

## Storage Wars: Adipose-liver Crosstalk as a Determinant of Liver Injury



Hepatic steatosis, or the accumulation of triglycerides in hepatocytes, is a shared phenotype of several liver diseases. Most notably, this includes metabolic dysfunction (MASLD) and alcohol-associated liver disease (ALD) but also includes ischemia-reperfusion injury (IRI) during liver transplantation. Despite differences in the underlying pathophysiology of these diseases, the factors governing steatosis and resultant inflammation and liver damage are not well-understood. Recent studies by Liss et al, Qian et al, Wickramasinghe et al, and Park et al provide compelling evidence that adipose tissue regulates both hepatic steatosis—and perhaps more broadly—the hepatic lipidome.<sup>1-4</sup> This highlights an important and underrecognized interorgan crosstalk between adipose tissue and the liver. Moreover, the data introduce critical distinctions between white and brown adipose depots in this signaling axis. All converge on the concept that adipose-liver interorgan communication broadly impacts liver disease outcomes across preclinical models of MASLD, ALD, and IRI. Collectively, their work raises important questions and may provide a targetable pathway with wide applicability across multiple mechanisms of liver injury (Figure 1).

The nature and outcome of adipose-liver crosstalk heavily depend on the type of adipose tissue. In the contexts discussed herein, white adipose tissue (WAT) negatively contributes to liver health, whereas brown adipose tissue may serve a protective role (Figure 1). Liss et al and Park et al demonstrate that WAT is not simply a passive bystander during liver injury. Rather, WAT may serve an active endocrine function by responding to systemic stress and driving liver injury following insult.<sup>1,2</sup> For example, in liver transplantation, IRI occurs once blood flow is reinitiated to the transplanted liver after an unavoidable period of ischemia.<sup>5</sup> During ischemia, liver cells undergo stress with cellular and metabolic changes; yet, reperfusion and rapid introduction of oxygenated blood flow trigger a large inflammatory cascade. This process was once considered primarily liver-intrinsic. However, Liss et al challenge this and provide preclinical evidence that WAT lipolysis is a major contributor to hepatic dysfunction after IRI. IRI triggers lipolysis in WAT, perhaps via circulating catecholamines, which drives steatosis in the liver. There is also evidence of harmful secondary signals extending beyond steatosis as evidenced by elevated proinflammatory transcripts in the liver and an altered hepatic lipidome. Pharmacologic or genetic inhibition of this pathway reduces liver IRI and is liver-protective.

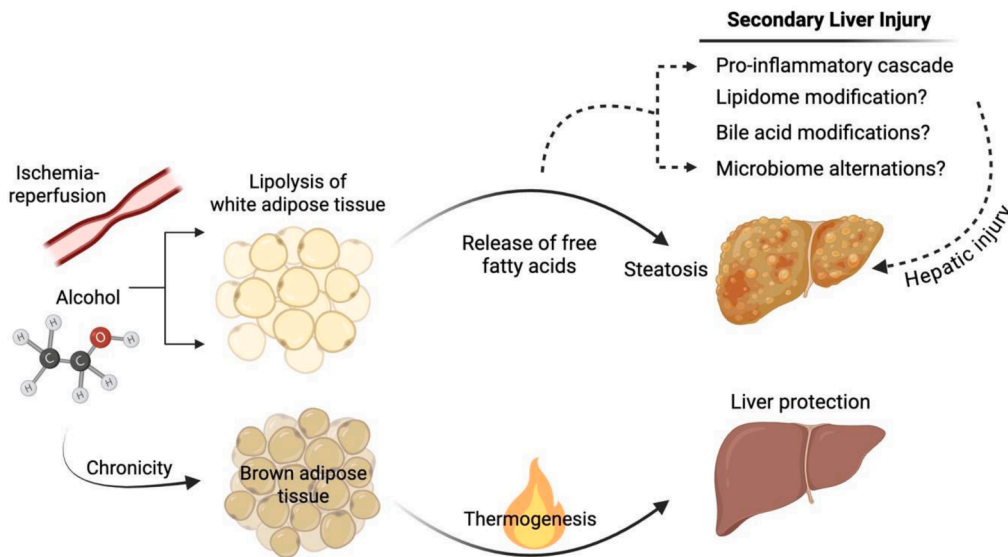
Park et al reported a similar mechanism for WAT in a model of ALD focused on a single ethanol binge in mice fed

a high-fat diet. This model led to WAT lipolysis, resulting in hepatic steatosis and inflammation. Transgenic mice with adipocytes unable to undergo apoptosis have reduced markers of lipolysis, serum free fatty acids, and liver injury. Wickramasinghe et al now demonstrate that lipolysis occurs through activation of sympathetic nerve b3 adrenergic receptors (Adrb3) in WAT following a single alcohol binge.<sup>2</sup> Ablating these sympathetic nerve fibers or deleting white adipose tissue-specific Adrb3 attenuates alcohol-induced lipolysis, hepatic steatosis and injury. This highlights an exacerbating role for WAT lipolysis in hepatic steatosis and acute injury in a preclinical model of ALD.

In contrast to WAT, a primary role of brown adipose tissue (BAT) is thermogenesis, acting as a “metabolic sink” for free fatty acids.<sup>6</sup> A study by Qian et al, investigating the role of BAT in liver injury, highlights a protective role for BAT in a model of chronic-plus-binge alcohol feeding. Their work shows that alcohol consumption activates BAT thermogenesis, providing an adaptive and protective response, which mitigates alcoholic liver injury by consuming excess free fatty acids that would otherwise target the liver.

Importantly, this study probes the complex impact of WAT and BAT on liver health.<sup>4</sup> By studying aged mice lacking the protein SQSTM1/p62, a key regulator of cellular metabolism, Qian et al show that the biggest risk factor for liver injury is activation of WAT and loss of protection from BAT. These mice were uniquely vulnerable to alcohol-induced liver injury for 2 interconnected reasons. First, WAT communication was in overdrive because the p62-deficient mice had developed obesity, and upon alcohol exposure, WAT lipolysis promoted liver injury. Secondly, the protective BAT activation that normally occurs in response to alcohol was completely blunted in these mice. This created a perfect storm that culminated in significant liver injury: a dysfunctional WAT undergoing lipolysis and increasing serum free fatty acids with a nonresponsive BAT failing to provide metabolic shielding. Interestingly, the acute binge model from Park et al did not find significant BAT changes, suggesting this protective BAT-liver axis may be more critical in chronic or “acute-on-chronic” disease states.<sup>2</sup>

These studies underscore the complex communication between WAT and BAT with the liver and raise several mechanistic and translational questions. Fundamentally, it will be crucial to understand how the release of lipolized free fatty acids drives liver injury and inflammation beyond substrate delivery and hepatic lipid accumulation. For example, the secondary effects of systemically available free fatty acids on the hepatic lipidome, immune signaling, bile acid composition, and the gut microbiome



**Figure 1.** Schematic of interorgan crosstalk between distinct adipose tissues and the liver during hepatic injury.

may exacerbate hepatic injury beyond simply driving steatosis (Figure 1).

If adipose-liver crosstalk is similar in human physiology, it may provide a targetable pathway to modify liver disease. For example, Liss et al lessened IRI in mice by pharmacological blockade of the axis with the atglistatin. Perhaps IRI could be attenuated in human liver transplant with a similar strategy, especially in high-risk patients with significant adiposity. This may be especially relevant as MASLD becomes the leading indication for liver transplant.<sup>7</sup> However, in light of overall high obesity prevalence in industrialized nations, managing the increased risk of liver injury in patients with significant adiposity across multiple pathophysiological contexts may be the next frontier in navigating the Storage Wars.

#### ABIGAIL E. RUSSI

Department of Pediatrics  
Indiana University School of Medicine  
Indianapolis, Indiana, and  
Herman B. Wells Center for Pediatric Research  
Indiana University School of Medicine  
Indianapolis, Indiana, and  
Nutrition and Molecular Metabolism Center  
Indiana University School of Medicine  
Indianapolis, Indiana

#### BRIAN J. DEBOSCH

Department of Pediatrics  
Indiana University School of Medicine  
Indianapolis, Indiana, and  
Herman B. Wells Center for Pediatric Research  
Indiana University School of Medicine  
Indianapolis, Indiana, and  
Nutrition and Molecular Metabolism Center  
Indiana University School of Medicine  
Indianapolis, Indiana, and  
Department of Anatomy, Cell Biology, and Physiology  
Indiana University School of Medicine  
Indianapolis, Indiana

## References

- Liss K, Goldman S, He M, et al. Inhibition of adipocyte lipolysis reduces liver injury in a mouse model of ischemia reperfusion injury. *Cell Mol Gastroenterol Hepatol* 2026;19:101679.
- Park SH, Seo W, Xu MJ, et al. Ethanol and its non-oxidative metabolites promote acute liver injury by inducing ER stress, adipocyte death, and lipolysis. *Cell Mol Gastroenterol Hepatol* 2023;15:281–306.
- Wickramasinghe PB, Caron A, Parupalli P, et al. Ablation of sympathetic nerve- $\beta_3$  adrenergic receptor-mediated adipose tissue lipolysis attenuates alcohol-induced liver injury in mice. *Cell Mol Gastroenterol Hepatol* 2026;20:101623.
- Qian H, Chao X, Wang S, et al. Loss of SQSTM1/p62 induces obesity and exacerbates alcohol-induced liver injury in aged mice. *Cell Mol Gastroenterol Hepatol* 2023;15:1027–1049.
- Liu J, Man K. Mechanistic insight and clinical implications of ischemia/reperfusion injury post liver transplantation. *Cell Mol Gastroenterol Hepatol* 2023;15:1463–1474.
- Ghesmati Z, Rashid M, Fayezi S, et al. An update on the secretory functions of brown, white, and beige adipose tissue: towards therapeutic applications. *Rev Endocr Metab Disord* 2024;25:279–308.
- Tincopa MA, Anstee QM, Loomba R. New and emerging treatments for metabolic dysfunction-associated steatohepatitis. *Cell Metab* 2024;36:912–926.

#### Correspondence

Address correspondence to: Brian J. DeBosch, MD, PhD, Department of Pediatrics, Indiana University School of Medicine, 1044 W. Walnut St, R4 302C Indianapolis, Indiana 46202. e-mail: [bdebosch@iu.edu](mailto:bdebosch@iu.edu).

#### Acknowledgments

The figure was created in <https://BioRender.com>.

#### Conflicts of interest

The authors disclose no conflicts.

#### Most current article

© 2026 The Authors. Published by Elsevier Inc. on behalf of the AGA Institute. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

2352-345X

<https://doi.org/10.1016/j.jcmgh.2025.101700>