Inflammation versus Host Defense in Obesity

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Obesity is characterized by a state of low-grade, chronic inflammation. Wang et al. (2014) report that immune cells from obese mice have decreased production of IL-22, a cytokine involved in immune responses and inflammation, and reveal therapeutic effects of exogenous IL-22 against obesity-linked metabolic dysfunctions.

Obesity is associated with increased inflammation, which is mainly evidenced by accumulation and proinflammatory polarization of macrophages/dendritic cells (DCs) and T cells in adipose tissue and skeletal muscle, and contributes to the development of insulin resistance and type 2 diabetes (Glass and Olefsky, 2012; Kratz et al., 2014; Wu et al., 2007). While alternatively activated macrophages, regulatory T cells, eosinophils, and invariant natural killer T cells are resident cells in lean adipose tissue and decreased in obese adipose tissue, "classically activated-like" or "metabolically activated," proinflammatory macrophages, T-cytotoxic 1 and T helper type 1 cells, neutrophils, B cells, and mast cells are increased in obese adipose tissue and mediate adipose tissue inflammation (Glass and Olefsky, 2012; Kratz et al., 2014). The mechanisms whereby inflammation contributes to obesity-linked metabolic dysfunctions remain incompletely understood. Increased secretion of proinflammatory cytokines may directly influence metabolic functions of insulin-responsive tissues/cells such as adipocytes and myocytes, causing insulin resistance in these tissues/cells. Adverse effects of proinflammatory cells/molecules on adipocytes/preadipocytes may also accelerate lipid transfer from adipocytes to skeletal muscle and liver, leading to ectopic lipid deposition and insulin resistance in these tissues and causing systemic metabolic dysfunctions (Glass and Olefsky, 2012; Wu et al., 2007). Therefore, anti-inflammation therapy is viewed as a promising strategy for obesity-linked metabolic dysfunctions and has indeed shown some promising effects (Glass and Olefsky, 2012). In contrast, Wang et al. (2014) now report impaired IL-22 induction in immune cells, leading to compromised host defense, in obese mice and unexpected beneficial effects of exogenous initerleukin-22 (IL-22) on obesity-related metabolic dysfunctions.

IL-22 is a cytokine mostly produced by activated DCs, innate lymphoid cells, and activated T cells, including Th22, Th17, and Th1 cells, that initiates immune responses against bacterial pathogens especially in epithelial cells (Sabat et al., 2014). IL-22 is thought to function as a proinflammatory cytokine, as it induces the production of leukocyte-attracting chemokines and acute-phase proteins in epithelial cells or hepatocytes (Sabat et al., 2014), which helps amplify the inflammatory process and enhances antimicrobial immunity. Indeed, recent reports showed increased Th22 frequency and IL-22 level in blood and enrichment of IL-22- and IL-17-producing T cells in adipose tissue of obese diabetic patients (Dalmas et al., 2014). Macrophage-derived IL-1β promoted adipose tissue T cell production of IL-22, which in turn increased macrophage release of IL-1β (Dalmas et al., 2014). Therefore, IL-22 may mediate amplification of IL-1β-driven adipose tissue inflammation and contribute to obesity-linked metabolic dysfunctions.

Recent studies have also recognized a connection between altered gut microbiota and obesity-related metabolic dysfunctions (Tremaroli and Bäckhed, 2012). Because of its crucial role in mucosal host defense, Wang et al. (2014) studied the biological importance of IL-22 production from immune cells in obese mice. In contrast to the reported increases in IL-22-producing T cells in blood and adipose tissue of obese humans (Dalmas et al., 2014), Wang et al. (2014) observed a defect in IL-22 induction in immune cells of diet-induced obese (DIO) mice and genetically obese leptin-deficient (ob/ob), or leptin receptor-deficient (db/db) mice under various immune challenges, which led to increased susceptibility to *C. rodentium* infection in these mice. Unexpectedly, they further demonstrated that deletion of IL-22 receptor caused greater weight gain and worsened insulin resistance in DIO mice. Treatment of DIO and db/db mice with exogenous IL-22 decreased food intake, reduced body weight and fat mass, and reversed obesity-related metabolic dysfunctions, with significant improvement of hyperglycemia and insulin resistance. Intriguingly, IL-22 treatment of DIO or db/db mice reduced serum lipopolysaccharide (LPS) levels, decreased adipose tissue inflammation, and activated STAT3 in liver and adipose tissue with improved lipid metabolism, including prevention of hepatic steatosis and induction of expression of genes involved in triglyceride lipolysis and fatty acid β-oxidation.

Multiple downstream functions of IL-22, including maintaining mucosal epithelial integrity, reducing inflammation, and alleviating metabolic functions, may all contribute to the beneficial effects of this cytokine on obesity-linked metabolic dysfunctions (Wang et al., 2014). The reductions in body weight and LPS levels observed in obese mice treated with IL-22 may have caused the decreased adipose tissue inflammation in the study

by Wang et al. (2014), though these results seem to oppose previous studies supporting a proinflammatory role of IL-22 in adipose tissue in humans and mice (Dalmas et al., 2014; Wang et al., 2011). The reasons for these IL-22-induced effects, weight reduction in particular, remain unknown and may be linked to the restoration of mucosal immunity. However, disruption of mucosal immunity by ablation of lymphotoxin has been shown to decrease IL-22 and reduce weight gain in DIO mice, whereas delivery of exogenous IL-22 restored weight gain in these mice (Upadhyay et al., 2012). These results point to an essential role of mucosal immunity mediated by the lymphotoxin-IL-22 pathway in weight gain, rather than weight loss, in DIO mice. In addition, Wang et al. (2014) found that STAT3 activation was associated with improved metabolism in liver and adipose tissue of obese mice treated with IL-22. However, previous studies do not support a beneficial role of STAT3 in hepatocyte and adipocyte metabolisms. In fact, STAT3 activation may mediate hepatocyte and adipocyte insulin resistance induced by IL-6, which is increased in obesity (Kristiansen and Mandrup-Poulsen, 2005). Therefore, further studies are needed to define the exact mechanisms whereby IL-22 treatment improves obesity-linked metabolic functions. In particular, it needs to be determined how IL-22 treatment of obese mice causes reductions in body weight and fat mass, which could account for most of the observed beneficial effects. Weight reduction by IL-22 cannot be explained solely by reduced food intake, as IL-22 treatment still decreased body weight in DIO mice in pair-feeding studies with normalized food intake (Wang et al., 2014). Therefore, effects of IL-22 on energy expenditure, and potential direct effects on metabolism of preadipocytes/adipocytes and skeletal muscle as well as their mechanisms, remain to be investigated.

A key challenge is now to determine whether IL-22 can be used as a therapy for obesity in humans. The study by Wang et al. (2014) supports this possibility, though IL-22 and constitutive activation of the STAT3 pathway have been involved in several types of human cancers (Sabat et al., 2014) and IL-22 overexpression in mouse adipose tissue results in spontaneous liposarcoma (Wang et al., 2011). Therefore, a better understanding of IL-22 mechanisms of action and examination of the potential oncogenic side effects are warranted before IL-22 can be used in humans for obesity-associated metabolic diseases.

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