

SUPPLEMENTARY MATERIAL

Supplementary Methods

Plasma sample collection

The plasma preparation was processed by the procedure as described previously with minor modifications (Liu et al., 2012). In brief, blood samples were put at 4 °C for 1 h after collection in EDTA tubes, then the blood was centrifuged at 3000 g at 4 °C for 15 min and the supernatant was collected.

Optimization of traditional AEC method to remove high abundance plasma proteins from HDL

A volume of 30 µL plasma for each sample was used for AEC lipoprotein separation. 5 main lipoprotein classes were separated following the methods reported previously except holding Buffer B at 7%, 8%, 9% and 10% for 10 min respectively before HDL elution to explore the removing effectiveness of high abundance plasma proteins from HDL (Hirowatari et al., 2003; Ji et al., 2014). Briefly, ionic strength of the elution buffer was altered by changing B% buffer as follows: (1) held B% buffer constant at 0% for 5 min; (2) increased B% buffer from 0 to 10% linearly over 5 min; (3) held B% buffer constant at 7%, 8%, 9% or 10% for 10 min; (4) held B% buffer constant at 20.5% for 10 min; (5) held B% buffer constant at 24.5% for 10 min; (6) held B% buffer constant at 27.5% for 10 min; (7) held B% buffer constant at 32.5% for 10 min; (8) increased B% buffer to 100% over 5 min; (9) held B% buffer constant for 5 min to wash the column; and then (10) reduced B% buffer to 0% and hold constant for 5 min to regenerate the column. The HPLC workstation, separation columns, mobile phase, flow rate and fraction collection methods were same with HiPL method.

Lipoprotein separation by FPLC

50 µL plasma was filtered by 0.22 µm Ultrafree-MC-GV centrifugal filters (Millipore) and was diluted to 200 µL with PBS. 200 µL diluted plasma from a single subject was applied directly to three Superose 6 gel filtration columns (10/300 GL; GE Healthcare) arranged in series on an AKTA FPLC system (GE Healthcare). The sample processed at a flow rate of 0.5 mL/min in PBS containing 1 mM EDTA as a running buffer. Eluate was collected as 47 1.5-mL fractions on a Frac 900 fraction collector (GE healthcare) maintained at 4 °C.

Extraction of lipid in each lipoprotein fraction

Lipid extraction was carried out by a methyl tert-butyl ether (MTBE) protocol described previously (Matyash et al., 2008). For lipidomics analysis of HFHC diet rabbits, 10 µL chloroform

solution containing 25 ng/ μ L of each 1,2-dibehenoyl-sn-glycero-3-phosphocholine (PC 22:0/22:0), 1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine (PE 14:0/14:0), N-heptadecanoyl-D-erythro-sphingosine (Cer d18:1/17:0), cholest-5-en-3 β -yl heptadecanoate (CE 17:0), triheptadecenoin (TAG 17:1/17:1/17:1), diheptadecenoin (DAG 17:1/17:1) was added as internal standards. For lipidomics analysis of ACS patients, 30 μ L internal standards mix of lipid classes in internal standards kit for lipidizer platform (Sciex, Foster City, CA) were added. Subsequently, a volume of 300 μ L methanol and then 1 ml MTBE was added to fractions redissolved by 50 μ L deionized water. Tubes were shaken for 1 h at room temperature. Upon addition of 250 μ L deionized water and shaking, phase separation was induced. The upper organic phase was collected, the lower aqueous phase re-extracted with MTBE. Upper phases were combined for lipidomics analysis and lower aqueous phases for proteomics analysis. The upper organic phase for lipidomics analysis was concentrated to dry under nitrogen. The solvent in the lower aqueous phase was removed in vacuo (SpeedVac, Thermo Fisher Scientific, San Jose, CA, USA). Lipid extracts were re-suspended in 200 μ L CHCl₃/MeOH 1:1 and stored at -80 °C.

Proteomics analysis

Protein digestion and stable isotope labeling

Trypsin digestion of protein from each sample was completed as previously described (Ning et al., 2008). TMT labeling was done following the manufacturer's instructions (Thermo Scientific, Rockford, IL). Briefly, for each 10-plex experiment, the tryptic digested peptides were reconstituted with 10 μ L 0.5 M TEAB buffer (pH 8.5). Each peptide solution was labeled at room temperature for 2 h with one-fifth of reagent vial (10-plex mass tag 126, 127N, 127C, 128N, 128C, 129N, 129C, 130N, 130C, 131) previously reconstituted with 300 μ L anhydrous acetonitrile (ACN). We labeled the same mixture of peptides from the analyzed samples in each TMT 10-plex plate as a reference channel. After 2 h, 8 μ L 5% hydroxylamine was added to each tube then incubated at room temperature for 15 min to quench the TMT reaction. The contents of all TMT reagent labeled sample tubes were combined into one tube for 10-plex experiments, respectively. Then, labeled samples were dried down by evaporation in a SpeedVac (Thermo Fisher Scientific, San Jose, CA, USA) to obtain a brown pellet. 100 μ L of water was added to the tube and the sample was dried completely. Prior to MS analysis, samples were desalted onto Empore C18 47 mm Disk (3-M).

LC-MS/MS analysis

For all samples, the peptides were resuspended in 12 μ L H₂O with 0.1% (v/v) TFA, and 3 μ L was taken for mass spectrometry analysis. Reverse-phase high-performance liquid chromatography (RP-HPLC) separation was achieved using an EASY-nLC 1000 LC system (Thermo Fisher

Scientific) equipped with a self-packed tip column (75 μm $\times$ 150 mm; C18, 3 μm) at a flow rate of 300 nL/min for 120 min and a linear gradient from 4% to 23% acetonitrile with 0.1% (v/v) formic acid. All mass spectral data were acquired on Orbitrap Fusion and Q Exactive HFX mass spectrometers (Thermo Fisher Scientific). For data acquisition on the Orbitrap Fusion instrument, a full scan was acquired in ranges m/z 300–1500 with high resolution (120000@ m/z 200) following data-dependent scans generated by HCD fragmentation. Resolution for MS/MS spectra was set to 50000 @ m/z 200. The normalized collision energy for MS2 was 33.0%. For data acquisition on the Q Exactive HFX instrument, a full scan was acquired in ranges m/z 300–1500 with high resolution (120000@ m/z 200) following data-dependent ‘top 15’ scans generated by HCD fragmentation. Resolution for MS/MS spectra was set to 60000 @ m/z 200. The normalized collision energy for MS2 was 28.0%. Data were acquired using Xcalibur software.

Data processing and quantification

All raw MS data were analyzed with the MaxQuant software (version 1.5.2.8). Parent ion and MS2 spectra were searched by the Andromeda search engine incorporated in the MaxQuant software against a Uniprot FASTA database corresponding with the species. A false discovery rate (FDR) of 0.01 for proteins and peptides, and a minimum peptide length of 7 amino acids were both required. Trypsin digestion was chosen as enzyme specificity. TMT tags on lysine residues and peptide N termini (229.162932 Da), and carbamidomethylation on cysteine were selected as fixed modifications, while protein N-terminal acetylation and methionine oxidation were selected as variable modifications. Search targeted variable modifications on acetylation (protein N-terminal) and oxidation (M). Maximally two missed cleavages were allowed. In quantification, a 10-plex TMT type was chosen in the item of reporter ion MS2 in MaxQuant software. Protein abundance was calculated from TMT reagent reporter ion intensities from MS/MS spectra. Relative ratio (ratio of ratio) was calculated as follows: firstly, the intensity of proteins in each channel were corrected by the reference channel to correct the cross-plate variation; secondly, in order to avoid the over- and under-estimation of protein quantification for each fraction due to the difference of protein content among 9 fractions, for example, over-estimation of the protein quantification in HDL and under-estimation in LDL and VLDL fractions due to much lower protein content in LDL and VLDL compared with HDL, the intensities after correction by reference channel were normalized by the average value in each channel to get protein ratios; thirdly, a value of 1.0 was assigned to the fraction containing the highest ratio for that particular protein and all other fractions were scaled from there (Gordon et al., 2010). The proteins quantified in more than 2/3 samples were used for the following analysis.

Lipidomics analysis

LC-MS/MS analysis for HFHC induced rabbits

The lipid samples were analyzed on AB Sciex TripleTOF 6600 Mass Spectrometers system (AB Sciex, Foster City, CA) coupled to a Shimadzu LC20ADXR system. A Kinetex C18 column (100 × 2.1 mm, 2.6 μm, Phenomenex, 00D-4462-an) at 40 °C was utilized to separate the lipids at a flow rate of 0.4 mL/min by a binary gradient of H₂O:MeOH:ACN(3:1:1) (mobile phase A) and IPA (mobile phase B), both containing 5 mM NH₄Ac. 2 μL sample was injected to the column and the sampler temperature was maintained at 4 °C. Linear gradient was set by changing B% mobile phase as follows: 0.5 min, 20% B; 1.5 min 40% B; 3 min 60% B; 13 min 98% B; 13.1 min 20% B; 17 min 20% B. The analytes were ionized in positive APCI mode, and parameters were set as follows: curtain gas (CUR): 35 psi; gas 1 (GS1):60 psi; gas 2 (GS2): 60 psi; ionspray voltage (ISVF): 5500V; temperature (TEM): 600 °C; decluttering potential (DP): 80 V. For TOF MS, accumulation was acquired in ranges m/z 200–1000 and accumulation time was 120 ms. For TOF MS/MS, accumulation was acquired in ranges m/z 50-1000; accumulation time was 70 ms; collision energy (CE) was set as 40 V; collision energy spread (CES) was 20 V.

Each lipid group database was exported by Lipidview software using the Lipidview method exporter tool and the extraction width was 20 mDa. Mass spectrums were compared to the exported database in Peakview software and the lipids which mass error less than 8 ppm and isotope ratio difference less than 10% were identified and then confirmed by characteristic product ion (PI) and neutral loss (NL). Characteristic PI m/z of PC, LPC, SM was 184(+), CE was 369.3(+) and Cer was 264.2(+). Characteristic NL m/z of PE was 141(+) and TAG/DAG was FA (+). Subsequent quantitative calculation all based on the peak area of confirmed lipids which were calculated using MultiQuant software. The method used for the lipid quantification of HFHC induced rabbits was similar to that used for the lipid quantification of ACS patients (see below).

LC-MS/MS analysis for ACS patients

Liquid chromatographic separation was performed on Shimadzu Nexera X2 LC-30AD system, coupled to SCIEX 5500 QTRAP Mass Spectrometer. Analyst 1.6.3 software (Sciex, Foster City, CA) was used for data acquirement. Waters ACQUITY UPLC BEH HILIC Column (130Å, 1.7 μm, 2.1 mm X 100 mm) was used for chromatographic separation. Five microliters of lipid extracts were injected into the column. The column temperature was maintained at 40 °C. A gradient system of two mobile phases, 1:1 (v/v) acetonitrile /water with 10 mM ammonium acetate (A) and pure acetonitrile (B), was used to elute the lipids from the column at a flow rate of 300 μL/min. The gradient was as follows: 0.1 min, 85% B; 7.5 min, 65% B; 8.5 min, 5% B; 11 min, 5% B; 15 min, 85% B. The total run time was 15 min.

The analytes were ionized in positive and negative ESI mode. Data were acquired in multiple reaction monitoring (MRM) mode. 631 MRM transitions were monitored in positive mode, and 401 transitions were monitored in negative mode. Nitrogen (99.999%) was applied as drying gas, nebulizer gas, and collision gas. The gas temperature was 500 °C. The curtain gas was set as 35.0 psi and collision gas set as medium. The pressure of ion source gas1 was 40 psi and gas2 was 50 psi. The ion spray voltage in positive mode was 5500 V and in negative mode was -4500 V.

Quantitative calculation all based on the peak area of confirmed transitions using MultiQuant 3.0 Software (Sciex, Foster City, CA). Internal standards kit for the Lipidizer platform (Sciex, Foster City, CA) contained multiple internal standards with different acyl chains for each lipid class, and we chose the internal standard for each lipid according to the similarity of the length of the acyl chain. The peak area of lipids was corrected by the corresponding internal standards to normalize the technical variability across injections. We calculated the lipid concentration by the formula as follows:

$$\frac{\text{Peak area (lipid)}}{\text{Peak area (internal standard)}} \times \text{Concentration (internal standard)}.$$

Then, in order to avoid the over- and under-estimation of the lipid quantification for each fraction due to the difference of total lipoprotein content among 9 fractions (especially among HDL subclasses), which might induce the similar distribution of lipid molecules, we calculated the percentage of lipids by normalizing the concentration of lipids using the total concentration of all measured lipids. The percentage of lipid class was the sum of the percentage of all lipids in this lipid class. The relative ratio (ratio of ratio) of the lipid class was the ratio of the lipid class percentage in each fraction to the maximum percentage of this lipid class in nine fractions.

Supplementary Discussion

According to the principle of constructing distribution correlation of APOA1 with other proteins and lipids in ACS patients, we performed PCC analysis between protein and lipid across the nine fractions separated by Lipo-HiPL methods for lipoproteins of rabbits and constructed the APOA1 interactome before and after HFHC diet (**Figure 3**). At Pre state, the proteins of APOM, SAA, GPLD1 (phosphatidylinositol-glycan-specific phospholipase D) and lipids of PC and PE correlated with APOA1, while proteins of APOE, DNAH8 (dynein heavy chain 8), CHMP4A (charged multivesicular body protein 4a) and lipids of TAG correlated with APOB, which suggested they were interacted molecules in the cargoes of HDL and LDL/VLDL respectively. The interactions of APOM, SAA, and GPLD1 with APOA1 were confirmed by the STRING database. It was reported that the proteins of APOM and GPLD1 correlated with APOA1 and distributed mainly in HDL (Xu and Dahlback, 1999; Deeg et al., 2001). The interaction of APOE with APOB was

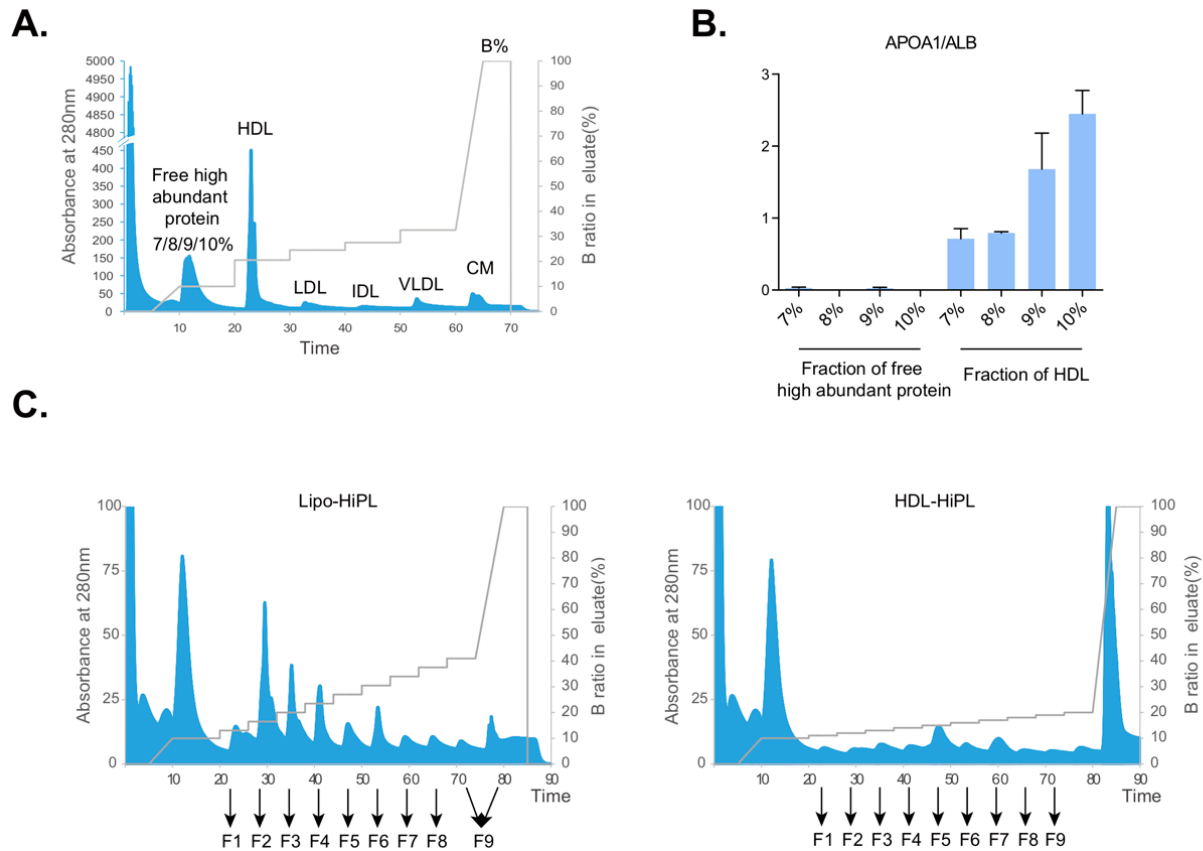
confirmed by the STRING database. However, the stable states were interrupted by the HFHC diet. For example, PCYOX1 (prenylcysteine oxidase 1), VNN1 (pantetheinase), and PM20D1 (N-fatty-acyl-amino acid synthase/hydrolase) joined into the LDL and VLDL cargoes after HFHC diet. PCYOX1 involved in the degradation of prenylated proteins and overproduction of hydrogen peroxide which could cause oxidative damage of LDL (Tschantz et al., 2001; Beigneux et al., 2002; Digits et al., 2002; Banfi et al., 2009; Gupta et al., 2010). VNN1 was a novel GPI-linked perivascular molecule and was required in the uptaking of angiogenic microparticles by endothelial cells (Aurrand-Lions et al., 1996; Povero et al., 2013). PM20D1 catalyzes the condensation of fatty acids and amino acids to generate N-acyl amino acids. N-acyl amino acids directly bind mitochondria and function as endogenous uncouplers of UCP1-independent respiration, which might be useful for treating obesity and associated disorders (Long et al., 2016).

Figure 4D showed the similar molecular profile dynamics between HFHC rabbits and ACS patients (**Figure 4D**). For example, GPLD1 increased in LDL/VLDL fractions in both HFHC induced rabbits and ACS patients. Considering the GPLD1 specifically cleaved glycosylphosphatidylinositol (GPI) anchors and VNN1 was a GPI-linked perivascular molecule (AurrandLions et al., 1996; Deeg et al., 2001), GPI-anchor could be highly correlated with ASCVD (arteriosclerotic cardiovascular disease) development. CHMP4A increased in LDL and had a highly similar dynamic profile with APOB in both HFHC induced rabbits and ACS patients. CHMP4A belongs to the chromatin-modifying protein/charged multivesicular body protein (CHMP) family. Since CHMP4A and CHMP4B can form novel membrane-attached filaments that can promote or stabilize negative curvature and outward budding (Hanson et al., 2008), we suppose that CHMP4A is an important structural protein in LDL and VLDL. Since PON1 (serum paraoxonase/arylesterase 1) protected lipid against oxidation and played beneficial effects in atherosclerosis-related processes (Litvinov et al., 2012), its decline in LDL of ACS patients and HFHC induced rabbits might enhance the ASCVD development. The lipoprotein lipase inhibition function of APOC3 suggested its incensement in LDL/VLDL of HFHC induced rabbits and ACS patients inhibited triglyceride metabolism. SAA1 increased in HDL and LDL fractions (especially in HDL fractions) in ACS patients and in LDL and VLDL in HFHC induced rabbits. SAA1 is a potential regulator of inflammation and endothelial dysfunction during the development of CVD (Hua et al., 2009), and previous research have shown that it increased in HDL of CVD patients in previous research (Riwanto et al., 2013). Together, most the dynamic changed molecules revealed by HiPL methods has important physiological functions related to the development of atherosclerosis, suggesting that HiPL methods are potential to find unknown therapeutic targets of CVD.

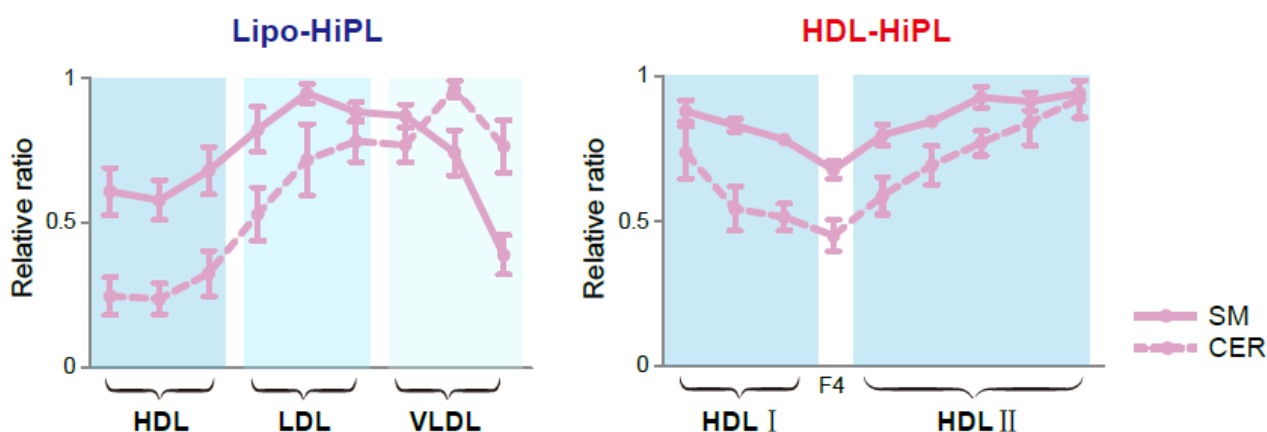
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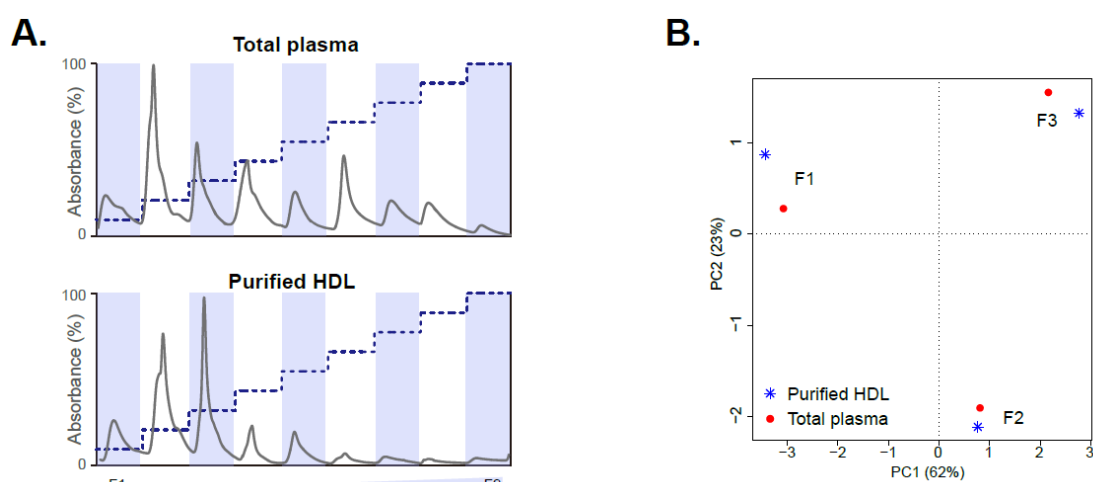
Supplementary Figures



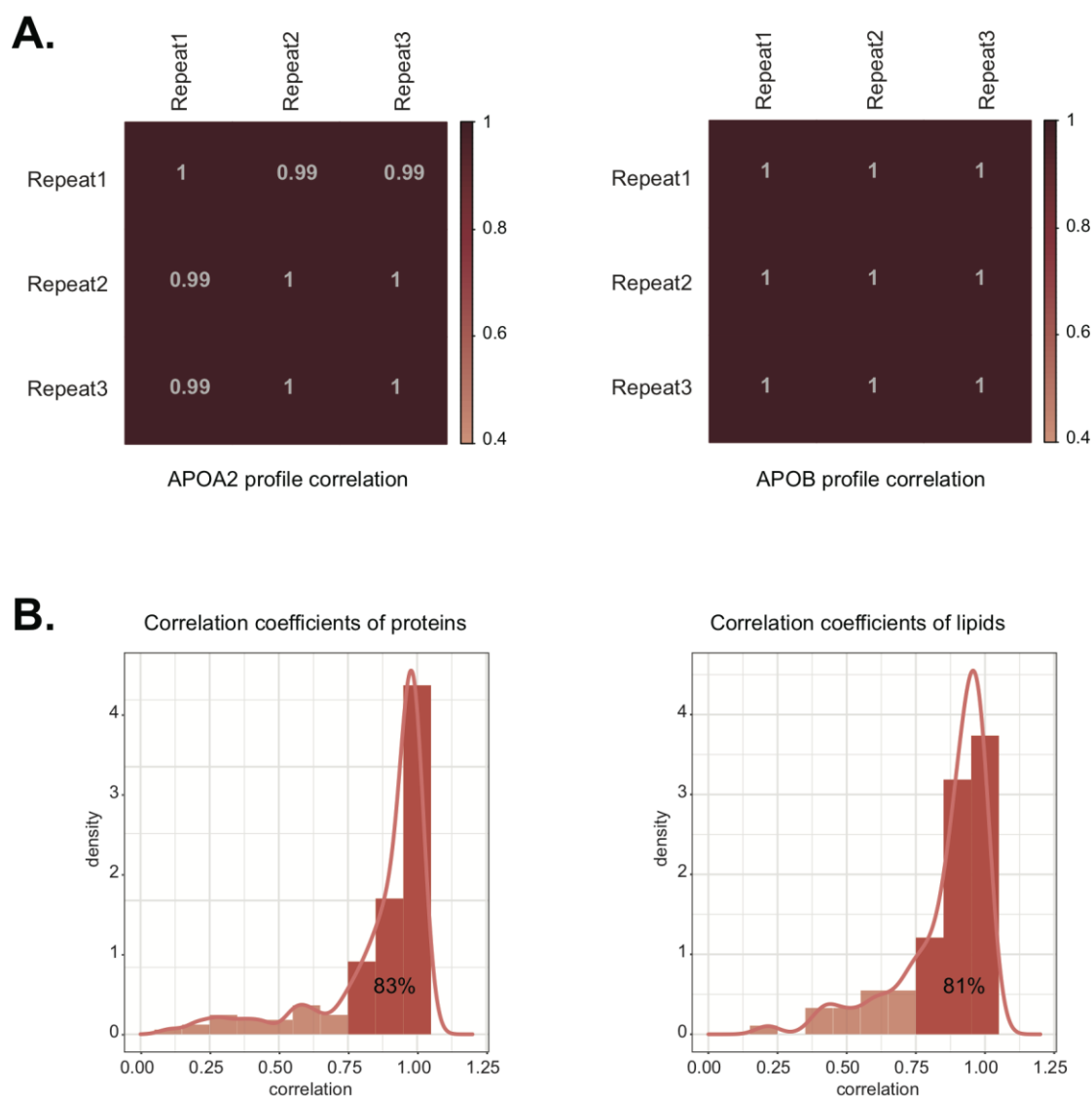
Supplemental Figure S1. Modified AEC method for lipoprotein separation. **A**, Separation chromatogram of plasma lipoproteins using traditional AEC method modified by keeping B ratio at 7%, 8%, 9%, and 10% for 10 min individually before HDL elution (healthy individual, n=3). **B**, The ratio of APOA1 to ALB in the fraction of high abundance protein and the HDL separated by keeping B ratio at 7%, 8%, 9% and 10% for 10 min individually (healthy individual; n = 3, the average ratio was presented). **C**, The entire and raw chromatograms by Lipo-HiPL and HDL-HiPL methods. To be noticed, the maximum absorbance at 280 nm of the peaks before 10 min was as high as 3500 mV and even higher. The maximum value of the ordinate axis was set as 100 mV to enlarge the lipoprotein chromatograms and increase the readability. In the Lipo-HiPL method, the last two peaks were merged to assure 9 lipoprotein fractions. In the HDL-HiPL method, the last two peaks were dropped and the first 9 HDL fractions were analyzed.



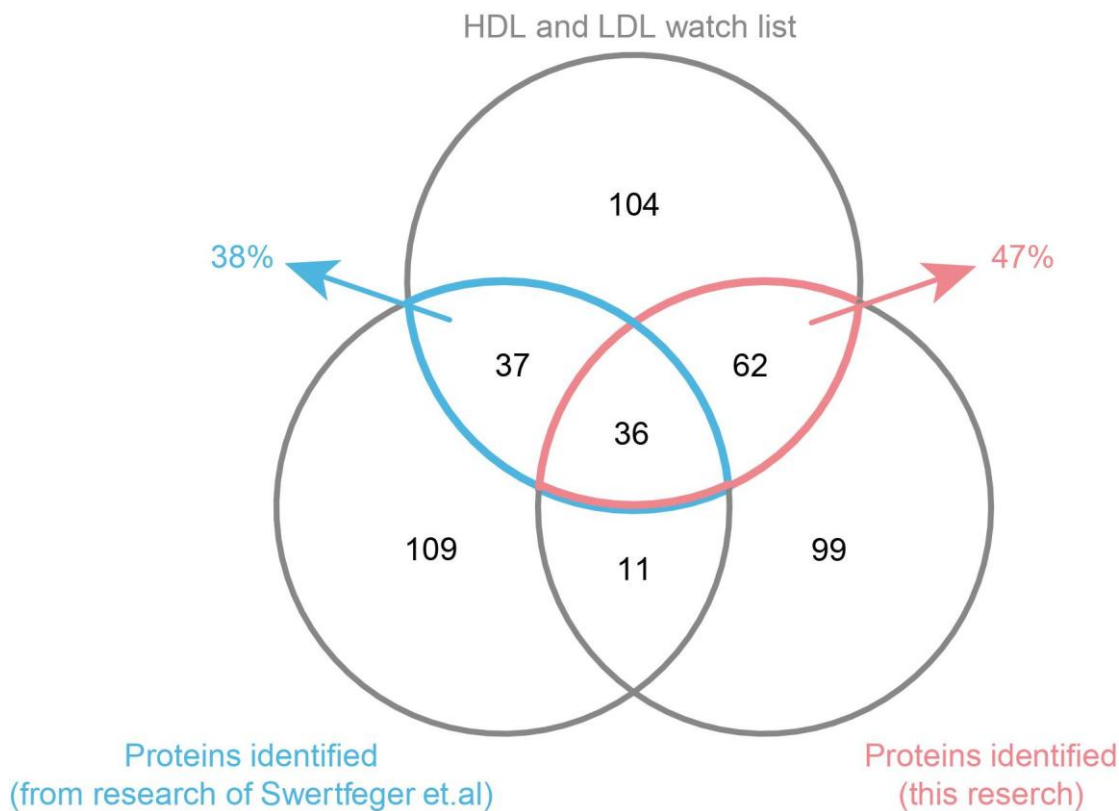
Supplemental Figure S2. Profiles of SM and CER in 9 fractions separated by the Lipo-HiPL method and HDL-HiPL method (healthy individual; n = 5, error bar: SEM). The relative ratio (ratio of ratio) of the lipid class was the ratio of the lipid class percentage in each fraction to the maximum percentage of this lipid class in nine fractions. The percentage of lipid class was the sum of the percentage of all lipids in this lipid class. See the Method part in the supplemental materials for the detailed calculation process of the relative ratio for lipids. SM, sphingomyelin; CER, ceramide.



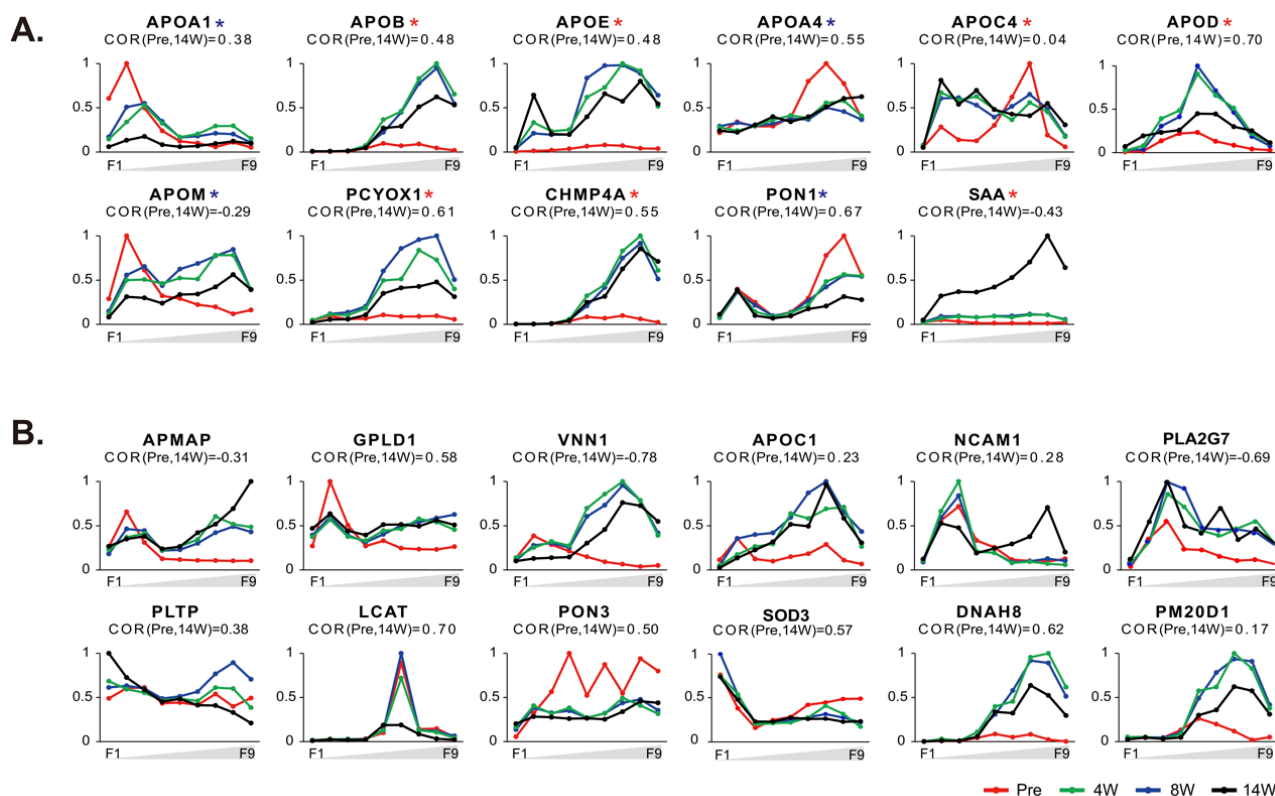
Supplemental Figure S3. HDL profile comparison between total plasma and HDL purified by FPLC using the Lipo-HiPL method. **A**, AEC of total plasma and HDL purified by FPLC (a plasma pool of 5 healthy individuals). To give a brief and overview picture of our HiPL method, the chromatographic peaks was only partial of retention time (from 20 min to 80 min) where the major lipoproteins eluted, and the absorbance (%) was the UV trace normalized by maximum value (it was drag-and-drop operation to zoom the specific region in the LC software). **B**, Principal components analysis (PCA) for protein profiles quantified continuously in the first 3 fractions of total plasma and purified HDL.



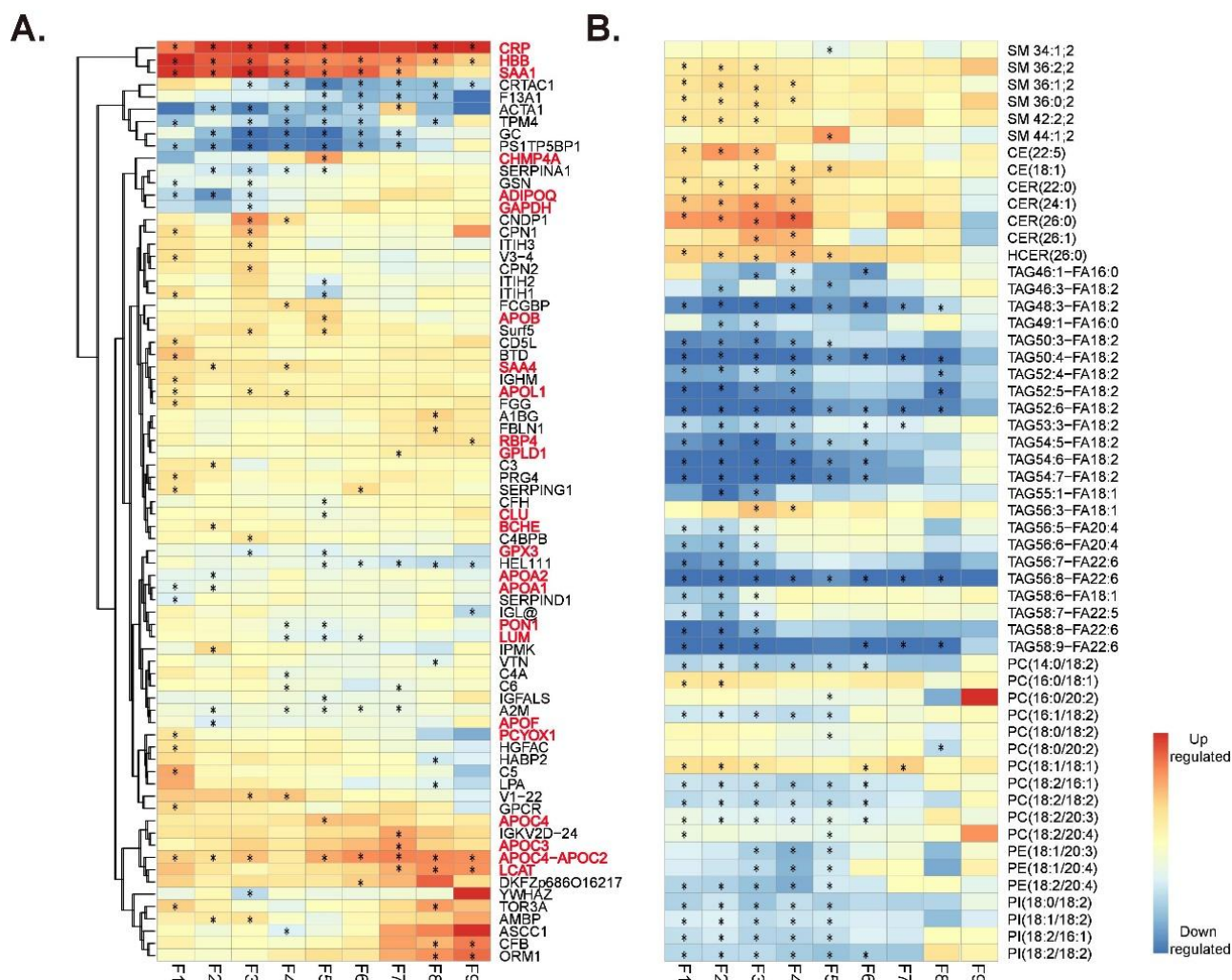
Supplemental Figure S4. Molecular correlation analysis among three repeats. **A**, The profile correlation of APOA2 and APOB among three repetitive separations using a plasma pool of five healthy individuals. **B**, Probability density diagrams of correlations of all quantified proteins and lipids among three repeats. Average value of three correlation coefficients were taken for analysis.



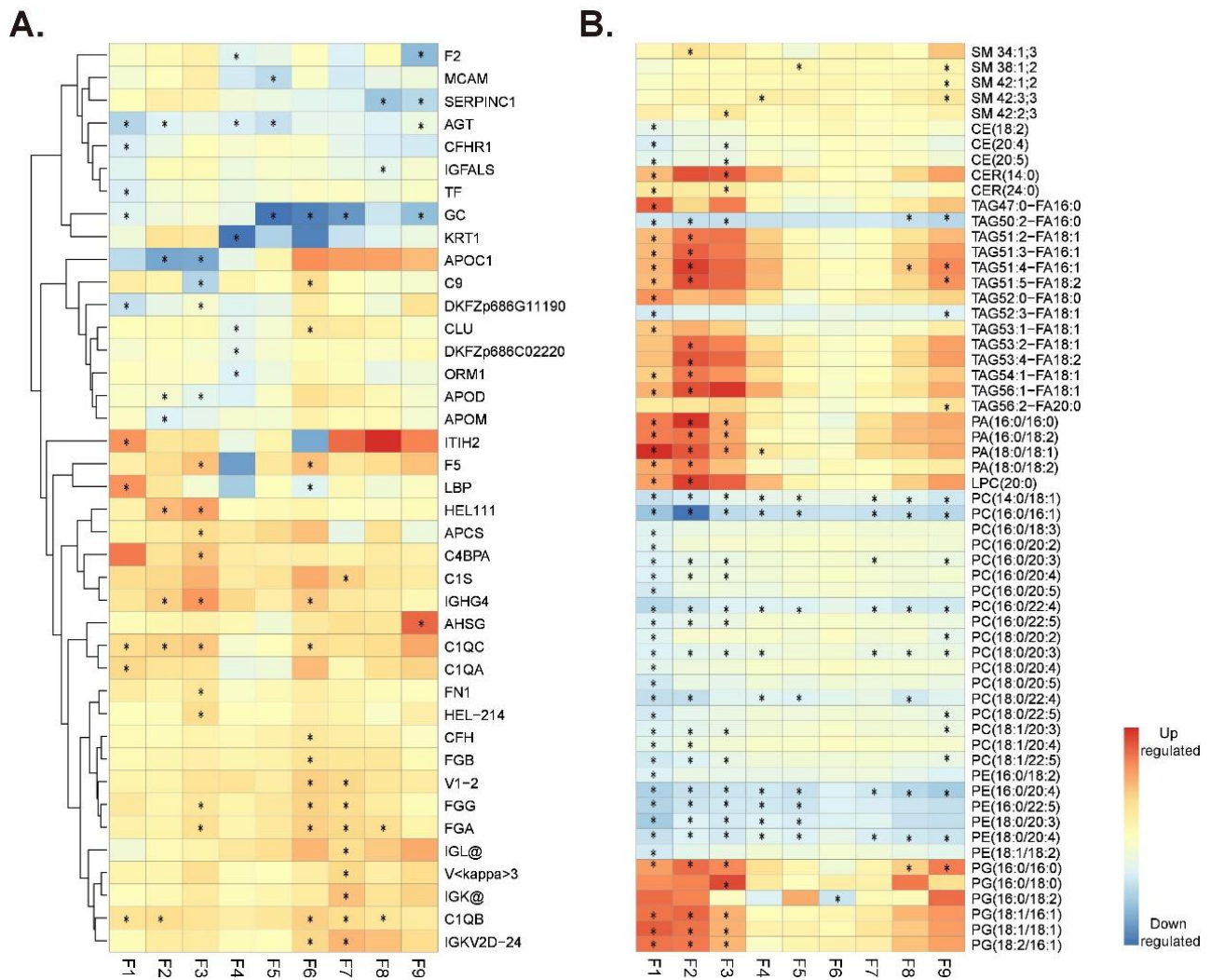
Supplemental Figure S5. Comparison of the ratio of lipoprotein-associated proteins to total identified proteins in result from Swertfeger’s research (Swertfeger et al., 2017) and our research. Lipoprotein-associated proteins were from the HDL and LDL watch list (<http://homepages.uc.edu/~davidswm/HDLproteome.html>). More details about HDL and LDL watch lists summarized by the Davidson lab could be seen on the website provided above. They contained 239 lipoprotein-associated proteins and 97 highly credible lipoprotein-related proteins. Briefly, the HDL watch list contained 229 HDL associated proteins identified by 17 labs from 2005-2014, in which 95 proteins were identified in at least 3 labs and considered to be highly credible HDL-related proteins. LDL watch list contained 60 LDL associated proteins identified by 4 labs from 2005-2014, in which 22 were identified in at least 2 labs and considered to be highly credible LDL-related proteins.



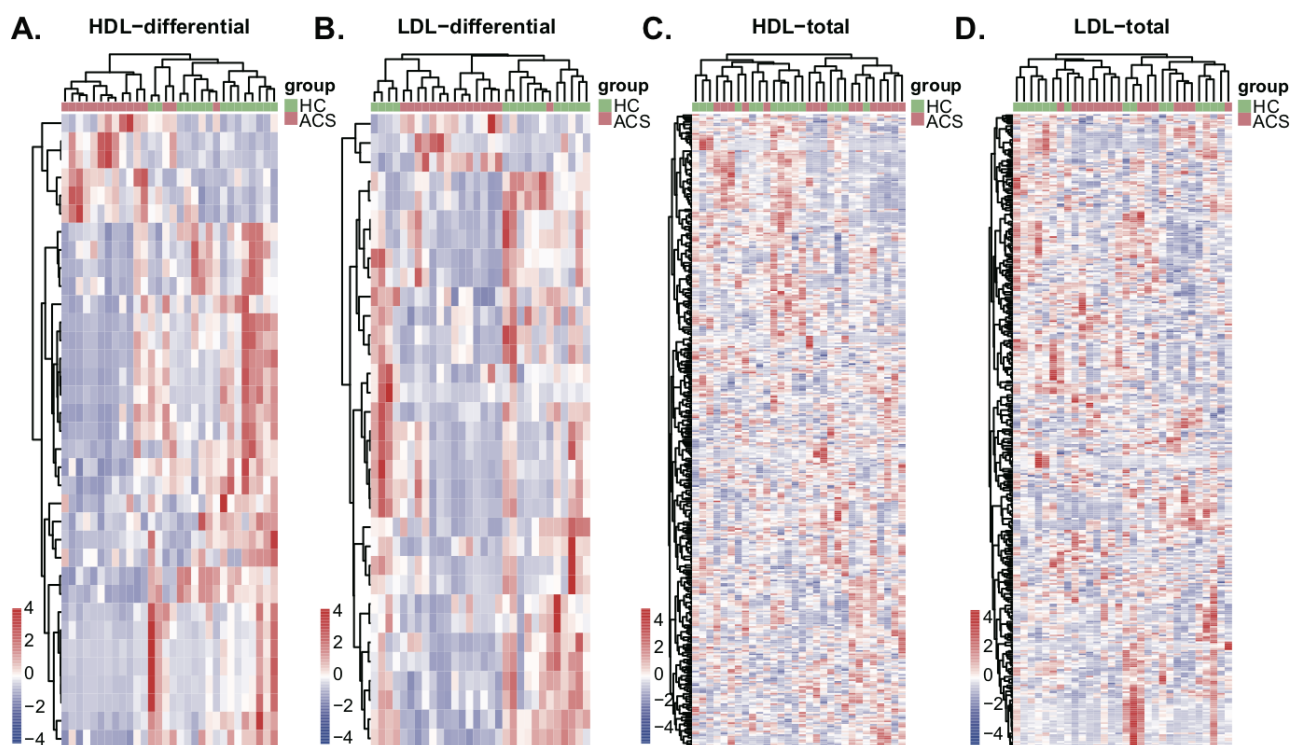
Supplemental Figure S6. Dynamics of protein profiles across nine lipoprotein subclasses of rabbits by Lipo-HiPL method during HFHC diet. **A**, Dynamic profiles of proteins having significantly quantitative variation at total plasma level 14 weeks after HFHC diet. **B**, Dynamic profiles of proteins having no significantly quantitative variation at total plasma level after HFHC diet. Each point was average of relative ratios of 3 individual samples (* : $P < 0.05$; red asterisk stood for up regulated and blue stood for down regulated after HFHC diet)



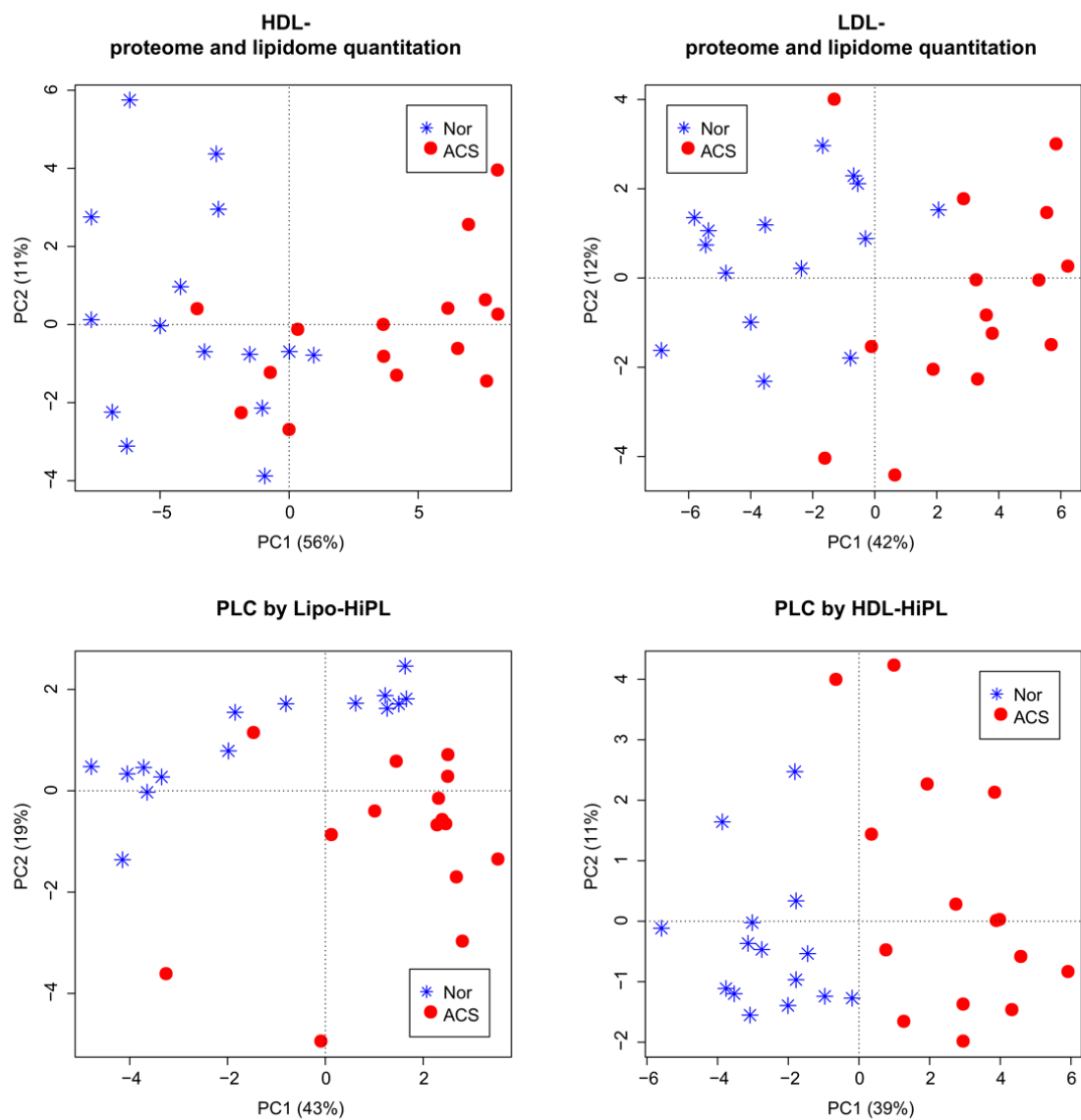
Supplemental Figure S7. Dynamic change of protein (A) and lipid (B) profiles by the Lipo-HiPL method in ACS patients. Red stood for up-regulated and blue stood for down-regulated in ACS patients, the darker of red or blue for each bin, the more significant the fold change; * : $P < 0.05$.



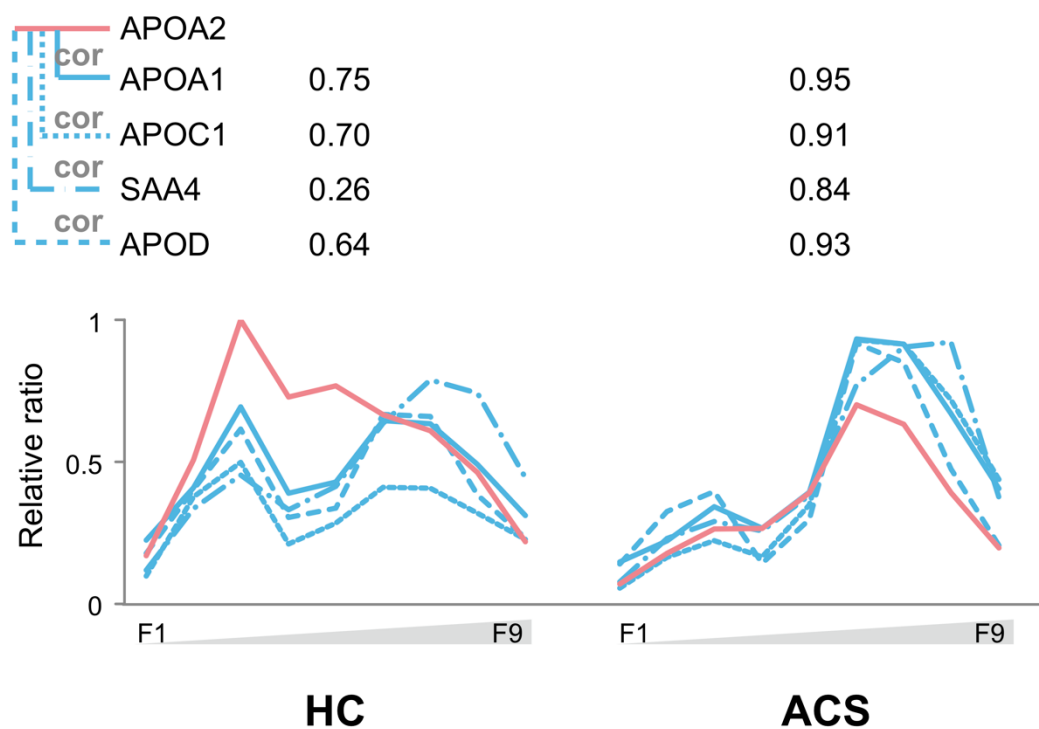
Supplemental Figure S8. Dynamic change of protein (A) and lipid (B) profiles could be observed by the HDL-HiPL method but not by the Lipo-HiPL method in ACS patients. Red stood for up-regulated, and blue stood for down-regulated in ACS patients, the darker of red or blue for each bin, the more significant the fold change; * : $P < 0.05$.



Supplemental Figure S9. HCA results of two groups (HC, ACS) using differential proteins and lipids with $p < 0.05$ and $FC > 1.5$ or < 0.667 in HDL (A) and LDL (B) and using all quantified proteins and lipids in HDL (C) and LDL (D).



Supplemental Figure S10. PCA analysis of two groups (HC, ACS) using direct proteome and lipidome quantification of HDL, LDL, and PLC feature by Lipo- and HDL-HiPL methods.



Supplemental Figure S11. Example of correlation-changed molecular pairs in figure 5F. Each point was the average of relative ratio of 15 individual samples and was normalized by the maximum of all fractions of two groups.

Supplementary Tables

Supplemental Table S7. List of 208 proteins identified in 9 lipoprotein subclasses.

A2M	C4BPA	EFEMP1	HEL-S-62p	LUM	SERPINA1
A30	C4BPB	F10	HEL-S-78p	MASP1	SERPINA3
ACTA1	C5	F11	HEL-S-89n	MASP2	SERPINA4
ACTN1	C6	F12	HEL-S-92n	MBL2	SERPINA5
ADIPOQ	C7	F13A1	HGFAC	MCAM	SERPINC1
AFM	C8A	F13B	HIST1H2BC	NCAM1	SERPIND1
AGT	C8B	F2	HP	NRP1	SERPINF1
AHSG	C8G	F5	HPR	OAF	SERPINF2
ALB	C9	F7	HPX	ORM2	SERPING1
AMBP	CAMP	F9 p22	HSPG2	PARVB	SPARCL1
APOA1	CD44	FAM173A	IGFALS	PCYOX1	SPP2
APOA2	CD5L	FBLN1	IGH@	PF4	SSFA2
APOA4	CDH5	FCGBP	IGHG4	PGLYRP2	Surf5
APOB	CELSR2	FCN2	IGHM	PI16	TF
APOC1	CETP	FERMT3	IGHV3OR16-13	PIGR	TGFBI
APOC2	CFB	FGA	IGJ	PLEK	TLN1
APOC3	CFH	FGG	IGK@	PLG	TOR3A
APOC4	CFHR1	FN1	IGKV1-27	PLTP	TRIM33
APOD	CFHR5	GAPDH	IGKV2D-24	PON1	UNQ172
APOE	CHMP4A	GC	IGKV2D-28	PON3	V<kappa>3
APOF	CLU	GP1BA	IGKV4-1	PPBP	V1-2
APOH	CNDP1	GPLD1	IGL@	PRG4	V1-22
APOL1	CP	GPX3	IGLC7	PROC	V1-5
APOM	CPN1	GSN	IPMK	PROS1	V2-17
ASCC1	CPN2	HABP2	ITIH1	PROZ	V2-7
AZGP1	CRTAC1	HBB	ITIH2	PS1TP5BP1	V3-4
BCHE	DKFZp686C15213	hCG_40889	ITIH3	PSAP	VCAM1
BTD	DKFZp686G11190	HEL111	ITIH4	PZP	VH3
C1QA	DKFZp686H17246	HEL-213	KLKB1	QSOX1	VH6DJ
C1QB	DKFZp686I04196	HEL-214	KNG1	RAA1	VTN
C1QC	DKFZp686I15212	HEL-S-108	KRT1	RBP4	VWF
C1S	DKFZp686K03196	HEL-S-153w	LBP	S100A9	XLKD1
C3	DKFZp686O16217	HEL-S-163pA	LCAT	SAA1	YWHAZ
C4A	DKFZp686P15220	HEL-S-37	LOC136242	SAA4	
C4B	ECM1	HEL-S-51	LPA	SEPP1	

Supplemental Table S12. Main clinical indexes of HC and ACS groups.

	HC	ACS	P (HC vs. ACS)
N (men/women)	15(13+2)	15(13+2)	
Age (years)	65.5 ±6.3	68 ±13.4	0.53
Triglycerides (mg/dl)	85.3 ±23.5	101.7 ±54.2	0.3
Total cholesterol (mg/dl)	146 ±17.7	149.7 ±29.9	0.68
HDL cholesterol (mg/dl)	39.7 ±5.7	37.8 ±6.8	0.42
LDL cholesterol (mg/dl)	95.4 ±16.5	106.2 ±31.7	0.25

Supplemental Table S17. Pearson correlation coefficients for the edges of the APOA1 interactomes in two groups (HC and ACS) constructed by Lipo-HiPL method.

HC			ACS		
nodes1	nodes2	correlation	nodes1	nodes2	correlation
APOA1	BCHE	0.849163	APOA1	BCHE	0.865197
APOA1	APOC1	0.972351	APOA1	APOC1	0.973235
APOA1	APOL1	0.850075	APOA1	APOL1	0.904502
APOA1	GPX3	0.945875	APOA1	GPX3	0.944466
APOA1	F12	0.75981	APOA1	SAA4	0.845492
APOA1	APOC3	0.938483	APOA1	APOC3	0.920404
APOA1	PLTP	0.973909	APOA1	PLTP	0.899819
APOA1	CDH5	0.862044	APOA1	CDH5	0.834832
APOA1	APOD	0.980286	APOA1	APOD	0.973358
APOA1	KLKB1	0.94613	APOA1	KLKB1	0.899536
APOA1	APOC2	0.909623	APOA1	APOC2	0.94949
APOA1	A2M	0.817771	APOA1	APOM	0.893022
APOA1	IGJ	0.891814	APOA1	HPR	0.76918
APOA1	APOA2	0.953068	APOA1	A2M	0.80149
APOA1	GC	0.798702	APOA1	APOA2	0.948599
APOA1	SERPIND1	0.750121	APOA1	APCS	0.757857
APOA1	APOA4	0.783628	APOA1	GC	0.960706
APOA1	ORM2	0.875645	APOA1	SERPIND1	0.798332
APOA1	PI16	0.780143	APOA1	SAA1	0.93455
APOA1	PC	0.898356	APOA1	ORM2	0.800567
APOA1	PC	0.899543	APOA1	CE	0.786751
APOA1	PC	0.921679	APOA1	LPC	0.885391
APOA1	PC	0.891951	APOA1	LPC	0.8631
APOA1	PC	0.897406	APOA1	PC	0.764268
APOA1	PC	0.927468	APOA1	PC	0.908837
APOA1	PC	0.935207	APOA1	PC	0.894445
APOA1	PC	0.954335	APOA1	PC	0.882922
APOA1	PC	0.945935	APOA1	PC	0.909005
APOA1	PC	0.825935	APOA1	PC	0.915558

APOA1	PC	0.835516	APOA1	PC	0.925378
APOA1	PC	0.923305	APOA1	PC	0.920874
APOA1	PC	0.901185	APOA1	PC	0.866756
APOA1	PC	0.942919	APOA1	PC	0.8552
APOA1	PC	0.9385	APOA1	PC	0.90973
APOA1	PC	0.897342	APOA1	PC	0.89095
APOA1	PC	0.924263	APOA1	PC	0.923878
APOA1	PE	0.927055	APOA1	PC	0.913191
APOA1	PE	0.915799	APOA1	PC	0.882325
APOA1	PE	0.953321	APOA1	PC	0.902702
APOA1	PE	0.935049	APOA1	PE	0.879533
APOA1	PE	0.945687	APOA1	PE	0.83591
APOA1	PE	0.940572	APOA1	PE	0.886013
APOA1	PE	0.912646	APOA1	PE	0.892672
APOA1	PE	0.932767	APOA1	PE	0.901181
APOA1	PE	0.934746	APOA1	PE	0.928791
APOA1	PE	0.947105	APOA1	PE	0.905498
APOA1	PI	0.958102	APOA1	PE	0.92095
APOA1	PI	0.949522	APOA1	PE	0.916959
APOA1	PI	0.951276	APOA1	PE	0.932386
APOA1	PI	0.954602	APOA1	PI	0.918509
APOA1	PI	0.957736	APOA1	PI	0.937686
			APOA1	PI	0.915036
			APOA1	PI	0.916288
			APOA1	PI	0.9263

Supplemental Table S18. Pearson correlation coefficients for the edges of the APOA1 interactomes in two groups (HC and ACS) constructed by HDL-HiPL method.

HC			ACS		
nodes1	nodes2	correlation	nodes1	nodes2	correlation
APOA1	APOC1	0.924313	APOA1	BCHE	0.949557
APOA1	APOD	0.965992	APOA1	APOC1	0.990604
APOA1	SAA1	0.771345	APOA1	APOL1	0.913554
APOA1	KRT1	0.765754	APOA1	SAA4	0.936353
APOA1	FCN3	0.754775	APOA1	APOE	0.775707
APOA1	APOA2	0.750729	APOA1	CD44	0.955698
			APOA1	APOC3	0.863247
			APOA1	APOD	0.934731
			APOA1	SAA1	0.851674
			APOA1	GC	0.895851
			APOA1	FCN3	0.974651
			APOA1	APOM	0.97037
			APOA1	HPR	0.903863
			APOA1	APOA2	0.946479
			APOA1	APOA4	0.810846
			APOA1	ORM2	0.778901
			APOA1	PS1TP5BP1	0.937276
			APOA1	HGFAC	0.881963
			APOA1	C1R	0.898653
			APOA1	PI16	0.877954
			APOA1	CER	0.774842
			APOA1	CER	0.774747
			APOA1	CER	0.798225
			APOA1	TAG	0.769171
			APOA1	TAG	0.777959
			APOA1	TAG	0.800218
			APOA1	PC	0.758592
			APOA1	PC	0.754747