Nature or Nurture? The Answer Is “Both” in Nonalcoholic Steatohepatitis

In the 4 decades since its initial description as a cause of chronic liver disease, nonalcoholic steatohepatitis (NASH) has become the most common cause of chronic liver disease worldwide. Epidemiologically, NASH tracks with the obesity epidemic, which has led to the recognition that environmental exposure to an obesogenic diet plays a key role in its pathogenesis. This nurture argument suggests that the majority of NASH sequelae can be explained and therefore remedied by dietary alteration. Although there is undoubtedly a dietary contributor to NASH pathogenesis, there is growing literature on how individual-specific differences contribute or compound NASH pathogenesis. Among these nature contributors is the role of the body’s immune system. In this issue of *Cellular and Molecular Gastroenterology and Hepatology*, Van Herck et al describe in the article “Diet reversal and immune modulation show key role for liver and adipose tissue T cells in murine nonalcoholic steatohepatitis” that T-cell subpopulations are modulated in the liver and adipose tissue of mice fed a NASH-inducing diet.

Van Herck et al examined the fate of several T-cell populations (T helper [Th]1, Th17, regulatory T [Treg], and cytotoxic T [Tc] cells) in both liver and adipose tissue in mice fed a NASH-inducing, high-fat, high-fructose diet. In the liver, this dietary model caused hepatic steatosis, inflammation, fibrosis, and an up-regulation of key lipogenic and hepatic stellate cell activation genes. In visceral adipose tissue (VAT), the model caused adipocyte hypertrophy, inflammation, dysregulation of critical lipid regulatory genes, and increased expression of the collagen synthetic genes, Col1a1 and Col3a1. In parallel with these histologic and metabolic changes in liver and adipose tissue were profound changes in several T-cell subpopulations. Namely, the liver, VAT, and blood compartment all had increased Th17 cells. VAT had increased proportions of Tc cells and reduced Treg cells. Van Herck et al additionally noted a positive correlation between liver inflammation (as quantified by the nonalcoholic fatty liver disease activity score [NAS]) and VAT Tc cells; and between NAS and liver and VAT Th17 cells. Conversely, there was a negative correlation between the NAS and VAT Treg cells.

Although the investigators initial results are consistent with several prior studies that have shown a shift from an anti-inflammatory T-cell program to an inflammatory one in NASH pathogenesis (reviewed by Van Herck et al), Van Herck et al advance those findings by showing that merely changing the diet from an obesogenic diet to a healthier one fails to reverse those changes. Namely, after 20 weeks of a high-fat, high-fructose diet, mice were placed on a Chow diet for an additional 12 weeks. Despite observing a reduction in body weight, improvement in metabolic parameters such as glucose tolerance, a regression of histologic NASH, improvement of adipocyte histology, and near-normalization of the lipid metabolic gene transcription signature in both the liver and VAT, the T-cell changes that were observed with NASH initiation did not revert to normal. Only administration of the T-cell–directed anti-CD8a antibody reduced the Tc subpopulation in VAT, liver, subcutaneous adipose tissue, blood, and spleen. Other T-cell subpopulations, such as Th17 cells, were not impacted by this therapy or by anti–interleukin 17A antibodies. Although these results may reflect the differences in adaptive immunity between mice and human beings, these results highlight that both nature (T-cell biology) and nurture (diet) impact NASH pathogenesis, and that strategies that address the nurture part of the equation in isolation may not be sufficient to completely ameliorate NASH.

In summary, Van Herck et al present a provocative analysis that reversal of diet from an obesogenic to a healthier diet does not reverse the liver or adipose tissue immunologic signature in NASH. Rather, immune-specific therapies may be needed in concert with dietary strategies to better address the systemic changes that characterize NASH pathogenesis.

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