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See related article on pg 2621

IL-17: Important for Host Defense, Autoimmunity, and Allergy?

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In this issue, Milovanovic and colleagues present evidence that IL-17a enhances IgE production, although the precise mechanism remains unclear. Their initial finding was that higher numbers of IL-17a-producing CD4$^+$ T cells were observed after polyclonal stimulation in a largely airway allergic population. These data add to the evidence that atopic disorders such as asthma and, possibly, atopic dermatitis (AD) may have distinct immunologic phenotypes. The hope is that by characterizing the immunologic basis of these common diseases we will be able to understand the heterogeneity observed in natural history, response to treatments, susceptibility to infections, genetic risk factors, and associations with other atopic disorders.

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IL-17 history and function

IL-17-producing T cells were initially described in autoimmune models (Aggarwal *et al.*, 2003; Cua *et al.*, 2003; Murphy *et al.*, 2003) and led to the characterization of a new T helper (Th) subset that extended our repertoire beyond Th1, Th2, and Th9. Th17 cells are thought to be associated with the development of autoimmune diseases, response to extracellular pathogens, and diseases characterized by chronic neutrophilic inflammation. IL-17a, one of the most studied Th17 cytokines, was first recognized for its innate immune actions (Fossiez *et al.*, 1996), consistent with its rapid production in response to microbial infections. For example, IL-17 has been shown to play a crucial role in host defense against *Staphylococcus aureus* skin infections (Ishigame *et al.*, 2009). This is consistent with the observation that T cells from subjects with hyper-IgE syndrome, which is characterized by recurrent and often severe pulmonary infections, eczema, staphylococcal abscesses, and mucocutaneous candidiasis, do not produce IL-17 (Milner *et al.*, 2008). Studies in recombinase activating gene (RAG)-deficient mice, which lack B and T cells, demonstrated that IL-17a could still be produced in response to IL-23, suggesting that there were non-T-cell sources for this cytokine (Uhlig *et al.*, 2006). This work was followed by multiple publications that demonstrated several cell types found within skin and mucosal surfaces produce IL-17a as part of an innate immune response (Cua and Tato, 2010). Therefore IL-17a can be considered part of both an innate and an adaptive immune system.

Immunologic classifications of allergic disorders

Allergic disorders affect up to 30% of the populations in developed countries and are caused by aberrant immune responses to allergens and other environmental stimuli. Current thinking has led to the recognition of at least two variants referred to as "atopic" (or extrinsic) and "nonatopic" (or intrinsic), which is probably best studied in asthma. Atopic asthmatics have more Th2-type airway inflammation characterized by IL-4-, IL-5-, and IL-13-secreting cells that result in tissue eosinophilia and increased serum IgE levels, whereas nonatopic asthmatics are characterized by increased IL-8-producing cells and tissue neutrophilia without elevations of IgE (Amin *et al.*, 2000). It has been suggested that IL-17a expression observed in some asthmatics is responsible for the tissue expression of CXCL8 and neutrophilia that is characteristic of the nonatopic variant. All individuals with atopic dermatitis (AD) are characterized by a lack of

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tissue neutrophilia, whereas those with nonatopic AD have slightly reduced tissue expression of IL-5 and IL-13 and normal IgE values (Novak and Bieber, 2003). Although the role of Th2 cells in allergic diseases is firmly established, it is now clear that $CD4^+$ cells are much more heterogeneous than originally thought, reflecting previously unsuspected degrees of plasticity in Th cell differentiation (O'Shea and Paul, 2010). A current challenge is to understand the role of other Th cell subsets and cytokines in allergic diseases, and it is intriguing to speculate that expansion of different Th cell lineages may result in different disease phenotypes.

> Milovanovic and colleagues' study presents provocative data suggesting that IL-17a enhances IgE production.

IL-17a expression in atopic disorders

In this issue, Milovanovic *et al.* (2010) report that IL-17a-producing T cells are expanded in the peripheral blood of allergic human subjects. Although several IL-17 family members have been implicated in mouse models of asthma and AD, only a few groups have found enhanced expression of IL-17a in humans with asthma (Hashimoto *et al.*, 2005; Molet *et al.*, 2001; Song *et al.*, 2008) or AD (Koga *et al.*, 2008; Toda *et al.*, 2003). In fact, some groups have noted the lack of IL-17a and the Th17 differentiation cytokine, IL-23, in the skin of AD subjects (Guttman-Yassky *et al.*, 2008; L. Beck, unpublished data), possibly explaining their propensity for skin infections. It has been suggested that IL-17a expression observed in some asthmatics is responsible for tissue expression of CXCL8 and neutrophilia that is characteristic of the nonatopic variant. In AD the characteristic downstream biological actions of IL-17a such as neutrophil recruitment, epidermal antimicrobial peptide production, and enhanced tight junction integrity are clearly not observed (De Benedetto *et al.*, 2009; Hurst *et al.*, 2002; Ong *et al.*, 2002; Ott *et al.*, 1994).

Although only about 30% of AD subjects experience recurrent *S. aureus* infections, greater than 90% are chronically colonized with this microbe, which would seem unlikely to occur in the context of IL-17 expression. Interestingly, Eyerich *et al.* (2009) recently observed that the Th2 cytokines (IL-4 and -13) present in AD lesions can partially inhibit IL-17-induced human beta defensin (hBD)-2 expression from human keratinocytes. This finding suggests that the balance of Th17 and Th2 cytokines may determine the quality of an innate immune response to extracellular pathogens. Importantly, Milovanovic and colleagues (2010) observed a significantly increased percentage of $IL\text{-}17a^+$-activated $CD4^+$ cells in only 6 of the 23 allergic donors. All 6 were asthmatics and presumably did not have AD. In contrast to the antagonism observed between IL-17a and Th2 cytokines in epidermal innate immune responsiveness, the authors observed synergy between these two cytokine profiles with regard to IgE production. In summary, their findings support and extend the growing literature demonstrating that IL-17a expression may define a unique allergic phenotype, but determining the relevance of these findings to immune responses in AD skin will require further study.

IL-17a promotes IgE production

Milovanovic and colleagues' study presents provocative data suggesting that IL-17a enhances IgE production. In a small subset of allergic patients compared with normal controls, they show higher numbers of IL-17a-producing CD4 T cells (Th17) after polyclonal activation of whole blood. After depletion of the Th17 cells *in vitro* from the allergic patients, IgE levels decrease. Furthermore, repleting IL-17a in the depleted cultures reversed the reduction in IgE. As an important control for their methodology they show that depletion of IFN-γ-secreting cells did not affect IgE production. Furthermore, blocking IL-17a affected only IgE and not IgG, IgM, or IgA production in peripheral blood mononuclear cells (PBMCs) from an atopic donor.

Effects of IL-17 on B cells have been described only in the BXD2 recombinant inbred mouse strain, which spontaneously develops glomerulonephritis and erosive arthritis. These mice have been shown to express IL-17 and develop spontaneous germinal centers, resulting in increased autoimmune antibodies (Hsu *et al.*, 2008). Germinal centers are sites of B- and T-cell interactions that result in active B-cell proliferation, somatic hypermutations, selection, and differentiation into memory B cells and plasma cells. In these BXD2 mice, IL-17 is thought to play an important role in the spontaneous development of germinal centers by retaining B cells and promoting CD4 T-cell and B-cell interactions. Mice lacking the IL-17 receptor have reduced germinal center B-cell development and decreased antibody responses (Hsu *et al.*, 2008). In this mouse strain, IL-17 affected B-cell activity, resulting in increases in autoimmune IgM and IgG levels, although IgE levels were not assessed. It is unclear how to reconcile this result with Milovanovic *et al.* (2010), who did not observe reductions in IgG and IgM levels with blocking IL-17a antibodies. One possible explanation is that the allergic donor PBMCs used for Milovanovic's studies had already experienced the class-switching effects of the Th2 cytokines (IL-4 and -13), although this and other possibilities will require further study.

Several mechanisms could account for IL-17a's ability to increase IgE secretion. For example, IL-17 could (i) augment IgE secretion of already existing IgE plasma cells, (ii) enhance differentiation of IgE-switched B cells to IgE-producing plasma cells, or (iii) promote class switching of memory B cells to IgE plasma cells. In this study, Milovanovic *et al.* provide evidence of the third mechanism. PBMC cultures stimulated for 10 days with IL-17 or anti-CD40 + IL-4 induced memory B-cell IgE class switching and differentiation into plasma cells as shown by similarly increased expression of ε germline transcription, a first step in the commitment of B cells to the

synthesis of IgE (Takhar *et al*., 2007). Increased activation-induced cytidine deamiase (AID) expression in these cultures also suggests the possibility that IL-17a could promote class switch recombination and somatic mutation, but further studies are needed to determine the precise molecular mechanisms involved. Another peculiarity of their results was that IL-17a did not increase IgE secretion in dose-escalation fashion; instead, it had an optimal concentration at 10 ng/ml, and the clinical relevance of such a high dose in tissue sites and/or secondary lymphoid organs will need to be addressed.

In summary, this work highlights the association of IL-17a and increased IgE secretion in human PBMCs. Whether the IL-17a-producing cells alone can increase IgE levels or whether these cells require IL-4 secretion simultaneously needs further study. Interestingly, a novel population of CD4 memory T cells (Th17/Th2) that produce both IL-17 and IL-4 has recently been described (Cosmi *et al*., 2010). Albeit extremely rare in healthy adults, IL-17 and -4-coproducing CD4 T cells were increased in the circulation of patients with severe asthma, which could explain the relationship between Th17 cells and increased IgE levels observed in this study. Perhaps this Th17/Th2 subset may identify a new phenotype with both neutrophilic infiltrates and increased IgE that lies somewhere between atopic and nonatopic asthma phenotypes. Further research investigating the expression and regulation of IL-17a and Th17 cytokines in general in humans with AD should be worthwhile. It will be important in future studies to consider the contribution of both the innate and the adaptive immune systems to IL-17a production and to determine where and how this interesting cytokine affects B-cell activation and antibody production.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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