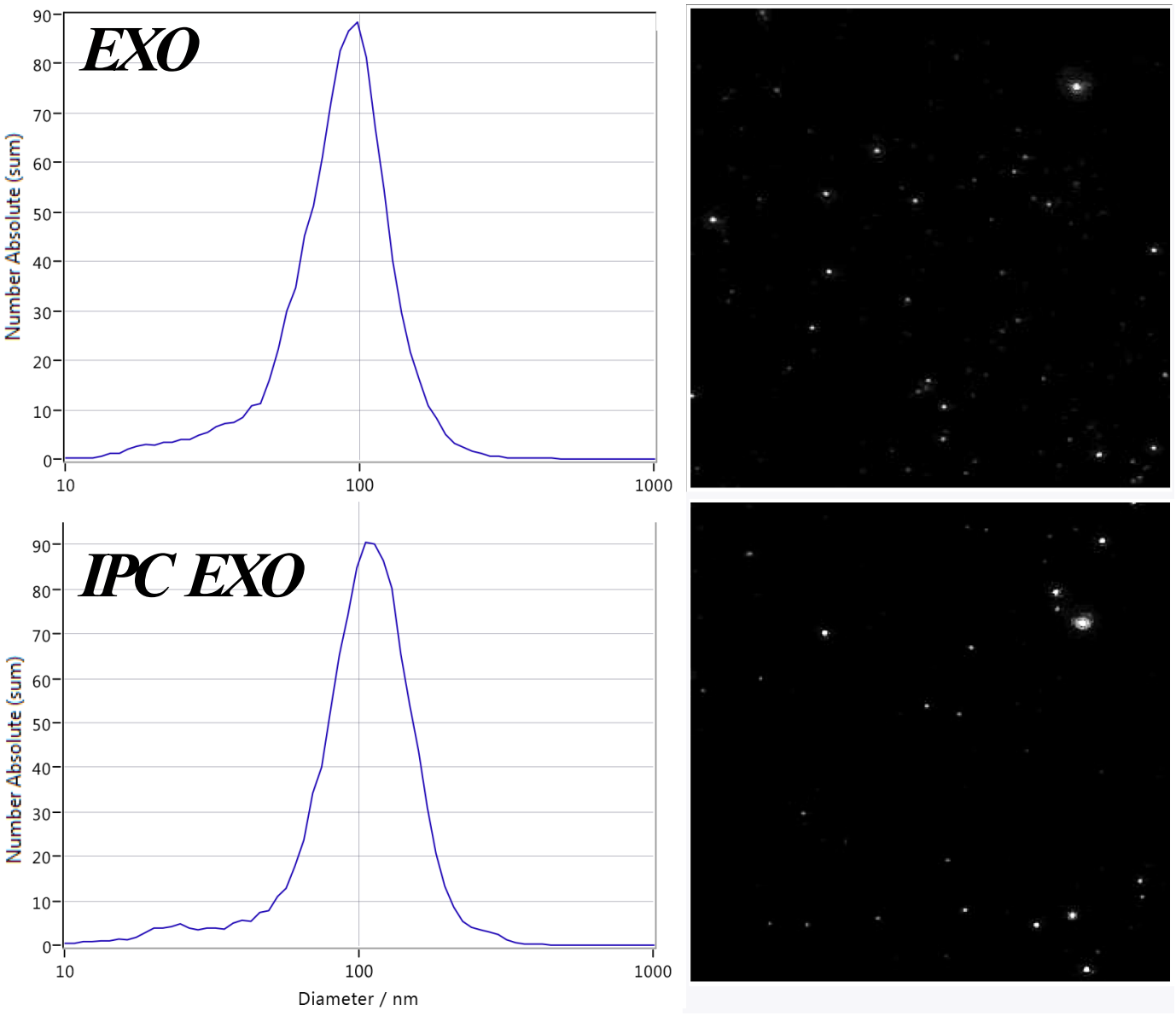


Figure 1S. Representative Nanotrack Plots and image of EV showing size distribution of EV.

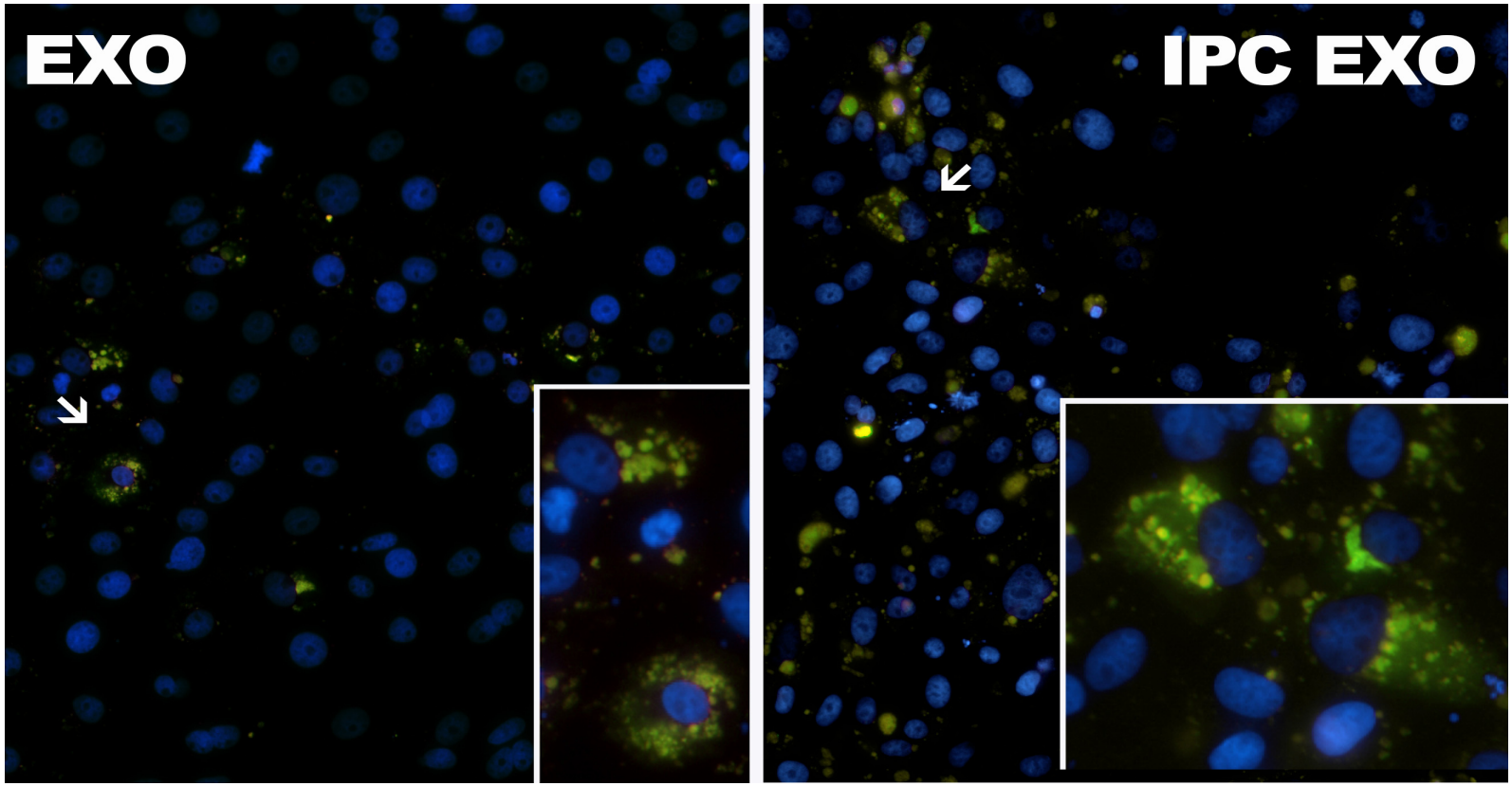


Figure 2S. Representative images of EV uptake by cultured renal tubular cells. EV, labeled with green exoglow, were rapidly taken up by cultured tubular cells exposed to Hoescht to label nuclei blue. Uptake of IPC EXO was greater than than of EXO ($p<0.05$). Insets show areas at arrows.

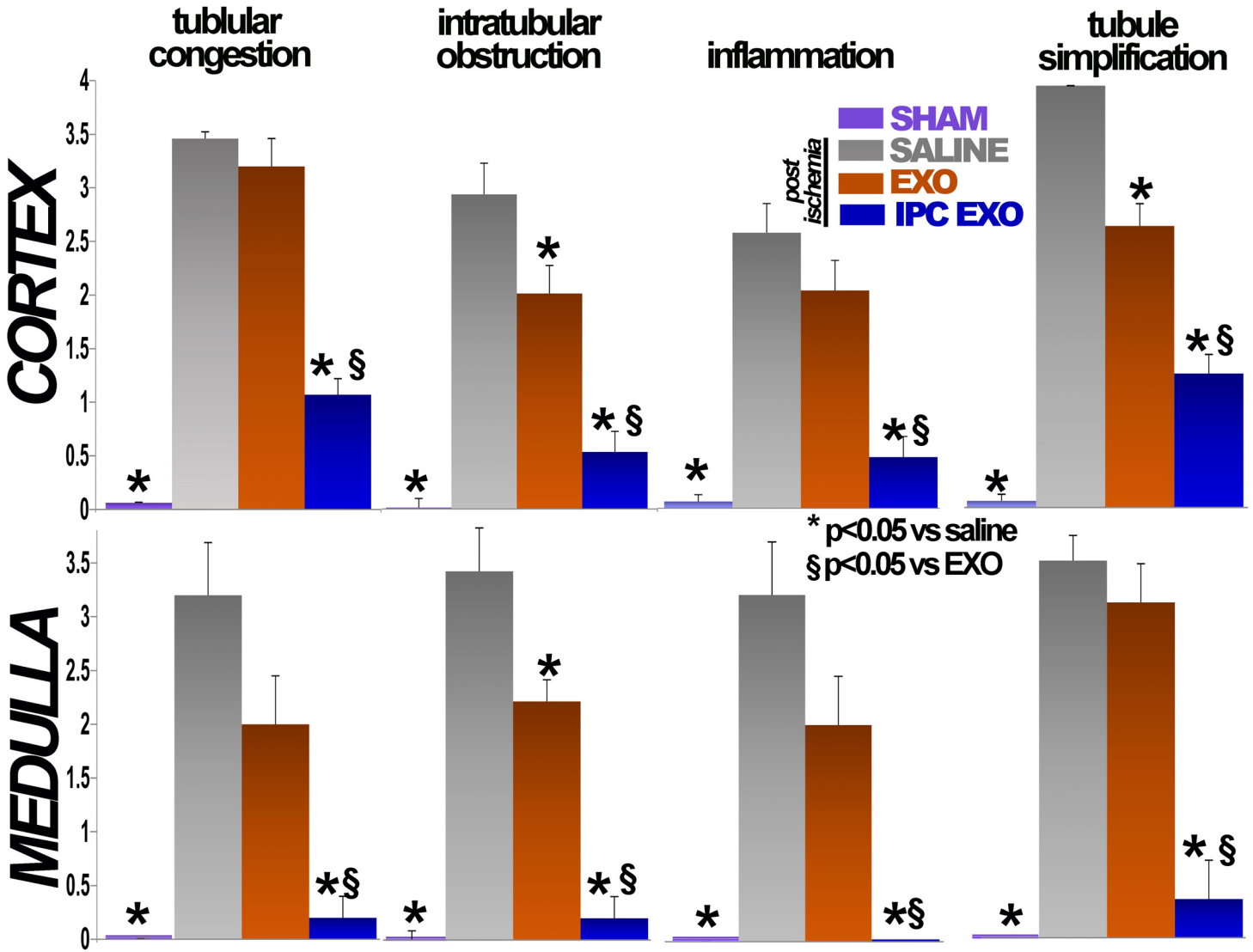


Figure 3S. Quantification of Histological Injury. Tubular congestion, intratubular obstruction (casts), inflammation and tubule simplification in blinded sections of cortex and medulla were graded on the follow scale: 0=none; 1+ = <10%, 2+ = 10-25%, 3+ = 26-75%, 4+ = >75%.

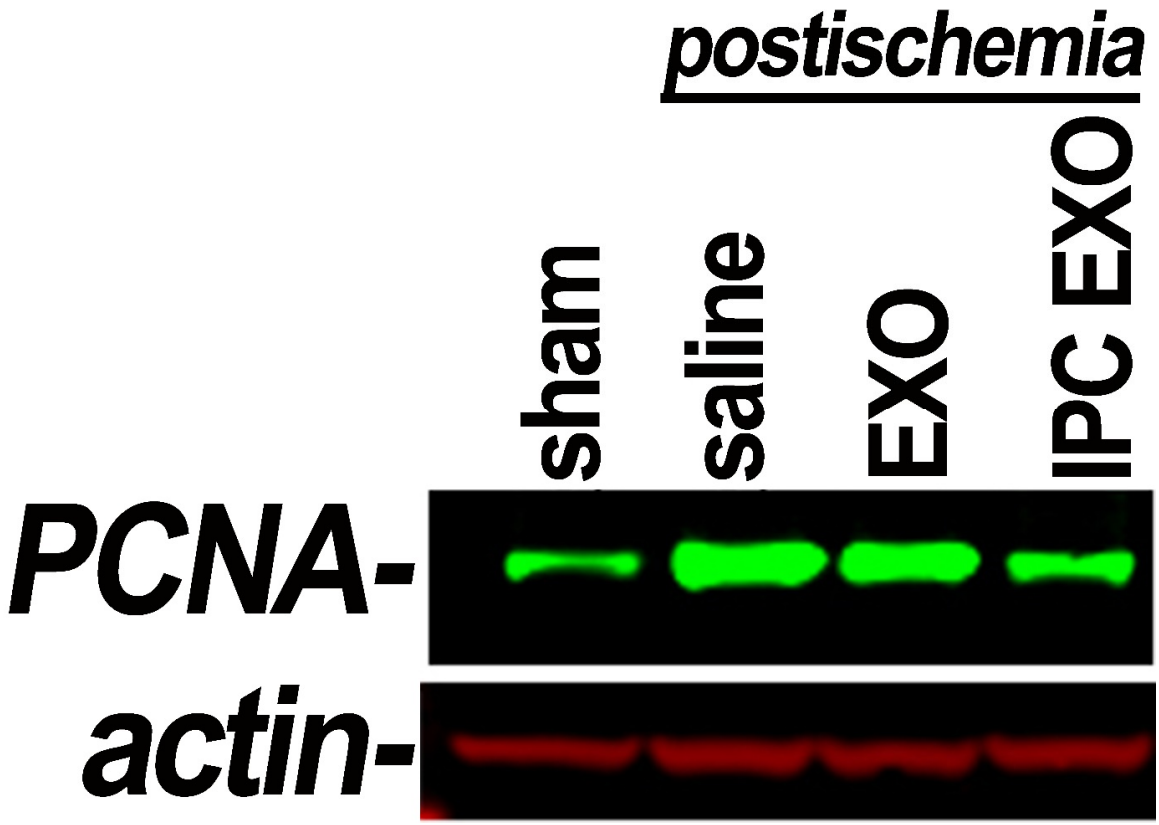
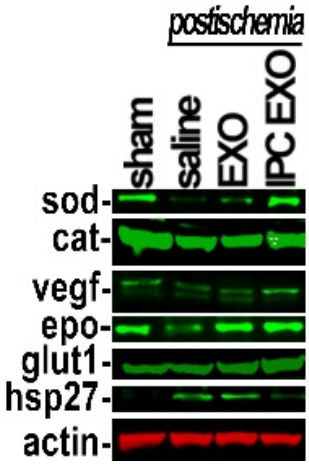


Figure 4S. Representative western blot of proliferative cell nuclear antigen (PCNA) protein levels in the four groups of rats (green), n = 2 blots: sham control, untreated ischemic (saline), ischemic treated with normoxic exosomes (exo) and ischemic treated with IPC exosomes (IPC exo). The corresponding actin levels are also included (red).



fold change

	Saline	EXO	IPC EXO
sod	0.25±0.06	0.52±0.13	0.84±0.15
cat	0.53±0.05	0.65±0.06	0.88±0.03
vegf	0.45±0.11	0.80±0.08	0.95±0.07
epo	0.54±0.11	0.73±0.15	0.88±0.25
glut1	0.45±0.11	0.63±0.08	0.81±0.14
hsp27	4.47±0.74	3.36±0.31	2.34±0.16

Figure 5S. Left, representative western blot of proteins suppressed by ischemia and partly supported by treatment with normoxic exosomes (exo) and IPC exosomes (IPC exo), n = 5: superoxide dismutase 1 (SOD, sham vs saline and IPC exo vs saline, $p < 0.05$); catalase (CAT, sham vs saline and IPC exo vs saline, $p < 0.05$); vascular endothelial growth factor (VEGF, IPC exo vs saline, $p < 0.01$); erythropoietin (EPO, sham vs saline and IPC exo vs saline, $p < 0.05$); glucose transporter 1 (GLUT1 or Slc2a1, sham vs saline and IPC exo vs saline, $p < 0.05$). In ischemia, heat shock protein 27 (hsp27) was increased ($P<0.05$), IPC exo limited its activation ($p<0.05$). Protein levels were all normalized for actin levels (red).

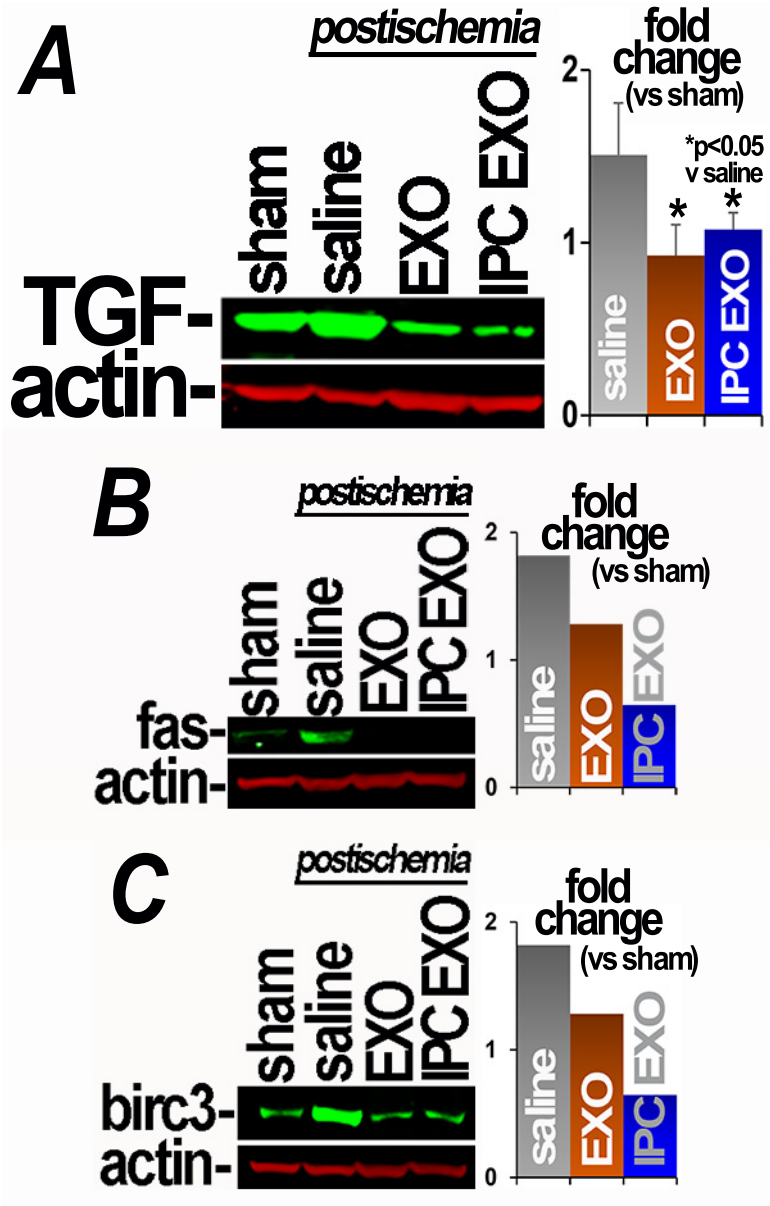
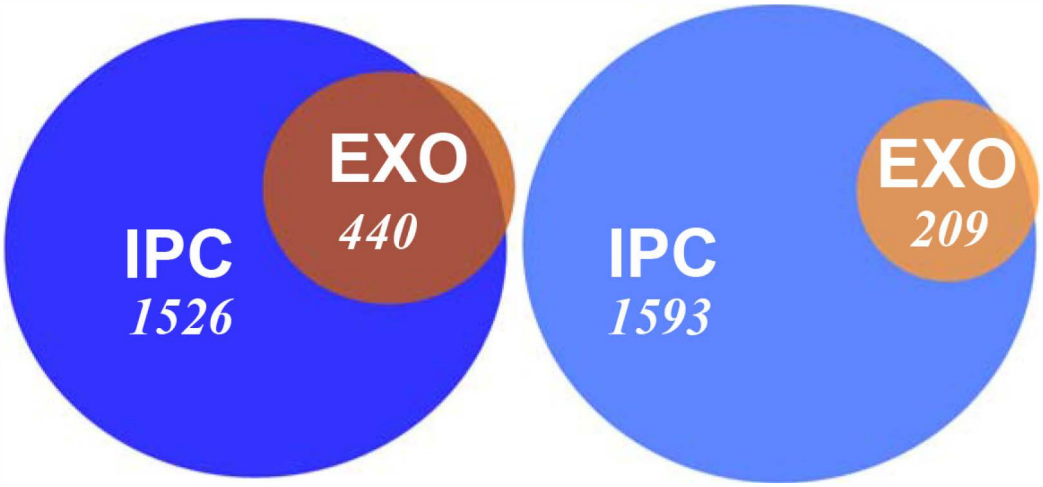


Figure 6S. Representative western blots: A, transforming growth factor (TGF); B, pro-apoptotic fas; and C, anti-apoptotic birc3 protein levels in four groups of rat kidneys (green): sham control, untreated postischemic (saline), postischemic treated with normoxic EV (EXO) and postischemic treated with IPC EV (IPC EV). The graphs shows the fold change in mean TGF/actin (n=3), fas/actin (n=2) and birc3/actin (n=2) band density as compared to sham.



Kegg pathway

Metabolic p=2.79e15

GO analysis

Transporter activity p=1.02e10

Number of transcripts	
Anti-apoptotic	39
Anti-inflammatory	29
Pro-vasculature	8
Anti-fibrosis	12

Figure 7S. Many transcripts were altered in untreated renal ischemia: either suppressed (left) or activated (right). IPC EXO treatment significantly restored 1526 suppressed genes, and significantly restored 1593 activated genes. Whereas EXO restored 440 suppressed genes and restored 209 activated genes ($p<0.05$ for all treatment groups with respect to untreated ischemia). Most genes restored by EXO overlapped the genes restored by IPC. The most significantly altered Kegg pathway was metabolic. The table categorizes 89 restored transcripts in both IPC EXO and EXO in potentially beneficial systems.

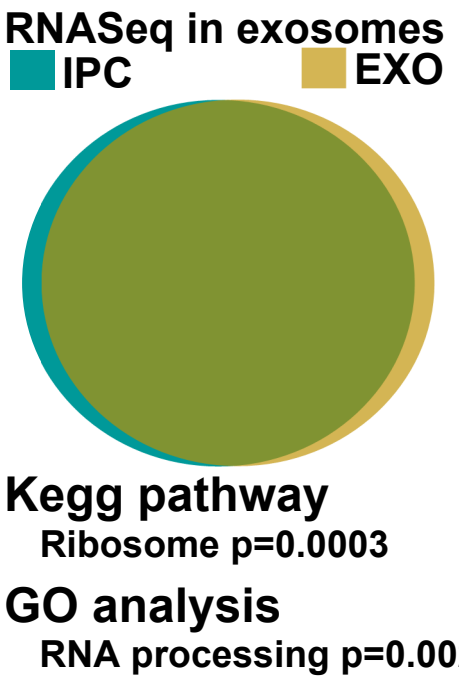


Figure 8S. RNA Seq in EV showed 24 differentially expressed transcripts between IPC and neutral EXO with the most altered pathway being the ribosome.

	heat inactivated EXO group	P value v saline	P value v EXO
24 h creatinine (mg/dl)	2.2±0.1	NS	NS
48 h creatinine (mg/dl)	1.62±0.3	NS	0.07
Weight (mg/300g body wt)	2.6±0.2	NS	<0.05
fraction damaged tubules	0.72±0.04	<0.05	<0.05
PMN/hpf	5.1±0.9	<0.05	<0.05
C3 pixel density	65±2.4	NS	<0.05
Fibrosis (% area)	0.19±0.001	NS	<0.05
Microvascular density	0.86±0.05	NS	NS

C, control RNA
S, size standard
H, heated IPC EXO RNA

Table 1S. Heat-inactivated EV are not protective. The table shows multiple parameters in postischemic rats that had been treated with heated EV at 24 and 48 hours postischemia. Although protein levels were not significantly different between control and heated EV, RNA was not found in EV after heat inactivation (right).

	NS v SHAM	EXO v SHAM	IPC V SHAM	IPC v NS
Pathway	**p value**	**p value**	**p value**	**p value**
Metabolic Pathways	9.47 e-92	2.75 e-35	---	1.39 e-41
Proliferation*	1.16 e -29	4.66 e-18	---	3.59 e-16
Focal adhesion	8.97 e-25	1.31 e-16	0.0029	3.51 e-09
Filtrate absorption#	5.83 e-21	8.32 e-15	0.0002	7.61 e-12
Cell cycle	3.88 e-20	1.20 e-16	---	8.18 e-17
ECM-receptor interaction	1.14 e-17	3.55 e-12	5.08 e-06	1.34 e-07
Oxidative phosphorylation	1.08 e-16	---	---	0.0155
Glutathione metabolism	1.74 e-14	---	---	2.28 e-08
Phagosome	1.99 e-14	1.76 e-10	---	2.42 e-11
Apoptosis	2.27 e-10	1.47 e-05	---	2.42 e-06
Cytokine-cytokine R interaction	5.74 e-14	8.15 e-11	---	1.33 e -09
DNA replication	2.67 e-07	--	---	1.48 e-08

In Kegg classification, pathway listed as cancer (*) protein digestion and absorption (#)

Table 2S. Differentially expressed Kegg pathways in untreated and EXO and EXO IPC treated renal ischemia. Data include the entire set of transcriptomes in the four groups of rats

gene	*fold change*	*P value*
Lrrc56	16.19684	3.26E-07
Drd4	78.49808	6.06E-06
Ptdss2	8.283269	2.55E-05
Phrf1	3.93936	0.0004027
Rn28s	0.270428	0.0005771
Rn45s	0.296246	0.0009219
Eps8l2	4.501065	0.0014974
Tmem80	10.53305	0.0022572
Ugt2b1	3.238392	0.002616
Ugt2b10	3.238402	0.002628
Mir3574	20.63152	0.0027636
Ddx39b	0.39594	0.0043904
Fau	0.689794	0.0055902
Rps6	2.338801	0.0061934
Rps13	1.380476	0.0085318
LOC102549726	0.307007	0.0151298
Rassf7	2.915573	0.0208718
Minos1	0.507992	0.0217366
Anxa1	1.300553	0.0255786
LOC100911483	0.411889	0.027246
Pfn1	0.68795	0.0275072
Mtap	0.233285	0.0393567
Clic1	0.629333	0.04683
Rnh1	0.512802	0.0486232
Tubb5	0.682995	0.0508805
Cox7a2l	1.670835	0.0540679
Eif3m	1.372874	0.0651085
Fam129b	0.774576	0.0735416
Ltb	0.29788	0.0866235
Atp6v1g2	0.29779	0.0877447
RT1-CE10	0.24278	0.0929345
Rps8	1.254032	0.0933281
Rps15a	0.754515	0.0955748
Eif3k	1.920594	0.1102808
Rpl17	1.272594	0.112006
Cd63	0.648305	0.112629
RT1-CE2	0.331922	0.1185701
Dynll1	0.650672	0.1206252
Ddt	0.503037	0.1212101
Cfdp1	1.415932	0.1224761
Atp5g3	0.693078	0.1231189
Rpl27	1.237502	0.1236026

Taldo1	1.604253	0.1238283
Rps3a	1.237234	0.1290179
Nrep	0.47773	0.1314657
Rbm3	1.341765	0.1332759
RT1-CE12	0.37312	0.1364004
Ube2s	0.610861	0.1428263
Pabpc1	1.257365	0.1488621
Rps24	0.821989	0.1493474
Cd24	1.250384	0.1529263
Psmb1	1.461866	0.153649
RT1-CE1	0.390259	0.1550898
Rpl30	1.303759	0.1646442
Ppp1ca	1.424261	0.1678137
Hnrnpa2b1	0.748745	0.175859
Hnrnpa1	1.245239	0.1778314
Skp1	1.304902	0.1832875
Pla2g16	1.719821	0.184658
Atp5b	0.8284	0.1946005
Eef2	0.822913	0.2015693
Rpsa	1.197804	0.2037134
Txn1	0.686598	0.2058584
Hsp90aa1	1.212961	0.2105127
Atp5g2	0.739137	0.2166733
Fkbp1a	0.806462	0.2166977
Atp6v1g1	0.743283	0.2295635
Fmr1	1.744195	0.2407201
Uqcr10	1.955778	0.242598
Akr1a1	0.846383	0.2449587
Cox7a2	0.756662	0.2480775
Rpl37	0.784878	0.2525435
Slc25a5	1.376195	0.2621689
S100a10	1.148694	0.2640821
Rps26	1.284187	0.2652901
Rps21	1.209257	0.2665313
Rpl24	1.153315	0.2680652
Eif3h	0.802052	0.2687002
Calm1	1.190372	0.2707449
Rps11	1.167072	0.2709647
Npm1	1.203589	0.2722887
Eif5a	0.856515	0.2767545
Eefsec	2.007712	0.2782998
Ccl2	0.703501	0.2837439
Rps20	0.834438	0.2862785
Gstp1	1.18054	0.295941

S100a11	0.856361	0.2967193
Anp32a	1.169359	0.2984425
Ncl	1.179824	0.3067983
Eif1	0.844571	0.3098891
Gabarap	1.229229	0.3104298
RT1-CE5	0.643873	0.3191237
Psma7	1.311407	0.3191301
Cox7c	1.314293	0.3209647
Tpm4	0.864358	0.3211267
Psmb4	0.838391	0.3238268
Hspa1b	0.764356	0.3257658
Gpx4	0.76898	0.3302108
Rps27a	1.16923	0.332307
Rplp1	1.157418	0.3365376
Oaz1	1.141339	0.3366418
Rpl31	1.16545	0.3380286
Sumo2	1.299053	0.3381638
Naca	0.885164	0.3398111
Irf7	0.413371	0.342284
Nap1l1	1.146845	0.3453079
Taf15	1.241188	0.3522772
Ptma	1.135475	0.3567916
Bex1	0.773795	0.3580473
Ap2m1	0.812035	0.3606806
Pgam1	0.818519	0.361135
Atp6v0c	0.769529	0.3666519
Tagln2	1.162377	0.3720678
Phf5a	0.684477	0.3747457
Btf3	1.144621	0.3779764
Rps23	1.117397	0.3789969
Cdc42se1	0.806276	0.3790978
Tceb2	0.781878	0.3807514
Rpl35a	0.825949	0.3985928
RT1-CE7	0.594312	0.4030576
Clta	0.845074	0.4047845
RT1-CE11	0.597632	0.4049716
LOC688869	0.787394	0.4211151
Rpl10a	0.893571	0.4272844
Ran	1.12744	0.427463
Cox5a	1.206173	0.4297347
Rpl29	1.12809	0.4352454
Myl12b	0.876199	0.4396517
Eif3g	0.825507	0.4412582
Ubxn1	1.143078	0.4422194

Pkm	0.837445	0.4492772
Rps25	1.131239	0.4495111
Ftl1	1.125947	0.4502224
Arpc3	1.231225	0.453335
Krt8	0.876578	0.4565726
Rpl5	1.124749	0.4582947
Cox4i1	0.84107	0.4584987
Eif2s1	0.817872	0.4587609
Rps18	1.102073	0.4589225
Tuba1c	0.885939	0.4617327
Mir1843b	0.513414	0.4633045
S100a6	1.239133	0.4651814
Tagln	0.845279	0.4759817
Mllt11	0.570966	0.480076
Gnb2l1	1.10397	0.4843559
Rps15	1.126447	0.4862987
Hint1	1.245795	0.4926176
Anxa5	0.872895	0.4939825
Slc25a4	1.164717	0.5028693
Rpl14	1.09488	0.5078502
RGD1560212	0.752566	0.5094949
Ywhae	0.844116	0.5124516
Hsp90ab1	1.09692	0.5128616
Rpl39	1.131763	0.5147275
Bc1	1.225677	0.5155934
Arpc2	0.881537	0.5170883
Nedd8	0.837991	0.5177774
Ost4	1.207691	0.5218714
Rps10	0.906872	0.5263327
Vamp8	0.668615	0.5275603
Sema6c	0.879467	0.5326785
Atp5h	0.800661	0.5533324
Net1	0.918908	0.556796
Setdb1	0.626909	0.5582528
Prr13	0.821144	0.5591506
Rpl22	1.130581	0.5647353
Ppia	1.087658	0.5656269
Actb	0.921363	0.5685723
Atp5g1	0.774983	0.5693493
Aldoa	0.926856	0.5742425
Gpx1	1.159759	0.5765184
Atpif1	1.197276	0.577025
Rpl26	1.079297	0.5790565
Dynlrb1	0.856332	0.5803291

Ubb	1.080049	0.5831251
Atp5i	0.823757	0.5832494
Rps7	1.074743	0.5854094
Rpl18a	0.918343	0.5869659
Rpl34	0.922835	0.587038
Mrpl17	1.19489	0.5889211
Hras	1.215426	0.5905863
Anxa2	0.927109	0.5943318
Gas5	0.761059	0.596497
Rpl19	0.921853	0.5974182
Ybx1	1.071817	0.598626
Ybx1-ps3	1.071805	0.5988658
Rpl36	0.918713	0.6059161
Mir186	1.490943	0.6061228
Rpl22l1	0.887405	0.607431
Gapdh	1.07394	0.6119164
Rpl18	0.936493	0.6121435
Mir7a-1	1.527482	0.6184054
Mgp	1.370084	0.6196138
Arpc1b	0.925357	0.6203871
Tpi1	1.094767	0.6272966
Fth1	1.087925	0.631166
Kif1c	0.937281	0.6403018
Rpl23	1.068558	0.6450173
Cdc37	0.907195	0.6451968
Cers2	0.903562	0.6490774
Prdx6	0.867922	0.6551477
Pebp1	0.903556	0.6553389
Atp5e	1.128412	0.6586591
Nsa2	1.124802	0.6593335
Deaf1	1.51687	0.6597719
Rps4x	0.936393	0.6661336
LOC689574	1.209821	0.6700299
Snrpd2	0.872997	0.6705857
Rpl10	0.942869	0.6768858
Atp5l	1.120157	0.6807349
Tuba4a	1.147543	0.6847105
Eef1a1	1.060202	0.6908095
Rpl7	1.06568	0.7003146
Apol9a	1.305528	0.7003316
Tnf	0.793562	0.7084428
Glrx3	1.079026	0.7093485
Rplp0	0.948217	0.7100793
Rpl35	1.08981	0.7117531

Spp1	1.087624	0.7177463
Rpl13	1.050367	0.7199709
Kctd10	1.049838	0.7221687
RT1-CE6	0.739749	0.7294701
Nme2	0.940854	0.7322649
Anp32b	1.06156	0.7323684
H2afz	0.922357	0.7332644
Atp5j	0.881965	0.7339682
Prdx2	1.052526	0.7448864
Ndufv3	1.168331	0.7453687
Actg1	0.952824	0.7459469
Rpl36al	0.912745	0.7519278
Pgk1	0.934738	0.7566777
Rpl37a-ps1	0.912298	0.7594105
Rpl21	0.950298	0.7597947
Rpl38	0.919155	0.7605254
Cox6c	0.921217	0.7606448
Lgals3	0.931137	0.7637967
Tpt1	1.046282	0.7694822
Csnk2b	1.089492	0.7708616
Calr	0.9617	0.7708902
Mir207	0.775739	0.7719874
Rps14	0.962285	0.7727725
Lta	0.835344	0.7737796
Rpl4	1.042309	0.7792766
Mir3064	1.240944	0.7817236
Rps12	1.035005	0.782746
Rpl32	1.036145	0.7861538
Mif	0.929525	0.7877495
Arpp19	0.849313	0.7889673
Cox7b	1.069265	0.8013971
Uba52	0.96798	0.8103173
Dstn	1.034023	0.8111642
Rpl41	0.964556	0.8118491
Gpx2	0.938774	0.8130104
Sat1	1.04026	0.8149929
Cfl1	0.974649	0.8201299
Myeov2	0.902782	0.8250237
Rps27	1.04381	0.8271308
Cdc42	1.037834	0.8358183
Tp53inp2	1.026886	0.8376532
Fxyd2	1.084099	0.8381056
Rpl6	0.973352	0.8382874
Coa3	1.07556	0.8384823

Chmp3	0.953033	0.8406023
Ccng1	0.968435	0.8428834
Atp5d	1.061233	0.8514214
Myl12a	1.023074	0.8532691
Atp5o	0.954268	0.8703125
Ndufa1	1.108824	0.8724803
Eno1	0.978673	0.8755616
Pmepa1	1.047201	0.876194
Tuba1a	0.974824	0.877689
Rps3	1.022198	0.8797707
RT1-CE3	1.122018	0.8829357
Rpl28	0.983611	0.8904055
Ndufb4	0.928273	0.8907963
Tomm20	1.036334	0.8942282
Tmsb4x	0.97827	0.8987523
Rpl3	1.01825	0.8990121
Ivns1abp	0.961778	0.9011038
Psmb7	1.029249	0.9038833
Tuba1b	0.98305	0.9061238
Mt2A	0.958631	0.9063594
Mir3583	1.096327	0.9178901
Rpl13a	0.984344	0.9241297
Snrpg	1.026437	0.9304076
Rpl9	0.98469	0.9334294
Prdx1	0.987126	0.9345581
Tmsb10	1.012851	0.9426112
Rpl23a	0.990667	0.9453443
Hspa8	0.991364	0.9453964
LOC252890	0.965323	0.9485038
Rps5	1.007585	0.9507977
Rps29	1.009315	0.9566838
Rps2	0.991934	0.9594823
Eef1g	0.993331	0.960309
Eif4a1	1.008239	0.9609216
Nfkbil1	0.974439	0.962564
Psma2	1.015447	0.9669022
Rps17	0.995146	0.9777611
Fam63a	1.005073	0.9827277
Tomm7	1.008497	0.983385
Prelid1	1.004061	0.9879881
Tpm1	0.997898	0.9890512
Tbca	0.99672	0.9916308
Cox17	1.004673	0.9931595
Rab13	1.001251	0.9948289

Ldha	0.999074	0.9953579
Rpl12	1.000357	0.997858
Uqcr11	0.99946	0.998225
Wbp5	0.999652	0.9988384
Psma6	0.999706	0.9988979
Rps28	0.999894	0.9995591

Table 3S. RNASeq in IPC and normoxic exosomes: fold change of IPC exosomes/ normoxic exosomes and p-values are presented.