Response to the Letter by Wu and Ballantyne

To the Editor:

Work in several laboratories, including that of Drs Wu and Ballantyne, have demonstrated that macrophages and T cells infiltrate adipose tissue (AT) during the metabolic syndrome.1 Because they are activated and secrete cytokines, it has been suggested that these immune cells may contribute to the development of insulin resistance. This idea gained support from reports of an increased prevalence of metabolic syndrome in patients with chronic inflammatory diseases such as psoriasis,2 Crohn’s disease,3 and rheumatoid arthritis. 4 These conditions, and rheumatoid arthritis in particular, are known to depend on adaptive immunity, with expanded T cell clones and HLA associations.

To identify the effect of T cell activation on AT metabolism, we studied AT of mice with increased T-cell activation.5 The Apoe-/- × CD4dnTGFbR mouse lacks functional transforming growth factor-β receptors on T cells, leading to enhanced T-cell activation and secretion of proinflammatory cytokines, in turn leading to macrophage activation and a hyperinflamed condition, in AT as in several other tissues including the artery wall. Because these mice are hyperlipidemic due to targeted Apoe genes, we had expected that they would develop also other features of the metabolic syndrome. To our surprise, this T cell–driven inflammation did not lead to increased insulin resistance. Therefore, we concluded that T-cell activation causes inflammation in AT but does not lead to insulin resistance.

A comparison of the AT gene expression pattern in these mice and ob/ob mice identified interleukin (IL)-6 as being reduced in T cell–driven inflammation but increased in ob/ob mice. We found that local cortisol production was the likely reason for the inhibited IL-6 production and showed that administration of IL-6 inhibited IL-6 production and showed that administration of IL-6 to induced IL-6 production and showed that administration of IL-6 to induced IL-6 production and showed that administration of IL-6 to induced IL-6 production and showed that administration of IL-6 to decreased insulin sensitivity in AT.

Wu and Ballantyne point out that it is too early to make any firm conclusions on the potential role of T cell–mediated AT inflammation in diet-induced obesity. We fully agree and it is important to note that we have not studied the effect of any particular diet on AT inflammation. Our approach was not to construct a situation that mimics human obesity as closely as possible but to determine the effect of T cell activation on AT inflammation. We compared AT inflammation in Apoe-/- × CD4dnTGFbR mice with that in ob/ob mice, in which obesity is attributable to a mutation in the leptin gene. These 2 mouse strains represent extreme conditions of T cell–driven inflammation and genetic obesity, respectively, and not the complex gene–environment interactions that likely contribute to obesity and insulin resistance in most humans with the metabolic syndrome. However, we are convinced that a reductionistic approach using genetic models is informative and can help us identify pathogenetic mechanisms of relevance also for common human disease conditions.

In this particular case, our approach shows that T cell–driven inflammation is not sufficient to cause insulin resistance in AT, even when combined with hyperlipidemia. Additional factors are needed to induce this condition and overcome the inhibition of IL-6 secretion. Some of these aspects were discussed in our article and in the accompanying editorial by Matter and Stein.6 We encourage Wu and Ballantyne, and other investigators, to study the interactions between immune cells and adipose tissue in diet-induced obesity.

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Disclosures

None.

Ariane Sultan

INSEERM ERI-25 and Université de Montpellier 1
Montpellier, France

Göran K. Hansson

Center for Molecular Medicine
Department of Medicine
Karolinska University Hospital
Karolinska Institutet
Stockholm, Sweden

E-mail Goran.Hansson@ki.se


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Ariane Sultan and Göran K. Hansson

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