APOC3 A43T Variant Promotes ApoC-III Catabolism and Accelerates TG-rich Lipoprotein Clearance in Mice and Humans


Humans with loss-of-function (LoF) variants in APOC3, the gene encoding apolipoprotein C-III (apoC-III), have significantly reduced plasma triglycerides (TG) and protection from coronary disease. These findings suggest that apoC-III may be a viable therapeutic target for decreasing vascular risk through TG reduction, and that elucidation of the protective mechanism of APOC3 LoF variants would inform such strategies. We report here the protective mechanism of the APOC3 A43T missense variant, one of four recently identified CAD-protective variants. By genotyping >8,000 human participants with low TG, we identified 17 APOC3 A43T carriers and phenotyped 6 carriers and 54 matched controls. A43T heterozygotes demonstrate a significant reduction in apoC-III levels relative to non-carriers (50% reduction, P<0.05), resulting in decreased plasma TG (50% reduction, P<0.05). We generated viral vectors expressing WT or A43T apoC-III and expressed these in humanized mouse models to further explore the mechanism of reduced apoC-III levels due to the A43T variant. Mice expressing human CETP and the apoC-III A43T variant exhibit reduced plasma apoC-III (50% reduction, P<0.0001) despite equal hepatic expression and secretion relative to controls expressing WT human apoC-III. These mice also exhibit reduced plasma TG and VLDL-C, and increased HDL-C relative to WT-expressing mice, fully recapitulating the protective lipoprotein profile of the human A43T carriers. Radioisotope-labeled apoC-III turnover studies showed that the A43T mutation causes a >3-fold higher apoC-III clearance rate in vivo (P<0.0001) due to defective integration into lipoprotein particles and accelerated renal catabolism (40% increase, P<0.01). This results in increased lipoprotein lipase (LPL) activity (27% increase, P<0.01) and faster chylomicron-TG clearance (97% increase, P<0.01) in vivo. We are currently performing analogous studies of WT vs. A43T apoC-III turnover and VLDL clearance in human APOC3 A43T carriers. Collectively, our results support the rationale for therapeutic efforts to target circulating apoC-III through disruption of its binding to lipoproteins, mirroring the genetics-driven approaches for targeting PCSK9 that have recently yielded novel therapies.

Disclosure Block: