METABOLIC DISEASE

Commensal bacteria (ab)use CD8$^+$ T cells to induce insulin resistance

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Chi Ma and Tim F. Greten*

Type I interferon–dependent expansion of intrahepatic CD8$^+$ T cells promotes systemic insulin resistance in obesity.

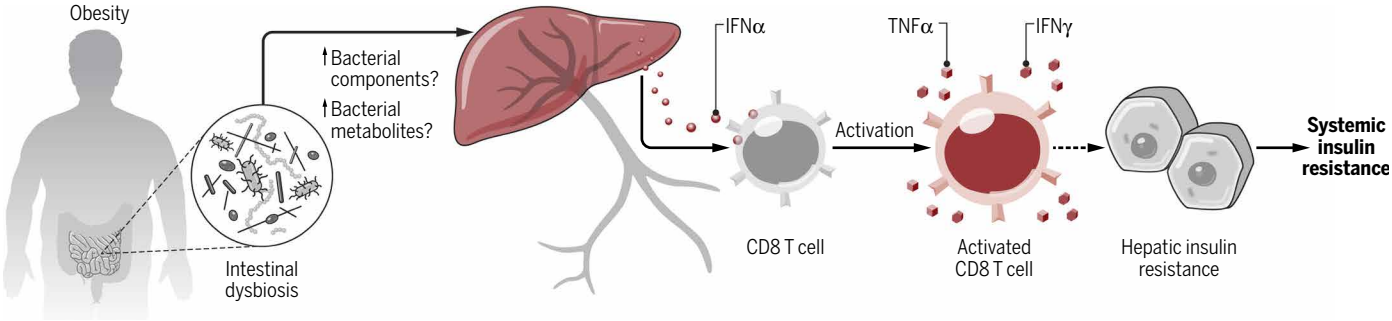

Fig. 1. IFN-I signaling mediates CD8$^+$ T cell activation and insulin resistance in obesity. Obesity has several systemic effects, one of them being changes in the composition of the intestinal microbiome. Ghazarian *et al.* propose that this microbial dysbiosis up-regulates IFN-Is in the liver and promotes activation and expansion of intrahepatic CD8$^+$ T cells, which contribute to hepatic and systemic insulin resistance.

Obesity has become a global pandemic. In 2014, about 40% of adults were overweight and 13% were obese worldwide (*1*). Obese individuals experience chronic low-grade inflammation that increases their susceptibility to a range of cardiovascular, fibrotic, and metabolic disorders in a variety of tissues. In the liver, this inflammation contributes to the development of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), which can lead to severe complications, such as cirrhosis and even hepatocellular carcinoma. The role of adaptive immunity in NAFLD remains poorly understood. In the current issue of *Science Immunology*, Ghazarian *et al.* report that inflammation in the form of type I interferon (IFN-I) signaling mediates the activation of CD8$^+$ T cells in the liver and contributes to systemic glucose dysregulation in patients with NAFLD and in mouse models of NAFLD (*2*).

Using high-fat diet (HFD)–fed mice, leptin-deficient (ob/ob) mice, and samples from patients with NAFLD, the authors observed a selective expansion of CD8$^+$ T cells in the liver in mice and humans. In comparison to mice fed a normal chow diet (NCD), the authors documented that intrahepatic CD8$^+$ T cells in HFD-fed mice were activated, produced more IFNγ and TNFα, and contributed to systemic insulin resistance; they documented similar observations in ob/ob mice and in NAFLD patients. In HFD-fed mice, selective blockade of the IFN-I signaling in CD8$^+$ T cells reversed activation of intrahepatic CD8$^+$ T cells and improved systemic insulin sensitivity. Furthermore, using broad-spectrum antibiotic treatment to deplete commensal bacteria in HFD-fed mice reduced IFN-I levels and the number of intrahepatic CD8$^+$ T cells. On the basis of these findings, Ghazarian *et al.* propose that increased liver IFN-I signaling and activation of CD8$^+$ T cells in the liver in NAFLD are linked to obesity-associated gut microbial dysbiosis (Fig. 1).

The authors and others have found activated intrahepatic CD8$^+$ and CD4$^+$ T cells in NAFLD (*3*, *4*), yet questions remain as to how intrahepatic T cells are being activated. Specifically, is the activation of intrahepatic T cells in NAFLD dependent on a particular antigen? In this study, the authors analyzed T cell receptor (TCR) repertoires of intrahepatic CD8$^+$ T cells in mice with NAFLD and found no significant changes in the repertoires as compared with control mice. Because antigen-dependent expansion results in a biased TCR repertoire, the authors propose that the activation of intrahepatic T cells in NAFLD is TCR-independent and represents bystander activation mediated by cytokines. Although the bystander activation hypothesis is not without precedent, these data are open to other interpretations as well. Innate-like lymphocytes such as innate lymphoid cells (ILCs), natural killer (NK) cells, and natural killer T (NKT) cells can rapidly respond to cytokines (*5*). Given that NK cells, NKT cells, and group 1 ILCs reside in the liver (*6*), it is unclear why intrahepatic CD8$^+$ T cells perform a function that conventionally associated with innate lymphocyte populations. Moreover, not all intrahepatic CD8$^+$ T cells are conventional CD8$^+$ T cells. In humans, CD8$^+$ mucosal-associated invariant cells, innate-like lymphocytes that recognize bacterial metabolites, are enriched in the liver and comprise ~20 to 50% of hepatic lymphocytes (*7*). Although the authors' claim that CD8$^+$ T cells are being activated in an antigen-independent fashion is intriguing, a conclusive demonstration

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will require further inroads into the biology of intrahepatic T cells and other liver-resident lymphoid cells.

The data reported by Ghazarian *et al.* support the idea that microbial dysbiosis links obesity with chronic inflammation and insulin resistance. Specifically, administration of oral broad-spectrum antibiotics that deplete commensal bacteria in HFD-fed mice did not affect weight gain but dampened inflammation in the liver and improved glucose tolerance in these mice. A contribution of the gut microbiome to immune regulation in NAFLD and other metabolic diseases has been suggested by previous studies (*8*). In fact, several groups have carried out gut metagenome sequencing in HFD-fed mice. Particularly noteworthy is the study by Rabot *et al.* (*9*) that documented that *Bacteroidetes* protected HFD-fed mice from developing glucose intolerance, whereas *Firmicutes* had the opposite effect. Whether the same microbes are regulating IFN-I levels and expansion of intrahepatic $CD8^+$ T cells in mice with NAFLD is worth testing. Equally interesting would be studies that define the bacterial components driving inflammation in NAFLD. It is plausible that the effects documented by Ghazarian *et al.* may be independent of bacterial components given the metabolic functions of intestinal microbiota, including vitamin synthesis, saccharolytic fermentation to produce short-chain fatty acids, and bile acid metabolism. For instance, levels of deoxycholic acid, a secondary bile acid that is also produced by intestinal bacteria, have been reported to increase in HFD-fed mice due to the expansion of *Clostridium* species (*10*).

In summary, Ghazarian *et al.* highlight the roles of IFN-I signaling and intrahepatic $CD8^+$ T cells in obesity-associated systemic insulin resistance and add to the growing recognition of the convergence of diet, inflammation, and the microbiome in the development of obesity-associated metabolic disease.

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Funding: This work was supported by the Intramural Research Program of the NIH/National Cancer Institute.

10.1126/sciimmunol.aan1473

Citation: C. Ma, T. F. Greten, Commensal bacteria (ab)use $CD8^+$ T cells to induce insulin resistance. *Sci. Immunol.* **2**, eaan1473 (2017).

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*Sci. Immunol.*2, (2017)
doi: 10.1126/sciimmunol.aan1473

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