SUPPLEMENTARY MATERIAL

Urinary EGF and MCP-1 and risk of CKD after cardiac surgery

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Supplemental Table 1. Baseline characteristics by post-operative urine MCP-1 tertiles

Variable (level, pg/ml)	All (N = 865)	Tertile 1 (4.7-143)	Tertile 2 (144-345)	Tertile 3 (346-11,683)
Age at the time of surgery	71.8 ± 9.0	71.5 ± 9.7	71.8 ± 8.2	72.1 ± 9.1
White race	837 (96.8)	280 (94.6)	293 (98.0)	264 (97.8)
Male sex	615 (71.1)	194 (65.5)	221 (73.9)	200 (74.1)
Diabetes	344 (39.8)	112 (37.8)	142 (47.5)	90 (33.3)
Hypertension	678 (78.4)	228 (77.0)	229 (76.6)	221 (81.9)
LVEF <35%	67 (7.7)	18 (6.1)	18 (6.0)	31 (11.5)
Previous myocardial infarction	216 (25.0)	55 (18.6)	94 (31.4)	67 (24.8)
Congestive heart failure	109 (12.6)	34 (11.5)	31 (10.4)	44 (16.3)
Mean pre-operative eGFR, mL/min/1.73m^2	69.5 ± 18.1	71.3 ± 16.6	69.7 ± 18.3	67.4 ± 19.3
CKD stage 3 or greater	263 (30.4)	81 (27.3%)	92 (30.8)	90 (33.3)
Mean pre-operative urine albumin/Cr ratio, mg/g	64.0 ± 187.2	43.5 ± 105.1	80.6 ± 249.7	67.9 ± 174.8
Perfusion time	108.1 ± 55.1	97.1 ± 41.9	99.6 ± 49.4	130.3 ± 67.0
Cross-clamp time	75.4 ± 42.5	70.2 ± 34.5	68.3 ± 39.6	89.5 ± 50.1
Surgery type				
- CABG and valve	189 (21.8)	56 (18.9)	53 (17.7)	80 (29.6)
- Other	9 (1.0)	2 (0.7)	2 (0.7)	5 (1.9)
- CABG only	432 (49.9)	153 (51.7)	175 (58.5)	104 (38.5)
- Valve only	235 (27.2)	85 (28.7)	69 (23.1)	81 (30.0)
Elective surgery	785 (90.8)	276 (93.2)	268 (89.6)	241 (89.3)

Data are presented as mean ± SD and frequency (%) for continuous and categorical variables, respectively

CABG = coronary artery bypass graft; CKD = chronic kidney disease; Cr = creatinine; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MCP-1 = major chemoattractant protein 1.

The number of patients per tertile: T1 n=296, T2 n=299, T3 n=270

Supplemental Table 2. CKD incidence or progression event rate		
Event	**n/N**	**Event Rate (per 1000 person-years)**
Composite CKD outcome overall	266/865	55.4 (49.2-62.5)
- CKD incidence	212/602	64.7 (56.6-74.1)
- CKD progression	54/263	35.4 (27.1-46.3)
Composite CKD outcome in those with AKI	105/271	73.9 (61.0-89.4)
Composite CKD outcome in those without AKI	161/594	47.7 (40.8-55.6)

AKI = acute kidney injury; CKD = chronic kidney disease.

Supplemental Table 3. Association of post-operative urine biomarker tertiles with risk of composite CKD outcome

Biomarker	Tertile	Adjusted HR for Urine Creatinine (95% CI)	Fully Adjusted* HR (95% CI)
Urine EGF (pg/mL)[‡]	Tertile 1 (83.5-417.8)	1.00 (referent)	1.00 (referent)
	Tertile 2 (420.5-1031)	0.84 (0.62-1.16)	0.91 (0.66-1.25)
	Tertile 3 (1033-19242)	0.59 (0.39-0.91) [†]	0.68 (0.43-1.07)
Urine MCP-1 (pg/mL)[‡]	Tertile 1 (4.7-143)	1.00 (referent)	1.00 (referent)
	Tertile 2 (144-345)	1.59 (1.15-1.22)[†]	1.46 (1.03-2.07)[†]
	Tertile 3 (346-11683)	1.68 (1.18-2.38)[†]	1.48 (0.99-2.22)
Urine EGF/MCP-1[‡]	Tertile 1 (0.01-1.77)	1.00 (referent)	1.00 (referent)
	Tertile 2 (1.78-5.42)	0.96 (0.72-1.26)	0.95 (0.70-1.29)
	Tertile 3 (5.44-108.73)	0.48 (0.34-0.67)[†]	0.50 (0.33-0.74)[†]

*Adjusted for age, sex, race, elective surgery, type of surgery, pre-operative eGFR, diabetes, hypertension, congestive heart failure, myocardial infarction, post-operative albuminuria, post-operative urine creatinine, AKI stage, cardiopulmonary bypass time, and study site

†: $P < 0.05$

‡: Log$_2$-transformed

Supplemental Table 4. Risk of composite CKD outcome by pre-operative urine biomarker level

Biomarker	Fully Adjusted* HR (95% CI)
Urine EGF (pg/mL)‡	0.99 (0.85-1.15)
Urine MCP-1 (pg/mL)‡	1.23 (1.10-1.38)†
Urine EGF/MCP-1‡	0.79 (0.71-0.89)†

*Adjusted for age, sex, race, elective surgery, type of surgery, pre-operative eGFR, diabetes, hypertension, congestive heart failure, myocardial infarction, pre-operative urinary albumin, pre-operative urinary creatinine, and study site

†: $P < 0.05$

‡: Log_2-transformed

Supplemental Table 5. Risk of CKD incidence or progression by post-operative urine biomarker level, adjusted for pre-operative level

Biomarker	**Fully Adjusted* HR (95% CI)**
Urine EGF (pg/mL)[‡]	0.84 (0.73-0.96)[†]
Urine MCP-1 (pg/mL)[‡]	1.08 (0.98-1.19)
Urine EGF/MCP-1[‡]	0.91 (0.83-0.99)[†]

* Adjusted for age, sex, race, elective surgery, type of surgery, pre-operative eGFR, diabetes, hypertension, congestive heart failure, myocardial infarction, post-operative albuminuria, post-operative urine creatinine, AKI stage, cardiopulmonary bypass time, and study site, and pre-operative biomarker level

†: $P < 0.05$

‡: Log$_2$-transformed

Supplemental Table 6. Basic clinical data of AKI patients included in the ScRNAseq analysis. Data derived from open access at KPMP.org

Tissue Type	Sex	Age (Years)	Race	KDIGO Stage	Baseline eGFR (ml/min/1.73m2)	Diabetes	Hypertension
AKI	Male	30-39	Black or African-American	Stage 2	90-99	Yes	Yes
AKI	Female	70-79	Black or African-American	Stage 2	70-79	Yes	Yes
AKI	Female	30-39	White	Stage 3	110-119	No	No
AKI	Male	40-49	Black or African-American	Stage 3	70-79	Yes	Yes
AKI	Male	50-59	Black or African-American	Stage 3	100-109	No	No
AKI	Male	30-39	Don't Know	Stage 2	120-129	No	No
AKI	Male	60-69	White	Stage 2	60-69	Yes	No
AKI	Male	70-79	White	Stage 3	70-79	Don't Know	No
AKI	Male	60-69	White	Stage 3	80-89	Yes	Yes
AKI	Male	60-69	White	Stage 3	70-79	No	Yes
AKI	Male	20-29	White	Stage 3	70-79	No	No
AKI	Female	60-69	White	Stage 3	50-59	Yes	No
AKI	Female	50-59	White	Stage 1	70-79	No	No
AKI	Male	20-29	Black or African-American	Stage 2	70-79	No	No

Supplemental Table 7. Top 20 canonical pathways (by P value enrichment) enriched in EGF co-regulated transcripts in DCT cells of patients with AKI. Pathways are only included when more than 3 molecules in the particular pathway are present in the signature. * denotes pathways that are also significantly enriched in the same analysis in TAL cells

Ingenuity Canonical Pathways	Molecules	P value	Z-score
Oxidative Phosphorylation*	MT-CO3,MT-ND1,MT-ND3,NDUFA13,NDUFA3,NDUFA7,NDUFB1	<0.001	-2.65
Mitochondrial Dysfunction*	BACE2,MT-CO3,MT-ND1,MT-ND3,NDUFA13,NDUFA3,NDUFA7,NDUFB1	<0.001	
ErbB Signaling	EGF,ERBB2,ERBB4,MAP2K6,PAK4,PIK3C2G	<0.001	-2.24
TR/RXR Activation*	ACACA,DIO2,NCOA4,PIK3C2G,THRA	0.001	
Sirtuin Signaling Pathway*	BCL2L11,GOT2,MT-ND1,MT-ND3,NDUFA13,NDUFA3,NDUFA7,NDUFB1,SCNN1A	0.002	2.83
PPARα/RXRα Activation*	ADIPOR1,GOT2,INSR,LPL,MAP2K6,PLCL1,STAT5B	0.002	-0.82
Telomerase Signaling	EGF,PIK3C2G,PPM1L,TERF2IP,TPP1	0.004	
Integrin Signaling	BCAR3,CAPN10,PAK4,PFN2,PIK3C2G,RHOQ,TSPAN7	0.004	-2.45
IL-15 Production	DSTYK,ERBB2,ERBB4,INSR,MAP2K6	0.006	-2.24
Insulin Secretion Signaling Pathway	GCGR,INSR,PIK3C2G,PLCL1,SCNN1A,STAT5B,VAMP2	0.009	-2.65
Semaphorin Neuronal Repulsive Signaling Pathway	ERBB2,MAP2K6,PAK4,PIK3C2G,SEMA6D	0.011	-0.45
Insulin Receptor Signaling	INSR,PIK3C2G,RHOQ,SCNN1A,VAMP2	0.011	-2.24
Senescence Pathway	CAPN10,MAP2K6,NF1,PHF1,PIK3C2G,PPM1L,RBL2	0.016	-1.13
FAK Signaling*	CAPN10,EGF,PAK4,PIK3C2G	0.017	
Neuregulin Signaling	EGF,ERBB2,ERBB4,STAT5B	0.018	-2.00
Sperm Motility	DSTYK,ERBB2,ERBB4,INSR,MAP2K6,PLCL1	0.020	
Pancreatic Adenocarcinoma Signaling	EGF,ERBB2,PIK3C2G,VEGFA	0.020	-2.00
Glioblastoma Multiforme Signaling	EGF,NF1,PIK3C2G,PLCL1,RHOQ	0.021	-2.00
Actin Cytoskeleton Signaling*	CYFIP2,EGF,KNG1,PAK4,PFN2,PIK3C2G	0.022	
LXR/RXR Activation	ACACA,HADH,KNG1,LPL	0.028	
Growth Hormone Signaling	IGFBP3,PIK3C2G,STAT5B	0.030	
Xenobiotic Metabolism CAR Signaling Pathway	ALDH5A1,ALDH6A1,HS6ST2,MAP2K6,PPM1L	0.035	-1.34
ILK Signaling	MAP2K6,PIK3C2G,PPM1L,RHOQ,VEGFA	0.035	-1.34
STAT3 Pathway	EGF,INSR,NDUFA13,VEGFA	0.040	-1.00
Axonal Guidance Signaling	EGF,ERBB2,NTN4,PAK4,PFN2,PIK3C2G,PLCL1,SEMA6D,VEGFA	0.047	

Supplemental Table 8. Top 20 canonical pathways (by *P* value enrichment) enriched in *CCL2* co-regulated transcripts in ATL cells of patients with AKI. Pathways are only included when more than 3 molecules in the particular pathway are present in the signature. * denotes pathways that are also significantly enriched in the same analysis in TAL cells

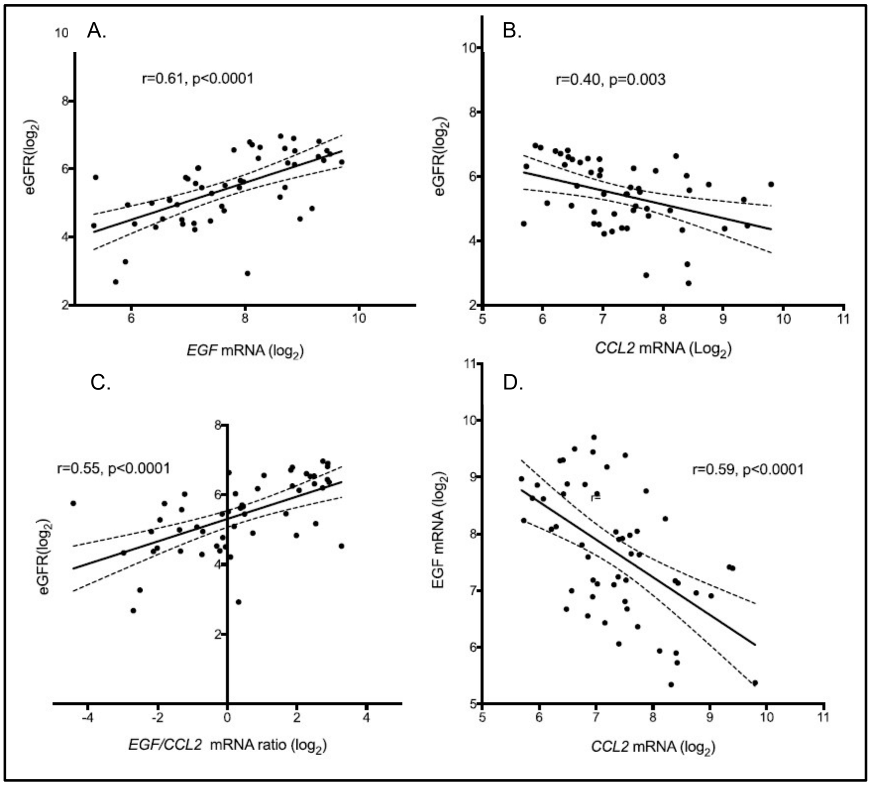
Ingenuity Canonical Pathways	Molecules	P value	Z-score
Hepatic Fibrosis Signaling Pathway	ATF4,CALM1 (includes others),CCL2,CCN2,CD40,CEBPB,CXCL8,EDN1,FGFR1,GNAI3,HIF1A,ICAM1,IKBKB,ITGA3,ITGAV,ITGB1,ITGB3,MYC,MYL12A,MYL12B,MYL6,MYL9,MYLK,NFKB2,NFKBIA,PDGFB,PRKCA,PRKCI,RAC1,RAP1B,RASD1,RHOB,RHOC,RHOG,RND3,RRAS2,SOD2,SPP1,STAT3,TGFB1	3.4E-09	5.284
EIF2 Signaling*	ACTB,ATF4,ATF5,EIF1,EIF2S2,EIF3A,EIF3G,EIF3J,EIF3M,EIF4A1,EIF4G1,EIF4G2,FAU,MYC,PABPC1,PPP1CA,PPP1CB,RAP1B,RASD1,RPL11,RPL12,RPL14,RPL18A,RPL19,RPL22,RPL22L1,RPL23,RPL24,RPL26,RPL27,RPL28,RPL29,RPL31,RPL32,RPL34,RPL35,RPL35A,RPL36,RPL36AL,RPL37,RPL38,RPL39,RPL41,RPL7,RPL7A,RPL8,RPLP0,RPLP1,RPLP2,RPS12,RPS13,RPS15,RPS15A,RPS16,RPS17,RPS18,RPS19,RPS21,RPS23,RPS24,RPS25,RPS26,RPS27A,RPS27L,RPS28,RPS7,RRAS2	1.3E-41	5.096
Integrin Signaling*	ACTB,ACTG1,ACTN1,ACTN4,ACTR3,ARF3,ARF4,ARF5,ARPC1B,ARPC2,ARPC3,ARPC4,ARPC5,ARPC5L,BCAR1,CAPNS1,CAV1,ILK,ITGA3,ITGAV,ITGB1,ITGB3,ITGB6,MYL12A,MYL12B,MYL9,MYLK,NEDD9,PDGFB,PFN1,PPP1CB,RAC1,RAP1B,RASD1,RHOB,RHOC,RHOG,RND3,RRAS2,VCL,ZYX	4.0E-18	5.096
Actin Cytoskeleton Signaling*	ACTB,ACTG1,ACTN1,ACTN4,ACTR3,ARPC1B,ARPC2,ARPC3,ARPC4,ARPC5,ARPC5L,BCAR1,BRK1,CFL1,DIAPH1,DIAPH3,FLNA,ITGA3,ITGAV,ITGB1,ITGB3,MSN,MYH9,MYL12A,MYL12B,MYL6,MYL9,MYLK,PDGFB,PFN1,PPP1CB,RAC1,RAP1B,RASD1,RRAS2,SLC9A1,TMSB10/TMSB4X,TRIO,VCL	1.6E-15	5.048
Signaling by Rho Family GTPases*	ACTB,ACTG1,ACTR3,ARPC1B,ARPC2,ARPC3,ARPC4,ARPC5,ARPC5L,CDC42EP1,CFL1,DIAPH3,GNAI3,GNB2,ITGA3,ITGAV,ITGB1,ITGB3,MSN,MYL12A,MYL12B,MYL6,MYL9,MYLK,NFKB2,PARD3,PRKCI,RAC1,RHOB,RHOC,RHOG,RND3,SLC9A1,STMN1,VIM	2.5E-11	4.536
Ephrin Receptor Signaling*	ACTR3,ARPC1B,ARPC2,ARPC3,ARPC4,ARPC5,ARPC5L,ATF4,BCAR1,CFL1,EFNA1,EFNB2,EPHA2,EPHB2,GNAI3,GNB2,ITGA3,ITGAV,ITGB1,ITGB3,PDGFB,PTPN11,RAC1,RAP1B,RASD1,RGS3,RRAS2,SDCBP,STAT3	1.1E-10	4.146
ILK Signaling*	ACTB,ACTG1,ACTN1,ACTN4,ATF4,CFL1,FLNA,HIF1A,ILK,IRS1,ITGB1,ITGB3,ITGB6,KRT18,MYC,MYH9,MYL6,MYL9,NFKB2,PPP1R14B,PPP2R5A,RAC1,RHOB,RHOC,RHOG,RND3,TMSB10/TMSB4X,VCL,VIM	1.3E-10	4.041
Actin Nucleation by ARP-WASP Complex*	ACTR3,ARPC1B,ARPC2,ARPC3,ARPC4,ARPC5,ARPC5L,ITGA3,ITGAV,ITGB1,ITGB3,RAC1,RAP1B,RASD1,RHOB,RHOC,RHOG,RND3,RRAS2	1.1E-10	4

Rac Signaling*	ACTR3,ARPC1B,ARPC2,ARPC3,ARPC4,ARPC5,ARPC5L,BRK1,CD44,CFL1,ITGA3,ITGAV,ITGB1,ITGB3,NFKB2,PARD3,PRKCI,RAC1,RAP1B,RASD1,RRAS2	4.4E-09	4
Regulation of Actin-based Motility by Rho*	ACTB,ACTR3,ARPC1B,ARPC2,ARPC3,ARPC4,ARPC5,ARPC5L,CFL1,ITGA3,ITGAV,ITGB1,ITGB3,MYL12A,MYL12B,MYL6,MYL9,MYLK,PFN1,PPP1CB,RAC1,RHOB,RHOC,RHOG,RND3	5.0E-14	3.838
mTOR Signaling*	EIF3A,EIF3G,EIF3J,EIF3M,EIF4A1,EIF4B,EIF4EBP1,EIF4G1,EIF4G2,FAU,FKBP1A,HIF1A,IRS1,PPP2R5A,PRKCA,PRKCI,RAC1,RAP1B,RASD1,RHEB,RHOB,RHOC,RHOG,RND3,RPS12,RPS13,RPS15,RPS15A,RPS16,RPS17,RPS18,RPS19,RPS21,RPS23,RPS24,RPS25,RPS26,RPS27A,RPS27L,RPS28,RPS7,RRAS2	4.0E-19	3.5
RhoA Signaling*	ACTB,ACTG1,ACTR3,ARPC1B,ARPC2,ARPC3,ARPC4,ARPC5,ARPC5L,CDC42EP1,CFL1,MSN,MYL12A,MYL12B,MYL6,MYL9,MYLK,PFN1,PPP1CB,RHPN2,RND3	5.9E-09	3.273
Remodeling of Epithelial Adherens Junctions*	ACTB,ACTG1,ACTN1,ACTN4,ACTR3,ARPC1B,ARPC2,ARPC3,ARPC4,ARPC5,ARPC5L,HGS,NME1,TUBA1A,TUBB,VCL,ZYX	3.6E-10	2.828
ERK/MAPK Signaling*	ATF4,BCAR1,DUSP1,EIF4EBP1,ELF3,ETS1,H3-3A/H3-3B,HSPB1,ITGA3,ITGAV,ITGB1,ITGB3,MYC,PPP1CA,PPP1CB,PPP1R14B,PPP2R5A,PRKCA,PRKCI,RAC1,RAP1B,RASD1,RRAS2,STAT1,STAT3,YWHAB,YWHAG,YWHAZ	2.5E-09	2.132
Regulation of eIF4 and p70S6K Signaling*	EIF1,EIF2S2,EIF3A,EIF3G,EIF3J,EIF3M,EIF4A1,EIF4EBP1,EIF4G1,EIF4G2,FAU,IRS1,ITGA3,ITGAV,ITGB1,ITGB3,PABPC1,PPP2R5A,RAP1B,RASD1,RPS12,RPS13,RPS15,RPS15A,RPS16,RPS17,RPS18,RPS19,RPS21,RPS23,RPS24,RPS25,RPS26,RPS27A,RPS27L,RPS28,RPS7,RRAS2	1.3E-19	1.633
Sirtuin Signaling Pathway*	ACLY,APEX1,BAX,CXCL8,EPAS1,GABARAP,GLS,H3-3A/H3-3B,HIF1A,MAP1LC3B,MYC,NAMPT,NDUFA2,NDUFA6,NDUFB3,NDUFB4,NDUFB6,NDUFS5,NDUFS6,NDUFS7,NDUFS8,NFKB2,PARP1,PGK1,POLR1D,POLR2F,SLC25A5,SLC2A1,SMARCA5,SOD2,STAT3,TIMM10,TIMM13,TIMM17A,TIMM8B,TUBA1A,VDAC1	1.0E-10	-1.4
Coronavirus Pathogenesis Pathway*	ATF4,BAX,CCL2,CXCL8,EEF1A1,FAU,IKBKB,KPNB1,NFKB2,NFKBIA,NPM1,PA2G4,RPS12,RPS13,RPS15,RPS15A,RPS16,RPS17,RPS18,RPS19,RPS21,RPS23,RPS24,RPS25,RPS26,RPS27A,RPS27L,RPS28,RPS7,STAT1,STAT3,TGFB1	1.0E-15	-3.053
RhoGDI Signaling*	ACTB,ACTG1,ACTR3,ARPC1B,ARPC2,ARPC3,ARPC4,ARPC5,ARPC5L,CD44,CFL1,GNAI3,GNB2,ITGA3,ITGAV,ITGB1,ITGB3,MSN,MYL12A,MYL12B,MYL6,MYL9,PRKCA,RAC1,RHOB,RHOC,RHOG,RND3	5.4E-10	-4.491
Epithelial Adherens Junction Signaling*	ACTB,ACTG1,ACTN1,ACTN4,ACTR3,ARPC1B,ARPC2,ARPC3,ARPC4,ARPC5,ARPC5L,FGFR1,MYH9,MYL6,MYL9,PARD3,RAC1,RAP1B,RASD1,RRAS2,TUBA1A,TUBB,VCL,ZYX	2.5E-09	
Mitochondrial Dysfunction*	COX17,COX6B1,COX7B,COX7C,CYCS,NDUFA2,NDUFA6,NDUFB3,NDUFB4,NDUFB6,NDUFS5,NDUFS6,NDUFS7,NDUFS8,OGDH,PARK7,PRDX3,PRDX5,PSENEN,SOD2,UQCR10,UQCRB,UQCRH,UQCRQ,VDAC1	5.9E-09	

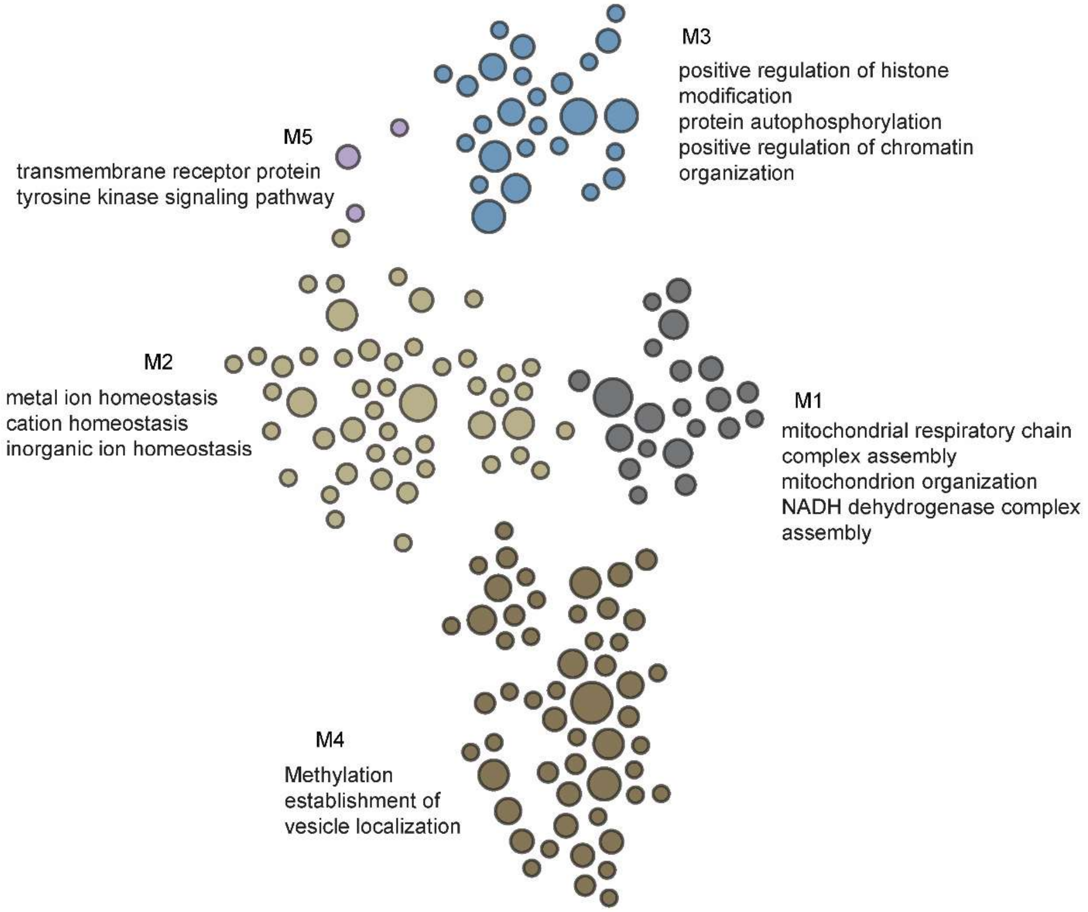
Supplemental Table 9. Common upstream regulators of *EGF* and *CCL2* coregulated transcripts in DCT and ATL cells

Upstream Transcriptional Regulators	Down-regulated Gene Signature in EGF$^-$ DCT Cells		Up-regulated Gene Signature in CCL2$^+$ ATL Cells	
	Activation Z-score	***P*-value of Overlap**	**Activation *Z*-score**	***P*-value of Overlap**
HIF1A	-1.89	0.0114	4.793	<0.0001
FOXO1	-2.18	0.0060	3.286	<0.0001
PPARGC1B	-2.21	0.0001	2.607	0.0017
SS18	-2.00	0.0004	2.236	0.0116
KDM5A	2.24	0.0090	-3.499	<0.0001
EZH2	2.20	0.0163	1.944	<0.0001

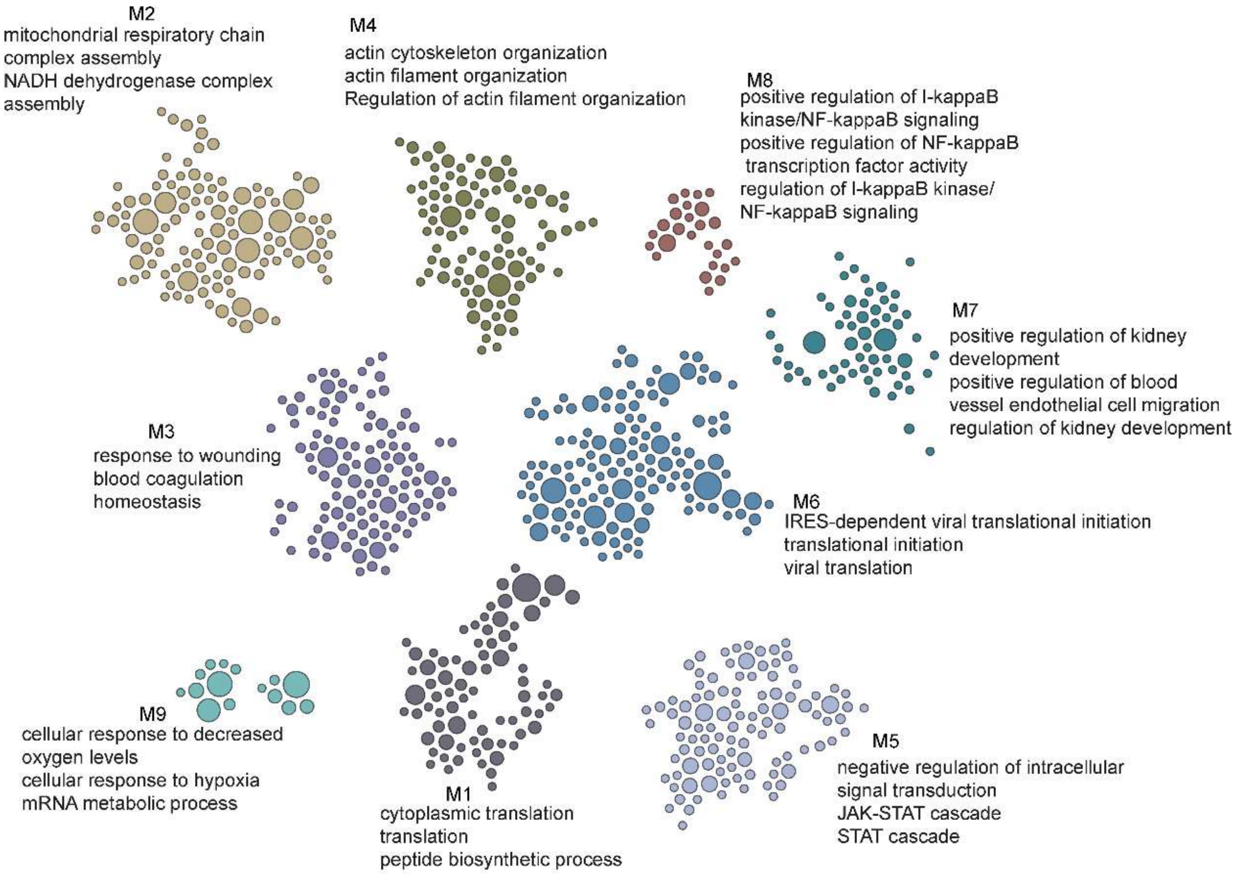
ATL = ascending thin loop of Henle; *CCL2* = gene encoding monocyte cheomoattractant protein-1 (MCP-1); DCT = distal convoluted tubule; EZH2 = Enhancer of zeste 2 polycomb repressive complex 2 subunit; FOXO1 = Forkhead box O1; HIF1A = Hypoxia-inducible factor 1 subunit alpha; KDM5A = Lysine Demethylase 5A; PPARGC1B = Peroxisome Proliferator Activated Receptor Gamma Coactivator 1 Beta; SS18 = SS18 Subunit Of BAF Chromatin Remodeling Complex.



Supplemental Figure 1. Association of *EGF* and *CCL2* mRNA levels in kidney tissue of patients with chronic kidney disease (diabetic kidney disease, hypertension-attributed kidney disease, and focal segmental glomerulosclerosis), and their correlation with eGFR. (A) *CCL2* = gene encoding monocyte chemoattractant protein-1 (MCP-1); *EGF* = epidermal growth factor; eGFR = estimated glomerular filtration rate.



Supplemental Figure 2. Functional summaries of repressed signatures in *EGF*$^-$ DCT cells in patients with AKI. Functional summary of repressed signature in *EGF*$^-$ DCT cells of patients with AKI – community clustering and enriched processes of the genes that are significantly down regulated in DCT cells that do not express *EGF* compared to *EGF*-expressing DCT cells. Each dot represents input gene, and the size of the dot indicates relative connectivity.



Supplemental Figure 3. Functional summaries of repressed signatures in *CCL2*⁺ ATL cells in patients with AKI. Functional summary of *CCL2*+ expression signature – community clustering and enriched processes of the genes that are significantly up-regulated in *CCL2*-expressing+ ATL cells compared to those that do not. NADH = nicotinamide adenine dinucleotide hydride; JAK-STAT= Janus kinase (JAK) - signal transducer and activator of transcription protein (STAT). Each dot represents input gene, and the size of the dot indicates relative connectivity.

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