

Supplementary data

Supplementary 1

Liquid chromatography with LC-MS/MS

LC-MS/MS was carried out using an Orbitrap Fusion Lumos Tribrid mass spectrometer (Thermo Scientific, Massachusetts, USA). Peptides were isolated using an UltiMate 3000 nanoLC system (Thermo Scientific, Massachusetts, USA). Peptide mixtures were loaded onto a C18 Acclaim PepMap NanoLC column with a 75 μ m inner diameter and a 25-cm length, which was filled with 2 μ m particles with a pore size of 100 Å (Thermo Science, USA). The mobile phase A was made up of 0.1 % formic acid in water, while the mobile phase B was made up of 100% acetonitrile and 0.1 % formic acid. A segmented gradient elution from 2% to 40% of solvent B was applied in 90 minutes using a 300 nL/min flow rate. A full-MS scan (externally tuned to a mass precision of 5 ppm with a resolution of 120000 at $m/z = 200$, auto gain control [AGC] set to $5e5$, and a maximum injection time of 50 ms) was performed in a data-dependent mode, followed by 3 s of high-energy collisional dissociation (HCD)-MS/MS of the most intense ions. HCD-MS/MS (with a resolution of 15000) was utilized to fragment multicharged ions. An AGC of $5e4$ was used for MS/MS analysis, with previously selected ions dynamically deleted for 180 seconds. The injection time was set to 50 milliseconds.

Exploration of proteomics database

Raw MS/MS data from the Proteome Discoverer kit was searched against the UniProt Knowledgebase human protein database (Swiss-prot) using the Mascot search method (version 2.2, Thermo Scientific). The following parameters were used in the search: MS/MS ion mass

tolerance of 0.02 Da, with up to two missed cleavages allowed; peptide mass tolerance was 10 ppm, and variable modifications such as deamidation, oxidation, phospho, carbamidomethyl, methyl, and acetyl were allowed. Based on a 1% false discovery rate (FDR). The protein content was determined by measuring the concentration of ions obtained from MS spectra of associated peptides. DAVID Bioinformatics Resources 6.8 was used to perform functional annotation clustering with gene ontology (GO) enrichment analysis allowing to examine the biological process involved and the enrichment of functional annotation clustering.

Supplementary Table 1: List of growth factors, cytokines and antioxidants found in PEVs by LC-MS/MS

Accession	Description
P42566	Epidermal growth factor receptor substrate 15 OS=Homo sapiens OX=9606 GN=EPS15 PE=1 SV=2
Q15582	Transforming growth factor-beta-induced protein ig-h3 OS=Homo sapiens OX=9606 GN=TGFB1 PE=1 SV=1
P17936	Insulin-like growth factor-binding protein 3 OS=Homo sapiens OX=9606 GN=IGFBP3 PE=1 SV=2
Q9UBC2	Epidermal growth factor receptor substrate 15-like 1 OS=Homo sapiens OX=9606 GN=EPS15L1 PE=1 SV=1
Q04756	Hepatocyte growth factor activator OS=Homo sapiens OX=9606 GN=HGFA1 PE=1 SV=1
P01344	Insulin-like growth factor II OS=Homo sapiens OX=9606 GN=IGF2 PE=1 SV=1
O43294	Transforming growth factor beta-1-induced transcript 1 protein OS=Homo sapiens OX=9606 GN=TGFB1I1 PE=1 SV=2
P62993	Growth factor receptor-bound protein 2 OS=Homo sapiens OX=9606 GN=GRB2 PE=1 SV=1
P01137	Transforming growth factor beta-1 proprotein OS=Homo sapiens OX=9606 GN=TGFB1 PE=1 SV=2
P35858	Insulin-like growth factor-binding protein complex acid labile subunit OS=Homo sapiens OX=9606 GN=IGFALS PE=1 SV=1
Q14766	Latent-transforming growth factor beta-binding protein 1 OS=Homo sapiens OX=9606 GN=LTBP1 PE=1 SV=4
Q9Y2Q3	Glutathione S-transferase kappa 1 OS=Homo sapiens OX=9606 GN=GSTK1 PE=1 SV=3
Q9UJC5	SH3 domain-binding glutamic acid-rich-like protein 2 OS=Homo sapiens OX=9606 GN=SH3BGRL2 PE=1 SV=2
Q9H299	SH3 domain-binding glutamic acid-rich-like protein 3 OS=Homo sapiens OX=9606 GN=SH3BGRL3 PE=1 SV=1
Q16775	Hydroxyacylglutathione hydrolase, mitochondrial OS=Homo sapiens OX=9606 GN=HAGH PE=1 SV=2
Q13162	Peroxiredoxin-4 OS=Homo sapiens OX=9606 GN=PRDX4 PE=1 SV=1
Q06830	Peroxiredoxin-1 OS=Homo sapiens OX=9606 GN=PRDX1 PE=1 SV=1
Q04760	Lactoylglutathione lyase OS=Homo sapiens OX=9606 GN=GLO1 PE=1 SV=4
P78417	Glutathione S-transferase omega-1 OS=Homo sapiens OX=9606 GN=GSTO1 PE=1 SV=2
P48637	Glutathione synthetase OS=Homo sapiens OX=9606 GN=GSS PE=1 SV=1
P48507	Glutamate--cysteine ligase regulatory subunit OS=Homo sapiens OX=9606 GN=GCLM PE=1 SV=1
P36969	Phospholipid hydroperoxide glutathione peroxidase OS=Homo sapiens OX=9606 GN=GPX4 PE=1 SV=3
P32119	Peroxiredoxin-2 OS=Homo sapiens OX=9606 GN=PRDX2 PE=1 SV=5
P30048	Thioredoxin-dependent peroxide reductase, mitochondrial OS=Homo sapiens OX=9606 GN=PRDX3 PE=1 SV=3

P30044	Peroxiredoxin-5, mitochondrial OS=Homo sapiens OX=9606 GN=PRDX5 PE=1 SV=4
P30041	Peroxiredoxin-6 OS=Homo sapiens OX=9606 GN=PRDX6 PE=1 SV=3
P22352	Glutathione peroxidase 3 OS=Homo sapiens OX=9606 GN=GPX3 PE=1 SV=2
P21266	Glutathione S-transferase Mu 3 OS=Homo sapiens OX=9606 GN=GSTM3 PE=1 SV=3
P10768	S-formylglutathione hydrolase OS=Homo sapiens OX=9606 GN=ESD PE=1 SV=2
P09488	Glutathione S-transferase Mu 1 OS=Homo sapiens OX=9606 GN=GSTM1 PE=1 SV=3
P09211	Glutathione S-transferase P OS=Homo sapiens OX=9606 GN=GSTP1 PE=1 SV=2
P07203	Glutathione peroxidase 1 OS=Homo sapiens OX=9606 GN=GPX1 PE=1 SV=4
P04179	Superoxide dismutase [Mn], mitochondrial OS=Homo sapiens OX=9606 GN=SOD2 PE=1 SV=3
P04040	Catalase OS=Homo sapiens OX=9606 GN=CAT PE=1 SV=3
P00441	Superoxide dismutase [Cu-Zn] OS=Homo sapiens OX=9606 GN=SOD1 PE=1 SV=2
P00390	Glutathione reductase, mitochondrial OS=Homo sapiens OX=9606 GN=GSR PE=1 SV=2
O76003	Glutaredoxin-3 OS=Homo sapiens OX=9606 GN=GLRX3 PE=1 SV=2
O75368	SH3 domain-binding glutamic acid-rich-like protein OS=Homo sapiens OX=9606 GN=SH3BGRL PE=1 SV=1

Supplementary Table 2: Biochemical analysis of platelet extracellular vesicles (PEVs)

Content	Mean	SD
Glucose (mg/dL)	87.67	12.50
Albumin (mg/dL)	27.70	0.12
Cholesterol (mg/dL)	17.33	0.58
Triglyceride (mg/dL)	15.00	6.08
Cl (mEq/L)	116.33	0.58
Na (mEq/L)	142.33	2.52
K (mEq/L)	3.23	0.06
Ca (mg/dL)	<1.2	
P (mg/dL)	1.43	0.21
Mg (mEq/L)	1.10	0.00
Fe (μ/dL)	76.70	3.79
TIBC (μg/dL)	266.70	5.03
UIB (μg/dL)	190.00	1.73
Ferritin (ng/mL)	45.33	15.14
Vitamin B12 (pg/mL)	87.07	39.32
Folate (ng/mL)	2.70	1.33
Fibrinogen (mg/mL)	<0.4	
Hemoglobin (g/dl)	0.13	0.12