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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

EDITORIAL

Macrophage-Specific SCAP Promotes Liver and Adipose Tissue Damage in a Lean NAFLD Model: Lean, Mean, Proinflammatory Machine

Nonalcoholic fatty liver disease (NAFLD) generally is described as an obesity-associated condition; nevertheless, NAFLD also is reported in nonobese and lean persons with global rates of nonobese NAFLD and lean NAFLD being 36%–45% and 7%–23%, respectively.[1] Lean NAFLD is characterized by reduced subcutaneous adipose tissue and ectopic fat deposition in the liver. In addition, lean NAFLD patients present with metabolic abnormalities, leaving them susceptible to the development of metabolic syndrome and severe liver disease.[2] In addition, this patient group presents with higher adverse adipokine profiles, contributing to persistent, low-grade inflammation (ie, metainflammation).[3] For these reasons, the cholesterol-rich Paigen diet is a suitable model to study lean NAFLD.[4]

Sterol regulatory element binding protein cleavage-activating protein (SCAP) is a cholesterol sensor that regulates intracellular cholesterol levels.[5] Inflammatory mediators increase SCAP activity, thereby disrupting intracellular cholesterol homeostasis, leading to atherosclerosis.[6] Furthermore, SCAP overexpression activates the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome, thus contributing to atherosclerosis development.[7] For these reasons, Huang et al[8] postulated that SCAP is an important mediator of cholesterol metabolism and metainflammation during lean NAFLD. Their study in the current issue of *Cellular and Molecular Gastroenterology and Hepatology* delineates the role of macrophage-specific SCAP in the Paigen diet model of lean NAFLD. Specifically, Huang et al[8] aimed to characterize the Paigen diet feeding model of lean NAFLD, to carefully characterize SCAP signaling in macrophages, and to determine how this can impact the liver and adipose tissue phenotypes. In addition, they evaluated signaling mechanisms downstream of SCAP in macrophages that mediate inflammatory responses.

Male macrophage-specific SCAP$^{-/-}$ mice (SCAP$^{\Delta M\varphi}$) and controls (age, 6–8 wk) were fed either a normal chow diet or a Paigen diet for 12 weeks. Huang et al[8] found that Paigen diet–fed control mice had a reduction in body weight accompanied with manifestations of metabolic syndrome. Paigen diet–fed control mice presented with enhanced liver weight but reduced epididymal white adipose tissue (eWAT) weight, along with smaller adipocyte size in eWAT but enhanced steatosis and lobular inflammation in the liver. Paigen diet–fed control mice had enhanced systemic inflammation and significant infiltration of macrophages to the eWAT and liver, which was accompanied with enhanced serum alanine aminotransferase (ALT) levels indicative of liver injury. These findings validate this as a model of lean NAFLD.

Considering the imbalance of lipid deposition in eWAT and liver, Huang et al[8] evaluated lipid metabolism genes. In Paigen diet–fed control mice, eWAT showed increased expression of lipolysis, synthesis, and lipid uptake genes; however, the liver had decreased lipolysis and increased synthesis and lipid uptake gene expression. These data suggest that imbalance of lipid metabolism in eWAT vs liver plays a role in the development of lean NAFLD.

As introduced earlier, metainflammation is an important process of lean NAFLD, and SCAP is a key inflammatory marker in macrophages. Macrophage SCAP expression was enhanced in eWAT and liver of Paigen diet–fed control mice, establishing the rationale for developing SCAP$^{\Delta M\varphi}$ mice. Chow-fed control and SCAP$^{\Delta M\varphi}$ mice had no differences in eWAT and liver lipid content and metabolism, metainflammation, or tissue structure. However, Paigen diet–fed SCAP$^{\Delta M\varphi}$ mice had an increase in eWAT adipocyte size and improvement of liver weight, lobular inflammation, and hepatic steatosis, as well as a reduced incidence of metabolic syndrome when compared with Paigen diet–fed control mice. Therefore, macrophage-specific deletion of SCAP may improve metabolic disturbances and eWAT and liver damage associated with lean NAFLD.

Investigating eWAT and liver injury further, Paigen diet–fed SCAP$^{\Delta MR\varphi}$ mice had reduced macrophage infiltration, expression of proinflammatory cytokines and serum ALT levels as compared with Paigen diet-fed controls. In addition, Paigen diet–fed SCAP$^{\Delta M\varphi}$ mice showed reduced eWAT lipolysis and lipid uptake but enhanced lipid synthesis gene expression compared with Paigen diet–fed controls, indicating restoration of adipocyte lipid storage. In the liver, Paigen diet–fed SCAP$^{\Delta M\varphi}$ mice had decreased lipid uptake and synthesis but unchanged lipolysis gene expression as compared with Paigen diet–fed controls. Macrophage–SCAP-dependent modulation of adipocyte and hepatocyte lipogenesis and inflammatory response were verified in vitro using co-culture systems. Therefore, macrophage–SCAP deletion may reverse dyslipidemia and metainflammation associated with lean NAFLD.

When delving into the mechanisms underlying these processes, Huang et al[8] first found that macrophage nuclear factor-κB (NF-κB) activity was up-regulated in Paigen diet–fed control mice, which was reduced in Paigen diet–fed SCAP$^{\Delta M\varphi}$ mice. Previous studies have found that stimulator of interferon genes (STING) promotes inflammation by activating NF-κB,[9] and within this study STING expression was enhanced in both the eWAT and liver of

Paigen diet–fed control mice but reduced in Paigen diet–fed SCAP$^{\Delta M\varphi}$ mice. Similarly, macrophage presence correlated with STING expression in both the liver and eWAT of Paigen diet–fed control mice that was blocked in Paigen diet–fed SCAP$^{\Delta M\varphi}$ mice. The SCAP/STING/NF-κB pathway was verified in vitro using overexpression and knockdown studies. Furthermore, SCAP was found to directly bind to STING, inducing translocation to the Golgi, in vitro. SCAP direct translocation of STING to the Golgi may be necessary for STING/NF-κB activation.

In the last set of studies, Huang et al[8] circled back to their Paigen diet model, but this time fed control or SCAP$^{\Delta M\varphi}$ mice for 16 weeks to induce hepatic fibrosis. Similar to 12 weeks of feeding, Paigen diet–fed SCAP$^{\Delta M\varphi}$ mice had reduced hepatic steatosis, lobular inflammation, macrophage infiltration, and ALT levels compared with Paigen diet–fed control mice. Paigen diet–fed SCAP$^{\Delta M\varphi}$ mice also had a significant amelioration of liver fibrosis compared with Paigen diet–fed control mice. These phenotypic changes were accompanied with reduced STING/NF-κB activation. Therefore, the macrophage-specific SCAP/STING/NF-κB pathway may modulate liver fibrogenesis in lean NAFLD.

The current consensus is that lean NAFLD is less severe than obese NAFLD; however, this concept has been challenged recently[10] and the utilization of a lean NAFLD model will be useful to evaluate pathogenesis and therapeutics. In an obese NAFLD model, the liver was shown to modulate obesity and white-to-brown fat conversion via paracrine signaling[11]; therefore, studies evaluating eWAT in lean NAFLD are novel. However, Huang et al[8] only investigated the eWAT or the liver separately, and studies determining crosstalk would be of interest. Furthermore, this study defines a damaging role for macrophages in both eWAT and liver inflammation, but also for liver fibrosis in lean NAFLD. These findings are provocative, considering the controversy regarding the reparative vs damaging roles of macrophages.[12] This segues into another notorious debate on macrophage polarization and the proinflammatory and anti-inflammatory properties of macrophages during disease. This study did not investigate polarization; however, it would be interesting to analyze this phenomenon in lean NAFLD. Lastly, it would be of interest to understand if these mechanisms can be therapeutically targeted in lean but also obese NAFLD, because these 2 etiologies can share similar pathogenic mechanisms. In summary, this study defines macrophage-specific SCAP signaling and the effects on eWAT and liver phenotypes in a model of lean NAFLD.

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Conflicts of interest
The authors disclose no conflicts.

Funding
Portions of this work were supported by Senior Research Career Scientist award 5IK6BX004601 (G.A.), Research Career Scientist award 5IK6BX005226 (H.F.), Veterans Affairs merit awards 1I01BX003031 (H.F.) and 5I01BX000574 (G.A.), and Career Development Award-2 1IK2BX005306 (L.K.) from the U.S. Department of Veterans Affairs, Biomedical Laboratory Research and Development Service; US National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases grants DK054811, DK115184, and DK110035 (G.A.), DK108959 and DK119421 (H.F.), and National Institutes of Health, National Institute on Alcohol Abuse and Alcoholism grant AA028711 (G.A.); The Hickam Endowed Chair, Gastroenterology, Indiana University (G.A.); and the Strategic Research Initiative, Indiana University (G.A. and H.F.). Portions of these studies were supported by resources at the Richard L. Roudebush VA Medical Center, Indianapolis, IN. The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

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2352-345X
https://doi.org/10.1016/j.jcmgh.2022.04.004