New study shows NKT cell subsets play a large role in the advancement of NAFLD

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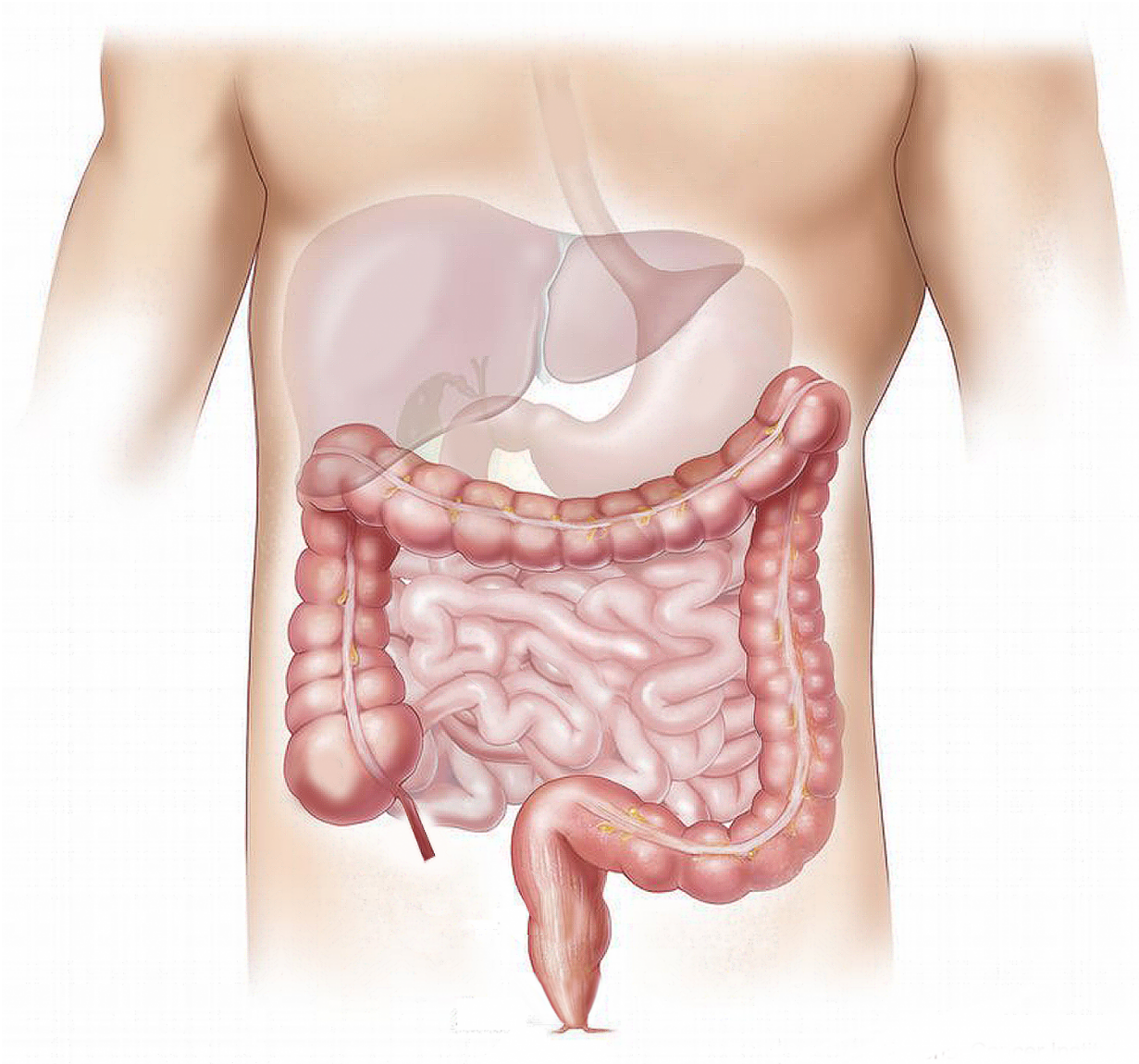

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Since 2015 it has been known that the gut microbiota could have a direct impact on nonalcoholic fatty liver disease (NAFLD), which affects up to 12% of adults and is a leading cause of chronic liver disease. In the November issue of the *Journal of Immunology*, released today, a report by Maricic et al. suggests that a genetic deficiency of iNKT cells has a strong impact on the microbial diversity and sheds new light on the role of type I natural killer T (or iNKT) cell subsets in the progression of nonalcoholic steatohepatitis (NASH), a form of NAFLD. The team, led by Vipin Kumar, represented a collaboration between multiple CMI member labs, including Rohit Loomba and Rob Knight as part of the CMI Seed Grant program.

This study indicates that the activation of a particular innate-like natural killer T cell subset plays a crucial role in the progression of nonalcoholic fatty liver disease and in the absence of or following inhibition of these cells mice are protected from the diet-induced fatty liver and fibrosis. Additionally, since microbiota can have a major impact on the NKT cell subsets, studies are underway to determine the influence of altered microbiota on these cells in liver disease. These studies have important implications for the development of novel strategies for the treatment of liver disease, stated Kumar.

Typical (wildtype) laboratory mice will develop steatosis and fibrosis in their livers, symptoms that typify human NASH, when fed a choline-deficient, l-amino acid-defined (CDAA) diet. However, mice deficient for the J alpha 18 gene of the T cell receptor (Jα18-/-) which lack iNKT cells did not develop these symptoms when fed on the same CDAA diet, suggesting a crucial role for these cells in the disease.

The impact of diet on inflammation and liver disease is well known and previous reports from Loomba's group in 2015 and 2017 had suggested

that gut microbiota could potentially have an impact on the inflammatory processes that lead to NASH.

Encouraged by these reports, the team used the protocols developed by the Earth Microbiome Project (EMP) to examined the gut microbiome of the mice and assessed whether the protection in iNKT cell-deficient mice (Jα18-/-) correlated with changes in microbial diversity. When the team examined the gut microbiome from the Jα18-/- mice, they observed not only a significant increase in the diversity of the microbial communities of Jα18-/- mice but also dramatic separation between Jα18-/- and CDAA-diet fed mice compared to wildtype mice on a normal diet.

Studies in mice often demonstrate such distinct clustering as both the housing environment and inherited effects from breeding can drive localized differentiation, but mice deficient for a the CD1d gene (CD1d-/-) that lack all NKT cells were similar in composition to the Jα18-/- mice, suggesting that the loss of the iNKT cell population may be driving this change.

Intriguingly, when we treated CDAA-fed mice with tazarotene, a drug that specifically depletes NKT-cells, these trends were not observed, suggesting that the impact of the loss of NKT cells may be a result of the absence of these mice during the early development of their gut microbiome and the immune system shaped by it, Austin Swafford, Director of Research at the Center for Microbiome Innovation explains.

As this study was the first reported analysis of the gut microbiome composition in Jα18-/- mice, the team is planning many follow-up experiments to examine the strain-level associations of the microbial community as well as effects on the metabolites detected in the samples.

More information: Igor Maricic et al. Differential Activation of

Hepatic Invariant NKT Cell Subsets Plays a Key Role in Progression of Nonalcoholic Steatohepatitis, *The Journal of Immunology* (2018). DOI: 10.4049/jimmunol.1800614