

Involvement of eosinophils in the onset of asthma

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When we read medical journals, every article provides new information, usually with surprise and sometimes with disappointment. In the November 2007 issue of the Journal, Lee et al report a gene-gene interaction of single nucleotide polymorphisms and the haplotypes of *CCR3* and the IL-5 receptor α -chain gene (*IL5RA*), which is associated with the eosinophil count, and they have also identified the effects of these genetic variations on the levels of those proteins in peripheral eosinophils. Although they did not find a positive association between the genetic variations of these molecules and asthma, this article provides allergy researchers with important information regarding the role of eosinophils in asthma.

Eosinophils are certainly the most enigmatic cells involved in allergic inflammation. After the first observation in the early 1920s, hundreds of studies showed a positive association between activation of eosinophils and the severity of allergic symptoms.^{2,3} A recent systematic review has indicated that the number of sputum eosinophils is an important clinical marker correlating with disease activity.⁴ In addition, elevated serum eosinophil cationic protein levels⁵ and cord blood eosinophilia⁶ were reported to precede wheeze and eczema, respectively. The remaining question is whether the eosinophilia is a cause or just a marker of allergic inflammation *in vivo* in human beings.

One of the definitive methods for proving the involvement of a specific molecule in the onset of a disease is to demonstrate a positive association between genetic polymorphism of the molecule and the prevalence of the disease. A single nucleotide polymorphism, a tiny variation of genetic sequence, modulates the production or the functional properties of the gene product, and shows association with the prevalence of the disease only if the molecule is a cause, not a marker.

IL-5 is a critical cytokine that regulates the differentiation, priming, activation, and survival of eosinophils.³ To date, only 1 study⁷ has demonstrated a positive association between a polymorphism of *IL5* or *IL5RA* and asthma, whereas several other studies, including the article by Lee et al,¹ negated this

association.^{8,9} It is notable that in some of those studies, including the article by Lee et al,¹ a positive association was found between polymorphisms in *IL5* or *IL5RA* and the eosinophil count. In sharp contrast, positive associations have frequently been reported between asthma and polymorphisms of the genes for IL-4, IL-13, and their receptors, even though all 3 of these T_H2 cytokines are mapped on the same gene locus, 5q31-33.¹⁰

On the other hand, CCR3, a receptor for RANTES, eotaxin-1, eotaxin-2, eotaxin-3, and monocyte chemoattractant proteins 3 and 4, plays a critical role in the selective recruitment and activation of eosinophils in allergic inflammatory sites.¹¹ To date, a couple of reports have demonstrated that polymorphisms of CCR3 or its ligands are associated with asthma,^{12,13} but such association cannot specify the involvement of eosinophils, because CCR3 is also expressed in basophils, T cells, and dendritic cells.

Very recently, IL-5 and eotaxin-2 (CCL24) double-transgenic mouse were shown to develop marked respiratory inflammation with the characteristics of severe asthma.¹⁴ Thus, it should be worth testing whether interaction of these 2 molecules is involved in the onset of asthma. In this context, again, the study by Lee et al¹ failed to detect any positive associations between asthma and the polymorphisms of *IL5RA* and *CCR3*, but interaction of those polymorphisms was clearly associated with the eosinophil count.¹ Of course, it is important to know whether the association can be replicated in an independent sample. Genetic analyses of the associated variants in different ethnic groups are necessary and desired. Further functional analyses of the genetic variants in eosinophils and other cell types would also be helpful. At least for now, however, it seems unlikely that IL-5 plays critical roles in the onset of asthma.

Researchers who are “eosinophiles” will probably read the article by Lee et al¹ with disappointment, just like 7 years ago when Leckie et al¹⁵ published an article showing no appreciable clinical efficacy for anti-IL-5 antibody therapy. Then, however, several subsequent studies revealed the presence of tissue-dwelling eosinophils in the lung.¹⁶ Thus, although IL-5 was apparently not a good target for the treatment of asthma, those subsequent findings gave new life to the hope that eosinophils could serve as a therapeutic target for asthma.

Will the same scenario unfold this time, too? Probably not, because this genetic linkage study by Lee et al¹ clearly demonstrates a positive association between the interaction of *IL5RA* and *CCR3* and the eosinophil count, and no association between the interaction and asthma. In other words, variations in *IL5RA* and *CCR3* showed no influence on the onset of asthma (and we presume that the eosinophil count does not, either).

As described by Bochner,¹⁷ the jury is still out regarding the verdict in the case of therapies versus eosinophils, whereas, for the case of eosinophils versus the onset of asthma, the article by Lee et al¹ failed to demonstrate any involvement of IL-5 in the onset of asthma. However, researchers who are "eosinophiles"

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should by no means be discouraged, because the possibilities of involvement of eosinophils in the onset of asthma and their involvement in the course of asthma, especially remodeling (ie, potential target for the therapeutic intervention), are separate issues. Indeed, since 2000, various investigators have piled up evidence that eosinophils play important roles, predominantly in the formation of airway remodeling.¹⁸ New therapeutic strategies that efficiently deplete tissue-dwelling eosinophils will further clarify the importance of eosinophils in the pathogenesis of asthma.

Further studies are surely necessary to prove the role of eosinophils or these eosinophil-related molecules by increasing the population or by selecting a certain asthma phenotype having, for example, symptoms related to airway remodeling. However, this study by Lee et al¹ may provide an efficient method for genetic studies regarding this complex disease. Genetic variations of *CCR3* and *IL5RA* were associated with objective phenotype markers—the protein levels and the number of circulating eosinophils. It is necessary to collect and arrange the numerous pieces of the jigsaw puzzles called asthma, and this study has contributed to that effort.

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