

Table S1. Viability% of the control and hypoxia treated cells measured by trypan blue dye exclusion test (Mean \pm SD values are shown with n=4 biological replicates).

Samples	Viability (mean \pm SD)
HL1 control	94.24 \pm 1.91
HL1 hypoxia	94.20 \pm 1.38
H9c2 control	94.56 \pm 2.42
H9c2 hypoxia	93.31 \pm 3.88
AC16 control	87.33 \pm 6.98
AC16 hypoxia	82.92 \pm 6.11

Table S2. Viability% of cells with serum starvation compared with differentiated control cells measured by Resazurin Cell Viability Assay. (Mean \pm SD values are shown with n=3 biological replicates).

Samples	Viability (mean \pm SD)
HL1	94.65 \pm 0.50
H9c2	92.84 \pm 1.99
AC16	102.39 \pm 2.17

Table S3. Antibodies used in our experiments.

Antibody	Manufacturer	Cat.No.	Clone
rabbit polyclonal anti-CD63 (C-terminal)	Sigma/Merck	SAB2109138	
mouse monoclonal anti-CD63	SantaCruz Biotechnology	MX-49.129.5	sc-5275
rabbit polyclonal anti-CD81	Sigma/Merck	SAB3500454	
mouse monoclonal anti-CD81	ThermoFisher	MA5-13548	1.3.3.22
rabbit polyclonal anti-TSG101	Sigma/Merck	HPA006161	
rabbit polyclonal anti-ALIX (C-terminal)	Sigma/Merck	SAB420047	
rabbit polyclonal anti-grp94 (C-terminal)	Sigma/Merck	G4420	
rabbit polyclonal anti-actin N terminal	Sigma/Merck	A2103	
goat-polyclonal anti-PDIA2	Sigma/Merck	SAB2501845	
goat anti-rabbit IgG-ATTO550	Sigma/Merck	43328	
goat anti-rabbit IgG ATTO488	Sigma/Merck	18772	
goat anti-mouse IgG CF488	Sigma/Merck	62197	
goat polyclonal anti-rabbit IgG Fc (HRP)	abcam	ab97200	
goat polyclonal anti-rabbit IgG H&L 10 nm gold pre-adsorbed	abcam	ab27234	
goat polyclonal anti-mouse IgG (whole molecule) 5 nm gold pre-adsorbed	Sigma/Merck	G7527	
donkey polyclonal anti-goat IgG (H+L) cross-adsorbed antibody Alexa Fluor 568	Invitrogen	A-11057	

Table S4. Protein/lipid ratio of H9c2 and AC16 cardiomyocyte-derived mEV and sEV fractions. (Mean \pm SD values are shown with n=3 biological replicates). EVs released under control and hypoxic conditions, within the same size and origin, do not differ significantly (unpaired student t-tests, $p>0,05$).

Samples	P/L ratio (mean \pm SD)
H9c2 mEV control	2.55 \pm 0.05
H9c2 mEV hypoxia	1.49 \pm 0.94
H9c2 sEV control	0.84 \pm 0.09
H9c2 sEV hypoxia	0.81 \pm 0.04
AC16 mEV control	1.57 \pm 0.32
AC16 mEV hypoxia	1.98 \pm 0.59
AC16 sEV control	4.9 \pm 1.19
AC16 sEV hypoxia	5.33 \pm 0.18

Table S5. ER resident proteins in EV, based on Vesiclepedia database

ER resident proteins												
ENPL (grp94/gp96/hsp90b1)		grp78 (hspa5, BiP, MIF2)		calnexin (CNX, IP90, P90)		calreticulin (CRT, RO, SSA, cC1qR)		grp170 (Hyou-1)		Erp29 (PDI-Db, PDIA9, ErP28)		
Sample source	Sample type	Sample source	Sample type	Sample source	Sample type	Sample source	Sample type	Sample source	Sample type	Sample source	Sample type	
Homo sapiens	brain cancer cells	EV (mEV+sEV)	brain cancer cells	EV (mEV+sEV)	brain cancer cells	EV (mEV+sEV)	brain cancer cells	EV (mEV+sEV)	brain cancer cells	EV (mEV+sEV)	brain cancer cells	EV (mEV+sEV)
	breast cancer cells	EV (mEV+sEV)	breast cancer cells	EV (mEV+sEV)	breast cancer cells	EV (mEV+sEV)	breast cancer cells	EV (mEV+sEV)	breast cancer cells	EV (mEV+sEV)	breast cancer cells	EV (mEV+sEV)
	bladder cancer cells	EV (mEV+sEV), EVs (sEV)	bladder cancer cells	EV (mEV+sEV), EVs (sEV)	bladder cancer cells	EV (mEV+sEV), EVs (sEV)	bladder cancer cells	EVs (sEV)	bladder cancer cells	EV (mEV+sEV), EVs (sEV)	bladder cancer cells	EV (mEV+sEV), EVs (sEV)
	colorectal cancer cells (CRC)	EV (mEV+sEV), mEV, exosomes (sEV)	colorectal cancer cells (CRC)	EV (mEV+sEV), mEV, exosome (sEV)	colorectal cancer cells (CRC)	EV (mEV+sEV), mEV, exosome (sEV)	colorectal cancer cells (CRC)	EV (mEV+sEV), mEV, exosomes (sEV)	colorectal cancer cells (CRC)	EV (mEV+sEV), mEV, exosomes (sEV)	colorectal cancer cells (CRC)	EV (mEV+sEV), mEV, exosomes (sEV)
	kidney cancer cells	EV (mEV+sEV),	kidney cancer cells	EV (mEV+sEV),	kidney cancer cells	EV (mEV+sEV),	kidney cancer cells	EV (mEV+sEV),	kidney cancer cells	EV (mEV+sEV),	kidney cancer cells	EV (mEV+sEV),
	lung cancer cells	EV (mEV+sEV),	lung cancer cells	EV (mEV+sEV),	lung cancer cells	EV (mEV+sEV),	lung cancer cells	EV (mEV+sEV),	lung cancer cells	EV (mEV+sEV),	lung cancer cells	EV (mEV+sEV),
	melanoma cells	EV (mEV+sEV), sEV	melanoma cells	EV (mEV+sEV), sEV	melanoma cells	EV (mEV+sEV), sEV	melanoma cells	EV (mEV+sEV)	melanoma cells	EV (mEV+sEV), sEV	melanoma cells	EV (mEV+sEV), sEV
	ovarian cancer cells	EV (mEV+sEV), exosomes (sEV)	ovarian cancer cells	exosomes (sEV)	ovarian cancer cells	(mEV+sEV), exosomes (sEV)	ovarian cancer cells	EV (mEV+sEV), exosomes (sEV)	ovarian cancer cells	EV (mEV+sEV), exosomes (sEV)	ovarian cancer cells	EV (mEV+sEV), exosomes (sEV)

prostate cancer cells	exosomes (sEV) EV	prostate cancer cells	exosomes (sEV) EV	prostate cancer cells	exosomes (sEV) EV	prostate cancer cells	exosomes (sEV) EV	prostate cancer cells	exosomes (sEV) EV	prostate cancer cells	exosomes (sEV) EV
leukemia cells	(mEV+sEV), exosomes (sEV), mEV, exosomes (sEV)	leukemia cells	(mEV+sEV), exosomes (sEV), mEV, exosomes (sEV)	leukemia cells	(mEV+sEV), exosomes (sEV), mEV, exosomes (sEV)	leukemia cells	EV (mEV+sEV)	leukemia cells	(mEV+sEV), exosomes (sEV), mEV, exosomes (sEV)	leukemia cells	EV (mEV+sEV), exosomes (sEV)
glioblastoma cells	mEV, exosomes (sEV)	glioblastoma cells	mEV, exosomes (sEV)	glioblastoma cells	mEV, exosomes (sEV)	glioblastoma cells	mEV, exosomes (sEV)	glioblastoma cells	mEV, exosomes (sEV)	glioblastoma cells	mEV, exosomes (sEV)
neuroblastoma cell	exosome	neuroblastoma cell	exosome	neuroblastoma cell	exosome	neuroblastoma cell	exosome	neuroblastoma cell	exosome	squamous carcinoma cells	exosomes (sEV)
astrocytoma cells	EV (mEV+sEV)	medulloblastoma cells	exosome (sEV)	astrocytoma cells	EV (mEV+sEV)	astrocytoma cells	EV (mEV+sEV)	astrocytoma cells	EV (mEV+sEV)	astrocytoma cells	EV (mEV+sEV)
B-cells	exosomes (sEV),sEV	squamous carcinoma cells	exosomes (sEV),	B-cells	sEV	T-cells	mEV, exosomes (sEV)	B-cells	exosomes (sEV)	T-cells	exosomes (sEV)
T-cells	mEV, exosomes (sEV)	osteosarcoma cells	matrix vesicles (sEV)	T-cells	mEV, exosomes (sEV)	dendritic cells (THP-1 monocyte derived)	EV (sEV, mEV)	T-cells	mEV, exosomes (sEV)	dendritic cells (THP-1 monocyte derived)	EV (sEV, mEV)
dendritic cells (THP-1 monocyte derived)	EV (sEV, mEV)	astrocytoma cells	EV (mEV+sEV)	dendritic cells (THP-1 monocyte derived)	EV (sEV, mEV)	neutrophil granulocytes	microparticles (sEV+mEV)	dendritic cells (THP-1 monocyte derived)	EV (sEV, mEV)	neutrophil granulocytes	microparticles (sEV+mEV)
neutrophil granulocytes	microparticles (sEV+mEV)	B-cells	exosomes (sEV),sEV	neutrophil granulocytes	microparticles (sEV+mEV)	Monocytes (THP-1)	microparticles (mEV)	neutrophil granulocytes	microparticles (sEV+mEV)	monocytes (THP-1)	microparticles (mEV)
endothelial cells	microparticles (mEV+sEV), mEV	T-cells	mEV, exosomes (sEV)	endothelial cells	EV(sEV), microparticles (mEV+sEV), mEV	Macrophages (U937)	exosomes (sEV)	Monocytes (THP-1)	microparticles (mEV)	endothelial cells	microparticles (mEV+sEV), mEV
platelets	microparticles (mEV+sEV)	dendritic cells (THP-1 monocyte derived)	EV (sEV, mEV)	platelets	microparticles (mEV+sEV)	endothelial cells	microparticles (mEV+sEV), mEV	endothelial cells	microparticles (mEV+sEV), mEV	platelets	microparticles (mEV+sEV)

bronchial epithelial cells	EV (sEV)	neutrophil granulocytes	microparticles (sEV+mEV)	retinal pigment epithelial cells	exosomes (sEV)	platelets	microparticles (mEV+sEV)	platelets	microparticles (mEV+sEV)	umbilical cord mesenchymal stem cells	mEV
retinal pigment epithelial cells	exosomes (sEV)	Monocytes (THP-1)	microparticles (mEV)	prostate epithelial cells	exosomes (sEV)	bronchial epithelial cells	EV (sEV)	bronchial epithelial cells	EV (sEV)	neonatal myoblast cells	mEV and exosomes (sEV)
prostate epithelial cells	exosomes (sEV)	endothelial cells	EV(sEV), microparticles (mEV+sEV), mEV	embryonic kidney cells	exosomes (sEV)	retinal pigment epithelial cells	exosomes (sEV)	retinal pigment epithelial cells	exosomes (sEV)	thymus (human derived thymic tissue)	exosomes (sEV)
urothelial cells	EV (sEV)	platelets	microparticles (mEV+sEV)	umbilical cord mesenchymal stem cells	mEV	prostate epithelial cells	exosomes (sEV)	urothelial cells	EV (sEV)	malignant pleural effusion (non-small lung cancer patient derived)	exosomes microvesicles ectosomes microparticles (mEV+sEV)
renal proximal tubule cells	exosomes	bronchial epithelial cells	EV (sEV)	mesenchymal stem cells	mEV, exosomes (sEV)	keratinocytes	exosomes (sEV)	neonatal myoblast cells	mEV and exosomes (sEV)	carotid atherosclerotic plaque	microparticles (mEV)
keratinocytes	exosomes (sEV)	retinal pigment epithelial cells	exosomes (sEV)	neonatal myoblast cells	mEV and exosomes (sEV)	embryonic kidney cells	exosomes (sEV)	thymus (human derived thymic tissue)	exosomes (sEV)	plasma	microparticles (sEV+mEV)
embryonic kidney cells	exosomes (sEV)	prostate epithelial cells	exosomes (sEV)	thymus (human derived thymic tissue)	exosomes (sEV)	umbilical cord mesenchymal stem cells	mEV	plasma	microparticles (sEV+mEV),	urine	exosomes (sEV)
umbilical cord mesenchymal stem cells	mEV	urothelial cells	EV (sEV)	carotid atherosclerotic plaque	microparticles (mEV)	placental mesenchymal stem cells	exosomes (sEV)	urine	exosomes (sEV)	breast milk	exosomes (sEV)
placental mesenchymal stem cells	exosomes (sEV)	embryonic kidney cells	exosomes (sEV)	plasma	microparticles (sEV+mEV),	mesenchymal stem cells	mEV, exosomes (sEV)	saliva	exosomes (sEV)		
mesenchymal stem cells	mEV, exosomes (sEV)	umbilical cord mesenchymal stem cells	mEV	urine	exosomes (sEV)	neonatal myoblast cells	mEV and exosomes (sEV)	breast milk	EV (sEV)		

neonatal myoblast cells	mEV and exosomes (sEV)	placental mesenchymal stem cells	exosomes (sEV)	breast milk	exosomes (sEV)	thymic TEC cells)	exosomes (sEV)
thymic TEC cells	exosomes (sEV)	mesenchymal stem cells	mEV, exosomes (sEV)			thymus (human derived thymic tissue)	exosomes (sEV)
thymus (human derived thymic tissue)	exosomes (sEV)	neonatal myoblast cells	mEV and exosomes (sEV)			malignant pleural effusion (non-small lung cancer patient derived)	exosomes microvesicles ectosomes microparticles (mEV+sEV)
malignant pleural effusion (non-small lung cancer patient derived)	exosomes/microvesicles/ectosomes/microparticles (mEV+sEV)	thymic TEC cells)	exosomes (sEV)			plasma	microparticles (sEV+mEV)
carotid atherosclerotic plaque	microparticles (mEV)	thymus (human derived thymic tissue)	exosomes (sEV)			serum (TBC patient)	exosomes (sEV)
		malignant pleural effusion (non-small lung cancer patient derived)	exosomes/microvesicles/ectosomes/microparticles (mEV+sEV)			urine	exosomes (sEV)
plasma	microparticles (sEV+mEV)	carotid atherosclerotic plaque	microparticles (mEV)			saliva	exosomes (sEV)
urine	exosomes (sEV)		microparticles (sEV+mEV), exosomes (sEV)			breast milk	exosomes (sEV)
saliva	exosomes (sEV)	plasma					

seminal plasma	exosomes (sEV)	urine	exosomes (sEV)
ascytes (CRC patient derived)	exosomes (sEV)	saliva	exosomes (sEV)
breast milk	EV (sEV)	seminal plasma	exosomes (sEV), prostasomes (mEV+sEV)
		breast milk	EV (sEV)

Mus
musculus

breast cancer cells	exosome (sEV)s	breast cancer cells	exosome (sEV)s	breast cancer cells	exosome (sEV)s	brain cancer cells	exosomes (sEV)	breast cancer cells	exosome (sEV)s	breast cancer cells	exosome (sEV)s
melanoma cells	EV (mEV + sEV)	melanoma cells	EV (mEV + sEV)	melanoma cells	EV (mEV + sEV)	breast cancer cells	exosome (sEV)	melanoma cells	EV (mEV + sEV)	melanoma cells	EV (mEV + sEV)
T-cells	exosome (sEV)	T-cells	exosome (sEV)	fibroblasts	exosomes (sEV)	melanoma cells	EV (mEV + sEV)	fibroblasts	exosomes (sEV)	embryonic fibroblasts	EV (mEV+sEV)
mast cells	exosome (sEV)	mast cells	exosome (sEV)	embryonic fibroblasts	exosomes (sEV), EV (mEV+sEV)	embryonic fibroblasts	(mEV+sEV)	embryonic fibroblasts	exosomes (sEV), EV (mEV+sEV)	pancreatic β -cells	exosomes (sEV)
myeloid derived suppressor cells	exosome (mEV+sEV)	myeloid derived suppressor cells	exosome (mEV+sEV)	pancreatic β -cells	exosomes (sEV)	pancreatic β -cells	exosomes (sEV)	myeloid derived suppressor cells	exosome (mEV+sEV)		
osteoblasts	sEV	osteoblasts	sEV	thymus	mEV						
fibroblasts	exosomes (sEV)	fibroblasts	exosomes (sEV)								

embryonic fibroblasts	exosomes (sEV), EV (mEV+sEV)	murine myoblasts	exosomes (sEV)
thymus	mEV	murine myotubes	exosomes (sEV)
		embryonic fibroblasts	EV (mEV+sEV)
		oligodendrocytes	exosomes (sEV)
		pancreatic β -cells	exosomes (sEV)
		thymus	mEV

Rattus norvegicus

insulinoma cell line	microparticles (mEV)	insulinoma cell line	microparticles (mEV)	insulinoma cell line	microparticles (mEV)	hepatocytes	exosomes (sEV)	NA	NA	NA	NA
reticulocytes	exosomes (sEV)	hepatocytes	exosomes (sEV)	hepatocytes	exosomes (sEV)	reticulocytes	exosomes (sEV)				
		retinal glial cells	exosomes (sEV)	reticulocytes	exosomes (sEV)						
		reticulocytes	exosomes (sEV)	plasma	microparticles (sEV)						
		plasma	microparticles (sEV)	pancreatic adenocarcinoma cells	exosomes (sEV)						
