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PROJECT SUMMARY

Cardiovascular disease (CVD) remains the leading cause of mortality in the western world despite the widespread success of statins. Genome-wide association studies (GWAS) have identified hundreds of genomic loci as significantly associated with plasma lipoprotein traits and coronary artery disease (CAD) in humans, many of which contain genes not previously implicated in metabolic disease pathogenesis. These loci could represent novel disease biology and new avenues for therapeutic intervention in CVD. The 8q24 locus, harboring the gene Tribbles-1 (*TRIB1*), is one of only two loci to associate with all plasma lipid traits (total cholesterol, LDL-C, HDL-C, triglycerides (TG)) and CAD, yet little is known about the mechanisms governing those associations. Interestingly, *TRIB1* significantly associates with plasma adiponectin levels as well, suggesting that *TRIB1* has a role in adipose biology. We present here data that mice with adipose-specific knockout of *Trib1* (Trib1_ASKO) have decreased plasma cholesterol and triglycerides, and increased circulating adiponectin. Preliminary investigations suggest that this finding is due in part to reduced hepatic cholesterol synthesis. Thus, it appears that adipose Trib1 affects hepatic lipid metabolism via crosstalk between the liver and adipose. This is consistent with the observation that Trib1_ASKO mice have altered adipokine secretion, yet previous work suggests that the cholesterol reduction observed in the Trib1_ASKO mice is likely adiponectin independent. How Trib1 effects adipokine secretion is unknown, and despite the established relationship between TRIB1 and the transcription factor C/EBPα, itself an important regulator of adipogenesis, our preliminary data suggests that the effects of Trib1 in the adipocyte are C/EBPα-independent. Finally, the altered plasma lipid profile in the Trib1_ASKO mice suggests that adipose TRIB1 regulates plasma lipoprotein metabolism, and thus it follows that the GWAS SNPs near *TRIB1* likely affect the function of adipose-specific *TRIB1*, presumably through altered gene expression. Currently, little is known about the regulation of *TRIB1* expression in adipose and the effects of common variation on this regulation. In this proposal, I outline a strategy for determining the cause of altered plasma lipids in Trib1_ASKO mice, the function of adipocyte TRIB1, and the adipose-specific effect of non-coding variation near *TRIB1*. *TRIB1* remains one of the most interesting genes to arise from plasma lipid and CAD GWAS studies, given the constellation of traits it associates with. The studies outlined in this proposal promise to elucidate novel functions of both this protein in adipose, and for adipose in regulating hepatic lipoprotein metabolism. These studies will further our understanding of CAD and dyslipidemia pathogenesis while unveiling novel avenues for therapeutic development targeting TRIB1 and adipose tissue.