-----------|
| miR-223 | Adults (143/44)                                | White blood cells | Increased in patients Higher in survivors than in non-survivors Negative correlation with lymphocyte apoptosis | (182)     |
| miR-223 | Adults (50 sepsis, 30 SIRS, 20 healthy controls) | Serum        | Decreased in sepsis vs SIRS patients and healthy controls                     | (242)     |
| miR-223 | Adults (137/84)                                | Serum        | No differential expression                                                     | (259)     |
| miR-223 | Adults (122/122)                               |             | Increased in sepsis Positive correlation with APACHE II and SOFA scores, and 28-day mortality | (260)     |
| miR-328 | Adults (110/89)                                | Serum        | Increased in sepsis patients Positive correlation with Scr, WBC, CRP, PCT, APACHE II score, and SOFA score | (261)     |
| miR-410-3p | Neonates (88 sepsis, 86 pneumonia) | Serum        | Decreased in sepsis versus pneumonia patients Correlation with levels of lncRNA NORAD | (262)     |
| miR-451a | Adults (98/65)                                | Serum        | Increased in patients Positive correlation with sepsis-induced cardiac dysfunction | (263)     |
| miR-452 | Adults (47 sepsis with AKI, 50 sepsis without AKI, 10 healthy controls) | Serum and urine | Increased in serum and urine of sepsis vs controls. Higher in patients with AKI vs no AKI | (264)     |
| miR-494-3p | -                                           | Blood        | Decreased in sepsis patients Downregulates TLR6 | (188)     |
| miR-495 | Adults (105/100)                               | Serum        | Decreased in patients Decreased in septic shock when compared to non-septic shock patients Negative correlation with sepsis-induced cardiac dysfunction | (255)     |
| miR-1184 | Children (30/30)                               | Serum        | Decreased in sepsis children | (191)     |
| miR-1184 | Neonates (72/56)                               | Serum        | Decreased in sepsis neonates Negative correlation with IL-16 | (192)     |

*Controls were neonates with respiratory infection or pneumonia.

AKI, acute kidney injury; ALI, acute lung injury; APACHE, acute physiology and chronic health evaluation; BALF, bronchoalveolar lavage fluid; CK, creatine kinase; CRP, C reactive protein; lncRNA, long noncoding RNA; NEAT1, nuclear enriched abundant transcript 1; NEC, necrotizing enterocolitis; NGAL, neutrophil gelatinase-associated lipocalin; PCT, procalcitonin; PSP, pancreatic stone protein; Scr, serum creatinine; SELP, P-selectin; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment; TLR, Toll like receptor; Treg, regulatory T cells; WBC, white blood cell.
3.1.3 miRNAs and host response to endotoxin (LPS)

Many studies analyzed miRNAs selected based on prior knowledge or miRNA screenings. While very instructive on a case-by-case basis, reductionist explorations tackle a small part of the role of miRNAs. A good illustration comes from reports on endotoxin, which is used as a model system to study host response to Gram-negative bacteria (Figure 3). The sensing of extracellular LPS by innate immune cells involves LPS binding protein (LBP), CD14, MD-2 and TLR4 (298, 299). TLR4, anchored at the cell membrane, recruits the adaptor molecule myeloid differentiation primary response 88 protein (MyD88). MyD88 activates a cascade of phosphorylation initiated at the level of IL-1 receptor (IL-1R)-associated kinase-1 (IRAK1) and TNF receptor-associated factor 6 (TRAF6), filling the NF-κB, IRFs and MAPK signaling pathways. These pathways control the transcription of immune response genes. Note that TLR4 shuttling to late endosome induces an alternative signaling through the adaptor molecule TIR domain-containing adaptor inducing IFNβ (TRIF). TRIF initiates IRF3 and late NF-κB activation, involved in the production of type I IFNs and IFN-inducible genes. For reasons of simplicity, this pathway is not described on Figure 3.

A few dozen of miRNAs, among which miR-15a, miR-16, miR-17-5p, miR-21, miR-25, miR-124-5p, miR-125b, miR-140-5p, miR-141, miR-146a, miR-149-5p, miR-155 miR-181c, miR-203-5p, miR-221, miR-326, miR-378, miR-448 and miR-466i, interfere at different levels with LPS sensing and LPS-induced signaling pathways (Figure 3). Note that miR-15a/16, miR-17-5p, miR-25, miR-125b, miR-141, miR-326 and miR-448 inhibit TLR4 expression, while miR-140-5p increases TLR4 expression. In addition, dozens of miRNAs among which miR-9-5p, miR-19a-5p, miR-29, miR-93, miR-98, miR-125, miR-221, miR-222, miR-223 and let-7a-5p target the expression of downstream proinflammatory and anti-inflammatory cytokines. Finally, the inflammatory response itself regulates the expression of proinflammatory and anti-inflammatory miRNAs (273–277, 300–302). These observations provide insight into the complexity of miRNAs interactions during host antimicrobial responses, and highlight the challenge of taking a comprehensive and integrated view of the impact of miRNAs on immune responses.

3.1.4 miRNAs and endotoxin tolerance

Exposure of isolated innate immune cells or whole body to low amounts of LPS induces a transient period of refractory response to subsequent exposure to LPS, generally attested by inhibition of cytokine production. This phenomenon is known as endotoxin tolerance. Expression studies suggest that miR-146a and miR-146b are involved in endotoxin tolerance in THP-1 human monocytic cells (303–305). miR-146a disrupts both transcription and translation of TNF gene in tolerant THP-1 cells (305). miR-146b is induced by the anti-inflammatory

![miRNAs and endotoxin sensing and signaling](image-url)
cytokines IL-10 and transforming growth factor (TGF)-β, but repressed by IFNγ which reverses endotoxin tolerance (304). Tolerance extends beyond LPS and TLR4 signaling. Bacterial lipoproteins recognized through TLR2 increase miR-146a expression and render THP-1 cells hypo-responsive to subsequent stimulation by *Salmonella typhimurium*. This is associated with a strong reduction of IRAK-1, phosphorylated inhibitory kappa B α (IkBα), and TNF production in tolerant THP-1 cells (306). Epigenetic mechanisms are involved in the establishment of tolerance. miR-146a and miR-155 are co-regulated in naïve and tolerant RAW 264.7 mouse macrophages. LPS stimulation induces histone 3 lysine 4 trimethylation (H3K4me3, a mark of transcriptionally active macrophages. LPS stimulation induces histone 3 lysine 4 trimethylation (H3K4me3, a mark of transcriptionally active genes) and NF-κB p65 binding to miR-146a and miR-155 gene loci. The induction of tolerance is associated with a shift towards repressive H3K9me3 mark and the recruitment of CCAAT/enhancer-binding protein (C/EBP) β and p50 inhibitory component of the NF-κB complex to miR-146a and miR-155 genes (307).

### 3.2 Examples of miRNAs studied as modulators of innate immune responses and biomarkers of sepsis

Table 1 summarizes observations about miRNAs obtained in cells exposed to MAMPs/DAMPs, and in animals and humans with sepsis. Table 2 summarizes observations about miRNAs as potential biomarkers of human sepsis. We will not describe all studies because it would be tedious if not impossible. We will focus on miR-15a, miR-16, miR-122, miR-143, miR-146a/b, miR-150, miR-155 and miR-223 taken as examples of important and versatile miRNAs, and because these miRNAs are discussed in several publications in the sepsis field. This selection is arbitrary, but we will nevertheless see that even a limited sample of miRNAs provides insight into the complexity by which miRNAs on impact sepsis. Observations reported in preceding chapters will not be repeated.

#### 3.2.1 miR-15a/16

MiR-15a and miR-16 are members of the miR-15 family comprising miR-15a, miR-15b, miR-16-1, miR-16-2, miR-195, and miR-497. miR-15a/16-1 cluster resides on human chromosome 13. miR-15a and miR-16 share the same seed sequence suggesting that they mediate similar biological functions.

##### 3.2.1.1 Anti-inflammatory activity

MiR-15a and miR-16 are commonly viewed as anti-inflammatory miRNAs. Bacterial infection and LPS increase miR-15a/16 in mouse bone-marrow derived macrophages, and in mouse lungs. miR-15a/16 target TLR4 and IRAK-1 in RAW 264.7 mouse macrophages exposed to LPS (78). In agreement, miR-15a/16 deficiency increases the expression of TLR4 through PU.1 (a transcription factor essential for TLR4 expression (308), and the phagocytosis and killing of *E. coli* by macrophages (77). Accordingly, miR-15a/16 knockout mice are resistant to CLP, *E. coli* and LPS-induced lethal sepsis (77). As an example of the connection between ncRNAs, the lncRNA SNHG16 downregulates the expression of miR-15a/16 and counter-regulates the inhibitory effects of miR-15a/16 on the expression of TLR4 in RAW 264.7 macrophages (209).

#### 3.2.1.2 Inflammatory activity

LPS increases miR-16 expression in human monocytic cells and biliary epithelial cells through the MAPK pathway. In a counter-regulatory manner, miR-16 suppresses silencing mediator for retinoid and thyroid hormone receptor, and increases NF-κB transcriptional activity and expression of IL-1α, IL-6 and IL-8 in LPS-stimulated cells (81). Similarly, miR-15a-5p is increased in RAW 264.7 macrophages exposed to LPS, targets TNF-induced protein 3–interacting protein 2, activates the NF-κB pathway and increases cytokine production (79). A miR-15a-5p inhibitor reduces IL-1β, IL-6 and TNF and inflammatory response in mice challenged with LPS (79).

#### 3.2.1.3 Biomarker value

MiR-15a and miR-16 are increased in patients with systemic inflammatory response syndrome (SIRS) and sepsis patients when compared to healthy controls (*n* = 66, 32, 24). miR-15a levels are higher in SIRS than in sepsis patients (206). The screening of 13 miRNAs (miR-15a, miR-16, miR-21, miR-27a, miR-34a, miR-126, miR-150, miR-155 miR-181b, miR-223, miR-125b, miR-146a, miR-486) in 62 adult sepsis patients and 32 healthy controls shows that miR-15a, miR-16, miR-21, miR-125b, miR-126, miR-146a, miR-155, miR-181b, miR-223 are increased in sepsis patients. MiR-15a is lower in patients with shock than in patients without shock (309). In a prospective observational study (117 survivors and 97 non-survivors with sepsis), a miRNome analysis shows that miR-15a (together with miR122, miR-193b* and miR483-5p) is increased in sepsis non-survivors, while miR-16 (and miR-223) is decreased (195).

Among seven miRNAs (miR-15a, miR-15b, miR-16, miR-206, miR-223, miR-378 and miR-451) measured in 46 neonatal sepsis patients, only miR-15a and miR-16 are increased, while miR-378 and miR-451 are decreased. Receiver operating characteristic (ROC) curve analyses suggest that miR-15a and miR-16 serum levels are good predictors of neonatal sepsis with area under the curves (AUCs) of 0.85 and 0.87 (78). MiR-15a and miR-16 are increased in the serum of neonates with sepsis when compared to neonates with respiratory infection or pneumonia without sepsis (*n* = 62 and 32) (309). Finally, two recent studies report increased miR-15b and miR-16a in small cohorts of sepsis neonates (25 sepsis and 25 controls) (211, 212).
Overall, miR-15a/16 drive anti-inflammatory or inflammatory action, and are commonly increased in sepsis patients. A link with disease severity seems more uncertain.

3.2.2 miR-122

miR-122 was identified 20 years ago as a liver specific miRNA in mice (227). miR-122 is encoded on chromosome 18 in humans, and has no close paralog. miR-122 has been especially studied in the context of host response to liver-tropic viruses.

3.2.2.1 Anti-inflammatory activity

miR-122 is decreased in the liver of patients with hepatocellular carcinoma (HCC). The upregulation of miR-122 in HepG2 human hepatocellular carcinoma cell lines inhibits TLR4 expression. Moreover, miR-122 decreases the proliferation and the production of TNF and IL-6 by HepG2 and Huh7 hepatocellular carcinoma cell lines (107).

3.2.2.2 Inflammatory activity

miR-122 targets suppressor of cytokine signaling protein (SOCS) 1 and SOCS3, inducing IFNα/β expression and decreasing hepatitis B virus (HBV) replication (103, 104). miR-122 targets the receptor tyrosine kinases (RTKs) insulin like growth factor 1 receptor (IGF1R), fibroblast growth factor receptor and myeloid-epithelial-reproductive tyrosine kinase. Then, miR-122 decreases STAT3 phosphorylation and increases IRF1 signaling and the expression of IFNs in response to hepatitis C virus (HCV) and the synthetic analog of doubled stranded RNA poly(I:C) (105). miR-122 targets heme oxygenase-1 and decreases HBV expression in hepatoma cells (106). Related to sepsis, miR-122-5p is increased in the heart of rats and in H9c2 rat cardiomyocytes challenged with LPS. Inhibition of miR-122-5p reduces myocardial injury through inhibition of inflammation, oxidative stress and apoptosis in endotoxemic rats (108).

3.2.2.3 Biomarker value

At least four studies have reported decreased miR-122 levels in patients with sepsis when compared to healthy controls (201, 207, 225, 227). miR-122 levels are lower in ARDS than in non-ARDS patients and show a negative correlation with 28-days mortality (227). In contrast with these observations, miR-122 is increased in sepsis patients and is an independent risk factor for 30-day mortality (195, 226). Moreover, the levels of miR-122 (but not miR-15a, miR-16, miR-19b*, miR-223 and miR-483-5p) are higher in patients with coagulation abnormalities than in patients with normal coagulation tested at days 1, 3, 7 and 10 of ICU admission (208). Finally, other studies do not point to miR-122 differential expression in sepsis patients and healthy controls (198, 228). Hence, the biomarker value of miR-122 remains questionable.

3.2.3 miR-143

miR-143 is encoded in a bicistronic locus with miR-145, but has no homology with miR-145. miR-143 is considered as an anti-inflammatory miRNA. Few studies looked at the mechanisms of action of miR-143 in the context of innate immune response and sepsis.

3.2.3.1 Anti-inflammatory activity

The quantification of 455 miRNAs in blood leukocytes from healthy volunteers infused 4 hours with endotoxin identified miR-143 as the only upregulated miRNA. High levels of miR-143 are linked to decreased expression of B-cell CLL/lymphoma 2, a regulator of apoptosis an innate immune signaling, and the silencing of inflammation-related target genes (128). Mycobacterial cell wall glycolipid (Ac2PIM) and muramyl dipeptide (MDP) are recognized by TLR2 and NOD2. In mouse macrophages, Ac2PIM induces miR-143. In turn, miR-143 targets the NOD2 signaling adaptors TGF-β activated kinase-1 (TA1) and receptor-interacting protein kinase 2. miR-143 suppresses PI3K/PKCα/MAPKβ/catenin-mediated expression of cyclooxygenase-2 (COX-2), SOCS3 and matrix metalloproteinase (MMP)-9 induced by MDP (129). Thus, miR-143 negatively regulates the NOD2 pathway, which may have consequences on the development of vaccines and Gram-positive bacteria sepsis.

miR-143 is the most significantly downregulated miRNA in nasal mucosal tissues from patients with allergic rhinitis (311). miR-143 dampens inflammatory responses in upper airways (130). Bronchial epithelium cells exposed to angiotensin II (AngII) and LPS increase miR-143 which targets angiotensin converting enzyme 2 (ACE2). A miR-143-3p inhibitor increases ACE2 and decreases inflammatory cytokines and apoptosis in cells exposed to AngII and LPS (132). ACE2 protects mice from ALI induced by sepsis (312), so miR-143 may be used to decrease lung inflammation involved in ARDS. In a mouse model of mycoplasma pneumonia, a miR-143-3p mimic reduces IL-2 and TNF, increases IL-10 and reduces alveolar epithelial cell apoptosis. A miR-143 mimic decreases TLR4, MyD88 and phosphorylated NF-κB p50 in lungs. miR-143 might be used to inhibit the TLR4/MyD88/NF-κB signaling pathway and normalize pulmonary inflammation during pneumonia (133).

Mesenchymal stem/stromal cells (MSCs) therapy improves sepsis outcome. Treating human umbilical cord MSCs with poly (I:C) decreases miR-143 and increases the anti-inflammatory power of MSCs on macrophages. miR-143 targets TAK1 involved in TLR3 signaling and COX-2. The infusion of poly (I:C)-activated MSCs improves survival of CLP mice, while the co-delivery of miR-143 reduces the survival benefit provided by MSCs (134). Targeting miR-143 might have therapeutic potential in dampening inflammatory responses in sepsis. No study reported inflammatory activity of miR-143.
3.2.3.2 Biomarker value

Microarray and RT-qPCR analyses have been used to explore miRNAs in T cells and whole blood in 34 healthy controls and 31 sepsis patients. Thirty five miRNAs are differentially regulated in sepsis patients. miR-143 (and miR-15a, miR-16, miR-93, miR-223 and miR-424) is increased in sepsis patients. miR-143 levels correlate with T cell immunoparalysis. The discriminatory power of miR-143 in T cells performs well, with an AUC of 0.95. miR-143 correlates positively with sequential organ failure assessment (SOFA; a clinical score based on the assessment of 6 variables representing an organ system: respiration, coagulation, liver, cardiovascular, central nervous system, renal) score (204). Another study reports higher blood levels of miR-143 in patients with sepsis than in patients with SIRS, and in SIRS patients than in healthy controls (n = 103/95/40). miR-143 levels correlate with disease severity, evaluated by SOFA and Acute Physiology And Chronic Health Evaluation (APACHE) II (a clinical score that estimates ICU mortality based on laboratory values, age and previous health conditions) scores (240).

In a prospective observational study, miR-143 is similarly expressed in sepsis survivors and non-survivors (n = 117/97) (195). In a cohort of 218 critically ill patients, among which 135 sepsis patients, miR-143 levels are similar to those measured in healthy controls (n = 103/95/40). miR-143 levels correlate with disease severity, evaluated by SOFA and Acute Physiology And Chronic Health Evaluation (APACHE) II (a clinical score that estimates ICU mortality based on laboratory values, age and previous health conditions) scores (240).

Contrary to the above, miR-143 serum levels are higher in sepsis patients than in patients with SIRS, and in SIRS patients than in healthy controls (n = 103/95/40). miR-143 levels correlate with disease severity, evaluated by SOFA and Acute Physiology And Chronic Health Evaluation (APACHE) II (a clinical score that estimates ICU mortality based on laboratory values, age and previous health conditions) scores (240).

In a prospective observational study, miR-143 is similarly expressed in sepsis survivors and non-survivors (n = 117/97) (195). In a cohort of 218 critically ill patients, among which 135 sepsis patients, miR-143 levels are similar to those measured in healthy controls (n = 103/95/40). miR-143 levels correlate with disease severity, evaluated by SOFA and Acute Physiology And Chronic Health Evaluation (APACHE) II (a clinical score that estimates ICU mortality based on laboratory values, age and previous health conditions) scores (240).

3.2.4.3 Biomarker value

miR-146a is increased in the blood of healthy subjects infused with endotoxin (251). Among 7 miRNAs measured in the serum of healthy controls, SIRS patients, and sepsis patients (n = 20/30/50), miR-146a and miR-223 are lower in sepsis patients (AUC = 0.804 and 0.858) (242). Similarly, reduced miR-146a levels discriminate sepsis from SIRS patients (AUC = 0.813) (243). In a pediatric study (n = 60/55 healthy and sepsis patients), miR-146a is decreased in blood and negatively correlated with the levels of C-reactive protein, procalcitonin (PCT), IL-6 and TNF. miR-146a levels correlate with sepsis severity and mortality, showing lower levels of miR-146a in non-surviving than in surviving patients (244). However, another study does not report differential expression of miR-146a in newborns with or without early-onset sepsis (n = 25/group) (237).

In contrast, miR-146a is increased in two studies analyzing adult patients (241, 245). In the first study (19 healthy controls, 102 sepsis, 44 severe sepsis), the AUCs of miR-146a and miR-155 for predicting 30-day mortality in ALL patients are 0.733 and 0.782 (241). In the second study (180 healthy controls, 180 sepsis patients with sepsis than in patients with SIRS, and in SIRS patients than in healthy controls (n = 103/95/40). miR-143 levels do not correlate with inflammatory markers, but correlate with indicators of organ failure (239).

3.2.4.4 Anti-inflammatory activity

The group of David Baltimore reported in 2006 the negative impact of miR-146a/b on signaling in innate immune cells (314). miR-146a/b is an immediate early-response NF-kB-dependent gene induced by microbial components and proinflammatory mediators. IRAK1 and TRAF6 are targets of miR-146a/b (314). Macrophages from miR-146a knockout mice are hyper-responsive to LPS, and miR-146a restrains inflammation, myeloid cell proliferation, and oncogenic transformation in vivo (315). miR-146a inhibits NF-kB signaling and expression of cytokines, ICAM-1 and E-selectin, and trafficking induced by MAMPs in monocytes, macrophages, DCs, endothelial cells and keratinocytes (137, 138, 159, 316, 317). miR-146a inhibits the expression of STAT1, IFNγ and TNF, and the cytotoxicity of natural killer cells (318). A miR-146a agomir (a synthetic chemically modified double-strand miRNA) inhibits macrophage inflammatory response and protects mice from LPS-mediated organ damage (141). The delivery of a miR-146a-expressing plasmid decreases inflammatory cytokines and organ injury, and increases survival of mice subjected to CLP (138).

3.2.4.5 Inflammatory activity

Exogenous single stranded miR-146a-5p induces inflammatory responses through activation of TLR7 and proteasome, and downregulation of IRAK-1. miR-146a knockout mouse show reduced inflammation and organ injury, improved cardiac function, and increased survival to acute sepsis induced by CLP (144). miR-146a-5p-mediated activation of TLR7 induces TNF, pulmonary inflammation, endothelial barrier disruption and ARDS in sepsis mice (145).
patients), miR-146a and miR-146b expression levels are predictors of sepsis risk (AUC = 0.774 and 0.897) (245). miR-146a and miR-146b positively correlate with APACHE II score, SOFA score, creatinine, CRP, IL-1β, IL-6, IL-17 and TNF. miR-146a and miR-146b are higher in survivors than in 28-day non-survivors. miR-146b has a better predictive value than miR-146a (AUC = 0.703 vs 0.599).

Overall, miR-146a is traditionally considered as anti-inflamatory, but 2 recent studies seem to contradict the uniform view. In the same manner, it remains unclear how miR-146a/b are modulated in human sepsis.

### 3.2.5 miR-150

miR-150 is encoded on human chromosome 19. miR-150 plays a role in hematopoiesis (319). miR-150 affects apoptosis, maturation and differentiation of lymphocytes and NK cells, and autoimmune diseases (320, 321). miR-150 is one of the four miRNAs (with miR-146b, miR-342, and let-7g) down-regulated in healthy subjects infused with LPS (128).

#### 3.2.5.1 Anti-inflammatory activity

miR-150 targets notch receptor 1, STAT1 and NF-kB to inhibit LPS-induced apoptosis and IL-1β, IL-6 and TNF, ICAM-1, VCAM-1 and E-selectin in RAW 264.7 macrophages, THP-1 monocyctic cells and endothelial cells (150, 154, 155). miR-150-5p is decreased in the heart of rats challenged with LPS. miR-150 decreases Akt2, cleaved caspase-3, Bax and apoptosis in rat heart and H9c2 cardiomyocytes (152). In a similar way, miR-150 decreases NF-kB, inhibits the NF-κB pathway, cytokine production, ER stress and apoptosis in LPS-stimulated human umbilical endothelial cells, H9c2 cardiomyocytes, IL-1β-stimulated chondrocytes, and pulmonary arterial endothelial cells from CLP mice (150, 151, 153). miR-150-5p interacts with X-inactive specific transcript IncRNA to regulate the c-Fos axis, thioredoxin-interacting protein-mediated pyroptosis and sepsis-induced myocardial injury (157). In sepsis mice with acute kidney injury (AKI), miR-150 targets MEKK3, inhibits LPS-induced c-Jun N-terminal kinase (JNK) pathway, apoptosis and inflammation (156). miR-150-5p+ mice show increased mortality from LPS and CLP. Rescuing miR-150 in lung endothelial cells decreases EGR2-dependent Ang2 expression, restores adherent junction reannealing and endothelial barrier function, and reduces mortality (149). miR-150 inhibits ARG1 and the expansion and immunosuppressive function of MDSCs (146) that expand during severe infections and have been associated with nosocomial infections, morbidity, and mortality in critically ill patients (17, 28, 322). miR-150-3p may have similar expression pattern and activity as miR-150-5p. miR-150-3p is one of the most downregulated exosomal miRNAs (with 146a-5p, 150-3p, 151a-3p) in heat stroke, associated with inflammatoty response and coagulation cascade (323).

#### 3.2.5.2 Inflammatoty activity

There is no formal demonstration of a proinflammatoty activity of miR-150. Though, miR-150 is increased (and not decreased) in the serum of mice ongoing CLP-induced sepsis and in rats challenged with LPS (147, 148).

### 3.2.6 miR-155

miR-155 is encoded on human chromosome 21. Its expression is increased by MAMPs, bacteria, viruses and parasites (267, 324–333). Captivatingly, the induction of miR-155 in macrophages is controlled by the molecular clock controller Bmal1, which in turn is repressed by miR-155. Thus, miR-155 is a regulatory component of the circadian rhythm, and of the circadian control of inflammation (267).

#### 3.2.6.1 Anti-inflammatory activity

miR-155 targets TGF-β activated kinase 1 binding protein 2 (TAB2) and negatively regulates the TLR/IL-1 signaling cascade...
in human DCs exposed to microbial stimuli (271). miR-155 inhibits caspase 1 and IL-1β by increasing autophagy through inhibition of TAB2. miR-155 agomir reduces lung pathology in mice with CLP (254). miR-155 inhibits IRF8-mediated antiviral response in Japanese encephalitis virus infected microglial cells (333). In Francisella tularensis-infected human macrophages, miR-155 downregulates MyD88 (327). The delivery of miR-155 inhibitor to mice challenged with LPS increases SOCS1, and reduces JAK and STAT3, cytokines, and kidney injury (325). In mice with CLP, a miR-155 mimic decreases JNK and β-arrestin 2 expression, reduces infiltration of macrophages and PMNs in the myocardium, and attenuates late sepsis-induced cardiac dysfunction (162). miR-155-deficient mice infected with H1N1 influenza virus and challenged 5 days later with Staphylococcus aureus show a robust induction of IL-17 and IL-23 and reduced bacterial burden in lungs. In a similar way, a miR-155 antagonist (i.e. anti-miRNAs, in the form of oligonucleotides silencing endogenous miRNAs) enhances lung bacterial clearance in mice (326). This could be relevant since post-influenza bacterial pneumonia is an important cause of morbidity and mortality.

The infection of astrocytes with Escherichia coli induces miR-146a and miR-155 expression. In a feedback loop mechanism, miR-146a and miR-155 inhibit TLR- and epithelial growth factor receptor (EGFR)-mediated NF-kB signaling pathway and inflammation. miR-146a and miR-155 antagonirs increase brain inflammation in mice infected with E. coli. Thus, miR-155 acts coordinately with miR-146a to safeguard the central nervous system from neuroinflammatory damages (334).

### 3.2.6.2 Inflammatory activity

Pioneer studies published in late 2000's linked miR-155 with inflammation and innate immunity. miR-155 has been identified as a target induced by inflammatory mediators in macrophages (324). Subsequently, miR-155 is shown to repress SOCS1 and Src homology 2 domain containing inositol polyphosphate 5-phosphatase 1 to increase LPS-induced cytokine production by mouse macrophages (269, 270).

miR-155 transgenic mice produce more TNF in response to LPS and are more sensitive to endotoxemia (335). miR-155 deficient mice have a reduced capacity to clear Streptococcus pneumoniae colonization from the nasopharynx, which is associated with impaired recruitment of macrophages and induction of protective T helper (Th) 17 immune responses (328). PMNs from miR-155-deficient septic mice express less NETs. miR-155 deficiency is associated with reduced accumulation of PMNs, NETs, edema and lung damage in mice with CLP (158). miR-155 is increased in endothelial cells from endotoxemic mice, and in the serum and bronchoalveolar lavage fluid (BALF) from septic patients with ARDS. miR-155 promotes vascular permeability and capillary leakage (159). miR-155 deficiency reduces endothelial activation and leukocyte adhesion and infiltration into the myocardium, myocardial edema and dysfunction, vasoplegia, and mortality in mice with endotoxia or CLP. miR-155 targets CD47 and angiotensin type 1 receptor to promote nitric oxide (NO)-mediated vasorelaxation and vasoplegia (161). Injection of a miR-155 inhibitor reduces inflammation and intestinal barrier dysfunction in mice with CLP (160).

#### 3.2.6.3 Biomarker value

The measure of 13 miRNAs in the plasma of 32 healthy controls and 62 patients with sepsis shows that 11 miRNAs including miR-155 are increased in patients. miR-155 levels are not associated with severity or outcome (309). A miRNome identifies 11 differentially expressed miRNAs in sepsis patients compared to healthy controls (n = 60/30), but only miR-155 is confirmed by PCR, miR-155 is elevated in patients, and positively correlates with SOFA score. miR-155 shows a good prediction value of 28-day survival (AUC = 0.763). Interestingly, miR-155 levels are proportional to the percentage of CD39+ regulatory T cells (201). Another study reports that miR-155 is increased in septic patients and is a valuable predictor of mortality (241). In a study analyzing 10 healthy controls and 10 sepsis patients with ARDS, miR-155 levels are elevated in BALF samples from sepsis patients (254). In a cohort of 156 sepsis patients of whom 41 with ALL and 32 with ARDS, miR-155 levels are higher in patients with ALL or ARDS, positively correlate with IL-1β and TNF, and negatively correlate with PaO2/FiO2 ratio. miR-155 AUC for diagnosing sepsis with ALI/ARDS is 0.87 (253). A study comparing 218 critically ill patients (135 with sepsis) with 76 healthy controls shows that, in critically ill patients ≤ 65 years, high miR-155 levels are associated with increased survival. This is not the case in patients older than 65 years (336). Finally, miR-155 is similarly expressed in peripheral blood from newborns with or without sepsis (237).

To summarize, there are strong arguments in favor of anti-inflammatory and proinflammatory activities of miR-155. miR-155 is usually increased in adults with sepsis, and associated with worse outcome. This is not observed in elderly and newborns, suggesting that miRNA-based biomarkers should be interpreted according to patient's age.

### 3.2.7 miR-223

miR-223 is encoded on chromosome X in mammals, and is highly conserved among species. miR-223 regulates hematopoiesis and triggers granulopoiesis and macrophage differentiation (337–340). miR-223 targets NLRP1, IGF1R, HSP90, C/EBPα, C/EBPβ, E2F1, forkhead box protein O1, NF-κB p65, nuclear factor I A, PBX/knotted 1 homeobox 1, STAT3 and STAT5, which accounts for a broad range of biological effects (338).

#### 3.2.7.1 Anti-inflammatory activity

miR-223 is predominantly expressed in myeloid cells and drives anti-inflammatory functions. miR-223 is involved in
macrophage polarization and activation, and negatively regulates neutrophil functions. miR-223 inhibits NF-κB p65 phosphorylation and IL-1β, IL-6, TNF and IL-12p40 expression in U-937 human mononuclear cells stimulated with LPS and IFNγ (341). NLRP3 is a sensor of the classical inflammasome involved in gasdermin-D processing, pyroptosis and secretion of IL-1β and IL-18 (342). miR-223 suppresses NLRP3 expression and IL-1β production in mouse macrophages and PMNs (343). Stimulation of macrophages with LPS, CpG DNA or poly(I:C) decreases miR-233 expression, which results in increased STAT3, NF-κB and MAPK signaling and production of IL-1β, IL-6 and TNF (344, 345). In the same line, PMN-derived miR-223 inhibits NLRP3 and IL-1β expression, and reduces pathogenesis in mice with DAMPs-induced ALI (346). miRNA-223 is upregulated in blood and lung parenchyma during experimental and human tuberculosis (347), and in monocytes from patients with tuberculosis (341). In a mouse model, miR-223 restricts the expression of CCL3, CXCL2 and IL-6 and the recruitment of PMNs into the lungs. miR-223 knockdown sensitizes mice to Mycobacterium tuberculosis lung infection through exacerbated PMN-dependent lethal inflammation (347). miR-223 promotes MMP-1 and MMP-9 activity in macrophages. M. tuberculosis infection via a miR-223/BMAL1 axis to subvert host defenses (348). Mechanical ventilation and Staphylococcus aureus-induced ALI is increased in miR-223 deficient mice. Pulmonary delivery of miR-223 using nanoparticles inhibits ALI. Interestingly, the transfer of miR-223 from PMNs to alveolar epithelial cells may be involved in attenuating lung inflammation (349).

3.2.7.2 Inflammatory activity

miR-223 increases in lungs of mice exposed to cigarette smoke and LPS and human in pulmonary cells and monocytes exposed to inflammatory cytokines. miR-223 targets histone deacetylase 2 (HDAC2), resulting in increased expression of fractalkine. miR-223 negatively correlates with HDAC2 expression in lungs from chronic obstructive pulmonary disease (COPD) patients (181). High miR-223 levels might contribute to stimulate the NF-κB pathway, and decrease corticosteroid response and disease severity in asthma and COPD (350).

3.2.7.3 Biomarker value

Studies evaluating miR-223 as a sepsis biomarker have generated contradictory results. When compared to healthy controls, miR-223 serum levels are either reduced (197, 237, 242), increased (182, 199, 204, 207) or not affected (259, 309) in patients. Observations using severity as a variable appear more consistent since miR-223 levels are lower in sepsis patients than in SIRS patients (242), and in patients with sepsis-induced cardiomyopathy than in healthy controls (238). Yet, miR-223 levels are either lower (182, 195) or higher (260) in sepsis non-survivors than in sepsis survivors (351). Finally, miRNAome studies have not pointed to miR-223 as a differentially expressed miRNA in sepsis (195, 196, 198, 202).

Overall, miR-223 is considered anti-inflammatory, albeit it might drive inflammatory effects by targeting HDAC2 in specific conditions. Clinical studies yielded heterogeneous results when assessing the potential of miR-223 as a biomarker of sepsis. However, a meta-analysis of 22 records, including 2210 sepsis, 426 SIRS, and 1076 healthy controls suggested that miR-223 could be used as an indicator for sepsis (351). It should be stressed however that miR-223 values were available in a subset of 6/22 studies.

3.2.8 Other miRNAs

Finally, we will describe few studies analyzing miRNAs in an unsupervised manner or in the context of specific clinical questions. A miRNAome analysis in critically ill patients with intra-abdominal sepsis or non-infective SIRS and healthy controls (n = 29/44/16) has detected 116 blood miRNAs increased in SIRS patients. miRNAs are more abundant in non-infectious SIRS than in sepsis patients. The top five differentially expressed miRNAs, miR-23a-5p, miR-26a-5p, miR-30a-5p, miR-30d-5p and miR-192-5p, discriminate severe sepsis from severe SIRS (AUC = 0.74-0.92). miRNA levels inversely correlate with IL-1, IL-6, IL-8, CRP and pancreatic stone protein (PSP), but not SOFA score. Hence, sepsis and non-infective SIRS are characterized by distinct changes in blood miRNAs, which may be used for diagnostic approaches in critically ill patients (196). However, except miR-23a, none of the short listed miRNAs are considered as sepsis biomarkers in previous studies (89, 249).

A recent study evaluated blood changes of miR-15a-5p, miR-155-5p, miR-192-5p, miR-423-5p in 46 sepsis patients treated with gentamicin, vancomycin (i.e. nephrotoxic antibiotics) or non-nephrotoxic antibiotics (n = 20/7/19). Small changes of miRNAs are observed in the different groups. miR-15a-5p at day 7 of gentamicin treatment provides good discrimination between AKI and non-AKI. miR-155-5p and miR-192-5p positively correlate with creatinine and neutrophil gelatinase-associated lipoprotein in patients receiving vancomycin (210). These data suggest that miRNAs expression might be modulated by antimicrobials, and may serve as diagnostic markers in sepsis patients receiving nephrotoxic antibiotics.

The expression of miR-146-3p, miR-147b, miR-155 and miR-223 (associated with inflammation, see 3.2) was assessed in the plasma of patients with bacterial sepsis or dengue
hemorrhagic fever and healthy controls (n = 130/69/82). miRNAs are increased in patients with sepsis when compared to patients with hemorrhagic fever or to healthy controls. miR-147b, alone or in combination with PCT, discriminates septic shock (AUC ≥ 0.8). Thus, miR-147b may be a biomarker to support clinical diagnosis of severe sepsis (247).

Necrotizing enterocolitis (NEC) is the most common and severe gastrointestinal pathology in preterm infants. A microarray-based screening has identified 230 upregulated miRNAs and 16 downregulated miRNAs in NEC when compared to sepsis and non-NEC/non-sepsis groups. Targeted analyses in a large cohort shows that miR-1290 can efficiently differentiate NEC from neonatal sepsis and neonatal inflammatory conditions such as bronchopulmonary dysplasia (200). Plasmatic miR-1290 expression may help differentiating NEC from neonatal sepsis.

4 Conclusions

Over the past decade, miRNAs have been the focus of intense research in the field of critical illness and sepsis. Our understanding of the modes of action and impact of miRNAs on host inflammatory and antimicrobial defenses has increased dramatically. However, this has not yet improved clinical management. Possibly, intervention strategies with miRNA mimics or miRNA antagonists could rebalance the dysregulated host response during sepsis (Figure 1). Unfortunately, no miRNA-based clinical trials have been registered for sepsis so far.

The data summarized in Table 1 and Figure 3 illustrate the complexity and wide range of action of miRNAs in inflammatory and infectious conditions. Some miRNAs have been ascribed both anti-inflammatory and proinflammatory activities. Many reasons may account for diverse observations, including differences between in vitro, ex vivo and in vivo settings, sterile and infectious models, organs and cell types examined, and kinetics. In in vivo sepsis models, a mediator may be beneficial or harmful depending on disease condition. For example, inhibition of macrophage migration inhibitory factor (a pleiotropic cytokine and central regulator of innate immune responses (352, 353)) increased susceptibility to infection but protected from lethal sepsis (354–357). Similarly, blocking TLR4 at the onset of infection induced mortality from otherwise non-lethal peritonitis, while therapeutic administration of anti-TLR4 antibodies protected mice from lethal Gram-negative bacterial sepsis (299).

Using miRNA as biomarker in sepsis holds more short-term potential than therapeutic opportunities. Many studies reported that miRNAs: 1) discriminate healthy donors from sepsis patients, 2) distinguish sepsis from non-infectious clinically-related diseases, 3) predict severity and/or the mortality, and 4) correlate with clinical parameters or cytokines. However, conflicting observations currently make translation to clinics challenging. So, how to use more efficiently miRNAs as biomarkers?

There is a crucial need for improvement and standardization of clinical studies in order to generate comprehensive views of miRNome during sepsis. We advocate for more stringent methodologies, in terms of both study design, clinical data collection, and miRNA investigation strategies. Importantly, small cohorts tends to exacerbate individual variations, whereas targeted techniques (e.g. RT-qPCR) fail to generate a global landscape of the miRNA fluctuations. Even if constraining, derivation and validation cohorts should be envisaged to corroborate and improve robustness of observations. A key objective would be to run unbiased miRNome analyses in large cohorts of well-defined critically-ill patients with or without sepsis.

Sepsis is a heterogeneous syndrome. Mediators detrimental during the overwhelming phase of sepsis might be beneficial during the later immunosuppressive phase, and miRNAs should not deviate from this principle (Figure 1). In fact, new types of clinical trials using a precision-medicine approach have been launched to adjust treatment (immunosuppressive or immuno-stimulant) given patients’ inflammatory status (see https://www.immunosep.eu/ as an example). We believe that studies should take into consideration the causative agent, the site of infection, medications and the inflammatory status to stratify patients. Bearing in mind disease progression, the timing of sampling should be recorded. Ideally, blood samples should be collected at hospital admission (ED, medical/surgical ICUs), and continued over time to have a longitudinal view of the expression miRNAs. For translational perspectives, it would be easier be detected miRNAs in serum or blood than in PBMCs or isolated vesicles.

Finally, miRNA expression levels are prone to be affected by individual parameters (age, sex, genetic, comorbidities...). Therefore, combination scores (including one or several miRNAs, demographic and/or clinical data) should also be considered. Along these lines, whole blood or single cell transcriptomic identified rather simple gene expression signatures to distinguish sterile inflammation from sepsis, sepsis from infection, viral infections from fungal and bacterial infections, peritonitis, and sepsis caused by community-acquired pneumonia (358–363). Ideally, polymorphisms affecting pri-, pre- and mature miRNA sequences or affecting the target gene sequence should be investigated as well (364).

Based on our current knowledge, clinical use of miRNA targeting in sepsis cannot be realistically envisaged. miRNAs might be used as biomarkers. However, further studies will be required to obtain robust results, in order to safely recommend the use of miRNAs as biomarkers of sepsis. This is a certainly an ambitious, but promising goal.
Author contributions

TR conceived the manuscript. TR and NA wrote the manuscript. NA, CT, ITS and TR revised the manuscript. All authors contributed to the article and approved the submitted version.

Funding

TR is supported by the Swiss National Science Foundation (SNSF; grant number 310030_207418), by the Horizon 2020 Marie Skłodowska-Curie Action: Innovative Training Network (MSCA-ESA-ITN, grant number 676129) and Horizon 2020 ImmunoSep (grant number 847422), by the Fondation Carigest/Promex Stiftung für die Forschung (Geneva, Switzerland) and the Fondation de Recherche en Biochimie (Epalinges, Switzerland). NA received a scholarship from the Porphyrogenis Foundation (Lausanne, Switzerland). CT and IS received a scholarship from the Société Académique Vaudoise (Lausanne, Switzerland).

Acknowledgments

We apologize for those studies that were not mentioned in this review.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Broz P, Monack DM. Newly described pattern recognition receptors team up against intracellular pathogens. Nat Rev Immunol (2013) 13:551–65. doi: 10.1038/nri3479
2. Savva A, Roger T. Targeting toll-like receptors: promising therapeutic strategies for the management of sepsis-associated pathology and infectious diseases. Front Immunol (2013) 4:387. doi: 10.3389/fimmu.2013.00387
3. Brubaker SW, Bonham KS, Zanoni I, Kagan JC. Innate immune pattern recognition: a cell biological perspective. Annu Rev Immunol (2015) 33:257–90. doi: 10.1146/annurev-immunol-032614-112240
4. Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell (2010) 140:805–20. doi: 10.1016/j.cell.2010.01.022
5. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA (2016) 315:801–10. doi: 10.1001/jama.2016.0287
6. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, et al. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. Lancet (2020) 395:200–11. doi: 10.1016/S0140-6736(19)32989-7
7. Prescott HC, Angus DC. Enhancing recovery from sepsis: a review. JAMA (2018) 319:62–75. doi: 10.1001/jama.2017.17687
8. Shankar-Hari M, Saha R, Wilson J, Prescott HC, Harrison D, Rowan K, et al. Rate and risk factors for rehospitalisation in sepsis survivors: systematic review and meta-analysis. Intensive Care Med (2020) 46:619–36. doi: 10.1007/s00134-019-05908-3
9. van der Poll T, Shankar-Hari M, Wiersinga WJ. The immunology of sepsis. Immunology (2021) 54:2450–64. doi: 10.1111/immu.2021.01012
10. Rubio I, Osuchowski MF, Shankar-Hari M, Skirecki T, Winkler MS, Lachmann G, et al. Current gaps in sepsis immunology: new opportunities for translational research. Lancet Infect Dis (2019) 19:e422–36. doi: 10.1016/S1473-3099(19)30567-5
11. Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent JL. Sepsis and septic shock. Nat Rev Dis Primers (2016) 2:16045. doi: 10.1038/nrdp.2016.45
12. Venet F, Monneret G. Advances in the understanding and treatment of sepsis-induced immunosuppression. Nat Rev Nephrol (2018) 14:121–37. doi: 10.1038/nrneph.2017.165
13. Torres LK, Pickkers P, van der Poll T. Sepsis-Induced Immunosuppression. Annu Rev Physiol (2022) 84:157–81. doi: 10.1146/annurev-physiol-061121-040214
14. Deutschman CS, Tracey KJ. Sepsis: current dogma and new perspectives. Immunity (2014) 40:463–75. doi: 10.1016/j.immuni.2014.04.001
15. Cohen J, Vincent JL, Adhikari NK, Machado FR, Angus DC, Calandra T, et al. Sepsis: a roadmap for future research. Lancet Infect Dis (2015) 15:381–614. doi: 10.1016/S1473-3099(15)70112-X
16. Ciardo E, Savva A, Roger T. Epigenetics in sepsis: targeting histone deacetylases. Int J Antimicrob Agents (2013) 42 Suppl:S8–12. doi: 10.1016/j.ijantimicag.2013.04.004
17. Schrijver IT, Theroule C, Roger T. Myeloid-Derived Suppressor Cells in Sepsis. Front Immunol (2019) 10.327. doi: 10.3389/fimmu.2019.00327
18. Cecconi M, Evans L, Levy M, Rhodes A. Sepsis and septic shock. Lancet (2018) 392:75–87. doi: 10.1016/S0140-6736(18)30696-2
19. Schlapbach LJ, Truck J, Roger T. Editorial: the immunology of sepsis—understanding host susceptibility, pathogenesis of disease, and avenues for future treatment. Front Immunol (2020) 11:1263. doi: 10.3389/fimmu.2020.01263
20. MiRa JC, Gentile LF, Mathias BJ, Efron PA, Brakenridge SC, Mohr AM, et al. Sepsis pathophysiology, chronic critical illness, and persistent inflammation-immunosuppression and catabolism syndrome. Crit Care Med (2017) 45:253–62. doi: 10.1097/CCM.0000000000003074
21. Safety WIPoC. (2001). Available at: http://www.inchem.org/documents/eh/ehc/ehc222.htm (Accessed 02.03.2021).
22. Pierrakos C, Vincent JL. Sepsis biomarkers: a review. Crit Care Clin (2010) 14:R15. doi: 10.1186/cc8872
23. Stanski NL, Wong HR. Prognostic and predictive enrichment in sepsis. Nat Rev Nephrol (2020) 16:20–31. doi: 10.1038/s41581-019-0199-3
24. Barichello T, Generoso JS, Singer M, Dal-Pizzol F. Biomarkers for sepsis more than just fever and leukocytosis—a narrative review. Crit Care (2022) 26:14. doi: 10.1186/s13054-021-03862-5
25. Opal SM, Wittebole X. Biomarkers of infection and sepsis. Crit Care Clin (2020) 36:11–22. doi: 10.1016/j.ccc.2019.08.002
26. Peters van Ton AM, Kox M, Abdo WF, Pickkers P. Precision immunotherapy for sepsis. Front Immunol (2018) 9:1926. doi: 10.3389/fimmu.2018.01926
primary microRNAs by the Microprocessor complex.

nsmb1167

Genes Dev complex in primary microRNA processing.
doi: 10.1038/nature03049

processing and subcellular localization.

human microRNAs.

Nat Biotechnol integrated expression atlas of MiRNAs and their promoters in human and mouse.

Caenorhabditis elegans. Cell

et al. Conservation of the sequence and temporal expression of let-7 heterochronic gene lin-14 by lin-4 mediates temporal pattern formation in C. elegans. Cell

nuclease mediates post-transcriptional gene silencing in Drosophila cells.

Frontiers inImmunology frontiersin.org26

et al. The 21-nucleotide let-7 RNA regulates developmental timing in C. elegans. Cell

cells. Cell

embo/cdf476

EMBO J (2001) 21:4663–70. doi: 10.1093/ emboj/cdf476

Science (2001) 294:853–8.
doi: 10.1126/science.1064921

et al. An estimate of the total number of true human MiRNAs. Nucleic Acids Res (2009) 47:3533–64. doi: 10.1093/nar/gkq497

die R, Abougessais I, Alam T, Arner E, Arner P, Ashoor H, et al. An integrated expression atlas of MiRNAs and their promoters in human and mouse. Nat Biotechnol (2017) 35:872–8. doi: 10.1038/nbt.3947

et al. Ye, Kim K, Han J, Yeom KH, Lee S, Baek SH, et al. MicroRNA genes are transcribed by RNA polymerase II. EMBO J (2004) 23:4051–60. doi: 10.1038/ sj.emboj.7600385

Borchert GM, Lanier W, Davidson BL. RNA polymerase III transcribes the转移 RNAs. Cell Res (2004) 143:122–20. doi: 10.1038/nrd1359

Lee Y, Kim M, Han J, Yeom KH, Lee S, Baek SH, et al. MicroRNA genes are transcribed by RNA polymerase II. EMBO J (2004) 23:4051–60. doi: 10.1038/sj.emboj.7600385

doi: 10.1093/embj/embf476

et al. The Drosha-DGCR8 complex in primary microRNA processing. Genes Dev (2004) 18:3106–27. doi: 10.1101/gad.1262504

Lin SL, Chang D, Wu DY, Ying SY. A novel RNA splicing-mediated gene silencing mechanism potential for genome evolution. Biochem Biophys Res Commun (2003) 301:754–60. doi: 10.1016/S0006-291X(02)02236-5

Lee Y, Hur I, Park SY, Kim YK, Suh MR, Kim VN. The role of PACT in the microRNA silencing pathway. EMBO J (2006) 25:522–32. doi: 10.1038/sj.emboj.7600942

Redfern AD, Colley SM, Brewer DJ, Ikeda N, Epis MR, Li X, et al. RNA-induced silencing complex (RISC). Proteins PACT, TRBP, and Dicer are IRA binding nuclear receptor coregulators. Proc Natl Acad Sci U.S.A. (2013) 110:6536– 41. doi: 10.1073/pnas.1301620110

Ramchandran R, Chaluvally-Raghavan P. MiRNA-mediated RNA activation in mammalian cells. Adv Exp Med Biol (2017) 983:81–9. doi: 10.1007/978-1-4939-9-6

Agarwal V, Bell GW, Nam JW, Bartel DP. Predictive effective microRNA target sites in mammalian miRNAs. Elife (2015) 4:e1–38. doi: 10.7554/eLife.05005

Kawatama T, Tomari Y. Making RISC. Trends Biochem Sci (2010) 35:368– 76. doi: 10.1016/j.tibs.2010.03.009

Yoda M, Kawatama T, Paroo Z, Ye X, Iwasaki S, Liu Q, et al. ATP-dependent human RISC assembly pathways. Nat Struct Mol Biol (2010) 17:17–23. doi: 10.1038/nsm.1733

Jo MH, Shin S, Jung SR, Kim E, Song JJ, Hohong S. Human argonaute 2 has diverse reaction pathways on target RNA. Mol Cell (2015) 59:117–24. doi: 10.1016/j.molcel.2015.04.027

De N, Young L, Lau PW, Meisner NC, Morrissey DV, MacRae II. Highly complementary target RNA targets promote release of guide RNAs from human Argonaute2. Mol Cell (2013) 50:344–55. doi: 10.1016/j.molcel.2013.04.001

et al. Alternative RISC assembly: binding and repression of microRNA-mRNA duplexes by human Ago proteins. RNA (2012) 18:2041–55. doi: 10.1261/rna.035675.112

Belter A, Gudanis D, Rolle K, Piwecka M, Gdaniec Z, Naskret-Barciszewska MZ, et al. Mature MiRNAs form secondary structure, which suggests their function beyond RISC. PloS One (2014) 9:e83384. doi: 10.1371/journal.pone.0113849

Guerrin SD, Aziz MJ, Hn, Wang H, He M, Al-Abed Y, et al. Extracellular microRNA 130b-3p inhibits eIC5P-induced inflammation. EMBO Rep (2020) 21: e84075. doi: 10.15252/embr.201948075

et al. Wang K, Zhang S, Weber J, Baxter D, Galas DJ. Export of microRNAs and microRNA-protein protective by mammalian cells. Nuclear Acids Res (2010) 38:7248–59. doi: 10.1093/nar/gkq601

et al. Chen X, Liang H, Zhang J, Ken K, Zhang CY. Secreted microRNAs: a new form of intercellular communication. Trends Cell Biol (2012) 22:125–32. doi: 10.1016/trends.cellb.2011.12.001

et al. Chen X, Ba Y, Ma L, Cai X, Yin Y, Wang K, et al. Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases. Cell Res (2008) 18:997–1006. doi: 10.1038/cr.2008.282

et al. Kosaka N, Iguchi H, Yoshioka Y, Takeshita F, Matsuki Y, Ochiya T. Mature MiRNAs form secondary structure, which suggests their function beyond RISC. Proc Natl Acad Sci U.S.A. (2019) 116:9207–12. doi: 10.1073/pnas.19023997

et al. Wang P, Zhang K, Zhang S, Weber J, Baxter D, Galas DJ. Export of microRNAs and microRNA-protein protective by mammalian cells. Nuclear Acids Res (2010) 38:7248–59. doi: 10.1093/nar/gkq601

et al. Chen X, Liang H, Zhang J, Ken K, Zhang CY. Secreted microRNAs: a new form of intercellular communication. Trends Cell Biol (2012) 22:125–32. doi: 10.1016/trends.cellb.2011.12.001

et al. Chen X, Ba Y, Ma L, Cai X, Yin Y, Wang K, et al. Characterization of miR-130b-3p regulates M1 macrophage polarization via targeting IRF1. J Cell Physiol (2022) 238:2008–22. doi: 10.1002/jcp.29987

et al. Wang K, Zhang S, Weber J, Baxter D, Galas DJ. Export of microRNAs and microRNA-protein protective by mammalian cells. Nuclear Acids Res (2010) 38:7248–59. doi: 10.1093/nar/gkq601
MALAT1 suppresses in sepsis. and C/EBPbeta synergize to induce MiR-21 and MiR-181b expression during infection. Infect Immun (2019) 88:4358–67. doi: 10.1145/1407672.1407672

Xue Z, Xi Q, Liu H, Guo X, Zhang J, et al. MiR-21 promotes NLPR3 inflammasome activation to mediate pyroptosis and endotoxic shock. Cell Death Dis (2019) 10:461. doi: 10.1038/s41419-019-1713-x

McClure C, Brudecki L, Ferguson DA, Yao QZ, 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) 82:8316–25. doi: 10.1128/FI.01945-14

McClure C, McPeak MB, Youssef D, Yao QZ, McCall CE, El Gazzar M. Stat3 and C/EBPbeta synergize to induce MiR-21 and MiR-181b expression during sepsis. Immunol Cell Biol (2017) 95:62–55. doi: 10.1038/jicb.2016.63

Xie W, Chen L, Chen L, Kou Q. Silencing of long non-coding RNA MALAT1 suppresses inflammation in septic mice: role of microRNA-23a in the down-regulation of MCEMP1 expression. Inflammation (2020) 43:608. doi: 10.1007/s10753-020-01251-8

Song W, Zhang T, Yang N, Zhang W, QW, et al. MicroRNA-22 supports robust innate immunity in hepatocytes by targeting the RTKs/STAT3 signaling pathway. F1000 Research (2018) 7:2055–16. doi: 10.7554/eLife.41159

Song W, Zhang T, Yang W, Chen Z, Wen R, Liu C. Inhibition of micro RNA-122-5p promotes lipopolysaccharide-induced myocardial injury by inhibiting oxidative stress, inflammation and apoptosis via targeting GIT1. BioMed Pharmacother (2021) 137:110638. doi: 10.1016/j.biopha.2021.110638

Zhang F, Fan X, Bai Y, Liu J, Zheng M, Chen J, et al. MiR-125b regulates procalcitonin production in monocytes by targeting Stat3. J Immunol (2016) 197:6108–16. doi: 10.4049/jimmunol.1502127

Li S, Zheng X, Yang S, Zhu Z. MicroRNA-98 protects sepsis mice from cardiac dysfunction, liver and lung injury by negatively regulating HMGAA2 through inhibiting NF-kappaB signaling pathway. Cell Cycle (2019) 18:1948–64. doi: 10.1002/cc.29138

Dong Z, Chen X, Wang W, Tian Z, et al. Exosomal derived from alveolar epithelial cells promote alveolar macrophage activation mediated by MiR-92a-3p in sepsis-induced acute lung injury. Front Cell Infect Microbiol (2021) 11:646546. doi: 10.3389/fcimb.2021.646546

Zhu J, Lin X, Yan C, Yang S, Zhu Z. MicroRNA-98 protects sepsis mice from cardiac dysfunction, liver and lung injury by negatively regulating HMGAA2 through inhibiting NF-kappaB signaling pathway. Cell Cycle (2019) 18:1948–64. doi: 10.1002/cc.29138

M. Antonakos et al. 10.3389/fimmu.2022.951798
kappaB pathway. *Int Immunopharmacol* (2020) 89:107016. doi: 10.1016/j.intimp.2020.107016

119. Yang P, Xiong W, Chen X, Liu J, Ye Z. Overexpression of MiR-129-5p mitigates sepsis-induced acute lung injury by targeting high mobility group box 1. *J Surg Res* (2020) 256:23–30. doi: 10.1016/j.jss.2020.05.101

120. Cui YL, Wang B, Gao HM, Xing YH, Li J, Li HJ, et al. Interleukin-18 and MiR-134 are associated with the downregulation of STAT1 in sepsis patients with thrombocytopenia. *Patient Prefer Adherence* (2016) 10:313–9. doi: 10.2147/PPA.S95588

121. Liu F, Li Y, Jiang R, Nie C, Zeng Z, Zhao N, et al. MiR-132 inhibits lipopolysaccharide-induced inflammation in alveolar macrophages by the cholinergic anti-inflammatory pathway. *Exp Lung Res* (2015) 41:261–9. doi: 10.3109/01903660.2015.1002206

122. Qin LY, Wang MX, Zhang H. MiR-133a alleviates renal injury caused by sepsis by targetting BNP3L. *Eur Rev Med Pharmacol Sci* (2020) 24:2632–9. doi: 10.26355/eurrev_202003_20532

123. Chen L, Xie W, Wang L, Zhang X, Liu F, Kou Q. MiRNA-133a aggravates inflammatory responses in sepsis by targeting SIRT1. *Int Immunopharmacol* (2020) 88:106848. doi: 10.1016/j.intimp.2020.106848

124. Zheng G, Pan M, Jin W, Jin G, Huang Y. MicroRNA-135a is up-regulated and aggravates myocardial depression in sepsis via regulating p38 MAPK/NF-kappaB pathway. *BioMed Research International* (2017) 45:6–12. doi: 10.1155/2017/01.029

125. Zhang X, Liu X, Chang R, Li Y. MiR-139-5p protects septic mice with acute lung injury by inhibiting Toll-like receptor 4/NF-kB signaling pathway. *Clinics (Sao Paulo)* (2021) 76:2249–54. doi: 10.6061/clinics/2021.076

126. Lin X, Wang Y. MiR-141 is negatively correlated with TLR4 in neonatal lung injury by targeting high mobility group box 1. *BioMed Biophys Res Commun* (2020) 256:23–8. doi: 10.1016/j.bbrc.2020.03.119

127. Zhen J, Chen W. MiR-142 inhibits cecal ligation and puncture (CLP)-induced inflammation in monocytes. *Stem Cells Transl Med* (2021) 10.e2484. doi: 10.1002/stem.2021.e2484

128. Schmidt WM, Spiel AO, Jilma B, Wolzt M, Müller M. Effects of 5,14-HEDGE, a 20-HETE mimetic, on lipopolysaccharide-induced changes in MyD88/TAK1/IKKbeta/IkappaB-alpha/NF-kappaB pathway and function through negative regulation of ARG-1 in sepsis. *Life Sci* (2021) 278:119626. doi: 10.1016/j.lfs.2021.119626

129. Prakhar P, Holla S, Ghorpade DS, Gilleron M, Puzo G, Udupa V, et al. MiR-29B-1 negatively regulates p38 MAPK/NF-kappaB inflammatory responses in monocytes. *Braz J Med Biol Res* (2021) 54:e16003. doi: 10.1590/1414-431X2021e16003

130. Chen J, Chen W. MiR-142 inhibitsecal ligation and puncture (CLP)-induced inflammation via inhibiting PD-L1 expression in macrophages and improves survival in septic mice. *BioMed Pharmacother* (2018) 97:1479–85. doi: 10.1016/j.biopha.2017.11.058

131. Schmidt WM, Spiel AO, Jilma B, Wolzt M, Müller M. Effects of 5,14-HEDGE, a 20-HETE mimetic, on lipopolysaccharide-induced changes in MyD88/TAK1/IKKbeta/kappaB-alpha/NF-kappaB pathway and function through negative regulation of ARG-1 in sepsis. *Life Sci* (2021) 278:119626. doi: 10.1016/j.lfs.2021.119626

132. Tacke F, Roderburg C, Bena F, Cardenas DV, Luedde M, Hippe HJ, et al. Levels of circulating MiR-134 are elevated in sepsis and predict mortality in critically ill patients. *Crit Care Med* (2024) 42:1096–104. doi: 10.1097/CCM.000000000000311

133. Sari AN, Korkmaz B, Serin MS, Kacan M, Unsal D, Burhanolugu CK, et al. Patient Prefer Health Surg Res (2020) 10:313–5. doi: 10.1155/2021-0313

134. Zhao X, Liu D, Gong W, Zhao G, Liu L, Yang L, et al. The toll-like receptor 4 (TLR4) via MyD88 signaling pathway in human leukocyte microRNA response to endotoxemia. *Biochem Biophys Res Commun* (2019) 490:3437–41. doi: 10.1016/j.bbrc.2018.12.190

135. Prakhar P, Holla S, Ghorpade DS, Gilleron M, Puzo G, Udupa V, et al. MiR-142 regulates inflammatory response and apoptosis by suppressing TLR4 in human umbilical vein endothelial cells. *Biochem Biophys Res Commun* (2018) 508:828–37. doi: 10.1016/j.bbrc.2018.04.168

136. Wei S, Liu Q. Long nonscoring RNA MALAT1 modulates sepsis-induced cardiac inflammation through the MiR-150-5p/NF-kappaB axis. *Int J Clin Exp Pathol* (2019) 12:3313–91

137. Zhu XG, Zhuo TN, Wen R, Liu CF. Overexpression of MiR-150-5p alleviates mitochondrial dysfunction in sepsis-induced Myocardial Depression. *BioMed Res Int* (2020) 2020:325368. doi: 10.1155/2020/325368

138. Liu Y, Yan N, Sui Z. MicroRNA-150 affects endoplasmic reticulum stress via MALAT1-MiR-150 axis-mediated NF-kappaB pathway in LPS-challenged HUVECs and septic mice. *Life Sci* (2021) 265:118744. doi: 10.1016/j.lfs.2021.118744

139. Deng X, Lin Z, Zuo C, Fu Y. Upregulation of MiR-150-5p alleviates LPS-induced inflammatory response and apoptosis of RAW264.7 macrophages by targeting Notch1. *Open Life Sci* (2020) 15:544–52. doi: 10.1515/ols-2020-0058

140. Chen S, Zhu H, Sun J, Zhu J, Qin L, Wan J. Anti-inflammatory effects of MiR-150 are associated with the downregulation of STAT1 in macrophages following lipopolysaccharide treatment. *Exp Ther Med* (2021) 22:1049. doi: 10.3892/etm.2021.10483

141. Shi L, Zhang J, Yuan Y, Xie C, Song Z, Zhu J. MiR-150-5p protects against septic acute kidney injury via repressing the MEEK/3IKV pathway. *Cell Signal* (2021) 86:101101. doi: 10.1016/j.cellsig.2021.101101

142. Wang X, Li XL, Qin J. The IncRNA IIX5/MiR-150-3p/Cox Fox axis regulates sepsis-induced myocardial injury via TNNIP-modulated pyroptosis. *Lab Invest* (2021) 101:1118–29. doi: 10.1038/s41374-021-00607-4

143. Hawser A, Taha D, Algaber A, Madhi R, Rahman M, Thorlacius H. MiR-150 regulates neutrophil extracellular trap formation and lung injury in abdominal sepsis. *J Leukoc Biol* (2022) 111:391–400. doi: 10.1007/JLB.3A1220-789RR

144. Etrudek V, Idouo TO, Schenk H, Seeliger B, Prasse A, Thamm K, et al. Role of endothelial microRNA-155 on capillary leak in systemic inflammation. *Crit Care* (2021) 25:76. doi: 10.1186/s13054-021-03500-0

145. Cao YY, Wang Z, Wang ZH, Jiang XG, Lu WH. Inhibition of MiR-155 alleviates sepsis-induced inflammation and intestinal barrier dysfunction by inactivating NF-kappaB signaling. *Int Immunopharmacol* (2021) 90:107218. doi: 10.1016/j.intimp.2020.107218
Antonakos et al.
immunoparalysis in sepsis. Mol Med (2018) 24:54. doi: 10.1186/s10020-018-0056-z

205. Zheng C, Qiu G, Ge M, Meng J, Zhang G, Wang J, et al. MiR-10a in Peripherally Blood Mononuclear Cells Is a Biomarker for Sepsis and Has Anti-Inflammatory Function. Mediators Inflam (2020) 2020:3479983. doi: 10.1155/2020/3479983

206. Wang H, Zhang P, Chen W, Feng D, Jia Y, Xie LX. Evidence for serum MiR-15b and MiR-16 levels as biomarkers that distinguish sepsis from systemic inflammatory response syndrome in human subjects. Clin Chim Acta (2012) 403:73-79. doi: 10.1016/j.ccl.2011-07-086

207. Wang H, Zhang P, Chen WJ, Feng D, Jia YH, Xie LX. Four serum microRNAs identified as diagnostic biomarkers of sepsis. J Trauma Acute Care Surg (2012) 73:850–4. doi: 10.1097/TA.0b013e3182525f50

208. Wang H, Deng J, Wang IY, Zhang P, Xin Z, Xiao K, et al. Serum MiR-122 levels are related to coagulation disorders in sepsis patients. Clin Chim Acta (2014) 432:92-35. doi: 10.1515/cia-2013-0389

209. Wang W, Liu C, Jang J, Zhang X, Du Y. LncRNA SNHG16 reverses the effects of MiR-15a-16 depletion by LPS-induced inflammatory pathway. BioMed Research International (2018) 2022:882-022.726-6. doi: 10.1186/s12979-022-00156-6

210. Peteyaova N, Martinike A, Zadrzal J, Klementa V, Pribylova L, Bris R, et al. Expression and 7-day time course of circulating microRNAs in septic patients treated with nephroprotective antibiotic agents. BMC Nephrol (2022) 23:111. doi: 10.1186/s12882-022-02726-6

211. Fouda E, Elrazek Midan DA, Ellaban R, El-Kousy S, Arafat E. The diagnostic and prognostic role of MiRNA 15b and MiRNA 378a in neonatal sepsis. Biochem Biophys Rep (2021) 28:100915. doi: 10.1016/j.bbrep.2021.100915

212. El-Hefnawy SM, Mostafa RG, El Zayat RS, Elfeshawy EM, Abd El-Bari HM, El-Menouh Elially MA. Biological and molecular study on serum MiRNA-16a and MiRNA-451 as neonatal sepsis biomarkers. Biochem Biophys Rep (2021) 25:100915. doi: 10.1016/j.bbrep.2021.100915

213. Xu H, Liu X, Ni H. Clinical significance of MiR-19b-3p in patients with sepsis and its regulatory role in the LPS-induced inflammatory response. Eur J Med Res (2020) 25:9. doi: 10.4103/ejmr.ejmr_020_04

214. Na L, Ding H, Xing E, Zhang Y, Gao J, Liu B, et al. The predictive value of microRNA-21 for sepsis risk and its correlation with disease severity, systemic inflammation, and 28-day mortality in sepsis patients. J Clin Lab Anal (2020) 34:e23103. doi: 10.1002/jcla.23103

215. Sankar S, Maruthai K, Bobby Z, Adhisivam B. MicroRNA Expression in Neonates with Late-onset Sepsis - A Cross-sectional Comparative Study. Immunol Invest (2021) 1-13. doi: 10.1080/08820139.2021.2020282:1-13

216. Zhang H, Che L, Wang Y, Zhou H, Gong H, Man X, et al. Deregulated microRNA-22-3p in patients with sepsis-induced acute kidney injury serves as a new biomarker to predict disease occurrence and 28-day survival outcomes. Int Urol Nephrol (2021) 53:2107–16. doi: 10.1007/s11255-021-02784-x

217. Fatmi T, Rehabi SA, Chabini N, Zervouki H, Azzaouh H, Elhabiri Y, et al. MiRNA-23b as a biomarker of culture-positive neonatal sepsis. Mol Med (2020) 26:964. doi: 10.2174/1573808020966662021091332

218. Yao L, Liu Z, Zhu J, Li B, Chai C, Tian Y. Clinical evaluation of circulating microRNA-25 level change in sepsis and its potential relationship with oxidative stress. Int J Clin Exp Pathol (2015) 8:7675–84. doi: 10.2147/ijcep.s83900

219. Zhang J, Wang CJ, Tang XM, Wei YK. Urinary MiR-26b as a potential biomarker for patients with sepsis-associated acute kidney injury: a Chinese population-based study. Eur Rev Med Pharmacol Sci (2018) 22:4604–10. doi: 10.26355/eurrev.201807.15518

220. Abdelaleem MO, Mohammed SR, El Sayed HS, Hussein SK, Ali DY, Abdelwahed MY, et al. Serum MiR-34a-5p and MiR-199-a-3p as new biomarkers of neonatal sepsis. PLoS One (2022) 17:e0262233. doi: 10.1371/journal.pone.0262233

221. Zhang C, Li X, Li N, Feng Z, Zhang C. MicroRNA-96 is down-regulated in sepsis neonates and attenuates LPS-induced inflammation, deteriorative disease condition, and predicts decreased survival of sepsis. BMC Med (2020) 99:e20729. doi: 10.1186/s1288-022-02792-9

222. Wang Q, Feng Q, Zhang Y, Zhou S, Chen H. Decreased microRNA 103 and microRNA 107 predict increased risks of acute respiratory distress syndrome and 28-day mortality in sepsis patients. Med (Baltimore) (2020) 99:e20729. doi: 10.1097/MD.0000000000012079

223. Abou El-Khier NT, Zaki ME, Alkasaby NM. Study of MicroRNA-122 as a diagnostic biomarker of sepsis. Egypt J Immunol (2019) 26:105–16.
Antonakos et al. 10.3389/fimmu.2022.951798

248. Roderburg C, Luedde M, Vargas Cardenas D, Vucur M, Scholten D, Frey N, et al. Circulating microRNA-150 serum levels predict survival in patients with critical illness and sepsis. PloS One (2013) 8:e54612. doi: 10.1371/journal.pone.0054612

249. Ma Y, Vilanoa 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: e75958. doi: 10.1371/journal.pone.0075918

250. How CK, Hou SK, Shih HC, Huang MS, Chiou SH, Lee CH, et al. Expression profile of microRNAs in gram-negative bacterial sepsis. Shock (2015) 43:121–7. doi:10.1097/SHK.0000000000000282

251. Braza-Boils A, Barwart T, Guttman C, Thomas MR, Judge HM, Joshi A, et al. Circulating MicroRNA levels indicate platelet and leukocyte activation in endotoxemia despite platelet P2Y12 inhibition. Int J Mol Sci (2020) 21:1–13. doi:10.3390/ijms21082897

252. Yang J, Liao Y, Dai Y, Hu L, Cui Y. Prediction of prognosis in sepsis patients by the SOFA score combined with MiR-150. Adv Clin Exp Med (2022) 31:19–15. doi:10.17217/acecm/20142536

253. Wang ZF, Yang YM, Fan H. Diagnostic value of MiR-155 for acute lung injury/acute respiratory distress syndrome in patients with sepsis. J Int Med Res (2020) 48:0300052943094700. doi:10.1177/0300052943094700

254. Liu P, Fei C, Zhao N, Wang Y, Liu Y, Li Y, et al. MiR-155 Alleviates Septic Lung Injury by Inducing Autophagy Via Inhibition of Transforming Growth Factor-beta Activated Binding Protein 2. Shock (2019) 48:61–8. doi:10.1097/SHK.0000000000000839

255. Liu G, Liu W, Guo J. Clinical significance of MiR-181a in patients with neonatal sepsis and its regulatory role in the lipopolysaccharide-induced inflammatory response. Exp Ther Med (2019) 17:3832–38. doi:10.3892/etm.2020.9388

256. Liang G, Wu Y, Guan Y, Dong Y, Jiang L, Mao G, et al. The correlations between the expression of serum MiR-206 and the severity and prognosis of sepsis. Ann Palliat Med (2020) 9:3222–34. doi:10.21037/apam-20-1391

257. Li M, Zhang H, Zuo YJ. MicroRNA-218 alleviates sepsis inflammation by negatively regulating VOPPI via JAK/STAT pathway. Eur Rev Med Pharmacol Sci (2018) 22:5260–6. doi:10.26355/eurev_201809_15827

258. Wu X, Yang J, Yu L, Long D. Plasma MiRNA-223 correlates with risk, inflammatory markers as well as prognosis in sepsis patients. Med (Baltimore) (2018) 97:e11352. doi:10.1097/MD.0000000000011352

259. Bena F, Tache F, Luode L, Trautwein C, Luedde T, Koch A, et al. Circulating microRNA-223 serum levels do not predict sepsis or survival in patients with critical illness. Dis Markers (2015) 2015:384208. doi:10.1155/2015/384208

260. Li N, Wu S, Yu L. The associations of long non-coding RNA tauineregulated gene 1 and microRNA-223 with general disease severity and mortality risk in sepsis patients. Med (Baltimore) (2020) 99:e23444. doi:10.1097/MD.000000000002437y

261. Sun B, Luan C, Guo L, Zhang B, Liu Y. Low expression of microRNA-328 can predict sepsis and alleviate sepsis-induced cardiac dysfunction and inflammatory response. Braz J Med Biol Res (2020) 53:e9501. doi:10.1590/1419-441120209501

262. Zhang H, Li L, Xi L, Xu Z, Zheng Y. Clinical significance of the Serum IncRNA NORD Expression in Patients with Neonatal Sepsis and Its Association with MiR-410-3p. J Inflammation Res (2011) 14:4818–8. doi:10.2147/JIR.S351985

263. Wang H, Cui W, Qiao L, Hu G. Overexpression of MiR-451a in sepsis and septic shock patients is involved in the regulation of sepsis-associated cardiac dysfunction and inflammation. Genet Mol Biol (2020) 43:e202000009. doi:10.1590/1678-6485-GMB-2020-0009

264. Liu Z, Yang D, Gao J, Xiang X, Hu X, Li S, et al. Discovery and validation of MiR-452 as an effective biomarker for acute kidney injury in sepsis. Theranostics (2020) 10:7150–75. doi:10.7150/thno.50093

265. Guo H, Tang Y, Ji L, Lin C, Ling X, Lu C, et al. MicroRNA-495 serves as a diagnostic biomarker in patients with sepsis and regulates sepsis-induced inflammation and cardiac dysfunction. Eur J Med Res (2019) 24:37. doi:10.1186/s40001-019-0396-3

266. Najad C, Stundon HJ, Gantzer MP. A guide to MIRNAs in inflammation and innate immune responses. FEBS J (2018) 285:3695–716. doi:10.1111/febs.14482

267. Curtis AM, Fagnoudes CT, Yang G, Polasch-Dermott EM, Wochal P, Miettirietik AF, et al. Circadian control of innate immunity and cell adhesion molecules during inflammation. FASEB J (2018) 32:4070–84. doi:10.1096/fj.201715368

268. Shu Z, Tan J, Miao Y, Zhang Q. The role of microvesicles containing microRNAs in vascular endothelial dysfunction. J Cell Mol Med (2019) 23:7933–45. doi:10.1111/jcmm.14716

269. Mandel J, Casari M, Stepanyan M, Martyanov A, Deppermann C. Beyond hemostasis: platelet innate immune interactions and thromboinflammation. Int J Mol Sci (2022) 23:1–30. doi:10.3390/ijms23073688
1. Meingen F, Xu Landen N, Wang A, Rethi B, Bouer C, Zuccolo M, et al. MiR-146a negatively regulates TLR2-induced inflammatory responses in keratinocytes. J Invest Dermatol (2014) 134:1931–40. doi: 10.1038/jid.2014.89

2. Xu D, Han Q, Hou Z, Zhang C, Zhang J. MiR-146a negatively regulates KC cell functions via STAT1 signaling. Cell Mol Immunol (2017) 14:712–21. doi: 10.1038/cmi.2015.113

3. He Y, Jang Y, Chen J. The role of MiR-150 in normal and malignant hematopoiesis. Oncogene (2014) 33:3887–93. doi: 10.1038/onc.2013.346

4. Cron MA, Mallard S, Truffaut F, Gualemi AV, Glihanni A, Fadel E, et al. Causes and consequences of MiR-150-5p dysregulation in myasthenia gravis. Front Immunol (2019) 10:539. doi: 10.3389/fimmu.2019.00539

5. Hu Z, Cui Y, Qiao X, He X, Li F, Luo C, et al. Silencing MiR-150 ameliorates experimental autoimmune encephalomyelitis. Front Neurosci (2019) 12:465. doi: 10.3389/fnins.2018.00465

6. Schrijver IT, Theroode C, Antonakos N, Regina J, Le Roy D, Bart PA, et al. COVID-19 rapidly increases MDSCs and prolongs innate immune dysfunctions. Eur J Immunol (2020). doi: 10.1002/eji.20209827

7. Li Y, Wen Q, Chen H, Wu X, Liu B, Li H, et al. Exosomes derived from heat stress cases carry miRNAs associated with inflammation and coagulation cascade. Front Immunol (2021) 12:624753. doi: 10.3389/fimmu.2021.624753

8. O’Connell RM, Taganov KD, Boldin MP, Cheng G, Baltimore D. MicroRNA-155 is induced during the macrophage inflammatory response. Proc Natl Acad Sci U.S.A. (2007) 104:1646–9. doi: 10.1073/pnas.0607311010

9. Ren Z, Cui Y, Xiong X, Wang C, Zhang Y. Inhibition of microRNA-155 alleviates lipopolysaccharide-induced kidney injury in mice. Int J Clin Exp Pathol (2017) 10:9362–71.

10. Podsadl A, Standford TJ, Ballinger MN, Eakin R, Park P, Kunkel SL, et al. MicroRNA-155 regulates host immune response to postviral bacterial pneumonia via TLR-3- and IFN-α signaling pathways. Am J Physiol Lung Cell Mol Physiol (2016) 310:L465–75. doi: 10.1152/ajplung.00224.2015

11. Bandypadhyay S, Long ME, Allen LA. Differential expression of microRNAs in Franciscella tularensis-infected human macrophages. MiR-155-dependent downregulation of MiR-206 inhibits the inflammatory response. PLoS One (2019) 9:e109525. doi: 10.1371/journal.pone.0109525

12. Verschoor CP, Dorrington MG, Novakowski KE, Kaiser J, Radford K, Nair P, et al. MicroRNA-155 is required for clearance of Streptococcus pneumoniae from the nasopharynx. Infect Immun (2014) 82:4824–33. doi: 10.1128/IAI.00251-14

13. Bittar A, De R, Melgar S, Aung KM, Rahman A, Qadir F, et al. Induction of immunomodulatory MiR-146a and MiR-155 in small intestinal epithelium of Vibrio cholerae infected patients at acute stage of cholera. PLoS One (2017) 12: e0173817. doi: 10.1371/journal.pone.0173817

14. Hucker O, Al-Hashemi J, Foedisch L, Poch O, Davideau JL, Tenenbaum H, et al. Identification and Characterization of MicroRNA Differentially Expressed in Macrophages Exposed to Porphyromonas gingivalis Infection. Infect Immun (2017) 85:1–12. doi: 10.1128/IAI.00771-16

15. Rothchild AC, Sisson JR, Shafiani S, Plaisier C, Min D, Mai D, et al. MiR-155 and MiR-146a collectively regulate monocyte functions. J Immunol (2016) 197:5501–7. doi: 10.4049/jimmunol.1600513

16. Eren RO, Reverte M, Rossi M, Hartley MA, Castiglioni P, Prevel F, et al. Mammalian innate immune response to a leishmaniasis-resident RNA virus increases macrophage survival to promote parasite persistence. Cell Host Microbe (2016) 20:318–28. doi: 10.1016/j.chom.2016.08.001

17. Pareek S, Roy Kumar, Bains J, Pan, Banerjee A, Vrati S. MiR-155 induction in microglial cells suppresses Japanese encephalitis virus replication and negatively modulates innate immune responses. J Neuroinf (2014) 11:97. doi: 10.1016/j.jneuroinf.2014.07.014

18. Yang B, Yang, Xu Bu, Fu Ji, Xu Q, Li L, et al. MiR-155 and MiR-146a collectively regulate meningitis Escherichia coli infection-mediated neuroinflammatory responses. J Neuroinflamm (2021) 18:114. doi: 10.1186/s12974-021-02165-4

19. Tili E, Michaille J, Cimino A, Costeuan A, Damiroz CD, Adair B, et al. Modulation of MiR-155 and MiR-124-1 levels following Pseudomonas aeruginosa/TNF-alpha stimulation and their possible roles in regulating the response to endotoxin shock. J Immunol (2017) 199:5802–9. doi: 10.4049/jimmunol.179.8.5802

20. Tacke F, Spelmann M, Luci M, Barquet J, Le Roy D, Cardenas BV, et al. MiR-155 Predicts Long-Term Mortality in Critically Ill Patients Younger than 65 Years. Mediators Inflamm (2019) 2019:6714080. doi: 10.1155/2019/6714080

21. Yuan JY, Wang F, Yu J, Yang GH, Liu XL, Zhang JW. MicroRNA-223 reversely regulates erythroid and megakaryocyte differentiation of K562 cells. Cell Mol Med (2009) 13:4551. doi: 10.1111/j.1582-4934.2008.00585.x

22. Aziz F. The emerging role of MiR-223 as novel potential diagnostic and therapeutic target for inflammatory disorders. Cell Mol Med (2016) 2016:1–6. doi: 10.1007/s10575-016-0403-3
339. Sun W, Shen W, Yang S, Hu F, Li H, Zhu TH. MiR-223 and MiR-142 attenuate hematopoietic cell proliferation, and MiR-223 positively regulates MiR-142 through LMO2 isoforms and CEBP-beta. *Cell Res* (2010) 20:1158–69. doi: 10.1038/cr.2010.134

340. Yuan X, Berg N, Lee JW, Le TT, Neudecker V, Jing N, et al. MicroRNA MiR-223 as regulator of innate immunity. *J Leukoc Biol* (2018) 104:515–24. doi: 10.1002/jlb.3MR0218-079R

341. Liu Y, Wang R, Jiang J, Yang B, Cao Z, Cheng X. MiR-223 is upregulated in monocyttes from patients with tuberculosis and regulates function of monocyte-derived macrophages. *Mol Immunol* (2015) 67:475–81. doi: 10.1016/j.molimm.2015.08.006

342. Chen KW, Demarco B, Brue P. Beyond inflamasomes: emerging function of gasdermin d during apoptosis and NETosis. *EMBO J* (2020) 39:e103397. doi:10.15252/embr.2019103397

343. Bauerfeind F, Rieger A, Schildberg FA, Knolle PA, Schmid-Burgk JL, Hornung V. NLRP3 inflammasome activity is negatively controlled by MiR-223. *J Immunol* (2012) 189:4175–81. doi: 10.4049/jimmunol.1201516

344. Chen Q, Wang H, Liu Y, Song Y, Lai L, Han Q, et al. Inducible microRNA-223 down-regulation promotes TLR-triggered IL-6 and IL-1beta production in macrophages by targeting STAT3. *PloS One* (2012) 7:e42971. doi: 10.1371/journal.pone.0042971

345. Zhang N, Fu L, Bu Y, Yao Y, Wang Y. Downregulated expression of MiR-223 promotes Toll-like receptor-activated inflammatory responses in macrophages by targeting RhoB. *Mol Immunol* (2017) 91:42–8. doi: 10.1016/j.molimm.2017.08.026

346. Feng Z, Qi S, Zhang Y, Qi Z, Yan L, Zhou J, et al. Ly6Gr+ neutrophil-derived MiR-223 inhibits the NLRP3 inflammasome in mitochondrial DAMP-induced acute lung injury. *Cell Death Dis* (2017) 8:e37549. doi: 10.1038/cddis.2017.549

347. Dorhoi A, Lannaconne M, Farinacci M, Fae KC, Schreiber J, Mora-Alves P, et al. MicroRNA-223 controls susceptibility to tuberculosis by regulating lung neutrophil recruitment. *J Clin Invest* (2013) 123:4836–48. doi: 10.1172/JCI67604

348. Lou J, Wang Y, Zhang Z, Qiu W. Activation of MMPs in Macrophages by Mysobacterial Infections involves the MiR-223–BMAL1 Signaling Pathway. *J Cell Biochem* (2017) 118:4804–12. doi: 10.1002/jcb.26150

349. Neudecker V, Brodsky KS, Clambey ET, Schmidt EP, Packard TA, Davenport B, et al. Neutrophil transfer of MiR-223 to lung epithelial cells dampens acute lung injury in mice. *Sci Transl Med* (2017) 9:1–19. doi: 10.1126/scitranslmed.aah5360

350. Rodell MP, Bracke KR, Heijnik IH, Maes T. MiR-223: A Key Regulator in the Innate Immune Response in Asthma and COPD. *Front Med (Lausanne)* (2020) 7:196. doi: 10.3389/fmed.2020.00196

351. Shen X, Zhang J, Huang Y, Tong J, Zhang L, Zhang Z, et al. Accuracy of circulating microRNAs in diagnosis of sepsis: a systematic review and meta-analysis. *J Intensive Care* (2020) 8:84. doi:10.1186/s40560-020-00497-6

352. Calandra T, Roger T. Macrophage migration inhibitory factor: a regulator of innate immunity. *Nat Rev Immunol* (2003) 3:791–800. doi: 10.1038/nri1200

353. Froidevaux C, Roger T, Martin G, Glausser MP, Calandra T. Macrophage migration inhibitory factor and innate immune responses to bacterial infections. *Crit Care Med* (2001) 29:S13–5. doi:10.1097/00003246-200110010-00006

354. Kershbaumer RJ, Rieger M, Volkel D, Le Roy D, Roger T, Garbaravicene J, et al. Neutralization of macrophage migration inhibitory factor (MIF) by fully human antibodies correlates with their specificity for the beta-sheet structure of MIF. *J Biol Chem* (2012) 287:7446–55. doi: 10.1074/jbc.M111.329864

355. Roger T, Delaloye J, Chanson AL, Giuday M, Le Roy D, Calandra T. Macrophage migration inhibitory factor deficiency is associated with impaired killing of gram-negative bacteria by macrophages and increased susceptibility to Klebsiella pneumoniae sepsis. *J Infect Dis* (2013) 207:331–9. doi:10.1093/infdis/jit673

356. Roger T, Schneider A, Weier M, Sweep FC, Le Roy D, Bernhagen J, et al. High expression levels of macrophage migration inhibitory factor sustain the innate immune responses of monocytes. *Proc Natl Acad Sci U.S.A.* (2016) 113:E997–1005. doi: 10.1073/pnas.1514018113

357. Savva A, Brouwer MC, Roger T, Valls Seron M, Le Roy D, Ferwerda B, et al. Functional polymorphisms of macrophage migration inhibitory factor as predictors of morbidity and mortality of pneumococcal meningitis. *Proc Natl Acad Sci U.S.A.* (2016) 113:5397–602. doi: 10.1073/pnas.1520727113

358. Sweeny TE, Shidham A, Wong HR, Khatri P. A comprehensive time-course-based multicohort analysis of sepsis and sterile inflammation reveals a robust diagnostic gene set. *Sci Transl Med* (2015). doi:10.1126/scitranslmed.aaf5993

359. McHugh L, Seldon TA, Branden RA, Kirk JT, Rapisarda A, Sutherland AJ, et al. A molecular host response assay to discriminate between sepsis and infection-negative systemic inflammation in critically ill patients: discovery and validation in independent cohorts. *PloS Med* (2015) 12:e1001916. doi: 10.1371/journal.pmed.1001916

360. Sweeny TE, Wong HR, Khatri P. Robust classification of bacterial and viral infections via integrated host gene expression diagnostics. *Sci Transl Med* (2016). doi:10.1126/scitranslmed.aaf7165

361. Sicluna BP, Klein Klowenberg PM, van Vught LA, Wiewel MA, Ong DS, Zwinderman AH, et al. A molecular biomarker to diagnose community-acquired pneumonia on intensive care unit admission. *Am J Respir Crit Care Med* (2015) 192:826–35. doi:10.1164/rcrm.201502-0355OC

362. Sicluna BP, van Vught LA, Zwinderman AH, Wiewel MA, Davenport EE, Burnham KL, et al. Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study. *Lancet Respir Med* (2017) 5:816–26. doi:10.1016/S2213-2600(17)30294-1

363. Reyes M, Filbin MR, Bhattacharyya RP, Billman K, Eisenhaure T, Hung DT, et al. An immune-cell signature of bacterial sepsis. *Nat Med* (2020) 26:333–40. doi: 10.1038/s41591-020-0752-4

364. Krolicki J, Sobolewska A, Lejnowski D, Collawn JF, Bartszewski R, microRNA single nucleotide polymorphism influences on microRNA biogenesis and mRNA target specificity. *Gene* (2018) 640:66–72. doi: 10.1016/j.gene.2017.10.021