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Non-alcoholic fatty liver disease (NAFLD) has emerged as the forerunner of more serious forms of liver disease such as non-alcoholic steatohepatitis (NASH) and also shows a strong association with atherosclerotic cardiovascular disease (CVD). As well as sharing risk factors such as obesity and insulin resistance, the association of NAFLD with CVD is likely driven by atherogenic dyslipidemia (increased VLDL, small dense LDL and reduced HDL) which in part reflects increased hepatic de novo lipogenesis. We have recently discovered a novel scaffolding protein called TTC39B (T39) that links high fat diet-induced metabolic responses to transcriptional programs regulating lipogenesis and cholesterol metabolism. Our studies suggest that inhibiting hepatic T39 might be a new strategy for treating NAFLD and CVD. Human genome wide association studies first showed that polymorphisms in the gene encoding T39 are associated with reduced *T39* expression and increased HDL. We showed that T39 promotes the ubiquitination and turnover of LXR and regulates levels of nuclear, active SREBP1 (nSREBP1) and hepatic lipogenic gene expression. Chow-fed *T39*^{-/-} mice showed increased HDL and increased *Abca1* expression in enterocytes, reflecting increased LXR levels. Western Diet (WD)-fed *T39*^{-/-}*Ldlr*^{-/-} mice had decreased lipogenic gene expression, protection from NAFLD and reduced atherosclerosis. Thus, deficiency of T39 activates a beneficial profile of gene expression that promotes cholesterol removal and inhibits lipogenesis. Our recent studies have shown that T39 interacts with the Retinoblastoma protein (RB) promoting its proteasomal degradation. This may be linked to the role of T39 in regulating the levels of nSREBP1 and LXR in proliferating cells and in hyperinsulinemic hepatocytes. The goal of this proposal is to elucidate the role of T39 in the regulation of hepatic lipogenesis, lipoproteins and atherosclerosis. We will evaluate a novel hypothesis that the interaction of T39 with RB links lipogenic genes and LXR to cell cycle genes in hepatocytes and enterocytes. This may pave the way for therapeutic inhibition of T39 potentially benefiting NAFLD and atherosclerosis.