Deuterium Fractionation and CO Depletion in Barnard 5

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Plasma proteomic profiling reveals distinct lipoprotein roles in atherosclerosis

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Background: Apolipoprotein B-containing lipoproteins - low-density lipoprotein (LDL), triglyceride-rich lipoproteins (TRL) and lipoprotein(a) [Lp(a)] - are central to atherosclerosis. While previous studies have revealed higher per-particle atherogenicity of TRL and Lp(a) compared with LDL, underlying mechanisms remain unclear.

Purpose: To identify plasma proteomic signatures of LDL, TRL, and Lp(a) and determine whether these signatures explain differences in lipoprotein atherogenicity and coronary artery disease (CAD) risk association.

Methods: We analyzed cross-sectional associations of LDL, TRL, and Lp(a) with 2,920 plasma proteins (high-throughput proximity extension assay) in 29,515 UK Biobank participants not on lipid-lowering therapy and free of CAD at baseline. In mutually adjusted models (including all three lipoproteins as independent variables and each protein as dependent variable) proteins were selected if significantly associated (multiple-testing corrected $P<3.5\times10^{-5}$) with LDL, TRL, or Lp(a). The protein selection was further validated using Mendelian randomization analysis with SNP sets relevant to each lipoprotein class. Final proteomic signatures that met both criteria were integrated into lipoprotein-specific multi-protein scores (MPS) using ridge penalization and mutual adjustment for other lipoproteins. We performed pathway enrichment analyses on these lipoprotein-specific MPS and examined their associations with CAD risk in Cox proportional hazards models.

Results: From the 2,920 proteins the selection process yielded 31 proteins robustly associated with LDL, 469 with TRL, and 43 with Lp(a) (Figure 1A). LDL-associated proteins had a signature primarily identifying them as involved in lipid metabolism. TRL- and Lp(a)-associated proteomic signatures, in contrast, showed substantial mutual overlap, and contributed to shared proinflammatory pathways (Figure 1B). In Cox models, 100 nmol/L higher levels were associated with a 3% (95% CI: 2-5%) higher CAD risk for LDL, 13% (95% CI: 6-22%) for TRL, and 22% (95% CI: 15-29%) for Lp(a). Correlations between MPS and particle counts were 0.64, 0.60, and 0.16 for LDL, TRL, and Lp(a), respectively. The LDL MPS was not independently associated with CAD risk once LDL particle count was included. In contrast, in mutually adjusted models, the TRL MPS remained strongly associated with CAD risk and fully explained TRL-related excess risk. The Lp(a) MPS remained independently associated with CAD risk alongside Lp(a) particle count (Figure 1C).

Conclusions: Plasma proteomics analysis reveals distinct signatures reflecting the diverse biological roles of LDL, TRL, and Lp(a). The higher per-particle atherogenicity of TRL and Lp(a) compared with LDL may be partially explained by shared proinflammatory processes.

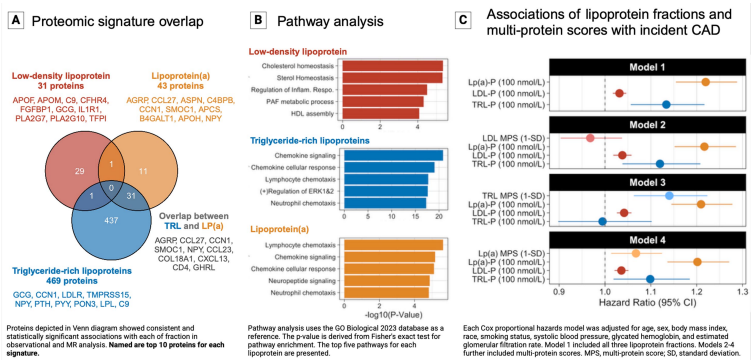

Figure 1. Overview of study results