Supplementary Table 2. Signaling pathways involved in kidney transplantation

Signaling pathway	CAN	IRI	Rejection	Biomarkers
VEGF-A				
In vitro studies and animal model	↑ Correlated with CADI score [23]. Accelerates allograft vasculopathy [24,25]			
Human studies	↑ Effects are time-dependent. Protective in the short term after kTx, increase of IF over the long term [26]		↑ In chronic renal allograft rejection [22]	
ET-1				
In vitro studies and animal model		↑ TNF-α, TGF-β stimulate ET-1 production in cultured MC, ECs, GECs, and RTECs [37–42].	↑ TNF-α, TGF-β stimulate ET-1 production in cultured MC, ECs, GECs, and RTECs [37–42] ↑ ET-1, ET-3, and receptors in chronic renal allograft rejection [43]	
Human studies	↑ CAN is associated with a higher level of ET-1 in kTx [44]. Increase of ETAR in intrarenal arteries with transplant renal arteriosclerosis [45]			
ANGPTs				
In vitro studies and animal model	↓ ANGPT1, ↑ ANGPT2, and Tie2 have a strong correlation with the Banff score [58]		Tie2 agonistic peptide administration enhances graft function [59]	
Human studies	↑ ANGPT2 levels are correlated with all-cause mortality [57]			
CXCL12/CXCR4/CXCR7				
In vitro studies and animal model	↑ Potentiate renal allografts fibrosis, promoting EMT [64,65] CXCR4 antagonist attenuate renal allograft fibrosis advancement [66]	Anti-CXCL12 antibodies could reduce IRI injury [67]		
Human studies	↑ Promoting transplants fibrosis [64]			
IL-6				
In vitro studies and animal model	↑ Intragraft induces IF and TA [77] IL-6 produced by podocyte regulates SOCS3 expression in ECs and induces immunosuppressive effect [83]	↑ IL-6 trans-signaling protects renal function [82]	↑ Intragraft with decreased Foxp3+ Tregs [75] Inhibition of donor IL-6 prevents humoral and cellular rejection [76]	
			↑ In the blood, urine, and biopsy tissue. Recipients with high blood IL-6 and IL-17 experienced rejection [80]. Donor IL-6 and IL-6R genotypes are associated with rejection [81]	

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Supplementary Table 2. Continued

Signaling pathway	CAN	IRI	Rejection	Biomarkers
EVs				
In vitro studies and animal model		EVs from MSCs, hiPSC-MSCs, RTECs, and EPCs exert renoprotection [91–94]	EVs from the plasma of patients with AMR induce EndMT and TS. RNase-mediated digestion of EVs cargo abolishes those effects [90]	
Human studies				Profiling kidney donors' urinary EVs or donors' preservation fluid can evaluate donor kidney quality and post-kTx graft function [87–89]

AKI, acute kidney injury; AMR, antibody-mediated allograft rejection; ANGPT, angiopoietin; CADI, chronic allograft damage index; CAN, chronic allograft nephropathy; ECs, endothelial cells; EMT, epithelial-mesenchymal transition; EPCs, endothelial progenitor cells; ET-1, endothelin-1; ETAR, ETA receptors; EVs, extracellular vesicles; GECs, glomerular epithelial; hiPSC-MSCs, human-induced pluripotent stem cell-derived MSCs; IL, interleukin; IF, interstitial fibrosis; IRI, ischemia-reperfusion injury; kTx, kidney transplantation; MC, mesangial cells; MSCs, mesenchymal stem cells; RTECs, renal tubular epithelial cells; SOCS3, suppressor of cytokine signaling 3; TA, tubular atrophy; TNF-α, tumor necrosis factor-alpha; TS, tubular senescence; TGF-β, transforming growth factor beta; VEGF-A, vascular endothelial growth factor A.