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CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

POINT-COUNTERPOINT

Inflammation: The Straw That Broke the NAFLD Liver!

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Nonalcoholic fatty liver disease (NAFLD) is a spectrum of conditions ranging from benign nonalcoholic fatty liver (NAFL) or bland steatosis to the more severe nonalcoholic steatohepatitis (NASH), characterized by excessive inflammation and varying degrees of fibrosis.[1] An estimated 20%–25% of patients with NAFL progress to NASH, and up to 25% of patients with NASH progress to cirrhosis.[1] Currently, NASH-related cirrhosis is the second leading indication for liver transplantation in the United States, and patients with NASH face an increased risk of developing hepatocellular carcinoma.[1] Despite the progress in understanding of the natural history of NAFLD over the last two decades, researchers continue to struggle in identifying the cellular and molecular mechanisms behind the progression of NAFL to NASH and the subsequent development of cirrhosis. In the following, I provide evidence suggesting that steatosis alone is insufficient to drive NAFLD progression, and argue for a multiple-hit model of NASH pathogenesis wherein various host-intrinsic and extrinsic insults promote hepatic inflammation fueling NAFLD progression.

NAFL is characterized by accumulation of fatty acids as triacylglycerol in hepatocytes in the absence of inflammation or liver injury.[1] Fat deposition in hepatocytes or hepatosteatosis is observed when hepatic fatty acid uptake and/or synthesis exceeds fatty acid catabolism via fatty acid oxidation and export as very low-density lipoproteins.[2] Unlike adipocytes, hepatocytes do not store fatty acids under homeostatic conditions. However, with insulin resistance, circulating free fatty acids are elevated because insulin does not sufficiently inhibit adipose tissue lipolysis. This increases fatty acid uptake in the hepatocyte resulting in a net increase in hepatic fatty acid deposition.[2] Although the precise molecular mechanisms and sequence of events leading to hepatic fatty acid accumulation in NAFLD are not well understood, insulin resistance is considered the primary driver of hepatosteatosis.[3] Hepatic insulin resistance prevents suppression of hepatic glucose production contributing to hyperglycemia, increased compensatory hyperinsulinemia, and fatty acid deposition in hepatocytes by promoting *de novo* lipogenesis.[3]

Hepatosteatosis compromises liver function by disrupting hepatic metabolism and in some instances causing hepatocyte apoptosis, which was deemed instrumental in promoting lipotoxicity-induced hepatic inflammation in NAFLD.[3] But given that apoptosis is a nonlytic, noninflammatory cell death pathway that has limited effects on the surrounding cells, steatosis-induced hepatocyte apoptosis may not substantially impact hepatic inflammation in NAFLD.[4] Evidence from animal studies suggests that fatty acid accumulation in hepatocytes is a mechanism to protect tissues from fatty acid–associated lipotoxicity.[5] Furthermore, animal models of hepatosteatosis where a high-fat diet or leptin deficiency resulted in substantial steatosis but not steatohepatitis suggest that hepatosteatosis may not drive NAFLD progression.[6] This was further corroborated by clinical evidence that a large proportion of the population with NAFL, which represents 20%–30% of the general population and as high as 75%–100% of obese individuals, are either slow progressors or nonprogressors.[1] As such, from a clinical perspective, NAFL is considered a benign condition that does not require clinical intervention.

Emphasis on the metabolic underpinnings of NAFLD led to the proposal of a sequential "two-hit" model to explain disease progression in patients with NAFLD. The "two-hit" model suggests that hepatic lipid accumulation provides the "first-hit" that sensitizes the liver to a "second-hit" of oxidative stress resulting in hepatic inflammation that fuels the progression of NAFLD. The "two-hit" model emphasized that inflammation is the primary driver of disease progression but fell short in recognizing the importance of environmental factors including diet and gut microbiota and the involvement of extrahepatic tissue in disease progression.[7] The current refined models (summarized next), supported by the last two decades of research, suggest that disease progression is a culmination of various host-intrinsic and extrinsic factors that contribute to chronic hepatic inflammation that in turn drive progression of NAFLD.[7]

New models of NAFLD progression are distinguished by their de-emphasis of lipotoxicity as a primary driver, with greater emphasis on the contribution of interactions among the gut, liver and adipose tissue, reflecting the recognition that NAFLD is a complex and heterogeneous disease.[8,9] The contribution of adipokines and inflammatory cytokines released by inflamed adipose tissue in promoting insulin resistance and steatosis are now well established.[9] However, the mechanisms of adipose tissue inflammation during

nutrient excess remain incompletely understood. Studies demonstrating that the components of a western diet activate various inflammatory pathways that in turn foster metabolic derangements provide a direct link between diet and inflammation in metabolic diseases including NAFLD.[10] Further demonstrating the overlap between inflammatory and metabolic pathways, numerous studies document that curbing either inflammation or its source not only reduces hepatic inflammation and fibrosis but also improves steatosis and metabolic syndrome.[8,9]

The role of gut microbiota has recently gained significant attention because of evidence demonstrating their involvement in modulating inflammation and metabolism in NAFLD.[11] Germ-free mice or mice treated with antibiotics to reduce gut microbial load do not develop NAFLD when placed on a western diet; this helped establish the critical role of gut microbiota in the pathogenesis of the disease.[12] The impact of gut permeability is emerging as another important factor in NAFLD that provides insights into the mechanisms of disease progression in a subset of individuals with NAFL. Both clinical and experimental data suggest that the consequence of diet-induced gut dysbiosis and intestinal epithelial barrier disruption increases translocation of gut microbial products, which promote hepatic inflammation and ultimately disease progression.[11]

Collectively, these recent advances serve to reinforce the adage "you are what you eat" by demonstrating that inflammatory pathways activated by caloric excess cause metabolic diseases including insulin resistance, type II diabetes, cardiovascular disease, and NASH in susceptible individuals.

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