A growing epidemic of obesity is threatening the health of millions of people around the world. In recent years, the fields of immunology and metabolism are rapidly converging (1). Studies have established that obesity is associated with systemic low-grade chronic inflammation, which may play a causal role in obesity-associated insulin resistance, type 2 diabetes, and other complications (2,3). Notably, many immune cells infiltrate and populate in tissues, such as adipose tissue, during obesity and influence nutrient metabolism and tissue inflammation (1). Despite these advances, however, how inflammatory responses are maintained at a low level in obesity remains poorly understood. This is an important question because an overt immune response in obesity would compromise the immune system’s ability to preserve immune “tolerance” of self while maintaining the ability to fight off foreign pathogens.

T lymphocytes, both CD4+ and CD8+ T cells, play an essential role in the initiation and regulation of adaptive immunity to foreign and native antigens. CD4+ T lymphocytes recognize polypeptides presented by class II major histocompatibility complex (MHC) molecules on the surface of antigen-presenting cells (APCs), such as macrophages and dendritic cells. Activated effector CD4+ T cells release cytokines that recruit other immune cells to the area, leading to inflammation. In addition to functionally distinct effector T-helper (Th) 1, Th2, and Th17 cells, CD4+ effector T cells can differentiate into immunosuppressive CD4+ CD25+ regulatory T (Treg) cells, an event regulated by the transcription factor forkhead box P3 (Foxp3) (4,5). In addition to their origin in thymus, Treg cells can arise in the periphery from CD4+ Foxp3− T cells. They are master regulators of peripheral lymphocytes and central for self-tolerance to control unwanted autoimmune response (6). Depletion of Tregs not only elicits autoimmunity, but also enhances immune response to non-self-antigens, as in the immune dysregulation, polyendocrinopathy, enteropathy, X-inked syndrome patients (6,7). These patients develop aggressive autoimmunity, including diabetes, thyroiditis, and eczema. Unlike CD8+ T cells, which increase in adipose tissue with obesity (8,9), Treg cells in abdominal adipose tissue of various obese mouse models as well as obese human patients decrease with adiposity (9,10). Manipulation of Treg levels in mice alters tissue inflammation and systemic metabolic parameters (9–11), pointing to Treg cells as negative regulators of proinflammatory responses in obesity.

To achieve self-tolerance, the immune system has evolved several mechanisms to ensure appropriate specificity and magnitude, thereby preventing potentially deleterious responses to self. As an essential regulatory mechanism, T-cell activation in response to antigens is dictated by both positive and negative costimulatory signals generated mainly by the interactions between the B7 family on the APC and their receptor CD28 family (6,12). Best-characterized members of the B7 ligand family are B7-1 and B7-2, and of the CD28 receptor family are activating CD28 and inhibitory cytotoxic T-cell–associated (CTLA)-4 (Fig. 1). CD28-mediated positive costimulation supports early stages of T-cell activation and proliferation and is important for the development of productive immune response. On the other hand, CTLA-4–mediated negative costimulation
controls homeostatic proliferation of naïve T cells, and thus is critical for the termination of immune response and prevention of inflammation-induced tissue damage (6,12). These costimulatory signals not only affect naïve and effector T cells, but also Treg cells (6,12). Indeed, mice deficient for either B7-1/B7-2 or CD28 or CTLA-4 exhibit Treg cell deficiency in both thymus and the periphery (13–16). However, whether and how the costimulatory signals are involved in metabolic regulation in obesity remains unclear.

In this issue, Zhong et al. (15) show that signals provided by B7-1/B7-2 tip the balance of metabolic regulation by regulating the homeostasis of Treg cells. Mice deficient in both B7-1 and B7-2 (hereafter the knockout mice) have normal body weight, while adipose tissue weight is significantly reduced and liver weight is increased compared with wild-type mice when fed a high-fat diet (HFD). Surprisingly, the knockout mice on an HFD are more insulin resistant and glucose intolerant. These metabolic changes are associated with elevated inflammation and increased abundance of macrophages in adipose tissue. Of importance, in human visceral adipose depot (but not in subcutaneous depot), there is a negative correlation between insulin resistance and the percent of B7-1/B7-2+ macrophages. Mechanistically, loss of B7-1 and B7-2 leads to a systemic reduction of Treg cells in several tissues, including adipose tissue, spleen, and lymph nodes. Adoptive transfer of Treg cells to the knockout mice improves metabolic parameters, suggesting that physiological effect of B7-1/B7-2 is mediated, at least in part, by Treg cells. Overall, the experiments support the model that B7-1/B7-2-mediated signals are important for the homeostasis of Treg cells and obesity-associated inflammation (Fig. 1).

Zhong et al. (15) provide important insights into how immunological balance is maintained in obesity. B7-1/B7-2 deficiency reduces the abundance of Treg cells, leading to increased inflammation and increased insulin resistance in obese mice fed an HFD. Thus, the downregulation of costimulatory signals in obese adipose tissue may be responsible for the reduction of Treg cells. These new findings raise many interesting questions. How are the levels of B7-1/B7-2 downregulated in adipose tissue with obesity? What is the role of adipocyte B7-1/B7-2 in the homeostasis of Treg cells? How does adipose microenvironment influence Treg-cell homeostasis and function? Last, as the two cohorts in this study are bred and reared separately, how do different gut microbiota structures influence their metabolic phenotypes? In the same vein, intestines harbor a large number of Treg cells and as Treg cells are critical for intestinal tolerance (17), it will be interesting to address how Treg cells in the intestines are affected and how the perturbation of gut Treg cells affect systemic inflammation and metabolic parameters in the obese knockout mice.

As we gain further insights into the functional significance and mechanism of these immunoregulatory pathways by both genetics and immunological approaches in obesity, these receptors and ligands are poised to become key targets for immunotherapy. The million dollar question is how to target the "costimulatory signals" therapeutically for a safe and effective treatment of type 2 diabetes.

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