

Response to Comment on: Meagher et al. Neutralization of Interleukin-16 Protects Nonobese Diabetic Mice From Autoimmune Type 1 Diabetes by a CCL4-Dependent Mechanism. *Diabetes* 2010;59:2862–2871

Craig Meagher,¹ William Cruikshank,² and Terry L. Delovitch¹

We thank Vendrame and Dotta (1) for their interesting perspective regarding our recently published study investigating the role of interleukin-16 (IL-16) in the development of insulinitis and type 1 diabetes in female NOD mice (2). On the basis of previous studies correlating suboptimal activation of caspase-3 with the development of autoimmunity in the clinical setting (3,4), they propose a similar condition might exist in NOD mice, resulting in defective secretion of mature IL-16. Although we have not directly examined this possibility, it must be considered that many studies have wrestled with the difficulty in detecting secreted IL-16 in several mouse strains used to examine inflammatory responses (2,5). This likely reflects the biology of mature IL-16, which is active at concentrations as low as 10^{-11} M, and indicates that the low levels of intrapancreatic mature IL-16 detected during the development of insulinitis is not restricted only to the NOD genetic background.

However, the notion that caspase-3 activation may be suboptimal in NOD mice is suggested by several articles reporting that T cells in NOD mice exhibit an altered signaling cascade downstream of the T-cell receptor, resulting in a hyporesponsive state of activation and resistance to activation-induced cell death (6–8). Importantly, although it may be that a reduction in caspase-3 activation leads to diminished IL-16 secretion, this correlation has not yet been proven and the level of activated caspase-3 required for cleavage of pro-IL-16 is unknown. Thus, in support of the perspective by Vendrame and Dotta, it is uncertain how a partial deficiency in caspase-3 activation would affect levels of IL-16 secretion; but clearly, based on our results, the level of caspase-3 activation occurring in lymphocytes is sufficient for the secretion of IL-16 and recruitment of T cells needed for disease pathology.

Collectively, a partial deficiency in caspase-3 activation may contribute to T-cell resistance to activation-induced cell death, which would enable autoreactive T cells to persist and may also facilitate their recruitment to islets via secretion of mature IL-16.

ACKNOWLEDGMENTS

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

REFERENCES

- Vendrame F, Dotta F. Comment on: Meagher et al. Neutralization of interleukin-16 protects nonobese diabetic mice from autoimmune type 1 diabetes by a CCL4-dependent mechanism. *Diabetes* 2010;59:2862–2871 (Letter). *Diabetes* 2011;60:e12. DOI: 10.2337/db10-1489
- Meagher C, Beilke J, Arreaza G, et al. Neutralization of interleukin-16 protects nonobese diabetic mice from autoimmune type 1 diabetes by a CCL4-dependent mechanism. *Diabetes* 2010;59:2862–2871
- Vendrame F, Santangelo C, Misasi R, et al. Defective lymphocyte caspase-3 expression in type 1 diabetes mellitus. *Eur J Endocrinol* 2005;152:119–125
- Vendrame F, Segni M, Grassetti D, et al. Impaired caspase-3 expression by peripheral T cells in chronic autoimmune thyroiditis and in autoimmune polyendocrine syndrome-2. *J Clin Endocrinol Metab* 2006;91:5064–5068
- Yoshimoto T, Wang CR, Yoneto T, Matsuzawa A, Cruikshank WW, Nariuchi H. Role of IL-16 in delayed-type hypersensitivity reaction. *Blood* 2000;95:2869–2874
- Salojin KV, Zhang J, Madrenas J, Delovitch TL. T-cell anergy and altered T-cell receptor signaling: effects on autoimmune disease. *Immunol Today* 1998;19:468–473
- Salojin K, Zhang J, Cameron M, et al. Impaired plasma membrane targeting of Grb2-murine son of sevenless (mSOS) complex and differential activation of the Fyn-T cell receptor (TCR)-zeta-Cbl pathway mediate T cell hyporesponsiveness in autoimmune nonobese diabetic mice. *J Exp Med* 1997; 186:887–897
- Arreaza G, Salojin K, Yang W, et al. Deficient activation and resistance to activation-induced apoptosis of CD8+ T cells is associated with defective peripheral tolerance in nonobese diabetic mice. *Clin Immunol* 2003;107: 103–115

From the ¹Department of Microbiology and Immunology, University of Western Ontario, London, Ontario, Canada; and ²The Pulmonary Center, Boston University, Boston, Massachusetts.

Corresponding author: Terry L. Delovitch, del@robarts.ca.
DOI: 10.2337/db10-1620

© 2011 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.