Increased IgE but Reduced Th2-Type Inflammation in Vitamin D Receptor-Deficient Mice

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LETTERS TO THE EDITOR

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The recent manuscript by Cantorna and colleagues reports that vitamin D receptor (VDR)-deficient mice fail to develop experimental allergic airway inflammation (1). The authors report that recruitment of inflammatory cells and induction of airway hyperreactivity following intranasal challenge with OVA in OVA-sensitized mice is severely dampened in the absence of VDR. The interpretation offered is that vitamin D is important for mounting a Th2-type immune response and that VDR might play an important role in regulating eosinophil and Th2 cell recruitment. However, in my opinion, the implications of the observation that VDR-deficient mice exhibit marked elevation in baseline serum IgE are not fully appreciated. Indeed, elevation of serum IgE is consistent with spontaneous enhancement of Th2 responses in VDR-deficient mice, which is in agreement with previous findings that VDR ablation results in augmented production of Th2 cytokines (2). As to the seemingly paradoxical observation that VDR-deficient mice fail to develop signs of allergic airway inflammation in response to allergen challenge despite the high IgE titer, I suggest that a potential explanation could invoke the so-called “IgE blocking hypothesis” (3). Specifically, the high amounts of spontaneous non-OVA specific IgE Abs reported in VDR-deficient mice might prevent mast cell sensitization by saturating FcεRI and thus prevent binding and aggregation by OVA-specific IgE. To analyze this, it would be important to document levels of anti-OVA-specific IgE following immunization and to show whether it is possible to induce passive mast cell sensitization by skin injection of OVA-specific IgE in VDR-deficient mice.

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The Authors Respond

The letter of Dr. D’Ambrosio offers an interesting but not entirely justified explanation of our data regarding the increased IgE levels in VDR KO mice that fail to develop experimental asthma. We agree that we probably have not “fully appreciated” the role of elevated baseline serum IgE in VDR KO mice. However, high IgE may or may not be due to spontaneous Th2 cell responses. Indeed, we have observed elevated baseline IgE levels in mice lacking the tyrosine kinase Itk, even in the absence of a significant Th2 response (1). In addition, our data contradict the findings by O’Kelly et al. cited above. We found that Th2 cell responses are not elevated in VDR KO mice and in fact our data suggest that Th2 cell responses are either not different or diminished (in terms of IL-4 secretion) in VDR deficiency (2). Only IgE production was elevated in the VDR KO mice. In addition, we feel that the reduced airways response observed in the VDR null mice is unlikely to be due to any “blocking effects” of circulating IgE interacting with FcεRI on mast cells for the following reasons. In our model, we induced allergic asthma in mice by immunizing with an adjuvant, followed by airway provocation with antigen. Under these conditions, airways responses observed 24 hours after challenging with allergen do not involve mast cells or the high affinity FcεRI (3–6). We therefore think it unlikely that IgE receptor blocking plays a role in the reduced AHR we observed in the VDR null mice. By contrast, more recent studies suggest that inducing airways hyperresponsiveness in the absence of adjuvant does require IgE, high affinity FcεRI, and mast cells in mice (7). Finally, as Dr. D’Ambrosio pointed out (in the paper by Yazdanbakhsh et al.) there are numerous examples of situations where elevated baseline IgE does not result in asthma and many possible mechanistic explanations. Therefore, we believe that without further experimentation it is premature to offer a single explanation for our data.

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