oxygen

MDPI

Systematic Review

Pre-Clinical Studies of MicroRNA-Based Therapies for Sepsis: A Scoping Review

Amin M. Ektesabi [1,2], Julia Simone [1], Chirag Vaswani [1,3], Greaton W. Tan [1,3], Yanbo Wang [1,3], Jacqueline L. Pavelick [1,2], Xiao Wu [1], Janice Tai [1], Sahil Gupta [1], James N. Tsoporis [1] and Claudia C. dos Santos [1,2,*]

[1] Keenan Research Centre for Biomedical Science, Unity Health—St. Michael's Hospital, Toronto, ON M5G 1W8, Canada; amin.ektesabi@mail.utoronto.ca (A.M.E.); c.vaswani@mail.utoronto.ca (C.V.); michaelyanbo.wang@mail.utoronto.ca (Y.W.); maxxiao.wu@mail.utoronto.ca (X.W.); janice.tai@mail.utoronto.ca (J.T.)
[2] Institute of Medical Sciences, Faculty of Medicine, University of Toronto, Toronto, ON M5S 1A8, Canada
[3] Department of Physiology, Temerty Faculty of Medicine, University of Toronto, Toronto, ON M5S 1A8, Canada
* Correspondence: claudia.santos@utoronto.ca; Tel.: +1-(416)-864-6060 (ext. 3198)

Abstract: Background: Sepsis is a severe and life-threatening condition triggered by a dysregulated response to infection, leading to organ failure and, often, death. The syndrome is expensive to treat, with survivors frequently experiencing reduced quality of life and enduring various long-term disabilities. The increasing understanding of RNA, RNA biology, and therapeutic potential offers an unprecedented opportunity to develop innovative therapy. Objective: This study is a scoping review focusing on pre-clinical studies of microRNA (miRNA)-based therapies for sepsis. Methodology: A scoping review. The search strategy identified papers published in PubMed until 15 October 2023, using the keywords (microRNA) AND (sepsis) AND (animal model). Inclusion criteria included papers that used either gain- or loss-of-function approaches, excluding papers that did not focus on microRNAs as therapy targets, did not include animal models, did not show organ failure-specific assessments, and focused on microRNAs as biomarkers. The PRISMA-ScR guideline was used in this study. Results: A total of 199 articles were identified that featured the terms "microRNA/miRNA/miR", "Sepsis", and "animal model". Of these, 51 articles (25.6%) employed miRNA-based therapeutic interventions in animal models of sepsis. Of these, 15 studies extended their inquiry to include or reference human clinical data. Key microRNAs of interest and their putative mechanisms of action in sepsis are highlighted. Conclusions: The body of work examined herein predominantly addresses various dimensions of sepsis-induced organ dysfunction, supporting the emerging role of miRNAs as potential therapeutic candidates. However, nearly 5% of papers on miR-based therapy have been retracted over the past 5 years, raising important concerns regarding the quality and complexity of the biology and models for assessing therapeutic potential.

Keywords: sepsis; microRNAs; inhibitors; mimics; antagomirs; infection; host response

Citation: Ektesabi, A.M.; Simone, J.; Vaswani, C.; Tan, G.W.; Wang, Y.; Pavelick, J.L.; Wu, X.; Tai, J.; Gupta, S.; Tsoporis, J.N.; et al. Pre-Clinical Studies of MicroRNA-Based Therapies for Sepsis: A Scoping Review. *Oxygen* **2024**, *4*, 20–36. https://doi.org/10.3390/oxygen4010002

Academic Editor: Gerardo Ferbeyre

Received: 1 December 2023
Revised: 18 January 2024
Accepted: 22 January 2024
Published: 29 January 2024

1. Introduction

Sepsis is a complex systemic disease of dysregulated response to infection associated with multi-organ dysfunction [1–3] for which no specific therapies exist. Current estimates are >48.9 million cases and 11.0 million deaths per year [4]. As the incidence rises (8.7% per year), the World Health Organization (WHO) has declared sepsis a global priority. Treating sepsis and related readmissions costs $62 and 3.5 billion annually, respectively [5]. Poor long-term outcomes in survivors are also increasingly recognized [6,7]. One intensive care unit (ICU) admission shortens the life span by four years [8]. Sequelae include physical, cognitive, and psychological disability [9]. Mortality in contemporary clinical trials ranges between 33 and 61% [10], and the failure of proposed therapies may be partially explained

by failure to unravel nuanced pathobiology, patient heterogeneity, and an overreliance on "one-size-fits-all" treatment approaches.

Sepsis-induced organ dysfunction is a multifaceted condition that affects various vital organs, including the lungs, kidneys, muscles, heart, and liver [11,12]. Characterized by a cascade of inflammatory and immunological processes, sepsis-induced organ dysfunction leads to reversible and irreversible physiological alterations in impacted organs, culminating in widespread tissue damage and organ failure [1]. A crucial unresolved problem is that mechanisms leading to organ failure may be organ-specific—therefore, not amenable to a single treatment approach.

MicroRNAs (miRs), 20–24 non-coding nucleotides, function at the post-transcriptional level by binding to regulatory sequences on target genes, orchestrating the response to infection, injury, inflammation, and oxidative stress. Their specificity and coordinated activity have made the development of a completely innovative class of drugs possible, with RNA itself acting as the drug target. The distinct advantage of RNA therapeutics includes unparalleled specificity, the ability to target traditionally undruggable targets, and the possibility of rapid and efficient regulation of RNA in situ. There are over 30 clinical trials of miR-based therapies that are being met with different degrees of success—this suggests that there may be important knowledge gaps that need to be considered [13]. Translating laboratory findings into successful clinical treatments is a tremendous challenge in sepsis. Careful consideration of the existing pre-clinical data is critical before embarking upon clinical studies.

To systematically map the research on the preclinical application of miRNA-based therapeutics for sepsis, as well as to identify and understand the current state of knowledge and existing data gaps, clarify how microRNA therapeutic targets are being selected and used in pre-clinical models, determine what sepsis-organ injury models are being used, and identify the types and available evidence for specific microRNAs.

2. Methods

The search strategy was conducted using prespecified eligibility criteria. Articles included had to be primary original publications that examined the use of miRNA mimics or inhibitors to treat sepsis-induced organ dysfunction in animal models of sepsis.

The information source and search strategy was limited to PubMed, which was searched until 15 October 2023, using the keywords (microRNA) AND (sepsis) AND (animal model). We specifically excluded papers that did not focus on microRNAs as the targets of therapy, that did not include animal models, that did not show organ failure-specific assessments, and that focused on microRNAs as biomarkers. The PRISMA-ScR guideline was used in this study.

Data revisions was performed by multiple reviewers who independently extracted data from each eligible article focused on miRNA interventions in sepsis animal models. A summary of miRNAs targeting genes and pathways, as well as an experimental model and the beneficial effect on the targeted organ, is presented in this scoping review. If there were any data on the regulation of oxidative stress pathways, we also included them in this study.

3. Results

The scoping review strategy is shown in Figure 1. A total of 199 articles were identified and reviewed, of which 51, representing approximately 25.6%, utilized miRNAs as a therapeutic intervention in preclinical models of sepsis. Table 1 summarizes the results. Figure 2 highlights key pathways modulated in preclinical studies of miR-based therapies. Key findings from the 15 studies that extended their inquiry to include or reference relevant findings from human clinical data are summarized below.

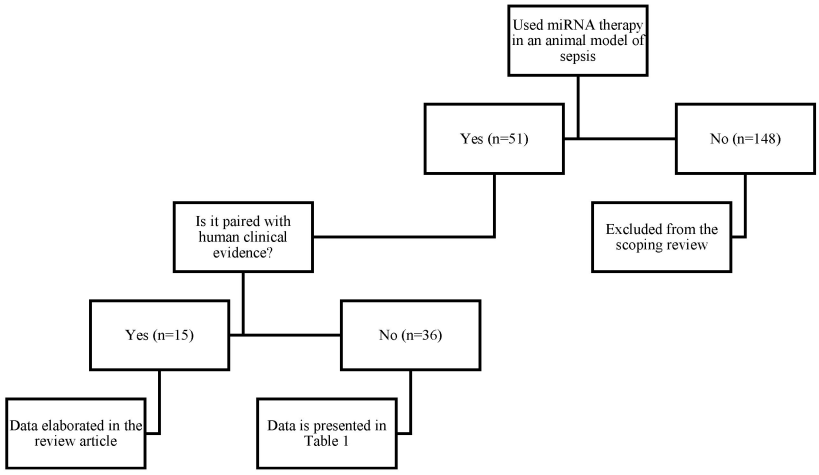

Figure 1. Selection process of articles utilizing miRNA therapy in preclinical sepsis models.

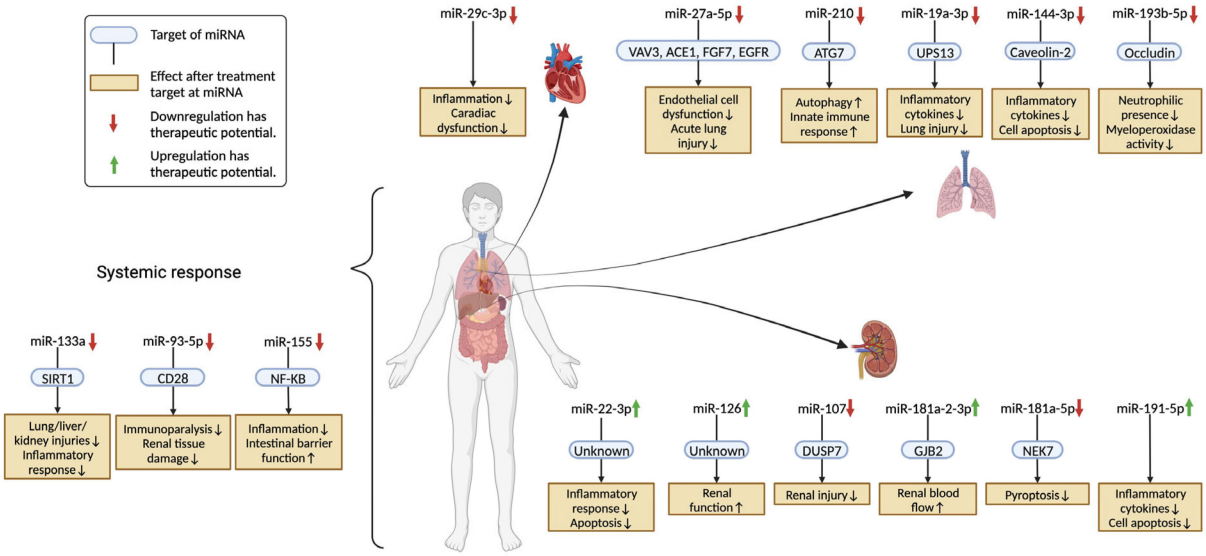

Figure 2. Schematic overview of miRNA therapeutic pathways in sepsis: bridging pre-clinical models and clinical evidence.

Table 1. Summary of reviewed articles on the use of miRNAs as therapeutic interventions in preclinical models of sepsis.

MiRNA Treatment of Interest	Species	Model	Effect	Change in Mortality	Clinical Relevance	Ref
MiR-155 mimic	Mouse (C57BL/6J)	CLP	Protected against cardiac dysfunction in late sepsis	Improved survival	Yes	[14]
MiR-140 siRNA	Mouse (BALB/c)	LPS (15 mg/kg)	Restored Wnt11 expression	Did not report	No evidence	[15]
MiR-203 mimic or inhibitor	Mouse (Kunming)	CLP	Reduced VNN1 expression	Did not report	Shown computationally	[16]
MiR-34b-3p agomiR	Mouse (C57BL/6N)	CLP	Reduced TNF-α, IL-1β, and IL-6	Improved survival	No evidence	[17]
MiR-214 mimic or inhibitor adenovirus	Mouse (Kunming)	CLP	Mimic reduced GLP-1R, AMPK, oxidative stress, and inflammation	Did not report	No evidence	[18]
MiR-126 overexpression vector	Mouse (C57BL/6J)	CLP, LPS (40 mg/kg)	Reduced proinflammatory mediators	Improved survival	Yes	[19]

Table 1. *Cont.*

MiRNA Treatment of Interest	Species	Model	Effect	Change in Mortality	Clinical Relevance	Ref
MiR-193b-5p inhibitor	Mouse (C57BL/6)	LPS (10 mg/kg)	Attenuated decreased occludin expression	Improved survival	Yes	[20]
MiR-27a-5p inhibitor	Mouse (C57BL/6)	LPS (dose unspecified)	Mitigated cellular infiltration but not protein and IgM leakage into alveolar space	Improved survival	No evidence	[21]
MiR-103a-3p agomiR lentivirus	Mouse (C57BL/6)	LPS (1 mg/kg)	Downregulated HMGB1, leading to attenuation of inflammatory response	Improved survival	Yes	[22]
MiR-101 agomiR	Rat (Sprague Dawley)	CLP	Improved left ventricle ejection fraction	Did not report	Yes	[23]
MiR-340-5p overexpression AAV	Mouse (C57BL/6J)	LPS (10 mg/kg)	Reduced myocardial oxidative stress injury and MyD88 expression	Did not report	No evidence	[24]
MiR-126 mimic or inhibitor	Rat (Sprague Dawley)	CLP	Mimic suppressed adhesion molecule expression and reduced immune cell accumulation in the myocardium	Mimic improved survival, inhibitor worsened survival	Shown in another study	[25]
MiR-210-3p inhibitor adenovirus	Mouse (strain unspecified)	CLP	Improved vascular density and autophagosome formation, increased ATG7 expression	Improved survival	Yes	[26]
MiR-21 mimic	Rat (Wistar)	CLP	Reduced sepsis-induced kidney cell apoptosis via the PTEN/PI3K/AKT signaling pathway	Did not report	No evidence	[27]
MiR-579-3p inhibitor lentivirus	Mouse (C57BL/6)	CLP	Enhanced SIRT1 expression, leading to reduced weight loss and renal injuries	Improved survival	No evidence	[28]
MiR-133a antagomiR	Mouse (C57BL/6J)	CLP	Reduced organ injury and inflammation, potentially through SIRT1 rescue	Did not report	Yes	[29]
MiR-93-5p antagomiR	Mouse (C57BL/6)	CLP	Reduced inflammatory monocytes and increased circulating effector memory T cells, especially of the CD4+ subset	Improved survival	Yes	[30]
MiR-130-3p mimic	Mouse (C57BL/6)	CLP	Reduced eCIRP-induced TNF-α and IL-6 proteins	Improved survival	No evidence	[31]
MiR-181-5p agomiR lentivirus	Mouse (C57BL/6J)	CLP	Alleviated sepsis-induced systemic inflammatory disease, may function as an HMGB1 antagonist	Improved survival	No evidence	[32]
MiR-19a-3p antagomiR	Mouse (C57BL/6)	LPS (1 mg/kg)	Reduced lung damage	Did not report	Reported in Chen et al. (2019)	[33]
MiR-21 mimic	Mouse (C57BL/6)	CLP	Ameliorated hyperoside-induced negative cardiac effects	Did not report	No evidence	[34]
MiR-22-3p mimic adenovirus	Rat (Sprague Dawley)	CLP	Protected against sepsis-induced acute kidney injury, possibly by repressing PTEN	Did not report	Yes	[35]
MiR-146a-expressing plasmid	Mouse (C57BL/6)	CLP	Prevented excessive inflammation and sepsis-induced multiple organ injury	Improved survival	No evidence	[36]
MiR-29c-3p antagomiR	Rat (Sprague Dawley)	CLP	Reduced sepsis-induced cardiac dysfunction and inflammatory response	Did not report	Yes	[37]

Table 1. *Cont.*

MiRNA Treatment of Interest	Species	Model	Effect	Change in Mortality	Clinical Relevance	Ref
MiR-205 agonist	Rat (Sprague Dawley)	CLP	Reduced kidney injury and protein expression of HMGB1 and PTEN	Did not report	No evidence	[38]
MiR-182-5p inhibitor lentivirus	Mouse (C57BL/6J)	*S. aureus* pneumonia	Repressed intestinal epithelial cell apoptosis and rescued the cell viability	Did not report	No evidence	[39]
MiR-23a-3p overexpression AAV	Mouse (C57BL/6)	CLP	Ameliorated sepsis-induced acute kidney injury, targeted FKBP5	Did not report	Yes	[40]
MiR-145 agomiR	Mouse (strain unspecified)	LPS (4 mL/kg)	Attenuated LPS-induced sepsis	Improved survival	No evidence	[41]
MiR-106b-5p inhibitor vector	Mouse (C57BL/6)	CLP	Reduced the cardioprotective effects of matrine administration	Did not report	No evidence	[42]
MiR-802 mimic	Mouse (BALB/c)	LPS (50 mg/kg)	Protected against LPS-induced acute lung injury by downregulating Peli2	Did not report	No evidence	[43]
MiR-926-3p inhibitor	Mouse (C57BL/6)	CLP	Enhanced autophagy through regulation of the mTOR signaling pathway	Did not report	Yes	[44]
MiR-144-3p agomiR or antagomiR	Mouse (BALB/c)	LPS (10 mg/kg)	AntagomiR alleviated inflammation and cell apoptosis induced by LPS	Did not report	Yes	[45]
MiR-130b agomiR	Mouse (C57BL/6J)	LPS (40 mg/kg)	Attenuated LPS-induced vascular inflammation	Did not report	No evidence	[46]
MiR-129-5p agomiR	Mouse (C57BL/6)	CLP	Attenuated inflammatory response, apoptosis, lung wet/dry weight ratio, and myeloperoxidase activity induced by CLP	Did not report	No evidence	[47]
MiR-199a antagomiR	Mouse (C57BL/6)	*Pseudomonas aeruginosa* burn	Protected lung tissue against sepsis-induced ARDS by upregulating SIRT1	Did not report	No evidence	[48]
MiR-181a-2-3p agomiR or antagomiR	Mouse (C57BL/6J)	CLP	AgomiR alleviated the inflammatory response and cell apoptosis by upregulating GJB2 expression	Did not report	Shown computationally	[49]
MiR-335 precursor or inhibitor	Mouse (Kunming)	CLP	Ameliorated myocardial injury following sepsis	Did not report	No evidence	[50]
MiR-34a agomiR or antagomiR	Mouse (C57BL/6)	CLP	AntagomiR reduced lung injury, inflammation, and oxidative stress, potentially through SIRT1 and ATG4B rescue	AgomiR worsened survival, antagomiR improved survival	No evidence	[51]
MiR-21 and miR181b antagomiR combination therapy	Mouse (BALB/c)	CLP	Restored Gr1+ CD11b+ cell differentiation and maturation	Improved survival	No evidence	[52]

Table 1. *Cont.*

MiRNA Treatment of Interest	Species	Model	Effect	Change in Mortality	Clinical Relevance	Ref
MiR-146a overexpression lentivirus	Mouse (C57BL/6)	CLP	Attenuated sepsis-induced cardiac dysfunction by preventing NF-κB activation, inflammatory cell infiltration, and inflammatory cytokine production via targeting of IRAK and TRAF6	Improved survival	No evidence	[36]
MiR-129-5p agomiR	Mouse (C57BL/6J)	LPS (20 mg/kg)	Reduced podocyte damage, inflammation, and apoptosis; targets the HMGB1/TLR2/TLR4/NF-κB axis	Improved survival	No evidence	[53]
MiR-124a agomiR or antagomiR	Mouse (BALB/c)	LPS (5 mg/kg)	AgomiR reduced LPS-induced cardiac dysfunction and apoptosis; targets STX2	Did not report	No evidence	[54]
MiR-217 agomiR or antagomiR	Mouse (C57BL/6)	CLP	AntagomiR demonstrated anti-inflammatory and anti-oxidant effects, beneficial effects reversed with SIRT1 inhibition	AgomiR worsened survival, antagomiR improved survival	No evidence	[55]
MiR-125b overexpression lentivirus	Mouse (C57BL/6)	CLP	Attenuated sepsis-induced cardiac dysfunction	Improved survival	No evidence	[56]
MiR-148a agomiR or antagomiR	Rat (Sprague Dawley)	CLP	AgomiR rescued CIRC-Ttc3 in sepsis-induced acute kidney injury	Did not report	No evidence	[57]
MiR-27a antagomiR	Mouse (C57BL/6)	LPS (5 mg/kg)	Reduced the beneficial effects of paclitaxel in reducing sepsis-induced liver injury	Worsened survival advantage conferred by paclitaxel	No evidence	[58]
MiR-26a-5p agomiR or antagomiR	Mouse (C57BL/6J)	LPS (10 mg/kg)	AgomiR suppressed LPS-induced inflammation and apoptosis of cardiomyocytes	Did not report	No evidence	[59]
MiR-93-5p mimic or inhibitor EVs	Mouse (C57BL/6)	CLP	Mimic EVs attenuated multiple organ injury, vascular leakage, inflammation, and apoptosis	Inhibitor worsened survival	Shown in previous work	[60]
MiR-107 inhibitor	Mouse (C57BL/6J)	LPS (8 mg/kg)	Reduced sepsis-induced acute kidney injury, potentially through DUSP7 rescue	Did not report	Yes	[61]

3.1. Acute Lung Injury (ALI)

3.1.1. miR-27a-5p [21]

Increased expression of miR-27a-5p was observed in patients with ARDS who died and were found to have diffuse alveolar damage (DAD) upon autopsy, as opposed to those without DAD. The guanine nucleotide exchange factor VAV3 was predicted and subsequently confirmed to be a key target of miR-27a-5p through a luciferase reporter system and siRNA knockdown. It was recognized that the regulatory role of miR-27a-5p was not restricted to VAV3, as other targets, including angiotensin-converting enzyme 1 (ACE1), Fibroblast Growth Factor 7 (FGF7), and epidermal growth factor receptor (EGFR), were also modulated, as demonstrated in both in vitro and in vivo studies. The Vav protein family, which includes Vav1, Vav2, and Vav3, is activated via tyrosine phosphorylation

triggered by specific receptor signals and is integral to various cellular functions and the immune response to bacterial products. In vitro and in vivo inhibition of miR-27a-5p was associated with a significant reduction in endothelial cell dysfunction and markers of acute lung injury, respectively. Further investigations are necessary to fully elucidate the roles of VAV3 and additional targets of miR-27a-5p.

In patients with sepsis, elevated circulating miR-27a levels were positively correlated with serum malondialdehyde, a marker of oxidative stress, and negatively correlated with serum glutathione peroxidase, another oxidative stress indicator. This suggests that miR-27a is closely linked with oxidative stress in sepsis [58].

3.1.2. miR-210 [62]

Extracellular vesicles (EVs) function as pivotal paracrine factors for facilitating intercellular communication, particularly as carriers of microRNAs. The encapsulation of miRNA-210 within these vesicles has been shown to reduce lung damage associated with sepsis, as evidenced in murine models of polymicrobial sepsis. Specifically, miR-210-3p has emerged as a potential influential agent in developing sepsis-induced acute lung injury [63]. The gene autophagy-related 7 (ATG7), essential for autophagosome formation and significant in the innate immune response to bacterial infections, is a likely target of miR-210-3p. Decreased ATG7 expression impairs the autophagic process [64]. Previous studies show an increase in miR-210 expression levels in the plasma of patients suffering from sepsis-induced acute kidney injury. Increased miR-210 was also correlated with higher mortality in septic patients [65]. While this miR was initially linked to sepsis-induced ALI, delivery of miR-210-3p via plasma EVs was found to attenuate lung injury. In a model of preclinical sepsis, miR-210-3p targets ATG7 to regulate autophagy and inflammatory activation in sepsis-induced ALI, suggesting that miR-210-3p may be a potentially promising therapeutic strategy for sepsis-induced ALI. Adenovirus-anti-miR-210-3p injections were used to knock down miR-210-3p in mice. The results also revealed that mice treated with anti-miR-210-3p exhibited a higher survival rate compared to those in the control group seven days following the induction of sepsis through cecal ligation and perforation surgery, thereby underscoring the pathophysiological significance of miR-210-3p and its critical role in the mechanisms leading to organ damage in sepsis, as well as its potential as a target for therapeutic interventions.

While miR-210-3p inhibitors abrogate them, the effects of oxidative stress in H9C2 cells are induced by septic serum. The promotion of stress-induced myocardial dysfunction (SIMD) pathogenesis by miR-210-3p, through targeting NDUFA4 which results in increased cardiomyocyte apoptosis and impaired mitochondrial function, was observed, emphasizing its significant role in oxidative stress responses [26].

3.1.3. miR-19a-3p [33]

The expression of miR-19a-3p in septic patients is increased [66]. Inflammatory responses in human and mouse immune cells, induced by lipopolysaccharide (LPS) stimulation, contributed to an increase in several miRNAs, including miR-19a-3p [67,68]. miR-19a-3p has been implicated in the regulation of a deubiquitination (DUB) enzyme, ubiquitin-specific protease 13 (USP13). Ubiquitination plays a vital role in TNF-α-mediated cell necrosis and sepsis-associated organ injury. Overexpression of USP13 was found to inhibit the secretion of inflammatory factors such as IL-6 and TNF-α [69]. Additionally, the inhibition of miR-19a-3p in LPS-treated mice showed an increase in expression of USP13, which ultimately resulted in reduced lung damage. These results imply that miR-19a-3p inhibition could mitigate sepsis-induced lung injury by increasing USP13 expression. This suggests that miR-19a-3p may be an effective marker and therapeutic target for treating sepsis-induced lung damage [70,71].

The expression of microRNAs such as miR-19a is controlled by ROS-sensitive transcription factors like NF-κB, indicating a link between microRNA dysregulation in tumorigenesis and oxidative stress [72].

3.1.4. miR-144-3p [45]

In malignant tumors, miR-144 has been reported to have tumor-suppressing properties [73,74]. Nonetheless, a pro-inflammatory effect of miR-144 was evidenced in a study on intracerebral hemorrhage, where the initiation of microglial autophagy and inflammation was facilitated by the regulation of the mammalian target of rapamycin (mTOR) through miR-144. In cases of congenital heart disease, miR-144 seems to target TBX1, affecting the proliferation and apoptosis of cardiomyocytes in a JAK2/STAT1-dependent manner.

Caveolae are membrane microdomains and Caveolin family proteins, such as Caveolin-1 and Caveolin-2, interface with the extracellular environment to transduce chemical or physical signals as a series of molecular events to the inside of the cell. The balance between Caveolin-1 and Caveolin-2 is important for the expression of nitric oxide synthase (iNOS) and progression toward sepsis. Caveolin-2 also inhibits the release of inflammatory cytokines like TNF-α, IL-1β, and IL-6 and suppresses cell apoptosis in murine models of acute lung injury [45]. Using dual luciferase reporter assays, Caveolin-2 was shown to be a direct target of miR-144-3p [45]. In LPS-induced ALI mouse models, the modulation of Caveolin-2 expression by miR-144-3p led to an increase in inflammatory response, oxidative stress, and apoptosis, suggesting that the inhibition of miR-144-3p may function therapeutically in sepsis. Additionally, in patients with septic ALI, the expression levels of miR-144-3p were significantly higher compared to healthy volunteers, highlighting its potential involvement in the pathology of septic ALI.

3.1.5. miR-193b-5p [20]

miR-193b-5p was identified as one of the top-regulated microRNAs in the lungs of septic mice treated with intravenous mesenchymal stromal cells. Using miRNA:mRNA paired analysis, this group identified the tight junction protein occludin as a critical target of miR-193b-5p. Occludin and tight junctions were preserved in miR-193b-deficient mice exposed to sepsis-induced lung injury. In a model of LPS-induced ALI, mice were randomized to receive either an inhibitor of miR-193b-5p, an equal volume of saline, or a non-coding RNA negative control, combined with high perfect (HPF) reagent administrated intratracheally. Assessments of lung microvascular permeability showed that the inhibition of miR-193b-5p significantly mitigated the loss of barrier function and reduced protein and IgM extravasation and neutrophil infiltration in the bronchoalveolar fluid. Lung tissues from mice treated with the inhibitor also had decreased myeloperoxidase activity. Importantly, the expression levels of miR-193b-5p were significantly increased in areas of biopsy-proven DAD compared to non-DAD in lungs from patients who died with ARDS. The relative contribution of occludin and the therapeutic potential of miR-193b-5p inhibition were further demonstrated in a model of virus-induced acute respiratory distress; the authors further demonstrated that miRNA administration in various tissues regulates genes associated with pattern recognition, macrophage activation, oxidative stress, inflammation, and phagocytosis [20].

3.2. Systemic Response

3.2.1. miR-133a [29]

Recent studies have demonstrated that miR-133a, a previously known muscle-specific microRNA, is significantly involved in various medical conditions such as fibrosis, cancer development, and inflammation [75,76]. miR-133a has been reported to be upregulated in sepsis and to regulate the NAD-dependent deacetylase sirtuin-1 (SIRT1). SIRT1 is involved in genomic maintenance, metabolic regulation, tumor inhibition, and inflammation. High expression of SIRT1, particularly in the thymus, is associated with immunity and reduced production of inflammatory cytokines in macrophages and dendritic cells. Mice lacking SIRT1 are highly susceptible to sepsis-induced inflammatory lung injury. This ties into the broader context where oxidative stress, a common factor in endothelial dysfunction and vascular diseases, is known to impair SIRT1 expression/activity, thus disrupting endothelial

homeostasis and emphasizing the interconnected roles of miR-133a, SIRT1, and oxidative stress in various medical conditions.

Circulating levels of miR-133a have been found to be significantly increased in sepsis patients compared to healthy individuals. In a preclinical model of polymicrobial sepsis induced by cecal ligation and puncture (CLP), miR133a was significantly increased compared to sham-operated animals, suggesting an upregulation of miR-133a in sepsis. Knockdown of miR-133a, in this CLP model, resulted in reduced lung, liver, and kidney injury, associated with a marked reduction in inflammation. In vitro, delivery of the miR-133a inhibitor was found to abrogate the inflammatory response to LPS in RAW264.7 macrophages. SIRT1 was identified as a target of miR-133a, and silencing of SIRT1 was shown to reverse the anti-inflammatory effects of the miR-133a inhibitor in LPS-stimulated sterile sepsis in an in-vitro cell model This study highlights the critical interaction between miR-133a and SIRT1 in sepsis pathology [29].

3.2.2. miR-93-5p [30]

Dragomir et al. have identified miR-93-5p as a promising therapeutic target for sepsis in their studies involving human samples and various mouse models. This group observed that miR-93-5p levels were upregulated in the peripheral blood mononuclear cells (PBMCs) of patients with sepsis and the plasma of mice subjected to CLP-induced sepsis. This upregulation was influenced further by the introduction of miR-K12-12, a viral miRNA demonstrated to bind to TLR8 and play a role in the pathophysiology of sepsis, leading to increased miR-93-5p levels. The expression of miR-93-5p across different immune cell types was also evaluated, suggesting its potential role in regulating immune cells.

This group noted an increase in miR-93-5p expression in sepsis models using both Gram-positive and Gram-negative bacteria in baboons, indicating that the dysregulation of miR-93-5p in sepsis might not depend on the type of causative bacteria. The plasma levels of miR-93-5p correlate with significant clinical parameters in sepsis, including various sepsis severity scores and the absolute lymphocyte count.

In treatment trials, mice treated with anti–miR-93-5p, compared to those that received a scrambled control miRNA, exhibited an immune response marked by increased levels of CD4+ and CD8+ effector memory T cells, decreased percentages of Ly6C^{hi} monocytes (monocytes expressing high levels of Ly6C) and F4/80+ mannose receptor C type-1 positive (MRC1, CD206) macrophages, and a reduction in PD-L1 expression on CSF1R+ monocytes, Ly6C^{hi} inflammatory monocytes, and F4/80+ macrophages. Treatment with anti-miR-93-5p mitigated CD8+ effector memory T-cell apoptosis seen in sepsis, particularly affecting the CD4+ subtype in both peripheral and lymphoid organs, which might help prevent immunoparalysis. Reductions in Ly6C^{hi} monocyte levels, normally protective against renal tissue damage during sepsis, underscore the potential of miR-93-5p as a target in sepsis therapy.

3.2.3. miR-155 [77]

In the scope of sepsis-induced intestinal barrier dysfunction, the role of microRNAs, specifically miRNA-155, emerges as pivotal yet not fully understood. Intestinal barrier dysfunction during sepsis is critically important as it allows the translocation of bacteria and their toxins from the gut into the systemic circulation, exacerbating the inflammatory response and potentially leading to multiple organ failure. In a model of sepsis induced by CLP, TNF-α-induced miR-155 expression was linked with intensified intestinal barrier failure. miR-155 has been implicated as a master regulator of nuclear factor kappa beta (NF-KB), a key transcription factor protein complex that controls transcription of DNA, cytokine production, oxidative stress, and cell survival. To study this connection, mice were administered a miR-155 inhibitor for three consecutive days, followed by CLP (pre-treatment). After 24 h, the expression of miR-155 and sepsis-induced injury was assessed. The miR-155 inhibitor significantly mitigated inflammation and enhanced intestinal barrier function, primarily by deactivating the NF-κB signaling pathway, which is also implicated

in oxidative stress responses. However, this study, which focused on pre-treatment and constrained to a 24 h model, did not assess mortality changes. It is also unclear whether the loss of intestinal barrier function in patients with sepsis is associated with an increase in circulating levels of miR-155. Further research will be required to elucidate the potential for miR-155 as a biomarker for intestinal barrier dysfunction and anti-miR-155-based therapy for sepsis.

3.3. Acute Kidney Injury (AKI)

3.3.1. miR-22-3p [35]

miR-22-3p was found to be significantly down-regulated in sepsis-induced acute kidney injury, both in vivo in a rat model and in vitro in LPS-induced HK-2 cells (human kidney 2 cells are a proximal tubular cell (PTC) line derived from normal kidney). The overexpression of miR-22-3p was observed to significantly suppress inflammation and cell apoptosis by targeting PTEN. These results suggested that miR-22-3p was protective in sepsis-induced acute kidney injury. Previous studies showed that the expression of miR-22-3p was significantly lower in patients with sepsis compared to healthy volunteers. In a rat sepsis-induced acute kidney injury model, the expression of miR-22-3p was substantially reduced. Overexpression of miR-22-3p was shown to reverse the pathological changes and reduce inflammatory expression levels in kidneys, indicating a protective role of miR-22-3p in acute kidney injury.

PTEN was identified as a direct target of miR-22-3p, and the down-regulation of PTEN by miR-22-3p was shown to suppress LPS-induced inflammation. These findings suggested that PTEN was a downstream functional regulator in the miR-22-3p-mediated modulation of sepsis-induced renal injury. Overexpression of miR-22-3p decreased the expression of p-65 and TLR4, as well as high-mobility group box 1 (HMGB1), which also heavily impacts the pathways regulating oxidative stress in kidneys. Taken together, in vitro and in vivo results demonstrated that the overexpression of miR-22-3p may exhibit beneficial effects by attenuating sepsis-induced or LPS-induced inflammation and apoptosis by targeting PTEN and inhibiting HMGB1/NF-Kb. These data suggest that the miR-22-3p/PTEN axis might be a promising therapeutic target for sepsis-induced acute kidney injury.

3.3.2. miR-126 [25]

Reductions in the levels of miR-126 found in the bloodstream during severe sepsis correlate with the incidence of acute kidney injury and increased mortality rates. A significant reduction in the circulating levels of miR-126 occurs within 24 h of sepsis onset in patients. A decrease in serum miR-126-3p is associated with severe sepsis. miR-126 has been found to play important roles in the regulation of both innate and adaptive immunity. In adaptive immunity, miR-126 cooperates with miR-135 to regulate T-helper type 2 (Th2) immune responses. In innate immunity, overexpression of miR-126 regulates Th1/Th17 responses affecting signal transduction and migration of immune cells [78,79]. In cell models, miR-126 was shown to target epidermal growth factor-like domain multiple 6 (EGFL6) and dyskeratosis congenita 1 (DKC1); miR-126 upregulation prevented podocyte injury in kidney cells [80]. In human microvascular endothelial cells, miR-126 administration prevented LPS-induced increases in HMGB1. Overexpression of miR-126 was found to protect against the breakdown of microvascular integrity and improve sepsis outcomes. The levels of the above oxidative stress molecules were reversed upon overexpression of miR-126 along with activation of the NF-κB signaling pathway [81]. Conversely, the survival rate in septic rats was decreased following the inhibition of miR-126, which influenced the differentiation of Th17/Treg through apoptosis, impacting the release and tissue infiltration of inflammatory factors [25].

Above and beyond the potential role of miR-126 as a biomarker of sepsis severity and acute kidney injury, various studies have looked at the therapeutic delivery of miR-126 for the treatment of periodontitis, cardiac tissue regeneration, hind limb ischemia-reperfusion injury, and CLP-induced sepsis [82–85]. In this CLP model, the team developed a nanoparti-

cle delivery system separately combining deacetylated poly-N-acetyl glucosamine (DEAC-pGlcNAc) polymers with miRNA-126-3p and miRNA-126-5p to test these combinations in vivo. Delivery of miR-126 in septic animals significantly improved survival, preserved vascular integrity, and modulated cytokine production. Further studies will be required to specifically determine the role of exogenous miR-126 regulation in sepsis-induced AKI.

3.3.3. miR-107 [61]

In septic patients with acute kidney injury, an elevation in miR-107 levels was observed within circulating endothelial cells, a finding echoed in the whole blood of LPS-exposed mice. miR-107 was implicated in the regulation of TNF-α secretion through its target, Dual-Specificity Phosphatase 7 (DUSP7), which acts on the substrates extracellular regulated kinase (ERK) 1 and ERK2 within an ERK-dependent pathway induced by LPS [86,87]. The suppression of miR-107 in septic AKI mouse models led to a noticeable reduction in renal injury. This inhibition preserved renal architecture, reduced tubular cell apoptosis and oxidative stress, maintained E-cadherin expression, and consequently diminished serum creatinine levels, underscoring the potential therapeutic benefits of targeting miR-107 in septic AKI.

3.3.4. miR-181a-2-3p [49]

Elevated levels of miR-181d-5p in the miR-181 family were linked to increased renal blood flow, demonstrating their protective effects in kidney disease [88]. In chronic obstructive pulmonary disease (COPD), the expression of miR-181a-2-3p was significantly reduced, and its silencing exacerbated COPD-related inflammation [49]. Through bioinformatics analysis, the gap junction beta-2 protein (GJB2) was identified as a target gene of miR-181a-2-3p, particularly in sepsis. The expression of GJB2 was higher in septic patients and lower in those recovering from sepsis-induced AKI, indicating its role as a critical gene in sepsis development and prognosis [49]. In the context of oxidative stress, miR-181a-2-3p inhibits oxidative stress by inhibiting early growth response factor 1 (EGR1) and NADPH oxidase 4 (NOX4) [89].

3.3.5. miR-181a-5p [90]

Various lines of evidence have implicated miR-181-5p in sepsis. In vitro, miR-181a-5p inhibition significantly inhibited LPS-enhanced inflammatory cytokine expression and NF-κB pathway activation, and these changes were eliminated by SIRT1 silencing; SIRT was found to be a direct target of miR-181a-5p. In vivo, miR-181a-5p inhibition significantly decreased the secretion of inflammatory factors and the plasma levels of biochemical markers of acute kidney injury (creatinine and blood urea nitrogen) and acute liver injury (aspartate aminotransferase and alanine aminotransferase). Importantly, the beneficial effects of miR-181-5p inhibition were abrogated by co-administration of a silencing RNA against SIRT1 [91]. In separate studies, miR-181-5p was found to be important in the pyroptosis of kidney cells in a septic model of AKI through downregulation of NEK7. NEK7 is a member of NIMA-related kinases (NEK proteins) that binds to NLRP3, acting downstream of potassium efflux to regulate NLRP3 oligomerization and activation. miR-181a-5p inhibits pyroptosis through the downregulation of NEK7 in LPS-induced HK-2 cells and CLP-induced mice, strongly suggesting that miR-181-5p may be an important therapeutic target for the treatment of sepsis-induced AKI [92]. In other independent studies, miR-181a-5p directly targeted the 3′ untranslated region of PPARα in vivo. PPARα plays a protective role in sepsis. Pparα deficiency impairs fatty acid utilization in the liver during sepsis. Hepatocyte Pparα deficiency worsens the outcome of bacterial infections. In a model of rat sterile sepsis induced by LPS, the long non-coding RNA (lncRNA) colorectal neoplasia differentially expressed (CRNDE) protected animals from sepsis-induced organ injury by "mopping" up circulating miR-181-5p, suggesting that endogenous mechanisms exist to reduce miR-181-5p levels and limit its injurious potential during sepsis [90].

3.3.6. miR-191-5p [93]

Studies revealed that miR-191-5p levels were notably lower in septic acute kidney injury (AKI) patients compared to healthy individuals, and this reduction was also significant when comparing septic AKI with septic non-AKI patients. Administration of miR-191-5p mimics in septic rat models demonstrated a marked reduction in renal injury scores, along with a substantial decrease in inflammatory cytokines and apoptotic proteins. These findings suggest a protective effect of miR-191-5p in septic AKI. Moreover, the miR-191-5p mimic significantly lowered serum TNF-α, IL-1β, and IL-6 levels in these models, pointing to miR-191-5p's potential as a therapeutic target for septic AKI.

3.4. Sepsis-Induced Cardiac Dysfunction

miR-29c-3p [37]

Sepsis patients have been found to have increased circulating miR-29c-3p levels; this was associated with increased clinical features of sepsis. Moreover, septic patients with cardiac dysfunction were found to have higher serum levels of miR-29c-3p compared to those without cardiac dysfunction, implying a correlation between increased miR-29c-3p levels and the severity of sepsis. Logistic regression analysis was used to determine that miR-29c-3p acted as an independent factor for cardiac dysfunction in sepsis patients.

In a rat model of sepsis, an increase in serum miR-29c-3p expression was observed; this was associated with marked cardiac dysfunction. Suppression of miR-29c-3p expression using a miR-29c-3p antagomir resulted in a notable improvement in cardiac function. These observations align with previous research, suggesting a regulatory role of miR-29c-3p in cardiac function during sepsis. The miR-29 family's relationship with the inflammatory response has been confirmed in several studies, such as the work of Chen et al., who demonstrated that restoring miR-29 levels in diabetic nephropathy inhibited the TGF-β/Smad3 pathway, reducing collagen matrix accumulation and inflammation. Therefore, the protective effects on cardiac function during sepsis might be attributed to the anti-inflammatory properties of antagonized miR-29c-3p, underlining its potential as a therapeutic target for mitigating cardiac dysfunction in septic conditions. In silico findings indicate that that miR-29c is a potential regulator of oxidative stress and the inflammatory response [94].

4. Discussion

MicroRNAs (miRNAs) are increasingly being recognized as promising therapeutic candidates for treating sepsis and sepsis-induced organ dysfunction. This scoping review has surveyed and summarized the most recent studies employing miRNA mimics, inhibitors, and other related products as tools to mitigate sepsis-induced organ dysfunction. We primarily focused on studies that exploited wither gain and loss of function in vivo and that we could link to clinically relevant human data.

The burgeoning field of miRNA-based therapeutics for sepsis is predicated on robust preclinical evidence. Such foundational data are indispensable for validating the efficacy and safety of miRNA-based interventions. Yet, our analysis also underscores the imperative of integrating clinical data. Preclinical scientists often take cues from these data to bolster the translational relevance of their work. However, the limited access to clinical samples in the research milieu poses a significant hurdle, one which may be partially circumvented through the strategic use of in silico databases. These repositories can provide predictive insights into miRNAs implicated in sepsis, bridging some of the gaps between bench research and clinical reality.

While this scoping review has delved into many preclinical studies, it is pertinent to reflect on the heterogeneity in the quality of the work presented. The scope of our review did not extend to a critical appraisal of these studies, yet we acknowledge the variance in experimental rigor as a crucial factor. Notably, studies employing short-term sepsis models, which last only a few hours, provide a limited understanding. Such models may reveal acute molecular and cellular responses but remain ambivalent on the long-term survivability and the chronic impact of sepsis, which are essential for evaluating miRNA

therapies. It is worth noticing that at this time, there are no active clinical trials for miRNA-based therapies for sepsis; however, using clinical data to validate pre-clinical results is the way to develop miRNA-based therapy. In cancer research, MRG-110, a miR-92a inhibitor, completed its phase 1 trial in 2019 [95].

A striking finding from our review, which included 199 articles that met our initial inclusion criteria, is that 11 of these studies (constituting approximately 5% of the total) have been retracted. Authors identified major gaps in the results section in addition to failure to timely respond to journals' questions as the main reason for the retraction of these articles. Further reasons for the retractions are as follows: Discrepancies in the research scope, inconsistencies in the presented results' framework, issues between the availability of data and the stated results section, inappropriate citations including citing retracted materials, incoherent, misleading and/or irrelevant content included in the article, and finally, dissatisfaction of the journal's chief editors with the entirety or specific parts of the presented data, and the authors' inability to address these issues. Considering the recent publication dates of most of these articles, the retraction rate is disconcertingly high. This prevalence of retractions within the miRNA–sepsis research domain necessitates a cautious interpretation of the current literature. It underscores the need for stringent peer review and post-publication scrutiny to ensure the reliability and credibility of the findings being disseminated. Finally, the authors want to acknowledge that our screening criteria were designed to balance inclusivity with relevance to our specific research focus. We understand this as a limitation and there may be articles left out because of our stringent screening method.

Funding: C.C.d.S. is funded by the Canadian Institutes of Health Research, The National Research Council of Canada, and the Nanomedicine Innovation Network. The APC was free of charge.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Singer, M.; Deutschman, C.S.; Seymour, C.W.; Shankar-Hari, M.; Annane, D.; Bauer, M.; Bellomo, R.; Bernard, G.R.; Chiche, J.D.; Coopersmith, C.M.; et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* **2016**, *315*, 801–810. [CrossRef] [PubMed]
2. Shankar-Hari, M.; Phillips, G.S.; Levy, M.L.; Seymour, C.W.; Liu, V.X.; Deutschman, C.S.; Angus, D.C.; Rubenfeld, G.D.; Singer, M.; Sepsis Definitions Task, F. Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* **2016**, *315*, 775–787. [CrossRef] [PubMed]
3. Seymour, C.W.; Liu, V.X.; Iwashyna, T.J.; Brunkhorst, F.M.; Rea, T.D.; Scherag, A.; Rubenfeld, G.; Kahn, J.M.; Shankar-Hari, M.; Singer, M.; et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* **2016**, *315*, 762–774. [CrossRef] [PubMed]
4. Rudd, K.E.; Johnson, S.C.; Agesa, K.M.; Shackelford, K.A.; Tsoi, D.; Kievlan, D.R.; Colombara, D.V.; Ikuta, K.S.; Kissoon, N.; Finfer, S.; et al. Global, regional, and national sepsis incidence and mortality, 1990–2017: Analysis for the Global Burden of Disease Study. *Lancet* **2020**, *395*, 200–211. [CrossRef] [PubMed]
5. Van den Berg, M.; van Beuningen, F.E.; Ter Maaten, J.C.; Bouma, H.R. Hospital-related costs of sepsis around the world: A systematic review exploring the economic burden of sepsis. *J. Crit. Care* **2022**, *71*, 154096. [CrossRef] [PubMed]
6. Prescott, H.C.; Angus, D.C. Postsepsis Morbidity. *JAMA* **2018**, *319*, 91. [CrossRef]
7. Prescott, H.C.; Angus, D.C. Enhancing Recovery From Sepsis: A Review. *JAMA* **2018**, *319*, 62–75. [CrossRef]
8. Cuthbertson, B.H.; Elders, A.; Hall, S.; Taylor, J.; MacLennan, G.; Mackirdy, F.; Mackenzie, S.J.; Scottish Critical Care Trials Group; Scottish Intensive Care Society Audit Group. Mortality and quality of life in the five years after severe sepsis. *Crit. Care* **2013**, *17*, R70. [CrossRef]
9. Herridge, M.S.; Chu, L.M.; Matte, A.; Tomlinson, G.; Chan, L.; Thomas, C.; Friedrich, J.O.; Mehta, S.; Lamontagne, F.; Levasseur, M.; et al. The RECOVER Program: Disability Risk Groups and 1-Year Outcome after 7 or More Days of Mechanical Ventilation. *Am. J. Respir. Crit. Care Med.* **2016**, *194*, 831–844. [CrossRef]
10. Ospina-Tascon, G.A.; Buchele, G.L.; Vincent, J.L. Multicenter, randomized, controlled trials evaluating mortality in intensive care: Doomed to fail? *Crit. Care Med.* **2008**, *36*, 1311–1322. [CrossRef]
11. Kaukonen, K.M.; Bailey, M.; Suzuki, S.; Pilcher, D.; Bellomo, R. Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. *JAMA* **2014**, *311*, 1308–1316. [CrossRef] [PubMed]
12. Ektesabi, A.M.; Mori, K.; Tsoporis, J.N.; Vaswani, C.M.; Gupta, S.; Walsh, C.; Varkouhi, A.K.; Mei, S.H.J.; Stewart, D.J.; Liles, W.C.; et al. Mesenchymal Stem/Stromal Cells Increase Cardiac miR-187-3p Expression in a Polymicrobial Animal Model of Sepsis. *Shock* **2021**, *56*, 133–141. [CrossRef] [PubMed]

13. Damase, T.R.; Sukhovershin, R.; Boada, C.; Taraballi, F.; Pettigrew, R.I.; Cooke, J.P. The Limitless Future of RNA Therapeutics. *Front. Bioeng. Biotechnol.* **2021**, *9*, 628137. [CrossRef] [PubMed]
14. Zhou, Y.; Song, Y.; Shaikh, Z.; Li, H.; Zhang, H.; Caudle, Y.; Zheng, S.; Yan, H.; Hu, D.; Stuart, C.; et al. MicroRNA-155 attenuates late sepsis-induced cardiac dysfunction through JNK and beta-arrestin 2. *Oncotarget* **2017**, *8*, 47317–47329. [CrossRef] [PubMed]
15. Liu, L.; Li, T.M.; Liu, X.R.; Bai, Y.P.; Li, J.; Tang, N.; Wang, X.B. MicroRNA-140 inhibits skeletal muscle glycolysis and atrophy in endotoxin-induced sepsis in mice via the WNT signaling pathway. *Am. J. Physiol. Cell Physiol.* **2019**, *317*, C189–C199. [CrossRef] [PubMed]
16. Ling, L.; Lu, H.T.; Wang, H.F.; Shen, M.J.; Zhang, H.B. MicroRNA-203 Acts as a Potent Suppressor in Septic Shock by Alleviating Lung Injury via Inhibition of VNN1. *Kidney Blood Press Res.* **2019**, *44*, 565–582. [CrossRef]
17. He, S.Y.; Wang, G.; Pei, Y.H.; Zhu, H.P. miR-34b-3p protects against acute kidney injury in sepsis mice via targeting ubiquitin-like protein 4A. *Kaohsiung J. Med. Sci.* **2020**, *36*, 817–824. [CrossRef]
18. Sang, Z.; Dong, S.; Zhang, P.; Wei, Y. miR-214 ameliorates sepsis-induced acute kidney injury via PTEN/AKT/mTOR-regulated autophagy. *Mol. Med. Rep.* **2021**, *24*, 683. [CrossRef]
19. Wang, H.F.; Wang, Y.Q.; Dou, L.; Gao, H.M.; Wang, B.; Luo, N.; Li, Y. Influences of up-regulation of miR-126 on septic inflammation and prognosis through AKT/Rac1 signaling pathway. *Eur. Rev. Med. Pharmacol. Sci.* **2019**, *23*, 2132–2138. [CrossRef]
20. Dos Santos, C.C.; Amatullah, H.; Vaswani, C.M.; Maron-Gutierrez, T.; Kim, M.; Mei, S.H.J.; Szaszi, K.; Monteiro, A.P.T.; Varkouhi, A.K.; Herreroz, R.; et al. Mesenchymal stromal (stem) cell therapy modulates miR-193b-5p expression to attenuate sepsis-induced acute lung injury. *Eur. Respir. J.* **2022**, *59*, 2004216. [CrossRef]
21. Younes, N.; Zhou, L.; Amatullah, H.; Mei, S.H.J.; Herrero, R.; Lorente, J.A.; Stewart, D.J.; Marsden, P.; Liles, W.C.; Hu, P.; et al. Mesenchymal stromal/stem cells modulate response to experimental sepsis-induced lung injury via regulation of miR-27a-5p in recipient mice. *Thorax* **2020**, *75*, 556–567. [CrossRef] [PubMed]
22. Chen, L.; Lu, Q.; Deng, F.; Peng, S.; Yuan, J.; Liu, C.; Du, X. miR-103a-3p Could Attenuate Sepsis-Induced Liver Injury by Targeting HMGB1. *Inflammation* **2020**, *43*, 2075–2086. [CrossRef] [PubMed]
23. Zhang, X.M.; Li, L.B.; Sun, C.H. The effect of myocardial infarction-associated transcript 2 (Mirt2) and miR-101 on sepsis-induced myocardial injury in rats. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 6299–6310. [CrossRef] [PubMed]
24. Zhang, C.; Zeng, L.; Cai, G.; Zhu, Y.; Xiong, Y.; Zhan, H.; Yang, Z. miR-340-5p Alleviates Oxidative Stress Injury by Targeting MyD88 in Sepsis-Induced Cardiomyopathy. *Oxid. Med. Cell Longev.* **2022**, *2022*, 2939279. [CrossRef] [PubMed]
25. Zou, Q.; Liu, C.; Hu, N.; Wang, W.; Wang, H. miR-126 ameliorates multiple organ dysfunction in septic rats by regulating the differentiation of Th17/Treg. *Mol. Biol. Rep.* **2022**, *49*, 2985–2998. [CrossRef] [PubMed]
26. Chen, D.; Hou, Y.; Cai, X. MiR-210-3p Enhances Cardiomyocyte Apoptosis and Mitochondrial Dysfunction by Targeting the NDUFA4 Gene in Sepsis-Induced Myocardial Dysfunction. *Int. Heart J.* **2021**, *62*, 636–646. [CrossRef] [PubMed]
27. Fu, D.; Dong, J.; Li, P.; Tang, C.; Cheng, W.; Xu, Z.; Zhou, W.; Ge, J.; Xia, C.; Zhang, Z. MiRNA-21 has effects to protect kidney injury induced by sepsis. *Biomed. Pharmacother.* **2017**, *94*, 1138–1144. [CrossRef] [PubMed]
28. Ling, H.; Li, Q.; Duan, Z.P.; Wang, Y.J.; Hu, B.Q.; Dai, X.G. LncRNA GAS5 inhibits miR-579-3p to activate SIRT1/PGC-1alpha/Nrf2 signaling pathway to reduce cell pyroptosis in sepsis-associated renal injury. *Am. J. Physiol. Cell Physiol.* **2021**, *321*, C117–C133. [CrossRef]
29. Chen, L.; Xie, W.; Wang, L.; Zhang, X.; Liu, E.; Kou, Q. MiRNA-133a aggravates inflammatory responses in sepsis by targeting SIRT1. *Int. Immunopharmacol.* **2020**, *88*, 106848. [CrossRef]
30. Dragomir, M.P.; Fuentes-Mattei, E.; Winkle, M.; Okubo, K.; Bayraktar, R.; Knutsen, E.; Qdaisat, A.; Chen, M.; Li, Y.; Shimizu, M.; et al. Anti-miR-93-5p therapy prolongs sepsis survival by restoring the peripheral immune response. *J. Clin. Investig.* **2023**, *133*, e158348. [CrossRef]
31. Borjas, T.; Jacob, A.; Kobritz, M.; Ma, G.; Tan, C.; Patel, V.; Coppa, G.F.; Aziz, M.; Wang, P. An engineered miRNA PS-OMe miR130 inhibits acute lung injury by targeting eCIRP in sepsis. *Mol. Med.* **2023**, *29*, 21. [CrossRef]
32. Ma, X.F.; Qin, J.; Guo, X.H. MiR-181-5p protects mice from sepsis via repressing HMGB1 in an experimental model. *Eur. Rev. Med. Pharmacol. Sci.* **2020**, *24*, 9712–9720. [CrossRef]
33. Ren, H.; Mu, W.; Xu, Q. miR-19a-3p inhibition alleviates sepsis-induced lung injury via enhancing USP13 expression. *Acta Biochim. Pol.* **2021**, *68*, 201–206. [CrossRef]
34. Zhang, J.; Liu, Y.; Liu, L. Hyperoside prevents sepsis-associated cardiac dysfunction through regulating cardiomyocyte viability and inflammation via inhibiting miR-21. *Biomed. Pharmacother.* **2021**, *138*, 111524. [CrossRef]
35. Wang, X.; Wang, Y.; Kong, M.; Yang, J. MiR-22-3p suppresses sepsis-induced acute kidney injury by targeting PTEN. *Biosci. Rep.* **2020**, *40*, BSR20200527. [CrossRef]
36. Funahashi, Y.; Kato, N.; Masuda, T.; Nishio, F.; Kitai, H.; Ishimoto, T.; Kosugi, T.; Tsuboi, N.; Matsuda, N.; Maruyama, S.; et al. miR-146a targeted to splenic macrophages prevents sepsis-induced multiple organ injury. *Lab. Investig.* **2019**, *99*, 1130–1142. [CrossRef]
37. Zhang, B.; Yu, L.; Sheng, Y. Clinical value and role of microRNA-29c-3p in sepsis-induced inflammation and cardiac dysfunction. *Eur. J. Med. Res.* **2021**, *26*, 90. [CrossRef] [PubMed]
38. Zhang, Y.; Xia, F.; Wu, J.; Yang, A.X.; Zhang, Y.Y.; Zhao, H.; Tao, W.Y. MiR-205 influences renal injury in sepsis rats through HMGB1-PTEN signaling pathway. *Eur. Rev. Med. Pharmacol. Sci.* **2019**, *23*, 10950–10956. [CrossRef] [PubMed]

39. Du, X.; Wei, J.; Tian, D.; Wu, M.; Yan, C.; Hu, P.; Wu, X.; Yang, W.; Yin, T. miR-182-5p contributes to intestinal injury in a murine model of Staphylococcus aureus pneumonia-induced sepsis via targeting surfactant protein D. *J. Cell. Physiol.* **2020**, *235*, 563–572. [CrossRef] [PubMed]
40. Xu, H.; Wang, Z. MicroRNA-23a-3p ameliorates acute kidney injury by targeting FKBP5 and NF-kappaB signaling in sepsis. *Cytokine* **2022**, *155*, 155898. [CrossRef] [PubMed]
41. Ma, F.; Li, Z.; Cao, J.; Kong, X.; Gong, G. A TGFBR2/SMAD2/DNMT1/miR-145 negative regulatory loop is responsible for LPS-induced sepsis. *Biomed. Pharmacother.* **2019**, *112*, 108626. [CrossRef]
42. Liu, Y.; Liu, L.; Zhang, J. Protective role of matrine in sepsis-associated cardiac dysfunction through regulating the lncRNA PTENP1/miR-106b-5p axis. *Biomed. Pharmacother.* **2021**, *134*, 111112. [CrossRef]
43. You, Q.; Wang, J.; Jia, D.; Jiang, L.; Chang, Y.; Li, W. MiR-802 alleviates lipopolysaccharide-induced acute lung injury by targeting Peli2. *Inflamm. Res.* **2020**, *69*, 75–85. [CrossRef]
44. Yan, F.; Wang, Q.; Yang, H.; Lv, H.; Qin, W. miR-926-3p influences myocardial injury in septic mice through regulation of mTOR signaling pathway by targeting TSC1. *Aging* **2023**, *15*, 3826–3838. [CrossRef] [PubMed]
45. Xu, R.; Shao, Z.; Cao, Q. MicroRNA-144-3p enhances LPS induced septic acute lung injury in mice through downregulating Caveolin-2. *Immunol. Lett.* **2021**, *231*, 18–25. [CrossRef]
46. Wang, P.; Zhang, X.; Li, F.; Yuan, K.; Li, M.; Zhang, J.; Li, B.; Liang, W. MiR-130b attenuates vascular inflammation via negatively regulating tumor progression locus 2 (Tpl2) expression. *Int. Immunopharmacol.* **2017**, *51*, 9–16. [CrossRef] [PubMed]
47. 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. [CrossRef] [PubMed]
48. Liu, Y.; Guan, H.; Zhang, J.L.; Zheng, Z.; Wang, H.T.; Tao, K.; Han, S.C.; Su, L.L.; Hu, D. Acute downregulation of miR-199a attenuates sepsis-induced acute lung injury by targeting SIRT1. *Am. J. Physiol. Cell Physiol.* **2018**, *314*, C449–C455. [CrossRef] [PubMed]
49. Yi, H.X.; Jiang, S.Y.; Yu, L.H.; Chen, K.; Yang, Z.X.; Wu, Q. MicroRNA 181a-2-3p Alleviates the Apoptosis of Renal Tubular Epithelial Cells via Targeting GJB2 in Sepsis-Induced Acute Kidney Injury. *Mol. Cell Biol.* **2021**, *41*, e0001621. [CrossRef] [PubMed]
50. Long, X.; Huang, Y.; He, J.; Zhang, X.; Zhou, Y.; Wei, Y.; Tang, Y.; Liu, L. Upregulation of miR-335 exerts protective effects against sepsis-induced myocardial injury. *Mol. Med. Rep.* **2021**, *24*, 806. [CrossRef] [PubMed]
51. Chen, S.; Ding, R.; Hu, Z.; Yin, X.; Xiao, F.; Zhang, W.; Yan, S.; Lv, C. MicroRNA-34a Inhibition Alleviates Lung Injury in Cecal Ligation and Puncture Induced Septic Mice. *Front. Immunol.* **2020**, *11*, 1829. [CrossRef]
52. McClure, C.; Ali, E.; Youssef, D.; Yao, Z.Q.; McCall, C.E.; El Gazzar, M. NFI-A disrupts myeloid cell differentiation and maturation in septic mice. *J. Leukoc. Biol.* **2016**, *99*, 201–211. [CrossRef]
53. Huang, X.; Hou, X.; Chuan, L.; Wei, S.; Wang, J.; Yang, X.; Ru, J. miR-129-5p alleviates LPS-induced acute kidney injury via targeting HMGB1/TLRs/NF-kappaB pathway. *Int. Immunopharmacol.* **2020**, *89 Pt A*, 107016. [CrossRef]
54. Diao, X.; Sun, S. PMicroRNA-124a regulates LPS-induced septic cardiac dysfunction by targeting STX2. *Biotechnol. Lett.* **2017**, *39*, 1335–1342. [CrossRef]
55. Yan, J.; Yang, F.; Wang, D.; Lu, Y.; Liu, L.; Wang, Z. MicroRNA-217 modulates inflammation, oxidative stress, and lung injury in septic mice via SIRT1. *Free Radic. Res.* **2021**, *55*, 1–10. [CrossRef] [PubMed]
56. Ma, H.; Wang, X.; Ha, T.; Gao, M.; Liu, L.; Wang, R.; Yu, K.; Kalbfleisch, J.H.; Kao, R.L.; Williams, D.L.; et al. MicroRNA-125b Prevents Cardiac Dysfunction in Polymicrobial Sepsis by Targeting TRAF6-Mediated Nuclear Factor kappaB Activation and p53-Mediated Apoptotic Signaling. *J. Infect. Dis.* **2016**, *214*, 1773–1783. [CrossRef] [PubMed]
57. Ma, X.; Zhu, G.; Jiao, T.; Shao, F. Effects of circular RNA Ttc3/miR-148a/Rcan2 axis on inflammation and oxidative stress in rats with acute kidney injury induced by sepsis. *Life Sci.* **2021**, *272*, 119233. [CrossRef] [PubMed]
58. Ou, Y.; An, R.; Wang, H.; Chen, L.; Shen, Y.; Cai, W.; Zhu, W. Oxidative stress-related circulating miRNA-27a is a potential biomarker for diagnosis and prognosis in patients with sepsis. *BMC Immunol.* **2022**, *23*, 14. [CrossRef]
59. Luo, Y.; Xu, H.; Yang, Z.; Lin, X.; Zhao, F.; Huang, Y.; Wang, Y.; Yang, X.; Li, H.; Wang, L.; et al. Long non-coding RNA MALAT1 silencing elevates microRNA-26a-5p to ameliorate myocardial injury in sepsis by reducing regulator of calcineurin 2. *Arch. Biochem. Biophys.* **2022**, *715*, 109047. [CrossRef]
60. He, Z.; Wang, H.; Yue, L. Endothelial progenitor cells-secreted extracellular vesicles containing microRNA-93-5p confer protection against sepsis-induced acute kidney injury via the KDM6B/H3K27me3/TNF-alpha axis. *Exp. Cell Res.* **2020**, *395*, 112173. [CrossRef]
61. Wang, S.; Zhang, Z.; Wang, J.; Miao, H. MiR-107 induces TNF-alpha secretion in endothelial cells causing tubular cell injury in patients with septic acute kidney injury. *Biochem. Biophys. Res. Commun.* **2017**, *483*, 45–51. [CrossRef]
62. Li, G.; Wang, B.; Ding, X.; Zhang, X.; Tang, J.; Lin, H. Plasma extracellular vesicle delivery of miR-210-3p by targeting ATG7 to promote sepsis-induced acute lung injury by regulating autophagy and activating inflammation. *Exp. Mol. Med.* **2021**, *53*, 1180–1191. [CrossRef]
63. Xu, J.; Feng, Y.; Jeyaram, A.; Jay, S.M.; Zou, L.; Chao, W. Circulating Plasma Extracellular Vesicles from Septic Mice Induce Inflammation via MicroRNA- and TLR7-Dependent Mechanisms. *J. Immunol.* **2018**, *201*, 3392–3400. [CrossRef] [PubMed]
64. Mandelbaum, J.; Rollins, N.; Shah, P.; Bowman, D.; Lee, J.Y.; Tayber, O.; Bernard, H.; LeRoy, P.; Li, P.; Koenig, E.; et al. Identification of a lung cancer cell line deficient in atg7-dependent autophagy. *Autophagy* **2015**. [CrossRef] [PubMed]

65. Avila-Bonilla, R.G.; Yocupicio-Monroy, M.; Marchat, L.A.; De Nova-Ocampo, M.A.; Del Angel, R.M.; Salas-Benito, J.S. Analysis of the miRNA profile in C6/36 cells persistently infected with dengue virus type 2. *Virus Res.* **2017**, *232*, 139–151. [CrossRef] [PubMed]
66. Chen, J.; Lin, M.; Zhang, S. Identification of key miRNA-mRNA pairs in septic mice by bioinformatics analysis. *Mol. Med. Rep.* **2019**, *20*, 3858–3866. [CrossRef] [PubMed]
67. Liu, F.; Li, Y.; Jiang, R.; Nie, C.; Zeng, Z.; Zhao, N.; Huang, C.; Shao, Q.; Ding, C.; Qing, C.; et al. miR-132 inhibits lipopolysaccharide-induced inflammation in alveolar macrophages by the cholinergic anti-inflammatory pathway. *Exp. Lung Res.* **2015**, *41*, 261–269. [CrossRef] [PubMed]
68. Huang, J.; Sun, Z.; Yan, W.; Zhu, Y.; Lin, Y.; Chen, J.; Shen, B.; Wang, J. Identification of microRNA as sepsis biomarker based on miRNAs regulatory network analysis. *Biomed. Res. Int.* **2014**, *2014*, 594350. [CrossRef] [PubMed]
69. Ma, X.J.; Guo, C.Y.; Yin, H.J.; Liu, Y.; Shi, D.Z. [Effect of activating blood circulation or activating blood circulation and detoxication on platelet activation, inflammation, and coagulation status in acute myocardial infarction rats]. *Zhongguo Zhong Xi Yi Jie He Za Zhi* **2014**, *34*, 1329–1334. [PubMed]
70. Wu, J.; Li, X. Plasma Tumor Necrosis Factor-alpha (TNF-alpha) Levels Correlate with Disease Severity in Spastic Diplegia, Triplegia, and Quadriplegia in Children with Cerebral Palsy. *Med. Sci. Monit.* **2015**, *21*, 3868–3874. [CrossRef]
71. Zhang, J.; Zhang, P.; Wei, Y.; Piao, H.L.; Wang, W.; Maddika, S.; Wang, M.; Chen, D.; Sun, Y.; Hung, M.C.; et al. Deubiquitylation and stabilization of PTEN by USP13. *Nat. Cell Biol.* **2013**, *15*, 1486–1494. [CrossRef]
72. Lu, C.; Zhou, D.; Wang, Q.; Liu, W.; Yu, F.; Wu, F.; Chen, C. Crosstalk of MicroRNAs and Oxidative Stress in the Pathogenesis of Cancer. *Oxid. Med. Cell Longev.* **2020**, *2020*, 2415324. [CrossRef]
73. Xiang, C.; Cui, S.P.; Ke, Y. MiR-144 inhibits cell proliferation of renal cell carcinoma by targeting MTOR. *J. Huazhong Univ. Sci. Technol. Med. Sci.* **2016**, *36*, 186–192. [CrossRef] [PubMed]
74. Cao, J.; Han, X.; Qi, X.; Jin, X.; Li, X. TUG1 promotes osteosarcoma tumorigenesis by upregulating EZH2 expression via miR-144-3p. *Int. J. Oncol.* **2017**, *51*, 1115–1123. [CrossRef] [PubMed]
75. Mitchelson, K.R.; Qin, W.Y. Roles of the canonical myomiRs miR-1, -133 and -206 in cell development and disease. *World J. Biol. Chem.* **2015**, *6*, 162–208. [CrossRef] [PubMed]
76. Essandoh, K.; Li, Y.; Huo, J.; Fan, G.C. MiRNA-Mediated Macrophage Polarization and its Potential Role in the Regulation of Inflammatory Response. *Shock* **2016**, *46*, 122–131. [CrossRef] [PubMed]
77. Cao, Y.Y.; Wang, Z.; Wang, Z.H.; Jiang, X.G.; Lu, W.H. Inhibition of miR-155 alleviates sepsis-induced inflammation and intestinal barrier dysfunction by inactivating NF-kappaB signaling. *Int. Immunopharmacol.* **2021**, *90*, 107218. [CrossRef]
78. Pandey, R.K.; Sundar, S.; Prajapati, V.K. Differential Expression of miRNA Regulates T Cell Differentiation and Plasticity During Visceral Leishmaniasis Infection. *Front. Microbiol.* **2016**, *7*, 206. [CrossRef]
79. Chen, C.; Zhang, L.; Huang, H.; Liu, S.; Liang, Y.; Xu, L.; Li, S.; Cheng, Y.; Tang, W. Serum miR-126-3p level is down-regulated in sepsis patients. *Int. J. Clin. Exp. Pathol.* **2018**, *11*, 2605–2612.
80. Su, J.; Ding, L. Upregulation of miR-126 inhibits podocyte injury in sepsis via EGFL6/DKC1 signaling pathway. *Mol. Med. Rep.* **2021**, *23*, 373. [CrossRef]
81. Nong, A.; Li, Q.; Huang, Z.; Xu, Y.; He, K.; Jia, Y.; Cen, Z.; Liao, L.; Huang, Y. MicroRNA miR-126 attenuates brain injury in septic rats via NF-kappaB signaling pathway. *Bioengineered* **2021**, *12*, 2639–2648. [CrossRef]
82. Luo, H.; Chen, D.; Li, R.; Li, R.; Teng, Y.; Cao, Y.; Zou, X.; Wang, W.; Zhou, C. Genetically engineered CXCR4-modified exosomes for delivery of miR-126 mimics to macrophages alleviate periodontitis. *J. Nanobiotechnol.* **2023**, *21*, 116. [CrossRef] [PubMed]
83. Shafei, S.; Khanmohammadi, M.; Ghanbari, H.; Nooshabadi, V.T.; Tafti, S.H.A.; Rabbani, S.; Kasaiyan, M.; Basiri, M.; Tavoosidana, G. Effectiveness of exosome mediated miR-126 and miR-146a delivery on cardiac tissue regeneration. *Cell Tissue Res.* **2022**, *390*, 71–92. [CrossRef] [PubMed]
84. Endo-Takahashi, Y.; Negishi, Y.; Nakamura, A.; Ukai, S.; Ooaku, K.; Oda, Y.; Sugimoto, K.; Moriyasu, F.; Takagi, N.; Suzuki, R.; et al. Systemic delivery of miR-126 by miRNA-loaded Bubble liposomes for the treatment of hindlimb ischemia. *Sci. Rep.* **2014**, *4*, 3883. [CrossRef] [PubMed]
85. Jones Buie, J.N.; Zhou, Y.; Goodwin, A.J.; Cook, J.A.; Vournakis, J.; Demcheva, M.; Broome, A.M.; Dixit, S.; Halushka, P.V.; Fan, H. Application of Deacetylated Poly-N-Acetyl Glucosamine Nanoparticles for the Delivery of miR-126 for the Treatment of Cecal Ligation and Puncture-Induced Sepsis. *Inflammation* **2019**, *42*, 170–184. [CrossRef]
86. Dumitru, C.D.; Ceci, J.D.; Tsatsanis, C.; Kontoyiannis, D.; Stamatakis, K.; Lin, J.H.; Patriotis, C.; Jenkins, N.A.; Copeland, N.G.; Kollias, G.; et al. TNF-alpha induction by LPS is regulated posttranscriptionally via a Tpl2/ERK-dependent pathway. *Cell* **2000**, *103*, 1071–1083. [CrossRef]
87. Owens, D.M.; Keyse, S.M. Differential regulation of MAP kinase signalling by dual-specificity protein phosphatases. *Oncogene* **2007**, *26*, 3203–3213. [CrossRef]
88. Klein, J.D.; Wang, X.H. Electrically stimulated acupuncture increases renal blood flow through exosome-carried miR-181. *Am. J. Physiol. Renal Physiol.* **2018**, *315*, F1542–F1549. [CrossRef] [PubMed]
89. Ma, J.; Shi, X.; Li, M.; Chen, S.; Gu, Q.; Zheng, J.; Li, D.; Wu, S.; Yang, H.; Li, X. MicroRNA-181a-2-3p shuttled by mesenchymal stem cell-secreted extracellular vesicles inhibits oxidative stress in Parkinson's disease by inhibiting EGR1 and NOX4. *Cell Death Discov.* **2022**, *8*, 33. [CrossRef]

90. Wang, J.; Song, J.; Li, Y.; Shao, J.; Xie, Z.; Sun, K. Down-regulation of LncRNA CRNDE aggravates kidney injury via increasing MiR-181a-5p in sepsis. *Int. Immunopharmacol.* **2020**, *79*, 105933. [CrossRef]
91. Huang, Z.; Xu, H. MicroRNA-181a-5p Regulates Inflammatory Response of Macrophages in Sepsis. *Open Med.* **2019**, *14*, 899–908. [CrossRef] [PubMed]
92. Zhang, M.; Zhi, D.; Lin, J.; Liu, P.; Wang, Y.; Duan, M. miR-181a-5p Inhibits Pyroptosis in Sepsis-Induced Acute Kidney Injury through Downregulation of NEK7. *J. Immunol. Res.* **2022**, *2022*, 1825490. [CrossRef] [PubMed]
93. Qin, Y.; Wang, G.; Peng, Z. MicroRNA-191-5p diminished sepsis-induced acute kidney injury through targeting oxidative stress responsive 1 in rat models. *Biosci. Rep.* **2019**, *39*, BSR20190548. [CrossRef] [PubMed]
94. Yang, J.; Hu, Q.C.; Wang, J.P.; Ren, Q.Q.; Wang, X.P.; Luoreng, Z.M.; Wei, D.W.; Ma, Y. RNA-Seq Reveals the Role of miR-29c in Regulating Inflammation and Oxidative Stress of Bovine Mammary Epithelial Cells. *Front. Vet. Sci.* **2022**, *9*, 865415. [CrossRef]
95. Abplanalp, W.T.; Fischer, A.; John, D.; Zeiher, A.M.; Gosgnach, W.; Darville, H.; Montgomery, R.; Pestano, L.; Allee, G.; Paty, I.; et al. Efficiency and Target Derepression of Anti-miR-92a: Results of a First in Human Study. *Nucleic Acid Ther.* **2020**, *30*, 335–345. [CrossRef]