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IL-21 Is a Major Negative Regulator of IRF4-Dependent Lipolysis Affecting Tregs in Adipose Tissue and Systemic Insulin Sensitivity

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PATHOPHYSIOLOGY

Obesity elicits immune cell infiltration of adipose tissue provoking chronic low-grade inflammation. Regulatory T cells (Tregs) are specifically reduced in adipose tissue of obese animals. Since interleukin (IL)-21 plays an important role in inducing and maintaining immune-mediated chronic inflammatory processes and negatively regulates Treg differentiation/activity, we hypothesized that it could play a role in obesity-induced insulin resistance. We found IL-21 and IL-21R mRNA expression upregulated in adipose tissue of high-fat diet (HFD) wild-type (WT) mice and in stromal vascular fraction from human obese subjects in parallel to macrophage and inflammatory markers. Interestingly, a larger infiltration of Treg cells was seen in the adipose tissue of IL-21 knockout (KO) mice compared with WT animals fed both normal diet and HFD. In a context of diet-induced obesity, IL-21 KO mice, compared with WT animals, exhibited lower body weight, improved insulin sensitivity, and decreased adipose and hepatic inflammation. This metabolic phenotype is accompanied by a higher induction of interferon regulatory factor 4 (IRF4), a transcriptional regulator of fasting lipolysis in adipose tissue. Our data suggest that IL-21 exerts negative regulation on IRF4 and Treg activity, developing and maintaining adipose tissue inflammation in the obesity state.

Obesity-associated tissue inflammation is now recognized as a major cause of decreased insulin sensitivity (1,2). Obesity, insulin resistance, and type 2 diabetes are closely associated with chronic inflammation characterized by abnormal cytokine production, increased acute-phase reactants and other mediators, and activation of a network of inflammatory signaling pathways (3,4). Excessive triglyceride accumulation within adipocytes leads to adipocyte hypertrophy and a dysregulation of adipokine secretory patterns. Adipocytes as well as cells of the stromal vascular fraction (SVF), including preadipocytes, fibroblasts, mesenchymal stem cells, and immune cells, contribute to the production of proinflammatory cytokines in obesity (3–5), with a pivotal role played by macrophages and T lymphocytes (6–8). In lean adipose tissue, T-helper (Th) type 2 cells produce anti-inflammatory cytokines such as interleukin (IL)-4, -10, and -13, which promote alternative activated M2 macrophage polarization (9). M2 polarization is also induced by regulatory T cells (Tregs) and eosinophils via IL-4. Conversely, in obese adipose tissue, investigators have observed an increase in the number of Th1 cytokines, M1 polarized macrophages, mast cells, B cells, and $CD8^+$ T cells, which contribute to

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