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Review

Review

MicroRNAs in septic acute kidney injury

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Abstract

Sepsis is a potentially fatal complication of burns and trauma that can cause acute kidney injury (AKI) with substantial morbidity and mortality, but this disease is poorly understood. Despite medical advances, effective therapeutic regimens for septic AKI remain uncommon. MicroRNAs (miRNAs) are endogenous non-coding RNAs that influence the translation of target messenger RNAs in a variety of biological processes. Emerging evidence has shown that miRNAs are intimately associated with septic AKI. The goal of this review was to summarize recent advances in the profound understanding of the functional role of miRNAs in septic AKI, as well as to provide new insights into miRNAs as feasible biomarkers and therapeutic targets for septic AKI.

Key words: MicroRNAs, Sepsis, Acute kidney injury, Biomarkers, Therapeutic targets

Highlights

- Recent advances in miRNAs in septic AKI are reviewed.
- The diagnosis and prognosis of septic AKI based on miRNA signatures are described.
- miRNA-meditated signaling and its therapeutic mechanisms against septic AKI are summarized.

Background

Sepsis, which is a serious condition that can cause multiple organ failure, is one of the leading causes of death after trauma, burns and critical surgery [1,2]. At the cellular and molecular levels, sepsis is characterized by an imbalance in the inflammatory response, mitochondrial damage, coagulopathy, immune dysfunction, autophagy and other pathophysiological processes that ultimately lead to organ malfunction [3]. Acute kidney injury (AKI) occurs in 50–60% of septic patients and has a mortality rate of 50–70% [4,5]. Moreover, sepsis is associated with ∼50% of AKI cases [6–9]. Recent evidence suggests that three fundamental mechanisms contribute to the development of septic AKI: microvascular dysfunction, inflammation and metabolic reprogramming [10]. Despite decades of clinical and experimental research, the pathophysiological mechanisms of septic AKI are still poorly understood [10–12]. As a result, treatments targeting the underlying mechanisms of organ dysfunction are limited, and current therapies primarily focus on etiological treatment (i.e. antibiotics, resuscitation) and organ support [13,14].

With the help of epigenetics and high-throughput sequencing technologies, as well as growing interest in non-coding RNAs (ncRNAs), including microRNAs (miRNAs), long-chain non-coding RNAs and circular RNAs, ncRNAs have been shown to regulate gene expression and interfere with cellular function on multiple levels. Recently, the role of miRNAs, which are short endogenous ncRNA molecules ranging between 19 to 25 nucleotides in length, in posttranscriptional

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regulation has been well investigated [15,16]. Specifically, miRNAs target hundreds of target-specific messenger RNAs to regulate the expression of hundreds of genes via their 3′ untranslated regions and prevent their transcription [15].

miRNAs are linked to the pathogenesis of septic AKI [2,17–19]. Clinical trials and animal experiments have demonstrated that modulating miRNA expression is beneficial in several diseases [20–23]. Some miRNAs are increased in the urine and plasma of patients with septic AKI, suggesting that they might be valuable diagnostic biomarkers [24–29]. Increasing evidence indicates that miRNAs could be therapeutic targets against septic AKI [30–35]. The current review aimed to evaluate the latest findings on the emerging role of miRNAs in septic AKI.

Review

miRNAs as potential biomarkers for septic AKI

Septic AKI is characterized by poor prognosis, primarily due to the lack of early and reliable diagnostic biomarkers, resulting in the delayed initiation of effective interventions [36]. Serum creatinine (Scr) and urine output have several limitations in the diagnosis of AKI [37,38]. In recent years, new biomarkers have been discovered, such as cystatin-C (Cys-C), neutrophil gelatinase-associated lipocalin (NGAL) and interleukin-18 (IL-18), but these markers are not sensitive enough to detect AKI [39]. However, it is vital to identify noninvasive biomarkers that are sensitive and specific to diagnose early-stage septic AKI.

Currently, nearly 4000 human miRNAs have been identified, and at least 30% may be effective biomarkers for humans [40]. miRNAs are the most promising transcriptomic biomarkers [41]. To date, various miRNAs in cells and tissues, as well as in plasma, serum, saliva and urine, have been investigated [25,29,42]. Because of their abundance and stability in body fluids, circulating miRNAs may function as disease fingerprints and novel molecular biomarkers [43]. Recent studies have highlighted the potential of miRNAs as biological markers for septic AKI [27,29]. Based on data from previously published experimental, animal and human investigations, 15 miRNAs are listed in Table 1.

miRNAs have emerged as interesting indicators of septic AKI, whether their expression is decreased or increased. Decreased expression of miR-22-3p in serum and urine has been identified in septic patients with AKI compared with non-AKI individuals [25,44]. In lipopolysaccharide (LPS)-induced septic AKI mice and septic AKI patients, urine miR-376b levels were dramatically decreased, which negatively correlated with Scr andBlood Urea Nitrogen (BUN) in septic patients. Furthermore, when compared to urinary tissue inhibitor metalloproteinase-2 (TIMP2) and insulin-like growth factor binding protein-7 (IGFBP7), urinary miR-376b had slightly better sensitivity (65 vs. 60%) for identifying AKI in septic patients and therefore may be a diagnostic tool for septic AKI [45]. A recent study demonstrated that the level of miR-574-5p was considerably decreased in septic AKI patients, which revealed that miR-574-5p might be a biomarker for predicting the development of AKI in septic patients [28]. Zhang *et al*. performed a TargetScanHuman examination and indicated that miR-124-3p.1 expression was downregulated in the serum of septic AKI patients, suggesting that an alteration in miR-124-3p.1 expression could help to detect early AKI [2]. Moreover, miR-15a-5p could be used as a biomarker for AKI in septic patients treated with gentamicin, and miR-15a-5p was statistically reduced in AKI patients [46]. Serum levels of miR-21-3p, in combination with Scr, Cys-C and kidney injury molecule 1 (KIM-1), were significantly increased in children with sepsis and could predict AKI onset with a sensitivity of 97% and specificity of 91.4% [47]. Another clinical study revealed that serum miR-320-3p levels were greatly enhanced in children with sepsis-induced AKI, and combining NGAL, KIM-1 and acute physiology and chronic health evaluation (APACHE) II scores could be effective for predicting prognosis in children [24]. Serum and urinary miR-452 levels increased early after LPS or cecal ligation puncture (CLP) in septic mice, occurring earlier than detectable renal dysfunction or tissue damage. Serum and urinary miR-452 levels were significantly higher in septic patients with AKI than in non-AKI patients [27]. Moreover, AKI in septic patients was detected by measuring miR-452 in urine with a sensitivity of 87.23%, which was higher than that in the arithmetic product of the concentrations of urinary TIMP2 and IGFBP7 ([TIMP2]∗[IGFBP7]. This result suggested that an increase in miR-452, particularly in urine, may be a useful biomarker for the early identification of AKI in patients with sepsis [27]. In addition, Wang *et al*. identified miR-20a as a promising biomarker for the early diagnosis of AKI in sepsis [48]. Urine miR-26b levels were increased in patients with septic AKI and could be used to identify AKI onset in patients with sepsis with a sensitivity of 90.8% and specificity of 75.0% [29].

Interestingly, emerging research suggests that miRNAs can also be used to predict the outcomes of patients with septic AKI. Septic patients with higher levels of miR-26b in their urine had a higher mortality rate, as shown by Kaplan–Meier analysis [29]. Low serum or urinary miR-22-3p expression was linked to poor 28-day survival in septic AKI patients, suggesting that a single miRNA could be a non-invasive biomarker for the prognosis of sepsis-induced AKI [25]. Lorenzen *et al*. revealed that plasma miR-210 was a reliable and independent predictor of survival in critically ill patients with AKI according to an analysis of 77 patients with AKI and 30 healthy controls [49]. The expression of 11 miRNAs was upregulated and 11 miRNAs were downregulated in the plasma of septic AKI patients. Of note, miR-210 and miR-494 were the two most increased miRNAs, whereas miR-205 was the most decreased. The sensitivities of miR-210, miR-494 and miR-205 were 81.0, 80.9 and 78.6%, and the specificities were 80.9, 72.1 and 90.5%, respectively. Similarly, serum miR-210, miR-494 and miR-205 showed prognostic value in

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Table 1. miRNAs as potential biomarkers of septic AKI

miRNA	Expression	Biofluid	Association with biomarker	Reference
miR-10a-5p	Upregulation	Blood (patients)	miR-29a	[51]
miR-15a-5p	Downregulation	Blood (patients)	-	[46]
miR-20a	Upregulation	Blood (rats)	-	[48]
miR-21-3p	Upregulation	Blood (patients)	Scr, Cys-C and KIM-1	[47]
miR-22-3p	Downregulation	Blood and urine (patients)	-	[25,44]
miR-26b	Upregulation	Urine (patients)	-	[29]
miR-29a	Upregulation	Blood (patients)	miR-10a-5p	[51]
miR-124-3p.1	Downregulation	Blood (patients)	-	[2]
miR-210	Upregulation	Blood (patients)	-	[49,50]
miR-205	Downregulation	Blood (patients)	-	[50]
miR-320- 3p	Upregulation	Blood (patients)	NGAL, KIM-1 and APACHE II scores	[24]
miR-376b	Downregulation	Urine (patients)	-	[45]
miR-452	Upregulation	Urine (mice)	-	[27]
		Blood and urine (patients)	-	
miR-494	Upregulation	Blood (patients)	-	[50]
miR-574-5p	Downregulation	Blood (patients)	-	[28]

miR microRNA, *Scr* serum creatinine, *Cys-C* Cystatin-C, *KIM-1* kidney injury molecule 1, *NGAL* neutrophil gelatinase-associated lipocalin, *APACHE* Acute Physiology and Chronic Health Evaluation

AKI induced by sepsis [50]. Additionally, the combined detection of miR-29a and miR-10a-5p demonstrated a superior area under the receiver operating characteristic value than the individual detection of miR-29a, miR-10a-5p, Cys-C, Scr and KIM-1. These two miRNAs have a high clinical reference value for the 28-day survival rate of septic AKI and have a wide range of applications [51].

Overall, several miRNAs in body fluids have been reported to be closely associated with the occurrence and prognosis of septic AKI. However, miRNAs need to be extensively evaluated before they may be used in clinical tests.

miRNA-meditated signaling pathways in septic AKI

miRNAs are involved in the pathogenesis of sepsis by regulating multiple signaling pathways, such as the nuclear factor-κB (NF-κB), phosphatase and tension homolog (PTEN) and C-Jun kinase enzyme (JNK) pathways [52–54] (Table 2).

NF-κB signaling pathway A vital mechanism that contributes to inflammation in injured kidneys is activation of theNF-κB pathway. As an essential transcription factor in the cytoplasm, NF-κB contains the dimeric subunits p50/p65, as well as the inhibitory subunit inhibitor of κB (IκB). Before activation, NF-κB dimers are bound to inhibitory IκB proteins (IκBα has been the most researched), and they are sequestered in the cytoplasm. Stimulus-induced degradation of IκBα proteins involves phosphorylation by the IκB kinase (IKK) complex, which consists of the catalytically active kinases IKKα and IKKβ and NF-κB essential modulator (NEMO) (the regulatory subunit IKKγ), which degrade NF-κB dimers via K48 polyubiquitination, resulting in rapid NF-κB activation. Activated NF-κB dimers are translocated into the nucleus and then act as transcription factors for multiple gene promoters, regulating a variety of pathological processes [55]. There is increasing evidence suggesting that the upregulation of NF-κB activity alleviates spetic AKI (Figure 1). For instance, miR210HG, which was upregulated in LPS-induced human HKC-8 cells, activated the NF-κB pathway by phosphorylating IκBα, translocating p65 into the nucleus and ameliorating inflammatory responses, whereas blocking the NF-κB signaling pathway improved renal function [56]. The overexpression of miR-30b promoted NF-κB signaling pathway activation, the release of inflammatory cytokines and apoptosis, but it inhibited LPS-induced autophagy in human kidney proximal tubular cells (HK-2) [54].

In contrast to the research mentioned above, numerous miRNAs may have renoprotective effects during the pathophysiological processes of sepsis-induced AKI. NF-κB activity was shown to be inhibited in HK-2 cells transfected with miR-146b mimics through the targeting of IL-1 receptor-associated kinase (IRAK1) [57]. miR-212-3p overexpression suppressed cell apoptosis by reducing the levels of mitogen-activated protein kinase 1 (MAPK1) and inhibiting the p38/NF-κB pathway in LPS-induced HK-2 cells [58]. Additionally, miR-129-5p levels were decreased in septic AKI models *in vivo* and *in vitro*, and the anti-inflammatory effects of miR-129-5p were partly mediated by inhibiting Toll-like receptors (TLRs)/NF-κB signaling [59]. In LPS-treated mouse kidney tubular cells (TCMK-1), miR-133a was significantly decreased and inhibited inflammation and apoptosis by targeting B-cell lymphoma-2 (Bcl-2)/adenovirus E1B 19 kDa interacting protein 3 (BNIP3) and blocking the NF-κB pathway [60]. A previous study showed that the overexpression of miR-34b-3p alleviated AKI in septic mice by downregulating ubiquitin-like protein 4A (UBL4A)/NF-κB [61]. Previous research has shown that the C-X-C motif chemokine ligand 12 (CXCL12)/C-X-C chemokine receptor

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Table 2. miRNAs-mediated signaling pathways in septic AKI

miRNA	Expression	Target genes	Signaling pPathway	Reference
miR210HG	Upregulation	-	NF-κB	[56]
miR-30b	Upregulation	-	JNK+ NF-κB pathway	[54]
miR-146b	Downregulation	IRAK1	NF-κB	[57]
miR-212-3p	Downregulation	MAPK1	p38/NF-κB	[58]
miR-129-5p	Downregulation	HMGB1	HMGB1/TLRs/NF-κB	[59]
miR-133a	Downregulation	BNIP3L	NF-κB	[60]
miR-34b-3p	Downregulation	UBL4A	NF-κB	[61]
miR -20a	Downregulation	CXCL12	NF-κB	[64]
miR-22-3p	Downregulation	CXCL12	NF-κB	[65]
		HMGB1	PTEN	[75]
miR-125a-5p	Downregulation	TRAF6	TRAF6/NF-κB TRAF6/TAK1	[69]
miR-495-3p	Downregulation	TRAF6	TRAF6/NF-κB	[70]
miR-590-3p	Downregulation	TRAF6	TLR4/TRAF6/NF-κB	[71]
miR-376b	Downregulation	NFKBIZ	NF-κB/miR-376b/NFKBIZ	[45]
miR-452	Upregulation	-	NF-κB/miR-452	[27]
miR-26a-5p	Upregulation	IL-6	NF-κB/miR-26a-5p/IL6	[30]
miR-21	Downregulation	PTEN	PTEN/P13K/AKT	[52]
miR-93	Downregulation	PTEN	PTEN/AKT/mTOR	[32]
miR-214	Downregulation	PTEN	PTEN/AKT/mTOR	[35]
miR-205	Downregulation	HMGB1	PTEN	[76]
miR-150-5p	Downregulation	MEKK3	MEKK3/JNK	[53]
miR-155	Downregulation	SOCS1	SOCS1/JAK2/STAT	[80]

miR microRNA, *NF-κB* nuclear factor-κB, *JNK* C-Jun Kinase enzyme, *IRAK1* interleukin 1 receptor associated kinase 1, *MAPK1* mitogen-activated protein kinase 1, *HMGB1* high mobility group box 1, *BNIP3L* BCL-2/adenovirus E1B 19 kDa interacting protein 3, *UBL4A* ubiquitin-like protein 4A, *CXCL12* chemokine (C-X-C motif) ligand 12, *TRAF6* TNF receptor-associated factor 6, *TAK1* transforming growth factor-beta-activated kinase 1, *TLR4* Toll-like receptor 4, *NFKBIZ* NF-kappaB inhibitor zeta, *IL-6* interleukin 6, *PTEN* phosphatase and tension homolog, *mTOR* mammalian target of rapamycin, *MEKK3* MEK kinase 3, *SOCS1* suppressor of cytokine signaling1, *JAK2* Janus kinase 2, *STAT* signal transducer of activators of transcription

type 4 (CXCR-4) axis can activate the NF-κB pathway and that both are involved in the expression of inflammatory and apoptotic genes [62,63]. miR-20a and miR-22-3p alleviated inflammation and apoptosis by inhibiting the NF-κB signaling pathways by targeting CXCL12 in LPS-treated HK-2 cells [64,65].

Accumulating evidence indicates that tumor necrosis factor (TNF) receptor-associated factor 6 (TRAF6) participates in the canonical NF-κB pathway [66]. Previous research has shown that LPS induced an inflammatory response via the NF-κB signaling pathway [67]. The canonical NF-κB pathway originates from lysine 63 in the ubiquitin (K63-Ub) chain, which serves as a platform for the formation of a signal complex composed of TAK1/TAB2, IKKα/IKKβ/NEMO [68]. This complex subsequently phosphorylates the IκBa protein, triggering NF-κB rapid activation [55] (Figure 1). miR-125a-5p expression was reduced in a mouse model of septic shock induced by LPS, but TRAF6 expression was significantly increased. Moreover, miR-125a-5p reduced LPS-induced acute inflammation in the kidney by targeting the TRAF6/NF-κB axis [69]. TRAF6 levels were significantly increased in serum samples from AKI patients and LPS-induced HK-2 cells, while miR-495-3p levels were noticeably decreased. In LPS-induced HK-2 cells, miR-495-3p directly targets TRAF6 through the NF-κB/p65 signaling pathway [70]. Ma *et al*. observed that the levels of miR-590-3p were markedly decreased in the kidneys of LPS-treated mice. Additionally, TRAF6 and TLR4/TRAF6/NF-κB inflammatory signaling-mediated apoptosis and the upregulation of proinflammatory cytokines in LPS-treated cells could be targeted by inhibiting miR-590-3p expression [71].

Recent research has shown that NF-κB regulates the transcription of miRNAs in addition to direct or indirect targets [72]. For instance, Liu *et al*. discovered that miR-376b levels in urine were significantly reduced in LPS-treated mice and septic patients with AKI. Notably, miR-376b downregulation induced nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor zeta (NFKBIZ) expresion, resulting in a negative feedback loop that limits NF-κB activation, inflammation and tubular cell death [45]. Similarly, there is evidence that NF-κB mediates the induction of miR-452 and miR-26a-5p [27,30]. In LPS-induced AKI mice, miR-452 was induced in renal tubular cells, and the binding of p65/NF-κB to the miR-452 gene promoter was increased more than 2-fold [27]. *In vitro* and *in vivo* models of septic AKI showed that miR-26a-5p expression in renal tubular cells was dramatically elevated in an NF-κB-dependent manner. The induction of miR-26a-5p decreased IL-6 expression, resulting in reduced renal tubular inflammation and protection against septic AKI [30].

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Table 3. miRNAs-mediated cellular mechanisms in septic AKI

miRNA	Expression	Target genes	Function	Reference
miR-152-3p	Upregulation	ERRFI1/STAT3	Facilitate apoptosis and inflammation	[91]
miR-128-3p	Upregulation	NRP1	Facilitate apoptosis and inflammation	[92]
miR-155-5p	Upregulation	WWC1	Facilitate apoptosis and inflammation	[93]
miR-106a	Upregulation	THBS2	Facilitate apoptosis and inflammation	[94]
miR-665	Upregulation	Bcl-2	Facilitate apoptosis and inflammation	[95]
miR-34b-5p	Upregulation	AQP2	Facilitate apoptosis and inflammation	[96]
miR-543	Upregulation	Bcl-2	Facilitate apoptosis and inflammation	[97]
miR-21	Upregulation	CDK6; PDCD4, PTEN	Facilitate cell apoptosis;	[111]
			Inhibit cell apoptosis	[112–114]
miR-545-3p	Upregulation	PPARA	Facilitate cell apoptosis, oxidative stress, inhibit cell viability	[98]
miR-122	Upregulation	VDR	Directly target VDR in renal tubular cells	[99]
miR-21-3p	Upregulation	FOXO1	Regulate the metabolism	[100]
miR-107	Upregulation	DUSP7	Induce TNF-α secretion	[101]
miR-19a	Downregulation	-	Inhibit cell apoptosis	[102]
miR-370-3p	Downregulation	HMGB1	Inhibit apoptosis and facilitate cell proliferation	[103]
miR-17-5p	Downregulation	-	Inhibit inflammation	[104]
miR-942-5p	Downregulation	FOXO3	Inhibit apoptosis and inflammation	[105]
miR-132-3p	Downregulation	HAVCR1	Inhibit apoptosis and inflammation	[19]
miR-21-5p	Downregulation	RUNX1	Inhibit apoptosis, inflammation and oxidative stress	[31]
miR-191-5p	Downregulation	OXSR1	Inhibit apoptosis and inflammation	[19]
miR-201-5p	Downregulation	NOTCH3	Inhibit apoptosis and inflammation	[106]
miR-26a-5p	Upregulation	-	Inhibit inflammation	[30]
miR-23a-3p	Downregulation	Wnt5a	Inhibit inflammation	[108]
miR-29b-3p	Downregulation	HDAC4	Inhibit apoptosis	[109]
miR-30c-5p	Downregulation	TXNIP	Inhibit pyroptosis	[33]
miR-93-5p	Upregulation	TXNIP	Facilitate pyroptosis	[115]
miR-150-5p	Downregulation	STAT3	Inhibit inflammation and oxidative stress	[53]
miR-21-5p	Downregulation	RUNX1	Inhibit oxidative stress	[31]
miR-199b-3p	Downregulation	Nrf2	Inhibit oxidative stress	[17]
miR-214	Downregulation	PTEN	Inhibit oxidative stress and autophagy	[35]
miR-214-5p	Upregulation	AMPK	Facilitate inflammation and oxidative stress	[34]
miR-545-3p	Upregulation	PPARA	Facilitate oxidative stress	[98]
miR-20a	Downregulation	CXCL12	Facilitate autophagy	[64]
miR-526b	Downregulation	ATG7	Facilitate cell viability, inhibit autophagy	[129]

miR microRNA, *ERRFI1* ERBB Receptor Feedback Inhibitor 1, *STAT3* signal transducer and activator of transcription 3, *NRP1* neuropilin-1, *WWC1* WW domain containing protein 1, *THBS2* thrombospondin 2, *Bcl-2* B-cell lymphoma-2, *AQP2* aquaponn-2, *CDK6* cyclin-dependent kinase 6, *PDCD4* programmed cell death 4, *PTEN* phosphatase and tension homolog, *PPARA* peroxisome proliferator activated receptor alpha, *VDR* vitamin D receptor, *FOXO* forkhead box protein O, *DUSP7* dual-specificity phosphatase 7, *TNF-α* tumor necrosis factor-alpha, *HMGB1* high mobility group box 1, *HAVCR1* hepatitis A virus cellular receptor 1, *RUNX1* Runt-related transcription factor 1, *OXSR1* oxidative-stress responsive 1, *NOTCH3* notch homolog 3, *Wnt5a* wingless-related MMTV integration site 5A, *HDAC4* histone deacetylase 4, *TXNIP* thioredoxin interacting protein, *Nrf2* nuclear factor erythroid 2-related factor 2, *AMPK* adenosine 5′-monophosphate (AMP)-activated protein kinase, *CXCL12* chemokine (C-X-C motif) ligand 12, *ATG7* autophagy related protein 7

Taken together, these findings suggested that many miRNAs targeted the adaptable transcription factor NF-κB and further reduced septic AKI by modifying the NF-κB signaling pathways. The miRNAs that are downstream and upstream of the NF-κB signaling pathway are potential targets against septic AKI.

PTEN signaling pathway PTEN is a well-known suppressor that controls inflammatory illnesses by activating the phosphoinositide-3-kinase (PI3K)/v-akt murine thymoma viral oncogene homolog (AKT) pathways [73], which is also important for angiogenesis, cell survival and other biological processes [74]. miRNA-21 overexpression prevented sepsis-induced kidney cell death via PTEN/PI3K/AKT signaling *in vitro* and *in vivo* [52]. In LPS-induced septic AKI mice, miR-93 was downregulated, which inhibited apoptosis, inflammation and the production of reactive oxygen species (ROS) via the PTEN/AKT/mammalian target of rapamycin (mTOR) pathway [32]. Similarly, miR-214 inhibited kidney autophagy, reduced oxidative stress and protected against AKI in septic mice by targeting the PTEN/AKT/mTOR pathway [35]. miR-22-3p improved septic AKI and inhibited the PTEN pathways and NF-κB signaling. Wang *et al*. discovered that the protective effect of miR-22-3p against septic AKI may be mediated by PTEN suppression [75]. Another study indicated that miR-205 could decrease renal

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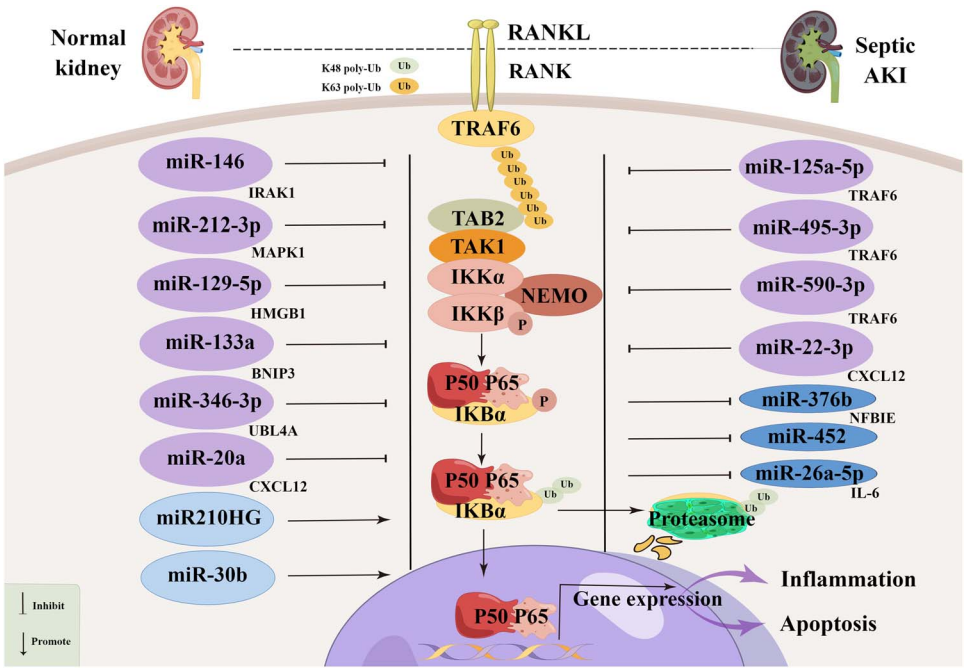


Figure 1. MicroRNAs (miRNAs) participate in the NF-κB pathway in septic acute kidney injury (AKI). RANK-derived canonical NF-κB pathways are outlined, and the K63-Ub chain generated by TRAF6 serves as a substrate for the formation of a signal complex that includes TAK1/TAB2, IKKα/IKKβ/NEMO (the regulatory subunit IKKγ). NF-κB, which is made up of the NF-κB dimers (p50/p65) and another inhibitory subunit IκB (IκBα has been the most studied). The IκBa kinase (IKK) complex, which consists of two catalytically active kinases, IKKα and IKKβ and NEMO, catalyzes the stimulus-induced degradation of IκBα proteins. Phosphorylated IκBa is ubiquitinated by K48 poly-Ub and degraded by proteasomes, causing NF-κB to rapidly activate, allowing bound NF-κB dimers to translocate to the nucleus and bind to multiple gene promoters, regulating various pathogenic processes. miRNAs have a role in the pathology of septic AKI via modulating the NF-κB signaling pathway

tubular epithelial apoptosis in rats with sepsis-induced renal injury via the high-mobility group box 1 (HMGB1)-PTEN signaling pathway [76]. Although a previous study suggested that miRNAs could alleviate AKI by decreasing PTEN expression, there is now a better understanding of the role of PTEN in septic AKI.

JNK signaling pathway All eukaryotic cells require MAPK, which is an intracellular signal transduction network primarily activated by MEK kinase 2 (MEKK2) [77]. The transduction of MAPK signals by MEKK3 is reported to be mediated by JNK [78]. JNK is closely related to septic AKI [79]. For instance, it was discovered that miR-150-5p was down-regulated in the serum of patients with septic AKI, in LPS-treated HK-2 cells and in an LPS-induced AKI animal model. Furthermore, miR-150-5p inhibited LPS-induced apoptosis, inflammatory responses and oxidative stress to protect against septic AKI by targeting signal transducer and activator of transcription 3 (STAT3) and inhibiting the MEKK3/JNK pathway [53]. The overexpression of miR-30b abrogated the LPS-induced decrease in HK-2 cell viability, inflammatory cytokine release, cell apoptosis and activation of the JNK and NF-κB signaling pathways but reduced LPS-induced HK-2 cell autophagy [54]. Another study discovered that inhibiting miR-155 could protect mice against LPS-induced kidney injury by altering the suppressor of cytokine signaling 1 (SOCS1)-Janus kinase 2 (JAK2)/STAT signaling pathway [80]. As stated previously, miRNAs can alleviate septic AKI by suppressing the JNK signaling pathway and thus improve apoptosis, inflammatory responses and oxidative stress, which may be a promising strategy for the treatment of septic AKI.

miRNA-mediated cellular mechanisms in septic AKI

The septic AKI animal model exhibits increased inflammatory response and oxidative stress, as well as tubular cell apoptosis and necrosis [81]. Inflammation and oxidative stress are considered to be the main pathogenesis of septic AKI [82]. Current evidence suggests that inhibiting pyroptosis can improve sepsis-induced AKI in mice [83]. Autophagy has been shown to play an important renoprotective role in septic AKI by inhibiting apoptosis [84,85]. There has been increasing evidence that miRNAs play a critical role in the cellular mechanisms of septic AKI (Table 3, Figure 2).

Inflammatory response and apoptosis The inflammatory response is crucial in the pathophysiology of septic AKI. Apoptosis and inflammation in kidney epithelial cells may cause septic AKI [86,87]. During sepsis, renal tubular epithelial cells in the nephron are apoptotic due to ischemia/reperfusion injury [88], and early septic AKI is associated with the activation of apoptosis [89]. As a result of calcium overload, cascade inflammation and oxygen-free radical release during sepsis, cell apoptosis may take

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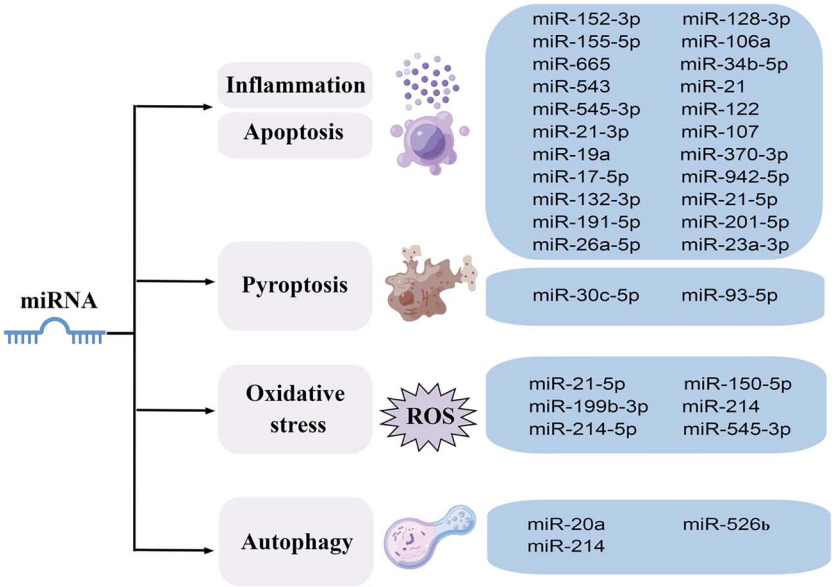


Figure 2. MicroRNAs (miRNAs, miR) are involved in the cellular mechanisms of septic acute kidney injury (AKI). miRNAs have a vital role in participating in regulating inflammation response, apoptosis, pyroptosis, oxidative stress and autophagy in septic AKI. *ROS* reactive oxygen species

place through both endogenous and exogenous pathways, facilitating the occurrence of septic AKI [90]. miR-152-3p was found to be increased in LPS-treated HK-2 and HEK293 cells, as well as in septic AKI patients. Targeting ERBB receptor feedback inhibitor 1 (ERRFI1) boosted apoptosis and inflammation and activated the STAT3 signaling pathway [91]. In LPS-induced septic renal injury, miR-128-3p promoted inflammatory cell infiltration, increased the production of inflammatory cytokines, decreased renal cell function and increased apoptosis [92]. miR-155-5p was upregulated in septic AKI animals and LPS-treated cells, whereas WW domain containing protein 1 (WWC1) inhibition exacerbated sepsis-induced AKI by increasing inflammation and apoptosis, indicating that it plays a role in the development of sepsis [93]. miR-106a was elevated in the serum of septic patients, CLP-induced mouse models and LPS-induced TCMK-1 cells, and it triggered inflammation and apoptosis in TCMK-1 cells by regulating thrombospondin 2 (THBS2) expression [94]. According to a recent study, the level of miR-665 was increased in LPS-treated HK-2 cells and kidneys of rat. Moreover, blocking miR-665 could inhibit LPS-induced inflammation and apoptosis by targeting Bcl-2 [95]. In septic AKI patients, serum miR-34b-5p expression was increased, and this factor targeted aquaporin-2 (AQP2) to facilitate LPS-induced renal cell apoptosis and the inflammatory response [96]. Furthermore, inhibiting miR-543 by targeting Bcl-2 could protect HK-2 cells from LPS-induced inflammation and apoptosis [97]. The upregulation of miR-545-3p in septic patient serum and LPS-induced HK-2 and HEK293 cells significantly reduced cell viability and increased cell apoptosis and migration by inhibiting peroxisome proliferator activated receptor alpha (PPARA) [98]. Moreover, miR-122 directly targeted vitamin D receptor (VDR) in renal tubular cells, and miR-122 induction contributed to the development of kidney injury by down-regulating VDR expression in an LPS-induced AKI model [99]. miR-21-3p was significantly increased in tubular epithelial cells during septic AKI. Severe metabolic alterations in tubular cells may play a critical role in the development of septic AKI via the influence of miR-21-3p on the AKT/cyclin-dependent kinase 2 (CDK2)-forkhead box protein O1 (FOXO1) pathway, resulting in cycle cell arrest and apoptosis [100]. Furthermore, an increase in miR-107 induces TNF-α secretion by targeting dual-specificity phosphatase 7 (DUSP7) in endothelial cells, which may directly lead to tubular cell injury in septic AKI [101].

To date, numerous miRNAs have been demonstrated to protect against septic AKI. LPS reduced the expression of miR-19a in MCT and RAW 264.7 cells, and miR-19a protected against septic AKI by suppressing tubular cell apoptosis [102]. In HK-2 cells damaged by LPS, the suppression of miR-370-3p decreased HMGB1 expression and reduced proliferation, but enhanced apoptosis as well as TNF-α and IL-6 secretion [103]. One study found that miR-17-5p levels were decreased in the serum of AKI patients and HK-2 cells induced by LPS. In addition, TNF-α, IL-6 and IL-1 were severely decreased in LPS-activated HK-2 cells that were transfected with miR-17-5p [104]. Similarly, miR-942-5p expression was reduced in HK-2 cells that were treated with LPS, and the overexpression of miR-942-5p inhibited LPS-induced inflammation and apoptosis in HK-2 cells via targeting FOXO3 [105]. miR-132-3p could protect against LPS-induced AKI in mice by targeting hepatitis A virus cellular receptor 1 (HAVCR1)/KIM-1 expression [19]. Zhang *et al*. reported that exosomal miR-21-5p reduced sepsis-related acute kidney damage by decreasing

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runt-related transcription factor 1 (RUNX1) expression [31]. Additionally, miR-191-5p, which is downregulated in CLP-induced septic kidney injury mice, can lower renal injury scores, the levels of inflammatory cytokines and apoptotic proteins by inhibiting oxidative-stress responsive 1 (OXSR1) expression [106]. Furthermore, miR-201-5p overexpression abrogated the LPS-induced inhibition of renal cell development, apoptosis and inflammation by suppressing TLR4/notch receptor 3 (NOTCH3) signal transduction [107]. miR-26a-5p has recently been found to inhibit inflammation and apoptosis, particularly IL-6 expression, thereby alleviating septic AKI [30]. Several studies have demonstrated increased serum levels of Wnt5a in patients with sepsis [108]. According to one study, miR-23a-3p expression was downregulated in the serum of sepsis patients with AKI and LPS-treated HK-2 cells. Furthermore, miR-23a-3p alleviated LPS-induced cell damage by targeting Wnt5a and reducing Wnt/β-catenin activity, which may be a novel therapeutic target for sepsis-associated AKI [109]. Moreover, the overexpressed of miR-29b-3p inhibited Mouse podocytes cells (MPC5) cell apoptosis by reducing HDAC4 histone deacetylase 4 (HDAC4) protein levels [110].

Notably, miR-21 is frequently analyzed in the context of sepsis. It has been shown that overexpression of miR-21 extends renal dysfunction and facilitates cell apoptosis in LPS-stimulated AKI mice [111]. Interestingly, several studies have yielded the opposite result, that miR-21 has renoprotective properties. miR-21 overexpression can reduce cell apoptosis and inflammation in the kidney via the PTEN/AKT and programmed cell death 4 (PDCD4)/NF-κB pathways, hence preventing kidney injury caused by sepsis [52,112–114]. The cause for these contradictory results is currently unknown. Thus, additional research is needed to determine whether miR-21 protects kidneys or has an aggravating effect in septic AKI.

Pyroptosis Pyroptosis, which is also referred to as inflammatory cell necrosis, is characterized by continual cell expansion, which allows cell contents to leak out and cause an inflammatory reaction. Pyroptosis is the dominant response to caspase-11/4/5 recognition of cytosolic LPS, and this recognition can also trigger nucleotide-binding oligomerization domain-, leucine-rich repeat- and pyrin domain-containing 3 (NLRP3)-mediated secretion of IL-1β/18, but only in a select subsets of cells [115]. MiR-30c-5p levels were reduced in septic mouse kidney tissues and HK-2 cells, and NLRP3 pathway-associated pyroptosis occurred in septic AKI. Furthermore, miR-30c-5p negatively regulates pyroptosis and sepsis-induced injury induced by the NLRP3 signaling pathway through thioredoxin-interacting protein (TXNIP) [33]. Juan *et al*. found that the exosomal miR-93-5p/TXNIP signaling pathway was crucial to the progression of sepsis-induced AKI [116]. The role of miRNAs in pyroptosis remains unknown, as does their specific role in septic AKI and more research is required in this area.

Oxidative stress Excessive inflammation and oxidative stress are involved in sepsis-induced AKI [117–119]. Notably, inflammatory cells can cause the overproduction of ROS, thereby reducing NO bioavailability [120]. This process can add to the superoxide pool and initiate a vicious cycle of oxidative stress, inflammation and vascular damage [121]. According to a recent study, superoxide dismutase (SOD) levels are decreased, malondialdehyde (MDA) levels are elevated and pathological damage is increased in kidney tissue during sepsis [122]. The overexpression of miR-150-5p reduced TNF-α, IL-6 and IL-1β levels, decreased BUN and Scr levels in septic AKI mice, and upregulated the expression of the antioxidant markers SOD and catalase, while downregulating the levels of MDA in the kidneys. miR-150-5p exerts a series of renoprotective effects by reducing inflammation and oxidative stress [53]. Moreover, exosomal miR-21-5p generated by Endothelial progenitor cells (EPCs) reduced sepsis-induced kidney injury by downregulating RUNX1 expression, resulting in endothelial protection in renal tissues during sepsis-induced AKI [31]. Previous studies have proven that the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway can alleviate septic AKI [123,124]. Nrf2 plays a crucial role in cellular defense and protection, and it has been reported that Nrf2 inhibits oxidative stress and inflammation [125,126]. For instance, it was suggested that the target of miR-199b-3p exerted renoprotection effects by inhibiting oxidative stress in LPS-treated cells [17]. miR-214 alleviated CLP-induced AKI by reducing oxidative stress through regulation of the PTEN/AKT/mTOR pathway [35]. However, miR-214-5p inhibition can mitigate septic AKI by suppressing oxidative stress, as evidenced by a significant increase in ROS and SOD levels and a decrease in MDA levels [34]. Additionally, a decrease in SOD levels and an increase in MDA levels after miR-545-3p overexpression in LPS-treated HK-2 and HEK293 cells demonstrated that inhibiting miR-545-3p protected against kidney injury by suppressing oxidative stress [98].

Autophagy Autophagy, which is a strictly controlled cellular catabolism process that is conserved from yeast to mammals, is essential for preserving cellular homeostasis by degrading cytoplasmic components [127,128]. Sepsis-induced AKI is associated with autophagy [129]. For instance, miR-20a promoted kidney injury in septic rats through autophagy [64]. Liu *et al*. demonstrated that excessive autophagy induced apoptosis in response to LPS stimulation, suggesting that autophagy was involved in sepsis-induced kidney damage. Furthermore, miR-526b may enhance cell viability by inhibiting autophagy and may be capable of targeting autophagy-related gene 7 (ATG7) in septic AKI [130]. A recent study demonstrated that miR-214 could attenuate AKI in septic mice by decreasing kidney autophagy through inhibition of the PTEN/AKT/mTOR pathway [35]. Overall, multiple lines of evidence suggest that miRNAs could play an important role in the pathophysiology of septic AKI, and as renoprotective

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treatments for AKI are researched, targeting autophagy will be a critical step forward.

Therapeutic potential of miRNAs in septic AKI

Studies have revealed that miRNA expression can be altered to mitigate kidney damage caused by sepsis. miRNAs play various roles in the development of septic AKI. Additional research has focused on miRNAs that are known to cause kidney damage, including miR-191-5p, miR-34b-3p, miR-93, miR-22-3p, miR-30c-5p, miR-150-5p and miR-23a-3p, via inhibiting inflammation, cell apoptosis and oxidative stress [32,33,53,61,65,106,109]. Some of these factors have shown promising therapeutic effects in animal models of septic AKI. For instance, in a septic AKI mouse model, the suppression of miR-214-5p, miR155, miR30b or miR106a showed significant renoprotective effects *in vivo* [54,80,94,34]. In addition, honokiol might alleviate septic AKI partly through the miR-218-5p/heme oxygenase 1 (HO-1) pathway [131]. Tian *et al*. found that dihydromyricetin regulated miR-199b-3p to affect the Nrf2 pathway, which might alleviate septic AKI [17]. Moreover, dexmedetomidine mitigated oxidative stress and inflammatory responses and reduced the severity of renal injury in LPS-treated rats by upregulating the expression level of miR-146a [132]. Another study revealed that human umbilical cord mesenchymal stem cell-derived exosomes decreased IL-1 receptor-associated kinase 4 (IRAK1) expression by increasing miR-146b levels, which improved sepsis-associated AKI and mouse survival [57]. Additionally, propofol and ginkgolide A have been shown to ameliorate septic AKI by modulating miRNA expression [17,133]. A few studies have demonstrated that xenon preconditioning and limb remote ischemic preconditioning can protect against septic AKI by upregulating the expression of miR-21 [112,113]. Research has shown that altering miRNA levels can reduce the severity of septic AKI, suggesting that it could be used as a treatment for septic AKI. However, more research is needed to determine the therapeutic effects of miRNAs on sepsis-induced AKI, and additional research is required to establish the efficacy and safety of miRNA regulation for clinical use.

Conclusions

In summary, sepsis is a serious complication of severe trauma, serious infection, large area burns and major surgery and has high mortality and morbidity, and concomitant AKI significantly worsens the prognosis of sepsis patients. The development of molecular biology and experimental techniques to analyze miRNAs has contributed to in-depth investigations of the pathological mechanisms of septic AKI. It has been gradually discovered that miRNAs have a promising future as potential biomarkers and therapeutic targets in septic AKI. However, miRNA studies on septic AKI should be validated in larger patient cohorts to demonstrate their applicability in clinical settings. A safer and more efficient method of medication delivery, as well as a more accurate technology for detecting miRNAs, will be required in future studies.

Abbreviations

AKI: Acute kidney injury; AKT: V-akt murine thymoma viral oncogene homolog; APACHE: Acute physiology and chronic health evaluation; AQP2: Aquaporin-2; ATG7: Autophagy-related gene 7; Bcl-2: B-cell lymphoma-2; BNIP3: Bcl-2/Adenovirus E1B 19 kDa interacting protein 3; BUN: Blood Urea Nitrogen; CDK2: Cyclin-dependent kinase 2; CLP: Cecal ligation puncture; CXCL12: C-X-C motif chemokine ligand 12; CXCR-4: C-X-C chemokine receptor type 4; Cys-C: Cystatin-C; DUSP7: Dual-specificity phosphatase 7; EPCs: Endothelial progenitor cells ; ERRFI1: ERBB receptor feedback inhibitor 1; FOXO1: Forkhead box protein O1; HAVCR1: Hepatitis A virus cellular receptor 1; HDAC4: Histone deacetylase 4; HMGB1: High-mobility group box 1; HO-1: heme oxygenase 1; IGFBP7: Insulin-like growth factor binding protein-7; IκB: Inhibitor of κB; IKK: IκB kinase; IL-18: Interleukin-18; IRAK1: Interleukin-1 receptor-associated kinase; IRAK1: Interleukin-1 receptor-associated kinase 4; JAK2: Janus kinase 2; JNK: C-Jun kinase enzyme; KIM-1: Kidney injury molecule 1; K63-Ub: lysine 63 of ubiquitin; lncRNA: Long-chain non-coding RNA; LPS: lipopolysaccharide; MAPK1: MEKK2: MEK kinase; Mitogen-activated protein kinase 1; miRNA: MicroRNA; mTOR: mammalian target of rapamycin; MDA: Malondialdehyde; ncRNA: Non-coding RNA; NEMO: NF-κB essential modulator; NF-κB: Nuclear factor-κB; NFKBIZ: Nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor zeta; NGAL: Neutrophil gelatinase-associated lipocalin; NLRP3: Nucleotide-binding oligomerization domain, leucine-rich repeat and pyrin domain-containing 3; NOTCH3: notch receptor 3; NRP1: neuropilin-1; OXSR1: Oxidative-stress responsive 1; PDCD4: Programmed cell death 4; PI3K: Phosphoinositide 3-kinase;PPARA: peroxisome proliferator activated receptor alpha; PTEN: Phosphatase and tension homolog; RUNX1: Runt-related transcription factor 1; nrf2: Nuclear factor erythroid 2-related factor 2; ROS: Reactive oxygen species; Scr: Serum creatinine; SOCS1: Suppressor of cytokine signaling 1; SOD: Superoxide dismutase; STAT: Signal transducer and activator of transcription; THBS2: Thrombospondin 2; TIMP2: Tissue inhibitor metalloproteinase-2; TLR: Toll-like receptor; TRAF6: TNF receptor-associated factor 6; TXNIP: Thioredoxin-interacting protein; UBL4A; Ubiquitin-like protein 4A; VDR: Vitamin D receptor; WWC1: WW domain containing protein 1.

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Authors'contributions

BW and JX defined the subject, reviewed the literature and wrote the manuscript. LM was responsible for the literature search and manuscript revision. PF reviewed the revised manuscript for important intellectual content. All the authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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