Paradigm shift in the immunopathogenesis of NAFLD

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In states of obesity, the development and fibrotic progression of nonalcoholic fatty liver disease (NAFLD) from nonalcoholic steatohepatitis (NASH) to cirrhosis has been proposed to stem from chronic, low-level type 1 inflammation in adipose tissue. However, new research challenges this view by showing instead that

NASH-associated fibrosis is actually driven by type 2 inflammation in the liver during obesity.

“We were interested in identifying the immunological mechanisms driving fibrosis in NAFLD, as the severity of liver fibrosis is prognostic for patients needing a liver transplant,” explains lead investigator Thomas Wynn. Having first shown that chronic (40-week) exposure of wild-type mice to a high-fat diet (HFD) induced the full sequelae of NAFLD, the researchers subjected mice deficient in both interleukin-4 (IL-4) and IL-10 (*Il4^{-/-};Il10^{-/-}*, which develop type 1 inflammation) to a HFD for 40 weeks. Surprisingly, although the *Il4^{-/-};Il10^{-/-}* mice developed obesity, they were highly resistant to NASH. RNA sequence analysis of the livers of these mice revealed increased hepatic expression of *Ifng* (which encodes interferon- γ (IFN γ)), suggesting that IFN γ is a protective factor against NASH. Consistent with this hypothesis, IFN γ -deficient mice (which develop type 2 inflammation) rapidly acquired NASH with evidence of fibrosis when fed a HFD. Mechanistically, this progression to

NASH was shown to be dependent upon transforming growth factor- β (TGF β) and IL-13 signalling pathways.

Finally, using patient biopsy samples, the researchers confirmed that type 2 inflammation (evidenced by an accumulation of eosinophils and increased type 2 cytokine production) is a hallmark of human fibrotic livers. “As fibrosis is the best predictor of patient outcomes and mortality in NAFLD, our findings could spur the development of new therapeutic avenues to halt progression of the disease and ultimately the need for liver transplantation,” speculates Wynn. “In particular, understanding how the TGF β –IL-13 axis interacts with and regulates other inflammatory pathways (such as IL-10, IL-17 and TNF) reported to be active in the metabolic syndrome and NASH will be crucial to developing therapeutics for both metabolic and fibrotic complications associated with obesity.”

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