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 read with great interest and appreciation the article by Meagher et al. (1). Here, treatment of NOD mice with anti–interleukin-16 (IL-16) antibodies results in type 1 diabetes prevention by interfering with $CD4^+$ T-cell recruitment to the pancreas. IL-16 is a chemoattractant factor for $CD4^+$ T cells that is released in its bioactive form by caspase-3 cleavage of pro–IL-16. In the current study, IL-16 is reported to be produced within the insulitic lesion by B220 B cells and $CD4^+$/$CD8^+$ T cells, rather than by the pancreatic islets. However, immunofluorescence studies with colocalization for IL-16 and active caspase-3 in islet-infiltrating cells show that although many lymphocytes constitutively express pro–IL-16, only a few stain for activated caspase-3 resulting in low levels of mature IL-16.

We have previously shown that patients who have type 1 diabetes or are affected by endocrinopathies such as autoimmune polyendocrine syndrome type 2 and autoimmune thyroiditis present a reduced expression of active caspase-3 in peripheral T cells (2,3). Similar findings have also been recently extended to the peripheral T cells of patients with multiple sclerosis (4). Importantly, in NOD mice treated with cyclophosphamide to accelerate diabetes development, active caspase-3 expression within the islets is rarely observed in $CD4^+$ and $CD8^+$ T cells (5).

Overall, we believe that these studies can explain the low levels of mature IL-16 detected in the inflamed islets. Although signal amplification with tyramide, similar to IL-16 stainings, could have improved the detection of active caspase-3, in our opinion a reduced expression of active caspase-3 in infiltrating T cells could account for the low levels of IL-16 detected in the insulitic lesion. The observation that the treatment of NOD mice with anti–IL-16 results in an increased apoptosis of $CD4^+$ T cells is not detrimental to this hypothesis because the exact mechanism underlying this process is unknown. In the NOD mouse, T cells may then be partially defective in IL-16 secretion, but still capable of releasing enough IL-16 for the recruitment of $CD4^+$ T cells and diabetes development.

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