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Supplementary information

Extracellular vesicles in kidney disease

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Supplementary Table 1 | Therapeutic use of extracellular vesicle in animal models of kidney damage.

Extracellular vesicle origin	Model	Type of injury	Dose	Effects	Refs
MSCs					
Bone Marrow	Glycerol	AKI	Single injection:15 μg $2.2x10^8$ EVs	Stimulation of tubular epithelial cells proliferation and apoptosis resistance	[1, 2]
	IRI	AKI	Single injection: 5×10^{10} EVs	Delivery of miR-199a-3p with Sema3A downregulation and AKT and ERK pathways activation	[3]
	Cisplatin	AKI	Single injection: 100 μg	Anti-apoptotic effect, by up-regulating anti-apoptotic genes	[4]
	Gentamicin	AKI	Single injection: 100 μg	Anti-inflammatory effect	[5]
	IRI	AKI	Single injection:200 μg	Anti-inflammatory effect; CCR2 EVs acting as decoy receptor to suppress CCL2 activity	[6]
	Cisplatin	CKD	Multiple injections: 100 μg followed by 50 μg every 4 days	Anti-apoptotic effect by up-regulating anti-apoptotic genes	[4]
	Remnant kidney	CKD	Single injection: 30 μg	Inhibition of fibrosis, interstitial lymphocyte infiltration and tubular atrophy	[7]
	UUO	CKD	Single injection: 30 μg	Decrease of serum creatinine and BUN	[8]
	UUO	CKD	Single: 0.5 mg/kg	Inhibition of fibrosis, by inhibiting the RhoA/ROCK pathway	[9]
	Type 1 diabetes	CKD	Multiple injections: $1x10^{10}$ EVs	Inhibition of fibrosis, via EV miRNA cargo	[10]
	Type 1 diabetes	CKD	Single injection: 100 μg/Kg	Induction of authophagy by increase of LC3 and Beclin-1 and decrease of mTOR and fibrotic markers	[11]
	Aristolochic acid nephropathy	CKD	Multiple injections: $1x10^{10}$ EVs	Inhibition of pro-fibrotic genes α-Sma, Tgfb1, and Col1a1	[12]
Human umbilical cord	Cisplatin	AKI	Single injection: 200 μg	Amelioration of oxidative stress and cell apoptosis, promotion of proliferation	[13]
	IRI	AKI	Single injection: 30 μg	Induction of HGF synthesis that facilitates cell dedifferentiation and growth	[14]
	UUO	CKD	Multiple injections: 200 μg (10mg/Kg)	Attenuation of fibrosis through inhibition of YAP activity by CK1δ/β-TRCP	[15]
	Sepsis/ cecal ligation	AKI	Single injection: 100 μg	Anti-inflammatory effect by miR-146b up-regulation and NF-κB activity inhibition	[16]
Wharton Jelly-	IRI	AKI	Single injection:100 μg	Anti-inflammatory effect through suppression of CX3CL1	[17]
	IRI	AKI	Single injection:100 μg	Inhibition of mitochondrial fission via miR-30	[18]
	Cyclosporine A	CKD	Multiple injections: 100 μg	Anti-oxidative property by inhibition of α-sma and ROS generation	[19]

Renal	IRI	AKI	Single injection: $2x10^7$ EVs	Pro-angiogenic effect with increase of peritubular capillaries and amelioration of microvascular rarefaction	[20]
	IRI	AKI	Single injection: $4x10^8$ EVs	Stimulation of tubular proliferation	[21]
Liver (HLSCs)	Aristolochic acid nephropathy	CKD	Multiple injections: $1x10^{10}$ EVs	Inhibition of fibrosis by reducing of pro-fibrotic genes α-Sma, Tgfb1, and Col1a1	[22]
	Type 1 diabetes	CKD	Multiple injections: $1x10^{10}$ EVs	Inhibition of fibrosis via miRNA transfer	[10]
Adipose tissue	Metabolic syndrome and renal artery stenosis	CKD	Single injection: $1x10^{10}$ EVs	Anti-inflammatory effect[84,85]; increase of T reg population[85]	[23] [24]
	Cisplatin	AKI	Double injections: 100 μg	Inhibition of apoptosis and inflammation by modulating Wnt/ TGF-β, and epithelial–mesenchymal transition signaling pathways.	[25]
	Sepsis/ cecal ligation	AKI	Single injection: 100 μg	Inhibition of inflammation and apoptosis through SIRT1 signaling pathway	[26]
	DOCA-salt hypertension	CKD	Multiple injections: $1.5x10^9$ EVs	Anti-inflammatory effect	[27]
	Spontaneous diabetes mice	CKD	Multiple injections	Promotion of autophagy flux and inhibition of apoptosis[93]; Amelioration of podocyte damage by transfer of miR-26a-5p[94]	[28] [29]
Embryonic	Remnant kidney	CKD	Multiple injections: 7 μg twice daily for 4 consecutive days	Reduction of tubular and glomerular damage	[30]
Human placenta	IRI	AKI	Multiple injections: 100 μg	Promotion of renal regeneration by Sox9+ cell activation	[31]
EPCs					
	IRI	AKI/CKD	Single injection: 30 μg	Promotion of renal regeneration by reprogramming hypoxic resident renal cells	[32]
	Thy1.1 glomerulonephritis	AKI	Single injection: 30 μg	Inhibition of antibody- and complement-mediated injury of mesangial cells	[33]
ECFCs					
	IRI	AKI	Single injection: 15 μg Single injection: 20 μg	Inhibition of endothelial cell apoptosis[82]; Renal protection via transfer of miR-486-5p targeting PTEN[83]	[34-36]
Human-induced pluripotent stem cells					
hiPSC-MSCs	IRI	AKI	Single injection: $1x10^{12}$ EVs	Anti-necroptosis effect via delivering SP1	[37]
hiPSCs	IRI	AKI	Single injection: $1x10^9$ EVs	Reduction of cell death and inflammatory	[38]
Embryonic stem cells					
ESC line	IRI	AKI	Double injections: 100 μg	Stimulation of proliferation and angiogenesis, inhibition of renal fibrosis	[39]
Renal tubular cells					

Kidney	IRI	AKI	Double injections: 100 μg	Reduction of tubular damage, neutrophil infiltration and fibrosis	[40]
Urine					
Urine	Glycerol	AKI	Single injection: $2x10^8$ EVs	Stimulation of tubular cell proliferation, reduction of inflammatory and injury markers, and restoration of endogenous Klotho loss	[41]
Urine-derived MSCs					
Urine	streptozotocin induced-diabetic nephropathy	CKD	Multiple injections: 100 μg	Inhibition of podocyte apoptosis and promotion of vascular regeneration	[42]

Studies administering extracellular vesicles, released by different sources, in models of AKI and CKD are listed, with the different modalities of administration and dosage. MSCs: mesenchymal stromal cells; EPCs: endothelial progenitor cells; ECFCs: endothelial colony forming cells; HLSCs: human liver stem cells; UUO: obstruction of the ureter; IRI: ischemia reperfusion injury; hiPSCs: human-induced pluripotent stem cells; ESCs: embryonic stem cells.

References

1. Bruno, S., et al. Mesenchymal stem cell-derived microvesicles protect against acute tubular injury. *J. Am. Soc. Nephrol.* **20**, 1053-1067 (2009).
2. Collino, F., et al. AKI recovery induced by mesenchymal stromal cell-derived extracellular vesicles carrying microRNA. *J. Am. Soc. Nephrol.* **26**, 2349-2360 (2015).
3. Zhu, G., et al. Exosomes from human-bone-marrow-derived mesenchymal stem cells protect against renal ischemia/reperfusion injury via transferring miR-199a-3p. *J. Cell. Physiol.* **234**, 23736-23749 (2019).
4. Bruno, S., et al. Microvesicles derived from mesenchymal stem cells enhance survival in a lethal model of acute kidney injury. *PLoS One* **7**, e33115 (2012).
5. Reis, L.A., Borges, F.T., Simões, M.J., Borges, A.A., Sinigaglia-Coimbra, R. & Schor, N. Bone marrow-derived mesenchymal stem cells repaired but did not prevent gentamicin-induced acute kidney injury through paracrine effects in rats. *PLoS One* **7**, e44092 (2012).
6. Shen, B., et al. CCR2 Positive Exosome Released by Mesenchymal Stem Cells Suppresses Macrophage Functions and Alleviates Ischemia/Reperfusion-Induced Renal Injury. *Stem Cells Int.* 1240301 (2016).
7. He, J., et al. Bone marrow stem cells-derived microvesicles protect against renal injury in the mouse remnant kidney model. *Nephrology (Carlton)* **17**, 493-500 (2012).

8. He, J., et al. Micro-vesicles derived from bone marrow stem cells protect the kidney both in vivo and in vitro by microRNA-dependent repairing. Nephrology (Carlton) 20, 591-600 (2015).
9. Shi, Z., Wang, Q., Zhang, Y. & Jiang, D. Extracellular vesicles produced by bone marrow mesenchymal stem cells attenuate renal fibrosis, in part by inhibiting the RhoA/ROCK pathway, in a UUO rat model. Stem Cell Res. Ther. 11, 253 (2020).
10. Grange, C., et al. Stem cell-derived extracellular vesicles inhibit and revert fibrosis progression in a mouse model of diabetic nephropathy. *Sci. Rep.* **9**, 4468 (2019).
11. Ebrahim, N., et al. Mesenchymal stem cell-derived exosomes ameliorated diabetic nephropathy by autophagy induction through the mTOR signaling pathway. *Cells* **7**, 226 (2018).
12. Kholia, S., et al. Mesenchymal Stem Cell Derived Extracellular Vesicles Ameliorate Kidney Injury in Aristolochic Acid Nephropathy. *Front. Cell Dev. Biol.* **8**, 188 (2020).
13. Zhou, Y., et al. Exosomes released by human umbilical cord mesenchymal stem cells protect against cisplatin-induced renal oxidative stress and apoptosis in vivo and in vitro. *Stem Cell Res. Ther.* **4**, 34 (2013).
14. Ju, G.Q., et al. Microvesicles derived from human umbilical cord mesenchymal stem cells facilitate tubular epithelial cell dedifferentiation and growth via hepatocyte growth factor induction. *PLoS One* **10**, e0121534 (2015).
15. Ji C., et al. Exosomes derived from hucMSC attenuate renal fibrosis through CK1δ/β-TRCP-mediated YAP degradation. *Cell Death Dis.* **11**, 327 (2020).
16. Zhang, R., et al. Human umbilical cord mesenchymal stem cell exosomes alleviate sepsis-associated acute kidney injury via regulating microRNA-146b expression. *Biotechnol. Lett.* **42**, 669-679 (2020).

17. Zou, X., et al. Microvesicles derived from human Wharton's Jelly mesenchymal stromal cells ameliorate renal ischemia-reperfusion injury in rats by suppressing CX3CL1. *Stem Cell Res. Ther.* **5**, 40 (2014).
18. Gu, D., Zou, X., Ju, G., Zhang, G., Bao, E. & Zhu, Y. Mesenchymal Stromal Cells Derived Extracellular Vesicles Ameliorate Acute Renal Ischemia Reperfusion Injury by Inhibition of Mitochondrial Fission through miR-30. *Stem Cells Int.* 2093940 (2016).
19. Zhang, G.Y., et al. Extracellular-vesicles derived from human Wharton-Jelly mesenchymal stromal cells ameliorated cyclosporin A-induced renal fibrosis in rats. *Int. J. Clin. Exp. Med.* **12**, 8943-8949 (2019).
20. Choi, H.Y., et al. Microparticles from kidney-derived mesenchymal stem cells act as carriers of proangiogenic signals and contribute to recovery from acute kidney injury. *PLoS One* **9**, e87853 (2014).
21. Ranghino, A., et al. The effects of glomerular and tubular renal progenitors and derived extracellular vesicles on recovery from acute kidney injury. *Stem Cell Res. Ther.* **8**, 24 (2017).
22. Kholia, S., et al. Human Liver Stem Cell-Derived Extracellular Vesicles Prevent Aristolochic Acid-Induced Kidney Fibrosis. *Front. Immunol.* **9**, 1639 (2018).
23. Eirin, A., et al. Mesenchymal stem cell-derived extracellular vesicles attenuate kidney inflammation. *Kidney Int.* **92**,114-124 (2017).
24. Song, T.R., et al. Mesenchymal stem cell-derived extracellular vesicles induce regulatory T cells to ameliorate chronic kidney injury. *Hypertension* **75**, 1223-1232 (2020).
25. De Almeida D.C., et al. A Regulatory miRNA-mRNA Network Is Associated with Tissue Repair Induced by Mesenchymal Stromal Cells in Acute Kidney Injury. *Front. Immunol.* **7**, 645 (2017).
26. Gao, F., Zuo, B., Wang, Y., Li, S., Yang, J. & Sun, D. Protective function of exosomes from adipose tissue-derived mesenchymal stem cells in acute kidney injury through SIRT1 pathway. *Life Sci.* **255**, 117719 (2020).

27. Lindoso, R.S., et al. Adipose Mesenchymal Cells-Derived EVs Alleviate DOCA-Salt-Induced Hypertension by Promoting Cardio-Renal Protection. *Mol. Ther. Methods Clin. Dev.* **16**, 63-77 (2019).
28. Jin, J., et al. Exosome secreted from adipose-derived stem cells attenuates diabetic nephropathy by promoting autophagy flux and inhibiting apoptosis in podocyte. *Stem Cell Res.* **10**, 95 (2019).
29. Duan, Y., et al. Adipose mesenchymal stem cell-derived extracellular vesicles containing microRNA-26a-5p target TLR4 and protect against diabetic nephropathy. *J. Biol. Chem.* **295**, 12868-12884 (2020).
30. Van Koppen, A., et al. Human embryonic mesenchymal stem cell-derived conditioned medium rescues kidney function in rats with established chronic kidney disease. *PLoS One* **7**, e38746 (2012).
31. Zhang, K., et al. In vivo two-photon microscopy reveals the contribution of Sox9+ cell to kidney regeneration in a mouse model with extracellular vesicle treatment. *J. Biol. Chem*. **295**, 12203-12213 (2020).
32. Cantaluppi, V., et al. Microvesicles derived from endothelial progenitor cells protect the kidney from ischemia-reperfusion injury by microRNA-dependent reprogramming of resident renal cells. *Kidney Int.* **82**, 412-427 (2012).
33. Cantaluppi, V., et al. Endothelial progenitor cell-derived extracellular vesicles protect from complement-mediated mesangial injury in experimental anti-Thy1.1 glomerulonephritis. *Nephrol. Dial. Transplant.* **30**, 410-422 (2015).
34. Burger, D., et al. Human Endothelial Colony-Forming Cells Protect against Acute Kidney Injury Role of Exosomes. *Am. J. Pathol.* **185**, 2309-2323 (2015).
35. Viñas, J.L., et al. Transfer of microRNA-486-5p from human endothelial colony forming cell-derived exosomes reduces ischemic kidney injury. *Kidney Int*. **90**, 1238-1250 (2016).

36. Viñas, JL., et al. Receptor-Ligand Interaction Mediates Targeting of Endothelial Colony Forming Cell-derived Exosomes to the Kidney after Ischemic Injury. *Sci. Rep.* **8**, 16320 (2018).
37. Yuan, X., et al. Extracellular vesicles from human-induced pluripotent stem cell-derived mesenchymal stromal cells (hiPSC-MSCs) protect against renal ischemia/reperfusion injury via delivering specificity protein (SP1) and transcriptional activating of sphingosine kinase 1 and inhibiting necroptosis. *Cell Death Dis.* **8**, 3200-3218 (2017).
38. Collino, F., et al. Extracellular Vesicles Derived from Induced Pluripotent Stem Cells Promote Renoprotection in Acute Kidney Injury Model. *Cells* **9**, 453 (2020).
39. Yu, L., et al. Embryonic stem cell-derived extracellular vesicles promote the recovery of kidney injury. *Stem Cell Res. Ther.* **12**, 379 (2021).
40. Dominguez, J.H., Liu, Y., Gao, H., Dominguez, J.M. 2nd., Xie, D. & Kelly, K.J. Renal Tubular Cell-Derived Extracellular Vesicles Accelerate the Recovery of Established Renal Ischemia Reperfusion Injury. *J. Am. Soc. Nephrol.* **28**, 3533-3544 (2017).
41. Grange, C., et al. Urinary Extracellular Vesicles Carrying Klotho Improve the Recovery of Renal Function in an Acute Tubular Injury Model. *Mol. Ther.* **28**, 490-502 (2020).
42. Jiang, Z.Z., et al. Exosomes secreted by human urine-derived stem cells could prevent kidney complications from type I diabetes in rats. *Stem Cell Res. Ther.* **7**, 24-37 (2016).