Inflammation, Adipose Tissue, and T Cells: What Is the “Straight Skinny” on Lean Versus Fat Mice?

To the Editor:

Obesity is associated with chronic inflammation in adipose tissue (AT), as evidenced by increased levels of cytokines/chemokines and accumulation and activation of macrophages and T cells,1–3 which are acknowledged as important contributors to insulin resistance in obesity. Recently, using Apoe−/− × CD4dnTGFβR mice, Sultan et al reported that T cell–mediated inflammation does not cause insulin resistance in lean mice.4 Compared to controls (Apoe−/− mice), lean Apoe−/− × CD4dnTGFβR mice showed increased inflammation in AT (but not specifically in AT), as indicated by increased content of T cells and macrophages, higher levels of tumor necrosis factor-α, interferon-γ, and monocyte chemoattractant protein-1, but a comparable level of interleukin (IL)-6.4 However, lean Apoe−/− × CD4dnTGFβR mice did not show worsened insulin resistance compared to Apoe−/− mice.5 Therefore, the authors concluded that T cell–mediated inflammation in AT does not cause insulin resistance in hyperlipidemic mice.4

We acknowledge Sultan et al for their report on the study of the role of T cell–mediated inflammation in insulin resistance.4 However, because of the following limitations of this study, we feel that it is too early to make any firm conclusions on the potential role of T cell–mediated AT inflammation in metabolic dysfunctions, particularly with diet-induced obesity, which is commonly accompanied by dyslipidemia.

First, Apoe−/− × CD4dnTGFβR mice displayed a unique inflammation pattern in AT, with unchanged IL-6 level compared to Apoe−/− controls but lower IL-6 level than B6 mice.4 However, obese mice showed increased IL-6 level compared to lean. Thus, this mouse model does not represent the AT inflammation pattern observed in obesity. In addition, obesity usually has little if any relevance to the T cell–mediated AT inflammation in obesity. The pathophysiology of the lipid disorders associated with insulin resistance and obesity, particularly as related to fatty acid metabolism, is markedly different than the Apoe−/− model. Second, the authors used lean mice.4 When we and others study the role of chronic AT inflammation in insulin resistance, we mostly refer to obese conditions and examine the contribution of obesity-related inflammation to metabolic dysfunctions. Results obtained in lean mice in a study of the role of inflammation per se in insulin resistance may have little direct relevance to obese conditions.

Third, this study used female mice.4 Most previous studies of obesity-related inflammation used male mice.1,5,6 As we showed previously,2 female mice were less predisposed to develop insulin resistance than male mice with obesity, even though they were maintained on the same type of high-fat diet for the same period of time. Therefore, it is unclear whether a sex effect existed in this study.4

Fourth, in addition to T cells, macrophages were also increased and activated in AT of Apoe−/− × CD4dnTGFβR. The absence of impaired insulin sensitivity in Apoe−/− × CD4dnTGFβR mice was also in conflict with a role of macrophage-mediated AT inflammation in insulin resistance, as previously demonstrated by several research laboratories.5,6

Fifth, the authors provided some evidence indicating that the lack of IL-6 upregulation may contribute to the absence of insulin resistance in Apoe−/− × CD4dnTGFβR mice.4 They also suggested that upregulation of 11β-HSD1 in AT of Apoe−/− × CD4dnTGFβR (compared to Apoe−/−) mice contributed to the lack of IL-6 upregulation in this mouse model. However, they did not show a significant difference between Apoe−/− × CD4dnTGFβR and Apoe−/− in AT IL-6 levels. Both Apoe−/− × CD4dnTGFβR and Apoe−/− mice had lower IL-6 levels in AT than B6. The authors might assume that the increased 11β-HSD1, which catalyzes generation of cortisol, in AT of Apoe−/− × CD4dnTGFβR may have counterbalanced the effect of the increased cytokines (tumor necrosis factor-α, monocyte chemoattractant protein-1, etc) on IL-6 regulation in Apoe−/− × CD4dnTGFβR because these cytokines were low in AT of Apoe−/− mice. However, the low levels of cytokines (including IL-6) in AT of Apoe−/− mice as compared to B6 were accompanied by insulin resistance, as the authors observed in Apoe−/− mice,6 which does not support a key role of IL-6 in insulin resistance.

In summary, Sultan et al reported some novel phenotypic changes of lean Apoe−/− × CD4dnTGFβR mice in AT and metabolic functions, which are caused by loss of TGFβ-dependent inhibition of T-cell activation.4 However, because of the limitations of this study, the potential contribution of T cell–mediated AT inflammation to insulin resistance with diet-induced obesity, which is the major mechanism driving this problem in humans, clearly requires additional study.

Sources of Funding

Supported by an American Heart Association Award and NIH grant R01DK078847.

Disclosures

None.

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Circ Res. 2009;105:e3-e4
doi: 10.1161/CIRCRESAHA.109.201244

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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