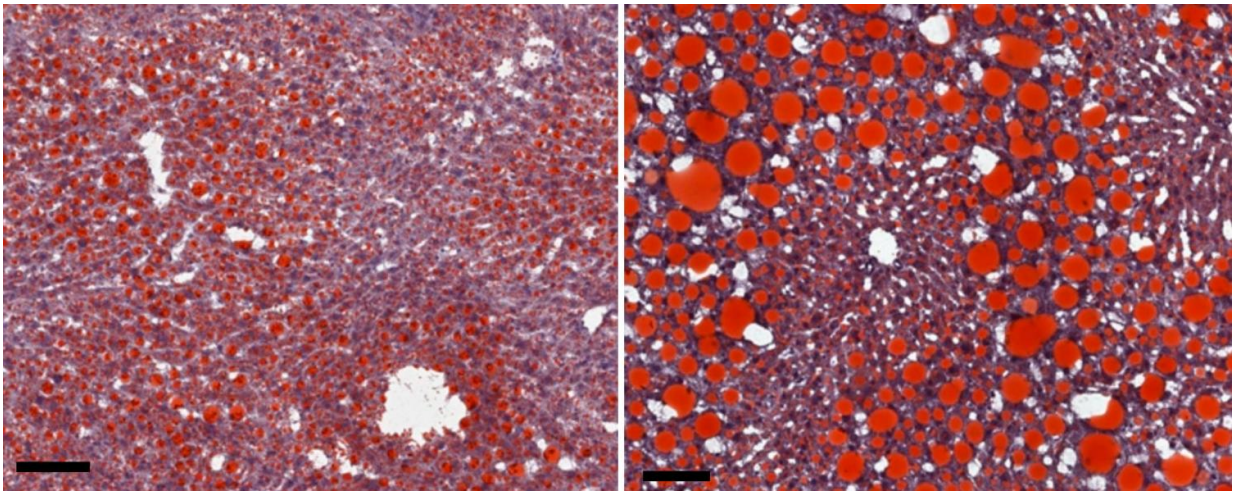


# Study sheds light on immune responses driving obesity-induced liver disease

June 28 2017

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The image on the left shows steatosis (fat build-up, red) in the liver of a normal mouse fed a high-fat diet. The right image shows markedly higher steatosis in the liver of a mouse lacking IFN-gamma fed a high-fat diet. Credit: NIAID

New findings from mouse models reveal that the type of immune response that helps maintain healthy metabolism in fatty tissues, called type 2 immunity, also drives obesity-induced nonalcoholic fatty liver disease (NAFLD). The work, led by scientists at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, shows that the inflammatory environment in the fatty liver is more complex than previously thought. These insights may inform the development of new NAFLD treatments as well as immune-altering

therapies for obesity and related health issues in people with NAFLD.

NAFLD affects an estimated 64 million people in the United States. Over time, it can progress to nonalcoholic steatohepatitis (NASH), eventually leading to liver damage and scarring. NAFLD is a leading indication for [liver transplantation](#).

Although the mechanisms regulating NAFLD progression have been unclear, scientists had suspected that the type of [immune response](#) that inflames fatty tissues during obesity, known as type 1 immunity, also worsens [liver disease](#). Unexpectedly, the NIAID-led team found that [obese mice](#) engineered to have strong type 1 immune responses were resistant to NASH. This protection was associated with activation of a type 1 immune molecule called IFN-gamma. Obese mice lacking IFN-gamma progressed rapidly to NASH and developed liver scarring.

Further experiments revealed that NASH-induced scarring depends on TGF-beta, a broad immune system regulator and target for experimental NASH therapies, and IL-13, a type 2 molecule produced by various immune cells, including eosinophils. Blocking TGF-beta in mouse models slowed NASH-driven liver scarring, but the number of eosinophils and amount of IL-13 produced in the liver increased to compensate for the lost TGF-beta function. Simultaneously blocking TGF-beta and IL-13 more effectively stopped liver scarring.

## INFLAMMATION AND OBESITY

*More than **one third** of adults in the United States are considered to be obese <sup>1</sup>*

Obesity places people at risk for inflammatory conditions including:



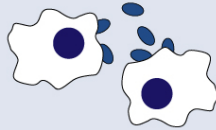
- Type 2 diabetes
- Heart disease
- High blood pressure
- Nonalcoholic fatty liver disease
- Joint inflammation
- Stroke
- Some types of cancer including breast, colon, and kidney

### TYPE ONE INFLAMMATION

Defends against bacteria and viruses

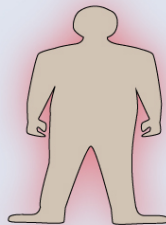


Cells engulf invading pathogens



Causes system-wide damage in obesity

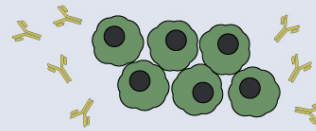
Chronic obesity has been tied to type one inflammation



### TYPE TWO INFLAMMATION

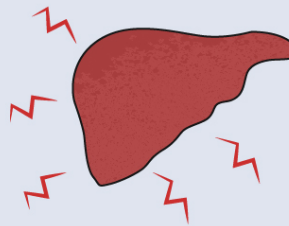


Defends against large parasites



Cells produce antibodies

Thought to protect healthy metabolic signaling in obesity



Type two inflammation may damage the liver in obesity

Science Translational Medicine | AAAS

<sup>1</sup> <https://www.niddk.nih.gov/health-information/health-statistics/overweight-obesity>

Infographic explaining how different types of inflammation are related to obesity and nonalcoholic fatty liver disease; Figure 7C, Biopsy samples from non-alcoholic fatty liver disease patients showing immune cell infiltration (arrows). Credit: Carla Schaffer / K.M. Hart et al. / AAAS

To determine whether these findings may be relevant to human disease,

the scientists examined liver biopsies from people with NASH. As in mice, the researchers observed evidence of type 2 inflammation and accumulation of eosinophils.

The researchers next plan to use mouse models to assess the specific roles of eosinophils in the liver and to study ways to specifically block the IL-13 and TGF-beta cell-signaling that leads to liver scarring.

**More information:** K.M. Hart et al., "Type 2 immunity is protective in metabolic disease but exacerbates NAFLD collaboratively with TGF- $\beta$ ," *Science Translational Medicine* (2017). [stm.sciencemag.org/lookup/doi/... scitranslmed.aal3694](https://stm.sciencemag.org/lookup/doi/10.1126/scitranslmed.aal3694)

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