

Comment on: Kim et al. Deficiency for Costimulatory Receptor 4-1BB Protects Against Obesity-Induced Inflammation and Metabolic Disorders. *Diabetes* 2011;60:3159–3168

Sandra E. Gomez-Mejiba and Dario C. Ramirez

In the December 2011 issue of *Diabetes*, Kim et al. (1) reported that 4-1BB (CD137/TNFRSF9) deficiency protected against high-fat diet-induced obesity, glucose intolerance, and fatty liver disease. They found that 4-1BB deficiency reduced number and activation of macrophages/CD8⁺ T cells/Th1 cells into adipose tissue, reduced circulating proinflammatory cytokines, and improved insulin sensitivity/liver pathology with respect to wild-type (WT) animals fed the same diet. This is an important advance in the field because antagonism of the 4-1BB/4-1BB ligand interaction (e.g., modulating its expression, blocking receptor/ligand interaction, and interfering signaling) could help reduce macrophage infiltration and adipose tissue inflammation in obesity. However, in an article published by the same laboratories in 2010 in *Endocrinology* (2), they found that 4-1BB stimulation with an agonistic antibody reduced weight gain and adiposity, increased energy expenditure, and improved insulin tolerance and fatty liver disease in mice fed a high-fat diet and genetically obese mice. The authors suggested that these effects would have been caused by 4-1BB-induced expansion/activation of CD8⁺ T cells and consequent increased energy expenditure. We are puzzled and wish to understand this apparent discrepancy between these two elegant studies (1,2) and why the first study was not discussed in the *Diabetes* article, which would help us understand the rationale of these apparently opposite results between these studies.

Inflammation and dysfunction of adipose tissue have emerged as important targets to reduce systemic inflammation and insulin resistance associated with obesity (3). As supported by an extensive body of evidence, most of the inflammatory cytokines produced by inflamed adipose tissue derives from fat-infiltrating and classically activated M1 macrophages (3). This infiltration and activation of macrophages into the metabolically stressed adipose tissue in obesity play critical roles in metabolic alterations associated to obesity (3). The work by Nishimura et al. (4) has highlighted the importance of CD8⁺ T cells in monocyte

infiltration, and differentiation and survival as macrophages into the obese adipose tissue (4). Moreover, 4-1BB expression increases upon activation in T cells and in inflamed vessel walls, where it promotes monocyte migration and macrophage differentiation, survival, and activation (5). This agrees with the data by Kim et al. (1) regarding increased expression of 4-1BB in adipose tissue of obese WT mice. Therefore, and opposite to what was reported in Kim et al. (2), we would have expected that administration of an antibody that agonizes 4-1BB signaling in obese WT mice would increase activation of CD8⁺ cells and promote more macrophage infiltration and activation into the fat tissue.

To facilitate the advancement in the field, it is necessary to have a clearer picture of how agonists or antagonists of 4-1BB and/or 4-1BB ligand change macrophage recruitment and activation in the metabolically stressed adipose tissue in obesity. Understanding of these processes will ensure mechanism-based interventions to reduce macrophage infiltration and consequent adipose tissue inflammation—a leading cause of metabolic complications of obesity.

ACKNOWLEDGMENTS

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Kim C-S, Kim JG, Lee B-J, et al. Deficiency for costimulatory receptor 4-1BB protects against obesity-induced inflammation and metabolic disorders. *Diabetes* 2011;60:3159–3168
2. Kim C-S, Tu TH, Kawada T, Kim B-S, Yu R. The immune signaling molecule 4-1BB stimulation reduces adiposity, insulin resistance, and hepatosteatosis in obese mice. *Endocrinology* 2010;151:4725–4735
3. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. *Annu Rev Physiol* 2010;72:219–246
4. Nishimura S, Manabe I, Nagasaki M, et al. CD8⁺ effector T cells contribute to macrophage recruitment and adipose tissue inflammation in obesity. *Nat Med* 2009;15:914–920
5. Drenkard D, Becke FM, Langstein J, et al. CD137 is expressed on blood vessel walls at sites of inflammation and enhances monocyte migratory activity. *FASEB J* 2007;21:456–463

From the Laboratory of Experimental and Therapeutic Medicine, Multidisciplinary Institute for Biological Investigations of San Luis, San Luis, Argentina, and the Department of Molecular Biology, National University of San Luis, San Luis, Argentina.

Corresponding author: Dario C. Ramirez, ramirezlabimibiosl@gmail.com.
DOI: 10.2337/db12-0128

© 2012 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.