SUPPLEMENTAL PROCEDURES

Reference Experiment 1: ERLIC

This experiment was performed as described in the section 'EXPERIMENTAL PROCEDURES' in the main manuscript except for the omission of ultracentrifugation (UC).

Plasma proteins were precipitated with 80% pre-chilled acetone (20mL) overnight at -20°C. Precipitated proteins were isolated by centrifugation at 1600 x g for 10min and then air dried on ice prior to in-solution tryptic digestion.

Reference Experiment 2: PUC

This experiment was performed as described in the section 'EXPERIMENTAL PROCEDURES' in the main manuscript except for the omission of glycopeptide enrichment by ERLIC.

Vacuum-dried peptides were reconstituted in 200µL mobile phase A (85% ACN, 0.1% HAc, 5mM CH_3COONH_4) and fractionated using a PolyWAX LP anion-exchange column (4.6 × 200mm, 5µm, 300Å; PolyLC, Columbia, MD) on a Shimadzu Prominence UFLC system (Kyoto, Japan). The UV spectra of the peptides were collected at 280nm. Whole proteome fractionation was performed using a 60min gradient elution of mobile phase A and mobile phase B (30% ACN, 0.1% FA) starting with 0 - 36% B over 30min, 36 −100% B over 20min, and then 100% B for 10min (flow rate 1mL/min). A total of 35 proteome fractions were collected, pooled into 20 fractions, and then vacuum dried. All peptide eluates were then deglycosylated using PNGaseF (New England Biolabs, Beverly, MA, USA) in 50mM ammonium acetate, pH 5. PNGaseF-treated peptides were then dried and reconstituted in 3% ACN, 0.1% FA for subsequent LC-MS/MS analysis.

Reference Experiment 3: Standard UC-ERLIC

This experiment was performed as described in the section 'EXPERIMENTAL PROCEDURES' in the main manuscript except that UC duration was 2h instead of 18h.

A total of 5mL pooled plasma was diluted with 25mL of 1 x phosphate buffered saline (PBS) and then differentially centrifuged at 200 x g (30min), 2,000 x g (30min) and 12,000 x g (60min) at 4°C to exclude intact cells and cellular debris. The resultant supernatant was aliquoted into a 25 x 89 mm polycarbonate tube (Type 50.2 Ti rotor, Beckman Coulter, California), and plasma extracellular vesicles were pelleted at 200,000 x g (2h, 4°C) using a Beckman L100-XP Ultracentrifuge (Beckman Coulter, California). The extracellular vesicles were re-suspended in PBS to remove residual contaminants and then pelleted at 200,000 x g (2h, 4°C).