

REVIEW

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Research progress on miR-124-3p in the field of kidney disease

Guanting Chen^{1,3}, Yaoxian Wang^{2,3*}, Linqi Zhang^{1,3*}, Kang Yang^{1,3}, Xixi Wang^{1,3} and Xu Chen^{1,3}

Abstract

MicroRNAs (miRNAs) are 18–25 nucleotides long, single-stranded, non-coding RNA molecules that regulate gene expression. They play a crucial role in maintaining normal cellular functions and homeostasis in organisms. Studies have shown that miR-124-3p is highly expressed in brain tissue and plays a significant role in nervous system development. It is also described as a tumor suppressor, regulating biological processes like cancer cell proliferation, apoptosis, migration, and invasion by controlling multiple downstream target genes. miR-124-3p has been found to be involved in the progression of various kidney diseases, including diabetic kidney disease, calcium oxalate kidney stones, acute kidney injury, lupus nephritis, and renal interstitial fibrosis. It mediates these processes through mechanisms like oxidative stress, inflammation, autophagy, and ferroptosis. To lay the foundation for future therapeutic strategies, this research group reviewed recent studies on the functional roles of miR-124-3p in renal diseases and the regulation of its downstream target genes. Additionally, the feasibility, limitations, and potential application of miR-124-3p as a diagnostic biomarker and therapeutic target were thoroughly investigated.

Keywords miR-124, miR-124-3p, Kidney, Function, Mechanism, Research progress

Background

The kidney is a vital organ with multiple physiological functions, including waste elimination, internal environmental balance, and endocrine homeostasis [1]. Diabetes, hypertension, primary glomerular diseases, and other kidney disorders often progress gradually with subtle initial symptoms, making them difficult to detect and frequently leading to Chronic Kidney Disease (CKD). The

complex pathophysiological mechanisms of CKD remain largely unexplained, and effective treatments are currently unavailable [2]. Therefore, researching new diagnostic and therapeutic targets and strategies is crucial for delaying CKD progression and improving patients' quality of life. Numerous studies have shown that microRNAs (miRNAs) regulate kidney physiological functions and the pathophysiological mechanisms of various kidney diseases. Among them, miR-124-3p, a subtype of miR-124, exhibits extensive biological functions and potential clinical applications, suggesting it could be a novel target for diagnosing and treating kidney diseases.

In this review, we summarize the role of miR-124-3p in kidney diseases and outline its mechanisms in Diabetic kidney disease (DKD), kidney stones, acute kidney injury (AKI), lupus nephritis (LN), and renal interstitial fibrosis (RIF). Finally, we emphasize the potential and challenges of miR-124-3p as a target for improving kidney function and disease diagnosis and treatment.

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The generation and function of miRNAs

MiRNAs are posttranscriptional regulators of protein-coding genes, mainly involved in gene expression regulation. They are short endogenous non-coding RNA molecules in eukaryotes, typically comprising 18–25 nucleotides [3]. There are currently more than 2,300 miRNAs with time- and tissue-dependent expression patterns in human cells [4]. miRNA coding sequences are generally found in exons, introns, or intergenic regions of protein-coding genes and are regulated by host genes and their promoters [5]. During biogenesis, the miRNA coding sequence is transcribed by RNA polymerase II or III into a hairpin-structured primary miRNA (pri-miRNA) that ranges from 300 to 1,000 bases in length. The pri-miRNA is cleaved in the nucleus by the Drosha-DGCR8 microprocessor complex to form a precursor miRNA (pre-miRNA) of about 70 bases. The pre-miRNA is transported from the nucleus to the cytoplasm by exportin-5, where it is cleaved by the RNase Dicer enzyme and the double-stranded RNA-binding protein TRBP to form a mature miRNA duplex. The miRNA duplex unwinds, and a single-stranded miRNA is incorporated into the RNA-induced silencing complex (RISC). By base-pairing with sequences in the 3'UTR or 5'UTR of target mRNAs, miRNAs can cause translational repression or mRNA degradation, inhibiting the expression of the target gene [6], as shown in Fig. 1. The relationships between miRNAs and their target mRNAs are complex. A single miRNA can regulate the transcription of multiple target genes, while a single gene or pathway is often regulated by multiple miRNAs, creating a powerful regulatory network [7]. It's estimated that miRNAs regulate up to 60% of protein-coding genes in the human body, making them key regulatory factors in cellular signaling [8].

Overview of miR-124-3p

The discovery of miRNAs in 1993 highlighted their significant role in gene expression regulation [9]. In 2004, Sun YQ et al. identified miRNAs specific to the kidneys [10], and in 2008, Harvey SJ et al. described the mechanisms by which miRNAs affect renal function [11]. It is now believed that miRNAs play a role in nearly every biological process in the human body. Generally, miRNAs influence a range of cellular biological processes, such as development, differentiation, proliferation, apoptosis, metabolism, and immune response, by precisely regulating gene expression under normal physiological conditions. Changes in miRNA expression are critical for regulating complex genetic networks and cellular signaling cascades. Imbalances in these regulatory mechanisms may contribute to the onset and progression of various diseases [12].

miR-124-3p has garnered significant attention among researchers in recent years. Lagos-Quintana M et al. first discovered miR-124 in mouse tissues in 2002 [13]. This miRNA is expressed in various tissues, with the highest specificity for brain tissue [14]. The miR-124 family includes miR-124-1, miR-124-2, and miR-124-3, located on chromosomal regions 8p23.1, 8q12.3, and 20q13.33, respectively [15]. These precursor RNAs undergo a series of biological processes to ultimately produce mature miR-124-3p, with sequences of 53 - UAAGGC ACGCGGUGAAUGCCAA-74, 62 - UAAGGCACGC GGUGAAUGCCAA-83, and 53 - UAAGGCACGCGG UGAAUGCCAA-74. Due to its high conservation, the mature sequence of miR-124-3p is identical in humans, mice, and rats [16]. (Another mature form of miR-124 is miR-124-5p, but studies on this variant are limited, and there are currently no publications related to kidney diseases. During our literature review, we found studies on

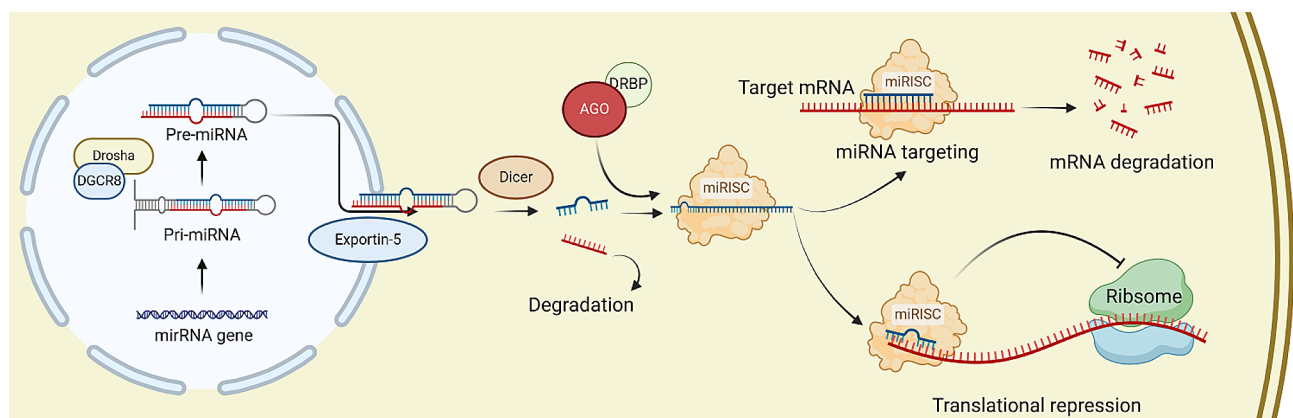


Fig. 1 Mechanism of miRNA action. The miRNA gene is transcribed by RNA polymerase II to generate the precursor pri-miRNA. This precursor is then cleaved by the ribonuclease Drosha and its cofactor DGCR8, producing a hairpin-shaped pre-miRNA. The pre-miRNA is exported to the cytoplasm by Exportin-5 and further processed by the nuclease Dicer, which removes the terminal stem-loop structure, yielding a mature miRNA duplex. Only one strand of the miRNA duplex is incorporated into the RISC, forming the miRNA-induced silencing complex (miRISC). This complex mediates either the degradation or translational repression of the target mRNA

miR-124, but they did not specify whether 3p or 5p forms were involved. However, through careful sequence alignment and comparison with known microRNA databases, we concluded that the miR-124 mentioned in these studies likely corresponds to miR-124-3p. Therefore, given the relevance and current research prospects of miR-124-3p, our review primarily focuses on this molecule. We recognize the potential importance of miR-124-5p, and as more studies are conducted, it will be an area for future investigation.)

Under normal physiological conditions, miR-124-3p is abundantly expressed in the nervous system, where it plays a critical role in neuronal differentiation and functional maintenance. This miRNA governs key processes, such as neuronal differentiation, synapse formation, and axon growth. Additionally, miR-124-3p demonstrates neuroprotective effects in some neurological disorders. Furthermore, miR-124-3p is involved in regulating immune responses, influencing inflammatory reactions and immune cell functions, and notably affecting monocyte differentiation and macrophage activity [17].

Macrophages are essential immune effector cells, derived from mature monocytes [18]. Macrophages can differentiate into the proinflammatory M1 type or the anti-inflammatory M2 type depending on the tissue microenvironment [19]. M1 macrophages express high levels of MHC complexes, activate adaptive immune responses, and produce nitric oxide, reactive oxygen species, and reactive nitrogen species to target cells while secreting cytokines to promote inflammation [20]. M2 macrophages, inducible by various cytokines, play key roles in tissue remodeling, regeneration, wound healing, and anti-inflammation. M2 macrophages can be subdivided into three subgroups based on stimuli: M2a, induced by IL-4 and/or IL-13, promote anti-inflammation, wound healing, and tissue fibrosis; M2b, induced by immune complexes with LPS and/or IL-1R ligands, have immunomodulatory functions; M2c, induced by IL-10, TGF- β , or glucocorticoids, contribute to immunosuppression, matrix deposition, and tissue remodeling [21, 22]. Multiple studies have described miRNA expression under various polarization conditions in human and mouse macrophages [23–25]. miR-124-3p is identified as a miRNA that promotes anti-inflammatory responses and M2 polarization in macrophages. Sun et al. found that miR-124-3p enhances the anti-inflammatory effect of cholinergic agonists and its overexpression protects mice from septic shock. Further research indicates that miR-124-3p regulates LPS-induced cytokine production by targeting STAT3, reducing IL-6 generation. Additionally, it decreases TNF- α release by targeting tumor necrosis factor- α converting enzyme (TACE) [26]. Veremeyko et al. demonstrated that monocytes show heterogeneity with distinct M1 and M2 activation pathways.

miR-124-3p is upregulated in macrophages treated with IL-4 and IL-13, facilitating the development and maintenance of the M2 phenotype. Knocking out miR-124-3p inhibits M2 markers CD206 and Ym1, while enhancing M1 markers CD86, iNOS, and TNF in M2 polarized macrophages [27].

In various diseases, changes in miRNAs and their subsequent transcriptional regulation of target proteins play a key role in the progression of pathology. According to the ENCORI database, miR-124-3p targets up to 2,509 mRNA molecules, affecting a wide range of cellular processes and biological functions, such as cell growth, differentiation, apoptosis, signal transduction, and metabolism [28]. Consequently, abnormal expression or malfunction of miR-124-3p could contribute to the development of various diseases. Early studies showed that miR-124-3p plays a significant regulatory role in tumor development and progression by promoting cancer cell migration and invasion [29–31]. Recent research has revealed that miR-124-3p also regulates neurological diseases [32], cardiovascular diseases [33], microglial cell polarization [34], vascular endothelial cell proliferation [35], and osteogenic differentiation [36]. It is closely linked to several physiological and pathological mechanisms, including inflammation [37], oxidative stress [38], ferroptosis [39], and autophagy [35]. In recent years, miR-124-3p has drawn increasing attention in kidney disease research. It influences the physiological and pathological states of glomerular endothelial cells, renal tubular epithelial cells, and mesangial cells by interacting with multiple target genes and interfering with downstream signaling pathways. Consequently, miR-124-3p is involved in the development and progression of diseases such as RIF, LN, AKI, and DKD.

The role of miR-124-3p in renal diseases

miR-124-3p is expressed in immune cells and various organs, with relatively higher expression in kidney tissue [40]. In many contexts, miR-124-3p is induced by inflammatory signals and acts as a negative regulator to maintain homeostasis. Its expression changes are considered key in regulating immune cells, inflammation, and immune responses [41]. Renal diseases and autoimmunity have a close interactive relationship. Their dysfunction can lead to the development of various renal diseases and, as the disease progresses, can also affect the normal function of the host's immune system. miR-124-3p is recognized as a common miRNA in fibrotic diseases, regulating epithelial-mesenchymal transition (EMT) by modulating the expression of genes such as E-cadherin, Vimentin, N-cadherin, Snail-1, and ZEB2 [42]. This aligns with the histopathological characteristics of CKD, marked by persistent renal tissue inflammation and excessive extracellular matrix deposition leading to

tubulointerstitial and glomerular fibrosis [43]. With the development of high-throughput omics technologies, studies have shown that miRNAs exhibit robust stability in urine [44], plasma [45], and tissues [46] and significant differential expression in various renal diseases [47–49], suggesting their potential as diagnostic biomarkers and therapeutic targets. For instance, miRNAs in renal biopsies correlate highly with pathological changes and progression rates in glomeruli, tubulointerstitium, and/or vascular compartments [50]. For diagnostic purposes, miRNAs in blood and urine have greater clinical application potential. miRNAs in plasma can be passively released from cells or actively secreted into the extracellular space in extracellular vesicles (such as exosomes) and other macromolecular complexes or lipoproteins. miRNAs in urine originate from urological system cells or are passively filtered from plasma. These miRNAs may therefore reflect renal or systemic pathological changes [50]. Based on this, exploring the expression pattern of miR-124-3p in the kidney and its relationship with disease progression may offer new perspectives for early diagnosis and intervention of renal diseases.

miR-124-3p and diabetic kidney disease

According to the International Diabetes Federation, the number of global diabetes patients reached 537 million in 2021 and is projected to rise to 784 million by 2045 [51, 52]. Approximately 30–40% of diabetes patients currently have concurrent DKD [53]. However, there is no effective early diagnostic method for DKD in clinical practice. Intervention measures mainly focus on strictly controlling blood glucose, lipids, and blood pressure to delay disease progression.

Pathological research shows that in patients with DKD, mitochondrial morphological changes are often observed in the proximal convoluted tubules. These changes include fragmentation into short rod-like or spherical shapes, accompanied by cristae rupture, blurring, or disappearance [54]. Recent studies have found increasing evidence of mitochondrial dysfunction in the renal tissues of patients with DKD and in animal models, indicating that mitochondrial dysfunction plays a significant role in the development of DKD [55]. Renal tubular epithelial cells contain abundant mitochondria and are responsible for reabsorbing glucose, amino acids, sodium, potassium, and phosphorus from the urine filtered by the glomerulus. These processes require a substantial amount of ATP. Mitochondrial oxidative phosphorylation, which produces ATP, also generates reactive oxygen species (ROS). Under normal physiological conditions, moderate levels of ROS support cell signaling. In a high-sugar, high-fat, and hypoxic environment, the renal tubules produce elevated levels of ROS and other harmful metabolites due to increased metabolic and excretory activity. This can

lead to mitochondrial oxidative stress, causing mitochondrial damage and dysfunction, ultimately resulting in cell injury or death [56]. Previous studies have shown that, in amyotrophic lateral sclerosis, normalizing miR-124 levels in the motor neurons of SOD1G93A transgenic mice can prevent disruptions in synaptic networks, mitochondrial dynamics irregularities, and excessive activation of microglia [57]. Additionally, miR-124-3p has been shown to be released from SH-SY5Y neuronal cells via exosomes, reducing microglia activation induced by interferon γ (IFN γ). This helps to control excessive microglia activation and protects neurons from mitochondrial oxidative damage [58]. Moreover, miR-124-3p promotes mitochondrial biogenesis, supports the tricarboxylic acid cycle, and enhances ATP synthesis, underscoring its close relationship with mitochondrial structure and function.

Recent studies indicate that mitochondrial biogenesis enhances oxidative phosphorylation capacity, reduces pathological oxidative stress, and aids in repairing mitochondrial dysfunction [59]. In mitochondrial biosynthesis, peroxisome proliferator-activated receptor gamma coactivator 1 α (PGC-1 α) plays a crucial regulatory role by increasing the expression of transcription factors and enhancing their activity through cooperative action [60]. PGC-1 α activation relies on cAMP response element-binding protein (CREB) and occurs through post-translational modification or increased transcription. Once activated, PGC-1 α moves to the cell nucleus, activating downstream nuclear respiratory factors 1/2 (NRF1/2). This increases the expression of mitochondrial transcription factor A (TFAM), which binds to the D-loop of mtDNA and activates mtDNA replication and transcription [61]. Subsequently, TFAM induces mitochondrial biogenesis by promoting mitochondrial expression, oxidative phosphorylation, and increasing intracellular ATP concentration. Additionally, other signaling pathways contribute to the transcriptional activation of mitochondrial biogenesis, including the AMPK/PGC-1 α pathway, the G β Y-AKT-eNOS-sGC pathway, the AKT/FOXO3a axis, and the assistance of sirtuins (such as SIRT1 and SIRT3) in transcription [62]. Purified mitochondria contain mature and precursor miRNAs [63]. Mitochondrial activity is involved in assembling the RNA-induced silencing complex (RISC) and the miRNA-mediated silencing process [64, 65], suggesting a functional link between miRNAs and mitochondria. Additionally, miRNAs regulate nuclear-encoded mitochondrial proteins [66] and mitochondrial metabolism [67, 68]. Current research identifies miR-124-3p as a key molecule affecting mitochondrial localization and function in primary motor neurons of mice. Vimentin, an intermediate filament protein associated with mitochondria in various cell types, is a critical target of miR-124 in this system [69]. By regulating Vimentin expression, miR-124 influences

mitochondrial function and distribution, affecting the morphology and function of motor neurons [70]. Furthermore, miR-124-3p promotes succinate accumulation in mitochondria by targeting and inhibiting stearoyl-CoA desaturase 1 (SCD1) expression. Succinate, an intermediate product of the tricarboxylic acid cycle, accumulates in mitochondria and stimulates mitochondrial complex II (succinate dehydrogenase). This enhances mitochondrial energy production, oxidative phosphorylation, and promotes mitochondrial biogenesis [71].

Therefore, miR-124-3p might also be involved in DKD associated with mitochondrial metabolic abnormalities (Fig. 2). Recent research by Liang LQ et al. found a significant downregulation of miR-124-3p expression in the renal tubular epithelial cells of db/db mice. Overexpressing miR-124-3p markedly enhances mitochondrial function, including improved mitochondrial energy metabolism and reduced oxidative stress. Further research shows that miR-124-3p regulates the expression of the mitochondrial function-related gene Sirt4 by suppressing FOXQ1, its direct target gene [72]. Sirt4 plays a key role in regulating mitochondrial function, impacting mitochondrial fusion and fission processes, and aiding in the removal of dysfunctional mitochondria. Specifically, increased Sirt4 expression effectively modulates mitochondrial dynamics, including fusion and fission,

and promotes the clearance of damaged mitochondria, thereby preserving normal mitochondrial function. In contrast, reduced Sirt4 expression leads to mitochondrial dysfunction, promoting ROS generation and contributing to the progression of DKD [73].

The glomerulus, the basic functional unit of the kidney, is a dense capillary cluster consisting of podocytes, endothelial cells, and mesangial cells [74]. Podocytes are terminally differentiated, highly specialized cells that adhere to the glomerular basement membrane (GBM). Along with glomerular endothelial cells and the GBM, they form the glomerular filtration barrier. Endothelial cells line the glomerular capillaries, while mesangial cells are mainly located in the mesangial region between the capillary walls. Both cell types are essential for maintaining glomerular homeostasis and reducing glomerular injury [75, 76]. As diabetic kidney disease (DKD) progresses, significant structural and functional changes occur in the glomerulus. Diabetes triggers adaptive pathological changes, such as thickening of the GBM, mesangial cell hypertrophy and proliferation, and increased mesangial matrix deposition. Glomerular endothelial cells show proliferation, endothelial integrity disruption, immature angiogenesis, and an increase in endothelial-mesenchymal transition [77]. At the same time, podocytes undergo cytoskeletal rearrangements, fusion or

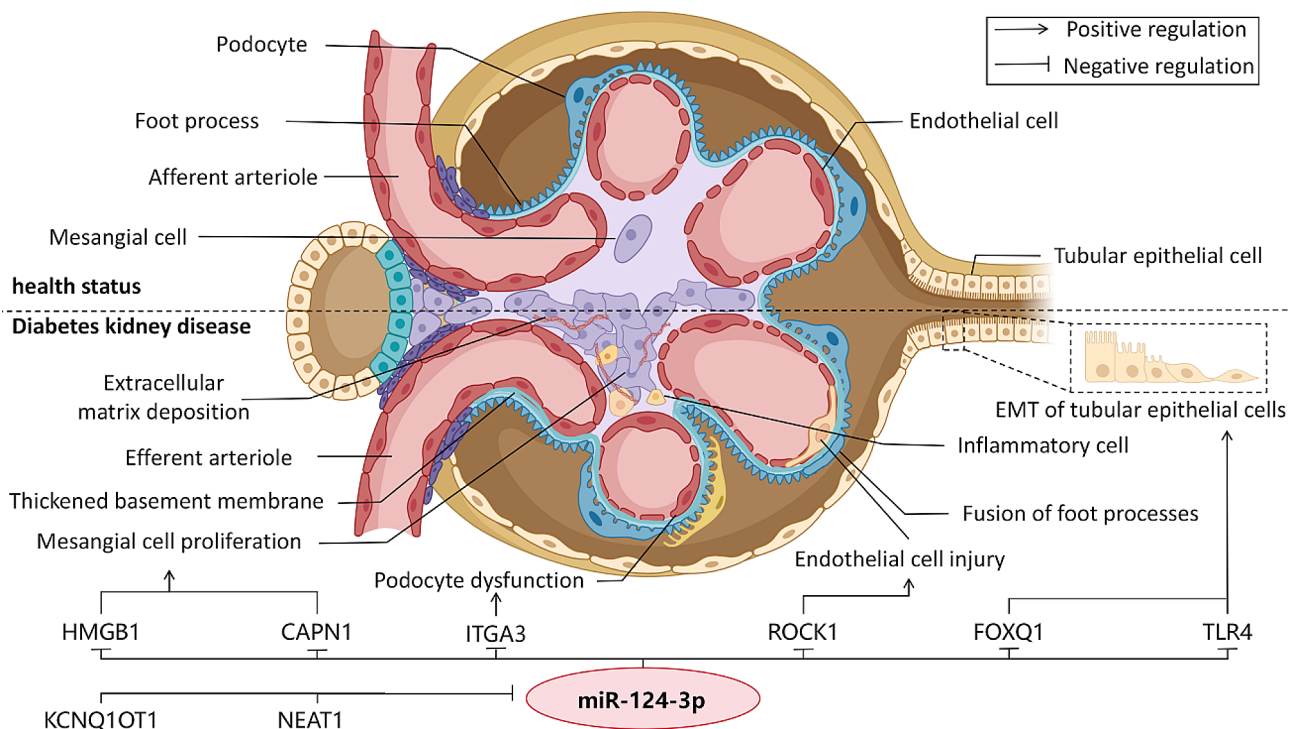


Fig. 2 miR-124-3p in diabetic kidney disease. The key pathological mechanisms of DKD include renal tubular fibrosis, thickening of the GBM, mesangial hypertrophy with abnormal proliferation, inflammatory cell infiltration, extracellular matrix (ECM) deposition, and podocyte foot process fusion or detachment. Multiple studies have shown that miR-124-3p plays a key role in the pathological progression of DKD, specifically exerting a protective effect on glomeruli. This microRNA can potentially reduce pathological processes like EMT, fibrosis, and inflammation by regulating key gene expression and modulating signaling pathways. These findings suggest potential therapeutic targets for the treatment of DKD

disappearance of foot processes, increased intercellular tight junctions, reduced slit diaphragm length, and even a decrease in podocyte count. These cellular abnormalities can increase glomerular capillary permeability and damage the glomerular filtration barrier, eventually causing proteinuria [78]. As a key microRNA, miR-124-3p plays a critical role in the glomerulus. For example, Peng H et al. found that under hyperglycemic conditions, miR-124 expression decreases in glomerular endothelial cells, while ROCK1 activity increases, leading to abnormalities in cell apoptosis and tight junction protein expression. The activation of ROCK1 can increase endothelial cell permeability, promote mesenchymal cell transdifferentiation, cause podocyte injury, and drive EMT. In contrast, overexpressing miR-124 can directly inhibit ROCK1 activity, reducing these types of damage [79]. Dong Li's team studied podocyte adhesion damage and its relationship with microRNAs. Using miRNA microarray analysis, they identified four microRNAs—miR-124, miR-190, miR-217, and miR-188—involved in podocyte adhesion damage under mechanical stress. Among these, miR-124 was found to target integrin $\alpha 3$ (ITGA3). Subsequent *in vivo* experiments revealed podocyte adhesion damage in streptozotocin (STZ)-induced uninephrectomized diabetic rats, indicated by elevated urinary podocytic nephrin, podocin, and albumin excretion, as well as reduced ITGA3 expression in renal cortical tissue. Furthermore, miRNAs showed differential regulation in the renal cortex of STZ-induced uninephrectomized diabetic rats, with significantly increased expression of miR-124. When miR-124 expression was inhibited in rats, podocyte adhesion improved significantly. These results suggest that miR-124 is related to podocyte adhesion damage and may be involved in the development of DKD [80–82]. Regarding mesangial cells, Lu H et al.'s study indicates that miR-124-3p can inhibit mesangial cell proliferation and fibrosis by negatively regulating high mobility group box 1 (HMGB1) [83]. Zhao N et al.'s study revealed another function of miR-124-3p: it reduces inflammatory responses and fibrosis by inhibiting the calpain-1 (CAPN1)/ β -catenin signaling pathway while inhibiting apoptosis in diabetic nephropathy models [84]. Additionally, Wang P et al.'s study found that miR-124-3p significantly reduces renal injury and fibrosis in STZ-induced DKD mice. This protective effect is related to miR-124-3p's inhibition of the Toll-like receptor 4 (TLR4)/nuclear factor κ B (NF- κ B) signaling pathway. By targeting and suppressing TLR4 transcription, it also inhibits downstream NF- κ B signaling, reducing the production of fibrosis-related factors, and slowing the progression of renal fibrosis [85]. Collectively, these studies illustrate the diverse role of miR-124-3p in regulating glomerular mesangial cell functions, including proliferation, fibrosis, inflammatory responses, and apoptosis.

These discoveries not only deepen our understanding of miR-124-3p's role in DKD but also offer valuable insights into developing new therapeutic strategies. However, more research is needed to clarify the specific regulatory mechanisms of miR-124-3p. Additionally, there is growing recognition of the importance of developing and testing miR-124-3p-targeted interventions in preclinical and clinical settings, which could offer new possibilities for future therapies.

MiR-124-3p and kidney stones

Kidney stones are closely associated with diet, exercise, and family history [86, 87]. Research indicates that the incidence of kidney stones is steadily increasing. The high recurrence rate can lead to various urinary system problems [88–90]. However, non-surgical treatments for recurrent kidney stones have limited effectiveness, and there are few preventive methods. Therefore, further research on the pathological mechanisms of kidney stones is crucial. Recent research suggests that the formation of CaOx stones, the primary component of kidney stones, is linked to an inflammatory response. Multiple clinical-pathological studies have demonstrated that renal interstitial CaOx crystals in patients with kidney stones and animal models are often surrounded by monocytes or macrophages, forming a vesicular structure [91]. *In vitro* and *in vivo* experiments have further confirmed that CaOx crystals stimulate renal tubular epithelial cells, leading to the release of cytokines such as osteopontin (OPN), monocyte chemoattractant protein-1 (MCP-1), cluster of differentiation 44 (CD44), and TGF- β . MCP-1 is thought to be the key trigger that initiates inflammation during the formation of calcium oxalate stones [92]. miR-124-3p has been identified as a major modulator of inflammation, demonstrating significant anti-inflammatory effects during the formation of CaOx crystals. Guo ZY et al. found through bioinformatics analysis and *in vitro* experiments that Lnc HOXA11-AS inhibits cell proliferation, induces cell apoptosis, and worsens cell damage during calcium oxalate crystallization-induced kidney injury. Overexpressing miR-124-3p, which competitively binds to HOXA11-AS, significantly mitigates these effects. Further research has shown that miR-124-3p reduces inflammation by targeting and suppressing the expression of MCP-1 [93] (Fig. 3). MCP-1, a member of the chemokine CC family, primarily regulates the movement of inflammatory cells. It can selectively recruit monocytes, neutrophils, and lymphocytes to sites of inflammation and tissue damage, playing a significant role in the initiation and maintenance of inflammatory responses [94]. When monocytes are attracted to the site of stone formation, they respond quickly to the surrounding inflammatory environment by releasing additional pro-inflammatory cytokines like TNF- α and IL-1 β .

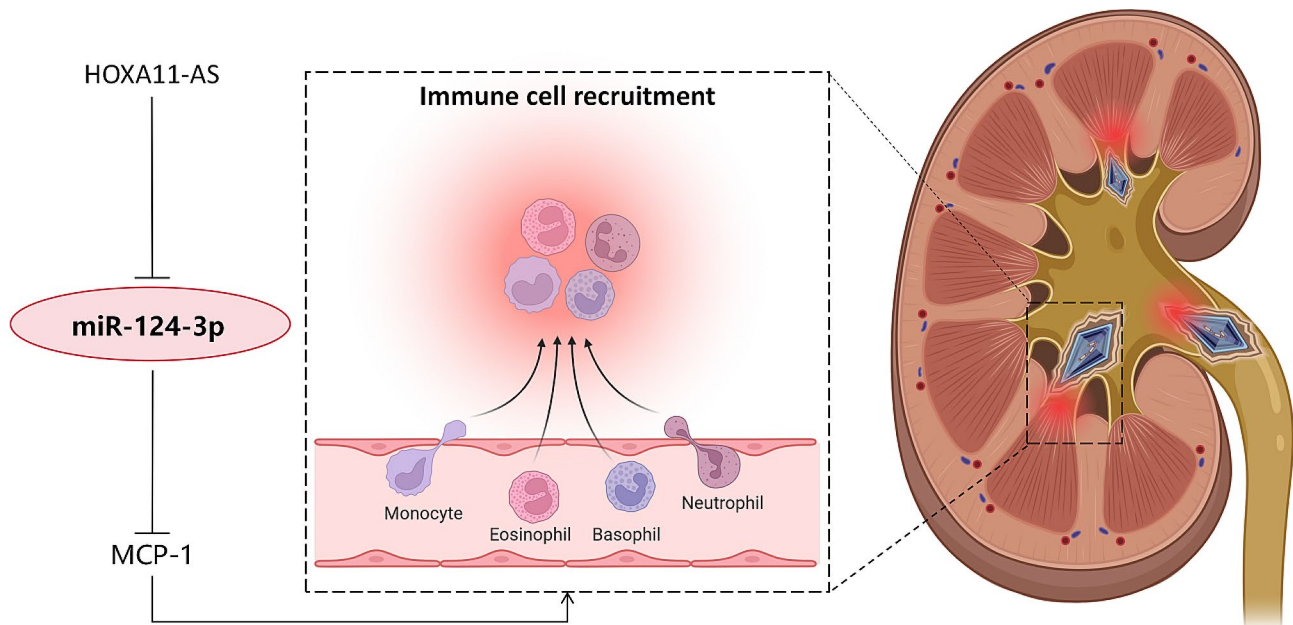


Fig. 3 miR-124-3p in kidney Stones. Kidney stones are classified into several types based on their composition, such as CaOx stones, phosphate stones, uric acid stones, and cystine stones. Among these, CaOx stones are the most common, making up about 60-90% of all kidney stones. It is now widely accepted that inflammation plays a key role in the formation of CaOx crystals. miR-124-3p provides renal protection by targeting and inhibiting MCP-1 expression, effectively reducing the inflammatory response

This, in turn, attracts a broader range of immune cells, including neutrophils and lymphocytes, to the inflamed area, creating a complex inflammatory network. In this inflammatory environment, the increased levels of calcium and oxalate ions promote the precipitation of CaOx crystals. These crystals further activate immune cells and stimulate the secretion of inflammatory mediators, leading to a self-perpetuating inflammatory cycle.

Currently, there are few publicly available research papers that directly explore the role of miR-124-3p in the pathology of kidney stones. The depth and breadth of research in this field require further enhancement. Given miR-124-3p's crucial role in inflammation regulation, a detailed investigation of its specific mechanisms in kidney stone formation could provide a theoretical basis for developing new prevention and treatment strategies.

MiR-124-3p and acute kidney injury

AKI refers to the sudden loss of kidney function within 7 days, characterized by increased serum creatinine (Scr) and decreased urine output, and is a major cause of CKD and ESRD [95, 96]. The etiology of AKI is diverse and not fully understood. Recent research indicates that inflammatory injury, cell cycle arrest, autophagy defects, ferroptosis, mitochondrial dysfunction, and metabolic reprogramming are closely related to its occurrence and development [97]. However, aside from kidney biopsy, current technologies cannot directly assess kidney injury. Pathological diagnosis also has drawbacks, such as

significant trauma and long detection times [98]. Therefore, finding highly sensitive and specific blood and urine markers has become a focus of recent clinical research.

Ischemia-reperfusion injury

Renal ischemia-reperfusion injury (RI/RI) is a common cause of AKI that rapidly activates the innate immune response in the kidney and induces collagen deposition. Even with blood reperfusion, restoring kidney function is challenging. The re-entry of a large amount of oxygen into the tissue produces ROS, triggers oxidative stress, and exacerbates damage and inflammation [99]. miR-124-3p has been shown to play a key role in AKI caused by RI/RI (Fig. 4). Significant differential expression of miR-124-3p has been noted in rat kidney tissue under various degrees of hypoxia, with its expression level negatively correlating with markers of renal injury. Additionally, miR-124-3p can indirectly regulate the expression of vascular endothelial growth factor (VEGF) by targeting mitogen-activated protein kinase 14 (Mapk14) [100]. Hypoxia-induced high expression of VEGF plays a key role in the kidney's self-protection mechanism. Mapk14 and VEGF are part of a regulatory loop. Inhibiting Mapk14 can boost VEGF-induced angiogenesis and reduce vascular permeability [101]. Moreover, miR-124-3p can inhibit endoplasmic reticulum stress (ERS) by targeting inositol-requiring enzyme 1 α (IRE-1 α), thereby protecting the kidney [102]. The endoplasmic reticulum (ER) is a key site for sensing damage or apoptotic signals.

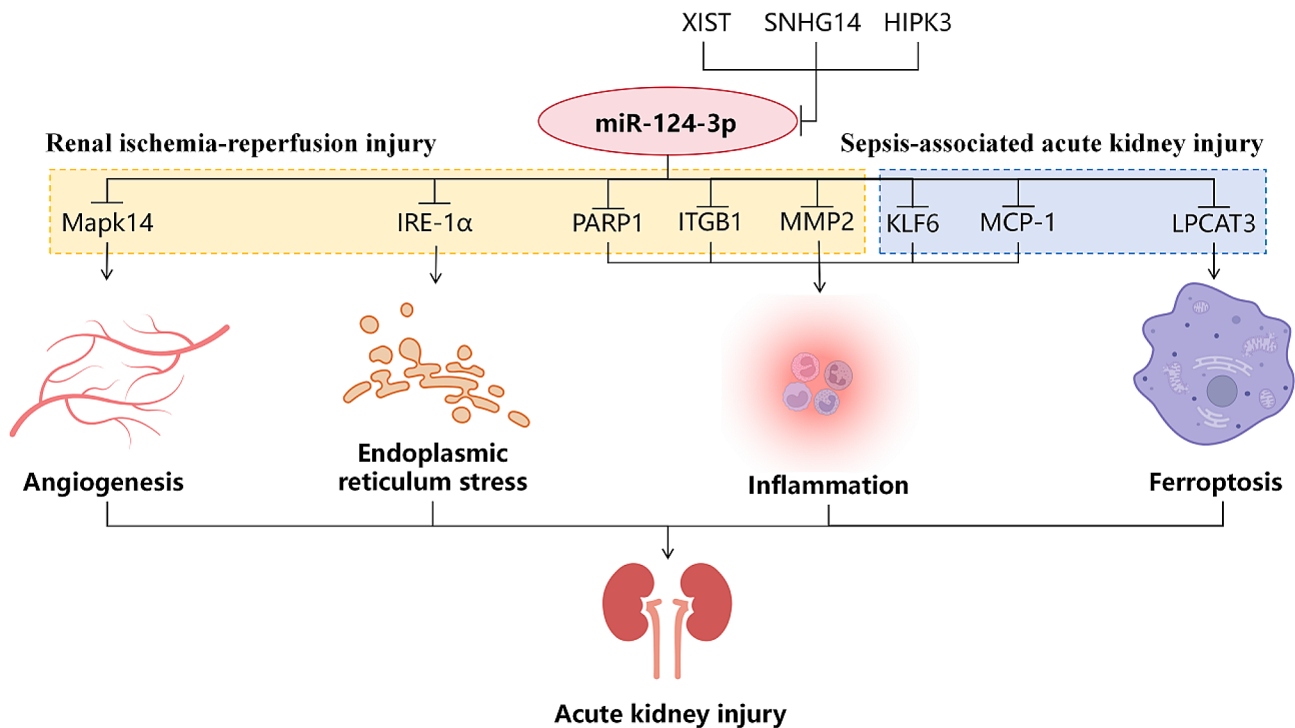


Fig. 4 miR-124-3p in acute kidney injury. AKI can be caused by various factors, with pathological features including tubular epithelial cell injury, inflammation, renal interstitial fibrosis, tubular atrophy, and vascular dysfunction. These pathological features interact synergistically, ultimately leading to the onset and progression of AKI. These pathological features interact synergistically, ultimately leading to the onset and progression of AKI. It protects the kidney from further damage and promotes renal recovery by intervening in target gene expression to regulate the survival, apoptosis, and proliferation of tubular epithelial cells, suppress inflammatory responses and renal interstitial fibrosis, and improve vascular function

During ischemia, reduced oxygen and glucose supply leads to the accumulation of misfolded and unfolded proteins in the ER, triggering ERS and activating the unfolded protein response (UPR). This activates IRE-1 α , which splices X-box binding protein-1 (XBP-1) mRNA into its mature form. XBP-1 then promotes the transcription and expression of various target genes, regulates ER formation, lipid synthesis, and glucose metabolism, and ultimately degrades misfolded proteins [103]. However, prolonged or intense ERS can overactivate UPR, inducing apoptosis and worsening RI/RI. Furthermore, calcium overload and ROS production during reperfusion can trigger oxidative stress, exacerbating UPR and apoptosis [104].

miR-124-3p plays a key role in regulating inflammation in AKI. A study has demonstrated that miR-124-3p has a highly conserved binding site in the 3' untranslated region (3'UTR) of poly (ADP-ribose) polymerase 1 (PARP1) and can exert renal protective effects by targeting and inhibiting PARP1 transcription [105]. PARP1 is a type of poly (ADP-ribose) polymerase that primarily repairs chromosomal DNA after mild activation caused by strand breaks or nicks. However, excessive activation of PARP1 can convert nicotinamide adenine dinucleotide (NAD⁺) into long PAR polymers, causing cytotoxic effects when transferred from the nucleus

to the cytoplasm [106]. Knocking out PARP1 can effectively reduce renal fibrosis and inflammatory responses in AKI mouse models [107]. Additionally, lncRNA XIST acts as a competitive sponge for miR-124-3p, preventing it from inhibiting its target gene, integrin β -1 (ITGB1). This blockage exacerbates apoptosis and inflammatory responses in NRK-52E cells treated with hypoxia/reoxygenation (H/R). Overexpressing miR-124-3p or inhibiting ITGB1 can reverse this effect [108]. Similarly, lncRNA SNHG14 competes with miR-124-3p for binding. In RI/RI rats and H/R-treated HK-2 cell models, silencing SNHG14 or overexpressing miR-124-3p can alleviate H/R-induced damage by regulating matrix metalloproteinase 2 (MMP2) expression. This includes reducing cell apoptosis, decreasing inflammatory factor release, and improving the oxidative stress response [109].

Sepsis-induced AKI

Sepsis is a systemic inflammatory disease resulting from infection. Nearly 50% of AKI cases in intensive care units are related to sepsis. These two conditions can coexist as a syndrome of acute dysfunction and organ injury, known as sepsis-associated acute kidney injury (SA-AKI) [110]. The mortality rate of SA-AKI is significantly higher than that of sepsis alone [111]. In recent years, studies have increasingly focused on the role of miRNAs, especially

miR-124-3p, in SA-AKI (Fig. 4). Research indicates that in a mouse model of disseminated *Candida* infection, upregulation of MCP-1 and downregulation of miR-124 are involved in the pathogenesis of SA-AKI. Adenovirus-mediated overexpression of miR-124 can inhibit MCP-1 expression, thereby reducing inflammatory cytokine levels in mice, alleviating acute kidney injury from disseminated *Candida* infection, and improving survival rates [112]. Additionally, studies have found that circHIPK3 expression is elevated in the serum of patients with SA-AKI and positively correlates with inflammatory factor levels. Downregulating HIPK3 expression can reduce kidney damage in SA-AKI mice, increase cell viability, and mitigate inflammatory responses and cellular senescence. Mechanistically, HIPK3 upregulates kruppel-like factor 6 (KLF6) expression by competitively binding to miR-124-3p. This promotes KLF6's binding to NOD-like receptor thermal protein domain associated protein 3 (NLRP3), activating NLRP3/caspase-1-mediated pyroptosis, thus worsening the inflammatory response in SA-AKI. At the same time, HIPK3 upregulates DNA methyltransferase1 (DNMT1) and DNMT3a expression by competitively binding to miR-148b-3p, increasing the methylation of the Klotho promoter, thus accelerating cellular senescence in SA-AKI. Downregulating miR-124-3p or miR-148b-3p significantly reduces the protective effect of HIPK3 silencing on SA-AKI [113]. Additionally, lipid metabolism disorders are closely linked to kidney injury [114]. Ferroptosis is an iron-dependent form of regulated necrosis caused by lipid peroxidation-mediated membrane damage, with phospholipids containing polyunsaturated fatty acids (PUFAs) as the primary substrate. This process is positively regulated by enzymes such as lysophosphatidylcholine acyltransferase 3 (LPCAT3) [115]. Thus, LPCAT3-mediated phospholipid metabolism disorders and the release of phospholipid-derived inflammatory mediators could be involved in the development of SA-AKI. In the serum of patients with SA-AKI, there is an increase in phosphatidylcholine content and LPCAT3 activity, along with a decrease in miR-124-3p expression. Further studies have shown that miR-124-3p negatively regulates LPCAT3 expression by binding to the 3' untranslated region of the LPCAT3 gene, affecting phospholipid metabolism and contributing to ferroptosis [116].

miR-124-3p and lupus nephritis

LN is a common and severe complication of systemic lupus erythematosus (SLE), significantly influenced by autoimmune dysregulation. Renal macrophages bind to immune complexes via Fc Gamma Receptors (FcγRs), leading to their deposition in the kidneys. This deposition activates the complement system, causing various pathological changes [117]. Recently, with the use of

novel immunosuppressive drugs like belimumab, mycophenolate mofetil, and anti-CD20 monoclonal antibodies, the survival rate of LN patients has significantly improved. However, about one-third of LN patients still progress to ESRD within 10–20 years [118]. Thus, there is an urgent need for new non-invasive biomarkers and therapeutic targets. Multiple studies show that miRNA expression is abnormal in the serum, kidney tissue, and urine of LN patients, indicating involvement in the disease's pathogenesis and progression [119, 120]. Recent prospective studies on miR-124-3p have shown differential expression in the serum of LN patients. Abdelsalam et al. studied serological markers of SLE and miR-124 expression in the serum of 50 LN patients and 50 healthy controls. They found that serum miR-124 expression was significantly lower in LN patients than in healthy controls and that it varied among LN patients with different clinical manifestations. Notably, patients with musculoskeletal involvement had the lowest serum miR-124 expression [121]. Zhang L et al. tested the serum of 62 subjects and found that serum miR-124 expression was significantly lower in LN patients compared to healthy controls. This reduction was even more pronounced in patients with active LN than in those with non-active LN and non-LN patients. Furthermore, miR-124 expression was negatively correlated with inflammatory markers like IL-1β, IL-6, and TNF-α. Cellular experiments show that transfection with a miR-124 mimic significantly inhibits mesangial cell proliferation and decreases the synthesis of inflammatory cytokines. The underlying mechanism involves targeting and suppressing the expression of TNF receptor-associated factor 6 (TRAF6) [122]. TRAF6 is a direct target of miR-124 and functions as an adaptor in inflammatory signaling pathways. It helps regulate intracellular TLR4/NF-κB signaling, inducing inflammation, apoptosis, and oxidative stress. Abnormal hyperactivity of TRAF6 often exacerbates renal injury during various kidney diseases [123]. Another study by Pan et al. found significantly reduced expression of miR-124-3p in LN tissues, serum, and cells. Their in vitro and in vivo studies indicated that HOXA11-OS acts as a competitive endogenous RNA (ceRNA) for miR-124-3p through sponge adsorption, promoting the expression of Cysteine-rich protein 61 (Cyr61) [124]. Cyr61 is a secreted extracellular matrix protein present at low levels under normal conditions. It has been found that serum Cyr61 levels are significantly elevated in SLE patients and are closely related to disease activity and inflammation [125]. HOXA11-OS promotes the expression of Cyr61 by competitively binding to miR-124-3p, thereby enhancing LN-IgG-induced podocyte autophagy and aggravating podocyte injury. When HOXA11-OS is knocked down, miR-124-3p significantly reduces kidney damage in lupus mice by targeting and inhibiting Cyr61 expression [124] (Fig. 5).

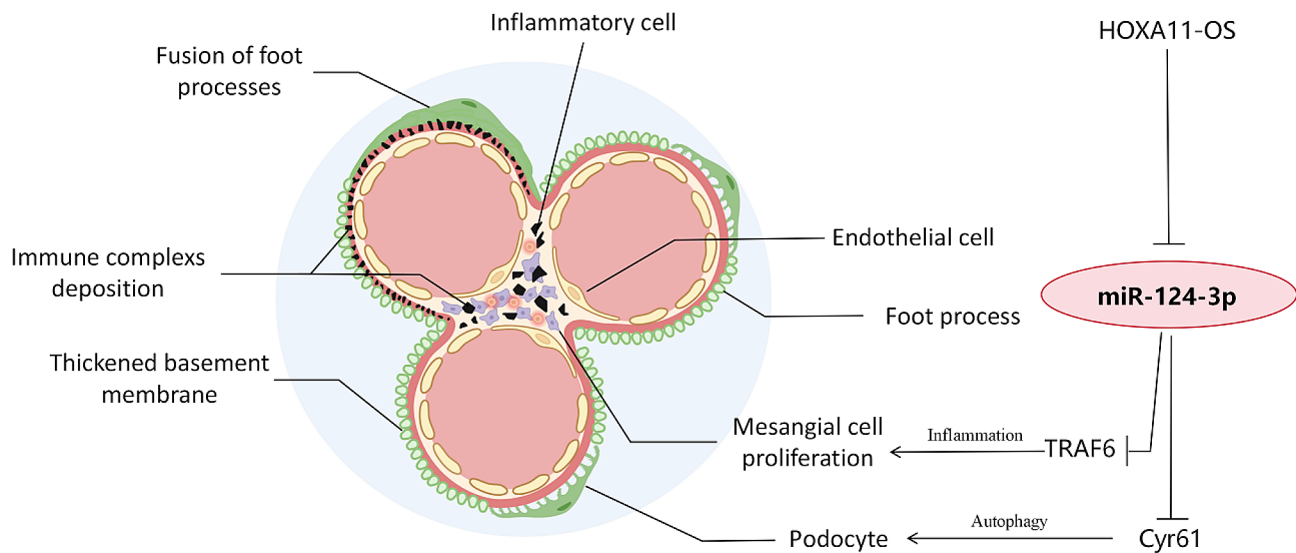


Fig. 5 miR-124-3p in lupus nephritis. The pathophysiology of LN is complex. In various glomerular compartments of LN patients, immune complex formation, activation of innate immune signaling pathways, infiltration of immune cells, and pro-inflammatory mediators can damage glomerular cells through multiple mechanisms. miR-124-3p plays a protective role in SLE by specifically inhibiting the expression of key molecules like TRAF6 and Cyr61. This targeted inhibition stops mesangial cell proliferation, reduces inflammatory reactions, prevents excessive podocyte autophagy, and effectively mitigates renal damage

MiR-124-3p and renal interstitial fibrosis

Renal interstitial fibrosis (RIF) is the final pathological outcome of various chronic and progressive kidney diseases, characterized by the replacement of normal renal interstitial and tubular structures with extensive extracellular matrix (ECM) accumulation [126]. Myofibroblast aggregation significantly contributes to ECM accumulation in the renal interstitium. The epithelial-mesenchymal transition (EMT) of renal tubular epithelial cells is an important source of myofibroblast generation and a key mechanism of RIF [127, 128]. miR-124-3p serves as a crucial regulatory factor, playing a central role in gene expression and the pathogenesis of numerous diseases. It is also one of the frequently studied miRNAs in fibrotic disorders. Numerous studies have established the substantial anti-RIF effect of miR-124-3p (Fig. 6). For example, Zhou Y et al. discovered that suppressing Lnc KCNQ1OT1 can directly target and upregulate miR-124-3p. This upregulation inhibits cell proliferation and downregulates α -SMA and FN, exerting an anti-RIF effect [129]. Furthermore, Zell S and colleagues used RNA microarray technology for an in-depth analysis of the expression of 46 EMT-related mRNAs and 342 miRNAs in hypoxia-induced renal proximal tubule epithelial cells. Their results indicated that under hypoxic conditions, renal proximal tubule epithelial cells displayed mesenchymal cell-like characteristics, including increased MMP2 expression and enhanced cell migration and proliferation. Among the analyzed miRNAs, 35 were upregulated, while 8 were downregulated. Notably, the decrease in miR-124 expression was strongly correlated

with increased MMP2 expression. miR-124 inhibits the migration and proliferation of renal epithelial cells under hypoxic conditions by targeting MMP2 [130]. MMPs form the primary enzyme system responsible for matrix degradation in the kidneys, exerting diverse degradative effects on the ECM. Their activity directly impacts the quantity of ECM expressed in renal tissue. MMP2, a prominent member of the MMP family, has been chiefly identified in the cytoplasm of glomerular mesangial cells and renal tubular epithelial cells [131]. Upon activation, MMP2 degrades Col IV and cleaves elastin, releasing biologically active fragments of ECM. This process disrupts the dense structural integrity among elastin fibers, facilitating the migration of renal interstitial fibroblasts beneath the epithelium. Consequently, this promotes EMT, ultimately contributing to RIF. The Notch signaling pathway, a highly conserved cellular mechanism, critically regulates the fate of various cell types [132]. Recent studies have revealed that dysregulation of Notch signaling significantly impacts the progression of fibrotic diseases [133]. Particularly in renal interstitial fibrosis, Notch1 emerges as the primary receptor mediating the effects of the Notch signaling pathway. Meanwhile, jagged 1 (JAG1) is the most extensively studied ligand in this pathway. Under external environmental stimuli, the Notch1 receptor interacts with the JAG1 ligand, initiating a cascade of events. This interaction leads to the release of the notch intracellular domain (NICD), which then translocates to the nucleus. Once in the nucleus, NICD activates the transcription of target genes closely associated with renal interstitial fibrosis [134], thereby

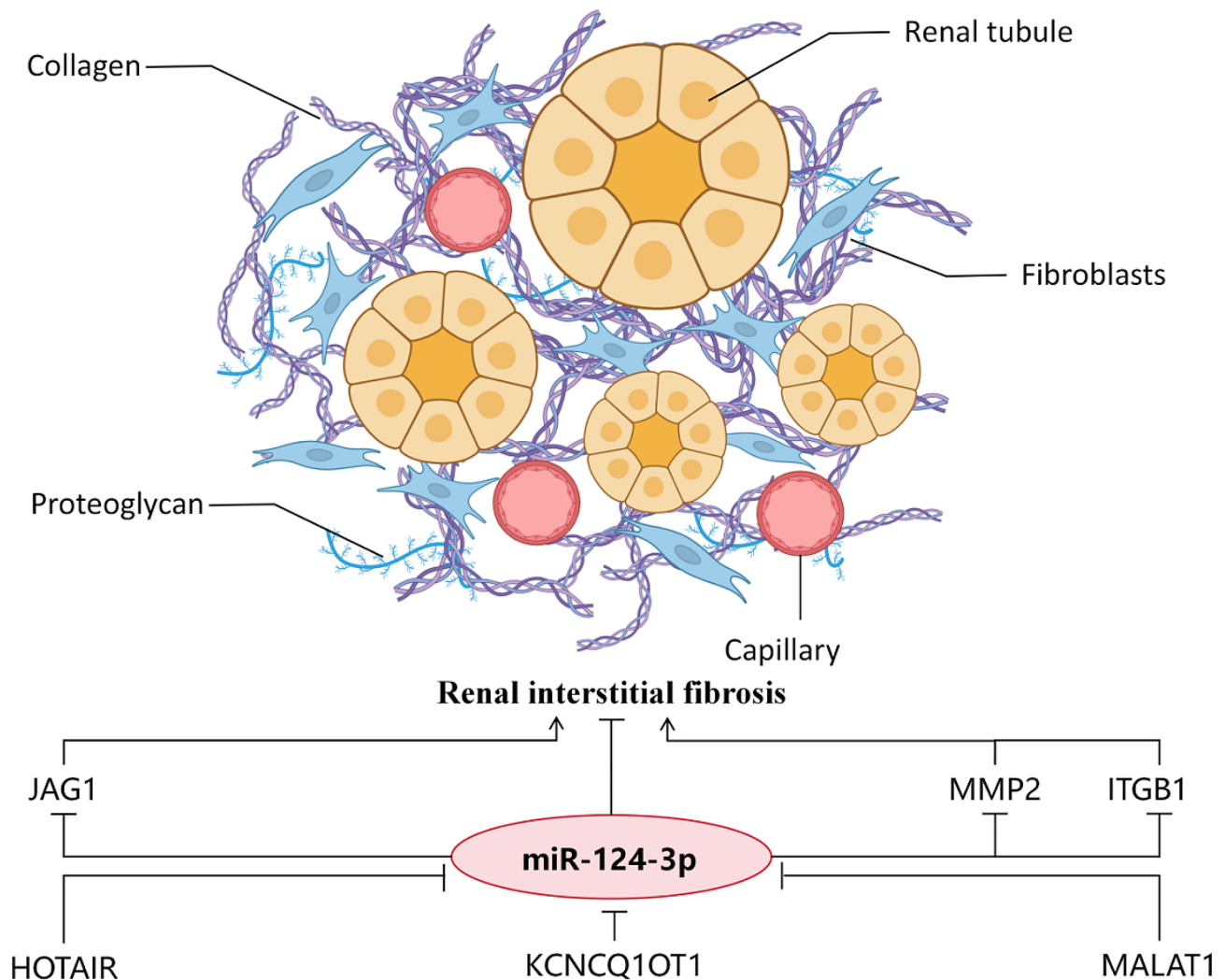


Fig. 6 miR-124-3p in renal interstitial fibrosis. RIF is a prevalent pathological feature of CKD advancing to ESRD, mainly characterized by myofibroblast proliferation and excessive ECM deposition. Studies suggest that miR-124-3p exhibits significant renoprotective effects in RIF progression, effectively inhibiting EMT advancement by modulating the expression of multiple target genes

promoting RIF progression. Qiu ZZ et al. established *in vivo/in vitro* models, revealing an interaction between Lnc HOTAIR and miR-124. This interaction directly targets JAG1, impacting the occurrence of RIF. In a UUO rat model, gastric lavage with Paeonol (PAE) reduced the expression of HOTAIR and JAG1 while increasing the expression of miR-124. Additionally, PAE inhibited HOTAIR-induced EMT and migration of NRK-49 F cells. HOTAIR activates the JAG1/Notch1 signaling pathway by inhibiting miR-124, an effect that PAE counteracts by increasing miR-124 expression [135]. Xia WP and colleagues observed significant overexpression of Lnc MALAT1 and ITGB1 in TGF- β 1-treated HK2/NRK-49 F cells and renal tissues from a UUO mouse model, while miR-124-3p expression was downregulated. Likewise, renal tissues from patients with obstructive nephropathy (ON) showed a similar expression pattern for MALAT1/

miR-124-3p/ITGB1 as observed in cell and animal experiments. Mechanistic studies revealed that MALAT1 competitively binds to miR-124-3p, thereby modulating ITGB1 expression and promoting RIF [136]. ITGB1, a crucial ECM receptor and the most abundantly expressed β -integrin subunit in the kidney [137], plays a pivotal role in regulating renal structure and function [138]. Recruiting ITGB1 can promote the development of RIF [139], while inhibiting its expression can effectively alleviate the EMT process induced by TGF- β 1 [140].

Research progress of miR-124-3p in clinic

The clinical application potential of miR-124-3p in kidney diseases is gradually emerging as research progresses on its functional basis. Preliminary studies have been conducted to explore the feasibility of using miR-124-3p as a biomarker for kidney diseases. For example, Xia WP et al.

reported a significant decrease in miR-124-3p expression in kidney tissues from patients with obstructive nephropathy compared to normal kidney tissues removed due to trauma [136]. Another study found a significant reduction in serum miR-124 expression in septic patients compared to healthy controls. miR-124 showed a negative correlation with serum levels of Scr, CRP, TNF- α , IL-1 β , IL-6, and IL-1 in septic patients in relation to disease status. Prognostic studies further indicated a close association between miR-124 and sepsis risk, where survivors exhibited significantly higher miR-124 expression than non-survivors, suggesting the potential of miR-124 as a promising biomarker for the diagnosis and prognosis of sepsis [141]. Apart from its diagnostic value in kidney diseases, miR-124-3p has shown remarkable diagnostic potential in other fields. In neuroscience, two notable studies have evaluated the extent of brain damage in patients who recovered from coma after cardiac arrest. In one study, researchers noted that serum miR-124 expression was significantly higher in patients with a poor prognosis compared to those with a favorable prognosis at 48 h post-cardiac arrest [142]. In another study, serum miR-124-3p levels were found to be significantly correlated with neurological outcomes at 6 months, where higher levels of miR-124-3p were associated with lower survival rates [143]. Furthermore, several studies have reported changes in the expression profile of miR-124-3p in patients with various types of cancer. These investigations have revealed significant alterations in miR-124-3p expression levels in cervical cancer, nasopharyngeal carcinoma, renal cell carcinoma, and other diseases, closely associated with the pathophysiological processes of these conditions [144–147].

Concurrently, therapeutic approaches targeting miR-124-3p are under investigation in clinical research. ABX464, a novel small molecule compound exhibiting a unique mechanism of action against HIV, falls within the quinoline derivative class [148]. In vitro and in vivo preclinical studies have both shown that ABX464 can increase miR-124-3p expression in humans [149]. Uncontrolled high cytokine expression significantly contributes to various inflammatory diseases. Currently, recombinant soluble receptors, antibodies, or signal inhibitors are commonly employed in clinical practice to target and inhibit cytokines for treating patients with glucocorticoid-refractory autoimmune diseases. However, due to the pleiotropic effects of cytokines and their crucial roles in various cells and pathways, blanket blockade of systemic cytokines poses significant risks. Hence, selectively inhibiting cytokines while preserving their activity at other sites is of paramount importance. miR-124-3p is negatively correlated with the inflammatory response [150]. Inducing miR-124-3p expression allows simultaneous targeting of multiple cytokines for downregulation,

thereby alleviating inflammatory responses. The selective induction of miR-124-3p biosynthesis by ABX464 limits the cell types responsive to ABX464-induced miR-124-3p expression. This prevents excessive miR-124-3p expression in all body cells, offering potential for selective cytokine inhibition while preserving the activity of other cytokines [151]. However, ABX464 is still in the research phase and has not yet been approved for clinical use. Further research and clinical trials are necessary to confirm its efficacy and safety. Nevertheless, this novel medical approach offers a new perspective.

Other miRNAs and kidney diseases

The establishment of human renal miRNA expression profiling through sequencing and microarray data, coupled with intensified research efforts, has led to an exponential increase in studies in this field, resulting in the identification of a growing number of miRNAs and their functions.

Reports suggest that miRNAs can impact the prognosis of RI/RI by regulating cellular apoptosis and inflammatory responses [152]. Among these miRNAs, miR-21 is the most extensively studied. Numerous studies have demonstrated the protective effect of miR-21 in AKI. In ischemic renal tissue, hypoxia-Inducible Factor 1- α (HIF1 α) responds to low oxygen levels, upregulating miR-21 to inhibit the expression of programmed Cell Death Protein 4 (PDCD4) and phosphatase and Tensin homolog (PTEN), thus reducing renal tubular cell apoptosis [153–155]. Moreover, miR-21 inhibits dendritic cell maturation via the PDCD4/NF- κ B pathway, thereby protecting renal tubular epithelial cells from ischemic injury by modulating renal inflammation [156]. Furthermore, miRNAs have potential effects on renal tubulointerstitial components during ischemia. For example, miR-126 and miR-218-2-5p protect kidneys from ischemia-reperfusion injury by preserving renal capillary density [157, 158]. Conversely, miR-150 promotes fibroblast activation, thereby accelerating the progression of renal fibrosis [159]. Podocytes, highly specialized epithelial cells situated on the outer surface of glomerular capillaries, play a crucial role in forming the glomerular filtration barrier. Recent research indicates that in mice with targeted deletion of Dicer specifically in podocytes, miR-23b, miR-24, and miR-26a are involved in maintaining podocyte differentiation, involving the loss of podocyte differentiation markers (synaptopodin, nephrin, and podocin) and foot process effacement [160]. Under high glucose conditions, upregulated miR-29c expression induces podocyte apoptosis by increasing Rho kinase activity through its targeting of sprouty homolog 1 (Spry1) [161]. miR-195 downregulates the expression of the target gene BCL2, subsequently activating caspase-3 and inducing podocyte apoptosis [162]. Besides regulating cellular apoptosis and

inflammatory responses, miRNAs also play critical roles in EMT (involving miR-26a, miR-30c, miR-29, etc.) [163, 164] and autophagy (involving miR-25-3p, miR-34a, miR-214-5p, etc.) [165–167].

However, it is crucial to note that miRNAs seem to have a dual role. For example, miR-21, which has renal protective effects as mentioned previously, is significantly increased in renal tissues of rat models with ischemia/reperfusion-induced AKI. By targeting ras-related protein Rab-11 A (Rab11a) and inhibiting autophagy, it can worsen kidney injury [168]. Furthermore, the expression levels of the same biomarker may vary among different diseases. For instance, miR-378a-3p is highly expressed in renal biopsy samples of patients with MN and focal segmental glomerulosclerosis (FSGS), remains unchanged in minimal change disease (MCD) and IgAN, but is down-regulated in DKD [169]. These findings highlight the complexity and diversity of miRNAs' involvement in kidney diseases. Therefore, it is imperative to further explore the specific mechanisms of miRNAs' actions in different diseases and dynamic shifts during disease progression. This will necessitate an integrated approach combining bioinformatics, clinical trials, and basic research data to accurately assess the potential impact of miRNAs in kidney diseases, paving the way for novel diagnostic and therapeutic strategies.

Prospects and summary

miR-124-3p, a conserved miRNA across multiple species, plays a crucial role in various cellular functions. This article summarizes the latest research progress on miR-124-3p in renal system diseases, particularly focusing on diabetic nephropathy, calcium oxalate kidney stones, acute kidney injury, lupus nephritis, and renal interstitial fibrosis. Besides renal diseases, abnormal expression of miR-124-3p is closely associated with the progression, drug resistance, and even prognosis of other diseases. Li H et al. utilized a chronic constriction injury (CCI) rat model and reported that knocking down SNHG16 can upregulate miR-124-3p expression, negatively regulating JAG1 to ameliorate mechanical allodynia and thermal hyperalgesia in CCI rats, while also reducing the concentration and mRNA expression of inflammatory cytokines [170]. Hu GR et al. reported that silencing of miR-124-3p eliminates hypoxia-induced decreases in H9c2 cell viability and increases apoptosis. It can inhibit inflammatory responses and apoptosis by targeting the NKRF/NF- κ B pathway, thereby suppressing acute myocardial infarction [171]. Luo Y et al. reported that Rab27A can regulate the miR-124-3p/STAT3/RelA axis, thus promoting apoptotic cell death and ROS production in inflammatory colon cells [172]. Overall, miR-124-3p is an important molecule with diverse functions and impacts on various diseases. Extensive research in the fields of kidney diseases,

neurological disorders, and oncology has provided valuable insights into the mechanistic roles of miR-124-3p in the pathogenesis and progression of diseases, warranting broader and more in-depth investigation.

The literature in this review clearly shows the significant role of miR-124-3p in renal protection, particularly through modulating inflammatory responses. Among these, MCP-1, frequently appearing in downstream pathways, plays a crucial role in kidney diseases. As one of the earliest discovered chemokines, MCP-1 has been extensively studied for decades. MCP-1 functions by binding to the G-protein-coupled CCR2 receptor on monocytes [173]. Its primary function is to regulate the transport of inflammatory cells, recruiting monocytes, neutrophils, and lymphocytes to sites of inflammation and tissue damage. MCP-1 is crucial for the initiation and maintenance of inflammatory responses and plays a key role in various physiological and pathological mechanisms. In the kidney, MCP-1 is expressed in renal tubular cells, smooth muscle cells, mesangial cells, and podocytes [174]. As a member of the CC chemokine family, MCP-1 recruits leukocytes to sites of inflammation caused by tissue damage or infection, inducing a cascade of inflammatory responses [175]. When kidney damage occurs, renal tubular epithelial cells release MCP-1, attracting monocytes, T-cells, and dendritic cells to the damaged site. These cells promote tissue remodeling and participate in kidney injury and subsequent adverse repair processes [176]. MCP-1 is easily detectable in serum and urine with good stability, making it a potential biomarker for monitoring disease activity and evaluating treatment effectiveness [177]. Research shows that MCP-1 changes significantly early in kidney injury. Increased urinary MCP-1 levels can predict renal fibrosis progression and are independently associated with a continuous decline in eGFR [178]. MCP-1 can induce an increase in inflammatory molecules in kidney cells, such as ICAM-1 and interstitial matrix molecules like fibronectin. In renal tubular epithelial cells, MCP-1 stimulates IL-6 secretion and ICAM-1 synthesis. In podocytes, MCP-1 binding to CCR2 leads to podocyte migration and significantly reduces nephrin mRNA and protein expression [174]. These findings provide important clues to deepen our understanding of kidney disease pathogenesis and develop new treatment strategies. Future research may find new methods to effectively prevent and treat kidney diseases by regulating miR-124-3p and MCP-1.

However, despite the promising prospects of miR-124-3p in the diagnosis and treatment of kidney diseases, we must still confront a number of challenges when utilizing it as a therapeutic target. Several studies mentioned above have indicated that the expression level of miR-124-3p predicts certain pathological events. In research on miRNAs as diagnostic markers for clinically

relevant diseases, these short noncoding RNAs within the human body possess characteristics such as strong stability and high sensitivity. By degrading or inhibiting the translation of mRNA, they regulate downstream gene transcription levels, intervening in cell activation, proliferation, transformation, apoptosis, and lipid metabolism [179]. miRNAs are valuable as early biomarkers for kidney injury and disease, complementing the detection of chronic kidney disease [180–182]. However, determining its specificity and stability *in vivo* is particularly important as a diagnostic marker. Recent studies have shown that miRNAs, with an average half-life of up to 119 h, can intervene in various physiological and pathological mechanisms in cells and can be stably expressed in blood or urine [6, 183, 184]. This stability makes miRNAs potential biomarkers with diagnostic significance for many kidney diseases. However, most free miRNAs in the body, released after cell apoptosis or necrosis [185], can still be degraded by endogenous RNA hydrolases under long-term exposure in blood or urine. With the current deepening research on exosomes, researchers have discovered that exosomes can ensure the integrity and functionality of transported active molecules due to their lipid bilayer characteristics when conveying information. Unlike free miRNA detection, which requires fresh samples, exosomes can be stored at -20 °C for up to 5 years without destroying their contents [186]. Therefore, compared to the direct detection of free miRNA expression, the detection of exosome-derived miRNAs may be more accurate and applicable to a wider range of experimental types [187]. Urine is an ideal source of noninvasive biomarkers, offering convenient and abundant sampling opportunities. After isolating and extracting exosomes, sample proteins become highly concentrated, potentially facilitating detection. Exosomes from different sources can carry their specific miRNAs and share similar expression profiles with tissue-derived miRNAs. Moreover, urinary exosomes, mostly secreted by the renal capsule and glomerular epithelial cells, potentially provide a richer and more specific set of markers [188, 189].

Additionally, numerous challenges arise during the clinical translation phase. Firstly, the small size and low abundance of miRNA molecules necessitate highly sensitive, specific, and streamlined techniques for the accurate extraction, detection, and quantification of miR-124-3p from large samples. Current detection methods, including real-time quantitative PCR and microarray analysis, provide relatively accurate results but are complex to operate and expensive, limiting their widespread clinical application. Moreover, various factors, such as sample source, collection time, and processing methods, can influence the expression level of miR-124-3p, introducing variability into the test results. For example, miR-124-3p expression levels may vary among different tissues or

bodily fluids, and fluctuations in expression levels can occur due to variations in collection time and processing methods. This variability not only complicates detection but also impacts the interpretation and comparison of results. More importantly, a lack of unified standards and validation processes for miR-124-3p detection currently exists. Various methods and standards adopted by different laboratories and research teams for testing significantly affect result comparability. Establishing unified standards and validation processes is imperative to ensure the accuracy and reliability of miR-124-3p test results and facilitate its clinical application.

The primary therapeutic challenge lies in achieving stability and efficiency in the targeted delivery of miRNAs *in vivo*, while mitigating potential off-target effects. miR-124-3p is expressed in various cell types and tissues, with multiple target genes, suggesting that changes in its expression levels could impact multiple genes and pathways in diverse tissues throughout the body. An illustrative case is the clinical trial of MRX34, a synthetic miR-34a mimic, evaluating its safety in patients with primary liver cancer and other specific solid tumors or hematological malignancies (clinicaltrials.gov, NCT01829971). The drug is administered intravenously, employing pH-sensitive liposome technology for precise delivery to tumor tissues. However, during a Phase 1b clinical trial, some patients experienced immune-related toxicities, and severe cytokine release syndrome occurred in some cases, leading to the termination of the study. It's important to note that miR-34a is a tumor suppressor miRNA, directly targeted by p53, capable of regulating numerous oncogenes [190]. However, it may also influence immune cell communication by modulating calcium signaling or chemokines [191, 192]. Animal studies additionally show that miR-34a mimics are absorbed not only by tumor tissues but also by the bone marrow and spleen [193]. Hence, further investigation and meticulous evaluation are necessary to ensure the safety and proper biodistribution of miRNA-targeted therapies in practical settings.

Current primary strategies for achieving intracellular targeting and effective uptake of miRNA therapy involve utilizing nanoscale carriers, virus-mediated artificial expression, and customizing therapeutic oligonucleotides through chemical modifications or the addition of biomolecular conjugates. A common feature of these strategies is the binding or encapsulation of nucleic acids by carriers, which shields their negative charges and safeguards the RNA from degradation. Non-pathogenic viral vectors, notably the adeno-associated virus delivery system, offer a means for intracellular delivery of miRNA therapy. This system ensures transient stability of the recombinant as a transcriptionally active episome within the nucleus of the host cell [194]. Chemical modifications, like locked

nucleic acid (LNA) alterations, improve the stability of oligonucleotides by decreasing the flexibility of the ribose ring and enhance cellular uptake via an endocytosis mechanism that remains incompletely understood [195]. Biomolecular conjugates, such as N-acetylgalactosamine (GalNAc), enhance targeted uptake of miRNA therapeutics by activating hepatocyte-specific asialoglycoprotein receptors [196]. The combined application of these strategies, including integrating LNA alterations or nanoscale carriers with cell type-specific biomolecular conjugates, has demonstrated promising outcomes in augmenting therapeutic efficacy and cell-targeting precision. Another challenge of miRNA-targeted therapy concerns its long-term efficacy and safety. Current clinical trials and studies primarily assess the efficacy and safety of miRNA therapy by monitoring changes in miRNA expression in disease contexts and conducting in-depth analyses of treatment-induced alterations in cellular signaling pathways. However, given the complexity of the miRNA regulatory network and the incomplete understanding of miRNA functions and mechanisms, additional clinical data and long-term follow-up studies are necessary to validate the long-term efficacy and safety of miRNA-targeted therapy. Lastly, to ensure functional impact, attention must also be given to the dosing of exogenous miRNAs. Dosages used in miRNA therapy frequently surpass the physiological range of endogenous miRNA expression, potentially resulting in unpredictable off-target effects. Because of dose-dependent miRNA-target interactions, varying concentrations of miRNAs can elicit markedly different effects in the body [197]. Additionally, overexpression of a single miRNA may displace other endogenous miRNAs in the RISC, potentially inducing toxic non-targeted effects [198]. Therefore, the dosage of miRNA therapeutics must be maintained within a specific range to achieve therapeutic effects. However, research in this area is still ongoing.

In studies investigating the regulation of kidney diseases by miR-124-3p, scientists are progressively unveiling its involvement in disease onset and progression, driven by the ongoing advancement of molecular targeted therapies. Furthermore, initial advancements have occurred in the exploration of novel biomarkers including lncRNAs, mRNAs, and circRNAs, offering novel avenues for early kidney disease diagnosis. Despite being somewhat distant from clinical implementation, these research achievements exhibit significant promise. In this context, researchers are endeavoring to tackle the challenges encountered in the clinical translation of these potential biomarkers.

1. Optimization of detection methods: Researchers need to continuously refine experimental techniques and analytical approaches to achieve precise and

sensitive detection, ensuring the accuracy and reliability of test results.

2. Establishment of diagnostic criteria: Researchers should establish standardized detection criteria for miR-124-3p and other potential biomarkers across various primary diseases and stages of CKD to enable more accurate disease diagnosis.
3. Comprehensive exploration of mechanistic pathways: Researchers need to delve deeper into the specific mechanisms through which miR-124-3p and other potential biomarkers function in kidney diseases, guiding the development of more targeted therapeutic approaches for clinical management.
4. Validation of clinical efficacy: It is imperative to validate the practical utility of miR-124-3p and other potential biomarkers in diagnosing and treating kidney diseases through large-scale, multicenter, prospective, high-quality evidence-based clinical studies.
5. Develop novel therapeutic strategies: Researchers should investigate new treatment approaches based on the regulation of miR-124-3p and other potential biomarkers. These approaches could include targeting overexpressed exosomes and their contents, as well as mediating intercellular communication, to delay or even reverse the progression of CKD.

In summary, substantial progress has been achieved in researching miR-124-3p and other potential biomarkers in kidney diseases; however, several challenges persist. Currently, effective interventions to repair or reverse refractory renal fibrosis in the clinical setting are lacking. Through future in-depth research and ongoing technological innovation, identifying and validating the molecular determinants of renal fibrosis onset could have profound implications for expanding clinical applications, potentially catalyzing revolutionary changes in the diagnosis and treatment of kidney disease.

In summary, although research on miR-124-3p in kidney diseases has made significant progress, it remains in its early stages. The limited published literature results in weak evidence for using miR-124-3p in the diagnosis and treatment of kidney diseases. The accuracy and reliability of miR-124-3p as a biomarker need validation through more high-level clinical trials. Currently, effective interventions for repairing or reversing refractory renal fibrosis are lacking in the clinical setting, though miR-124-3p has shown potential therapeutic value. However, this potential treatment strategy remains theoretical, requiring more research to explore its feasibility and safety. Future research advancements and continuous technological innovations focusing on identifying and validating the molecular determinants of renal fibrosis

may profoundly broaden clinical applications and revolutionize the diagnosis and treatment of kidney diseases.

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Author contributions

YK and WXX participated in the review of relevant literature, CGT drafted the manuscript, and participated in the revision of the manuscript. CX helped draft the manuscript and drew the figures. WYX and ZLQ participated in the revision of the manuscript. All authors have read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

- Wallace MA. Anatomy and physiology of the kidney. *Aorn J*. 1998;68(5):800. [https://doi.org/10.1016/s0001-2092\(06\)62377-6](https://doi.org/10.1016/s0001-2092(06)62377-6).
- Tang PC, Chan AS, Zhang CB, García Córdoba CA, Zhang YY, To KF, et al. TGF- β 1 signaling: Immune dynamics of chronic kidney diseases. *Front Med (Lausanne)*. 2021;8:628519. <https://doi.org/10.3389/fmed.2021.628519>.
- Alles J, Fehlmann T, Fischer U, Backes C, Galata V, Minet M, et al. An estimate of the total number of true human miRNAs. *Nucleic Acids Res*. 2019;47(7):3353–64. <https://doi.org/10.1093/nar/gkz097>.
- Kozomara A, Birgaoanu M, Griffiths-Jones S. miRBase: from microRNA sequences to function. *Nucleic Acids Res*. 2019;47(D1):D155–62. <https://doi.org/10.1093/nar/gky1141>.
- Olena AF, Patton JG. Genomic organization of microRNAs. *J Cell Physiol*. 2010;222(3):540–5. <https://doi.org/10.1002/jcp.21993>.
- Diener C, Keller A, Meese E. Emerging concepts of miRNA therapeutics: from cells to clinic. *Trends Genet*. 2022;38(6):613–26. <https://doi.org/10.1016/j.tig.2022.02.006>.
- Geibert L, MacRae IJ. Regulation of microRNA function in animals. *Nat Rev Mol Cell Bio*. 2019;20(1):21–37. <https://doi.org/10.1038/s41580-018-0045-7>.
- Li C, Wang F, Miao P, Yan L, Liu S, Wang X, et al. miR-138 increases depressive-like behaviors by targeting SIRT1 in Hippocampus. *Neuropsych Dis Treat*. 2020;16:949–57. <https://doi.org/10.2147/NDT.S237558>.
- Lee RC, Feinbaum RL, Ambros V. The C. Elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. *Cell*. 1993;75(5):843–54. [https://doi.org/10.1016/0092-8674\(93\)90529-y](https://doi.org/10.1016/0092-8674(93)90529-y).
- Sun Y, Koo S, White N, Peralta E, Esau C, Dean NM, et al. Development of a micro-array to detect human and mouse microRNAs and characterization of expression in human organs. *Nucleic Acids Res*. 2004;32(22):e188. <https://doi.org/10.1093/nar/gnh186>.
- Harvey SJ, Jarad G, Cunningham J, Goldberg S, Schermer B, Harfe BD, et al. Podocyte-specific deletion of dicer alters cytoskeletal dynamics and causes glomerular disease. *J Am Soc Nephrol*. 2008;19(11):2150–8. <https://doi.org/10.1681/ASN.2008020233>.
- Ho P, Clark IM, Le LTT. MicroRNA-Based diagnosis and therapy. *Int J Mol Sci*. 2022;23(13):7167. <https://doi.org/10.3390/ijms23137167>.
- Lagos-Quintana M, Rauhut R, Yalcin A, Meyer J, Lendeckel W, Tuschl T, et al. Identification of tissue-specific microRNAs from mouse. *Curr Biol*. 2002;12(9):735–9. [https://doi.org/10.1016/s0960-9822\(02\)00809-6](https://doi.org/10.1016/s0960-9822(02)00809-6).
- Mishima T, Mizuguchi Y, Kawahigashi Y, Takizawa T, Takizawa T. RT-PCR-based analysis of microRNA (miR-1 and -124) expression in mouse CNS. *Brain Res*. 2007;1131(1):37–43. <https://doi.org/10.1016/j.brainres.2006.11.035>.
- Ben GR, Ben AO, Ziadi S, Ben DM, Trimeche M. Methylation of miR-124a-1, miR-124a-2, and miR-124a-3 genes correlates with aggressive and advanced breast cancer disease. *Tumour Biol*. 2014;35(5):4047–56. <https://doi.org/10.1007/s13277-013-1530-4>.
- Qin Z, Liu X. miR-124, a potential therapeutic target in colorectal cancer. *Oncotargets Ther*. 2019;12:749–51. <https://doi.org/10.2147/OTT.S179501>.
- Li Q, Liu S, Yan J, Sun MZ, Greenaway FT. The potential role of miR-124-3p in tumorigenesis and other related diseases. *Mol Biol Rep*. 2021;48(4):3579–91. <https://doi.org/10.1007/s11033-021-06347-4>.
- Yang J, Zhang L, Yu C, Yang XF, Wang H. Monocyte and macrophage differentiation: circulation inflammatory monocyte as biomarker for inflammatory diseases. *Biomark Res*. 2014;2(1):1. <https://doi.org/10.1186/2050-7771-2-1>.
- Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. *J Clin Invest*. 2012;122(3):787–95. <https://doi.org/10.1172/JCI59643>.
- Gentek R, Molawi K, Sieweke MH. Tissue macrophage identity and self-renewal. *Immunol Rev*. 2014;262(1):56–73. <https://doi.org/10.1111/imr.12224>.
- Tang PM, Nikolic-Paterson DJ, Lan HY. Macrophages: versatile players in renal inflammation and fibrosis. *Nat Rev Nephrol*. 2019;15(3):144–58. <https://doi.org/10.1038/s41581-019-0110-2>.
- Chen T, Cao Q, Wang Y, Harris DCH. M2 macrophages in kidney disease: biology, therapies, and perspectives. *Kidney Int*. 2019;95(4):760–73. <https://doi.org/10.1016/j.kint.2018.10.041>.
- Zhang Y, Zhang M, Zhong M, Suo Q, Lv K. Expression profiles of miRNAs in polarized macrophages. *Int J Mol Med*. 2013;31(4):797–802. <https://doi.org/10.3892/ijmm.2013.1260>.
- Cobos Jiménez V, Bradley EJ, Willemsen AM, van Kampen AH, Baas F, Kootstra NA. Next-generation sequencing of microRNAs uncovers expression signatures in polarized macrophages. *Physiol Genomics*. 2014;46(3):91–103. <https://doi.org/10.1152/physiolgenomics.00140.2013>.
- Graff JW, Dickson AM, Clay G, McCaffrey AP, Wilson ME. Identifying functional microRNAs in macrophages with polarized phenotypes. *J Biol Chem*. 2012;287(26):21816–25. <https://doi.org/10.1074/jbc.M111.327031>.
- Sun Y, Li Q, Gui H, Xu DP, Yang YL, Su DF, et al. MicroRNA-124 mediates the cholinergic anti-inflammatory action through inhibiting the production of pro-inflammatory cytokines. *Cell Res*. 2013;23(11):1270–83. <https://doi.org/10.1038/cr.2013.116>.
- Veremeyko T, Siddiqui S, Sotnikov I, Yung A, Ponomarev ED. IL-4/IL-13-dependent and independent expression of miR-124 and its contribution to M2 phenotype of monocytic cells in normal conditions and during allergic inflammation. *PLoS ONE*. 2013;8(12):e81774. <https://doi.org/10.1371/journal.pone.0081774>.
- Li JH, Liu S, Zhou H, Qu LH, Yang JH. starBase v2.0: decoding miRNA-cRNA, miRNA-ncRNA and protein-RNA interaction networks from large-scale CLIP-Seq data. *Nucleic Acids Res*. 2014;42(Database issue):D92–7. <https://doi.org/10.1093/nar/gkt1248>.
- Xu X, Li S, Lin Y, Chen H, Hu Z, Mao Y, et al. MicroRNA-124-3p inhibits cell migration and invasion in bladder cancer cells by targeting ROCK1. *J Transl Med*. 2013;11:276. <https://doi.org/10.1186/1479-5876-11-276>.
- Eguía-Aguilar P, Pérezpeña-Díazconti M, Benadón-Darszon E, Chico-Ponce DLF, Gordillo-Domínguez L, Torres-García S, et al. Reductions in the expression of miR-124-3p, miR-128-1, and miR-221-3p in pediatric astrocytomas are related to high-grade supratentorial, and recurrent tumors in Mexican children. *Child Nerv Syst*. 2014;30(7):1173–81. <https://doi.org/10.1007/s00381-014-2416-5>.
- Li H, Xie S, Liu M, Chen Z, Liu X, Wang L, et al. The clinical significance of downregulation of miR-124-3p, miR-146a-5p, miR-155-5p and miR-335-5p in gastric cancer tumorigenesis. *Int J Oncol*. 2014;45(1):197–208. <https://doi.org/10.3892/ijo.2014.2415>.
- Ge X, Guo M, Hu T, Li W, Huang S, Yin Z, et al. Increased Microglial Exosomal Mir-124-3p alleviates neurodegeneration and improves cognitive outcome after mTBI. *Mol Ther*. 2020;28(2):503–22. <https://doi.org/10.1016/j.ymthe.2019.11.017>.

33. Wei YJ, Wang JF, Cheng F, Xu HJ, Chen JJ, Xiong J, et al. Mir-124-3p targeted SIRT1 to regulate cell apoptosis, inflammatory response, and oxidative stress in acute myocardial infarction in rats via modulation of the FGF21/ CREB/PGC1 α pathway. *J Physiol Biochem*. 2021;77(4):577–87. <https://doi.org/10.1007/s13105-021-00822-z>.
34. Jiang D, Gong F, Ge X, Lv C, Huang C, Feng S, et al. Neuron-derived exosomes-transmitted mir-124-3p protect traumatically injured spinal cord by suppressing the activation of neurotoxic microglia and astrocytes. *J Nanobiotechnol*. 2020;18(1):105. <https://doi.org/10.1186/s12951-020-00665-8>.
35. Zhao J, Wang Y, Wang D, Yan W, Zhang S, Li D, et al. MiR-124-3p attenuates brain microvascular endothelial cell injury in vitro by promoting autophagy. *Histol Histopathol*. 2022;37(2):159–68. <https://doi.org/10.14670/HH-18-406>.
36. Cao Y, Lv Q, Li Y, Astragaloside IV. Improves tibial defect in rats and promotes proliferation and osteogenic differentiation of hBMSCs through MiR-124-3p. *J STAT3 Axis*. *J Nat Prod*. 2021;84(2):287–97. <https://doi.org/10.1021/acs.jnatprod.0c00975>.
37. Zhang S, Dong D, Zhang Y, Wang J, Liu L, Zhao Y, et al. MiR-124-3p relieves allergic rhinitis by inhibiting dipeptidyl peptidase-4. *Int Immunopharmacol*. 2021;101(Pt B):108279. <https://doi.org/10.1016/j.intimp.2021.108279>.
38. Guo X, Li C, Wang Y, Jiang C, Yang L. Long non-coding RNA nuclear paraspeckle assembly transcript 1 downregulation protects lens epithelial cells from oxidative stress-induced apoptosis by regulating the microRNA-124-3p/death-associated protein kinase 1 axis in age-related cataract. *Int Ophthalmol*. 2023;43(9):3413–24. <https://doi.org/10.1007/s10792-023-02749-4>.
39. Wu L, Tian X, Zuo H, Zheng W, Li X, Yuan M, et al. MiR-124-3p delivered by exosomes from heme oxygenase-1 modified bone marrow mesenchymal stem cells inhibits ferroptosis to attenuate ischemia-reperfusion injury in steatotic grafts. *J Nanobiotechnol*. 2022;20(1):196. <https://doi.org/10.1186/s12951-022-01407-8>.
40. Stelzer G, Rosen N, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, et al. Curr Protoc Bioinf. 2016;54(0):1. <https://doi.org/10.1002/cpbi.5>. The GeneCards Suite: From Gene Data Mining to Disease Genome Sequence Analyses.
41. Qin Z, Wang PY, Su DF, Liu X. miRNA-124 in Immune System and Immune disorders. *Front Immunol*. 2016;7(0):406. <https://doi.org/10.3389/fimmu.2016.00406>.
42. Ghafouri-Fard S, Shoorai H, Bahroudi Z, Abak A, Majidpoor J, Taheri M. An update on the role of miR-124 in the pathogenesis of human disorders. *Biomed Pharmacother*. 2021;135(0):111198. <https://doi.org/10.1016/j.biopha.2020.111198>.
43. Tang PC, Chan AS, Zhang CB, García Córdoba CA, Zhang YY, To KF, et al. TGF- β 1 signaling: Immune dynamics of chronic kidney diseases. *Front Med (Lausanne)*. 2021;8(0):628519. <https://doi.org/10.3389/fmed.2021.628519>.
44. Mall C, Rocke DM, Durbin-Johnson B, Weiss RH. Stability of miRNA in human urine supports its biomarker potential. *Biomark Med*. 2013;7(4):623–31. <https://doi.org/10.2217/bmm.13.44>.
45. Mitchell PS, Parkin RK, Kroh EM, Fritz BR, Wyman SK, Pogoseva-Agadjanyan EL, et al. Circulating microRNAs as stable blood-based markers for cancer detection. *Proc Natl Acad Sci U S A*. 2008;105(30):10513–8. <https://doi.org/10.1073/pnas.0804549105>.
46. Xi Y, Nakajima G, Gavin E, Morris CG, Kudo K, Hayashi K, et al. Systematic analysis of microRNA expression of RNA extracted from fresh frozen and formalin-fixed paraffin-embedded samples. *RNA*. 2007;13(10):1668–74. <https://doi.org/10.1261/ma.642907>.
47. Gholaminejad A, Abdul Tehrani H, Gholami Fesharaki M. Identification of candidate microRNA biomarkers in diabetic nephropathy: a meta-analysis of profiling studies. *J Nephrol*. 2018;31(6):813–31. <https://doi.org/10.1007/s40620-018-0511-5>.
48. Zhu H, Leung SW. Identification of microRNA biomarkers in type 2 diabetes: a meta-analysis of controlled profiling studies. *Diabetologia*. 2015;58(5):900–11. <https://doi.org/10.1007/s00125-015-3510-2>.
49. Roointan A, Gholaminejad A, Shojale B, Hudkins KL, Gheisari Y. Candidate microRNA biomarkers in Lupus Nephritis: a Meta-analysis of profiling studies in kidney, blood and urine samples. *Mol Diagn Ther*. 2023;27(2):141–58. <https://doi.org/10.1007/s40291-022-00627-w>.
50. Garmaa G, Bunduc S, Kóti T, Hegyi P, Csopor D, Ganbat D, et al. A systematic review and Meta-analysis of microRNA profiling studies in chronic kidney diseases. *Noncoding RNA*. 2024;10(3):30. <https://doi.org/10.3390/nrna10030030>.
51. de Boer IH, Khunti K, Sadusky T, Tuttle KR, Neumiller JJ, Rhee CM, et al. Diabetes management in chronic kidney disease: a Consensus Report by the American Diabetes Association (ADA) and kidney disease: improving global outcomes (KDIGO). *Diabetes Care*. 2022;45(12):3075–90. <https://doi.org/10.2337/dci22-0027>.
52. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in chronic kidney disease. *Kidney Int*. 2022;102(5S):S1–127. <https://doi.org/10.1016/j.kint.2022.06.008>.
53. Umanath K, Lewis JB. Update on Diabetic Nephropathy: Core Curriculum 2018. *Am J Kidney Dis*. 2018;71(6):884–95. <https://doi.org/10.1053/ajkd.2017.10.026>.
54. Jiang H, Shao X, Jia S, Qu L, Weng C, Shen X, et al. The Mitochondria-targeted metabolic tubular Injury in Diabetic kidney disease. *Cell Physiol Biochem*. 2019;52(2):156–71. <https://doi.org/10.33594/000000011>.
55. Forbes JM, Thorburn DR. Mitochondrial dysfunction in diabetic kidney disease. *Nat Rev Nephrol*. 2018;14(5):291–312. <https://doi.org/10.1038/nrneph.2018.9>.
56. Tang C, Cai J, Yin XM, Weinberg JM, Venkatachalam MA, Dong Z, et al. Mitochondrial quality control in kidney injury and repair. *Nat Rev Nephrol*. 2021;17(5):299–318. <https://doi.org/10.1038/s41581-020-00369-0>.
57. Vaz AR, Vizinha D, Morais H, Colaço AR, Loch-Neckel G, Barbosa M, et al. Overexpression of miR-124 in motor neurons plays a key role in ALS pathological processes. *Int J Mol Sci*. 2021;22(11):6128. <https://doi.org/10.3390/ijms22116128>.
58. Garcia G, Fernandes A, Stein F, Brites D. Protective signature of IFN γ -Stimulated Microglia relies on Mir-124-3p regulation from the Secretome released by mutant APP Swedish neuronal cells. *Front Pharmacol*. 2022;13:833066. <https://doi.org/10.3389/fphar.2022.833066>.
59. Tian L, Cao WJ, Yue RJ, Yuan Y, Guo XH, Qin DM, et al. Pretreatment with Tiliain improves mitochondrial energy metabolism and oxidative stress in rats with myocardial ischemia/reperfusion injury via AMPK/SIRT1/PGC-1 α signaling pathway. *J Pharmacol Sci*. 2019;139(4):352–60. <https://doi.org/10.1016/j.jphs.2019.02.008>.
60. Fontecha-Barriuso M, Martín-Sánchez D, Martínez-Moreno JM, Monsalve M, Ramos AM, Sánchez-Niño MD, et al. The role of PGC-1 α and mitochondrial Biogenesis in kidney diseases. *Biomolecules*. 2020;10(2):347. <https://doi.org/10.3390/biom10020347>.
61. Lehman JJ, Barger PM, Kovacs A, Saffitz JE, Medeiros DM, Kelly DP. Peroxisome proliferator-activated receptor gamma coactivator-1 promotes cardiac mitochondrial biogenesis. *J Clin Invest*. 2000;106(7):847–56. <https://doi.org/10.1172/JCI10268>.
62. Popov LD. Mitochondrial biogenesis: an update. *J Cell Mol Med*. 2020;24(9):4892–9. <https://doi.org/10.1111/jcmm.15194>.
63. Hathaway QA, Pinti MV, Durr AJ, Waris S, Shepherd DL, Hollander JM. Regulating microRNA expression: at the heart of diabetes mellitus and the mitochondrion. *Am J Physiol Heart Circ Physiol*. 2018;314(2):H293–310. <https://doi.org/10.1152/ajpheart.00520.2017>.
64. Huang L, Mollet S, Souquere S, Le Roy F, Ernoul-Lange M, Pierron G, et al. Mitochondria associate with P-bodies and modulate microRNA-mediated RNA interference. *J Biol Chem*. 2011;286(27):24219–30. <https://doi.org/10.1074/jbc.M111.240259>.
65. Yoda M, Kawamata T, Paroo Z, Ye X, Iwasaki S, Liu Q, et al. ATP-dependent human RISC assembly pathways. *Nat Struct Mol Biol*. 2010;17(1):17–23. <https://doi.org/10.1038/nsmb.1733>.
66. Zhang X, Zuo X, Yang B, Li Z, Xue Y, Zhou Y, et al. MicroRNA directly enhances mitochondrial translation during muscle differentiation. *Cell*. 2014;158(3):607–19. <https://doi.org/10.1016/j.cell.2014.05.047>.
67. Carrer M, Liu N, Grueter CE, Williams AH, Frisard MI, Hulver MW, et al. Control of mitochondrial metabolism and systemic energy homeostasis by microRNAs 378 and 378*. *Proc Natl Acad Sci U S A*. 2012;109(38):15330–5. <https://doi.org/10.1073/pnas.1207605109>.
68. Chan SY, Zhang YY, Hemann C, Mahoney CE, Zweier JL, Loscalzo J. MicroRNA-210 controls mitochondrial metabolism during hypoxia by repressing the iron-sulfur cluster assembly proteins ISCU1/2. *Cell Metab*. 2009;10(4):273–84. <https://doi.org/10.1016/j.cmet.2009.08.015>.
69. Chernouvanenko IS, Matveeva EA, Gelfand VI, Goldman RD, Minin AA. Mitochondrial membrane potential is regulated by vimentin intermediate filaments. *FASEB J*. 2015;29(3):820–7. <https://doi.org/10.1096/fj.14-259903>.
70. Li Q, Wang L, Liu H, Ren W, Zhang Z, Xia B, et al. Roles of miR-124-3p/Scd1 in urolithin A-induced brown adipocyte differentiation and succinate-dependent regulation of mitochondrial complex II. *Biochem Biophys Res Commun*. 2022;606:174–81. <https://doi.org/10.1016/j.bbrc.2022.03.112>.
71. Yardeni T, Fine R, Joshi Y, Gradus-Perry T, Kozar N, Reichenstein I, et al. High content image analysis reveals function of miR-124 upstream of Vimentin in

- regulating motor neuron mitochondria. *Sci Rep-Uk*. 2018;8(1):59. <https://doi.org/10.1038/s41598-017-17878-x>.
72. Liang L, Wo C, Yuan Y, Cao H, Tan W, Zhou X, et al. Mir-124-3p improves mitochondrial function of renal tubular epithelial cells in db/db mice. *Faseb J*. 2023;37(3):e22794. <https://doi.org/10.1096/fj.202201202RR>.
73. Xu X, Zhang L, Hua F, Zhang C, Zhang C, Mi X, et al. FOXM1-activated SIRT4 inhibits NF- κ B signaling and NLRP3 inflammasome to alleviate kidney injury and podocyte pyroptosis in diabetic nephropathy. *Exp Cell Res*. 2021;408(2):112863. <https://doi.org/10.1016/j.yexcr.2021.112863>.
74. Li T, Shen K, Li J, Leung S, Zhu T, Shi Y, et al. Glomerular endothelial cells are the coordinator in the Development of Diabetic Nephropathy. *Front Med-Lausanne*. 2021;8:655639. <https://doi.org/10.3389/fmed.2021.655639>.
75. Yang H, Fang X, Shen Y, Yao W, Chen D, Shen L, et al. MiR-153-3p reduces extracellular matrix accumulation in high glucose-stimulated human glomerular mesangial cells via targeting PAQR3 in diabetic nephropathy. *Endocrinol Diab Nutr*. 2022;69(1):34–42. <https://doi.org/10.1016/j.endien.2022.01.007>.
76. Daehn IS, Duffield JS. The glomerular filtration barrier: a structural target for novel kidney therapies. *Nat Rev Drug Discov*. 2021;20(10):770–88. <https://doi.org/10.1038/s41573-021-00242-0>.
77. Li M, Deng L, Xu G. METTL14 promotes glomerular endothelial cell injury and diabetic nephropathy via m6A modification of α -klotho. *Mol Med*. 2021;27(1):106. <https://doi.org/10.1186/s10020-021-00365-5>.
78. Thomas MC, Brownlee M, Susztak K, Sharma K, Jandeleit-Dahm KA, Zoungas S, et al. Diabetic kidney disease. *Nat Rev Dis Primers*. 2015;1:15018. <https://doi.org/10.1038/nrdp.2015.18>.
79. Yi M, Peng H, Yang J, Wang J, Li Y, Tan Z, et al. MicroRNA-124 inhibits rho associated kinase 1 activity to ameliorate the damages of glomerular endothelial cells caused by high glucose. *Ch J Nephrol*. 2017;33(01):30–6. <https://doi.org/10.3760/cmaj.issn.1001-7097.2017.01.005>. (Chinese journal).
80. Li D, Lu Z, Jia J, Zheng Z, Lin S. Changes in microRNAs associated with podocytic adhesion under mechanical stress. *J Renin-Angio-Aldo S*. 2013;14(2):97–102. <https://doi.org/10.1177/1470320312460071>.
81. Li D, Lu Z, Jia J, Zheng Z, Lin S. MiR-124 is related to podocytic adhesive capacity damage in STZ-induced uninephrectomized diabetic rats. *Kidney Blood Press R*. 2013;37(4–5):422–31. <https://doi.org/10.1159/000355721>.
82. Li D, Lu Z, Jia J, Zheng Z, Lin S. Curcumin ameliorates podocytic adhesive capacity damage under mechanical stress by inhibiting miR-124 expression. *Kidney Blood Press R*. 2013;38(1):61–71. <https://doi.org/10.1159/000355755>.
83. Lu H, Shi H, Xie Z, Li Q, Li J. Effects of LncRNA KCNQT1 Targeting Regulation on miR-124-3p/HMGB1 axison proliferation, apoptosis and fibrosis of Human Mesangial cells Induced by High glucose. *Prog Mod Biomed*. 2023;23(14):2625–31. <https://doi.org/10.13241/j.cnki.pmb.2023.14.005>. (Chinese journal).
84. Zhao N, Du L, Ma Y, Wang Y, Ma J, Fang Z, et al. LncRNA NEAT1/microRNA-124 regulates cell viability, inflammation and fibrosis in high-glucose-treated mesangial cells. *Exp Ther Med*. 2022;24(2):507. <https://doi.org/10.3892/etm.2022.11434>.
85. Zhang S, Xu L, Liang R, Yang C, Wang P. Baicalin suppresses renal fibrosis through microRNA-124/TLR4/NF- κ B axis in streptozotocin-induced diabetic nephropathy mice and high glucose-treated human proximal tubule epithelial cells. *J Physiol Biochem*. 2020;76(3):407–16. <https://doi.org/10.1007/s13105-020-00747-z>.
86. Alexander RT, Fuster DG, Dimke H. Mechanisms underlying Calcium Nephrolithiasis. *Annu Rev Physiol*. 2022;84:559–83. <https://doi.org/10.1146/annurev-physiol-052521-121822>.
87. Wang Q, Wang Y, Yang C, Wang J, Shi Y, Wang H, et al. Trends of Urolithiasis in China: A National Study based on hospitalized patients from 2013 to 2018. *Kidney Dis-Basel*. 2023;9(1):49–57. <https://doi.org/10.1159/000527967>.
88. Chewcharat A, Curhan G. Trends in the prevalence of kidney stones in the United States from 2007 to 2016. *Urolithiasis*. 2021;49(1):27–39. <https://doi.org/10.1007/s00240-020-01210-w>.
89. Moe OW. Kidney stones: pathophysiology and medical management. *Lancet*. 2006;367(9507):333–44. [https://doi.org/10.1016/S0140-6736\(06\)68071-9](https://doi.org/10.1016/S0140-6736(06)68071-9).
90. Miano R, Germani S, Vespasiani G. Stones and urinary tract infections. *Urol Int*. 2007;79(Suppl 1):32–6. <https://doi.org/10.1159/000104439>.
91. Liu Q, Liu Y, Guan X, Wu J, He Z, Kang J, et al. Effect of M2 macrophages on Injury and apoptosis of Renal Tubular Epithelial cells Induced by Calcium Oxalate crystals. *Kidney Blood Press R*. 2019;44(4):777–91. <https://doi.org/10.1159/000501558>.
92. Khan SR. Crystal-induced inflammation of the kidneys: results from human studies, animal models, and tissue-culture studies. *Clin Exp Nephrol*. 2004;8(2):75–88. <https://doi.org/10.1007/s10157-004-0292-0>.
93. Li Y, Yan G, Zhang J, Chen W, Ding T, Yin Y, et al. LncRNA HOXA11-AS regulates calcium oxalate crystal-induced renal inflammation via miR-124-3p/MCP-1. *J Cell Mol Med*. 2020;24(1):238–49. <https://doi.org/10.1111/jcmm.14706>.
94. Lin Z, Shi JL, Chen M, Zheng ZM, Li MQ, Shao J, et al. CCL2: an important cytokine in normal and pathological pregnancies: a review. *Front Immunol*. 2022;13:1053457. <https://doi.org/10.3389/fimmu.2022.1053457>.
95. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. *Nephron*. 2012;120(4):c179–84. <https://doi.org/10.1159/000339789>.
96. Lewington AJ, Cerdá J, Mehta RL. Raising awareness of acute kidney injury: a global perspective of a silent killer. *Kidney Int*. 2013;84(3):457–67. <https://doi.org/10.1038/ki.2013.153>.
97. Pickkers P, Darmon M, Hoste E, Joannidis M, Legrand M, Ostermann M, et al. Acute kidney injury in the critically ill: an updated review on pathophysiology and management. *Intens Care Med*. 2021;47(8):835–50. <https://doi.org/10.1007/s00134-021-06454-7>.
98. Bhatraju PK, Zelnick LR, Chinchilli VM, Moledina DG, Coca SG, Parikh CR, et al. Association between early recovery of kidney function after acute kidney injury and Long-Term Clinical outcomes. *Jama Netw Open*. 2020;3(4):e202682. <https://doi.org/10.1001/jamanetworkopen.2020.2682>.
99. Pabla N, Bajwa A. Role of mitochondrial therapy for ischemic-reperfusion Injury and Acute kidney Injury. *Nephron*. 2022;146(3):253–8. <https://doi.org/10.1159/000520698>.
100. Xu Y, Zhu Y, Xu J, Mao H, Li J, Zhu X, et al. Analysis of microRNA expression in rat kidneys after VEGF inhibitor treatment under different degrees of hypoxia. *Physiol Genomics*. 2023;55(11):504–16. <https://doi.org/10.1152/physiolgenomics.00023.2023>.
101. Yang J, Xu H, Chen K, Zheng D, Liu S, Zhou X, et al. Platelets-derived miR-200a-3p modulate the expression of ET-1 and VEGFA in endothelial cells by targeting MAPK14. *Front Physiol*. 2022;13:893102. <https://doi.org/10.3389/fphys.2022.893102>.
102. Ding C, Dou M, Wang Y, Li Y, Wang Y, Zheng J, et al. miR-124/IRE-1 α affects renal ischemia/reperfusion injury by regulating endoplasmic reticulum stress in renal tubular epithelial cells. *Acta Bioch Bioph Sin*. 2020;52(2):160–7. <https://doi.org/10.1093/abbs/gmz150>.
103. Wang Y, Tian J, Qiao X, Su X, Mi Y, Zhang R, et al. Intermedin protects against renal ischemia-reperfusion injury by inhibiting endoplasmic reticulum stress. *Bmc Nephrol*. 2015;16:169. <https://doi.org/10.1186/s12882-015-0157-7>.
104. Lin CL. Attenuation of endoplasmic reticulum stress as a treatment strategy against ischemia/reperfusion injury. *Neural Regen Res*. 2015;10(12):1930–1. <https://doi.org/10.4103/1673-5374.169615>.
105. Ke J, Zhao F, Luo Y, Deng F, Wu X. MiR-124 negatively regulated PARP1 to alleviate renal ischemia-reperfusion injury by inhibiting TNF α /RIP1/RIP3 pathway. *Int J Biol Sci*. 2021;17(8):2099–111. <https://doi.org/10.7150/ijbs.58163>.
106. Alemasova EE, Lavrik OI. Poly(ADP-ribosyl)ation by PARP1: reaction mechanism and regulatory proteins. *Nucleic Acids Res*. 2019;47(8):3811–27. <https://doi.org/10.1093/nar/gkz120>.
107. Zheng J, Devalaraja-Narashimha K, Singaravelu K, Padanilam BJ. Poly(ADP-ribose) polymerase-1 gene ablation protects mice from ischemic renal injury. *Am J Physiol-Renal*. 2005;288(2):F387–98. <https://doi.org/10.1152/ajprenal.00436.2003>.
108. Chen F, Hu Y, Xie Y, Zhao Z, Ma L, Li Z, et al. Total glucosides of Paeony Alleviate Cell apoptosis and inflammation by targeting the long noncoding RNA XIST/MicroRNA-124-3p/ITGB1 Axis in Renal Ischemia/Reperfusion Injury. *Mediat Inflamm*. 2020;220:8869511. <https://doi.org/10.1155/2020/8869511>.
109. Xue Q, Yang L, Wang H, Han S. Silence of long noncoding RNA SNHG14 alleviates Ischemia/Reperfusion-Induced Acute kidney Injury by regulating miR-124-3p/MMP2 Axis. *Biomed Res Int*. 2021;221:8884438. <https://doi.org/10.1155/2021/8884438>.
110. Paterson CW, Ford ML, Coopersmith CM. Breaking the bond between tetra-nectin and HMGB1 in sepsis. *Sci Transl Med*. 2020;12(539):eabb2575. <https://doi.org/10.1126/scitranslmed.abb2575>.
111. Menon S, Symons JM, Selewski DT. Acute kidney Injury. *Pediatr Rev*. 2023;44(5):265–79. <https://doi.org/10.1542/pir.2021-005438>.
112. Li XY, Zhang YQ, Xu G, Li SH, Li H. miR-124/MCP-1 signaling pathway modulates the protective effect of itraconazole on acute kidney injury in a mouse model of disseminated candidiasis. *Int J Mol Med*. 2018;41(6):3468–76. <https://doi.org/10.3892/ijmm.2018.3564>.
113. Han J, Li W, Zhang J, Guan Y, Huang Y, Li X, et al. Mechanism of circHIPK3-miRNA-124-3p/miRNA-148b-3p-Mediated inflammatory responses and cell senescence in Candida albicans-Induced septic acute kidney Injury. *Geron-tology*. 2022;68(10):1145–65. <https://doi.org/10.1159/000523910>.

114. Xiong W, Xiong Z, Song A, Lei C, Ye C, Zhang C, et al. Relieving lipid accumulation through UCP1 suppresses the progression of acute kidney injury by promoting the AMPK/ULK1/autophagy pathway. *Theranostics*. 2021;11(10):4637–54. <https://doi.org/10.7150/thno.56082>.
115. Liang D, Minikes AM, Jiang X. Ferroptosis at the intersection of lipid metabolism and cellular signaling. *Mol Cell*. 2022;82(12):2215–27. <https://doi.org/10.1016/j.molcel.2022.03.002>.
116. Zhang H, Wu H, Qian J, Sun L, Sang L, Wang P, et al. The regulation of LPCAT3 by miR-124-3p.1 in acute kidney injury suppresses cell proliferation by disrupting phospholipid metabolism. *Biochem Biophys Res Commun*. 2022;604:37–42. <https://doi.org/10.1016/j.bbrc.2022.03.009>.
117. Chang A, Clark MR, Ko K. Cellular aspects of the pathogenesis of lupus nephritis. *Curr Opin Rheumatol*. 2021;33(2):197–204. <https://doi.org/10.1097/BOR.0000000000000777>.
118. Elalouf O, Keeling SO, Touma Z. Subcutaneous belimumab in the treatment of systemic lupus erythematosus. *Immunotherapy-Uk*. 2018;10(13):1163–73. <https://doi.org/10.2217/imt-2018-0061>.
119. Ye H, Su B, Ni H, Li L, Chen X, You X, et al. microRNA-199a may be involved in the pathogenesis of lupus nephritis via modulating the activation of NF- κ B by targeting Klotho. *Mol Immunol*. 2018;103:235–42. <https://doi.org/10.1016/j.molimm.2018.10.003>.
120. Kong J, Li L, Lu Z, Song J, Yan J, Yang J, et al. MicroRNA-155 suppresses Mesangial Cell Proliferation and TGF- β 1 production via inhibiting CXCR5-ERK Signaling Pathway in Lupus Nephritis. *Inflammation*. 2019;42(1):255–63. <https://doi.org/10.1007/s10753-018-0889-1>.
121. Abdelsalam M, Zaki M, Abo EN, Foda SM, Osman A. Study of MicroRNA-124 in patients with Lupus Nephritis. *Endocr Metab Immune*. 2024. <https://doi.org/10.2174/0118715303250919231010073608>.
122. Zhang L, Zhang X, Si F. MicroRNA-124 represents a novel diagnostic marker in human lupus nephritis and plays an inhibitory effect on the growth and inflammation of renal mesangial cells by targeting TRAF6. *Int J Clin Exp Pathol*. 2019;12(5):1578–88.
123. Portillo JA, Greene JA, Schwartz I, Subauste MC, Subauste CS. Blockade of CD40-TRAF2,3 or CD40-TRAF6 is sufficient to inhibit pro-inflammatory responses in non-haematopoietic cells. *Immunology*. 2015;144(1):21–33. <https://doi.org/10.1111/imm.12361>.
124. Pan X, Chen S, Shen R, Liu S, You Y. HOXA11-OS participates in lupus nephritis by targeting mir-124-3p mediating Cyr61 to regulate podocyte autophagy. *Mol Med*. 2022;28(1):138. <https://doi.org/10.1186/s10020-022-00570-w>.
125. Guo P, Ma Y, Deng G, Li L, Gong Y, Yang F, et al. CYR61, regulated by mir-22-3p and MALAT1, promotes autophagy in HK-2 cell inflammatory model. *Transl Androl Urol*. 2021;10(8):3486–500. <https://doi.org/10.21037/tau-21-623>.
126. Nakagawa M, Izawa T, Kuwamura M, Yamate J. Analyses of damage-associated molecular patterns, particularly biglycan, in cisplatin-induced rat progressive renal fibrosis. *J Toxicol Pathol*. 2023;36(3):181–5. <https://doi.org/10.1293/tox.2022-0148>.
127. Sheng L, Zhuang S. New insights into the role and mechanism of partial epithelial-mesenchymal transition in kidney fibrosis. *Front Physiol*. 2020;11:569322. <https://doi.org/10.3389/fphys.2020.569322>.
128. Cruz-Solbes AS, Youker K. Epithelial to mesenchymal transition (EMT) and endothelial to mesenchymal transition (EndMT): role and implications in kidney fibrosis. *Results Probl Cell Differ*. 2017;60:345–72. https://doi.org/10.1007/978-3-319-51436-9_13.
129. Hao J, Zhou Y, Yu W, Li H, He D. Silencing of LncRNA KCNQ1OT1 confers an inhibitory effect on renal fibrosis through repressing mir-124-3p activity. *Bioengineered*. 2022;13(4):10399–411. <https://doi.org/10.1080/21655979.2022.2056816>.
130. Zell S, Schmitt R, Witting S, Kreipe HH, Hussein K, Becker JU, et al. Hypoxia induces mesenchymal gene expression in renal tubular epithelial cells: an in vitro model of kidney transplant fibrosis. *Nephron Extra*. 2013;3(1):50–8. <https://doi.org/10.1159/000351046>.
131. Cheng Z, Liu L, Wang Z, Cai Y, Xu Q, Chen P, et al. Hypoxia activates src and promotes endocytosis which decreases MMP-2 activity and aggravates renal interstitial fibrosis. *Int J Mol Sci*. 2018;19(2):581. <https://doi.org/10.3390/ijms19020581>.
132. Siebel C, Lendahl U. Notch Signaling in Development, tissue homeostasis, and Disease. *Physiol Rev*. 2017;97(4):1235–94. <https://doi.org/10.1152/physrev.00005.2017>.
133. Zhang Y, Jin D, Kang X, Zhou R, Sun Y, Lian F, et al. Signaling pathways involved in Diabetic Renal Fibrosis. *Front Cell Dev Biol*. 2021;9:696542. <https://doi.org/10.3389/fcell.2021.696542>.
134. Yu C, Xiong C, Tang J, Hou X, Liu N, Bayliss G, et al. Histone demethylase JMJD3 protects against renal fibrosis by suppressing TGF β and notch signaling and preserving PTEN expression. *Theranostics*. 2021;11(6):2706–21. <https://doi.org/10.7150/thno.48679>.
135. Zhou H, Gao L, Yu ZH, Hong SJ, Zhang ZW, Qiu ZZ et al. LncRNA HOTAIR promotes renal interstitial fibrosis by regulating Notch1 pathway via the modulation of miR-124. *Nephrology*. 2019; 24(4):472–480. <https://doi.org/10.1111/nep.13394>.
136. Xia W, Chen X, Zhu Z, Chen H, Li B, Wang K, et al. Knockdown of LncRNA MALAT1 attenuates renal interstitial fibrosis through miR-124-3p/ITGB1 axis. *Sci Rep-Uk*. 2023;13(1):18076. <https://doi.org/10.1038/s41598-023-45188-y>.
137. Mamuya FA, Xie D, Lei L, Huang M, Tsuji K, Capen DE, et al. Deletion of β 1-integrin in collecting duct principal cells leads to tubular injury and renal medullary fibrosis. *Am J Physiol-Renal*. 2017;313(4):F1026–37. <https://doi.org/10.1152/ajprenal.00038.2017>.
138. Wu W, Kitamura S, Truong DM, Rieg T, Vallon V, Sakurai H, et al. Beta1-integrin is required for kidney collecting duct morphogenesis and maintenance of renal function. *Am J Physiol-Renal*. 2009;297(1):F210–7. <https://doi.org/10.1152/ajprenal.00060.2008>.
139. Hu K, Wu C, Mars WM, Liu Y. Tissue-type plasminogen activator promotes murine myofibroblast activation through LDL receptor-related protein 1-mediated integrin signaling. *J Clin Invest*. 2007;117(12):3821–32. <https://doi.org/10.1172/JCI32301>.
140. Yeh YC, Wei WC, Wang YK, Lin SC, Sung JM, Tang MJ, et al. Transforming growth factor- β 1 induces Smad3-dependent β 1 integrin gene expression in epithelial-to-mesenchymal transition during chronic tubulointerstitial fibrosis. *Am J Pathol*. 2010;177(4):1743–54. <https://doi.org/10.2353/ajpath.2010.091183>.
141. He F, Zhang C, Huang Q. Long noncoding RNA nuclear enriched abundant transcript 1/miRNA-124 axis correlates with increased disease risk, elevated inflammation, deteriorative disease condition, and predicts decreased survival of sepsis. *Medicine*. 2019;98(32):e16470. <https://doi.org/10.1097/MD.00000000000016470>.
142. Gilje P, Gidlöf O, Rundgren M, Cronberg T, Al-Mashat M, Olde B, et al. The brain-enriched microRNA miR-124 in plasma predicts neurological outcome after cardiac arrest. *Crit Care*. 2014;18(2):R40. <https://doi.org/10.1186/cc13753>.
143. Devaux Y, Dankiewicz J, Salgado-Somoza A, Stamat P, Collignon O, Gilje P, et al. Association of circulating MicroRNA-124-3p levels with outcomes after out-of-hospital cardiac arrest: a Substudy of a Randomized Clinical Trial. *Jama Cardiol*. 2016;1(3):305–13. <https://doi.org/10.1001/jamacardio.2016.0480>.
144. Rogeri CD, Silveira H, Causin RL, Villa LL, Stein MD, de Carvalho AC, et al. Methylation of the hsa-miR-124, SOX1, TERT, and LMX1A genes as biomarkers for precursor lesions in cervical cancer. *Gynecol Oncol*. 2018;150(3):545–51. <https://doi.org/10.1016/j.ygyno.2018.06.014>.
145. Murray MJ, Raby KL, Saini HK, Bailey S, Wool SV, Tunncliffe JM, et al. Solid tumors of childhood display specific serum microRNA profiles. *Cancer Epidemiol Biomarkers*. 2015;24(2):350–60. <https://doi.org/10.1158/1055-9965.EPI-14-0669>.
146. Xu X, Lu J, Wang F, Liu X, Peng X, Yu B, et al. Dynamic changes in plasma MicroRNAs have potential predictive values in monitoring recurrence and metastasis of nasopharyngeal carcinoma. *Biomed Res Int*. 2018;218:7329195. <https://doi.org/10.1155/2018/7329195>.
147. Li R, Chen W, Lu C, Li X, Chen X, Huang G, et al. A four-microRNA panel in serum may serve as potential biomarker for renal cell carcinoma diagnosis. *Front Oncol*. 2022;12:1076303. <https://doi.org/10.3389/fonc.2022.1076303>.
148. Campos N, Myburgh R, Garcel A, Vautrin A, Lapasset L, Nadal ES, et al. Long lasting control of viral rebound with a new drug ABX464 targeting rev - mediated viral RNA biogenesis. *Retrovirology*. 2015;12:30. <https://doi.org/10.1186/s12977-015-0159-3>.
149. Vautrin A, Manchon L, Garcel A, Campos N, Lapasset L, Laafer AM, et al. Both anti-inflammatory and antiviral properties of novel drug candidate ABX464 are mediated by modulation of RNA splicing. *Sci Rep-Uk*. 2019;9(1):792. <https://doi.org/10.1038/s41598-018-37813-y>.
150. He X, Jing Z, Cheng G. MicroRNAs: new regulators of toll-like receptor signalling pathways. *Biomed Res Int*. 2014;214:945169. <https://doi.org/10.1155/2014/945169>.
151. Tazi J, Begon-Pescia C, Campos N, Apolot C, Garcel A, Scherrer D, et al. Specific and selective induction of miR-124 in immune cells by the quinoline ABX464: a transformative therapy for inflammatory diseases. *Drug Discov Today*. 2021;26(4):1030–9. <https://doi.org/10.1016/j.drudis.2020.12.019>.

152. Mahtal N, Lenoir O, Tinel C, Anglicheau D, Tharaux PL. MicroRNAs in kidney injury and disease. *Nat Rev Nephrol*. 2022;18(10):643–62. <https://doi.org/10.1038/s41581-022-00608-6>.
153. Xu X, Kriegl AJ, Liu Y, Usa K, Mladinov D, Liu H, et al. Delayed ischemic preconditioning contributes to renal protection by upregulation of miR-21. *Kidney Int*. 2012;82(11):1167–75. <https://doi.org/10.1038/ki.2012.241>.
154. Hu H, Jiang W, Xi X, Zou C, Ye Z. MicroRNA-21 attenuates renal ischemia reperfusion injury via targeting caspase signaling in mice. *Am J Nephrol*. 2014;40(3):215–23. <https://doi.org/10.1159/000368202>.
155. Jia P, Teng J, Zou J, Fang Y, Zhang X, Bosnjak ZJ, et al. miR-21 contributes to xenon-conferred amelioration of renal ischemia-reperfusion injury in mice. *Anesthesiology*. 2013;119(3):621–30. <https://doi.org/10.1097/ALN.0b013e318298e5f1>.
156. Song N, Zhang T, Xu X, Lu Z, Yu X, Fang Y, et al. miR-21 protects against Ischemia/Reperfusion-Induced Acute kidney Injury by preventing epithelial cell apoptosis and inhibiting dendritic cell maturation. *Front Physiol*. 2018;9:790. <https://doi.org/10.3389/fphys.2018.00790>.
157. Bijkerk R, van Solingen C, de Boer HC, van der Pol P, Khairoun M, de Bruin RG, et al. Hematopoietic microRNA-126 protects against renal ischemia/reperfusion injury by promoting vascular integrity. *J Am Soc Nephrol*. 2014;25(8):1710–22. <https://doi.org/10.1681/ASN.2013060640>.
158. Wang X, Liu J, Yin W, Abdi F, Pang PD, Fucci QA, et al. miR-218 expressed in endothelial progenitor cells contributes to the development and repair of the kidney microvasculature. *Am J Pathol*. 2020;190(3):642–59. <https://doi.org/10.1016/j.ajpath.2019.11.014>.
159. Guan H, Peng R, Mao L, Fang F, Xu B, Chen M, et al. Injured tubular epithelial cells activate fibroblasts to promote kidney fibrosis through mir-150-containing exosomes. *Exp Cell Res*. 2020;392(2):112007. <https://doi.org/10.1016/j.yexcr.2020.112007>.
160. Ho J, Ng KH, Rosen S, Dostal A, Gregory RI, Kreidberg JA, et al. Podocyte-specific loss of functional microRNAs leads to rapid glomerular and tubular injury. *J Am Soc Nephrol*. 2008;19(11):2069–75. <https://doi.org/10.1681/ASN.2008020162>.
161. Long J, Wang Y, Wang W, Chang BH, Danesh FR. MicroRNA-29c is a signature microRNA under high glucose conditions that targets sprouty homolog 1, and its in vivo knockdown prevents progression of diabetic nephropathy. *J Biol Chem*. 2011;286(13):11837–48. <https://doi.org/10.1074/jbc.M110.194969>.
162. Chen YQ, Wang XX, Yao XM, Zhang DL, Yang XF, Tian SF, et al. MicroRNA-195 promotes apoptosis in mouse podocytes via enhanced caspase activity driven by BCL2 insufficiency. *Am J Nephrol*. 2011;34(6):549–59. <https://doi.org/10.1159/000333809>.
163. Zheng Z, Guan M, Jia Y, Wang D, Pang R, Lv F, et al. The coordinated roles of miR-26a and miR-30c in regulating TGFβ1-induced epithelial-to-mesenchymal transition in diabetic nephropathy. *Sci Rep-Uk*. 2016;6:37492. <https://doi.org/10.1038/srep37492>.
164. Tung CW, Ho C, Hsu YC, Huang SC, Shih YH, Lin CL, et al. MicroRNA-29a attenuates Diabetic glomerular Injury through modulating cannabinoid receptor 1 signaling. *Molecules*. 2019;24(2):264. <https://doi.org/10.3390/molecules24020264>.
165. Liu XJ, Hong Q, Wang Z, Yu YY, Zou X, Xu LH, et al. MicroRNA-34a suppresses autophagy in tubular epithelial cells in Acute kidney Injury. *Am J Nephrol*. 2015;42(2):168–75. <https://doi.org/10.1159/000439185>.
166. 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(4):683. <https://doi.org/10.3892/mmr.2021.12322>.
167. Liu G, Kang X, Guo P, Shang Y, Du R, Wang X, et al. Mir-25-3p promotes proliferation and inhibits autophagy of renal cells in polycystic kidney mice by regulating ATG14-Beclin 1. *Ren Fail*. 2020;42(1):333–42. <https://doi.org/10.1080/0886022X.2020.1745236>.
168. Liu X, Hong Q, Wang Z, Yu Y, Zou X, Xu L, et al. MiR-21 inhibits autophagy by targeting Rab11a in renal ischemia/reperfusion. *Exp Cell Res*. 2015;338(1):64–9. <https://doi.org/10.1016/j.yexcr.2015.08.010>.
169. Müller-Deile J, Dannenberg J, Schroder P, Lin MH, Miner JH, Chen R, et al. Podocytes regulate the glomerular basement membrane protein nephrin by means of miR-378a-3p in glomerular diseases. *Kidney Int*. 2017;92(4):836–49. <https://doi.org/10.1016/j.kint.2017.03.005>.
170. Li H, Fan L, Zhang Y, Cao Y, Liu X. SNHG16 aggravates chronic constriction injury-induced neuropathic pain in rats via binding with mir-124-3p and mir-141-3p to upregulate JAG1. *Brain Res Bull*. 2020;165:228–37. <https://doi.org/10.1016/j.brainresbull.2020.09.025>.
171. Hu G, Ma L, Dong F, Hu X, Liu S, Sun H, et al. Inhibition of microRNA-124-3p protects against acute myocardial infarction by suppressing the apoptosis of cardiomyocytes. *Mol Med Rep*. 2019;20(4):3379–87. <https://doi.org/10.3892/mmr.2019.10565>.
172. Luo Y, Yu MH, Yan YR, Zhou Y, Qin SL, Huang YZ, et al. Rab27A promotes cellular apoptosis and ROS production by regulating the miRNA-124-3p/STAT3/RelA signalling pathway in ulcerative colitis. *J Cell Mol Med*. 2020;24(19):11330–42. <https://doi.org/10.1111/jcmm.15726>.
173. Kim MJ, Tam FW. Urinary monocyte chemoattractant protein-1 in renal disease. *Clin Chim Acta*. 2011;412(23–24):2022–30. <https://doi.org/10.1016/j.cca.2011.07.023>.
174. Haller H, Bertram A, Nadrowitz F, Menne J. Monocyte chemoattractant protein-1 and the kidney. *Curr Opin Nephrol Hypertens*. 2016;25(1):42–9. <https://doi.org/10.1097/MNH.0000000000000186>.
175. Lin Z, Shi JL, Chen M, Zheng ZM, Li MQ, Shao J. CCL2: an important cytokine in normal and pathological pregnancies: a review. *Front Immunol*. 2023;13:1053457. <https://doi.org/10.3389/fimmu.2022.1053457>.
176. Lv W, Booz GW, Wang Y, Fan F, Roman RJ. Inflammation and renal fibrosis: recent developments on key signaling molecules as potential therapeutic targets. *Eur J Pharmacol*. 2018;820:65–76. <https://doi.org/10.1016/j.ejphar.2017.12.016>.
177. Xu L, Sharkey D, Cantley LG, Tubular GM-CSF, Promotes Late. MCP-1/CCR2-Mediated fibrosis and inflammation after Ischemia/Reperfusion Injury. *J Am Soc Nephrol*. 2019;30(10):1825–40. <https://doi.org/10.1681/ASN.2019010068>.
178. Moloi MW, Rusch JA, Omar F, Ekrikpo U, Dandara C, Bello AK, et al. Urinary MCP-1 and TWEAK as non-invasive markers of disease activity and treatment response in patients with lupus nephritis in South Africa. *Int Urol Nephrol*. 2021;53(9):1865–73. <https://doi.org/10.1007/s11255-020-02780-9>.
179. Lv W, Fan F, Wang Y, Gonzalez-Fernandez E, Wang C, Yang L, et al. Therapeutic potential of microRNAs for the treatment of renal fibrosis and CKD. *Physiol Genomics*. 2018;50(1):20–34. <https://doi.org/10.1152/physiolgenomics.00039.2017>.
180. Ichii O, Horino T. MicroRNAs associated with the development of kidney diseases in humans and animals. *J Toxicol Pathol*. 2018;31(1):23–34. <https://doi.org/10.1293/tox.2017-0051>.
181. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL. Epidemiology of Acute Kidney Injury in critically ill children and young adults. *New Engl J Med*. 2017;376(1):11–20. <https://doi.org/10.1056/NEJMoa1611391>.
182. Ramachandran K, Saikumar J, Bijol V, Koyner JL, Qian J, Betensky RA, et al. Human miRNome profiling identifies microRNAs differentially present in the urine after kidney injury. *Clin Chem*. 2013;59(12):1742–52. <https://doi.org/10.1373/clinchem.2013.210245>.
183. Fichtlscherer S, De Rosa S, Fox H, Schwietz T, Fischer A, Liebetrau C, et al. Circulating microRNAs in patients with coronary artery disease. *Circ Res*. 2010;107(5):677–84. <https://doi.org/10.1161/CIRCRESAHA.109.215566>.
184. Gantier MP, McCoy CE, Rusinova I, Saulep D, Wang D, Xu D, et al. Analysis of microRNA turnover in mammalian cells following Dicer1 ablation. *Nucleic Acids Res*. 2011;39(13):5692–703. <https://doi.org/10.1093/nar/gkr148>.
185. Garcia-Martin R, Wang G, Brandão BB, Zanotto TM, Shah S, Kumar PS, et al. MicroRNA sequence codes for small extracellular vesicle release and cellular retention. *Nature*. 2022;601(7893):446–51. <https://doi.org/10.1038/s41586-021-04234-3>.
186. Wang K, Zhang S, Weber J, Baxter D, Galas DJ. Export of microRNAs and microRNA-protective protein by mammalian cells. *Nucleic Acids Res*. 2010;38(20):7248–59. <https://doi.org/10.1093/nar/gkq601>.
187. Nik MKN, Shahidan W. Non-exosomal and exosomal circulatory MicroRNAs: which are more valid as biomarkers? *Front Pharmacol*. 2019;10:1500. <https://doi.org/10.3389/fphar.2019.01500>.
188. Manier S, Liu CJ, Avet-Loiseau H, Park J, Shi J, Campigotto F, et al. Prognostic role of circulating exosomal miRNAs in multiple myeloma. *Blood*. 2017;129(17):2429–36. <https://doi.org/10.1182/blood-2016-09-742296>.
189. Shao L, Zhang Y, Lan B, Wang J, Zhang Z, Zhang L, et al. MiRNA-Sequence indicates that mesenchymal stem cells and Exosomes have similar mechanism to Enhance Cardiac Repair. *Biomed Res Int*. 2017;217:4150705. <https://doi.org/10.1155/2017/4150705>.
190. Saito Y, Nakaoka T, Saito H. microRNA-34a as a Therapeutic Agent against Human Cancer. *J Clin Med*. 2015;4(11):1951–9. <https://doi.org/10.3390/jcm4111951>.
191. Hart M, Nickl L, Walch-Rueckheim B, Krammes L, Rheinheimer S, Diener C, et al. Wrinkle in the plan: miR-34a-5p impacts chemokine signaling by modulating CXCL10/CXCL11/CXCR3-axis in CD4+, CD8+ T cells, and M1 macrophages. *J Immunother Cancer*. 2020;8(2):e001617. <https://doi.org/10.1136/jitc-2020-001617>.

192. Diener C, Hart M, Alansary D, Poth V, Walch-Rückheim B, Menegatti J, et al. Modulation of intracellular calcium signaling by microRNA-34a-5p. *Cell Death Dis.* 2018;9(10):1008. <https://doi.org/10.1038/s41419-018-1050-7>.
193. Kelnar K, Bader AG. A qRT-PCR method for determining the Biodistribution Profile of a miR-34a Mimic. *Methods Mol Biol.* 2015;1317:125–33. https://doi.org/10.1007/978-1-4939-2727-2_8.
194. Herrera-Carrillo E, Liu YP, Berkhout B. Improving miRNA delivery by optimizing miRNA expression cassettes in Diverse Virus vectors. *Hum Gene Ther Method.* 2017;28(4):177–90. <https://doi.org/10.1089/hgtb.2017.036>.
195. Deprey K, Batistatou N, Kritzer JA. A critical analysis of methods used to investigate the cellular uptake and subcellular localization of RNA therapeutics. *Nucleic Acids Res.* 2020;48(14):7623–39. <https://doi.org/10.1093/nar/gkaa576>.
196. Prakash TP, Graham MJ, Yu J, Carty R, Low A, Chappell A, et al. Targeted delivery of antisense oligonucleotides to hepatocytes using triantennary N-acetyl galactosamine improves potency 10-fold in mice. *Nucleic Acids Res.* 2014;42(13):8796–807. <https://doi.org/10.1093/nar/gku531>.
197. Narayan N, Morenos L, Phipson B, Willis SN, Brumatti G, Eggers S, et al. Functionally distinct roles for different miR-155 expression levels through contrasting effects on gene expression, in acute myeloid leukaemia. *Leukemia.* 2017;31(4):808–20. <https://doi.org/10.1038/leu.2016.279>.
198. Jacquet K, Vidal-Cruchez O, Rezzonico R, Nicolini VJ, Mograbi B, Hofman P, et al. New technologies for improved relevance in miRNA research. *Trends Genet.* 2021;37(12):1060–3. <https://doi.org/10.1016/j.tig.2021.08.006>.

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