

Simultaneous Metabolomics and Proteomics Analysis of Plasma-derived Extracellular Vesicles

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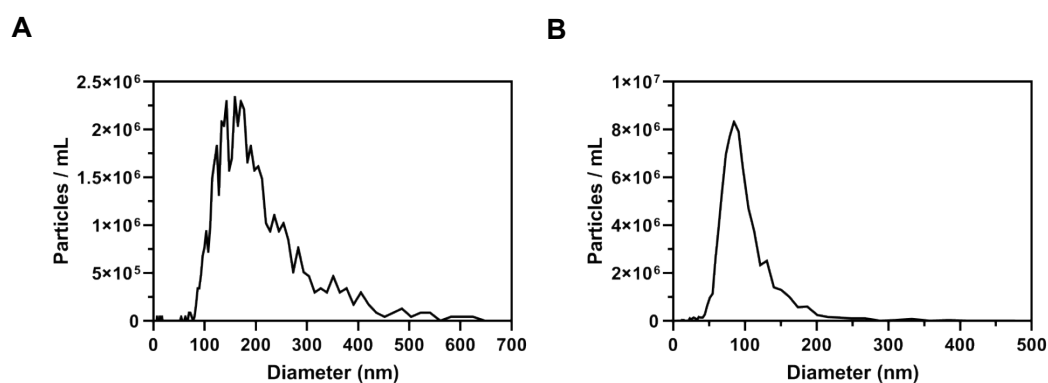


Figure S1. Size distribution of the isolated microvesicles (A) and exosomes (B) measured using Zeta View Nanoparticle tracking analysis (NTA).

A

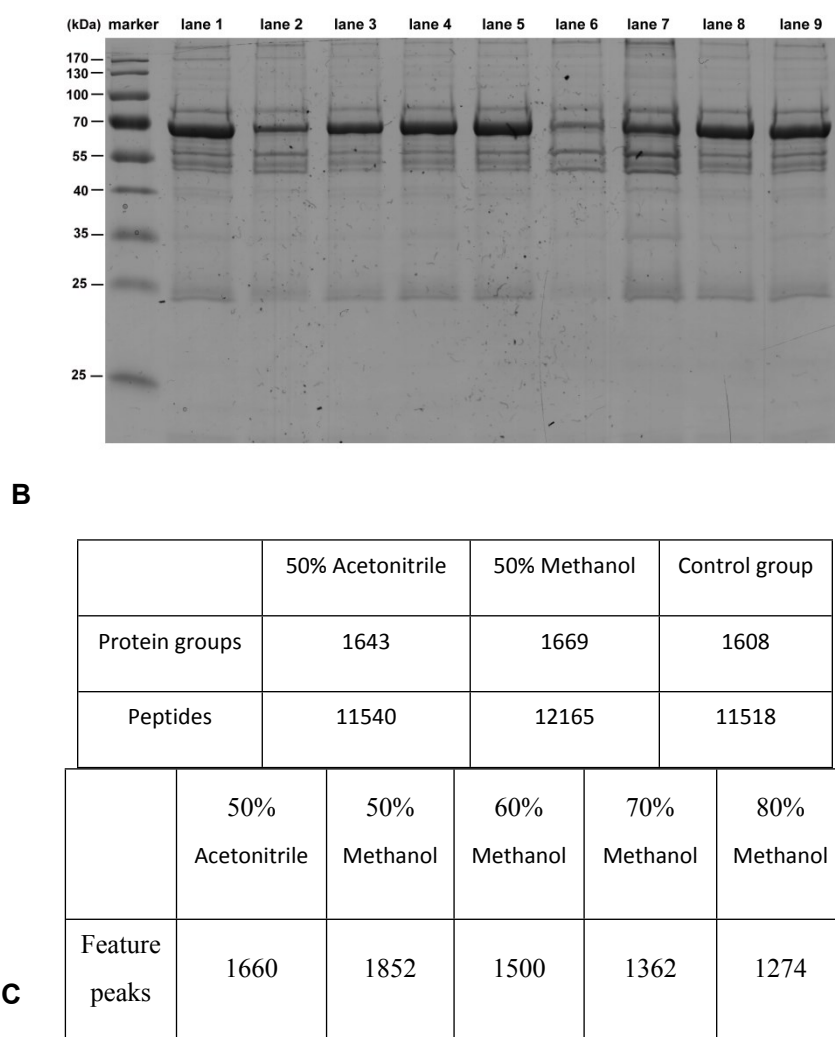


Figure S2. Optimization of the extraction conditions for metabolites and proteins. (A) SDS-PAGE image of the proteins obtained from microvesicles without extraction of metabolites (lane 1: the control group), with extraction of metabolites using different concentration of acetonitrile (lane 2-5: 50%, 60%, 70%, 80%) or methanol (lane 6-9: 50%, 60%, 70%, 80%). 10 µg of proteins were loaded per lane. (B) The number of protein groups and peptides identified from microvesicles with 50% acetonitrile treatment, with 50% methanol treatment and without organic solvent treatment. (C) The number of feature peaks identified in positive detection mode from the metabolites extracted using 50% acetonitrile and different concentration of methanol (50%, 60%, 70%, 80%).

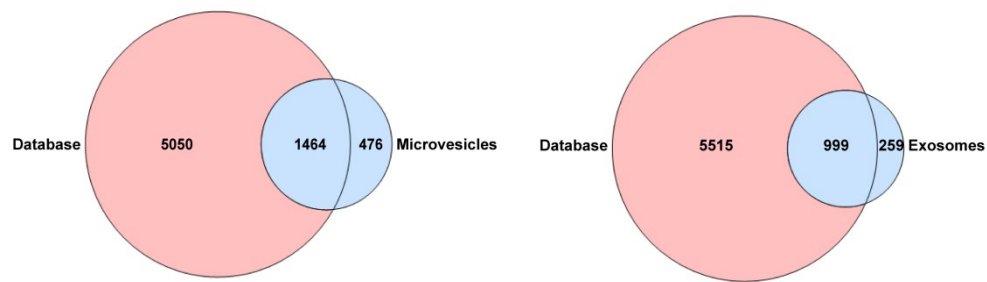


Figure S3. Venn diagrams showing the overlap between the exosome database from ExoCarta and EVs data from our experiments. There was a 79% overlap between the exosome database and our proteins identified from exosomes and a 75% overlap between the exosome database and our proteins identified from microvesicles.

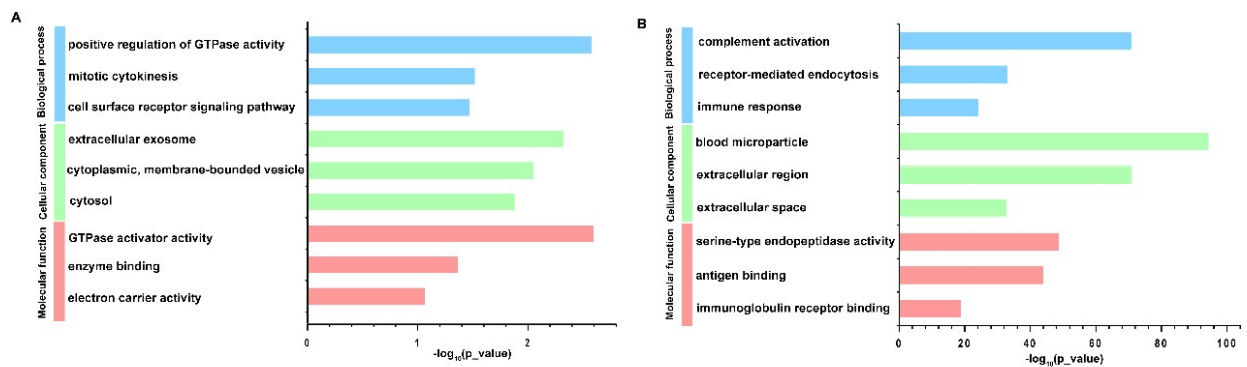


Figure S4. Gene ontology analysis of the up-regulated proteins in exosomes (A) and the up-regulated proteins in microvesicles (B). The three gene ontology categories (biological process, cellular component and molecular function) are displayed in different colors.

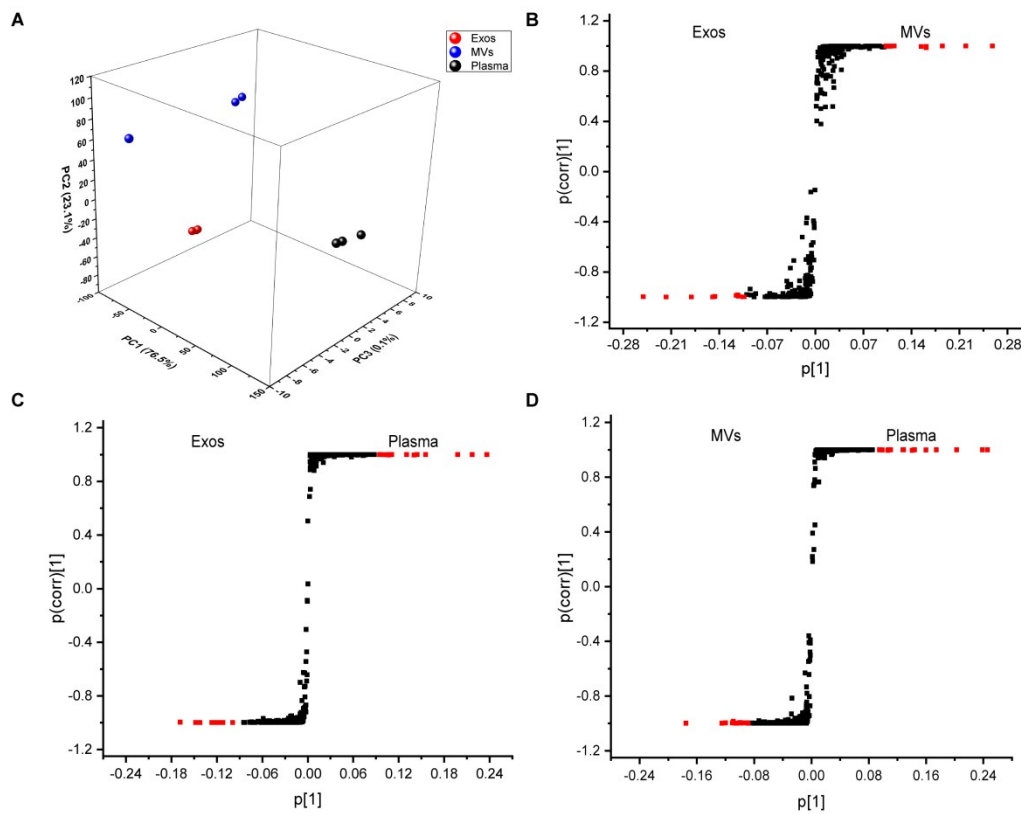
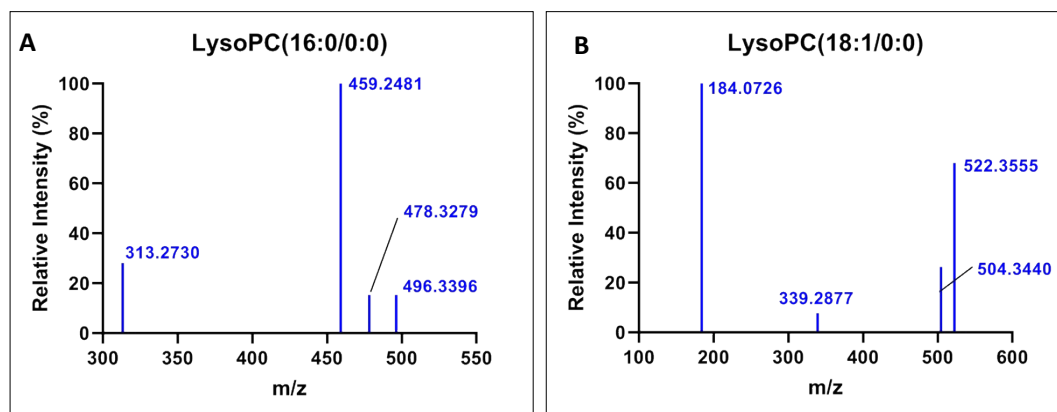


Figure S5. PCA analysis of metabolites from exosomes, microvesicles and plasma identified in negative ion mode (A). S-plot of OPLS-DA models of metabolites identified in negative ion mode: exosomes vs. microvesicles (B), exosomes vs. plasma (C), microvesicles vs. plasma (D). Metabolites with $\text{VIP} > 2$ are colored in red.



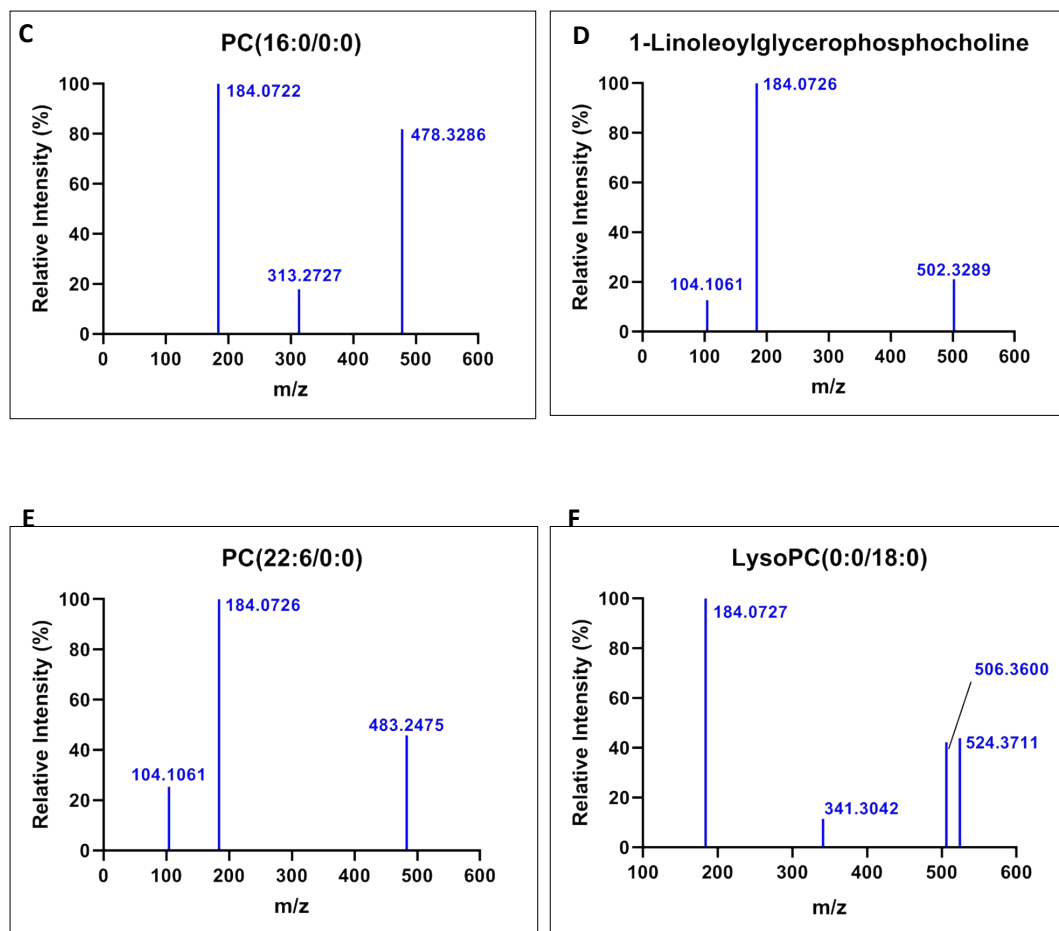


Figure S6. Typical MS/MS spectra of several validated differential metabolites.

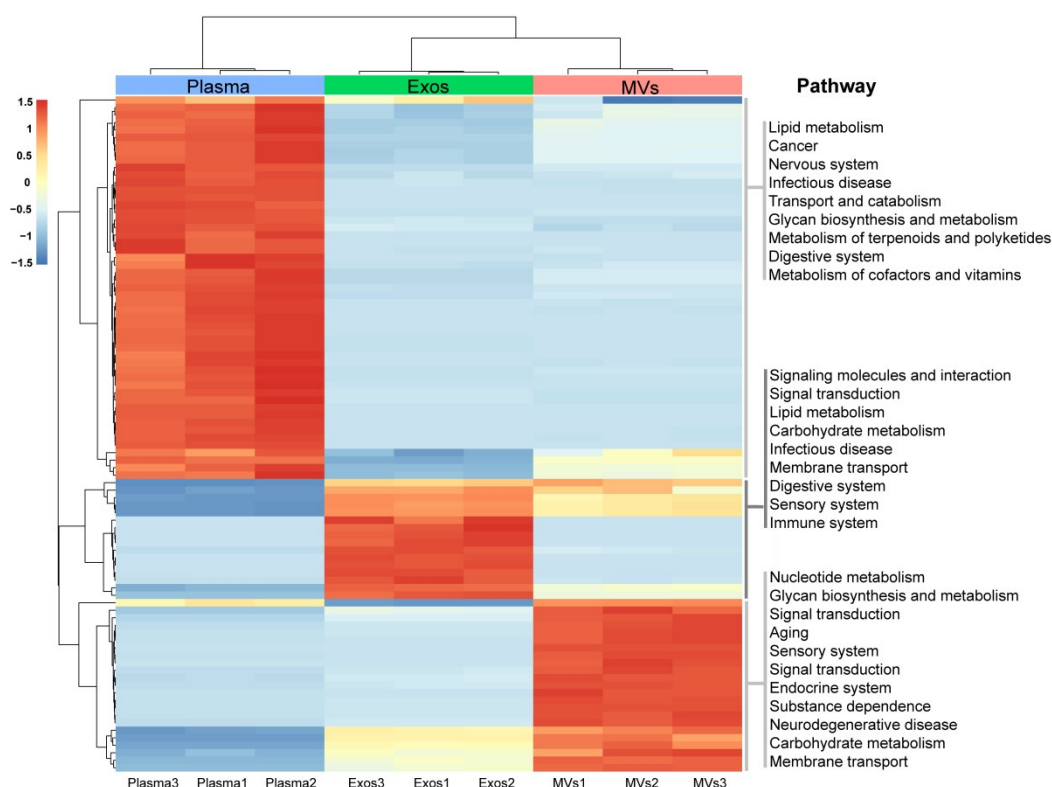


Figure S7. Heatmap of differential metabolites identified among microvesicles, plasma, and exosomes. The expression changes of metabolites are shown on a relative scale, with depletion colored in blue and enrichment colored in red. Clusters from the heatmap underwent metabolites KEGG pathway enrichment analysis. Significantly enriched KEGG terms are shown on the right.

Table S1. Identification of differential proteins between exosomes and microvesicles.

Protein ID	Gene ID	Gene Name	Up-regulated in
O15371	8664	eukaryotic translation initiation factor 3 subunit D(EIF3D)	exosomes
P33527	4363	ATP binding cassette subfamily C member 1(ABCC1)	exosomes
Q12982	663	BCL2 interacting protein 2(BNIP2)	exosomes
O43665	6001	regulator of G-protein signaling 10(RGS10)	exosomes
P62837	7322	ubiquitin conjugating enzyme E2 D2(UBE2D2)	exosomes
P53990	9798	IST1, ESCRT-III associated factor(IST1)	exosomes
O75489	4722	NADH:ubiquinone oxidoreductase core subunit S3(NDUF53)	exosomes

P30086	5037	phosphatidylethanolamine binding protein 1(PEBP1)	exosomes
Q9H299	83442	SH3 domain binding glutamate rich protein like 3(SH3BGRL3)	exosomes
Q9H0U3	84061	magnesium transporter 1(MAGT1)	exosomes
Q96QS1	10077	tetraspanin 32(TSPAN32)	exosomes
P20936	5921	RAS p21 protein activator 1(RASA1)	exosomes
P46939	7402	utrophin(UTRN)	exosomes
O14817	7106	tetraspanin 4(TSPAN4)	exosomes
P17252	5578	protein kinase C alpha(PRKCA)	exosomes
Q96K49	84910	transmembrane protein 87B(TMEM87B)	exosomes
Q9Y5X1	51429	sorting nexin 9(SNX9)	exosomes
O95858	23555	tetraspanin 15(TSPAN15)	exosomes
O14548	9167	cytochrome c oxidase subunit 7A2 like(COX7A2L)	exosomes
P47712	5321	phospholipase A2 group IVA(PLA2G4A)	exosomes
P04433	28876	immunoglobulin kappa variable 3D-11(IGKV3D-11)	microvesicles
P01880	3495	immunoglobulin heavy constant delta(IGHD)	microvesicles
P35858	3483	insulin like growth factor binding protein acid labile subunit(IGFALS)	microvesicles
O14791	8542	apolipoprotein L1(APOL1)	microvesicles
P19652	5005	orosomucoid 2(ORM2)	microvesicles
Q03591	3078	complement factor H related 1(CFHR1)	microvesicles
P15169	1369	carboxypeptidase N subunit 1(CPN1)	microvesicles
P13671	729	complement C6(C6)	microvesicles
P0C0L5	721	complement C4B (Chido blood group)(C4B)	microvesicles
Q969X1	64114	transmembrane BAX inhibitor motif containing 1(TMBIM1)	microvesicles

P01719	28796	immunoglobulin lambda variable 3-21(IGLV3-21)	microvesicles
P00747	5340	plasminogen(PLG)	microvesicles
P00748	2161	coagulation factor XII(F12)	microvesicles
P01714	28797	immunoglobulin lambda variable 3-19(IGLV3-19)	microvesicles
P01834	3514	immunoglobulin kappa constant(IGKC)	microvesicles
P02647	335	apolipoprotein A1(APOA1)	microvesicles
P01833	5284	polymeric immunoglobulin receptor(PIGR)	microvesicles
P01877	3494	immunoglobulin heavy constant alpha 2 (A2m marker)(IGHA2)	microvesicles
P01876	3493	immunoglobulin heavy constant alpha 1(IGHA1)	microvesicles
P80748	28796	immunoglobulin lambda variable 3-21(IGLV3-21)	microvesicles
P02763	5004	orosomucoid 1(ORM1)	microvesicles
P07358	732	complement C8 beta chain(C8B)	microvesicles
P01871	3507	immunoglobulin heavy constant mu(IGHM)	microvesicles
P04003	722	complement component 4 binding protein alpha(C4BPA)	microvesicles
P07357	731	complement C8 alpha chain(C8A)	microvesicles
P02760	259	alpha-1-microglobulin/bikunin precursor(AMBP)	microvesicles
P01031	727	complement C5(C5)	microvesicles
P03952	3818	kallikrein B1(KLKB1)	microvesicles
P08603	3075	complement factor H(CFH)	microvesicles
P01591	3512	joining chain of multimeric IgA and IgM(JCHAIN)	microvesicles
B9A064	100423062	immunoglobulin lambda like polypeptide 5(IGLL5)	microvesicles
P23083	388077	immunoglobulin heavy variable 1/OR15-1 (non-functional)(IGHV1OR15-1)	microvesicles
P04208	28822	immunoglobulin lambda variable 1-47(IGLV1-47)	microvesicles

P10643	730	complement C7(C7)	microvesicles
Q9NWZ3	51135	interleukin 1 receptor associated kinase 4(IRAK4)	microvesicles
P00738	3240	haptoglobin(HP)	microvesicles
P00739	3250	haptoglobin-related protein(HPR)	microvesicles
P00736	715	complement C1r(C1R)	microvesicles
P27918	5199	complement factor properdin(CFP)	microvesicles
P00734	2147	coagulation factor II, thrombin(F2)	microvesicles
P07360	733	complement C8 gamma chain(C8G)	microvesicles
P01702	28820	immunoglobulin lambda variable 1-51(IGLV1-51)	microvesicles
P01743	28465	immunoglobulin heavy variable 1-46(IGHV1-46)	microvesicles
P01620	28912	immunoglobulin kappa variable 3-20(IGKV3-20)	microvesicles
P01861	3503	immunoglobulin heavy constant gamma 4 (G4m marker)(IGHG4)	microvesicles
P02751	2335	fibronectin 1(FN1)	microvesicles
P01024	718	complement C3(C3)	microvesicles
P01860	3502	immunoglobulin heavy constant gamma 3 (G3m marker)(IGHG3)	microvesicles
P04211	28776	immunoglobulin lambda variable 7-43(IGLV7-43)	microvesicles
P01023	2	alpha-2-macroglobulin(A2M)	microvesicles
P01781	28452	immunoglobulin heavy variable 3-7(IGHV3-7)	microvesicles
P00450	1356	ceruloplasmin(CP)	microvesicles
Q08380	3959	galectin 3 binding protein(LGALS3BP)	microvesicles
P19823	3698	inter-alpha-trypsin inhibitor heavy chain 2(ITIH2)	microvesicles
P01859	3501	immunoglobulin heavy constant gamma 2 (G2m marker)(IGHG2)	microvesicles
P01617	28883	immunoglobulin kappa variable 2D-28(IGKV2D-28)	microvesicles

P19827	3697	inter-alpha-trypsin inhibitor heavy chain 1(ITIH1)	microvesicles
P01857	3500	immunoglobulin heavy constant gamma 1 (G1m marker)(IGHG1)	microvesicles
P02748	735	complement C9(C9)	microvesicles
P02747	714	complement C1q C chain(C1QC)	microvesicles
P02746	713	complement C1q B chain(C1QB)	microvesicles
P06681	717	complement C2(C2)	microvesicles
P01019	183	angiotensinogen(AGT)	microvesicles
P01613	28896	immunoglobulin kappa variable 1D-33(IGKV1D-33)	microvesicles
P02745	712	complement C1q A chain(C1QA)	microvesicles
P22792	1370	carboxypeptidase N subunit 2(CPN2)	microvesicles
Q16610	1893	extracellular matrix protein 1(ECM1)	microvesicles
P09871	716	complement C1s(C1S)	microvesicles
P01610	28937	immunoglobulin kappa variable 1-17(IGKV1-17)	microvesicles
P20851	725	complement component 4 binding protein beta(C4BPB)	microvesicles
P05156	3426	complement factor I(CFI)	microvesicles
P01772	28434	immunoglobulin heavy variable 3-33(IGHV3-33)	microvesicles
Q15485	2220	ficolin 2(FCN2)	microvesicles
O75636	8547	ficolin 3(FCN3)	microvesicles
Q15848	9370	adiponectin, C1Q and collagen domain containing(ADIPOQ)	microvesicles
P48740	5648	mannan binding lectin serine peptidase 1(MASP1)	microvesicles
P55056	346	apolipoprotein C4(APOC4)	microvesicles
O43866	922	CD5 molecule like(CD5L)	microvesicles
Q9Y6R7	8857	Fc fragment of IgG binding protein(FCGBP)	microvesicles

P05160	2165	coagulation factor XIII B chain(F13B)	microvesicles
P01602	28299	immunoglobulin kappa variable 1-5(IGKV1-5)	microvesicles
P02656	345	apolipoprotein C3(APOC3)	microvesicles
Q9Y385	51465	ubiquitin conjugating enzyme E2 J1(UBE2J1)	microvesicles
P02655	344	apolipoprotein C2(APOC2)	microvesicles
P01764	28442	immunoglobulin heavy variable 3-23(IGHV3-23)	microvesicles
P02654	341	apolipoprotein C1(APOC1)	microvesicles
P01763	28424	immunoglobulin heavy variable 3-48(IGHV3-48)	microvesicles
P04275	7450	von Willebrand factor(VWF)	microvesicles
P00751	629	complement factor B(CFB)	microvesicles
P02774	2638	GC, vitamin D binding protein(GC)	microvesicles
P20742	5858	PZP, alpha-2-macroglobulin like(PZP)	microvesicles
P07225	5627	protein S (alpha)(PROS1)	microvesicles

Table S2. Tentative identification of different metabolites among exosomes, microvesicles and plasma.

Compound name	Formula	Adducts	m/z	Mass Error (ppm)	Different between Exos and MVs	Different between Exos and plasma	Different between MVs and plasma
Corchoroside E	C ₄₁ H ₆₄ O ₁₉	M+Na	883.3951	1.9498	√		
Vulgaxanthin I	C ₁₄ H ₁₇ N ₃ O ₇	M+Na	362.0968	2.8844	√		
4,8,12,15,18-Icosapentaenoic acid	C ₂₀ H ₃₀ O ₂	M+H-H ₂ O, M+H	303.2312	-4.1425	√		
Eldecalcitol	C ₃₀ H ₅₀ O ₅	M+H, M+Na	491.3703	-5.5992		√	√

Pelargonidin 3-sophoroside	$C_{28}H_{33}O_{14}^+$	M+Na	616.1763	0.116	√		
{[8-(2,4-dihydroxyphenyl)-7-(3,7-dimethylocta-2,6-dien-1-yl)-5-hydroxy-2-methyl-6-oxo-2H,6H-pyrano[3,2-g]chromen-2-yl]methoxy}sulfonic acid	$C_{30}H_{32}O_{10}S$	M+K	623.1357	1.5447	√	√	√
Bilirubin	$C_{33}H_{36}N_4O_6$	M+H, M+Na	585.2708	0.139		√	√
Calendulose H methyl ester	$C_{49}H_{78}O_{19}$	M+Na	993.5072	4.4004	√		√
N-icosanoyl sphingosine 1-phosphate	$C_{38}H_{76}NO_6P$	M+Na	696.5263	-5.8592	√		
LysoPC(16:0/0:0)	$C_{24}H_{50}NO_7P$	M+H-H ₂ O	478.329	-0.3929		√	√
LysoPC(18:2)	$C_{26}H_{50}NO_7P$	M+Cl, M+FA-H	542.3212	-3.1415		√	√
LysoPC(20:4)	$C_{28}H_{50}NO_7P$	M+H-H ₂ O, M+Na	566.3208	-3.2379		√	√
1-Linoleoylglycerophosphocholine	$C_{26}H_{50}NO_7P$	M+H, M+Na	520.3396	-0.4054			√
PE(19:1/0:0)	$C_{24}H_{48}NO_7P$	M+H, M+Na	494.3236	-0.9546		√	√
Heptaethylene glycol	$C_{14}H_{30}O_8$	M+Na, M+K	349.1832	-0.2933	√	√	√
TG(8:0/13:0/12:0)	$C_{36}H_{68}O_6$	M+Na	619.4912	0.6408		√	√
TG(15:0/18:2/18:0)	$C_{54}H_{100}O_6$	M+H-H ₂ O	827.7561	8.7832	√		√
LysoPC(0:0/18:0)	$C_{26}H_{54}NO_7P$	M+H-H ₂ O, M+H, M+Na	524.3711	0.0579	√	√	√
LysoPC(18:1/0:0)	$C_{26}H_{52}NO_7P$	M+H, M+Na	522.3553	-0.1985	√	√	√
1-Eicosatrienoyl-glycero-3-phosphate	$C_{23}H_{41}O_7P$	M+Na	483.2475	-1.6505		√	

LysoPA(0:0/18:1)	C ₂₁ H ₄₁ O ₇ P	M+Na	459.2477	-1.0908		√	√
Sucrose	C ₁₂ H ₂₂ O ₁₁	M+Na	365.1052	-0.5922	√	√	
Octaethylene glycol	C ₁₆ H ₃₄ O ₉	M+H, M+NH ₄ , M+Na, M+K	393.2093	-1.672	√	√	√
1-Docosenoyl-glycero-3-phosphate	C ₂₅ H ₄₉ O ₇ P	M+Na	515.3126	3.6981		√	
PC(16:0/0:0)	C ₂₄ H ₅₀ NO ₇ P	M+H, M+Na	496.3398	0.0634	√	√	√
Hexaethylene glycol	C ₁₂ H ₂₆ O ₇	M+Na	305.1566	-1.5532	√	√	√
3-Tritriacontanone	C ₃₃ H ₆₆ O	M+NH ₄	496.5489	7.7066		√	√
PC(22:6/0:0)	C ₃₀ H ₅₀ NO ₇ P	M+H	568.3384	-2.3201		√	√
Desglucocoroloside	C ₂₉ H ₄₄ O ₇	M+NH ₄	522.3454	5.6109		√	√
LysoPC(20:3)	C ₂₈ H ₅₂ NO ₇ P	M+H	546.3551	-0.6312		√	√
LysoPE(18:2/0:0)	C ₂₃ H ₄₄ NO ₇ P	M+H-H ₂ O, M+H, M+Na, M+K	478.2924	-0.9198		√	√
2-[(5-Hydroxypentyl)oxy]-9,10-secocholesta-5,7,10-triene-1,3,25-triol	C ₃₂ H ₅₄ O ₅	M+H-H ₂ O, M+H, M+Na	541.3857	-1.7497		√	√
Gadobenic acid	C ₂₂ H ₃₁ GdN ₃ O ₁₁	M+K	710.079	-6.1329	√		√
1,26-Hexacosanediol diferulate	C ₄₆ H ₇₀ O ₈	M+H, M+NH ₄ , M+Na	773.4946	-2.882		√	√
MG(0:0/20:2/0:0)	C ₂₃ H ₄₂ O ₄	M+NH ₄	400.3412	-2.3226	√		
PE(P-16:0/0:0)	C ₂₁ H ₄₄ NO ₆ P	M+H	438.2974	-1.2591	√		
Feruloyl-beta-sitosterol	C ₃₉ H ₅₈ O ₄	M+NH ₄	608.4729	9.4972	√		

Glycerol tripropanoate	C ₁₂ H ₂₀ O ₆	M+H	261.1305	-10.5158	√	√	√
Digitoxigenin 3-[glucosyl-(1->6)-glucosyl-(1->4)-2,6-dideoxyribohexoside]	C ₄₁ H ₆₄ O ₁₇	M+Na	851.3991	-5.4202	√		
PC(o-16:0/16:1)	C ₄₀ H ₈₀ NO ₇ P	M+Na	740.5525	-5.4632	√		
PC(22:6/18:2)	C ₄₈ H ₈₀ NO ₈ P	M+H	830.5669	-3.0956	√	√	√
Crustecdysone	C ₂₇ H ₄₄ O ₇	M+NH ₄	498.3455	6.2628		√	√
Deshydroxy-C-1027 chromophore	C ₄₃ H ₄₂ ClN ₃ O ₁₂	M+H	828.2586	6.8095	√		√
Met His Lys	C ₁₇ H ₃₀ N ₆ O ₄ S	M+H-H ₂ O, M+H, M+NH ₄ , M+Na, M+K	437.1932	-4.2786	√	√	√
Edetic Acid	C ₁₀ H ₁₆ N ₂ O ₈	M+H	293.0974	-1.8555	√	√	√
2,6,10,14-Tetramethylpentadecanoic acid	C ₁₉ H ₃₈ O ₂	M+NH ₄	316.3205	-1.5265	√	√	√
CE(15M5)	C ₅₂ H ₈₈ O ₃	M+H-H ₂ O	743.6775	9.7543	√		
L-2-Amino-4-methylenepentanedioic acid	C ₆ H ₉ NO ₄	M+H	160.0598	-4.1446		√	√
Gentamicin C2b	C ₂₀ H ₄₁ N ₅ O ₇	M+H	464.3131	11.299	√		
4,7-Dihydroxy-N,N,N-trimethyl-10-oxo-3,5,9-trioxa-4-phosphahexacos-18-en-1-aminium 4-oxide	C ₂₅ H ₅₁ NO ₇ P ⁺	M+NH ₄	526.3769	6.6169		√	
DG(15:0/0:0/18:4n3)	C ₃₆ H ₆₂ O ₅	M+Na	597.4489	-0.1003		√	√
Adenosine 3'-monophosphate	C ₁₀ H ₁₄ N ₅ O ₇ P	M+H	348.0699	-1.4091	√		
Geranyl-PP	C ₁₀ H ₂₀ O ₇ P ₂	M+H	315.0795	11.9819	√	√	√
Tetraethylene glycol	C ₈ H ₁₈ O ₅	M+Na	217.1042	-2.3614	√	√	√
22-Acetylpriverogenin B	C ₃₂ H ₅₂ O ₅	M+H	517.3853	-6.6173		√	√
DG(13:0/20:3/0:0)[iso2]	C ₃₆ H ₆₄ O ₅	M+H	577.4825	-0.2085		√	√

Jurubine	C ₃₃ H ₅₇ NO ₈	M+NH ₄	613.4436	2.2576		√	√
DG(18:4/20:5/0:0)	C ₄₁ H ₆₂ O ₅	M+NH ₄	652.4996	9.5301	√		
Nb-Palmitoyltryptamine	C ₂₆ H ₄₂ N ₂ O	M+Na	421.3168	-5.4652	√		√
3-Hydroxy-2-(stearylino)-4-octadecen-1-yl beta-D-erythro-hexopyranosiduronic acid	C ₄₂ H ₇₉ NO ₉	M+NH ₄	759.6103	1.3373		√	
4-Hydroxy-N,N,N-trimethyl-10-oxo-7-(stearylino)-3,5,9-trioxa-4-phosphaheptacosan-1-aminium 4-oxide	C ₄₄ H ₈₉ NO ₈ P ⁺	M+H-H ₂ O	773.6277	-1.2455	√	√	√
N-1-(beta-D-erythro-Hexopyranosyloxy)-3-hydroxy-2-octadecanyl]docosanamide	C ₄₆ H ₉₁ NO ₈	M+H-H ₂ O	768.6721	1.1858	√	√	√
Labadoside	C ₃₈ H ₄₂ O ₁₆	M+NH ₄	772.274	-9.4558	√	√	
PE-NMe(18:4/20:0)	C ₄₄ H ₈₀ NO ₈ P	M+Na	804.5525	1.4805	√		
5,9-Dihydroxy-2-(2-hydroxy-2-propenyl)-1-(1-hydroxy-3,5,6-trimethoxy-10-methyl-9-oxo-9,10-dihydro-2-acridinyl)-10-methoxy-11-methyl-1,11-dihydrofuro[2,3-c]acridin-6(2H)-one	C ₃₇ H ₃₆ N ₂ O ₁₁	M-H	683.225	0.5729	√	√	
Ethylenediaminetetraacetic acid	C ₁₀ H ₁₆ N ₂ O ₈	M-H ₂ O-H, M-H	291.0827	-2.4101	√	√	√
Plerixafor	C ₂₈ H ₅₄ N ₈	M+Cl	537.4148	-3.4114		√	√
PE(P-16:0e/0:0)	C ₂₁ H ₄₄ NO ₆ P	M-H	436.2828	-1.3626	√		
2-Palmitoyl-sn-glycero-3-phosphocholine	C ₂₄ H ₅₀ NO ₇ P	M+Cl, M+FA-H	540.3294	-2.0908		√	√
3-(13,14-Dihydroxy-17-triaconten-1-yl)-5-methyl-2(5H)-furanone	C ₃₅ H ₆₄ O ₄	M+FA-H	593.4775	-2.1624		√	√
LysoPE(0:0/20:1)	C ₂₅ H ₅₀ NO ₇ P	M-H	506.324	-2.4608		√	√
2-Linoleoyl-sn-glycero-3-	C ₂₃ H ₄₄ NO ₇ P	M-H	476.277	-2.5918			√

phosphoethanolamine							
LysoPE(18:0/0:0)	C ₂₃ H ₄₈ NO ₇ P	M-H	480.3089	-1.4224	√		√
Adenosine 3',5'-bisphosphate	C ₁₀ H ₁₅ N ₅ O ₁₀ P ₂	M-H	426.0213	-1.867	√		
1-Pentadecanoyl-sn-glycero-3-phosphocholine	C ₂₃ H ₄₈ NO ₇ P	M-H	480.3087	-1.8051		√	√
Norethindrone acetate	C ₂₂ H ₂₈ O ₃	M-H	339.1992	7.6159		√	√
1-Heptadecanoyl-sn-glycero-3-phosphocholine	C ₂₅ H ₅₂ NO ₇ P	M-H	508.34	-1.6035		√	√
2-icosadienoy-sn-glycero-3-phosphoethanolamine	C ₂₅ H ₄₈ NO ₇ P	M-H	504.3082	-2.7025		√	√
4-Undecylbenzenesulfonic acid	C ₁₇ H ₂₈ O ₃ S	M-H	311.1678	-2.7916		√	√
2-Dodecylbenzenesulfonic acid	C ₁₈ H ₃₀ O ₃ S	M-H	325.1835	-2.4226	√	√	√
Testosterone sulfate	C ₁₉ H ₂₈ O ₅ S	M-H	367.1578	-1.7925		√	√
Glycogen	C ₂₄ H ₄₂ O ₂₁	M+Cl	701.1905	-1.2112	√		
N-Acetyl-D-galactosamine 1-phosphate	C ₈ H ₁₆ NO ₉ P	M+FA-H	346.0553	2.888			√
Inosinic acid	C ₁₀ H ₁₃ N ₄ O ₈ P	M-H	347.0392	-1.818	√		√
4-(Hydroxymethyl)-2-[2-(4-hydroxyphenyl)ethyl]-7-methyl-6,7-dihydro-5H-cyclopenta[c]pyridinium	C ₁₈ H ₂₂ NO ₂ ⁺	M-H ₂ O-H	265.1468	0.6298	√		
Cellobiose	C ₁₂ H ₂₂ O ₁₁	M-H	341.1085	-1.1805	√	√	
Inosine 5'-monophosphate (IMP)	C ₁₀ H ₁₃ N ₄ O ₈ P	M-H	347.0394	-1.3182	√		√
8-HETE	C ₂₀ H ₃₂ O ₃	M-H ₂ O-H, M-H	319.2273	-1.7562	√		
Raffinose	C ₁₈ H ₃₂ O ₁₆	M+Cl	539.138	-0.8977			√
3-(19,20-Dihydroxytriacetyl)-5-methyl-2(5H)-furanone	C ₃₅ H ₆₆ O ₄	M+FA-H	595.4929	-2.5898		√	√

Table S3. List of m/z values for the MS/MS spectrum of validated differential metabolites.

Compound name	Peak m/z (measured)	Peak m/z (database)
Bilirubin	299.1388	299.1391
	584.2621	584.2617
LysoPC(16:0/0:0)	313.273	313.27
	459.2481	459.23
	478.3279	478.324
	496.3396	496.337
LysoPC(0:0/18:0)	184.0727	184.0733
	341.3042	341.305
	506.36	506.3605
	524.3711	524.3711
LysoPC(18:1/0:0)	184.0726	184.0733
	339.2877	339.2894
	504.344	504.3449
	522.3555	522.3554
Sucrose	203.0522	203.0521
	365.1052	365.1035
PC(16:0/0:0)	184.0722	184.0731
	313.2727	313.2732
	478.3286	478.3297
PC(22:6/0:0)	104.1061	104.107
	184.0726	184.073

	483.2475	483.251
1-Linoleoylglycerophosphocholine	104.1061	104.107
	184.0726	184.073
	502.3289	502.329
Deshydroxy-C-1027 chromophore	810.2486	810.242
DG(15:0/0:0/18:4n3)	557.4551	557.4564
	575.4664	575.467
Geranyl-PP	315.0794	315.0763
PE(P-16:0)	420.2856	420.287
DG(15:0/0:0/18:4n3)	557.4557	557.4564
LysoPE(18:2)	337.2728	337.274
PE(19:1)	476.3114	476.3161
MG(0:0/20:2/0:0)	400.3411	400.3427
LysoPC(20:3)	458.248	458.251
Centamicin C2b	446.2987	446.297
Adenosine 3'-monophosphate	136.0609	136.0614
DG(13:0/20:3/0:0)	559.4716	559.472
PC(22:6/18:2)	745.4761	745.48
PE(P-16:0/0:0)	239.237	239.238
	436.2827	436.2833
LysoPE(0:0/20:1)	506.3239	506.3252
LysoPE(18:0/0:0)	283.2634	283.2643
Norethinrone acetate	183.0114	183.0102

	339.1992	339.201
1-Heptadecanoyl-sn-glycero-3-phosphocholine	508.3399	508.3386
	283.2634	283.2627
2-Dodecylbenzenesulfonic acid	325.1828	325.1837
Inosinic acid	135.0307	135.0302
Inosine 5'-monophosphate	92.0246	92.025
	135.0305	135.0302
Glycogen	545.1701	545.1718
LysoPC(18:2/0:0)	504.2666	504.3083
Feruloyl-beta-sitosterol	561.4087	561.3938
Met His Lys	119.0846	119.0851