Supplemental Information

Extracellular Vesicle and Particle Biomarkers

Define Multiple Human Cancers

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 Table S1. Related to Figure 1. Patient information for surgically resected tissue samples and plasma samples.

Tissue samples

Cancer type	sample size (% male)	average age (yr)	stage (%)
Lung adenocarcinoma	18 (33.3)	63.6 (23-88)	I(38.9); II(27.8); III(11.1); IV(22.2)
Pancreatic ductal adenocarcinoma	21 (66.7)	68.9 (51-83)	I(4.8); II(71.4); III(23.8)
Neuroblastoma	9 (36.4)	10.7 (2-35)	IV(100)
Osteosarcoma	7 (57.1)	19 (14-25)	IV(100)
Breast cancer	6 (0)	66.7 (57-73)	IV(100)
Melanoma	5 (NA)	NA	III(100)
Colorectal cancer	3 (33.3)	63.7 (52-77)	0(33.3); II(66.7)
Hepatoblastoma	3 (100)	2.3 (2-3)	IV(100)
MPNST (malignant peripheral nerve sheath tumor)	1 (100)	16	IV(100)
Fibrolabellar hepatocellular carcinoma	2 (100)	15.5 (15-16)	IV(100)
Wilms tumor	2 (100)	3 (1-5)	IV(100)
Immature teratoma	1 (0)	14	IV(100)
Desmoplastic small-round-cell tumor	1 (100)	14	IV(100)
Embryonal rhabdomyosarcoma	2 (0)	5.5 (3-8)	IV(100)
Epithelioid sarcoma	1 (0)	16 ´	IV(100)
Synovial sarcoma	1 (100)	54	IV(100)
Renal cell carcinoma	1 (100)	60	IV(100)
Anasplastic ependymoma	1 (0)	10	IV(100)
Total	85		

Plasma samples

Cancer type	sample size (% male)	average age (yr)	stage (%)
Lung adenocarcinoma	12 (41.7)	60.7 (23-78)	I(50.0); II(41.7); III(8.3)
Pancreatic ductal adenocarcinoma	9 (66.7)	69.9 (51-82)	II(77.8); III(22.2)
Neuroblastoma	15 (66.7)	7 (1-34)	III(6.7); IV(93.3)
Osteosarcoma	5 (80)	21.6 (14-35)	IV(100)
Breast cancer	8 (0)	52.1 (38-61)	II(25); III(12.5); IV(62.5)
Melanoma	1 (NA)	NA	NA
Colorectal cancer	3 (33.3)	63.7 (52-77)	0(33.3); II(66.7)
Hepatoblastoma	1 (100)	2	IV(100)
Germinoma	1 (NA)	NA	NA
MPNST (malignant peripheral nerve	1 (100)	16	IV(100)
sheath tumor)			
Fibrolabellar hepatocellular carcinoma	2 (100)	15.5 (15-16)	IV(100)
Wilms tumor	1 (100)	1	IV(100)
Mesothelioma	15 (73.3)	64.3 (41-83)	I(13.3); III(6.7); IV(6.7); NA(73.3)
DSRCT (desmoplastic small-round-	1 (100)	14	IV(100)
cell tumor)			
Hodgkin's lymphoma	1 (0)	19	IV(100)
Anasplastic ependymoma	1 (0)	10	IV(100)
Total	77		
Adult control	28 (46.4%)	43.5 (32-78)	NA
Pediatric control	15 (80%)	7.2 (3-19)	NA
Total	43		

Plasma samples for validation experiment (ELISA and targeted mass spectrometry)

Cancer type	sample size (% male)	average age (yr)	stage (%)
Lung adenocarcinoma	8 (12.5)	67.5 (48-80)	I (25.0); II (75.0)
Pancreatic ductal adenocarcinoma	15 (86.7)	69.7 (54-87)	I (33.3); II (33.3); III (33.3)
Total	23		
Healthy controls	15 (13.3)	45.1 (34-59)	NA
Total	15		

Table S2. Related to figure 1. Gene ontology analysis using Metascape (http://metascape.org/) for the 13 common EVP cargo proteins detected in more than 50% of human samples.

Category	Term	Description	Proteins	Log P	Log (q-value)
Reactome Gene Sets	R-HSA-109582	Hemostasis	A2M,ACTB,FLNA,FN1,HBB,JCHAIN,LGALS3BP,RAP1B,YV	-10.9	-6.6
GO Biological Processes	GO:0045055	regulated exocytosis	A2M,B2M,STOM,FLNA,FN1,GSN,HBB,LGALS3BP,RAP1B	-10.2	-6.2
GO Biological Processes	GO:0042060	wound healing	A2M,ACTB,FLNA,FN1,GSN,HBB,YWHAZ,MSN	-8.0	-4.2
Reactome Gene Sets	R-HSA-6802948	Signaling by high-kinase activity BRAF mutants	ACTB,FN1,RAP1B,FLNA	-5.9	-2.7
GO Biological Processes	GO:1905475	regulation of protein localization to membrane	ACTB,STOM,GSN,YWHAZ,MSN,RAP1B,FLNA,FN1	-5.7	-2.6
GO Biological Processes	GO:0006897	endocytosis	ACTB,B2M,GSN,HBB,JCHAIN,LGALS3BP	-5.5	-2.5
KEGG Pathway	hsa05205	Proteoglycans in cancer	ACTB,FLNA,FN1,MSN,GSN,B2M	-5.3	-2.3
KEGG Pathway	hsa04810	Regulation of actin cytoskeleton	ACTB,FN1,GSN,MSN,HBB,FLNA,JCHAIN,YWHAZ,B2M	-5.2	-2.3
Reactome Gene Sets	R-HSA-1280215	Cytokine Signaling in Immune system	B2M,FN1,MSN,RAP1B,YWHAZ,ACTB,GSN,FLNA,STOM	-4.4	-1.8
GO Biological Processes	GO:0003014	renal system process	GSN,HBB,JCHAIN,ACTB,YWHAZ,STOM	-4.4	-1.7
GO Biological Processes	GO:0009636	response to toxic substance	ACTB,GSN,HBB,PRDX2,B2M	-3.7	-1.1
GO Biological Processes	GO:0034762	regulation of transmembrane transport	ACTB,STOM,FLNA,GSN,RAP1B	-2.4	-0.1
Reactome Gene Sets	R-HSA-382551	Transport of small molecules	A2M,STOM,HBB	-2.1	0.0

Table S4. Related to Figure 2. Complete list of tumor-enriched EVP proteins in lung adenocarcinoma. A total 123 proteins were identified across 14 LuCa pairs by mass spectrometry based on the following parameters:≥10-fold difference in levels, FDR <0.05, and positivity in ≥50% tumors.. Bolded proteins are exclusively expressed in tumor tissues

protein	false discovery rate (FDR)	log ₁₀ fold change (tumor / normal)	posivitiy in tumor tissue (n=14)	posivitiy in normal tissue (n=22)	Positivity in adjacent tissue (n=14)	Positivity in distant tissue (n=8)
FHL2	0.012	5.4	79%	9%	7%	13%
XRN2	0.012	5.4	79%	9%	14%	0%
GLRX	0.012	4.9	86%	23%	36%	0%
HDLBP	0.012	4.8	86%	27%	36%	13%
SRRT	0.032	4.7	79%	18%	29%	0%
RCC1	0.012	4.6	79%	23%	36%	0%
AP3S1	0.012	4.6	86%	27%	29%	25%
SNRPD3	0.012	4.6	79%	18%	21%	13%
NOP2	0.022	4.6	64%	5%	7%	0%
RPL22	0.012	4.5	86%	36%	43%	25%
DNAJC7	0.022	4.5	64%	5%	7%	0%
STK39	0.012	4.5	71%	14%	14%	13%
SRP54	0.012	4.3	86%	32%	43%	13%
DHX36	0.012	4.3	86%	27%	36%	13%
ELAVL1	0.022	4.3	64%	9%	7%	13%
THBS2	0.012	4.3	71%	18%	29%	0%
ACO2	0.040	4.3	86%	32%	43%	13%
ACBD3	0.022	4.2	71%	18%	21%	13%
SRP9	0.012	4.1	57%	5%	7%	0%
THOC2	0.012	4.1	79%	23%	29%	13%
HNRNPC	0.012	4.1	100%	55%	79%	13%
EIF5B	0.012	4.1	93%	41%	43%	38%
RALY	0.012	4.0	57%	5%	7%	0%
UCHL5	0.022	4.0	57%	5%	0%	13%
KHDRBS1	0.040	4.0	79%	32%	50%	0%
SF3B6	0.040	4.0	86%	36%	57%	0%
WDR44	0.012	4.0	93%	41%	50%	25%
BABAM2	0.022	4.0	86%	36%	50%	13%
HTATIP2	0.012	3.9	50%	0%	0%	0%
CSTF3	0.012	3.9	57%	5%	7%	0%
RPL38	0.012	3.9	57%	9%	7%	13%
RPL35A	0.040	3.9	86%	41%	50%	25%
POLR2L	0.012	3.8	64%	14%	14%	13%
NUP43	0.012	3.8	64%	14%	14%	13%
CKAP5	0.012	3.8	64%	14%	21%	0%
FBLIM1	0.022	3.8	71%	23%	21%	25%
GLA	0.012	3.8	57%	9%	14%	0%
				9%		
DCPS	0.040	3.8	57%		14%	0%
TPRKB	0.022	3.8	71%	23%	29%	13%
ESRP1	0.040	3.8	64%	14%	14%	13%
PABPC4	0.022	3.8	100%	55%	71%	25%
GORASP2	0.022	3.8	71%	27%	36%	13%
VCAN	0.048	3.7	71%	27%	21%	38%
RPS17	0.032	3.7	64%	18%	21%	13%
PGM2L1	0.022	3.7	79%	32%	14%	63%
RANGAP1	0.022	3.7	86%	41%	43%	38%
COG5	0.012	3.7	57%	9%	14%	0%
LSM4	0.012	3.7	71%	27%	36%	13%
CTNNBL1	0.040	3.6	71%	23%	29%	13%
FEN1	0.040	3.6	50%	5%	7%	0%
CPSF7	0.032	3.6	79%	32%	43%	13%
TEP1	0.012	3.6	93%	45%	36%	63%
DHX16	0.040	3.6	57%	14%	14%	13%
METTL1	0.032	3.6	50%	0%	0%	0%
TBC1D8B	0.048	3.5	57%	14%	21%	0%
POLR2C	0.022	3.5	64%	18%	21%	13%
PSPC1	0.022	3.5	64%	23%	29%	13%
	0.022	3.5	64%	18%	29%	0%

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PSMID4	RRP12	0.040	3.4	50%	5%	7%	0%
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HERC							
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KHSRP	RAE1						
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HEATRSB	KHSRP	0.048	3.3	79%	36%	43%	25%
PAICS				50%			
DBR1							
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	SUPT16H	0.022	1.0	100%	91%	86%	100%

 Table S5. Related to Figure 3. List of Damage-associated molecular pattern (DAMP) molecules in this study.

Туре	# of molecu	lle Proteins
S100s	18	S100A1, S100A10, S100A11, S100A12, S100A13, S100A14, S100A16, S100A2, S100A3, S100A4, S100A6, S100A7, S100A7A, S100A8, S100A9, S100B, S100G, S100P
TLRs	6	TLR2, TLR3, TLR4, TLR6, TLR7, TLR8
Annexins	13	ANXA1, ANXA10, ANXA11, ANXA13, ANXA2, ANXA2P2, ANXA3, ANXA4, ANXA5, ANXA6, ANXA7, ANXA8, ANXA9
HMG molecules	12	HMG20A, HMG20B, HMGA1, HMGA2, HMGB1, HMGB2, HMGB3, HMGN1, HMGN2, HMGN3, HMGN4, HMGN5
Integrins	28	ITGA1, ITGA10, ITGA11, ITGA2, ITGA2B, ITGA3, ITGA4, ITGA5, ITGA6, ITGA7, ITGA8, ITGA9, ITGAD, ITGAE, ITGAL, ITGAL, ITGAM, ITGAV, ITGAX, ITGB1, ITGB1BP1, ITGB2, ITGB3, ITGB4, ITGB5, ITGB6, ITGB7, ITGB8, ITGBL1
scavenger receptors	7	scavenger receptors, MSR1, SCARA3, SCARB1, SCARB2, SCARF1, SCARF2, SSC5D
chemokine receptors	6	CCR1, CCR7, CCRL2, CXCR1, CXCR2, CXCR4
Galectins	11	CLC, LGALS1, LGALS2, LGALS3, LGALS3BP, LGALS4, LGALS7, LGALS8, LGALS9, LGALS9B, LGALSL
Fibrinogen	5	FGA, FGB, FGG, FGL1, FGL2
ECM glycoproteins	43	ACAN, ASPN, BCAN, BGN, CEMIP, CHAD, CHADL, CSPG4, DCN, FMOD, HABP2, HAPLN1, HAPLN3, HAPLN4, HAS1, HAS2, HAS3, HSPG2, HYAL2, HYAL3, IMPG2, KERA, LUM, LYVE1, MGEA5, NCAN, OGN, OMD, PAPLN,
Fibronectin	12	Fibronectin, ELFN2, FANK1, FLRT1, FLRT2, FLRT3, FN1, FNDC1, FNDC3A, FSD1, FSD1L, FSD2, IGFN1
Thioredoxin	15	TMX1, TMX2, TMX3, TMX4, TXN, TXN2, TXNDC12, TXNDC17, TXNDC5, TXNDC9, TXNIP, TXNL1, TXNL4A, TXNRD1, TXNRD2
Purinergic receptor	5	P2RX1, P2RX3, P2RX4, P2RX7, P2RY2
Others	14	A2M (CD91), AGER, BCL2, BSG, CALR, CALR3, CD14, CD2, CD36, CD44, FPR1, HAVCR2, IL1R1, IL6ST
Total	195	

Table S6. Related to Figure 4. Proteins defined as predictive for distinguishing tumor versus non-tumor based on tumor tissue-derived EVPs *versus* non-tumor tissue-derived EVP comparison.

protein	protein name	log₁₀ fold change (tumor / normal)	posivitiy in normal tissue (n=66)	posivitiy in tumor tissue (n=85)
THBS2	thrombospondin 2	5.1	12%	74%
VCAN	versican	5.1	17%	75%
SRRT	serrate, RNA effector molecule	4.1	9%	62%
TNC	tenascin C	3.5	9%	54%
DPYSL2	dihydropyrimidinase like 2	3.6	55%	98%
AHCY	adenosylhomocysteinase	3.2	62%	96%
DNAJA1	DnaJ heat shock protein family (Hsp40) member A1	3.3	45%	85%
PGK1	phosphoglycerate kinase 1	2.3	79%	100%
EHD2	EH domain containing 2	1.0	68%	87%
ADH1B	alcohol dehydrogenase 1B (class I), beta polypeptide	-0.6	67%	64%
CAVIN1	caveolae associated protein 1	-1.1	53%	42%
FGGY	FGGY carbohydrate kinase domain containing	-1.2	20%	4%
ABCA3	ATP binding cassette subfamily A member 3	-1.7	32%	12%
STX11	syntaxin 11	-2.8	38%	1%
CAVIN2	caveolae associated protein 2	-3.8	53%	7%
CD36	CD36 molecule	-4.3	71%	20%

Table S7. Related to Figure 6. Proteins defined as predictive for distinguishing tumor *versus* non-tumor based on tumor plasma EVPs versus healthy control plasma-derived EVPs comparison.

protein	protein name	log ₁₀ fold change (tumor / normal)	posivitiy in normal plasma (n=43)	posivitiy in tumor plasma (n=77)
IGLC2	immunoglobulin lambda constant 2	4.6	12%	56%
KRT17	keratin 17	3.0	7%	43%
IGHG1	immunoglobulin heavy constant gamma 1	2.6	12%	36%
KRT6B	keratin 6B	2.4	7%	35%
FTL	ferritin light chain	2.2	49%	70%
RDX	radixin	1.9	0%	25%
CFL1	cofilin 1	1.9	26%	49%
PRSS1	protease, serine 1	1.8	0%	22%
TUBA1C	tubulin alpha 1c	1.8	7%	30%
ADAMTS13	ADAM metallopeptidase with thrombospondin type 1 motif 13	1.8	12%	35%
IGKV6D-21	immunoglobulin kappa variable 6D-21	1.7	16%	38%
YWHAQ	tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein theta	1.7	16%	38%
POTEI	POTE ankyrin domain family member I	1.4	0%	17%
POTEE	POTE ankyrin domain family member F	1.2	0%	14%
VWF	von Willebrand factor	0.9	98%	97%
ACTG1	actin gamma 1	-2.1	93%	64%
IGLV3-27	immunoglobulin lambda variable 3-27	-2.1	86%	57%
IGKV1D-12	immunoglobulin kappa variable 1D-12	-2.2	58%	25%
F11	coagulation factor XI	-2.3	91%	58%
C1RL	complement C1r subcomponent like	-2.4	86%	64%
ATRN	attractin	-2.4	84%	53%
BCHE	butyrylcholinesterase	-2.4	84%	53%
IGHV3-35	immunoglobulin heavy variable 3-35	-2.5	70%	43%
IGKV1-17	immunoglobulin kappa variable 1-17	-2.7	100%	66%
C1QTNF3	C1q and TNF related 3	-3.0	63%	25%
IGHV3-20	immunoglobulin heavy variable 3-20	-3.2	86%	55%
IGHV3OR15-7	immunoglobulin heavy variable 3/OR15-7	-3.3	79%	39%
COLEC11	collectin subfamily member 11	-3.4	84%	40%
IGHD	immunoglobulin heavy constant delta	-3.5	77%	35%
IGKV3D-11	immunoglobulin kappa variable 3D-11	-3.6	100%	61%
IGHV3OR16-10	immunoglobulin heavy variable 3/OR16-10	-3.9	86%	47%
IGKV2D-24	immunoglobulin kappa variable 2D-24	- 4.1	86%	39%
IGKV2-40	immunoglobulin kappa variable 2-40	-4.1	88%	44%
IGKV1-27	immunoglobulin kappa variable 1-27	-4.4	79%	22%
IGHV3OR16-9	immunoglobulin heavy variable 3/OR16-9	-4.4	88%	44%
IGLV5-45	immunoglobulin lambda variable 5-45	-4.4	72%	18%
IGHV3OR16-13	immunoglobulin heavy variable 3/OR16-13	-4.6	77%	27%
IGHV1-46	immunoglobulin heavy variable 1-46	-4.7	72%	16%
IGHV4-39	immunoglobulin heavy variable 4-39	-5.0	93%	38%
IGHV3-11	immunoglobulin heavy variable 3-11	-5.0	95%	43%
IGLC3	immunoglobulin lambda constant 3	-5.2	77%	27%
IGKV1-6	immunoglobulin kappa variable 1-6	-5.5	67%	1%
PON3	paraoxonase 3	-5.6	72%	5%
IGHV3-21	immunoglobulin heavy variable 3-21	-5.7	70%	9%
IGHV7-4-1	immunoglobulin heavy variable 3-2-1	-5.7 -5.8	74%	10%
IGKV2D-30	immunoglobulin heavy variable 7-4-1	-5.6 -6.0	67%	0%
IGLC6	immunoglobulin kappa variable 2D-30 immunoglobulin lambda constant 6	-0.0 -7.1	70%	1%
IGLUU	mimunogiobulin iambua constant o	-1.1	1070	1 70

Table S8. Related to STAR Methods. Targeted peptides from top 20 PaCa plasma EVP markers. Peptides were identified from the fractionated library and targeted in a PRM experiment. LRRC26 were not identified in the fractionated library.

Protein	Sequence	m/z
CA2	VVDVLDSIK	494.2899
CA2	LNFNGEGEPEELMVDNWRPAQPLK	928.4528
CD55	LTCLQNLK	495.2758
GLIPR2	EAQQYSEALASTR	727.3489
KRAS	LVVVGAGGVGK	478.2999
P4HB	NFEDVAFDEK	607.2726
PEBP1	VLTPTQVK	443.2735
PEBP1	GNDISSGTVLSDYVGSGPPK	975.4741
PSMA4	LLDEVFFSEK	613.8192
PSMA4	SALALAIK	393.7577
PACSIN2	ASLMNDDFEK	585.2604
PACSIN2	ADPSLNPEQLK	606.3199
TGM2	LVVNFESDK	525.7772
TGM2	TVEIPDPVEAGEEVK	806.4084
PTPRJ	GDPLGTEGGLDASNTER	844.8867
PTPRJ	QQADSNCGFAEEYEDLK	668.6134
ABCB1	LVTMQTAGNEVELENAADESK	750.3574
ABCB1	NTTGALTTR	467.7527
ABCB1	VVQEALDK	451.253
XPNPEP2	TVHWGTPSAFQK	453.5659
XPNPEP2	GTVDEFSGAEIVDK	733.8526
XPNPEP2	LIFPAATSGR	516.7961
ADGRG6	TGLFQDVGPQRK	673.3628
ADGRG6	TQEVHHPICAFWDLNK	665.6566
ADGRG6	TIDELAFK	468.7555
ABCB11	ILLLDEATSALDTESEK	924.4762
ABCB11	VNVQFLR	438.2581
ABCB11	SLNIQWLR	515.2944
ITGA1	EYAQRIPSGGDGK	689.3411
ITGA1	DSNTDILLVGAPMYMGTEK	1027.991
ITGA1	WVLIGSPLVGQPK	697.4135
LTF	QVLLHQQAK	532.8135
LTF	SNLCALCIGDEQGENK	904.4007
LTF	DVTVLQNTDGNNNEAWAK	994.9688
ALPL	SVGIVTTTR	467.2717
ALPL	FPFVALSK	454.7662
ALPL	LNTNVAK	380.2217
SRI	LSPQAVNSIAK	564.324
SRI	SGTVDPQELQK	601.3076
SRI	ALTTMGFRLSPQAVNSIAK	669.0334
BAIAP2L1	LNESLDENFK	604.794
BAIAP2L1	TIFPHTAGSNK	586.8076
BAIAP2L1	VNNSTGTSEDPSLQR	802.8797