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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

# Rebuttal to: Liver Steatosis is a Driving Factor of Inflammation

See Point-Counterpoint articles on pages 1267 and 1273

Hepatosteatosis, a hallmark of alcoholic and nonalcoholic fatty liver disease (NAFLD), is characterized by accumulation of lipid storage organelles called lipid droplets (LDs) within hepatocytes. LDs primarily function to maintain cellular metabolism and protect cells from lipotoxicity by storing excess free fatty acids and cholesterol esters during nutrient excess. Conversely, LDs serve as energy sources during periods of nutrient deprivation or tissue growth.[1] During chronic or excess caloric intake when lipid availability exceeds the capacity of LDs to sequester excess free fatty acids, LDs accumulate in hepatocytes. LD accumulation within hepatocytes, however, does not equate to cellular dysfunction,[1] and evidence supporting a link between excessive LD accumulation in hepatocytes and NAFLD progression is, at best, correlative. Excess circulating free fatty acids and lipid intermediates, in the event of failed sequestration into LDs, however, contribute to hepatic inflammation by inducing lipotoxicity and activation of immune cells.[2]

Mooli and coworkers in the accompanying point-counterpoint article argue that lipotoxicity-induced pyroptosis is the major driver of disease progression in NAFLD. Although pyroptosis does promote hepatic inflammation in NAFLD, it might be a hasty assumption to suggest that excess lipids are the most influential promoter of pyroptosis in NAFLD.[3] NAFLD is associated with increased translocation of some of the most potent inducers of hepatocyte pyroptosis: gut microbial products.[3,4] Studies have shown that even short-term exposure to a western diet increases the translocation of gut microbial products in healthy subjects and the resulting endotoxemia not only galvanizes hepatic inflammation but also hepatosteatosis suggesting that gut microbial products also have a function in LD accumulation in hepatocytes.[5–7] Although these new studies provide experimental support that inflammation contributes to the metabolic abnormalities associated with nutrient excess, there is ample evidence of this concept in the literature. We have become too focused on identifying the metabolic components of inflammation and have ignored the abundant evidence that genetic and pharmacologic manipulation of inflammatory pathways or depletion of gut microbiota not only reduce hepatosteatosis but also attenuate metabolic derangements associated with chronic high calorie intake.[6,8–10]

Lastly, I would like to emphasize that the liver is a heterogeneous organ, not only critical for metabolism but also instrumental in modulating local and systemic immunity.[11] The inextricably linked interactions between the various cells of the liver including epithelial, endothelial and immune cells are integral to maintaining immunotolerance, which is essential for normal liver function and tissue homeostasis. Changes in the liver microenvironment during times of excessive nutrient intake disrupts this balance resulting in sustained inflammation, which promotes the development and progression of chronic liver diseases, including NAFLD. Moving forward, striving for a holistic approach to understanding how various cells of the liver and organs connected to the liver influence liver physiology is foundational to obtaining a deeper understanding of the mechanisms underlying NAFLD progression.

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**Conflicts of interest**
The authors disclose no conflicts.

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