Supplementary Table 1. GO biological functions of transcripts modulated in EV- and MSC-CTRL in respect to –Dsh samples. Genes commonly modulated in EV-CTRL and MSC-CTRL in respect to -Dsh were analyzed. Genes with log2 (FC) ≥ 1 and log2(FC) ≤ -1 were respectively considered as up- or down-regulated.

down -CTRL vs -Dsh				
Term	**Count**	**%**	**PValue**	**Genes**
ECM-receptor interaction	10	9,52	2,66E-09	TNC, COL3A1, COL1A2, ITGB4, COL1A1, THBS1, THBS2, COL5A2, COL5A1, FN1
Focal adhesion	11	10,48	5,06E-07	TNC, COL3A1, COL1A2, ITGB4, COL1A1, THBS1, FLNC, THBS2, COL5A2, COL5A1, FN1
Complement and coagulation cascades	3	2,86	9,17E-02	C3AR1, C5AR1, F13A1
up -CTRL vs -Dsh				
Term	**Count**	**%**	**PValue**	**Genes**
Butanoate metabolism	6	0,35	1,19E-04	ACSM2, ACSM1, OXCT1, ABAT, AACS, ACSM5
Glycine, serine and threonine metabolism	5	0,29	8,11E-04	ALAS2, DMGDH, AGXT2, GNMT, CBS
Tryptophan metabolism	5	0,29	1,90E-03	AADAT, HAAO, ACMSD, KMO, INMT
Alanine, aspartate and glutamate metabolism	4	0,23	7,27E-03	ASS1, ACY3, ABAT, AGXT2
Primary bile acid biosynthesis	3	0,18	1,67E-02	CYP7B1, AMACR, AKR1D1
Drug metabolism	5	0,29	1,78E-02	FMO5, FMO2, CYP2A5, CYP2E1, CYP2A4
Complement and coagulation cascades	5	0,29	1,78E-02	C8A, F13B, SERPINF2, SERPINA1D, SERPINC1
Valine, leucine and isoleucine degradation	4	0,23	2,33E-02	ALDH6A1, IVD, OXCT1, ABAT
Drug metabolism	4	0,23	2,61E-02	UPB1, CYP2A5, UPP2, CYP2A4
Lysine biosynthesis	2	0,12	2,67E-02	AADAT, AASS
beta-Alanine metabolism	3	0,18	3,45E-02	CNDP1, UPB1, ABAT
Tyrosine metabolism	4	1,28	5,22E-02	HGD, GSTZ1, HPD, FAH
Steroid hormone biosynthesis	4	1,28	7,39E-02	HSD3B2, CYP7B1, AKR1C18, AKR1D1
Selenoamino acid metabolism	3	0,96	8,85E-02	CTH, GGT1, CBS

Supplementary Table 2. List of the miRNA couples expressed in EV-CTRL and showing a significant statistical correlation with the down-regulated RNA targets in EV-CTRL versus AKI samples. miRNAs expressed in EV-CTRL were clustered into families, according to their seed sequence, and scanned the 3'-UTR of AKI-expressed genes for perfect seed-match occurrences (6-8mers). Genes predicted to be a target of at least two miRNA family were considered (*p<0.05,* Hypergeometric distribution).

SEED1	SEED2	Observed	Expected	P value	mirna_seed1	mirna_seed2
AGACGG	GGGUCU	32	796	0,015	hsa-miR-483-5p	hsa-miR-193a-5p
AACGGA	GGCUCA	31	776	0,018	hsa-miR-191	hsa-miR-24
AGACGG	CAGUGC	37	972	0,021	hsa-miR-483-5p	hsa-miR-148b hsa-miR-148a
AGGAGC	GAGGGG	100	3076	0,021	hsa-miR-28	hsa-miR-423-5p
GAGGGG	GAGUUG	65	1900	0,024	hsa-miR-423-5p	hsa-miR-571
AGACGG	GGUAGA	27	684	0,030	hsa-miR-483-5p	mmu-miR-379
GAGGGG	GGGUCU	81	2470	0,031	hsa-miR-423-5p	hsa-miR-193a-5p
GCGGGG	GGUAGA	26	665	0,036	hsa-miR-744	mmu-miR-379
AGACGG	UCCUUG	33	889	0,037	hsa-miR-483-5p	hsa-miR-502
GAGUUG	GGGUCU	55	1614	0,039	hsa-miR-571	hsa-miR-193a-5p
AGACGG	AGGUAG	29	766	0,040	hsa-miR-483-5p	hsa-miR-196b
AACGGA	GGGUCU	25	647	0,044	hsa-miR-191	hsa-miR-193a-5p
ACCCGU	UGUGCG	9	175	0,047	hsa-miR-99a	hsa-miR-210
AGCCCU	GAGGGG	93	2942	0,048	mmu-miR-129-3p	hsa-miR-423-5p
GAGGGG	GCGGGG	44	1273	0,05	hsa-miR-423-5p	hsa-miR-744

Supplementary Table 3. GO biological functions of predicted targets of miRNA-EVs. Genes down-regulated in EV-CTRL (log2 (FC) ≤ -1, EV-CTRL vs AKI), but not in EV-Dsh treatment in respect to AKI were analyzed. The list of predicted targets was established using as background all genes on the whole Refseq annotation and predicted to be a target of at least two miRNAs.

Term	Count	%	PValue	Genes
ECM-receptor interaction	8	4,848485	0,000	SDC1, ITGA5, ITGB4, COL6A1, THBS1, THBS2, COL5A1, FN1
Dilated cardiomyopathy	6	3,636364	0,003	DES, ADCY7, ITGA5, TGFB3, ITGB4, TPM2
Focal adhesion	8	4,848485	0,004	RAC2, ITGA5, ITGB4, COL6A1, THBS1, THBS2, COL5A1, FN1
Hypertrophic cardiomyopathy (HCM)	5	3,030303	0,011	DES, ITGA5, TGFB3, ITGB4, TPM2
Wnt signaling pathway	6	3,636364	0,019	WNT4, NKD1, NKD2, RAC2, NFATC4, FZD2
p53 signaling pathway	4	2,424242	0,035	SERPINE1, RPRM, SFN, THBS1
Chemokine signaling pathway	6	3,636364	0,041	CCR5, CXCL14, RAC2, ADCY7, CCL9, CCL4
Cytokine-cytokine receptor interaction	7	4,242424	0,041	CCR5, CXCL14, CSF2RB2, TGFB3, CCL9, CCL4, TNFSF8
Complement and coagulation cascades	4	2,424242	0,043	C1QA, C5AR1, SERPINE1, F7
Pathways in cancer	8	4,848485	0,050	WNT4, RAC2, TGFB3, FGF11, BIRC5, FZD2, RUNX1, FN1