Potential role of ACE2-related microRNAs in COVID-19-associated nephropathy

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A B S T R A C T

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for coronavirus disease (COVID-19), potentially have severe kidney adverse effects. This organ expressed angiotensin-converting enzyme 2 (ACE2), the transmembrane protein which facilitate the entering of the virus into the cell. Therefore, early detection of the kidney manifestations of COVID-19 is crucial. Previous studies showed ACE2 role in various indications of this disease, especially in kidney effects. The MicroRNAs (miRNAs) in this organ affected ACE2 expression. Therefore, this review aims at summarizing the literature of a novel miRNA-based therapy and its potential applications in COVID-19-associated nephropathy. Furthermore, previous studies were analyzed for the kidney manifestations of COVID-19 and the miRNAs role that were published on the online databases, namely MEDLINE (PubMed) and Scopus. Several miRNAs, particularly miR-18 (which was upregulated in nephropathy), played a crucial role in ACE2 expression. Therefore, the antimiR-18 roles were summarized in various primate models that aided in developing the therapy for ACE2 related diseases.

1. Introduction

The coronavirus disease (COVID-19), which is a pandemic infection has greatly affected every individual across the world and scientists from all disciplines are working hard to assess the situation and make it benefit humanity. This disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1], and leads to rapid activation of innate immune cells, especially in patients with severe symptoms. This novel coronavirus primarily manifests as an acute respiratory illness accompanied by interstitial and alveolar pneumonia, however, it also affect multiple organs, such as heart, digestive tract, blood, central nervous system, and the kidney [2–4].

The levels of various proinflammatory effector cytokines are elevated in COVID-19, especially in critically ill patients with acute kidney injury (AKI). Moreover, some T cell-derived cytokines, such as IL-17 also increased [5]. Similar to other infectious diseases, vaccine for COVID-19 need a quite long period of time to be developed. Therefore, it is necessary to act early in order to inhibit the disease progression by discovering an alternative-novel therapy.

Nephrologists should identify the kidney manifestations' symptoms

of COVID-19 very early to efficiently manage such adverse conditions. Furthermore, it is important to protect the immunocompromised patients with kidney disease from a viral infection. However, there is limited literature on the kidney adverse effects of SARS-CoV-2, especially in pediatric COVID-19 patients. A study by Batle et al. showed that AKI is one of the key manifestations of SARS-CoV-2 infection [6]. The knowledge about the other viruses adversely affecting the kidneys, particularly the glomerulus, helped in understanding SARS-CoV-2 potential in causing kidney disorders. Some pediatric kidney diseases caused by viruses include IgA nephropathy, focal segmental glomerulosclerosis (FSGS), and human immunodeficiency virus-associated nephropathy (HIVAN).

These kidney disorders mainly involve the impaired expression of genes, especially those constituting the podocytes. Furthermore, the podocyte cytoskeletal protein is also involved in apoptosis and injury [7]. An abnormal podocyte structure disrupts the glomerular functions, leading to excessive protein loss through urine [8], which triggers the release of proinflammatory mediators causing further kidney disorder via tubular cell damage. Some fibrogenic proinflammatory mediators lead to extracellular matrix (ECM) deposition causing sclerosis that

further develop into hyalinosis and fibrosis [9]. These fibrotic lesions further trigger the release of fibrogenic proinflammatory mediators, therefore, leading to chronic progressive and end-stage kidney disease [7].

The MicroRNAs (miRNAs) have the ability to influence the expression of some genes, and its based therapy have great potential in future medicine [10–12]. Currently, the understanding of how COVID-19 affects kidney disease patients treated with cytokine inhibitors is variably limited. Therefore, this study aims to explore the kidney pathogenesis of SARS-CoV-2, notably the role of suspected miRNAs as a potential novel modality to treat and prevent kidney manifestations of COVID-19 [13].

1.1. The pathological mechanism of SARS-CoV-2 infection

The genome of coronavirus (CoV) consists of unique structures such as an *N*-terminal fragment within the spike protein encoded by the *spike (S), membrane (M), envelope (E), and nucleocapsid (N) genes* [14]. A typical CoV genome has at least six open reading frames (ORFs) with the first (ORF1a/b) occupying two-thirds the length of the entire genome, and encoding 16 non-structural proteins (nsp 1-16). A frameshift mutation between ORF1 a and b produces two polypeptides, pp1 a and ab. These polypeptides are converted into 16 nsps by the virally encoded chymotrypsin-like protease (3CLpro) or Mpro, and one or two papain-like proteases. Meanwhile, all the structural and accessory proteins are translated from the sgRNAs of CoVs. The four main structural proteins, S, M, E, and N, are encoded by the ORFs 10 and 11 which are occupying one-third portion of the genome near the 3-terminus [4,15,16]. Besides these, different CoVs encode unique structural and accessory proteins, such as the HE, 3a/b, and 4a/b, which play vital roles in genome maintenance and viral replication [15]. Among the viral proteins in the CoV membrane, the M glycoprotein is most abundant, leaving a short NH2-terminal domain outside the virus and an extended COOH terminus (cytoplasmic domain) inside [17]. The S protein is a type I membrane glycoprotein constituting the peplomers, which primarily induces the neutralizing antibodies. The molecular interaction between the envelope proteins determines the formation and composition of the coronaviral membrane. The M glycoprotein plays a predominant role in the intracellular formation of the virus particles in the absence of the S. While in the presence of tunicamycin, coronavirus grows and produces spikeless, noninfectious virions containing M and devoiding S [14,17].

1.2. The role of ACE2 in SARS-CoV-2 infection

The angiotensin-converting enzyme 2 (ACE2), an S1 surface receptor, and transmembrane protease serine 2 (TMPRSS2) within the endosome facilitate endocytosis of the viral particles into the cells. Meanwhile, majority of the ACE2 receptors are located in the respiratory and gastrointestinal epithelium, heart, blood vessels, and kidneys [1]. The SARS-CoV-2 enters the host cell via five steps, namely adhesion, penetration, biosynthesis, maturation, and release. The viral affinity to the host cells is directly correlated to the disease severity, since the host protease activates the S1 and S2 subunits of the S protein. Furthermore, the S2 aids the viral entry into the host cells by endocytosis or membrane fusion. Also, within the cell, the virus undergoes nuclear replication (by sending the genetic material to the nucleus) and released out of the cell after maturation [1,4]. Therefore, the link between cardiovascular complications and infection is related to ACE2, which is found to be a functional receptor for SARS-CoV-2 [18,19].

ACE2, an important proinflammatory mediator in AKI or glomerular disorders associated with COVID-19, is upregulated by the miRNAs. In this review, the miRNAs involved in ACE2 expression and the therapeutic potentials of antiMiR and miRNA profiling in kidney diseases were explored. Some of the ACE2-associated-microRNAs are mentioned in Table 1.

The SARS-CoV-2 binds to ACE2 via the S glycoprotein that facilitates the virus entry into the host cells, mediated by the protease enzyme (TMPRSS2), that catalyzes the attachment of the viral receptor (spike protein) to its cellular ligand (ACE2) [1,15]. After the virus enters the host cell and is uncoated, the genome is transcribed and then translated [48]. Furthermore, the CoV genome replication and transcription occur in the host cell cytoplasmic membrane and involve coordinated processes of continuous and discontinuous RNA synthesis, mediated by the viral replicase protein complex, encoded by the 20-kb *replicase* gene [49] that comprises 16 viral subunits and a few cellular proteins. In addition with the RNA-dependent RNA polymerases, helicases, and proteases activities common to RNA viruses, the CoV replicase plays a crucial role in employing a variety of RNA processing enzymes. These enzymes are not found in other RNA viruses and include putative sequence-specific endoribonucleases [50]. The receptor-binding domain of SARS-CoV-2 has a high affinity for ACE2, which serves as the binding site for COVID-19 [51,52]. The SARS-CoV-2 infection leads to an intense cytokine response triggering a series of inflammatory mediators in the host. While in some COVID-19 patients, a cytokine storm resembling secondary haemophagocytic lymphohistiocytosis (a hyperinflammatory state) is triggered by viral infections [13]. Although several cytokines induced by SARS-CoV-2 are essential for the inflammatory response, they do not play a role in viral clearance, which is primarily dependent on other cytokines such as IL-15, type I interferons, and IFNγ [13]. Verdechia et al. stated that ACE2 down-regulation induced by the cell entry of SARS-CoV, NL63, and SARS-CoV-2 is particularly detrimental in patients with pre-existing ACE2 deficiency. The degree of ACE2 deficiency is associated with a variety of conditions, including older age, hypertension, diabetes, and cardiovascular disease. In a setting of enhanced ACE2 deficiency produced by viral invasion, the marked dysregulation between the 'adverse' ACE → Angiotensin II → AT1 axis, and the 'protective' ACE2 → Angiotensin 1-7 → Mas axis contribute to the progression of inflammatory and thrombotic processes [53].

1.3. The pathological mechanism of common virus-associated kidney diseases

The molecular mechanisms underlying virus-induced glomerular injury, cell infection, kidney damage by upregulated cytokines and proinflammatory factors, and the deposition of immune complexes are fully understood [54,55]. The host's genetic factors influence the formation of all glomerular lesions, which is secondary to the viral infections [55]. Previous studies have detected the presence of intracellular viral genome and proteins of HIV and parvovirus B19 in the glomerular epithelial and endothelial cells, indicating that these viruses directly affect kidney cytokine production, cell injury, proliferation, apoptosis, and dysregulation or dedifferentiation [55–57]. The deposition of circulating immune complexes containing viral antigens, *in situ* immune complex formation after a planted viral antigen, or autoantibody formation against intrinsic antigens lead to glomerulonephritis [56]. Several HIV antigens, such as p24 and gp41, have been found in the circulating immune complexes, acting as antibody targets, also, p24 is found in the eluted glomerular immune deposits [54,56]. Generally, hepatitis B and C do not directly infect the glomerular or tubular cells, yet they cause immune system dysfunctions [58–60]. The increased numbers of circulating immune complexes is found in hepatitis B patients with glomerulonephritis [58]. All the major hepatitis of B antigens (core, surface, and e) are identified in the immune complex deposits, with the e antigens associating with the subepithelial and core, while the surface antigens with the mesangial and subendothelial immune deposits [58]. The hepatitis C envelope protein E2, which is associated with circulating anti-hepatitis C antibodies and immune complex formation, induce the production of rheumatoid factor and cryoglobulins [58,59,61]. Moreover, it has been previously shown that parvovirus B19 also stimulates the production of antibodies and

Table 1
A list of miRNAs involved in ACE2 expression regulation.

miRNAs	Origin	Species	Pathology	Target genes involved in COVID-19-associated nephropathy		Ref #
				Established genes	Functions of genes	
miR-18a	Kidney	C57Bl/6 mice	Hypoxia/reoxygenation endothelial cell injury	ACE2	Synthesize inactive Ang 1–9 from Ang 1 to produce the vasodilatory and antiproliferative molecule Ang 1–7 from Ang II	[20]
miR-125b	Kidney	Mice	Regulate VEGF receptor-2 phosphorylation Activation of serine/threonine protein kinase Akt	TSP-1	Inhibit Id-1	[21]
miR-125b	Kidney (Tubular epithelial cells HK-2)	Human	Tubular apoptosis	ACE2	Tubular apoptosis and synthesize inactive Ang 1–9 from Ang 1 to produce the vasodilatory and antiproliferative molecule Ang 1–7 from Ang II	[22]
miR-132	Myocardium, arteries, and kidney	Mice	Vasoconstriction, catecholamines release, blood pressure elevation	AGT1R, MMP9	Takes part in cardiovascular control	[23]
miR-143	Kidney, heart, blood vessels, lung	Mice	AMP-activated protein kinase (AMP) Kα2 suppresses endothelial ACE expression via the phosphorylation of p53 and upregulation of miR-143/415	ACE2, ERK5, NPR3, CALD1	Actin stress fibers, ACE, KLF5, myocardin, MRTF-B, calmodulin kinase II-δ modulate gene expression. ERK1/2, p38 mitogene activatedprotein kinase (MAPK), and Akt signaling pathways are involved in an altered phenotype of VSMCs under various conditions	[24–28]
miR-145, -27a, 27b	Kidney, heart, blood vessels, lung	Mice	Regulate the kidney sympathetic nerve activity, and decreasing the secretion of renin	ACE, ACE2, AGTR2 ERK5, NPR3, CALD1	Activation of the ERK1/2 Signaling Pathway	[29–35]
miR-155	Kidney, heart, blood vessels (Mice) Serum (Human)	Wistar Kyoto Mice and human	Vasoconstriction, catecholamines release, blood pressure elevation	AGT1R, AT1R, ACE, ACE2	Encoding angiotensin II receptor, type 1 (AGTR1), the most important receptor for angiotensin II	[36,37–40]
miR-181a	Serum	Human	Regulate the kidney sympathetic nerve activity and decreasing the secretion of renin	ACE2	Tubular apoptosis and synthesize inactive Ang 1–9 from Ang 1 to produce the vasodilatory and antiproliferative molecule Ang 1–7 from Ang II	[41,42]
miR-200	Heart (Atrial)	Mice	Remodeling and fibrosis	ACE	Remodeling and subsequent fibrosis	[31]
miR-421	Heart (Atrial)	Mice	Remodeling, fibrosis	ACE2	Synthesize inactive Ang 1–9 from Angland to produce the vasodilatory and antiproliferative molecule Ang 1–7 from Ang II	[24,31,32]
miR-483-3p		Mice	Regulate the kidney sympathetic nerve activity and decreasing renin secretion	ACE1, ACE2, AT, AGT2R	Synthesize inactive Ang 1–9 from Angland to produce the vasodilatory and antiproliferative molecule Ang 1–7 from Ang II	[41,43]
miR-4262	Lung	Mice (bleomycin-induced)	Acute lung injury	ACE2	Proapoptotic and Synthesize inactive Ang 1–9 from Ang 1 to produce the vasodilatory and antiproliferative molecule Ang 1–7 from Ang II	[26]
miR-365	Aorta	Mice	Inhibition of vascular smooth muscle cells (VSMCs) proliferation by post-transcriptional cyclin D1 regulation	Cyclin D1	functional gene in rat VSMCs	[27]
miR-126		Mice	Vascular dysfunction mediator	SPRED-1, PIK3 regulatory subunit-2, VCAM-1, CXCL12, RhoB	Inhibits growth-factor-mediated activation of MAP kinase, negatively regulates hematopoiesis of bone marrow, inhibits fibroblast growth factor (FGF) differentiation by inhibiting FGF-mediated phosphorylation of ERK1/2, attenuates actin stress fiber formation via inhibition of TESK1-mediated phosphorylation of cofilin, Inhibits TGFB-induced epithelial-to-mesenchymal transition	[27,28]
miR-221/222		Mice	Regulation of inflammation and vascular remodeling	ETS1, VCAM1, MCP	Leukocyte-endothelial cell adhesion, interacts with integrin alpha-4/beta-1 (ITGA4/ITGB1) on leukocytes, and mediates both adhesion and signal transduction, responsible leukocyte migration to the inflammation site	[27,28,44]
miR-130a		Mice	Regulation of VSMCs proliferation	GAX	A growth arrest-specific homeobox, which inhibits proliferation, differentiation, and VSMCs migration	[45]

(continued on next page)

Table 1 (*continued*)

miRNAs	Origin	Species	Pathology	Target genes involved in COVID-19-associated nephropathy		Ref #
				Established genes	Functions of genes	
miR-19b; −29; −132/212; −181b;	Mice	Mice	Promotion of fibrosis and cardiovascular remodeling	ACE2, AGT1R	Synthesize inactive Ang 1–9 from Ang 1 to produce the vasodilatory and antiproliferative molecule Ang 1–7 from Ang II	[23,33–35,46]
miR-146a	Heart	Mice	Inhibition of inflammation	ACE2, MMP16, TIMP3	Synthesize inactive Ang 1–9 from Ang 1 to produce the vasodilatory and antiproliferative molecule Ang 1–7 from Ang II	[41]
miR-133a; −208; −1	Heart	C57BL/6 J mice	Regulation of cardiovascular hypertrophy and dysfunction	AGT1R	The essential receptor synthesize inactive Ang 1–9 from Ang 1 to produce the vasodilatory and antiproliferative molecule Ang 1–7 from Ang II process	[32]
miR-424; −503	Lung	Mice	Inhibition of VSMCs proliferation	FGF2, FGFR1	A potent mitogen, induce angiogenesis, mediates phosphorylation of ERK1/2	[7,47]

immune complexes [57].

1.4. The pathological mechanism underlying the effect of SARS-CoV-2 on the kidney

The renin-angiotensin system (RAS) is essential for physiological homeostasis maintenance. Although renin was discovered over a hundred years ago, the various aspects of RAS are still not fully understood. However, there is an increasing interest in understanding the pathophysiological roles of the monocarboxyl peptidase, and ACE2 in the kidneys. The ACE converts the decapeptides angiotensin I (ATI) and II (ATII) into angiotensin-(1–9) (Ang-1–9) and angiotensin-(1–7) (Ang-1–7), respectively, by eliminating the two distal amino acids. The ACE further metabolizes Ang-1–9 to Ang-1–7 [62]. Therefore, the ATII activation leading the microangiopathy, hypercoagulability, hypoxic cellularity, glomerular, and tubular injury (Fig. 2). Most studies have indicated that ACE2-mediated responses counteract those generated by ACE-mediated production of angiotensin II and promote vasodilation, natriuresis, and cytoprotection. The mice with a global deletion of ACE2 show increased responsiveness to RAS activation [63], while the maternal with ACE2 deficiency show increased concentrations of angiotensin II in the placenta, resulting in restricted fetal growth [64]. The ACE2 plays a role in the regulation of oxidative stress in the paraventricular nuclei and the rostral ventrolateral medulla that modulates the sympathetic tone and blood pressure [65]. The ACE2 also have some RAS-independent effects, for instance, it serves as a lung receptor with binding affinity for coronavirus and the virus causing severe acute respiratory syndrome. Moreover, the ACE2-deficient mice do not develop lung injury upon exposure to the coronavirus [66]. The ACE2 converts ATI and ATII to Ang-1-7, and modulates the available ATII to the activated ATII type I receptors. The Ang-1–7 acts as a ligand for the Mas receptor that mediates vasodilation, natriuresis, and blood pressure [67]. The abnormalities in ACE2 expression and activity are implicated in various disorders, including hypertension, cardiovascular disease, and diabetic kidney disease (DKD). The DKD patients show an increase in the ACE/ACE2 ratio in the glomerulus and tubulointerstitium due to the decreased ACE2 expression [68]. Previous studies in diabetic mice with either a global deletion or pharmacologic inhibition of ACE2 have shown an exacerbated DKD development [68].

The podocytes in the kidneys express various components of RAS, such as the (pro)renin receptor, angiotensinogen, ACE, and the angiotensin II type 1 receptor, as well as ACE2 [69]. All the previous studies support the hypothesis that the severity of many diseases includes SARS-CoV-2 infection with kidney involvement, is influenced by ACE2 expression.

2. COVID-19 associated nephropathy

As an impact of SARS-CoV-2 infection, ACE2 pathways down-regulation lead to myocardial injury, fibrosis, and inflammation [1,4,19]. In line with these findings, several reports linked SARS-CoV-2 infection with myocardial damage and heart failure, accompanied by acute respiratory distress syndrome (ARDS), arrhythmias, coagulopathy, and acute kidney injury (AKI) [19,70,71]. Some previous studies have shown that SARS-CoV-2 directly or indirectly affect the kidneys and cause podocyte injury. Na et al. reported protein loss in 30.3% of patients during antiviral treatment [72]. Meanwhile, podocyte injuries usually lead to protein loss through the urine, and release proinflammatory mediators, such as transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and chemokine ligand 1 (CXCL1), causing mesangial matrix deposition, glomerular sclerosis, hyalinosis, and fibrosis [7,70,73]. The increased glomerular filtration due to barrier defects causes the elevation in the single-nephron glomerular filtration rate (SNGFR), leading to hypertrophy. Also, hyperfiltration triggers oxidative stress, further contributing to glomerular injury, causing the

deposition of the mesangial matrix and fibrosis [7,70,73]. The fibrotic tissues trigger the release of profibrotic inflammatory mediators to progressive kidney injury. Based on the pathological mechanisms, the clinical signs of COVID-19-associated nephropathy include AKI, glomerular nephrosis, and progressive chronic kidney disease (CKD), with symptoms such as hypertension, fluid and electrolyte imbalance, metabolic acidosis or alkalosis, and swelling [7,70,73].

Some studies reported a lower incidence (3–9%) of AKI in COVID-19 patients [74–77]. However, recent research reported a higher frequency of kidney involvement, i.e., 34% of 59 COVID-19 patients developed massive albuminuria on the first day of admission, and 63% developed proteinuria during their stay in hospital [78,79]. The blood urea nitrogen (BUN) was elevated in 27% overall, and in two-thirds of patients that died. The computed tomography (CT) scan of the kidneys showed reduced density, indicating inflammation or oedema [76]. A recent study by Cheng et al. reported that amongst 710 hospitalized COVID-19 patients, 44% had proteinuria and hematuria, while 26.7% had hematuria on admission [79]. The prevalence of elevated serum creatinine and blood urea nitrogen was 15.5% and 14.1%, respectively [79]. AKI was an independent risk factor for patients' in-hospital [76,78,79].

2.1. miRNAs

MiRNAs are small (about 22 nucleotides) non-coding RNAs known to regulate the post-transcriptional expression affecting various cellular processes, such as cell proliferation, apoptosis, and differentiation [80]. They block the target genes by binding to the 3′UTR during transcription, repressing the messenger RNA and promoting their degradation by cleavage [81–83]. More than 2000 miRNAs have been identified in humans, one miRNA targets several genes, while multiple miRNAs regulate one gene [83–86]. The miRNAs regulate about 60% of the human protein-coding genes, indicating their significant role in expression [82,84,85,87]. The miRNAs is seen in body liquid, such as plasma and serum samples, while those circulating freely act on the recipient cells regulating the target gene expression [88–91]. The miRNAs derived from the kidney and urinary tract and are passively filtered through the glomerulus and secreted by kidney tubules [92]. These miRNAs serve as biomarkers for diagnosis, prognosis, or therapeutic response of various diseases [81,84,92–96]. miRNAs are present in the body fluids, such as plasma and serum, acting as endocrine signals to regulate target genes in the recipient cells [97,98]. These miRNAs are at least partially encased in extracellular vesicles, such as exosomes [99]. The deletions of Dicer, an RNase III enzyme required for miRNA biogenesis, highlight the miRNAs pivotal roles in juxtaglomerular cells, tubular epithelial cells, and in podocytes [84]. For example, the miR-93 leads to glomerular injury by activating VEGF [100], while the miR-192 accelerates collagen formation in the glomerular mesangial cells and promotes TGF-β/Smad 3-induced tubulointerstitial fibrosis in mice with diabetic nephropathy [101,102]. These studies indicate that miRNAs play an essential role in glomerular disease development, particularly those associated with podocytes [84]. The urinary miRNAs that serves as biomarkers for the diagnosis, prognosis, or responses to therapy in various diseases is derived from the kidney and urinary tract and are passively filtered.

3. Modality of miRNA testing

The modality of miRNA testing is changing rapidly, due to the rapid advances in next-generation sequencing (NGS). The conventional approaches to miRNA clinical testing, include small RNA sequencing, quantitative miRNA real-time reverse-transcription PCR (qRT-PCR), miRNA microarray, multiplexed miRNA detection with color-coded probe pairs, and Nanostring nCounter gene expression system [36].

3.1. The potential roles of miRNAs in the kidney

Certain miRNAs are essential for kidney function, and changes in their levels lead to various conditions, such as diabetic kidney disease (DKD), acute kidney injury, lupus nephritis, and polycystic kidney disease. Therefore, miRNAs are potential therapeutic targets for kidney disorders [84,103–106]. They are also potential markers for diagnosing and monitoring various kidney diseases, such as DKD, due to their stability in urine and blood [101,107–109]. Moreover, the urine and serum of DKD patients contain miRNAs correlated with specific stages of kidney disease, fibrosis, and CKD progression [110–112].

Rudnicki et al. reported that miR-30d, miR-140-3p, miR-532-3p, miR-194, miR-190, miR-204, and miR-206 were downregulated in progressive CKD cases [113]. Chung et al. showed that miR-192 was highly upregulated in progressive kidney fibrosis in a mouse and rat model of kidney disease [101]. Lorenzen et al. reported that miR-210 was a reliable marker of acute rejection and a predictor of long-term graft function ([79], while the human CKD and kidney transplant study by Ulbing et al. showed significant changes in the levels of systemic miR-223-3p and miR-93-5p based on CKD stages, as well as inflammation and other bone parameters [86,102,114]. Zhang C et al. reported that the levels of urinary miR-196a significantly increased in focal-segmental glomerulosclerosis (FSGS) during massive proteinuria, compared with those in complete remission state. They also found an association between urinary miR-196a and proteinuria, and also estimated glomerular filtration rate (eGFR), interstitial fibrosis, and tubular atrophy. This study also showed that patients with higher levels of urinary miR-196a had a greater reduction in kidney survival, compared to those with lower urinary miR-196a [115]. Liu Y et al. reported that miR-29 regulates the expression of collagens and other genes related to the extracellular matrix (ECM) in the kidney medulla of SS and SS-13BN rats [108]. Wang et al. showed that stable miR-10 and miR-30d are present in human and animal (Male C57BL/6J mice) urine, while the elevation of urinary miR-10a and miR-30d levels serve as a novel biomarker for kidney injury [116]. Furthermore, miR-93 modulates the expression of VEGF and its downstream, which is crucial in DKD pathogenesis [86,102,117]. The high glucose concentration led to the overexpression of miR-377 in human mesangial cells. Moreover, Wang Q et al. reported that miR-377 is associated with an increased expression of protein and fibronectin in a DKD mouse model [118]. Ma J et al. reported that miR-93 overexpression prevented TGF-β1-stimulated EMT and kidney fibrogenesis via modulation of Orai1 expression [86,100,102]. Furthermore, Phua YL et Al. showed that stromal miRNAs are required for healthy kidney development and formation of the kidney vascular network, particularly for glomerular mesangial cells' maintenance [119]. Chen YK et al. reported that miR-195 promotes apoptosis of podocytes under high-glucose conditions via enhanced caspase cascades of BCL2 [105]. The miR-93 facilitates glomerular injury by activating VEGF [86,100,102]. Furthermore, miR-192 accelerates collagen formation in the glomerular mesangial cells and promotes TGF-β/Smad 3-induced tubulointerstitial fibrosis in mice models of diabetic nephropathy. These studies indicated that miRNAs play essential roles in glomerular disease development, particularly podocyte-associated disorders, tubular atrophy, extracellular matrix (ECM) collagen deposition, fibrosis, and podocyte apoptosis, through various pathways.

Exosomes in urine are reliable tool for the analysis of miRNAs in kidney diseases, since many miRNAs originated from the kidney cells [87]. The expression of various miRNAs are dysregulated in different kidney conditions, for instance, the aberrations of miRNA expression in kidney fibrosis was described in a recent meta-analysis, identifying five upregulated (miR-142–3p, miR-223–3p, miR-21–5p, miR-142–5p, miR-214–3p) and two downregulated (miR-29c-3p, miR-200a-3p) miRNAs [120].

In a cohort of 90 CKD patients at stages 3–5, Chen et al. showed that the levels of miR-125b, miR-145, and miR-155 are significantly lower
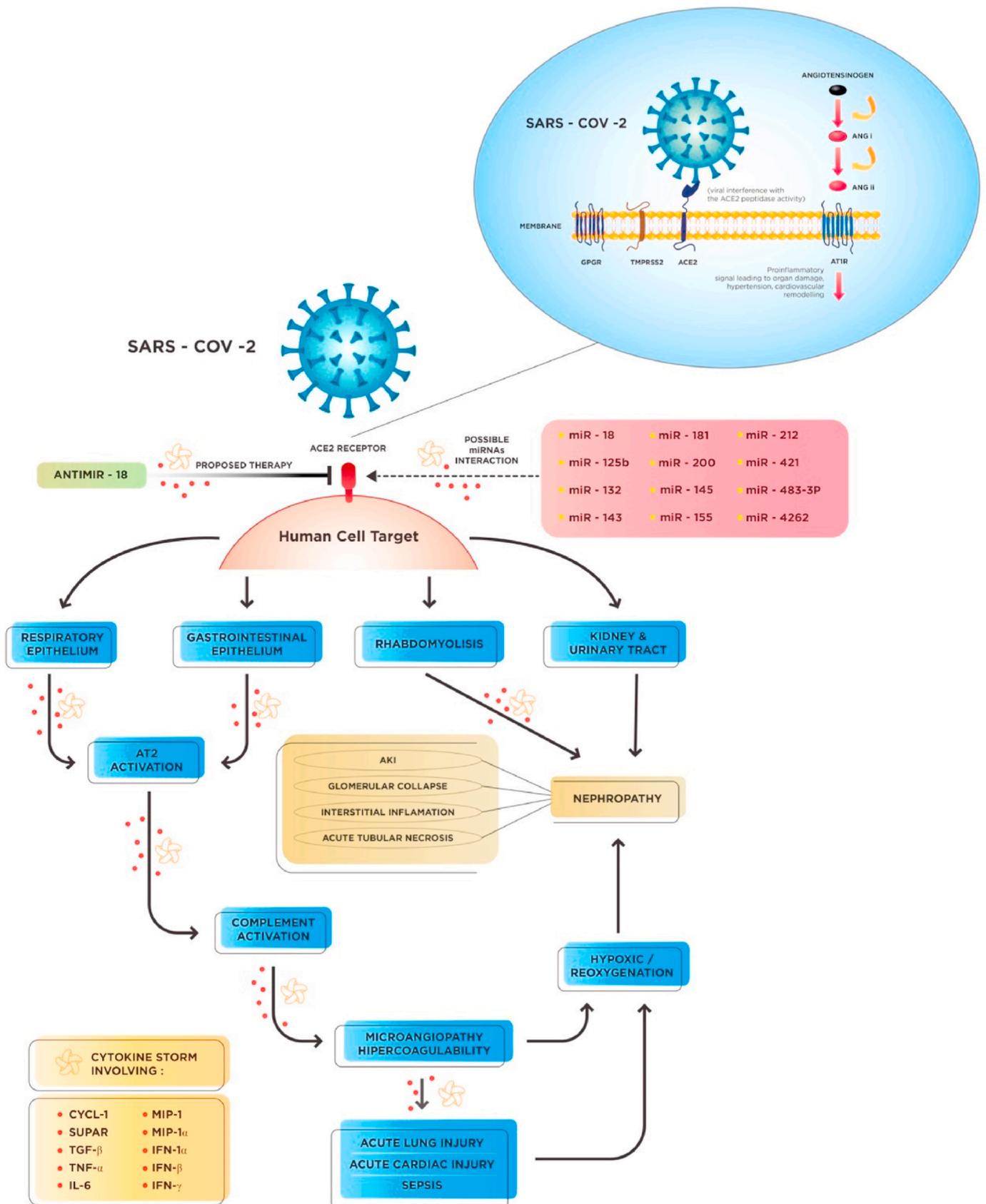
Fig. 1. The SARS-CoV-2 infection impact on the podocyte cytoskeletal protein. (A) Normal glomerulus without podocyte, mesangial cell, and parietal epithelial cell impairment. (B) Injured podocyte leads to glomerular sclerosis. (C) Podocyte integrity with normal cytoskeletal proteins expression. (D) Impairment in podocyte integrity, effacement, apoptosis, and collapse, as virus abnormality impact. The virus makes the cytokine-storm and the proinflammatory mediators responsible for podocyte apoptosis, collapse, and effacement, to clinically manifest as AKI and protein-loss.

than in healthy controls [121]. In another study in a CKD murine model, the miR-223 series is shown to decrease, this is later confirmed in CKD patients at stage 4 and 5 [114]. This indicated that some miRNAs involved in podocyte skeletal protein expression, leading to various steroid-resistant nephrotic syndrome (SRNS) entity (Fig. 1).

The MiRNAs exist in body fluids, including plasma and serum samples, acting as endocrine signals to regulate target genes in recipient cells [97,98]. These miRNAs are at least in part, encased in extracellular vesicles, including exosomes [92,122]. The urinary miRNAs is derived from the kidney and urinary tract, and passively filtered through the glomerulus and released from kidney tubules [92,123,115,116,124,124,124,125].

The MiR-17, miR-451, miR-106a, and miR-19b serve as biomarkers for diagnosis, prognosis, or therapeutic response in various diseases [104,109,115,124]. Therefore, miRNAs have gained importance as biomarkers and offer useful perspectives for the clinical management of kidney disease as an addition to GFR and albuminuria testing [110].

A study conducted by Chu et al. (2014) showed that Dicer ablation occurs in the early metanephric mesenchyme in severe kidney dysgenesis despite the normal specification of nephron progenitors and ureteric bud outgrowth. The kidney dysgenesis is due to marked apoptosis associated with increased Bim expression just after the initial inductive events in metanephric kidney development. These studies indicated a model where miRNAs modulate the balance between survival and apoptosis in the metanephric mesenchyme by targeting the proapoptotic protein Bim [106]. Therefore, the change between baseline miRNAs profiling with those on the follow-up period are essential

modality for therapeutic result monitoring.

Deletions of Dicer, an RNase III enzyme required for miRNA biogenesis in kidney cells, highlighted the miRNAs pivotal role in juxtaglomerular and tubular epithelial cells, and in podocytes [106]. Several miRNAs, including miR-192, -194, − 204, − 215, and − 216, are highly expressed in the kidney, as compared with other human organs [107,108]. In the fibrotic kidney, the miR-192 expression increased significantly in diabetic-mice glomeruli [83,109–111]. Kato et al. also reported the upregulation of miR-192 in fibrotic kidney disease is associated with the activation of TGF-β/Smad signaling, which regulates expression positively by Smad 3, and negatively by Smad7-dependent mechanism [83]. The miR-93 has been shown to facilitate glomerular injury through the activation of vascular endothelial growth factor (VEGF) [86,102]. Meanwhile, the MiR-192 accelerates collagen formation in glomerular mesangial cells in models of diabetic kidney disease (DKD), and also promotes TGF-β/Smad3-induced tubulointerstitial fibrosis. Some studies indicated that miRNAs play essential roles in the development of glomerular diseases, particularly podocyte-associated disorders [70,77]. According to this study, some antimiR-192 and antimiR-93 were conducted in the fibrotic kidney of animal models [102].

MicroRNAs are popularly known as kidney biomarkers and offered useful perspectives for the future clinical management of kidney disease as an addition to GFR and albuminuria testing [85]. The development of new therapeutic techniques involving miRNAs for future use in the diagnosis, treatment, and prevention of kidney diseases is promising [86]. Meanwhile, some are specifically linked to kidney infections, such

Fig. 2. Pathological mechanism underlying the kidney manifestations of SARS-CoV-2 involving proinflammatory mediators and miR expression. Several miRNAs involve in ACE2 expression, while most of them are affected in other organs, and miR-18 and -125b are specifically expressed in the kidney. Currently, only antimir-18 has a good evidence-based study as an ACE2 expression silencer.

as DKD, FSGS, IgA nephropathy, and others. The urine and serum of individuals with kidney disease contain sediments of miRNAs that correlate with specific stages of kidney disease, fibrosis, and function decrease. Exosomes in urine are excellent tools for microRNAs analysis in kidney diseases, since they originate from kidney cells [86,92,95,96,98,122,20,126–128].

MicroRNAs is detected in the kidney and expressed as deregulation in pathological conditions [92,129,130]. The aberrations of miRNA expression in kidney fibrosis were described in a recent meta-analysis that identified five upregulated (miR-142–3p, miR-223–3p, miR-21–5p, miR-142–5p, miR-214–3p) and two downregulated (miR-29c-3p, miR-200a-3p) miRNAs [73,101,115,131–133]. In a cohort of 90 CKD patients at stages of 3–5, Chen et al. showed that miR-125b, miR-145, and miR-155 levels decreased compared to the healthy control [99]. In CKD murine model, it was found that miR-223 decreased, this was recently confirmed in stage 4 and 5 patients [11].

3.2. ACE2 involvement in SARS-CoV-2 infection

The angiotensin-converting enzyme 2 (ACE2) is an enzyme of the renin-angiotensin-aldosterone system (RAAS), which catalyzes the conversion of angiotensin I (Ang I) into Ang (1–9) and Ang II into Ang (1–7) [130]. The ACE2 is widely expressed in lungs, heart tissue, intestine, kidneys, central nervous system, testis, and liver. During the 20 years from its discovery, the investigations targeting the enzyme's complex role established ACE2 as an important regulator in hypertension, heart failure (HF), myocardial infarction (MI), DM, and lung diseases [19,134,135]. Some evidences showed that ACE2 provides vascular protective effects by counteracting the essential effects of Ang II. Moreover, ACE2 possesses potential for developing new avenues in treating vascular diseases [131,132]. Zhang et al. reported that ACE2 ease the development of early atherosclerotic lesions by improving endothelial cells (EC) function [112]. The antiatherosclerotic effect of ACE2 involves the downregulation of the Ang II-activated reactive oxygen species (ROS). Endtmann et al. recently reported that Ang II, through type 1 angiotensin (AT1) receptor and oxidative stress, impairs EPC function in vitro and in vivo, while Ang II induces EPC aging through activation of NADPH oxidase [133]. Donoghue et al. [134] found that ACE2 emerged as a negative regulator of the RAAS and participated in the pathophysiology of hypertension. The Ang II is directly cleaved by ACE2 to give angiotensin (1–7), which functions contrarily to ACE/Ang II/AGT1R signaling [135,136].

3.3. Role of miRNAs in ACE2 expression

Interestingly, Chen et al. (2020) and Liu et al. (2019) reported many microRNAs involved in ACE2 expression, which have not been reported elsewhere [136,137]. Currently, only a few of them are well studied (Table 1).

Some experts discovered miRNAs affecting ACE2-associated nephropathy; these miRNAs are listed in Table 1.

Gu et al. conducted a miRNAs study using hypertensive rats, and found that chronic aerobic exercise training improved RAAS balance, decreased blood pressure by down-regulation of the expression of miR-143. The result was accompanied by significantly elevated circulating ACE2 and angiotensin (1–7) levels [120,121]. Another study conducted by Lambert et al. showed that miR-421 (located on chromosome X q13.2) could decrease the ACE2 protein expression by translational repression [128,137,21]. Jackson et al. in their study with BPH/2J mice models, found a negative correlation between miR-181a and renin [22]. Marques et al. found that in hypertensive patients, there was a downregulation of miR-181a, accompanied by an increase in renin mRNA [126]. Generally, miR-181a expression by destabilizing mRNA, keeps renin low. Therefore, miR-181a upregulation decrease blood pressure by suppressing the kidney sympathetic nerve activity and reduce the renin secretion [127]. Ang II, an RAAS effector, is produced when ACE

hydrolyzes Ang I, while the increased ACE expression is associated with high blood pressure. Interestingly, Kohlstedt et al. [23] found that the shear stress-mediated ACE expression is down-regulated by miR-145 [122,23]. Hu et al. [124] discovered that miR-145 overexpression induced downregulation of ACE protein without reducing the ACE mRNA level. Therefore, miR-145 overexpression contributes to ACE upregulation, increasing blood pressure, by alternate post-transcriptional effects [122,124]. Also, activating the ERK1/2 signaling pathway suppresses miR-145 expression, promote ACE, and increase blood pressure [124]. Then, Eskildsen et al. in their study using rats model showed that after ten days of sustained Ang II-induced hypertension in the subjects, the miR-132/-212 expression increased in the myocardium, arteries, and kidney [119]. There was a positive correlation between the degree of increase in miR-132/miRNA-212 and blood pressure in vitro and in vivo [23,33,138,139]. Recent studies have shown that miR-155 (located on chromosome 21) regulates the expression of AGT1R mRNA by targeting the 3′-untranslated region to silence AGT1R mRNA expression [125]. Angiotensin II has two categories, namely Ang II type 1 (AGT1R) and Ang II type 2 receptor (AGT2R). The AGT1R takes part in a variety of physiological and pathological mechanisms involving the cardiovascular control. These include vasoconstriction, the release of catecholamines, and blood pressure evaluation [127].

Another ACE2-associated miRNA study conducted by Bao et al. using a bleomycin-induced mouse model for acute lung injury (ALI), analyzed the mRNA and protein levels of an antiapoptotic protein Bcl-2 in the ALI-mice that have been treated w/o ACE2. The miR-4262 levels were analyzed in the mouse lung, while the Bcl-2-targeting miRNAs were predicted using bioinformatics algorithms and an applied luciferase reporter assay to examine the effects of miR-4262 on the Bcl-2 protein translation upon their binding to 3′- UTR of Bcl-2 mRNA. The adeno-associated viruses carrying either miR-4262 mimics or antisense were injected into ALI-mice without ACE2 and analyzed, for their effects on the apoptosis in mouse lung cells using Western blot. The results showed that the ACE2-induced suppression of miR-4262, partially contributed to the inhibition of the PEC apoptosis [129]. The miR-4262 is a promising novel treatment for ACE2 and ARDS [127].

Recent studies indicated that miR-124 and miR-135a potentially suppress the NR3C2 expression by reducing the amount of mineralocorticoid receptor protein rather than at the mRNA level [24,25]. The NR3C2 deficient mice died in the neonatal period, due to severe water and sodium loss [26]. Therefore, miR-124 and miR-135a are responsible for blood pressure reduction through RAAS modulation [127]. Kemp et al. [27] found that miR-483-3p inhibited luciferase expression bearing 3′-UTRs of 4 different RAAS-related genes (angiotensinogen, ACE-1, ACE-2, and AGTR2) [127,20]. As an Ang II-regulated miRNA, miR-483-3p was reversed by antimir-483-3p [127,20]. The suppressing angiotensinogen and ACE-1 eventually block the production of Ang II and decrease blood pressure. Nevertheless, evidence showed that AGT2R and ACE-2 oppose the AGT1R-mediated vasoconstrictor action of Ang II, being a part of the "protective arm of RAAS." [127,20].

Another interesting ACE2 associated-miRNA found by Huang et al. [118] is miR-125b, which directly targets the 3′-UTR of ACE2 mRNA. The study was conducted based on bioinformatic analysis with TargetScan software (http://www.targetscan.org/vert_71/), which predicted that miR-125b was potentially targeted at 3′-UTR of ACE2 mRNA. Therefore, the luciferase reporter assays was performed using wild-type or mutated ACE2 3′-UTR constructs to confirm that miR-125b acts as a negative regulator of ACE2. The result showed that co-transfection with miR-125b mimics significantly ($p < 0.05$) decreased the activity of the reporter harboring wild-type ACE2 3′-UTR. However, the activity of the reporter carrying the mutated ACE2 3′-UTR was unaltered by miR-125b. These results indicated that ACE2 is a direct target of miR-125b [118].

Zhang et al. showed that EPC-EXs (endothelial progenitor cells exosomes) elicit anti-oxidative and antiapoptosis [20]. This is

evidenced by protecting ECs from hypoxic/reoxygenation (H/R)-induced injury, which is associated with decreased ROS/Nox2 and increased NO/eNOS levels [20]. However, the levels of miR-18a and ACE2 are reduced in Ang II-induced aging ECs [20]. The neuron overexpression of ACE2 protects cells against oxygen-glucose deprived-induced injury, which correlated with the changes in Nox2/Nox 4 expression and ROS production [20,37]. This data showed that ACE2-EPC-EXs (ACE2-primed endothelial progenitor cells exosomes) are more effective than EPC-EXs in decreasing apoptosis, ROS overproduction, and increasing EC function through downregulating Nox2 and upregulating eNOS [20]. Based on the data of ACE2-EPC-EXs co-culture, the differences of the ROS/Nox2/apoptosis decline and the eNOS/NO/tube formation appeared to be more in Ang II-induced aging ECs than that of young ECs H/R injury [20]. This mechanism is attributed to the higher level of ACE2 in aging ECs after co-incubation with ACE2-EPC-EXs [20]. These observations are supported by the previous study, which showed that ACE2 could protect the brain from ischemic injury with a tendency of age-dependence [20,39,40]. The ACE2 transfection leads to an upregulation of miR-18a in EPCs, EPC-EXs, and ECs [20]. This data showed that miR-18a is a mediator that enhance the protective effects of ACE2-EPC-EXs in aging ECs under H/R condition [20]. To investigate the role of miR-18a in ACE2-EPC-EXs, its expression in the parent cells is knocked down [20]. It was observed that the miR-18a level in ACE2-EPC-EXs is downregulated [20]. More substantially, the protective effects in ACE2-EPCs-EXs *anti*-miR-18a group were decreased, indicating that miR-18a participates in the protective effects that emerged from ACE2-EPC-EXs. Besides, to confirm whether ACE2 could affect miR-18a expression [20,140], the ACE2-specific DX600 inhibitor is used [20]. It was also found that DX600 blocked ACE2-induced miR-18a in the EPCs, EPCEXs, and ECs after coincubation [20]. More importantly, the changes of the miR-18a level were associated with the EC functions [20]. DX600 or *anti*-miR-18a partially blocked the beneficial effects of ACE2-EPC-EXs on H/R-injured ECs [20]. This data further confirmed that ACE2 promotes miR-18a expression, while ACE2-EPC-EXs protect ECs from H/R-induced dysfunction through ACE2, EPC-EXs, and miR-18a [20]. Overall, ACE2-EPC-EXs exhibited greater anti-oxidative and antiapoptosis effects on aging than on the young ECs, and also undergo H/R injury through miR-18a and subsequently downregulation of the Nox2/ROS pathway [20]. Further experiments is applied to examine the protective roles of ACE2-EPC-EXs in vivo and determine their targets on miR-18a [20]. These approaches greatly enrich the understanding of the molecular basis of ACE2-mediated protection against ACE-associated nephropathy and also made clear the antimir-18 development as a novel therapy.

The miR-18a increased thrombospondin-1 production and decreased the inhibitor of DNA-binding protein 1, a transcriptional repressor of thrombospondin-1. It also reduced vascular endothelial growth factor (VEGF)-A and VEGF-D levels, and improved tubule formation. It was effectively internalized by arteriovenous malformation derived from brain endothelial cells (AVM-BECs) in the absence of extraneous transfection reagents [38]. Ferreira et al. reported VEGF-D overexpression in AVM and the capacity of miR-18a to induce AVM-BECs to function more normal. The miR-18a role in the VEGF-D level highlights the clinical potential of microRNA as a treatment for AVM and other vascular diseases [38–40]. Furthermore, miR-18a is part of the miR-17 and miR-92 cluster, which is associated with tumor angiogenesis. However, when evaluated individually, miR-17, miR-18a, miR-19a, and miR-20a have antiangiogenic activity [30]. miRNA have different and opposing roles depending on the cell type and the physiological/pathological context. miR-18a inhibits Dicer expression, a key enzyme involved in miRNA biogenesis. Dicer silencing induces TSP-1 expression [38–40], a potent inhibitor of endothelial cell migration, proliferation, and survival [117]. Ferreira et al. also showed that increased TSP-1 induced by miR-18a treatment correlated with the inhibition of Id-1 expression. Meanwhile, Id-1 is widely overexpressed in most human cancers, therefore, representing a promising target for

anticancer therapies [38–40] The strongest miR-18a effect is found on cells subjected to arterial flow [132]. The angiogenesis is regulated by several endogenous growth factors, particularly VEGF-A. The TSP-1 antagonizes VEGF-A bioavailability and activity by inactivating metalloproteinase-9, which suppresses the release of VEGF-A from the extracellular matrix. The endothelial cells treated with the 3 TSP-1 types 1 (the active domain of TSP-1) decreased VEGF receptor-2 phosphorylation and the activation of serine/threonine-protein kinase Akt [21,38–40]. Moreover, Ferreira et al. showed that VEGF-A, VEGF-D, a key lymphangiogenic, and proangiogenic factors were upregulated in AVM, while miR-18a significantly decreased both VEGF-A and VEGF-D released, through TSP-1 [38,39]. The therapeutic potential of miR-18a is becoming increasingly apparent by its ability to regulate cell proliferation and induce a structural vascular network, which requires the efficient formation of 3-dimensional tubules [38–40]. The miR-18a is also internalized and functionally relevant without the aid of a transfection reagent, demonstrating its potential on clinical application [132]. These findings support the potential use of miR-18a to improve the functionally aberrant AVM-BECs and emphasize the relevance of VEGF-D in vascular dysfunction. Eventually, the use of this miRNA is very potential to be further developed in advancing AVM treatment as a non-invasive, effective, and biocompatible therapeutic agent [38–40].

Using data mining and bioinformatic tools, Wicik et al. described the ACE2 interaction network and evaluated its expression [19]. The study found 1954 miRNAs regulating components of the ACE2 interaction network [19]. The analysis of the top 10 miRNAs regulating each network (complete network, heart, lung, nervous system tissues, and virus-infection proteins network), five of them were shared between all networks (hsa-miR-302c-5p, hsa-miR-27a-3p, hsa-miR-1305, hsa-miR-587, hsa-miR-26b-5p) [19]. The signaling pathways associated with the 36 genes regulated by the top miRNAs, included RAS, AGE-RAGE, and Apelin [71].

Most of the mentioned miRNAs above involve in ACE2 expression in the kidney, heart, blood vessels, and lung. Also, most of those mentioned in Table 1 act as gene enhancer, while few act as gene silencer, i. e miR-19, -27, −29, −155, −365, −421, and −424. Mir-145 and miR-155 have relatively evidence as an ACE2 gene enhancer. While mir-19b, −29, −132, −181, and −212 have relative evidence as gene silencer. The mir-29 has a strong evidence as fibrotic-protecting miRNA [108,120,126,33,141–147]. The upregulation of miR-130 is reported in relapsing INS, however, its target is on GAX, a growth arrest-specific homeobox, which inhibits proliferation, differentiation, and migration of VSMCs (Table 1). i.e., miR-18 and miR-125b are specifically expressed in the kidney, acting as ACE2 gene enhancer.

A study by Zhang et al. showed that ACE2 upregulated miR-18a and ACE2-EPC-EXs (ACE2-primed endothelial progenitor cells exosomes) as an antimir-18 and protected endothelial cells from hypoxic/reoxygenation (H/R) -induced dysfunction in adult C5BJ/6 mice. Also, ACE2-EPC-EXs exhibited antioxidative and antiapoptotic effects on endothelial cells (EC). While, the antimiR-18 inhibited ACE2 expression by downregulating the Nox2/ROS pathway and protected endothelial cells from hypoxic/reoxygenation [20].

3.4. Future possible ACE2-related intervention

Based on this literature review, most of the ACE2-associated miRNAs affected multiorgans, therefore, their antimir therapy potentially lead to some adverse reactions. The disease severity which depend on ACE2 receptor, include SARS-CoV-2 infection, therefore, miR-29 is a fibrotic gene silencer for the disease severity prevention. Based on this review, miR-29 has a quite strong evidence and it is recommended for further study using animal models.

AntimiR-18 is also a potential novel therapy in ACE2-related disease, such as hypertension, CKD, nephropathy, and SARS-CoV-2 infection. Therefore, a study is recommended on ACE2 expression and antimir-18 with primate models.
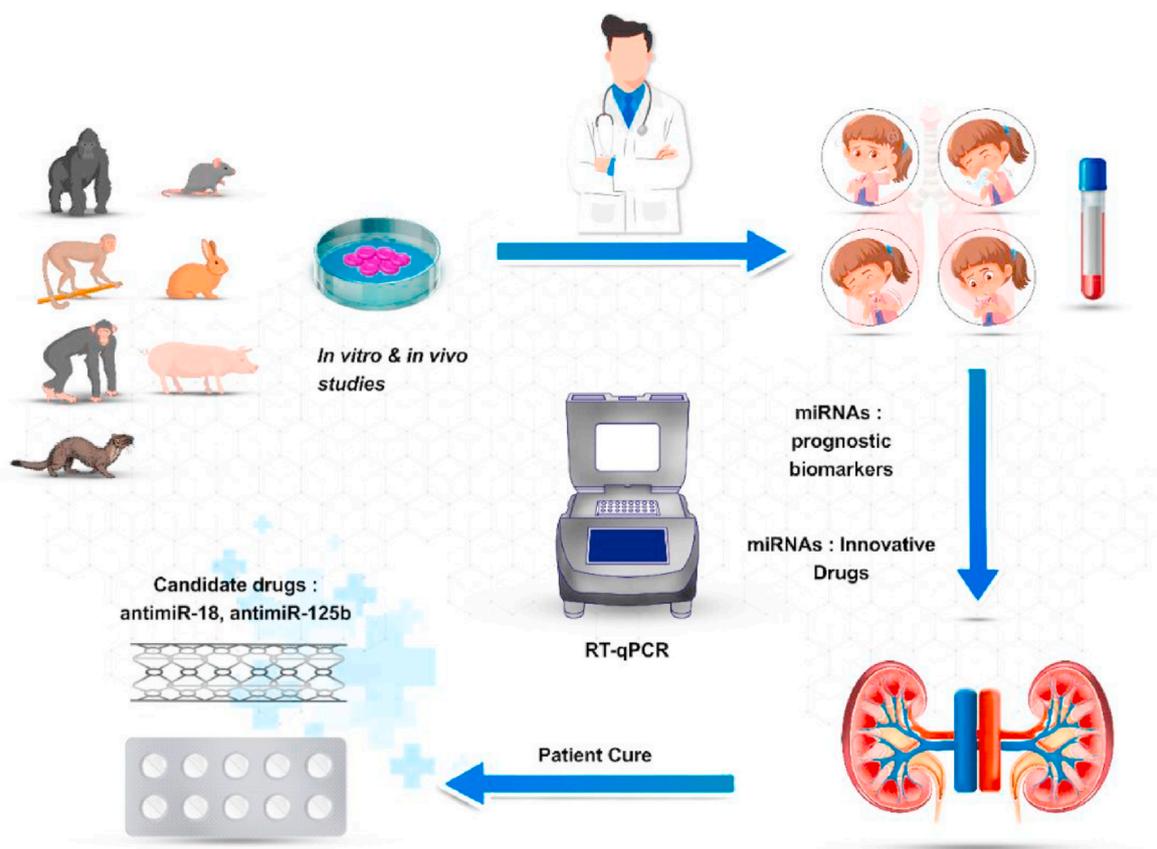
Fig. 3. The miRNAs potential in kidney disease, a bench to bedside approach (in vitro and in vivo models) are used to screen the most useful miRNAs in ACE2 associated nephropathy. The patient samples are screened using high-throughput techniques. The miRNAs is further used as innovative therapeutic approach to improve kidney function in the ACE2-associated nephropathy patients.

Moreover, the review of ACE2 expression with antimiR-125b has not been published even in mice, therefore, a study is also recommended for this phenomenon.

4. Antimir therapy

Antimir, a novel therapy for the future have been developed through several stages, from the search of target miRNA sequences to the design of the *anti*-miRNA oligonucleotides (AMO), the selection of an adequate chemical structure, and its validation [148–151]. Currently, there are two drugs using locked nucleic acids (LNA) [148], the first is Miravirsen from Santaris Pharma, developed to treat hepatitis C virus (HCV) infection by targeting miR-122 [148,149], which is now in phase 2 of clinical trials. Furthermore, the MiRagen Therapeutics company has entered phase 1 of clinical trials for MRG106-11-101 LNA-antimiR®, designed to control the activity of miR-155 in malignancy [148,152], which is responsible in the differentiation, proliferation, and function of blood and lymph cells. The in vitro tests conducted using the developed AMO, successfully inhibited miR-155 activity in lymphoma cells, restoring normal function, and reducing aberrant cell proliferation [148,152]. Mostly, miRNAs affected more than one organ, therefore, it is difficult to determine antimir therapy for each disease [148]. In addition, the miRNAs mapping for each disease and the results of the antimir study with animal models, from mice to primate, is evidently needed (Fig. 3). Also, the interaction between the miRNAs, ACE2, and nephropathy is essential in developing antimir therapy for ACE2-related nephropathy, including those related to SARS-CoV-2 infection.

5. Concluding remarks

The kidney manifestations of COVID-19 infection include AKI, interstitial nephritis, podocyte apoptosis, collapse glomerulonephritis, and progressive CKD. The proinflammatory mediators play an essential role in these manifestations. Meanwhile, specific miRNAs, notably those related to ACE2 expression, are responsible for the increased circulatory proinflammatory mediator levels. The MiRNA-based therapy, notably antimiR-18 and antimir-125b are novel potential ACE2-related therapeutic options for nephropathy associated with COVID-19 (Fig. 3). Moreover, further studies related to antimiR-18 and antimiR-125b are absolutely necessary.

Declaration of competing interest

We declare that no conflict of interest in this study.

References

[1] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T.S. Schiergens, G. Herrler, N.H. Wu, A. Nitsche, M.A. Müller, C. Drosten, S. Pöhlmann, SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell 181 (2) (2020) 271–280, https://doi.org/10.1016/j.cell.2020.02.052 e8.
[2] M. Moghtaderi, Continuous Renal Replacement Therapy (CRRT) in Patients with COVID-19 Infection vol. 8, (2020), pp. 4–7 2.
[3] K.R. Na, H.R. Kim, Y. Ham, D.E. Choi, K.W. Lee, J.Y. Moon, Y. Kim, S. Cheon,

K.M. Sohn, J. Kim, S. Kim, H. Jeong, J.W. Jeon, Acute Kidney Injury and Kidney Damage in COVID-19 Patients vol. 35, (2019), pp. 1–9 2020.

[4] L. Mousavizadeh, S. Ghasemi, Genotype and phenotype of COVID-19: their roles in pathogenesis, J. Microbiol. Immunol. Infect. (2020), https://doi.org/10.1016/j.jmii.2020.03.022 0–4.

[5] Z. Liu, X.R. Huang, H.Y. Chen, E. Fung, J. Liu, H.Y. Lan, Deletion of angiotensin-converting enzyme-2 promotes hypertensive nephropathy by targeting smad 7 for ubiquitin degradation, Hypertension 70 (4) (2017) 822–830, https://doi.org/10.1161/HYPERTENSIONAHA.117.09600.

[6] M. Ye, J. Wysocki, J. William, M.J. Soler, I. Cokic, D. Batlle, Glomerular localization and expression of angiotensin-converting enzyme 2 and angiotensin-converting enzyme: implications for albuminuria in diabetes, J. Am. Soc. Nephrol. 17 (11) (2006) 3067–3075, https://doi.org/10.1681/ASN.2006050423.

[7] K. Reidy, F.J. Kaskel, Pathophysiology of focal segmental glomerulosclerosis, Pediatr. Nephrol. (2007), https://doi.org/10.1007/s00467-006-0357-2.

[8] V.D. D'Agati, F.J. Kaskel, R.J. Falk, Focal segmental glomerulosclerosis, N. Engl. J. Med. 2398–411 (2011), https://doi.org/10.1056/NEJMra1106556.

[9] K. Reidy, F.J. Kaskel, Pathophysiology of focal segmental glomerulo-sclerosis:350–354, (2007), https://doi.org/10.1007/s00467-006-0357-2.

[10] M. Ulbing, A.H. Kirsch, B. Leber, S. Lemesch, J. Münzker, N. Schweighofer, D. Hofer, O. Trummer, A.R. Rosenkranz, H. Müller, K. Eller, V. Stadlbauer, B. Obermayer-Pietsch, MicroRNAs 223-3p and 93-5p in patients with chronic kidney disease before and after renal transplantation, Bone 95 (2017) 115–123, https://doi.org/10.1016/j.bone.2016.11.016.

[11] V.M. Meuth, L. Metzinger, Non-coding RNA Research miR-223 and other miRNA's evaluation in chronic kidney disease : innovative biomarkers and therapeutic tools, Non-Coding RNA Res. 4 (1) (2019) 30–35, https://doi.org/10.1016/j.ncrna.2019.01.002.

[12] V. Metzinger-Le Meuth, O. Fourdinier, N. Charnaux, Z.A. Massy, L. Metzinger, The expanding roles of microRNAs in kidney pathophysiology, Nephrol. Dial. Transplant. (2019) 7–15, https://doi.org/10.1093/ndt/gfy140.

[13] G. Schett, M. Sticherling, M.F. Neurath, COVID-19: risk for cytokine targeting in chronic inflammatory diseases? Nat. Rev. Immunol. 20 (5) (2020) 271–272, https://doi.org/10.1038/s41577-020-0312-7.

[14] P.C.Y. Woo, Y. Huang, S.K.P. Lau, K.Y. Yuen, Coronavirus genomics and bioinformatics analysis, Viruses 2 (8) (2010) 1805–1820, https://doi.org/10.3390/v2081803.

[15] S Van Boheemen, M De Graaf, C. Lauber, T.M. Bestebroer, V.S. Raj, Zaki AM:, osterhaus ADME:, haagmans BL:, gorbalenya AE:, snijder E:, fouchier RAM: genomic characterization of a newly discovered coronavirus, mBio 3 (6) (2012) 1–9, https://doi.org/10.1128/mBio.00473-12.

[16] J.H.C.M. Kreijtz, Y. Süzer, R. Bodewes, A. Schwantes, G. Van Amerongen, R.J. Verburgh, G. De Mutsert, J. Van Den Brand, S.E. Van Trierum, T. Kuiken, R.A.M. Fouchier, A.D.M.E. Osterhaus, G. Sutter, G.F. Rimmelzwaan, Evaluation of a modified vaccinia virus Ankara (MVA)-based candidate pandemic influenza A/H1N1 vaccine in the ferret model, J. Gen. Virol. 91 (11) (2010) 2745–2752, https://doi.org/10.1099/vir.0.024885-0.

[17] C.A.M. de Haan, L. Kuo, P.S. Masters, H. Vennema, P.J.M. Rottier, Coronavirus particle assembly: primary structure requirements of the membrane protein, J. Virol. 72 (8) (1998) 6838–6850, https://doi.org/10.1128/jvi.72.8.6838-6850.1998.

[18] K. Wang, M. Gheblawi, G.Y. Oudit, Angiotensin converting enzyme 2: a double-edged sword, Circulation (2020) 426–428, https://doi.org/10.1161/circulationaha.120.047049.

[19] Z. Wicik, C. Eyileten, D. Jakubik, R. Pavao, J.M. Siller-Matula, M. Postula, ACE2 interaction networks in COVID-19: a physiological framework for prediction of outcome in patients with cardiovascular risk factors, BioRxiv 5 (13) (2020) 094714, , https://doi.org/10.1101/2020.05.13.094714 2020.

[20] C. Zhang, J. Wang, X. Ma, W. Wang, B. Zhao, Y. Chen, C. Chen, J.C. Bihl, ACE2-EPC-EXs protect ageing ECs against hypoxia/reoxygenation-induced injury through the miR-18a/Nox2/ROS pathway, J. Cell Mol. Med. 22 (3) (2018) 1873–1882, https://doi.org/10.1111/jcmm.13471.

[21] P.R. Lawler, J. Lawler, Molecular basis for the regulation of angiogenesis by thrombospondin-1 and -2, Cold Spring Harbor Perspect. Med. 2 (5) (2012) 1–13, https://doi.org/10.1101/cshperspect.a006627.

[22] Y.F. Huang, Y. Zhang, C.X. Liu, J. Huang, G.H. Ding, MicroRNA-125b contributes to high glucose-induced reactive oxygen species generation and apoptosis in HK-2 renal tubular epithelial cells by targeting angiotensin-converting enzyme 2, Eur. Rev. Med. Pharmacol. Sci. 20 (19) (2016) 4055–4062.

[23] T.V. Eskildsen, P.L. Jeppesen, M. Schneider, A.Y. Nossent, Angiotensin II Regulates microRNA-132/-212 in Hypertensive Rats and Humans (March):11190–207, (2013), https://doi.org/10.3390/ijms140611190.

[24] Q. Gu, B. Wang, X. Zhang, Y. Ma, J. Liu, X. Wang, Contribution of renin – angiotensin system to exercise-induced attenuation of aortic remodeling and improvement of endothelial function in spontaneously hypertensive rats 23:298–305, (2014), https://doi.org/10.1016/j.carpath.2014.05.006.

[25] Z. Peng, J. Mao, X. Chen, F. Cai, W. Gu, H. Fu, H. Shen, J. Wang, X. Jin, X. Zhu, A. Liu, Q. Shu, L. Du, Serum suPAR levels help differentiate steroid resistance from steroid-sensitive nephrotic syndrome in children, Pediatr. Nephrol. 30 (2) (2015) 301–307, https://doi.org/10.1007/s00467-014-2892-6.

[26] H. Bao, F. Gao, G. Xie, Z. Liu, Angiotensin-converting enzyme 2 inhibits apoptosis of pulmonary endothelial cells during acute lung injury through suppressing MiR-4262, Cell. Physiol. Biochem. 37 (2) (2015) 759–767, https://doi.org/10.1159/000430393.

[27] M.H. Kim, O. Ham, S.Y. Lee, E. Choi, C.Y. Lee, J.H. Park, J. Lee, H.H. Seo, M. Seung, E. Choi, P.K. Min, K.C. Hwang, MicroRNA-365 inhibits the proliferation

[28] of vascular smooth muscle cells by targeting cyclin D1, J. Cell. Biochem. 115 (10) (2014) 1752–1761, https://doi.org/10.1002/jcb.24841.

[28] S. Bátkai, T. Thum, MicroRNAs in hypertension: mechanisms and therapeutic targets, Curr. Hypertens. Rep. 14 (1) (2012) 79–87, https://doi.org/10.1007/s11906-011-0235-6.

[29] A. Iio, T. Takagi, K. Miki, T. Naoe, A. Nakayama, Y. Akao, Biochimica et Biophysica Acta through host gene NCR143/145 in cancer cells, BBA Gene Regul. Mech. 1829 (10) (2013) 1102–1110, https://doi.org/10.1016/j.bbagrm.2013.07.010.

[30] B. Hu, J. Song, H. Qu, C. Bi, X. Huang, X. Liu, M. Zhang, Mechanical stretch suppresses microRNA-145 expression by activating extracellular signal-regulated kinase 1/2 and upregulating angiotensin-converting enzyme to alter vascular smooth muscle cell phenotype 9(5):1–10, (2014), https://doi.org/10.1371/journal.pone.0096338.

[31] D.W. Lambert, L.A. Lambert, N.E. Clarke, N.M. Hooper, K.E. Porter, A.J. Turner, Angiotensin-converting enzyme 2 is subject to post-transcriptional regulation by miR-421, Clin. Sci. 127 (4) (2014) 243–249, https://doi.org/10.1042/CS20130420.

[32] A.F. Ceylan-Isik, M.R. Kandadi, X. Xu, Y. Hua, A.J. Chicco, J. Ren, S. Nair, Apelin administration ameliorates high fat diet-induced cardiac hypertrophy and contractile dysfunction, J. Mol. Cell. Cardiol. 63 (85) (2013) 4–13, https://doi.org/10.1016/j.yjmcc.2013.07.002.

[33] P.L. Jeppesen, G.L. Christensen, M. Schneider, A.Y. Nossent, H.B. Jensen, D.C. Andersen, T. Eskildsen, S. Gammeltoft, J.L. Hansen, S.P. Sheikh, Angiotensin II type 1 receptor signalling regulates microRNA differentially in cardiac fibroblasts and myocytes, Br. J. Pharmacol. 164 (2) (2011) 394–404, https://doi.org/10.1111/j.1476-5381.2011.01375.x.

[34] A. Sen, P. Most, K. Peppel, Induction of microRNA-138 by pro-inflammatory cytokines causes endothelial cell dysfunction, FEBS Lett. 588 (6) (2014) 906–914, https://doi.org/10.1016/j.febslet.2014.01.033.

[35] L. Chen, R. Xu, H. Yu, Q. Chang, J. Zhong, The ACE2/Apelin signaling , microRNAs , and hypertension, (2015), pp. 5–10, https://doi.org/10.1155/2015/896861 2015.

[36] D. Gustafson, K. Tyryshkin, N. Renwick, microRNA-guided diagnostics in clinical samples, Best Pract. Res. Clin. Endocrinol. Metabol. 30 (5) (2016) 563–575, https://doi.org/10.1016/j.beem.2016.07.002.

[37] G. Ceolotto, I. Papparella, A. Bortoluzzi, G. Strapazzon, F. Ragazzo, P. Bratti, A.S.C. Fabricio, E. Squarcina, M. Gion, P. Palatini, A. Semplicini, Interplay between miR-155, AT1R A1166C polymorphism, and AT1R expression in young untreated hypertensives, Am. J. Hypertens. 24 (2) (2011) 241–246, https://doi.org/10.1038/ajh.2010.211.

[38] R. Ferreira, T. Santos, A. Amar, S.M. Tahara, T.C. Chen, S.L. Giannotta, F.M. Hofman, Malformation endothelial cell function:293–297, (2013), https://doi.org/10.1161/STROKEAHA.113.003578.

[39] O.G. Bhalala, L. Pan, V. Sahni, T.L. McGuire, K. Gruner, W.G. Tourtellotte, J.A. Kessler, microRNA-21 regulates astrocytic response following spinal cord injury, J. Neurosci. 32 (50) (2012) 17935–17947, https://doi.org/10.1523/JNEUROSCI.3860-12.2012.

[40] T. Li, Y. Tian, Q. Li, H. Chen, H. Lv, W. Xie, Han J: the neurexin/N-ethylmaleimide-sensitive factor (NSF) interaction regulates short term synaptic depression, J. Biol. Chem. 290 (29) (2015) 17656–17667, https://doi.org/10.1074/jbc.M115.644583.

[41] H.B. Wang, J. Yang, The role of renin-angiotensin aldosterone system related micro-ribonucleic acids in hypertension, Saudi Med. J. 36 (10) (2015) 1151–1155, https://doi.org/10.15537/smj.2015.10.12458.

[42] F.Z. Marques, A.E. Campain, M. Tomaszewski, E. Zukowska-szczechowska, Y.H.J. Yang, F.J. Charchar, B.J. Morris, Gene expression profiling reveals renin mRNA overexpression in human hypertensive kidneys and a role for MicroRNAs, (2011), pp. 1093–1098, https://doi.org/10.1161/HYPERTENSIONAHA.111.180729.

[43] Cardiovascular IN:, function R: NIH public access 465(1):99–110, 2014. Doi: 10.1007/s00424-012-1146-3AT.

[44] E. Bronze-Da-Rocha, MicroRNAs expression profiles in cardiovascular diseases, BioMed Res. Int. 2014 (2014), https://doi.org/10.1155/2014/985408.

[45] W.H. Wu, C.P. Hu, X.P. Chen, W.F. Zhang, X.W. Li, X.M. Xiong, Y.J. Li, MicroRNA-130a mediates proliferation of vascular smooth muscle cells in hypertension, Am. J. Hypertens. 24 (10) (2011) 1087–1093, https://doi.org/10.1038/ajh.2011.116.

[46] S. Gao, T.W. Liu, Z. Wang, Z.Y. Jiao, J. Cai, H.J. Chi, X.C. Yang, Downregulation of MicroRNA-19b contributes to angiotensin II-induced overexpression of connective tissue growth factor in cardiomyocytes, Cardiol. 127 (2) (2014) 114–120, https://doi.org/10.1159/000355429.

[47] J. Kim, Y. Kang, Y. Kojima, J.K. Lighthouse, X. Hu, A. Aldred, D.L. Mclean, H. Park, S.A. Comhair, D.M. Greif, 503 is disrupted in pulmonary, Arter. Hypertens. 19 (1) (2013) 74–82, https://doi.org/10.1038/nm.3040 Endothelial.

[48] P. Vats, H. Saini, R. Sirohiya, A Review Article on Phytochemicals New Line of Treatment of Sars Covid-19 vol. 15, (2020), pp. 36–46, https://doi.org/10.9790/3008-1503043646 3.

[49] Phelan: 乳鼠心肌提取 HHS Public Access, Physiol. Behav. 176 (1) (2018) 139–148, https://doi.org/10.1016/j.physbeh.2017.03.040.

[50] J. Ziebuhr, The coronavirus replicase, Curr. Top. Microbiol. Immunol. 287 (2005) 57–94, https://doi.org/10.1007/3-540-26765-4_3.

[51] Y. Chen, Q. Liu, D. Guo, Emerging coronaviruses: genome structure, replication, and pathogenesis, J. Med. Virol. 92 (4) (2020) 418–423, https://doi.org/10.1002/jmv.25681.

[52] P. Prabakaran, X. Xiao, D.S. Dimitrov, A model of the ACE2 structure and function as a SARS-CoV receptor, Biochem. Biophys. Res. Commun. 314 (1) (2004)

235–241, https://doi.org/10.1016/j.bbrc.2003.12.081.

[53] Since January 2020 Elsevier Has Created a COVID-19 Resource Centre with Free Information in English and Mandarin on the Novel Coronavirus COVID- 19 . The COVID-19 Resource Centre Is Hosted on Elsevier Connect , the company ' s public news and information (January), 2020.

[54] P. Chandra, J.B. Kopp, Viruses and collapsing glomerulopathy : a brief critical review:1–5, (2013), https://doi.org/10.1093/ckj/sft002.

[55] S.E. Wenderfer, Viral-associated Glomerulopathies in Children:1929 vol. 38, (2015), https://doi.org/10.1007/s00467-015-3057-y.

[56] M.J. Ross, Advances in the pathogenesis of HIV-associated kidney diseases, Kidney Int. 86 (2) (2014) 266–274, https://doi.org/10.1038/ki.2014.167.

[57] M. Waldman, J.B. Kopp, Parvovirus B19 and the Kidney:47–56, (2007), https://doi.org/10.2215/CJN.01060307.

[58] A. Gupta, R.J. Quigg, Glomerular diseases associated with hepatitis B and C, Adv. Chron. Kidney Dis. 22 (5) (2015) 343–351, https://doi.org/10.1053/j.ackd.2015.06.003.

[59] A. Ozkok, A. Yildiz, Hepatitis c virus associated glomerulopathies 20(24):7544–7554, (2014), https://doi.org/10.3748/wjg.v20.i24.7544.

[60] B. Colvin, M. Trebbin, D.D. Agati, C Viral Glomerulonephritis Infection Is Associated and Immunotactoid with Fibrillary Glomerulopathy:2244–52, (1998).

[61] N. Kamar, L. Rostaing, L. Alric, Treatment of hepatitis C-virus-related glomerulonephritis:436–439, (2006), https://doi.org/10.1038/sj.ki.5000142.

[62] J.L. Guy, D.W. Lambert, F.J. Warner, N.M. Hooper, A.J. Turner, Membrane-associated zinc peptidase families: comparing ACE and ACE2, Biochim. Biophys. Acta Protein Proteomics 1751 (1) (2005) 2–8, https://doi.org/10.1016/j.bbapap.2004.10.010.

[63] S.B. Gurley, T.M. Coffman, Angiotensin-converting enzyme 2 gene targeting studies in mice: mixed messages, Exp. Physiol. 93 (5) (2008) 538–542, https://doi.org/10.1113/expphysiol.2007.040014.

[64] M.S. Bharadwaj, W.B. Strawn, L. Groban, L.M. Yamaleyeva, M.C. Chappell, C. Horta, K. Atkins, L. Firmes, S.B. Gurley, K.B. Brosnihan, Angiotensin-converting enzyme 2 deficiency is associated with impaired gestational weight gain and fetal growth restriction, Hypertension 58 (5) (2011) 852–858, https://doi.org/10.1161/HYPERTENSIONAHA.111.179358.

[65] L. Huang, D.J. Sexton, K. Skogerson, M. Devlin, R. Smith, I. Sanyal, T. Parry, R. Kent, J. Enright, Q long Wu, G. Conley, D. DeOliveira, L. Morganelli, M. Ducar, C.R. Wescott, R.C. Ladner, Novel peptide inhibitors of angiotensin-converting enzyme 2, J. Biol. Chem. 278 (18) (2003) 15532–15540, https://doi.org/10.1074/jbc.M212934200.

[66] K. Kuba, Y. Imai, S. Rao, H. Gao, F. Guo, B. Guan, Y. Huan, P. Yang, Y. Zhang, W. Deng, L. Bao, B. Zhang, G. Liu, Z. Wang, M. Chappell, Y. Liu, D. Zheng, A. Leibbrandt, T. Wada, A.S. Slutsky, D. Liu, C. Qin, C. Jiang, J.M. Penninger, A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury, Nat. Med. 11 (8) (2005) 875–879, https://doi.org/10.1038/nm1267.

[67] R.A.S. Santos, A.C. Simoes e Silva, C. Maric, D.M.R. Silva, R.P. Machado, I. De Buhr, S. Heringer-Walther, S.V.B. Pinheiro, M.T. Lopes, M. Bader, E.P. Mendes, V.S. Lemos, M.J. Campagnole-Santos, H.P. Schultheiss, R. Speth, T. Walther, Angiotensin-(1-7) is an endogenous ligand for the G protein-coupled receptor Mas, Proc. Natl. Acad. Sci. U. S. A. 100 (14) (2003) 8258–8263, https://doi.org/10.1073/pnas.1432869100.

[68] H.N. Reich, G.Y. Oudit, J.M. Penninger, J.W. Scholey, A.M. Herzenberg, Decreased glomerular and tubular expression of ACE2 in patients with type 2 diabetes and kidney disease, Kidney Int. 74 (12) (2008) 1610–1616, https://doi.org/10.1038/ki.2008.497.

[69] R.V. Durvasula, S.J. Shankland, Activation of a local renin angiotensin system in podocytes by glucose, Am. J. Physiol. Ren. Physiol. 294 (4) (2008) F830–F839, https://doi.org/10.1152/ajprenal.00266.2007.

[70] C. Lu, D. Zhou, Q. Wang, W. Liu, F. Yu, F. Wu, C. Chen, Review Article Crosstalk of MicroRNAs and Oxidative Stress in the Pathogenesis of Cancer Production through Targeting Multiple 2020, (2020).

[71] I.-Y. Chen, S.C. Chang, H.-Y. Wu, T.-C. Yu, W.-C. Wei, S. Lin, C.-L. Chien, M.-F. Chang, Upregulation of the chemokine (C-C motif) ligand 2 via a severe acute respiratory syndrome coronavirus spike-ACE2 signaling pathway, J. Virol. 84 (15) (2010) 7703–7712, https://doi.org/10.1128/JVI.02560-09.

[72] Na KR:, Kim HR:, Ham Y:, Choi DE:, Lee KW:, Moon JY:, Kim Y:, Cheon S:, Sohn KM:, Kim J:, Kim S:, Jeong H:, Jeon JW:, Kim Y: v O I Is R N O L a V O I Is N O L a V O I Is R N O L a 35(December 2019), 2020.

[73] Y. Isaka, Targeting TGF- β signaling in kidney fibrosis:1–13, (2018), https://doi.org/10.3390/ijms19092532.

[74] W. Guan, Z. Ni, Y. Hu, W. Liang, C. Ou, J. He, L. Liu, H. Shan, C. Lei, D.S.C. Hui, B. Du, L. Li, G. Zeng, K. Yuen, R. Chen, C. Tang, T. Wang, P. Chen, J. Xiang, S. Li, J. Wang, Z. Liang, Y. Peng, L. Wei, Y. Liu, Y. Hu, P. Peng, J. Wang, J. Liu, Z. Chen, G. Li, Z. Zheng, S. Qiu, J. Luo, C. Ye, S. Zhu, Disease, In China, 2020, (2019), https://doi.org/10.1056/NEJMoa2002032.

[75] N. Chen, M. Zhou, X. Dong, J. Qu, F. Gong, Y. Han, Y. Qiu, J. Wang, Y. Liu, Y. Wei, J. Xia, T. Yu, Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan , China : a descriptive study, Lancet 395 (10223) (2020) 507–513, https://doi.org/10.1016/S0140-6736(20)30211-7.

[76] Y. Cheng, R. Luo, K. Wang, M. Zhang, Z. Wang, L. Dong, Kidney Impairment Is Associated with In-Hospital Death of COVID- 19 Patients, (2020).

[77] M. Outcomes, Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China, (2020), https://doi.org/10.1001/jama.2020.1585 1–9.

[78] Volunteers A–ncov, Z. Li, M. Wu, J. Guo, J. Yao, X. Liao, Until 24 : 00 of February 7 2020 , 31774 Laboratory-Confirmed Cases of Novel Coronavirus (2019-nCoV)

Infection Have Been Reported , Including 6101 Severe Cases in Critical Conditions and 722 Deaths . The Critical and Urgent Need at This Moment Is to Fin, (2019).

[79] S. Naicker, C.W. Yang, S.J. Hwang, B.C. Liu, J.H. Chen, V. Jha, The Novel Coronavirus 2019 epidemic and kidneys, Kidney Int. 97 (5) (2020) 824–828, https://doi.org/10.1016/j.kint.2020.03.001.

[80] J.C. He, M. Husain, M. Sunamoto, V.D.D. Agati, M.E. Klotman, R. Iyengar, P.E. Klotman, Nef stimulates proliferation of glomerular podocytes through activation of Src- dependent Stat 3 and MAPK1 , 2 pathways 114(5), (2004), https://doi.org/10.1172/JCI200421004 (The).

[81] L. He, G.J. Hannon, Harbor CS: MicroRNAs : SMALL RNAs with A BIG ROLE IN GENE REGULATION, (2004), https://doi.org/10.1038/nrg1379 5(July).

[82] D.W. Padmashree, N.R. Swamy, Molecular signaling cascade of miRNAs in causing Diabetes Nephropathy, Bioinformation 9 (8) (2013) 401–408.

[83] D.P. Bartel, MicroRNAs: target recognition and regulatory functions, Cell (2009) 215–233, https://doi.org/10.1016/j.cell.2009.01.002.

[84] K. Bhatt, M. Kato, R. Natarajan, Mini-review: emerging roles of microRNAs in the pathophysiology of renal diseases, Am. J. Physiol. Physiol. 310 (2) (2016) F109–F118, https://doi.org/10.1152/ajprenal.00387.2015.

[85] R.C. Friedman, K.K. Farh, C.B. Burge, D.P. Bartel, Most mammalian mRNAs are conserved targets of microRNAs:92–105, (2009), https://doi.org/10.1101/gr.082701.108.

[86] LR do Nascimento, C.P. Domingueti, MicroRNAs: new biomarkers and promising therapeutic targets for diabetic kidney disease, J. Bras. Nefrol. 41 (3) (2019) 412–422, https://doi.org/10.1590/2175-8239-JBN-2018-0165.

[87] M. Kato, N.E. Castro, R. Natarajan, MicroRNAs: potential mediators and biomarkers of diabetic complications, Free Radic. Biol. Med. 64 (2013) 85–94, https://doi.org/10.1016/j.freeradbiomed.2013.06.009.

[88] M. Tanaka, K. Oikawa, M. Takanashi, M. Kudo, J. Ohyashiki, K. Ohyashiki, M. Kuroda, Down-regulation of miR-92 in human plasma is a novel marker for acute leukemia patients 4(5):1–5, (2009), https://doi.org/10.1371/journal.pone.0005532.

[89] P.S. Mitchell, R.K. Parkin, E.M. Kroh, B.R. Fritz, S.K. Wyman, E.L. Pogosova-Agadjanyan, A. Peterson, J. Noteboom, K.C. O'Briant, A. Allen, D.W. Lin, N. Urban, C.W. Drescher, B.S. Knudsen, D.L. Stirewalt, R. Gentleman, R.L. Vessella, P.S. Nelson, D.B. Martin, M. Tewari, Circulating microRNAs as stable blood-based markers for cancer detection, Proc. Natl. Acad. Sci. U. S. A. 105 (30) (2008) 10513–10518, https://doi.org/10.1073/pnas.0804549105.

[90] O.F. Laterza, L. Lim, P.W. Garrett-engele, K. Vlasakova, N. Muniappa, W.K. Tanaka, J.M. Johnson, J.F. Sina, T.L. Fare, F.D. Sistare, W.E. Glaab, Plasma MicroRNAs as Sensitive and Specific Biomarkers of Tissue Injury METHODS : 1983, (2009), https://doi.org/10.1373/clinchem.2009.131797.

[91] J. Siracusa, N. Koulmann, M. Goriot, S. Bourdon, Data in Brief Circulating levels of non-muscle-speci fi c miRNAs in response to acute muscle damage in rat, Data Br. 18 (2018) 190–197, https://doi.org/10.1016/j.dib.2018.02.076.

[92] A. Ramezani, J.M. Devaney, S. Cohen, M.R. Wing, R. Scott, S. Knoblach, R. Singhal, L. Howard, J.B. Kopp, D.S. Raj, Circulating and urinary microRNA profile in focal segmental glomerulosclerosis: a pilot study, Eur. J. Clin. Invest. 45 (4) (2015) 394–404, https://doi.org/10.1111/eci.12420.

[93] K. Ramachandran, J. Saikumar, V. Bijol, J.L. Koyner, J. Qian, R.A. Betensky, Human miRNome profiling identifies MicroRNAs differentially present in the urine after kidney, Injury 1752 (2013), https://doi.org/10.1373/clinchem.2013.210245.

[94] G. Wang, C. Szeto, Quantification of gene expression in urinary sediment for the study of renal diseases:494–499, (2007), https://doi.org/10.1111/j.1440-1797.2007.00836.x.

[95] F. Barutta, M. Tricarico, A. Corbelli, L. Annaratone, S. Pinach, S. Grimaldi, G. Bruno, D. Cimino, D. Taverna, M.C. Deregibus, M.P. Rastaldi, P.C. Perin, G. Gruden, Urinary exosomal MicroRNAs in incipient diabetic nephropathy, PLoS One 8 (11) (2013) 1–8, https://doi.org/10.1371/journal.pone.0073798.

[96] B.W.M. Balkom Van, T. Pisitkun, M.C. Verhaar, M.A. Knepper, Exosomes and the Kidney : Prospects for Diagnosis and Therapy of Renal Diseases (January), (2020), https://doi.org/10.1038/ki.2011.292.

[97] M. Kato, L. Arce, M. Wang, S. Putta, L. Lanting, R. Natarajan, A microRNA circuit mediates Transforming Growth Factor-ß1 autoregulation in renal glomerular mesangial cells, Kidney Int. 80 (4) (2011 August) 358–368, https://doi.org/10.1038/ki.2011.43.

[98] M.H. Sohel, Extracellular/circulating MicroRNAs: release mechanisms, functions and challenges, Achiev. Life Sci. 10 (2) (2016) 175–186, https://doi.org/10.1016/j.als.2016.11.007.

[99] H. Dong, J. Lei, L. Ding, Y. Wen, H. Ju, X. Zhang, MicroRNA: function, detection, and bioanalysis, Chem. Rev. 113 (8) (2013) 6207–6233, https://doi.org/10.1021/cr300362f.

[100] J. Ma, L. Zhang, J. Hao, N. Li, J. Tang, L. Hao, Up-regulation of microRNA-93 inhibits TGF-β1-induced EMT and renal fibrogenesis by down-regulation of Orai1, J. Pharmacol. Sci. 136 (4) (2018) 218–227, https://doi.org/10.1016/j.jphs.2017.12.010.

[101] A.C.K. Chung, X.R. Huang, X. Meng, H.Y. Lan, miR-192 mediates TGF-β/Smad 3-driven renal fibrosis, J. Am. Soc. Nephrol. 21 (8) (2010) 1317–1325, https://doi.org/10.1681/ASN.2010020134.

[102] X. Yang, X. Wang, F. Nie, T. Liu, X. Yu, H. Wang, Q. Li, R. Peng, Z. Mao, Q. Zhou, G. Li, MiR-135 family members mediate podocyte injury through the activation of Wnt/β-catenin signaling, Int. J. Mol. Med. 36 (3) (2015) 669–677, https://doi.org/10.3892/ijmm.2015.2259.

[103] A. Loboda, M. Sobczak, A. Jozkowicz, J. Dulak, TGF- ? 1/Smads and miR-21 in Renal Fibrosis and Inflammation 2016, (2016).

[104] J. Li, B. Liu, H. Xue, Q.Q. Zhou, L. Peng, MiR-217 Is a useful diagnostic biomarker

and regulates human podocyte cells apoptosis via targeting tnfsf11 in membranous nephropathy, BioMed Res. Int. 2017 (2017), https://doi.org/10.1155/2017/2168767.

[105] Y.Q. Chen, X.X. Wang, X.M. Yao, D.L. Zhang, X.F. Yang, S.F. Tian, N.S. Wang, MicroRNA-195 promotes apoptosis in mouse podocytes via enhanced caspase activity driven by BCL2 insufficiency, Am. J. Nephrol. 34 (6) (2011) 549–559, https://doi.org/10.1159/000333809.

[106] C. Yang, P.C. Fan, C.C. Chen, C.C. Peng, C.H. Chang, C.H. Yang, L.J. Chu, Y.C. Chen, C.W. Yang, Y.S. Chang, P.H. Chu, A circulating miRNA signature for early diagnosis of acute kidney injury following acute myocardial infarction, J. Transl. Med. 17 (1) (2019) 1–12, https://doi.org/10.1186/s12967-019-1890-7.

[107] V. Metzinger-Le Meuth, L. Metzinger, miR-223 and other miRNA's evaluation in chronic kidney disease: innovative biomarkers and therapeutic tools, Non-Coding RNA Res. 4 (1) (2019) 30–35, https://doi.org/10.1016/j.ncrna.2019.01.002.

[108] Y. Liu, N.E. Taylor, L. Lu, K. Usa, A.W. Cowley, N.R. Ferreri, N.C. Yeo, M. Liang, Renal medullary MicroRNAs in dahl salt-sensitive rats: MiR-29b regulates several collagens and related genes, Hypertension 55 (4) (2010) 974–982, https://doi.org/10.1161/HYPERTENSIONAHA.109.144428.

[109] R. Li, A.C.K. Chung, Y. Dong, W. Yang, X. Zhong, H.Y. Lan, The microRNA miR-433 promotes renal fibrosis by amplifying the TGF-β/Smad 3-Azin1 pathway, Kidney Int. 84 (6) (2013) 1129–1144, https://doi.org/10.1038/ki.2013.272.

[110] R. Nassirpour, D. Raj, R. Townsend, C. Argyropoulos, MicroRNA biomarkers in clinical renal disease: from diabetic nephropathy renal transplantation and beyond, Food Chem. Toxicol. 98 (2016) 73–88, https://doi.org/10.1016/j.fct.2016.02.018.

[111] C. Hill, A. Flyvbjerg, R. Rasch, M. Bak, A. Logan, Transforming growth factor-β2 antibody attenuates fibrosis in the experimental diabetic rat kidney, J. Endocrinol. 170 (3) (2001) 647–651, https://doi.org/10.1677/joe.0.1700647.

[112] M. Lassila, K. Fukami, K. Jandeleit-Dahm, T. Semple, P. Carmeliet, M.E. Cooper, A.R. Kitching, Plasminogen activator inhibitor-1 production is pathogenetic in experimental murine diabetic renal disease, Diabetologia 50 (6) (2007) 1315–1326, https://doi.org/10.1007/s00125-007-0652-x.

[113] M. Rudnicki, P. Perco, B. D'haene, J. Leierer, A. Heinzel, I. Mühlberger, N. Schweibert, J. Sunzenauer, H. Regele, A. Kronbichler, P. Mestdagh, J. Vandesompele, B. Mayer, G. Mayer, Renal microRNA- and RNA-profiles in progressive chronic kidney disease, Eur. J. Clin. Invest. 46 (3) (2016) 213–226, https://doi.org/10.1111/eci.12585.

[114] M. Ulbing, A.H. Kirsch, B. Leber, S. Lemesch, J. Münzker, N. Schweighofer, D. Hofer, O. Trummer, A.R. Rosenkranz, H. Müller, K. Eller, V. Stadlbauer, B. Obermayer-Pietsch, MicroRNAs 223-3p and 93-5p in patients with chronic kidney disease before and after renal transplantation, Bone 95 (2017) 115–123, https://doi.org/10.1016/j.bone.2016.11.016.

[115] C. Zhang, S. Liang, S. Cheng, W. Li, X. Wang, C. Zheng, C. Zeng, S. Shi, L. Xie, K. Zen, Z. Liu, Urinary miR-196a predicts disease progression in patients with chronic kidney disease, J. Transl. Med. 16 (1) (2018) 1–12, https://doi.org/10.1186/s12967-018-1470-2.

[116] N. Wang, Y. Zhou, L. Jiang, D. Li, J. Yang, C.Y. Zhang, K. Zen, Urinary MicroRNA-10a and MicroRNA-30d serve as novel, sensitive and specific biomarkers for kidney injury, PLoS One 7 (12) (2012), https://doi.org/10.1371/journal.pone.0051140.

[117] J. Long, Y. Wang, W. Wang, B.H.J. Chang, F.R. Danesh, Identification of microRNA-93 as a novel regulator of vascular endothelial growth factor in hyperglycemic conditions, J. Biol. Chem. 285 (30) (2010) 23457–23465, https://doi.org/10.1074/jbc.M110.136168.

[118] Q. Wang, Y. Wang, A.W. Minto, J. Wang, Q. Shi, X. Li, R.J. Quigg, MicroRNA-377 is up-regulated and can lead to increased fibronectin production in diabetic nephropathy, Faseb. J. 22 (12) (2008) 4126–4135, https://doi.org/10.1096/fj.08-112326.

[119] Y.L. Phua, J.Y.S. Chu, A.K. Marrone, A.J. Bodnar, S. Sims-Lucas, J. Ho, Renal stromal miRNAs are required for normal nephrogenesis and glomerular mesangial survival, Phys. Rep. 3 (10) (2015) 1–19, https://doi.org/10.14814/phy2.12537.

[120] A. Gholaminejad, H. Abdul Tehrani, M. Gholami Fesharaki, Identification of candidate microRNA biomarkers in renal fibrosis: a meta-analysis of profiling studies, Biomarkers (2018) 713–724, https://doi.org/10.1080/1354750X.2018.1488275.

[121] N.X. Chen, K. Kiattisunthorn, K.D. O'Neill, X. Chen, R.N. Moorthi, V.H. Gattone, M.R. Allen, S.M. Moe, Decreased MicroRNA is involved in the vascular remodeling abnormalities in chronic kidney disease (CKD), PLoS One 8 (5) (2013), https://doi.org/10.1371/journal.pone.0064558.

[122] A. Turchinovich, L. Weiz, A. Langheinz, B. Burwinkel, Characterization of extracellular circulating microRNA, Nucleic Acids Res. 39 (16) (2011) 7223–7233, https://doi.org/10.1093/nar/gkr254.

[123] J.M. Lorenzen, I. Volkmann, J. Fiedler, M. Schmidt, I. Scheffner, H. Haller, W. Gwinner, T. Thum, Urinary miR-210 as a mediator of acute T-cell mediated rejection in renal allograft recipients, Am. J. Transplant. 11 (10) (2011) 2221–2227, https://doi.org/10.1111/j.1600-6143.2011.03679.x.

[124] W. Zhang, C. Zhang, H. Chen, L. Li, Y. Tu, C. Liu, S. Shi, K. Zen, Z. Liu, Evaluation of microRNAs miR-196a, miR-30a-5p, and miR-490 as biomarkers of disease activity among patients with FSGS, Clin. J. Am. Soc. Nephrol. 9 (9) (2014) 1545–1552, https://doi.org/10.2215/CJN.11561113.

[125] G. Wang, B.C.H. Kwan, F.M.M. Lai, K.M. Chow, P.K.T. Li, C.C. Szeto, Elevated levels of miR-146a and miR-155 in kidney biopsy and urine from patients with IgA nephropathy, Dis. Markers 30 (4) (2011) 171–179, https://doi.org/10.3233/DMA-2011-0766.

[126] L.L. Lv, Y.H. Cao, H.F. Ni, M. Xu, D. Liu, H. Liu, P.S. Chen, B.C. Liu, MicroRNA-29c in urinary exosome/microvesicle as a biomarker of renal fibrosis, Am. J. Physiol.

[127] Ren. Physiol. 305 (8) (2013) 1220–1227, https://doi.org/10.1152/ajprenal.00148.2013.

[127] J.D. Arroyo, J.R. Chevillet, E.M. Kroh, I.K. Ruf, C.C. Pritchard, D.F. Gibson, P.S. Mitchell, C.F. Bennett, E.L. Pogosova-Agadjanyan, D.L. Stirewalt, J.F. Tait, M. Tewari, Argonaute 2 complexes carry a population of circulating microRNAs independent of vesicles in human plasma, Proc. Natl. Acad. Sci. U. S. A. 108 (12) (2011) 5003–5008, https://doi.org/10.1073/pnas.1019055108.

[128] H. Zhou, H. Kajiyama, T. Tsuji, X. Hu, A. Leelahavanichkul, S. Vento, R. Frank, J.B. Kopp, H. Trachtman, R.A. Star, P.S.T. Yuen, Urinary exosomal wilms' tumor-1 as a potential biomarker for podocyte injury, Am. J. Physiol. Ren. Physiol. 305 (4) (2013), https://doi.org/10.1152/ajprenal.00056.2013.

[129] V. Metzinger-Le Meuth, O. Fourdinier, N. Charnaux, Z.A. Massy, L. Metzinger, The expanding roles of microRNAs in kidney pathophysiology, Nephrol. Dial. Transplant. 34 (1) (2019) 7–15, https://doi.org/10.1093/ndt/gfy140.

[130] S.D. Deshpande, S. Putta, M. Wang, J.Y. Lai, M. Bitzer, R.G. Nelson, L.L. Lanting, M. Kato, R. Natarajan, Transforming growth factor-βinduced cross talk between p53 and a MicroRNA in the pathogenesis of diabetic nephropathy, Diabetes 62 (9) (2013) 3151–3162, https://doi.org/10.2337/db13-0305.

[131] B. Wang, P. Koh, C. Winbanks, M.T. Coughlan, A. McClelland, A. Watson, K. Jandeleit-Dahm, W.C. Burns, M.C. Thomas, M.E. Cooper, P. Kantharidis, MiR-200a prevents renal fibrogenesis through repression of TGF-β2 expression, Diabetes 60 (1) (2011) 280–287, https://doi.org/10.2337/db10-0892.

[132] F. He, F. Peng, X. Xia, C. Zhao, Q. Luo, W. Guan, Z. Li, X. Yu, F. Huang, MiR-135a promotes renal fibrosis in diabetic nephropathy by regulating TRPC1, Diabetologia 57 (8) (2014) 1726–1736, https://doi.org/10.1007/s00125-014-3282-0.

[133] L. Denby, V. Ramdas, R. Lu, B.R. Conway, J.S. Grant, B. Dickinson, A.B. Aurora, J.D. McClure, D. Kipgen, C. Delles, E. Van Rooij, A.H. Baker, MicroRNA-214 antagonism protects against renal fibrosis, J. Am. Soc. Nephrol. 25 (1) (2014) 65–80, https://doi.org/10.1681/ASN.2013010072.

[134] M. Gheblawi, K. Wang, A. Viveiros, Q. Nguyen, J. Zhong, A.J. Turner, M.K. Raizada, M.B. Grant, G.Y. Oudit, Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System, (2020), https://doi.org/10.1161/CIRCRESAHA.120.317015 1456–74.

[135] V.B. Patel, J. Zhong, M.B. Grant, G.Y. Oudit, Hosp. R HHS Publ. Access 118 (8) (2017) 1313–1326, https://doi.org/10.1161/CIRCRESAHA.116.307708 (Role).

[136] Y. Chen, X. Wang, MiRDB: an online database for prediction of functional microRNA targets, Nucleic Acids Res. 48 (D1) (2020) D127–D131, https://doi.org/10.1093/nar/gkz757.

[137] W. Liu, X. Wang, Prediction of functional microRNA targets by integrative modeling of microRNA binding and target expression data, Genome Biol. 20 (1) (2019) 1–10, https://doi.org/10.1186/s13059-019-1629-z.

[138] E.E. Bouhassira, California institute for regenerative medicine, SAGE Encycl. Stem Cell Res. 1 (2015), https://doi.org/10.4135/9781483347660.n64.

[139] X. Jiang, Q. Ning, J. Wang, Angiotensin II induced differentially expressed microRNAs in adult rat cardiac fibroblasts, J. Physiol. Sci. 63 (1) (2013) 31–38, https://doi.org/10.1007/s12576-012-0230-y.

[140] B. Song, Z.Z. Zhang, J.C. Zhong, X.Y. Yu, G.Y. Oudit, H.Y. Jin, L. Lu, Y Le Xu, Z. Kassiri, W.F. Shen, P.J. Gao, D.L. Zhu, Loss of angiotensin-converting enzyme 2 exacerbates myocardial injury via activation of the CTGF-fractalkine signaling pathway, Circ. J. 77 (12) (2013) 2997–3006, https://doi.org/10.1253/circj.CJ-13-0805.

[141] E. Van Rooij, L.B. Sutherland, J.E. Thatcher, J.M. DiMaio, R.H. Naseem, W.S. Marshall, J.A. Hill, E.N. Olson, Dysregulation of microRNAs after myocardial infarction reveals a role of miR-29 in cardiac fibrosis, Proc. Natl. Acad. Sci. U. S. A. 105 (35) (2008) 13027–13032, https://doi.org/10.1073/pnas.0805038105.

[142] B. Wang, R. Komers, R. Carew, C.E. Winbanks, B. Xu, M. Herman-Edelstein, P. Koh, M. Thomas, K. Jandeleit-Dahm, P. Gregorevic, M.E. Cooper, P. Kantharidis, Suppression of microRNA-29 expression by TGF-β1 promotes collagen expression and renal fibrosis, J. Am. Soc. Nephrol. 23 (2) (2012) 252–265, https://doi.org/10.1681/ASN.2011010055.

[143] Z. Zhu, J. Yin, D.C. Li, Z.Q. Mao, Role of microRNAs in the treatment of type 2 diabetes mellitus with Roux-en-Y gastric bypass, Braz. J. Med. Biol. Res. 50 (3) (2017) 6–11, https://doi.org/10.1590/1414-431X20175817.

[144] D.G. Padmashree, N. Swamy, Molecular signaling cascade of miRNAs in causing Diabetes Nephropathy, Bioinformation 9 (8) (2013) 401–408, https://doi.org/10.6026/97320630009401.

[145] M. Kato, TGF-β-induced signaling circuit loops mediated by microRNAs as new therapeutic targets for renal fibrosis? Kidney Int. 84 (6) (2013) 1067–1069, https://doi.org/10.1038/ki.2013.297.

[146] L. Cushing, P.P. Kuang, J. Qian, F. Shao, J. Wu, F. Little, V.J. Thannickal, W.V. Cardoso, J. Lü, miR-29 is a major regulator of genes associated with pulmonary fibrosis, Am. J. Respir. Cell Mol. Biol. 45 (2) (2011) 287–294, https://doi.org/10.1165/rcmb.2010-0323OC.

[147] A.J. Kriegel, Y. Liu, Y. Fang, X. Ding, M. Liang, The miR-29 family: genomics, cell biology, and relevance to renal and cardiovascular injury, Physiol. Genom. 44 (4) (2012) 237–244, https://doi.org/10.1152/physiolgenomics.00141.2011.

[148] J.F. Lima, L. Cerqueira, C. Figueiredo, C. Oliveira, N.F. Azevedo, Anti-miRNA oligonucleotides: a comprehensive guide for design, RNA Biol. 15 (3) (2018) 338–352, https://doi.org/10.1080/15476286.2018.1445959.

[149] M.H. Van Der Ree, A.J. Van Der Meer, J. De Bruijne, R. Maan, A. Van Vliet, T.M. Welzel, S. Zeuzem, E.J. Lawitz, M. Rodriguez-Torres, V. Kupcova, A. Wiercinska-Drapalo, M.R. Hodges, Janssen HLA:, Reesink HW: long-term safety and efficacy of microRNA-targeted therapy in chronic hepatitis C patients, Antivir. Res. 111 (2014) 53–59, https://doi.org/10.1016/j.antiviral.2014.08.015.

[150] J. Krützfeldt, N. Rajewsky, R. Braich, K.G. Rajeev, T. Tuschl, M. Manoharan,

M. Stoffel, Silencing of microRNAs in vivo with 'antagomirs', Nature 438 (7068) (2005) 685–689, https://doi.org/10.1038/nature04303.

[151] J. Elmén, M. Lindow, A. Silahtaroglu, M. Bak, M. Christensen, A. Lind-Thomsen, M. Hedtjärn, J.B. Hansen, H.F. Hansen, E.M. Straarup, K. McCullagh, P. Kearney, S. Kauppinen, Antagonism of microRNA-122 in mice by systemically administered LNA-antimiR leads to up-regulation of a large set of predicted target mRNAs in the liver, Nucleic Acids Res. 36 (4) (2008) 1153–1162, https://doi.org/10.1093/nar/gkm1113.

[152] K.A. Lennox, R. Owczarzy, D.M. Thomas, J.A. Walder, M.A. Behlke, Improved performance of anti-miRNA oligonucleotides using a novel non-nucleotide modifier, Mol. Ther. Nucleic Acids 2 (2013) e117, https://doi.org/10.1038/mtna.2013.46.