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

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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 insulitis 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 insulitis 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.

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REFERENCES

1. 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
2. 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
3. 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
4. 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
5. 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
6. 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
7. 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
8. 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

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