Review Article

The extracellular miRNA fingerprint of kidney disease: a narrative review

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Background and Objective: MicroRNAs (miRNAs) are small non-coding RNA molecules that post-transcriptionally regulate gene expression by binding to their target mRNAs. In kidney, miRNAs have been implicated the development of several diseases, including chronic and acute kidney disease, diabetic nephropathy (DN), hypertensive nephropathy, kidney immune diseases and polycystic kidney disease (PKD), among others. The association of miRNA levels in bodily fluids with disease progression, suggests their role as mediators of renal pathophysiology and their use as biomarkers. This review discusses current knowledge of miRNA function in kidney diseases, focusing on their participation in cellular communication and their value as biomarkers.

Methods: Bibliography search strategy includes publications in English from peer-reviewed journals listed in PubMed database from 2000–January 2022.

Key Content and Findings: A rapidly growing kidney disease-specific extracellular miRNA signature coupled to cellular export/import mechanisms involving vesicle trafficking, protein carriers and miRNA leakage has been identified in the last decade due to the developments in genomics and bioinformatics. However, besides attempts to model the complexity of the networks and regulatory mechanisms of miRNAs involved in each kidney disease, in the majority of cases definitive or causative roles have not been established yet.

Conclusions: MiRNAs provide the opportunity to explore novel serum and urine biomarkers of kidney disease, as well as potential therapeutic targets.

Keywords: Extracellular microRNAs (extracellular miRNAs); kidney disease; biomarkers

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Introduction

MicroRNA (miRNA) biogenesis and function

Noncoding RNAs (ncRNAs) have arisen as a new paradigm in gene regulation and cell differentiation (1). Further of ribosomal RNAs (rRNAs) and transfer RNAs (tRNAs) involved in protein synthesis, regulatory ncRNAs classify based on their size: those shorter than 200 nucleotides (nt) are called short non-coding RNAs and include miRNAs, short interfering RNAs (siRNAs), small nuclear RNA (snRNA), small nucleolar RNA (snoRNA) and piwi-interacting RNAs (piRNAs), whereas those longer than 200 nt are called long non-coding RNAs (lncRNAs) and include linear [long intergenic (lincRNA), intronic RNA, enhancer RNA (eRNA), natural antisense transcripts (NAT)] and circular RNA (circRNA) (2). They can regulate gene expression at transcriptional or post-transcriptional level by modulating chromatin structure, RNA maturation and protein synthesis/transport (3).

MiRNAs are a large family of conserved, small, non-coding RNAs of 19–25 nt long that repress the translation and/or degradation of their target mRNAs (4). Since the discovery of the first miRNA, Lin-4, in *Caenorhabditis elegans* in 1993, thousands of miRNAs have been uncovered in many multicellular organisms (5,6). At present, there are more than 2,600 and 1,900 mature miRNAs described

in human and mouse, respectively (7). This regulatory system is based on base-pair complementarity between miRNAs and target sequences mainly located in the 3' untranslated region (UTR) of mRNAs. However, functional miRNA binding sites can also be found in the 5' UTR and open reading frame regions (ORFs) (8). This feature makes possible that a single miRNA can potentially target hundreds mRNAs and that one mRNA can be regulated by several miRNAs, with cooperative repression achieved by binding closely spaced target sites (9). This dynamic interaction relies on many factors, including the subcellular location, the abundance of miRNAs and target mRNAs and the affinity of miRNA-mRNA interactions (10). MiRNAs are transcribed by RNA polymerase II as a long precursor RNA primary miRNA (pri-miRNA) which is processed by the DROSHA-DGCR8 in the nucleus, resulting in a precursor miRNA (pre-miRNA) of ~70 nt in length. Once exported into the cytoplasm, it is shortened by DICER, yielding a ~22-nt mature miRNA. There, miRNAs associate with specific mRNAs within the multiprotein complex of Argonaute proteins, the core of the RNA-induced silencing complex (RISC) (11). One strand of the miRNA ('guide strand') is loaded into argonaute (AGO), whereas the other strand ('passenger strand') is eliminated. Alternative cleavage by DROSHA or DICER leads to the generation of isomiRs (9). Further, multiple non-canonical miRNA biogenesis pathways have been discovered, which include Drosha/DGCR8- and Dicer-independent processing routes (10). MiRNAs show very specific expression patterns that differ among tissues and cell types and are involved in virtually every cellular process, including development, differentiation, stress response and apoptosis (12).

Extracellular miRNAs

Although miRNAs function cell-intrinsically, miRNAs can be found in mostly every body fluid which support their role in the communication between cells and tissues. MiRNAs can be exported by cells through two main routes: (I) active transport via extracellular vesicles (EVs) and (II) transport as part of protein-miRNA complexes; which confer them protection from degradation by ribonucleases. Further, there can be some passive leakage of miRNAs from damaged cells (*Figure 1*) (13).

EVs are classified based on their size and biogenesis: exosomes (30–200 nm), microvesicles (MVs) (100–1,000 nm) and apoptotic bodies (ABs) (>1,000 nm). Their heterogeneity of cargoes includes lipids, proteins, metabolites and nucleic acids. Exosomes, also termed small EVs, are generated through the endocytic pathway through the translocation of multivesicular bodies (MVBs) to the plasma membrane, where they undergo fusion and release their contents through the process of exocytosis involving both endosomal sorting complex required for transport (ESCRT)-dependent or ESCRT-independent ceramide-mediated pathways (14). Their characteristic composition of surface proteins facilitates a selective targeting of recipient cells (15). The main proteins incorporated in exosomes are members of the tetraspanin family (CD9, CD63 and CD81), ESCRT proteins (Alix, TSG101), integrins, heat shock proteins (Hsp), actin and flotillins (14). A growing evidence indicates a selective active loading or sorting of miRNAs into these vesicles (16,17). Some studies suggest the involvement of AGO2 and other RNA-binding proteins in the regulation of this miRNA loading (18). Other RNA-binding proteins such as Y-box protein 1 (19), nucleophosmin 1 (NPM1) (20), neutral sphingomyelinase 2 (nSMase2) (21) and hnRNPA2B (22) also confer specificity to this process. The EXOmotif GGAG present in some miRNAs can be recognized by hnRNPA2B1, thus controlling the loading of these miRNAs. Interestingly, sumoylation of hnRNPA2B1 seems to be essential for the binding of hnRNPA2B1 to miRNAs (22). Recently, Garcia-Martin *et al.* identified sequence patterns in miRNAs which determine their secretion in EVs (EXOmotifs) or cellular retention (CELLmotifs), defining cell-type-specific EV miRNA profiles (23).

MVs and ABs are EVs formed by direct outward budding and fission of the plasma membrane in living and dying cells, respectively, and their surface protein largely depend on their cellular membrane of origin (24). MVs generation mostly occur in lipid-rich plasma membrane microdomains (lipid rafts/caveolae). Although the mechanism of miRNA uploading into MVs is largely unknown, Collino *et al.* demonstrated that the ribonucleoproteins T-cell internal antigen-1 (TIA), TIA-1-related (TIAR) and AU-rich element-binding protein (HuR) are involved in the selected miRNA pattern in MVs (25). Many MV-encapsulated miRNAs can also be associated with RISC proteins such as AGO2, which increase their stability and functionality in recipient cells (26). Phosphatidylserine is a distinctive element of ABs. Zernecke *et al.* firstly showed that miR-126-enriched ABs shed by endothelial cells could alter chemokine responses in neighboring cells (27). However, there are very few studies investigating the AB-encapsulated miRNA effects and a limited understanding about the specificity and selectivity of miRNA loading into ABs.

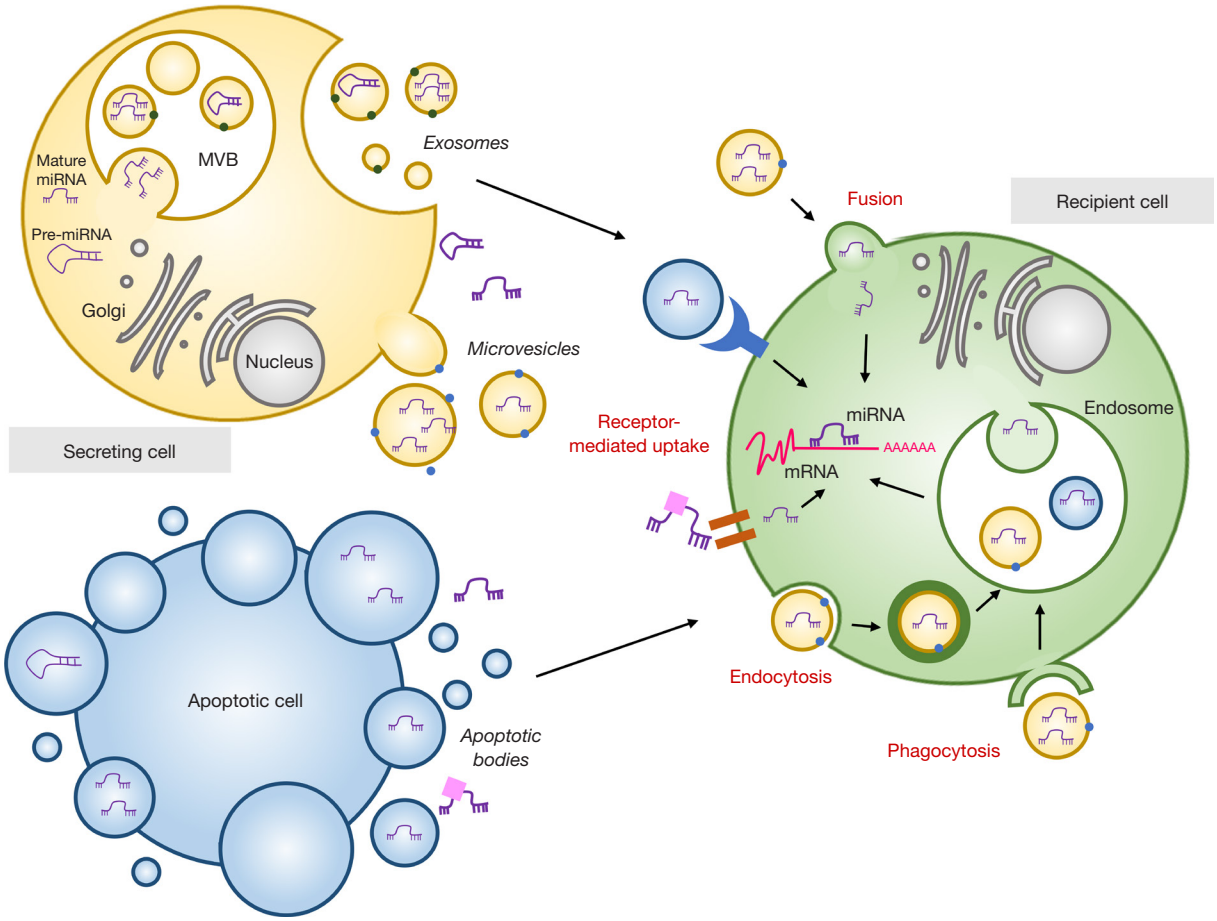

Figure 1 Intercellular miRNA transference. Extracellular miRNAs participate in the communication between cells. MiRNAs (mature miRNAs and pre-miRNAs) are exported by cells through extracellular vesicles (exosomes, microvesicles and apoptotic bodies), as part of protein-miRNA complexes or passive leakage. Uptake mechanisms from vesicle-associated extracellular miRNAs are phagocytosis, endocytosis and direct fusion with the target-cell plasma membrane, while vesicle-free secreted miRNAs are taken up by specific cell surface receptors. Following internalization, miRNAs released in the cytoplasm can repress target gene expression. miRNA, microRNA; MVB, multivesicular bodies.

MiRNAs can also be transported in vesicle-free systems, such as RNA-binding proteins or low-density (LDL) and high-density lipoproteins (HDL) (28). More than half of the miRNAs found in serum may be bound to ribonucleoproteins, such as AGO2, NPM1 and ribosomal protein L10a and L5 (20,29). Of note, the profile of miRNAs bound to vesicle-free systems differs from that found in EVs, indicating complementary and independent mechanisms of miRNA transport (28).

Many research groups have demonstrated that extracellular miRNAs are functional in recipient cells. However, the mechanisms of miRNA uptake are not fully understood. There is evidence that vesicle-associated extracellular miRNAs can be internalized by recipient cells through endocytosis, phagocytosis or the direct fusion with the target-cell plasma membrane. Interaction can operate through two main mechanisms: receptor-ligand binding and direct release of EV content in target cells (*Figure 1*). Vesicle-free secreted miRNAs may be taken up by specific cell surface receptors. Particularly, miRNAs associated with HDL interact with the HDL receptor and scavenger receptor BI (SR-BI). MiRNAs have also been shown to be transferred via direct cell-cell contact and gap junctions (10).

The fact that many circulating miRNAs dynamically exhibit a bio-fluids-specific profile in relation to a pathophysiological state, not only constitutes a specific

Table 1 Search strategy summary

Criterion	Specification
Date of search	January 2022
Databases and other sources searched	PubMed
Search terms used	"Extracellular miRNAs" OR "kidney disease" OR "biomarkers"
Timeframe	2000–January 2022
Inclusion and exclusion criteria	Only articles written in English language and published in peer-reviewed journals were included
Selection process	Selection process was carried out by the author

miRNAs, microRNAs.

mechanism for intercellular communication, but also gives rise to the miRNA application as diagnostic and prognostic biomarkers (10). Particularly, miRNAs-based biomarkers in blood and urine have generated a strong interest in the field of nephrology. This review discusses the up-to-date knowledge of miRNA function in kidney diseases, focusing on their participation in cellular communication and their value as biomarkers. We present the following article in accordance with the Narrative Review reporting checklist (available at https://exrna.amegroups.com/article/view/10.21037/exrna-22-2/rc).

Methods

Bibliography search strategy includes publications in English from peer-reviewed journals listed in PubMed database from 2000–January 2022. Search terms used were: "extracellular miRNAs" OR "kidney disease" OR "biomarkers" (*Table 1*).

Extracellular miRNAs in renal pathophysiology

Chronic kidney disease (CKD)

CKD is a clinical condition with maintained reduction of renal function which is present in 30–40% of patients with highly prevalent pathologies such as diabetes mellitus and hypertension (30). It leads to tubulointerstitial and glomerular fibrosis as a result of excessive deposition of extracellular matrix of proteins (ECM), such as hyaluronic acid, fibronectin (FN), proteoglycans and interstitial collagens in association with a persistent inflammatory response, tubular epithelial cell (TEC) dedifferentiation and loss and rarefaction of the peritubular microvasculature (30). Myofibroblasts, derived from fibroblasts and PDGFRβ$^+$/PDGFRα$^+$ mesenchymal cells in the kidney, are the principal cells responsible for producing ECM (31).

Regulation of kidney fibrosis by miRNAs

MiRNAs have raised as powerful dynamic regulators of fibrotic processes [fibromiRs, (32)]. It mainly occurs thought the regulation of transforming growth factor beta 1 (TGF-β1) signaling in a cell-dependent and context-dependent manner (33). In keeping, Dicer1 deficiency promotes fibrosis in different organs by upregulating Smad2/3 (34,35). TGF-β signaling, in turn, can regulate the transcription of miRNAs by binding Smad proteins to Smad-binding elements (SBEs) in the DNA. In addition, Smad-activated auxiliary factors such as the RNA helicase p68, a component of the Drosha microprocessor complex, can promote the recruitment of Drosha/DGCR8 to specific pri-miRNAs (36).

Gomez *et al.* identified 24 miRNAs commonly upregulated both in human CKD and in animal models of kidney fibrosis, suggesting a "fibrotic" miR signature in the kidney (37). Cell-specific small RNA-sequencing (sRNA-seq) on TECs, endothelial cells, PDGFR-β$^+$ cells and macrophages also show a differential miRNA profile in injured kidneys (38).

MiRNA-mediated control of kidney fibrosis mainly occurs thought the regulation of crucial signaling pathways associated with epithelial dedifferentiation, myofibroblast activation, matrix deposition and inflammation (*Table 2*) (113). MiR-21 regulates TGF-β-induced signaling pathways by targeting Smad7 and phosphatase and tensin homology (PTEN) and, in turn, is upregulated by TGF-β in TECs promoting renal fibrosis (39,40). Other miRNAs regulating TGF-β signaling are: miR-433 which contributes to renal fibrosis by amplifying the TGF-β/Smad3-Azin1 pathway (42), miR-23b targeting TGF-β receptor type II (TGF-βRII), SMAD3 and TGF-β, suggesting a negative feedback loop-regulating TGF-β signaling (43), and miRNA-196a/b, which mitigate renal fibrosis by targeting TGF-βRII (44). Although the contribution of epithelial to mesenchymal transition (EMT) to fibrosis is seriously questioned (31), some miRNAs have been closely related to it. MiR-200a targets include EMT-related factors such as TGF-β2, β-catenin and the Zinc finger E-box binding homeobox 1 (ZEB1), which negatively modulates E-cadherin (45-47). Let-7d and miR-214 has been

Table 2 MiRNAs in chronic and acute kidney injury, diabetic nephropathy, hypertensive nephropathy, kidney immune diseases and polycystic kidney disease

miRNAs	Level during disease	Target	Effect	Reference(s)
Chronic kidney injury				
miR-21	Up	SMAD7, PTEN, PPARA, MMPs, TIMPs	ECM*, mitochondrial dysfunction*	(39-41)
miR-433	Up	AZIN1	ECM*	(42)
miR-23	Up	TGFBRII, SMAD3, TGFB	ECM#	(43)
miR-196	Up	TGFBRII	ECM#	(44)
miR-200a	Up	TGFB2, CTNNB1, ZEB1/2	EMT#	(45-47)
Let-7	Down	TGFBRI, HMGA2	EMT*	(48,49)
miR-214	Up	SNAIL, TWIST, ND6, ND4	EMT*	(50,51)
miR-27	Up	PPARG	Mitochondrial dysfunction*	(52)
miR-33/-150/-495	Up	CPT1A	Mitochondrial dysfunction*	(53,54)
miR-29	Up	COLs, FBNs, LMNAs, ELNs	ECM#	(55)
miR-132	Up	FOXO3A, P300	Fibroblast proliferation#	(56)
miR-503	Down	RAF1	Fibroblast proliferation#	(57)
Acute kidney injury				
miR-21	Up	PDCD4, PTEC, PPARA, NFKB	Apoptosis#, inflammation#	(58,59)
miR-494	Up	ATF-3	Apoptosis*, inflammation*	(60)
miR-24	Up	H2A.X, HO-1	Apoptosis*	(61)
miR-194	Down	RHEB	ROS#, inflammation#	(62)
miR-181	Up	BCL-2	Apoptosis*	(63)
miR-489	Up	PARP1	Apoptosis#	(64)
miR-150	Up	MYB	Apoptosis*, inflammation*	(65)
miR-16	Up	BCL2	Apoptosis*	(66)
miR-107	Up	DUSP7	Inflammation*	(67)
miR-183	Up	SIRT1	Fibrosis*, apoptosis*	(68)
Diabetic nephropathy				
miR-192	Up	ZEB1/2	ECM*	(69)
miR-200b/c	Up	ZEB1, FOG2	ECM*	(70)
miR-216/-217	Up	PTEN	Cellular hypertrophy*	(71)
miR-21	Up	SMAD7, MMP-7, TIMP1	ECM*	(41,72)
miR-23	Down	SNON	ECM*, EMT*	(73)
miR-29a	Down	HDAC	Podocyte damage*	(74)
miR-29c	Up	SPRY-1	Apoptosis*, ECM*	(75)
miR-25	Down	NOX4	ROS*	(76)
miR-30/-130b	Up	SNAIL1, CTGF, GIPR2	EMT#	(77-79)

Table 2 (*continued*)

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miRNAs	Level during disease	Target	Effect	Reference(s)
miR-10	Up	NLRP3	Inflammation#	(80)
miR-45	Up	PSHD11, LMP7, P65	Inflammation#	(81,82)
miR-377	Up	P21, Mn-SOD	ROS*, autophagy#	(83)
miR-214	Up	ULK1, PTEN	Autophagy#, ECM*, cellular hypertrophy*	(84,85)
miR-150	Up	SIRT1	Autophagy#	(86)
Hypertensive nephropathy				
miR-29	Up	COL1A1	ECM#	(87)
miR-204	Down	SHP2	ECM*	(88)
miR-192	Up	ZEB1/2	ECM*	(89)
miR-155	Up	AGTR1	ECM#	(90)
miR-21	Up	PPARA	ECM*	(91)
miR-103	Up	SNRK	ECM*, inflammation*	(92)
miR-429	Up	ZEB1	EMT#	(93)
Kidney immune diseases				
Let7a miR-148/-196	Up	GALNT2, C1GALT1	Aberrant IgA glycosylation*	(94-96)
miR-223	Down	KPNA3/1	Endothelial cell proliferation*	(97)
miR-100	Down	IL-8	Inflammation*	(98)
miR-877	Down	IL-1β	Inflammation*	(98)
miR-200bc miR-429	Up	TWEAK	Inflammation#	(99)
miR-21	Up	PTEN	ECM*	(100)
miR-146	Up	TRAF6	Inflammation#	(101)
miR-150	Up	SOCS1	ECM*	(102)
miR-422	Up	KLK4	ROS*, inflammation*	(103)
miR-10	Down	IL-8	Inflammation*	(104)
Polycystic kidney disease				
miR-17	Up	PKD1/2, PPARA	Cyst growth*	(105,106)
miR-92	Up	HNF1B	Cyst growth*	(105)
miR-20/-106a	Down	KLF12	Cell proliferation*	(107)
miR-365	Up	PKHD1	ECM#	(108)
miR-192/-194	Down	ZEB2, CADH2	EMT*	(109)
miR-21	Up	PDCD4	Apoptosis#	(110)
miR-199a	Up	CDKN1C/P53	Cell proliferation*	(111)
miR-214	Up	TLR4	Inflammation#	(112)

* and # represent enhanced or repressed process, respectively. miRNA, microRNA; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; ROS, reactive oxygen species.

described as regulators of key EMT genes SNAIL and TWIST (48-50). Metabolic derangement, particularly mitochondrial impairment in TECs, is now identified as a key culprit in fibrogenesis (114). MiR-21 promote fibrosis by silencing metabolic pathways targeting peroxisome proliferator-activated receptor alpha (PPAR-α) and MPV17-like protein (39). MiRNA-27a also promotes fibrosis via suppressing PPAR-γ pathway (52), while disruption of mitochondrial oxidative phosphorylation during CKD is also a consequence of miR-214 increase, by targeting the mitochondrial genes MT-ND6 and MT-ND4L (51). Impairment of renal fatty acid oxidation during fibrosis progression is a process controlled by miR-33 (115), miR-150 and miR-495 (53). Other miRNAs can regulate ECM production during CKD. TGF-β/Smad3 signaling inhibits miR-29 in TECs which targets collagens, fibrillins, laminins and elastin (55). MiR-21 also has a role in ECM homeostasis through the regulation of metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) (41). MiRNA-132 and miR-503 can reduce renal fibrosis by selectively inhibiting myofibroblast proliferation (56,57).

Extracellular miRNAs in renal fibrosis: potential biomarkers

In the kidney, EVs can be originated from all segments of the nephron and have an important role as signaling messengers, regulating the phenotype of renal and extrarenal cell types controlling various biological processes including programmed cell death, angiogenesis, inflammation, immunosuppression and regeneration, and subsequently, the outcome of kidney injury (116).

Crosstalk between kidney cells, including injured and uninjured TECs, fibroblasts and immune cells, has emerging as a crucial mechanism during fibrogenesis which involves EVs shuttled miRNAs (*Figure 2*) (117). TGF-β1 mRNA is secreted by injured TECs and transported to interstitial fibroblasts through exosomes (118). Hypoxia-injured proximal TECs (PTECs) promote fibroblast activation by shuttling exosomes containing miR-150 (119). In fibrotic tissue, secreted miR-21-containing MVs from injured and senescent TECs promote EMT in neighboring cells by targeting PI3K-Akt and PPARα-HIF-1α pathways, respectively (120-122), while MV-secreted miR-216a promotes EMT and aggravates renal fibrosis through the PTEN/Akt pathway (123). By contrast, miR-34a is secreted by interstitial fibroblasts and transported via MVs toward TECs, inducing apoptosis and tubular atrophy (124).

Urine and serum levels of some fibromiRs correlate with proteinuria and kidney function in CKD patients (*Figure 3*). Muralidharan *et al.* provided an extracellular miRNA signature of 384 urinary and 266 circulatory miRNAs differentially expressed between patients with estimated glomerular filtration rate (eGFR) ≥30 versus <30 mL/min/1.73 m^2. Thus, let-7a and miR-423 showed lower levels in urine and plasma of patients with eGFR <30, respectively while the presence of miR-130, miR-1825 and miR-1281 was upregulated in urine and plasma of patients with eGFR <30; which was confirmed in albumin/TGF-β1-treated mice and TECs (125). Increased serum and urinary miRNA-21 levels, the best characterized miRNA in CKD, parallel the severity of kidney fibrosis and renal loss of function (126,127). In another cohort of CKD patients, increased miR-29 and miR-196a and decreased miR-155, miR-214, miR-200a and miR-93 levels were observed in urine, while increased miR-155, miR-214 and miR-200a and reduced miR-29a and miR-93 were found in serum of CKD patients, suggesting their use as potential non-invasive disease biomarkers (128). Another study examined miR-126 and miR-223 in serum of 601 CKD patients with a follow-up for 6 years, noticing that the level of both miRNAs had decreased along time (129). Serum miR-483 and miR-363 were identified by next generation sequencing as potential diagnostic biomarkers associated with CKD severity (130). By the same approach, Khurana *et al.* identified 30 differentially expressed ncRNAs in urinary exosomes from CKD patients. Among them, miRNA-181a was 200-fold decreased and appeared as the most robust and stable potential biomarker (131). Ichii *et al.* found increased levels of miR-146a in urine sediments of mice with CKD (132).

Acute kidney injury (AKI)

AKI is characterized by the rapid decline of renal function due to ischemia, nephrotoxicity, sepsis, obstruction of urinary tract or bladder outflow obstruction which can lead to tubular necroinflammation. AKI is a predisposing cause and an occasional precedent of CKD, whereas CKD is a major risk factor for AKI (133).

Regulation of AKI by miRNAs

The importance of miRNAs in AKI was first evidenced by the conspicuous protective effect observed in PTEC-specific *Dicer* knockout mice where over 80% miRNAs were depleted (134). Altered expression of >50 miRNAs have been described to play protective and pathogenic roles

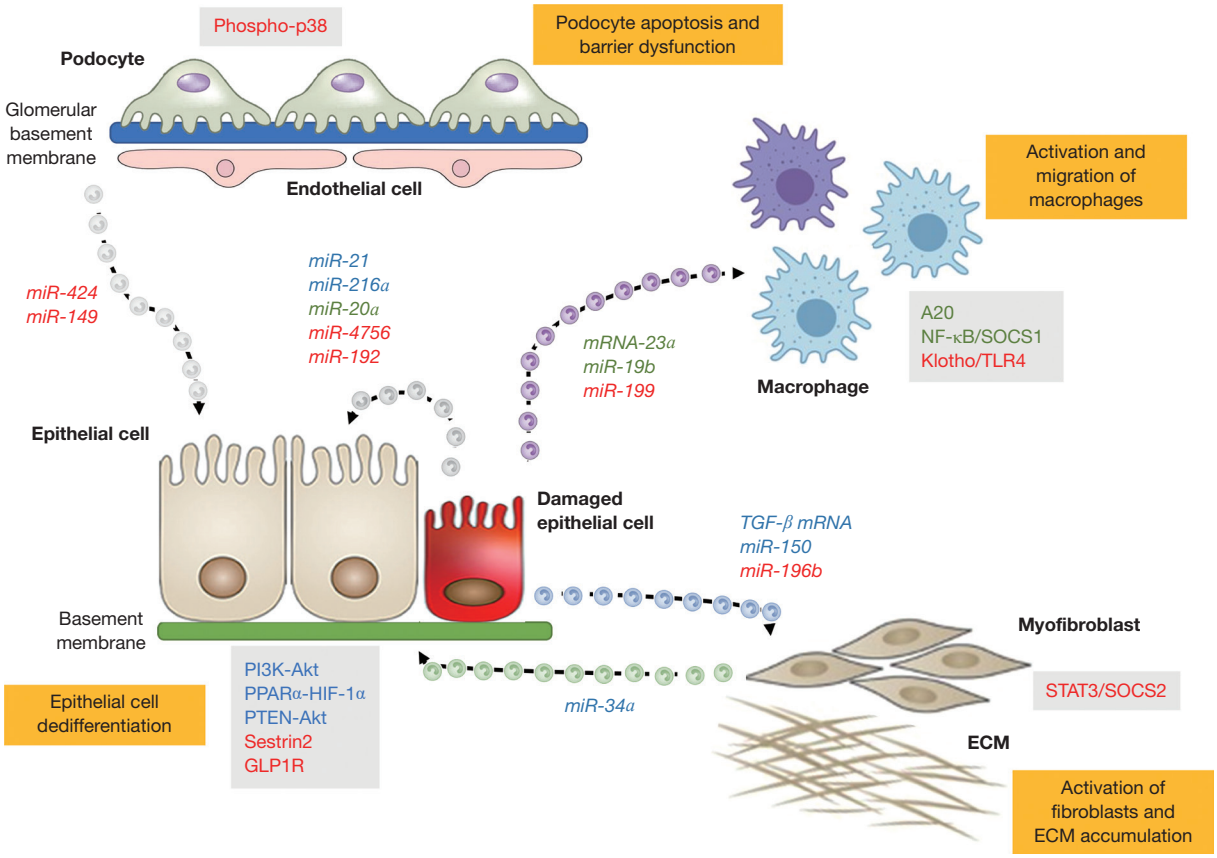

Figure 2 EV miRNA-mediated cellular crosstalk in kidney injury. EV-borne miRNAs contribute to cell-to-cell communication and regulates signaling pathways associated with the pathogenesis of kidney disease such as podocyte apoptosis, glomerular barrier disfunction, activation and migration of macrophages, epithelial cell dedifferentiation, activation of fibroblasts and ECM accumulation. Names in blue, green and red represent EV miRNAs in chronic and acute kidney disease and diabetic nephropathy, respectively. Names in grey squares represent miRNA target genes for these kidney diseases. A20, TNF alpha induced protein 3; NF-κB, nuclear factor-kappa B; SOCS1, suppressor of cytokine signaling 1; TLR4, toll like receptor 4; STAT3, signal transducer and activator of transcription 3; SOCS2, suppressor of cytokine signaling 2; PI3K, phosphoinositide 3-kinases; AKT, protein kinase B; PPAR-α, peroxisome proliferator-activated receptor alpha; HIF-1α, hypoxia-inducible factor-1; PTEN, phosphatase and tensin homology; GLP1R, glucagon-like peptide 1 receptor; ECM, extracellular matrix proteins; EV, extracellular vesicle; miRNA, microRNA.

in the development of AKI including miR-21, miR-205, miR-127 and miR-494 (60,135-137). Cell-enriched miRNA analysis in AKI shows macrophage-enhanced miR-18a and miR-16 and PTEC-enhanced miR-194 (38).

Inflammation and apoptosis are the main responses regulated by miRNAs during AKI (*Table 2*). MiRNA-21 inhibits apoptosis by targeting programmed cell death protein-4 (PDCD4) and PTEN (138), while showing an anti-inflammatory role by targeting PPAR-α and nuclear factor-kappa B (NF-κB) (58,59). MiR-494 is up-regulated in AKI repressing activating transcription factor-3 (ATF-3) which increases inflammatory mediators (60). In turn, miR-219 downregulation triggers a proinflammatory phenotype of macrophages increasing the expression of Mincle during AKI (139). Other miRNAs such as miR-24 (61), miR-181 (63), miR-150 (65), miR-16 (66) and miR-183 (68) stimulate apoptosis during AKI, while miR-489 is induced via hypoxia-inducible factor-1 (HIF-1α) to protect from apoptosis (64). Endothelial activation also plays a key role in septic AKI, involving altered vascular reactivity, permeability and adherence of leukocytes. It has been described that increased miR-107 induces tumor necrosis factor alpha (TNF-α) secretion by targeting dual-specificity phosphatase 7 (DUSP7) in endothelial cells (67).

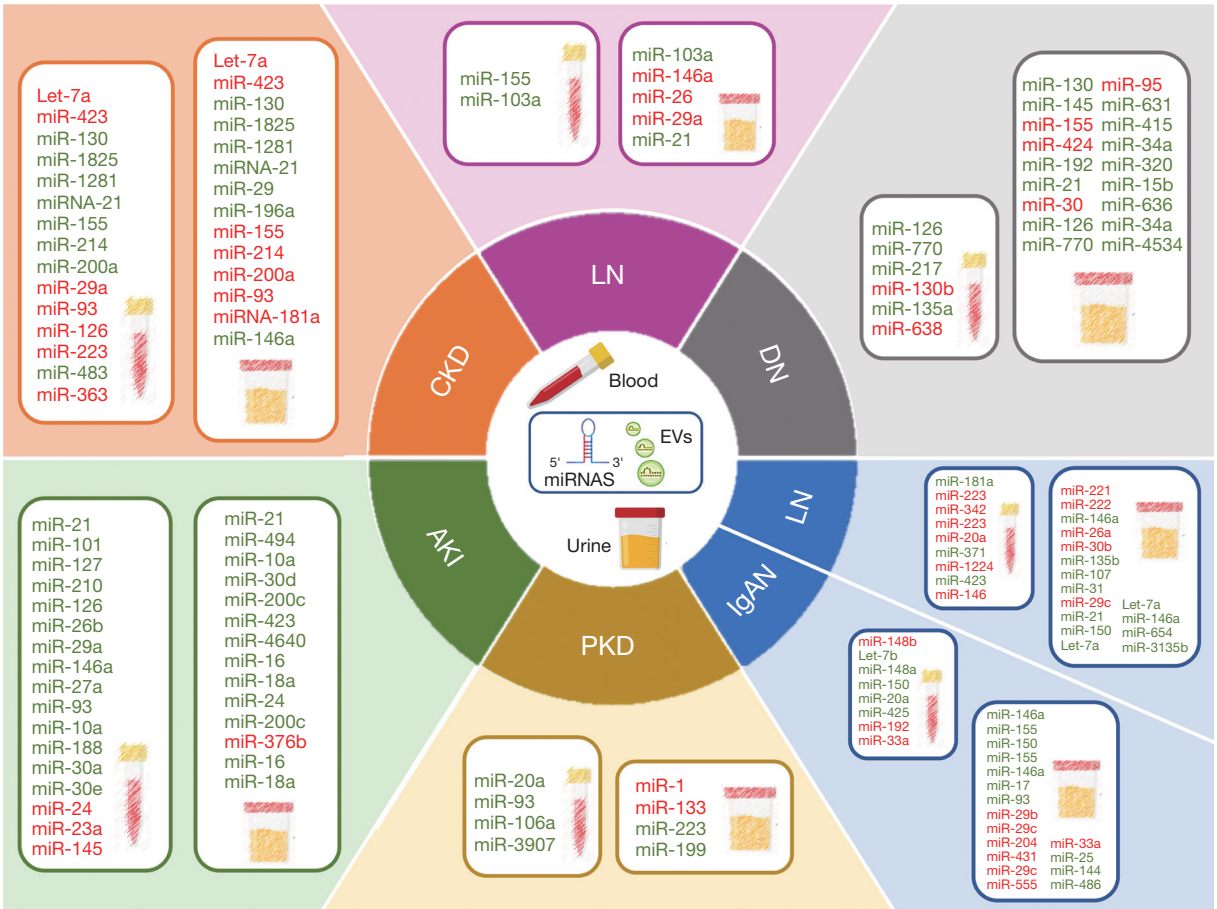

Figure 3 Blood and urine miRNAs as potential biomarkers of renal disease. Names in green and red represent enhanced or repressed miRNAs, respectively. EV, extracellular vesicle; CKD, chronic kidney disease; DN, diabetic nephropathy; AKI, acute kidney injury; PKD, polycystic kidney disease; IgAN, IgA nephropathy; LN, lupus nephritis; miRNA, microRNA.

Extracellular miRNAs in AKI: potential biomarkers

EV-borne miRNAs also participate in cell-to-cell communication during AKI (*Figure 2*). Hypoxia-injured PTECs trigger the pro-inflammatory phenotype of macrophages by exosomal miR-23a and miR-19b transferring which suppress the activity of the ubiquitin editor A20 and NF-κB/SOCS1, respectively (140,141). MiR-20a is enriched in hypoxia-derived tubular exosomes and protects against TECs mitochondrial failure and apoptosis (142). In turn, miR-191 secreted by platelet-derived MVs induces apoptosis of TECs in AKI by targeting cystathionine-β-synthase (CBS) (143).

There is an urgent need to identify sensitive and specific early markers for AKI that overcomes the limitations of traditional serum creatinine and blood urea nitrogen values which change only after significant kidney injury with a substantial time delay. Some serum and urine miRNAs have raised as promising early indicators of this disease (*Figure 3*) (144). It has been described that increased serum and urinary miRNA-21 levels parallel the severity of AKI (145). Other miRNAs with differential urine levels are miR-494, miR-10a, miR-30d, miR-200c, miR-423 and miR-4640 (60,146,147). MiRNA profiling of urinary exosomes shows that miRNA concentration tracks with AKI progression, including miR-16, miR-24 and miR-200c. Complementarity, miR-9a, miR-141, miR-200c and miR-429 were associated to AKI recovery stage (148). Several miRNAs, including miR-101, miR-127, miR-210, miR-126, miR-26b, miR-29a, miR-146a, miR-27a, miR-93 and miR-10a have also been reported to be altered in serum of AKI patients (149). Noteworthy, miR-210 predicted AKI mortality in intensive care unit patients (150).

Specific serum and urine miRNA signatures have been associated with the different casualties of AKI. Pavkovic

et al. detected more than 20-fold changes in 11 urinary miRNAs of the cisplatin-induced AKI model, which are associated with DNA damage response, cell cycle dysregulation and apoptosis (151). In different models of contrast-induced AKI, increased miR-188, miR-30a and miR-30e levels are detected in plasma (152). Decreased urinary miR-376b is proposed as a useful biomarker for the diagnosis or identification of AKI in patients with sepsis. Mechanistically, miR-376b is suppressed by NF-κB in TECs, leading to the induction of its target gene NF-κB inhibitor zeta (NFKBIZ), which limits inflammation and cell death (153). A significant upregulation of miR-16 and miR-18a was observed in the first-passed urine of patients who developed delayed graft function (DGF), the typical first clinical AKI manifestation occurring following renal transplantation (38). Decreased serum miR-24, miR-23a and miR-145 levels were reported in post-myocardial infarction AKI pathogenesis (154).

Diabetic nephropathy (DN)

DN is a complication of type 1 and 2 diabetes mellitus, with a global incidence of 9%. It is histologically characterized by early tubular cell atrophy followed by mesangial cell (MCs) hypertrophy, podocyte dysfunction, glomerulosclerosis, renal fibrosis and matrix expansion. DN main contributors are hyperglycaemia and insulin resistance (155).

Regulation of DN by miRNAs

First evidences of the involvement of miRNAs in DN were observed in mice with podocyte-specific deletion of *Dicer* or *Drosha*, which exhibited severe renal phenotypes including proteinuria, podocyte foot process effacement and apoptosis, glomerulosclerosis and tubulointerstitial fibrosis (*Table 2*) (156,157).

MiR-192 is a master miRNA regulator of DN (158). MiR-192 upregulates collagen genes in MCs by targeting the transcriptional repressors ZEB1/2 (69). Of interest, miR-192 upregulates other miRNAs, including miR-216a/miR-217 and miR-200b/c whose targets promote cellular hypertrophy (71). MiR-21 and miR-23 also promote renal fibrogenesis and hypertrophy by regulating TGF-β signaling (41,73). Inflammation is an early event during DN. MiR-10 negatively regulates inflammation by targeting activation of the NLRP3 inflammasome (80), while miR-45 downregulates the 26S proteasome non-ATPase regulatory subunit 11 (PSMD11), multifunctional protease 7 (LMP7) and NF-κB p65 (81,82). Redox and autophagy imbalance are also drivers of DN. Enhanced expression of miR-377 increases FN levels by targeting p21-activated kinase and manganese superoxide dismutase (MnSOD) (83). MiR-214 and miR-150 control autophagy during DN by regulating the PI3K/AKT/mTOR and SIRT1/p53/AMPK pathways, respectively (84,85). Other miRNAs modulate the high-glucose (HG)-induced homeostasis imbalance in DN. HG induce apoptosis of mouse podocytes by downregulating miR-29a and increasing miR-29c expression. Low levels of miR-29a correlate with enhanced levels of its target histone deacetylase (HDAC), which modulates the acetylation status of nephrin (74). MiR-29c promotes apoptosis and FN synthesis by inhibition of sprouty RTK signaling antagonist 1 (SPRY1) (75). Other miRNAs involved in the HG-induced response are miR-25 (76), miR-30c and miR-130b (77-79), which modulate reactive oxigen species (ROS) and EMT, respectively.

Extracellular miRNAs in DN: potential biomarkers

EV miRNAs also participate in the cellular crosstalk during DN (*Figure 2*). EVs enriched in miR-196b from TECs mediate fibroblast activation and promotes renal fibrosis in diabetic mice through the activation of the signal transducer and activator of transcription 3 (STAT3)/suppressor of cytokine signaling 2 (SOCS2) signaling pathway (159). MiR-199a is increased in EVs from human serum albumin (HSA)-induced TECs which triggers kidney macrophage M1 polarization by targeting the Klotho/toll like receptor 4 (TLR4) pathway (160). EVs enriched in miR-4756 are also produced by HSA-induced TECs and promote EMT and endoplasmic reticulum stress by targeting Sestrin2 (161). EVs from HG-stimulated TECs favors renal fibrosis by transferring miR-192 to healthy recipient TECs and targeting glucagon-like peptide 1 receptor (GLP1R) (162). EVs from injured podocytes containing miRNA-424 and miR-149 induce apoptosis and p38 phosphorylation in TECs (163).

Many of the altered urinary miRNAs in type 1 DN patients are associated renal fibrosis-associated pathways (*Figure 3*) (164). Urinary exosomes from diabetic patients with microalbuminuria are enriched in miR-130 and miR-145 while have reduced miR-155 and miR-424 levels (165). Urine miR-192 and miR-21 are significantly increased while miR-30b levels are decreased in diabetic patients with altered kidney function (166-169). Interestingly, miR-415 was found to be elevated in urinary exosomes prior to albuminuria and glomerulosclerosis which suggest its use as an early biomarker (170). Park *et al.* identified miR-126

and the miR-770 family in urine and blood as promising predictive markers of DN progression (171). Serum miR-217 levels positively correlates with severity of diabetes nephropathy (172). By contrast, reduced serum miR-130b correlate with it (173). Urinary sediment miR-95 and miR-631 also reflect the severity and prognosis of DN (174). MiR-135a levels are upregulated in serum and renal tissue from patients with DN and db/db mice, and correlate with microalbuminuria and renal fibrosis scores (175). MiR-34a and miR-320c are upregulated in the urinary exosomes of type 2 DN (176,177). MiR-34a regulates MC proliferation and glomerular hypertrophy by targeting growth arrest-specific 1 (GAS1) (178), while miR-320c protects TECs from damage by downregulating Bone Morphogenetic Protein 6 (BMP6) (179). Other potential biomarkers for type 2 DN are miR-15b, miR-636, miR-34a and miR-4534 in urine (177,180) and miR-638 in serum (181).

Hypertensive nephropathy

Hypertension affects 25–30% population worldwide. Under chronicity, elevated blood pressure damages renal vessels and impairs GFR, promoting nephropathy characterized by renal fibrosis, tubular and glomerular hypertrophy. In turn, about 80% of CKD patients eventually develop hypertension as a consequence of an unbalanced renin-angiotensin-aldosterone system (RAS) (182).

Regulation of hypertensive nephropathy by miRNAs

The miRNA profile of human hypertensive nephrosclerosis biopsies revealed differential expression, showing higher levels of miR-200a, miR-200b, miR-141, miR-429, miR-146, miR-132, miR-192 and miR-205 (183,184).

High salt intake, one of the risk factors of hypertension, increases miR-29b expression in renal medulla in non-salt sensitive rats. Due to several collagen genes are miR-29b target genes, its increase may have a protective role (*Table 2*) (87). In the same model, miR-204 is downregulated and promotes the protein tyrosine phosphatase nonreceptor type 11 (SHP2)/p-STAT3 signaling, exacerbating renal interstitial fibrosis (88). Angiotensin (Ang) II, the main peptide of the RAS, can exert both a vasoconstrictor effect and a pro-inflammatory action in post-glomerular arteries (185). MiR-155 controls blood pressure by downregulating the expression of the Ang II type 1 receptor (AGTR1) (90). In the same vein, miR-21 mediates Ang II-induced kidney fibrosis via amplifying the TGF-β1/Smad3 pathway by targeting PPAR-α (91), while miR-103a contributes to Ang II-induced renal inflammation and fibrosis through the SNF related kinase (SNRK)/NF-κB/p65 regulatory axis (92).

Extracellular miRNAs in hypertensive nephropathy: potential biomarkers

Gildea *et al.* identified 45 urinary exosomal miRNAs associated with salt sensitivity or inverse salt sensitivity (*Figure 3*) (186). Upregulated expression of miR-155 has been reported in plasma of renal transplant recipients (187). In patients with hypertensive nephropathy, miR-103a was upregulated in urine and serum. Interestingly, patients with a positive response to angiotensin-converting enzyme inhibitor or β-blocker treatment displaying a reduction in their albumin–creatinine ratio showed a decrease in miR-103a, suggesting this miRNA as a dynamic biomarker reflecting the pathological status and treatment response (188). MiR-146a, miR-26 and miR-29a from urinary exosomes correlates with albuminuria in essential hypertension (189-191), while higher urinary miR-21 levels are detected earlier than urinary albumin (184).

Kidney immune diseases

IgA nephropathy (IgAN) and lupus nephritis (LN) are the main kidney immune diseases. IgAN is the most common form of primary glomerulonephritis. It is characterized by the aberrant glycosylation of immunoglobulin A (IgA1) and consequently alters the synthesis and binding of antibodies directed against this IgA1 form, generating an immune complex that accumulates in the glomerular mesangium. It activates MCs, enhancing proliferation and secretion of ECM, cytokines and chemokines and leading to renal injury (192). LN is an autoimmune disorder with a complex pathophysiology whose immunological hallmark is the production of a range of autoantibodies directed at ubiquitous nuclear components (193).

Regulation of IgAN by miRNAs

MiRNA expression profiling of kidney biopsies from patients with IgAN showed that dysregulated levels of miRNAs related to fibrosis (downregulation of miR-200c and upregulation of miR-192, miR-141 and miR-205) (194) and to the immune response (upregulation of miR-155 and miR-146a) (195), associated with disease severity and progression. MiR-150 has been proposed as a potential functional mediator of kidney fibrosis progression in IgAN (196). Let-7a and miR-148b/miR-196b control *N*-

acetylgalactosaminyltransferase 2 (GALNT2) and 1β,1,3 galactosyltransferase 1 (C1GALT1), respectively, enzymes which are involved in aberrant IgA glycosylation (94-96).

MiRNAs regulates IgA features in different renal cell types (*Table 2*). Glomerular endothelial cells of patients with IgAN showed decreased levels of miR-223, contributing to cellular proliferation. This miRNA targets importin α4 and α5 (KPNA3/1), responsible for the nuclear transport of NF-κB p65 and STAT3 (97). Downregulation of miR-100 and miR-877 controls overproduction of interleukin 8 (IL-8) and IL-1β in MCs activated by secretory IgA from IgAN patients (98). By contrast, miR-200bc/429 cluster alleviates inflammation in podocytes from IgAN patients by targeting TNF-related weak inducer of apoptosis (TWEAK)/FN14 (99). Of note, miR-21 promotes fibrogenic activation in podocytes and TECs by activating the PTEN/Akt pathway activation in IgAN (100).

Extracellular miRNAs in IgAN: potential biomarkers

Several studies have described the serum and urine miRNome of IgAN patients postulating some miRNAs as potential biomarkers (*Figure 3*). Serum miR-148b and miR-let-7b levels were reported to discriminate patients with IgAN from both controls and patients with other forms of glomerulonephritis (197). Plasma content in miR-148a, miR-150, miR-20a and miR-425 is increased in IgAN patients, especially in the early-stage (198), while IgAN patients with lower miR-192 levels are more likely to have renal function decline (199). Elevated urinary levels of miRNA-146a and miRNA-155 in IgAN patients, correlate with proteinuria but inversely correlate with urinary expression of the cytokines IL-1β and TNF-α (195). Other potential biomarkers of IgAN are miR-150, miR-155, miR-146a, miR-17 and miR-93—which are found at increased levels—and miR-29b, miR-29c, miR-204, miR-431 and miR-555—which are found at decreased levels—in the urine of patients with IgAN (200,201). These changes have also been reported in miR-29c and miR-146a urinary exosomes (202). Levels of miR-33a both in serum, urine and kidney tissues decrease with the severity of renal injury and the progression of renal failure in IgAN patients (54). Increased levels of miR-25, miR-144 and miR-486 in urinary sediment, mainly derived from urinary erythrocytes, could also be non-invasive candidate biomarkers for IgAN (203).

Regulation of lupus nephritis by miRNAs

MiRNA expression evaluation in kidney biopsies from class II LN patients (characterized by pure mesangial involvement), identified 36 upregulated and 30 downregulated miRNAs (204). In patients with LN, disease severity correlates and glomerular and tubulointerstitial expression of miR-638, miR-198 and miR-146a (205). MiR-150 has also been demonstrated to promote renal fibrogenesis by targeting the suppressor of cytokine signaling 1 (SOCS1), a negative regulator of the JAK/STAT signaling pathway, which controls cell proliferation, inflammation and fibrosis (*Table 2*) (206). MCs contribute to the pathogenesis of LN through both the secretion of proinflammatory cytokines and matrix protein deposition. MiR-422a is upregulated in MCs and TECs from renal LN biopsies. This miRNA targets kallikrein related peptidase 4 (KLK4) which belongs to the kallikrein-kinin system and have pleiotropic effects in inflammation, oxidative stress and vascular function (103). IL-8, essential in type III hypersensitivity and a major characteristic of LN, was confirmed as a direct target of miR-10a in MCs (104).

Extracellular miRNAs in lupus nephritis: potential biomarkers

Some miRNAs have emerged as potential LN biomarkers (*Figure 3*). MiR-181a was increased while miR-223 was decreased in serum samples from LN patients, whose levels correlate with markers of this disease (68). MiRNA expression profiles in plasma, urinary sediment and peripheral blood mononuclear cells (PBMCs) revealed a group of miRNAs associated with LN (miR-342, miR-223 and miR-20a in plasma, miR-221 and miR-222 in urinary sediment, and miR-371, miR-1224 and miR-423 in PBMCs), which are promising disease biomarkers (207-209). Although, miR-146 expression is increased in the glomerulus, the levels are decreased in PBMCs from patients with LN. However, miR-146 enrichment in urinary exosomes associates with renal damage and can discriminate patients with active from inactive LN patients (210). Levels of miR-26a and miR-30b are decreased in the kidneys and urine of LN patients and promote MC proliferation (211). Urinary exosomal miR-135b, miR-107 and miR-31 levels are higher in treatment responder patients. These are mainly produced in TECs and are engulfed by endothelial and MCs where target HIF-1α, reducing proliferation and inflammation (212). Decreased urinary exosome-associated miR-29c appears to be a predictor of early renal fibrosis in LN (213), while in the case of miR-21, miR-150 and let-7a correlate with the clinical stage (214). MiR-146a, miR-654 and miR-3135b in urinary exosomes possess a predictive value in type IV LN complicated by cellular crescent (215).

Polycystic kidney disease (PKD)

PKD is a genetic kidney disorder characterized by the growth of cysts in the kidneys, due to mutations or dysregulated expression of either polycystic kidney disease 1 (*PKD1*) or 2 (*PKD2*) gene, which encode for polycystin 1 and 2, respectively, with an autosomal dominant (ADPKD) pattern of inheritance, or the polycystic kidney and hepatic disease 1 (PKHD1) gene which encodes for fibrocystin/polyductin, resulting in an autosomal recessive (ARPKD) disease. Aberrant expression of these genes leads to disrupted cell division, proliferation and impaired cell-matrix and/or cell-cell interactions (216).

Regulation of PKD by miRNAs

Genetic profiling assays revealed alterations in miRNA expression profiles in PKD, most of them directly regulating the expression of PKD1, PKD2, PKHD and cell proliferation-related genes (*Table 2*) (217). Thus, the dysregulated miRNAs miR-214, miR-31, miR-199a, miR-21, miR-34a, miR-132 and miR-146b are believed to target major pathways in autosomal dominant PKD (218). Pandey *et al.* predicted and verified several miRNAs (miRs-10a, miR-30a, miR-96, miR-126, miR-182, miR-200a, miR-204, miR-429 and miR-488): mRNA reciprocal interactions in a PKD mouse model (217).

The miR-17~92 cluster is upregulated in the kidney of various PKD mouse models and its overexpression produces cysts. Particularly, miR-17 targets PKD1 and PKD2 whereas miR-92 inhibits PKHD1 through the transcription factor hepatocyte nuclear factor 1 homeobox B (HNF-1β). It has been described that the cellular myelocytomatosis oncogene (C-MYC) transcriptionally activates the miR-17~92 cluster, which regulates the mechanistic target of rapamycin kinase (mTOR) and TGF-β pathways, both of which are implicated in cyst growth (105). Tran *et al.* demonstrated that the binding of miR-17 to PKD2 is antagonized by the RNA-binding protein bicaudal C homolog 1 (BICC1), thus regulating PKD2 gene dosage (219).

MiRNAs have a key role in cyst expansion which is associated with EMT. PKHD1 is a direct target of miR-365 and is involved in the decrease of E-cadherin and destruction of ECM (108). MiR-192 and miR-194, whose levels are downregulated by hypermethylation of their promoter region, directly target ZEB2 and cadherin-2, which are involved in EMT. MiR-199a inhibitor suppresses proliferation of cystic cells and induces cell apoptosis by targeting cyclin dependent kinase inhibitor 1C (*CDKN1C*)/*p57*, a negative regulator of cell proliferation by inhibiting G1 cyclin-dependent kinases (111).

Extracellular miRNAs in PKD: potential biomarkers

The role of EVs in ADPKD progression have not drawn considerable attention so far (*Figure 3*). Of note, EVs generated from cystic TECs display increased levels of miR-200b, miR-200c, miR-429 and miR-21 levels which promote cyst growth in ADPKD by inducing epithelial cell proliferation, fibroblast activation and macrophage recruitment (220).

The serum and urine miRNA profile in ADPKD patients differ substantially depending on the stage of CKD. Serum exosomal levels of miR-17 family members miR-20a, miR-93 and miR-106a significantly drop after hemodialysis in ADPKD patients (221). In urine from ADPKD patients, dysregulated miRNAs have previously involved in kidney tumor suppression (miR-1 and miR-133). Others miRNAs have presumed inflammatory and fibroblast cell origin (miR-223/miR-199) (222). Increased levels of miR-3907 in the circulation can predict ADPKD progression (223).

Clinical applications and perspectives

Since early 1940s, the mainstay of renal functional monitoring has not progress significantly. So, the increased estimated prevalence of kidney diseases urgently demands novel biomarkers to enhance early diagnosis, guide prognosis and monitor response to treatment (224). The importance of miRNAs in the kidney field has gained widespread interest over the last decade not only enabling to understand in-depth the pathways involved in kidney pathophysiology, but also as biomarkers circulating in biofluids. In kidney diseases, urine is the preferred source of biomarkers due to its direct access to the damaged tissues of the kidney and urinary tract. Although a kidney disease-specific blood and urine miRNA signature has been identified in patients and mouse models, no definitive data have yet been translated to the clinic (225). There is limited knowledge about the cell type of origin and functional role of circulating miRNA and therefore, if they are tissue/disease-specific or represent more general pathologies like inflammation. Understanding the cell specificity of miRNAs' expression in the kidney is essential to contextualize whole-tissue miRNA changes and target validation, which would improve the rational selection of biomarkers. Identification of host cell-derived protein

Table 3 Nephroprotective action of MSC-EVs containing miRNAs

MSC source	*In vivo* model	miRNA	EV subtype	Pathophysiological effects	Target gene	Reference(s)
Bone marrow	UUO	miR-144	Exosomes	Tubular basement membrane integrity	*tPA*	(232)
Bone marrow	UUO	Let-7c	Exosomes	ECM accumulation	*TGFBRI*	(233)
Muscle	UUO	miR-29	Exosomes	ECM accumulation	*TGFB3*	(234)
Endothelium	IRI	miR-126, miR-296	Microvesicles	Capillary rarefaction, glomerulosclerosis, tubulointerstitial fibrosis	*SPRED1*, *VCAM1*, *PIK3R2*, *HGS*	(235)
Epithelium	Glycerol	miR-10a, miR-486, miR-127	Exosomes	Necrosis	*Non-described*	(236)
Umbilical cord	CLP	miR-146b	Exosomes	Inflammation, apoptosis	*IRAK1*	(237)
Bone marrow	IRI	miR-199a	Exosomes	Apoptosis	*SEMA3A*	(238)
Non-described	Cisplatin	miR-1184	Exosomes	Inflammation, apoptosis	*FOXO4*	(239)
hWJMSCs	IRI	miR-30b/c/d	EVs	Mitochondrial fission, apoptosis	*DRP1*	(240)
ECFC	IRI	miR-486	Exosomes	Apoptosis	*PTEN*	(241)
Placenta	IRI	miR-200a	EVs	Oxidative stress, mitochondrial fragmentation	*KEAP1*	(242)
Umbilical cord	STZ	miR-451	MVs	Apoptosis, EMT, ECM accumulation	*P15*, *P19*	(243)
Bone marrow	STZ	Let-7a	Exosomes	Apoptosis, oxidative stress, EMT, ECM accumulation	*USP22*	(244)
Adipose	db/db	miR-26	Exosomes	Apoptosis	*TLR4*	(245)

The treatment with MSC-EVs reduces the pathophysiological effects indicated in mouse models of chronic (UUO) and acute (IRI, glycerol, CLP, cisplatin) kidney disease and diabetic nephropathy (STZ, db/db transgenic mouse), respectively. MSC, mesenchymal stem cell; EV, extracellular vesicle; miRNA, microRNA; UUO, unilateral ureteral obstruction; ECM, extracellular matrix; IRI, ischemia reperfusion injury; CLP, cecal ligation and puncture; STZ, streptozotocin. MV, microvesicle; EMT, epithelial-mesenchymal transition.

surface markers among EVs surface proteins would allow to determine their cellular origin (226). Further, unification of methodology for extracellular RNA isolation, purification and detection by combining-omics technologies, including proteomic, transcriptomic, and metabolomic methods, as well as to standardize EVs classification is needed to provide more robust biomarkers. Consideration of the distinct miRNA half-lives, conservation degree between species and variability between patients, evaluating variables such as age, gender, ethnicity, additional medication or the presence of comorbidities in large cohort studies are also essential steps for their clinical translation (227).

While a miRNA-based therapy that either restores or blocks miRNA expression and activity by using miRNA mimics or antagomirs is very appealing, the potential of miRNAs as an effective therapy has been limited so far to experimental models and two ongoing clinical trials (clinicaltrials.gov, NCT03373786, NCT04536688), mainly due to the lack of reliable organ- and cell-specific delivery methods and off-target effects on other genes. Some new synthesis and delivery methodology include locked nucleic-acids (LNA) (228) coupled to lipid-based nanoparticles, FDA-approved poly-lactic-co-glycolic acid (PLGA)-based nanoparticles, cell and/or tissue-specific antibodies/peptides and ultrasound microbubble-mediated gene transference (229,230). EVs have also gained prominence as drug delivery vehicles. The process of loading EVs with specific cargos, including miRNA analogues, can be attained by manipulating parental cells (endogenous loading) or the isolated EVs (exogenous loading) themselves. Furthermore, to boost their delivery and biodistribution, EVs can be engineered to recognize specific cell surface receptors (231). How to obtain exosomes on a large scale for clinical treatment will also be a focus of future studies. In this line, several studies describe the renoprotective effect of EVs derived from multipotent mesenchymal stem cells (MSCs), emerging as a potential powerful cell-free therapeutic strategy. In some kidney diseases, content analysis of this MSC-derived EV identified that transported miRNAs can underlie this response (*Table 3*) (246). Future studies

are directed to integrate circulating and renal miRNA expression data along renal cell types to generate a complete kidney expression atlas in injury and repair conditions coupled to ligand-receptor networks between EVs and kidney cells, as well as to develop new technology for single-vesicle analysis, which undoubtedly will unleash their full potential as therapeutic targets and biomarkers.

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