Table S1 : Implication of miR-21-5p in human renal pathology.

Kidney disease	Renal expression of miR-21-5p	Circulating miR-21-5p	Urinary level of miR-21-5p	Other expression of miR-21-5p	References
Acute kidney injury (AKI)			Elevated urinary level of miR-21-5p in AKI patients. No association with AKI no recovery at 90 days.		[1]
		Increased miR-21-5p level after cardiopulmonary bypass surgery with ischemic preconditioning.			[2]
		Increased miR-21-5p level in AKI patients. miR-21-5p associated with AKI clinical stage.	Higher level of miR-21-5p in AKI patients.		[3]
		Lower serum and urinary levels of miR-21-5p in patients with cardiac surgery-associated AKI.			[4]
		Elevated levels of miR-21-5p in acute tubular necrosis and Hepatorenal Syndrom.			[5]
		Decreased circulating miR-21-5p associated with post cardiac surgery AKI			[6]
	Increased renal expression of miR-21-5p in transplanted patients with acute tubular necrosis		Increased urinary level of miR-21-5p after: - acetaminophen-induced AKI - cisplatin-induced AKI		[7]
		Increased urinary and circulating miR-21-5p levels in patients with post cardiac surgery AKI			[8]

			Increased urinary level of miR-21-5p in patients with AKI		[9]
			Increased urinary level of miR-21-5p in patients with AKI		[10]
Nephrolithiasis	Increased miR-21-5p expression		Increased miR-21-5p urinary level		[11]
papillary renal cell carcinoma		Increased miR-21-5p levels			[12]
Nephroangiosclerosis			Increased urinary level of miR-21-5p associated with a better renal outcome		[13]
Diabetic nephropathy			Increased urinary exosomal expression of miR-21-5p associated with: - higher serum creatinine level - lower eGFR		[14]
	Increased miR-21-5p glomerular expression negatively associated with eGFR				[15]
		Increased circulating miR-21-5p level associated with - a low eGFR - a high proteinuria - IRC progression			[16]
		Increased circulating miR-21-5p level associated with renal function worsening			[17]

		Increased circulating miR-21-5p level is not associated with nephropathy			[18]
	Increased renal miR-21-5p level associated with - kidney function worsening - proteinuria - fibrosis (glomerular and interstitial)				[19]
	Increased glomerular miR-21-5p expression associated with proteinuria				[20]
	Increased renal miR-21-5p level				[21]
			Increased urinary levels of miR-21-5p		[22]
			Increased urinary levels of miR-21-5p associated with : - a better renal function - less fibrotic lesions		[23]
			Increased urinary levels of miR-21-5p associated with a better renal outcome		[13]
Kidney transplantation			Increased urinary levels of miR-21-5p in patients with moderate and severe IFTA		[24]
			Increased urinary levels of miR-21-5p in patients with insterstitial fibrosis and tubular atrophy		[25]

				Increased levels of miR-21-5p in hypothermic machine perfusate associated with a worse renal function	[26]
	Increased renal miR-21-3p level in patients developing post-transplant AKI				[27]
	Increased miR-21-5p level in patients with high IF/TA grade	Increased circulating miR-21-5p level in patients with grade 3 IF/TA			[28]
	Increased renal miR-21-5p level associated with graft function, graft survival and renal fibrosis				[29]
IgA nephropathy	Increased miR-21-5p expression				[30]
	Increased miR-21-5p level associated with - glomerular and intestitial fibrosis - renal survival				[31]
	Increased glomerular and tubular miR-21-5p associated with : - glomerular and intestitial fibrosis - proteinuria - renal function				[32]
			Increased urinary levels of miR-21-5p associated with a better renal function		[33]

			Increased urinary levels of miR-21-5p associated with a better renal outcome		[13]
Minimal change nephrotic syndrome			Increased urinary levels of miR-21-5p		[22]
Polycystic Kidney Diseases	miR-21-5p is increased in cyst walls				[34]
Uremic Vascular Calcification		Increased levels of miR-21-5p			[35]
Chronic Kidney Disease			Increased urinary levels of miR-21-5p		[36-37]

AKI : Acute Kidney Injury ; DFG : Débit de filtration glomérulaire ; IF/TA : Interstitial Fibrosis / Tubular Atroph ; eGFR : estimated Glomerular Filtration Rate ; ESRD: End Stage Renal Disease ; CKD: Chronic Kidney Diseease ; VC: Vascular Calcification ; IFTA: Interstitial Fibrosis and Tubular Atrophy

Table S2 : Implication of miR-21a-5p in animal models of acute and chronic renal pathologies.

Kidney disease	miR-21a-5p role	Animal model	Expression of miR-21a-5p	Molecular target : (*cell type* : **miR-21a-5p direct target**)	Référence
Acute Kidney Injury (AKI)	Protective	Cecal ligation and puncture (CLP) in rats Overexpression of miR-21a-5p (agomir)	miR-21a-5p ↘ in kidney <u>Overexpression of miR-21a-5p :</u> ↗ renal function ↘ histological injuries ↘ apoptosis, inflammatory and oxidative stress response	*Endothelial progenitor cells (rat) :* **RUNX1**	[38]
		Ischemia-reperfusion mouse model Inhibition of miR-21a-5p (KO in dendritic cells)	miR-21a-5p ↘ in dendritic cells <u>Inhibition of miR-21a-5p :</u> ↘ renal function ↗ histological injuries	*Bone Marrow Derived Dendritic Cell (human) :* **CCR7**	[39]
		Ischemia-reperfusion mouse model Cobalt chloride (protective) Inhibition of miR-21a-5p (LNA)	miR-21a-5p ↗ kidney <u>Inhibition of miR-21a-5p :</u> ↘ renal function ↗ histological injuries	*Umbilical vein endothelial cells (human) :* **thrombospondin-1**	[40]
		Ischemia-reperfusion mouse model Delayed ischemic preconditioning (protective) Inhibition of miR-21a-5p (LNA)	miR-21a-5p ↗ whole kidney after preconditioning <u>Inhibition of miR-21a-5p</u> : Loss of preconditioning benefit (renal function, histology)	*HK2* (Human renal epithelial cells) : **PHD2** – HIF1	[41]
		Ischemia-reperfusion rat model Ghrelin (protective)	miR-21a-5p ↗ miR-21a-5p ↗↗ with ghreline	*NRK-52E cells* (Rat renal epithelial cells) : **PTEN** –Akt **Bcl2**	[42]
		Ischemia-reperfusion mouse model Ischemic preconditioning (protective)	miR-21a-5p ↗ 24h after preconditioning	*HEK-296* (human embryonic kidney) and *HK-2 :*	[43]

				MKK3 – p38 MAPK – IL-6/TNF-α	
		Ischemia-reperfusion rat model Inhibition of miR-21a-5p (oligonucleotides)	miR-21a-5p ↗ whole kidney <u>Inhibition of miR-21a-5p</u> : ↘ renal function ↗ histological injuries	*Cellules NRK-52E* : **Rab11a**	[44]
		Ischemia-reperfusion mouse model, Preconditioning with xenon (protective) Inhibition of miR-21a-5p (LNA)	miR-21a-5p ↗ kidney miR-21a-5p ↗↗ with xenon <u>Inhibition of miR-21a-5p</u> : Loss of xenon benefit (renal function, histology)		[45]
AKI	protective	Injections of gentamycine in rats Preconditioning with xenon (protective)	miR-21a-5p ↗ kidney miR-21a-5p ↗↗ with xenon		[46]
		Ischemia-reperfusion mouse model Ischemic preconditioning (protective) Inhibition of miR-21a-5p (LNA)	miR-21a-5p ↗ whole kidney after preconditioning (4h-4 days) <u>Inhibition of miR-21a-5p</u> : Loss of preconditioning benefit (renal function, histology) No effect in absence of preconditioning	*Epithelial renal cells (human)* : **PDCD4** HIF1	[47]
		Ischemia-reperfusion mouse model	miR-21a-5p ↗ kidney (D1 to D30)	*Tubular cells (mouse)* : **PDCD4**	[48]
	deleterious	Aristolochic acid treated mice Inhibition of miR-21a-5p (KO or LNA)	miR-21a-5p ↗ kidney <u>Inhibition of miR-21a-5p :</u> Protection against fibrosis injuries ↗ renal function	*HK2 :* **Wnt2b**	[49]
		Ischemia-reperfusion rat model	miR-21a-5p ↗ kidney		[50]

		Vitamin D3 and erythropoietin preconditioning			
		Ischemia-reperfusion mouse model Administration of erythropoietin (protective)	miR-21a-5p ↗ kidney Erythropoietin ↘ miR-21a-5p kidney		[51]
		Cisplatin injections in rat	Urinary miR-21a-5p ↗		[52]
		Ischemia-reperfusion mouse model	miR-21a-5p ↗ kidney miR-21a-5p ↗↗ 24h post reperfusion		[53]
		Ischemia-reperfusion rat model Gentamycine-induced AKI in rats	miR-21a-5p ↗ cortex ↗↗ medulla ↘ miR-21-a-5p in blood ↗ miR-21-5p in urine miR-21a-5p ↗ cortex and medulla ↘ miR-21a-5p in blood and urine		[10]
		Ischemia-reperfusion mouse model Inhibition of miR-21a-5p (KO or oligonucleotide)	↗ miR-21a-5p kidney <u>Inhibition of miR-21a-5p :</u> Protection against fibrosis injuries	*Myofibrobasts, renal epithelial cells* : ERK/MAPK **PPARα** MPV17-like **RECK**	[54]
		HMOX1$^{-/-}$ mice with low salt diet and injection of Cyclosporin A	miR-21a-5p ↗ whole kidney		[55]
		Low salt diet in mice and injection of Cyclosporin A	miR-21a-5p ↗ whole kidney Up to 2 weeks of treatment then decrease	*Proximal tubular cells (human) :* **PTEN** – Akt	[56]

Renal transplantation	deleterious	Streptozotocin (STZ)-induced diabetic mice Inhibition of miR-21a-5p (KO)	miR-21a-5p ↗ kidney <u>KO miR-21a-5p</u> : ↗ proteinuria ↘ renal function ↗ glomerulosclerosis	*Podocytes (mice)* : **SMAD7** **PDCD4** p53 **TIMP3**	[20]
		db/db mice Overexpression of miR-21a-5p (plasmide)	miR-21a-5p ↘ whole kidney <u>Overexpression of miR-21a-5p</u> : ↘ mesangial proliferation ↘ albuminuria	*Mesangial cells (mouse) :* **PTEN** - PI3K - Akt	[57]
Diabetic nephropathy (DN)	protective	STZ-induced DN rats Inhibition of miR-21a-5p (oligonucleotides)	miR-21a-5p ↗ kidney <u>Inhibition of miR-21a-5p :</u> ↘ inflammatory response and progression of the disease ↘ renal function	*Podocytes (mouse) :* **TIMP3**	[58]
		KK-Ay mice + high fat diet (diabetus + moderate obesity)	miR-21a-5p ↗ kidney and serum		[59]
	deleterious	STZ-induced diabetic mice Treatment with C66 (curcumin analogue) Inhibition of miR-21a-5p (LNA)	C66 ↘ miR-21a-5p kidney <u>Inhibition of miR-21a-5p :</u> - ↘ albuminuria - ↘ renal fibrosis		[60]

		KK-Ay mice + high fat diet (diabetus + moderate obesity) Inhibition of miR-21a-5p (antagomir)	miR-21a-5p correlated expression in kidney and sera circulating miR-21a- ↗ associated with : - albuminuria - altered renal function - glomerular injuries <u>Inhibition of miR-21a-5p :</u> improvement of albuminuria, renal function and glomerular injuries	*HKC (Human Kidney Cells)* : **SMAD 7**	[61]
		KK-Ay mice + high fat diet Inhibition of miR-21a-5p (lentivirus)	miR-21a-5p ↗ whole kidney <u>Inhibition of miR-21a-5p :</u> - ↘ EMT and fibrosis markers - ↘ albuminuria	*HKC (Human Kidney Cells)* + TGF-ß: TGF-ß – SMAD 3 / **SMAD 7** α-SMA, E-cadherin	[61]
		KK-Ay mice Inhibition of miR-21a-5p (oligonucleotide)	miR-21a-5p ↗ whole kidney associated with à albuminuria, renal failure and glomerular sclerosis <u>Inhibition of miR-21a-5p</u> : ↘ injuries		[62]
		Streptozotocin-induced diabetic mice TIMP3$^{-/-}$ mice	miR-21a-5p ↗ whole kidney	*Mesangial cells (mice)* : **TIMP3** SirT1	[21]
	Deleterious	db/db mice Inhibition of miR-21a-5p (ultrasound-microbubble-mediated miR-21 small hairpin RNA transfer)	miR-21a-5p ↗ whole kidney <u>inhibition of miR-21a-5p</u> : - improvement of renal function - inhibition of renal fibrosis and inflammation	*Tubular and mesangial cellsn (rat) :* **SMAD 7** TGF-ß NFκB	[63]

		OVE26 mice (Type 1 diabetus)	miR-21a-5p ↗ renal cortex	*Mesangial cells (rat and human)*: **PTEN** – AKT – GSK3ß - Tor complex 1	[64]
		NOD mice (Non Obese Diabetic mice) PDCD4$^{-/-}$ (type 1 diabetus)	miR-21a-5p ↗ ß islands	*ß cells (mice)* : **PDCD4** – NFκB	[65]
		Col4a3 $^{-/-}$ mice Inhibition of miR-21a-5p (oligonucleotide)	miR-21a-5p ↗ kidney <u>Inhibition of miR-21a-5p</u> : Protection against disease progression and improvement of survival ↘ albuminuria ↘ expression markers of kidney injury, fibrosis, inflammation, mitochondrial function and lipid metabolism		[32]
Alport nephropathy	deleterious	Col4a3 $^{-/-}$ mice Inhibition of miR-21a-5p (oligonucleotide)	miR-21a-5p ↗ whole kidney <u>Inhibition of miR-21a-5p</u> : Improvement of renal function and proteinuria Survival increased ↘ glomerular and interstitial fibrosis	*Proximal tubular cells, podocytes, fibroblasts (mice and human) :* **PPAR-α** – RXR (Retinoid X Receptor)	[66]
Glomerulonephritis	deleterious	Nephrotoxic serum injections in rat (contains antibodies against the glomerular basement membrane)	Urinary miR-21a-5p ↗		[67]
		Glomerulonephritis induced by anti-Thy 1.1 in rats	miR-21a-5p ↗ kidney		[68]

				Circulating T cells (human lupus disease) : **PDCD4**	[69]
Polycystic renal disease	deleterious	Kif3a$^{-/-}$ mice Pkd1$^{-/-}$ mice Pkd2$^{-/-}$ mice Hnf-1ß$^{-/-}$ mice miR-21$^{-/-}$ mice	miR-21a-5p ↗ whole kidney and cysts KO miR-21a-5p : ↘ cysts Improvement of renal function	*Renal epithelial cells (mice)* : **PDCD4**	[70]
Kidney Stone Disease	deleterious	Calcium oxalate crystal deposition induced by injection of glyoxylate in mice Inhibition of miR-21a-5p (oligonucleotides)	miR-21a-5p ↗ kidney Inhibition of miR-21a-5p : ↘ creatinemia ↘ renal tubular injury ↘ lipid accumulation	*HK2 :* **PPARα**	[34]
Renal fibrosis / Chronic kidney disease	deleterious	TGF-ß transgenic mice (model of glomerular sclerosis) Inhibition of miR-21a-5p (KO)	miR-21a-5p ↗ kidney KO miR-21a-5p : ↗ proteinuria ↗ glomerusclerosis	*Podocytes (mice)* : **SMAD7** **PDCD4** **p53** **TIMP3**	[11]
		UUO mice	miR-21a-5p ↗ kidney	*Epithelial renal cells (mice) :* SPRY1/ERK/NFκB signalling pathway	[20]
		Angiotensin II-treated mice Inhibition of miR-21a-5p (lentivirus)	↗ miR-21a-5p cortical kidney Inhibition of miR-21a-5p : ↘ albuminuria Protection against fibrosis	*HK2 :* **PPARα**	[71]

	deleterious	UUO mice	↗ miR-21a-5p kidney	*HK2 :* ERK1/2	[72]
		Adenine-induced renal fibrosis mouse model	↗ miR-21a-5p cortical kidney		[73]
		Unilateral ureteral obstruction mice (UUO)	↗ miR-21a-5p kidney D4-D28	*Fibroblasts (mice)* : α-SMA, collagen 1A1	[19]
		UUO mice Inhibition of miR-21a-5p (KO or oligonucleotide)	↗ miR-21a-5p kidney <u>Inhibition of miR-21a-5p :</u> Protection against fibrosis	*Myofibrobases, renal epithelial cells (mice)* : ERK/MAPK **PPARα** MPV17 **RECK**	[28]
		UUO mice SMAD3$^{-/-}$ (protective) Inhibition of miR-21a-5p (shRNA)	↗ miR-21a-5p kidney ↘ miR-21a-5p kidney SMAD3$^{-/-}$ with UUO <u>Inhibition of miR-21a-5p</u> : Improvement of histological injuries		[54]
		UUO mice Inhibition of miR-21a-5p (LNA)	↗ miR-21a-5p- kidney <u>Inhibition of miR-21a-5p</u> : Improvement of histological injuries		[75]
		UUO rats SHRSP rats (hypertensive rats)	miR-21a-5p ↗ kidney		[76]

Abbreviations : AKI : Acute Kidney Injury ; CLP : cecal ligation and puncture ; DN : diabetic nephropathy ; HKC : Human Kidney Cells ; KO : Knock Out ; LNA : Locked Nucleic Acid ; UUO : Ureteral Unilateral Obstruction; shRNA : small hairpin RNA, SHRSP : Spontaneously hypertensive rat stroke-prone ; STZ : Streptozotocin

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