Hepatic transforming growth factor-? 1 stimulated clone-22 D1 controls systemic cholesterol metabolism.

Disturbances in lipid homeostasis are hallmarks of severe metabolic disorders and their long-term complications, including obesity, diabetes, and atherosclerosis. Whereas elevation of triglyceride (TG)-rich very-low-density lipoproteins (VLDL) has been identified as a risk factor for cardiovascular complications, high-density lipoprotein (HDL)-associated cholesterol confers atheroprotection under obese and/or diabetic conditions. Here we show that hepatocyte-specific deficiency of transcription factor transforming growth factor ? 1-stimulated clone (TSC) 22 D1 led to a substantial reduction in HDL levels in both wild-type and obese mice, mediated through the transcriptional down-regulation of the HDL formation pathway in liver. Indeed, overexpression of TSC22D1 promoted high levels of HDL cholesterol in healthy animals, and hepatic expression of TSC22D1 was found to be aberrantly regulated in disease models of opposing energy availability. The hepatic TSC22D1 transcription factor complex may thus represent an attractive target in HDL raising strategies in obesity/diabetes-related dyslipidemia and atheroprotection.