Recent studies project an exponential increase in type 2 diabetes mellitus, obesity, and the metabolic syndrome not only in Western but also in developing countries. This perspective suggests an alarming rise in morbidity, mortality, and health care costs associated with these diseases. Thus, for improving prevention, diagnosis, and therapy of these diseases, we need a better understanding of the genetic, molecular, cellular, and environmental interactions that govern these metabolic derangements.

Chronic inflammation plays a pivotal role in insulin resistance and obesity that shares many pathogenetic aspects with atherogenesis. Hotamisligil and coworkers were the first to describe a role of proinflammatory cytokines in obesity. They reported an increase in tumor necrosis factor (TNF)α in the white adipose tissue of obese mice that correlated with insulin resistance. Meanwhile, this notion has been extended from mice to men and to other cytokines such as monocyte chemoattractant protein (MCP)-1, interleukin (IL)-1, and IL-6 that have been found to be involved in obesity and insulin resistance.

At the cellular level, most reports have highlighted macrophages as the key directors of this inflammatory concert. Less is known about the role of adaptive immunity in obesity. Recent studies reveal that obese mice and men also exhibit an increase in adipose tissue T cells and the corresponding chemokines such as RANTES (regulated on activation, normal T-cell expressed and secreted) or cytokines such as interferon (IFN)-γ. Nevertheless, the relevance of T cells in this context remains to be determined.

In this issue of *Circulation Research*, Sultan et al describe the effects of T cell-mediated inflammation in lean atherosclerotic mice focusing on the role of IL-6 on insulin resistance in adipose tissue. The authors used *ApoE−/−; CD4dnTGFbR* mice that display enhanced T cell activation attributable to disrupted TGF-β signaling and observed increased number of macrophages and CD4+ T cells, as well as enhanced expression and secretion of TNFα, IFNγ, and MCP-1 in adipose tissue. Unexpectedly, IL-6 was not elevated, but lower in *ApoE−/−; CD4dnTGFbR* compared with obese *ob/ob* and even wild-type mice. In line with this observation, adipose insulin sensitivity remained unchanged unless IL-6 was administered exogenously. The authors conclude that T cell inflammation in adipose tissue induces a variety of proinflammatory cytokines, that is, however, not sufficient for inducing IL-6 and adipose tissue insulin resistance.

Is IL-6 expression actively suppressed in the adipose tissue of *ApoE−/−; CD4dnTGFbR* mice? To address this question, Sultan et al analyzed the transcriptional regulation of IL-6. The IL-6 promoter contains several repressive glucocorticoid response elements. The authors found an increased expression of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) in adipose tissue of *ApoE−/−; CD4dnTGFbR* mice, an enzyme that is expressed by CD4+ T cells and drives the interconversion between inactive 11-ketoglucocorticoids and their active derivatives such as cortisol. These findings suggest that CD4+ T cells express more 11β-HSD1 on adipose tissue infiltration, consequently secreting more cortisol that in turn will repress IL-6 secretion in neighboring adipocytes. A recent study suggests that basal 11β-HSD1 activity is low but enhanced in mononuclear leukocytes after migration into sites of inflammation. Nevertheless, further studies have to be performed to verify if the same holds true for CD4+ T cells on adipose tissue infiltration. Taken together, these observations suggest that activated CD4+ T cells may exhibit a dual role in adipose tissue: they confer inflammatory effects via induction of proinflammatory cytokines and suppress IL-6-mediated insulin resistance (Figure).

Of note, the effects of IL-6 on metabolic diseases are not uniform and reflect the complex interplay of multiple factors. IL-6 serum levels positively correlate with obesity in humans and predict the risk of developing insulin resistance and type 2 diabetes. Chronic infusion of IL-6 into the portal vein induced hepatic insulin resistance in mice. Furthermore, activation of the mitogen-activated protein kinase c-Jun N-terminal kinase (JNK1) in adipose tissue can cause insulin resistance in the liver via increased IL-6 secretion by adipocytes. Conversely, transgenic nonobese diabetic (NOD) mice overexpressing human IL-6 in pancreatic β cells had lower fasting glucose levels, delayed onset of diabetes, and consequently prolonged survival compared with NOD mice. Moreover, IL-6-deficient mice develop mature-onset obesity by direct actions of IL-6 on the brain. These studies imply that the effects of IL-6 on insulin resistance are controversial and differ from tissue to tissue. Finally, expression of IL-6 remained unchanged in 3T3-L1 adipocytes on IFNγ stimulation, thereby casting doubts whether T cells do at all enhance IL-6 stimulation in adipocytes.

*ApoE−/−; CD4dnTGFbR* mice have been previously studied for addressing the role of increased T cells in atherogenesis: compared with age-matched *ApoE−/−* littermates, *ApoE−/−; CD4dnTGFbR* mice showed an increase in aortic...
lesions, plaque T cells, macrophages, and IFNγ mRNA, as well as enhanced plasma levels of IFNγ and TNFα. Thus, this model was an interesting choice to address the effects of hyperlipidemia- and T cell–driven inflammation in lean mice on adipose tissue metabolism. However, these stimuli were not sufficient to induce insulin resistance in mice without obesity. This was to be expected given previous reports about normal insulin sensitivity in LDL-R-deficient mice19,20 or our own results in ApoE-deficient animals (C. Lohmann, N. Schäfer, T. von Lukowicz, M.A.S. Stein, J. Borén, S. Rütti, W. Wahl, M.Y. Donath, T.F. Löscher, C.M. Matter, unpublished observations, 2009). Moreover, obese mice exhibit insulin resistance and infiltration with T cells in their visceral adipose tissue which may even appear before macrophages.21 Interestingly, Sultan et al10 observed more macrophages in ApoE−/− CD4dnTGFβR mice, suggesting that CD4+ T cells attract more macrophages into the adipose tissue. In light of these findings, analyses in lean and obese mice single mutant CD4dnTGFβR mice would provide suitable models for further dissecting the causal role of T cell–mediated inflammation and the corresponding metabolic response. 

Taken together, we learn from Sultan et al10 that enhanced T cell activation in lean atherosclerotic mice attract and stimulate T cells and macrophages in adipose tissue without affecting insulin resistance. Activated T cells in adipose tissue may play a dual role: they exert proinflammatory effects by stimulating TNFα, IFNγ, and MCP-1 without elevating IL-6. On the other hand, stimulation of T cells may even actively suppress IL-6 expression by simultaneous activation of 11β-HSD1 in adipose tissue. In between these 2 positions, it is conceivable that elevated T cells, in the absence of obesity, are only bystanders, without playing a critical role. Thus, the effects of T cells and their mediators on insulin resistance may vary in different tissues and physiological contexts: their relevance remains to be proven.

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