

Letter to the Editor

A novel non-IgE-mediated pathway of mite-induced inflammation

To the Editor:

In a recent article published in the *Journal of Immunology*, Barrett et al¹ demonstrated that mite and *Aspergillus fumigatus* extracts stimulate the production of cysteinyl leukotrienes from bone marrow-derived dendritic and pulmonary CD11c⁺ cells through a glycan C-type lectin receptor (Dectin-2) interaction involving FcR γ and Syk signaling that activates arachidonic acid metabolism.

Previously, a number of clinical and experimental observations had called our attention to the existence of important connections between IgE-mediated diseases and leukotriene-mediated inflammation. We had observed that a large proportion of patients with hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs), a condition that is accompanied by increased production of leukotrienes, were atopic and had IgE-mediated sensitivity to mite allergens.² This observation has been recently confirmed in another study in which we found significantly increased total and mite-specific IgE levels in patients with NSAID hypersensitivity compared with those seen in healthy control subjects.³ In tropical countries in which high relative humidity and temperature are optimal for mite proliferation, mite allergens are the main source of sensitization and allergic respiratory disease.

A second clinical observation, also reported by Spanish investigators and others, was that most patients with anaphylaxis after the ingestion of mite-contaminated foods frequently exhibit hypersensitivity to NSAIDs.⁴ We designated the association of allergic rhinitis, aspirin/NSAID hypersensitivity, and severe reactions to mite-contaminated foodstuffs as a "new aspirin triad." To understand this association, we performed a study in collaboration with Canadian investigators in which it was demonstrated that mite allergenic extracts inhibited COX-1 *in vitro*. We postulated that mite-induced human allergic diseases could be accompanied, at least in a subset of the patient population, by a dysregulation of leukotriene biosynthesis, metabolism, or both similar to the disturbances described in patients with NSAID hypersensitivity.

In concordance with that hypothesis, various genetic polymorphisms that involve leukotriene C₄ (LTC₄) synthase and cysteinyl leukotriene receptors have been observed in patients with hypersensitivity to NSAIDs; in that context it is important to mention that so-called atopic genes are located in the 5q22-q35 region of human chromosome 5, close to the *LTC4S* gene.

Diverse lines of evidence also support a dysregulation of leukotriene pathways in subjects with mite allergy. Acevedo et al⁵ described an association of the A-444C allele of the *LTC4S* gene and IgE response to mite allergens, and we have observed that NSAID-sensitive patients show stronger skin test responses and increased specific IgE antibodies to *Blomia tropicalis* than atopic non-NSAID-sensitive subjects.³

Cysteinyl leukotrienes modulate the allergic response, as evidenced in various studies in which it has been shown that leukotrienes enhance IgE and IgG production by human B cells, whereas *LTC4S* knockout mice have a markedly reduced antigen-induced T_H2 pulmonary inflammation. Additionally, it has been demonstrated that IL-4 and IL-13 modulate the number

of cysteinyl leukotriene type 1 and 2 receptors on T, B, and antigen-presenting cells.

Furthermore, various groups of investigators have observed that aspirin enhances food-dependent exercise-induced anaphylaxis⁶ and facilitates anaphylaxis induced by food allergens.⁷⁻¹⁰ These effects could be due to an increased gut permeability, resulting in enhanced opportunity for sensitization at the immunocompetent cell-rich gastrointestinal submucosa.

Bachert et al¹¹ have proposed a role for staphylococcal enterotoxins, which, through the V β receptor on T lymphocytes, allow polyclonal IgE production, including IgE to house dust mite, in nasal polyps, the lungs, and possibly the skin. It would be interesting to investigate in the future whether aspirin-hypersensitive patients with urticaria and angioedema and those with oral anaphylaxis to mites have superantigen-induced immune stimulation from concomitant staphylococcal infection that enhances their susceptibility to mite-induced disease.

The elegant demonstration of Barrett et al¹ on the increased leukotriene production induced by mites perfectly fits into the puzzle that we have been trying to solve for many years to explain the interactions between mite-induced allergy and NSAID hypersensitivity.¹² These observations might have important therapeutic implications in regard to the pharmacologic inhibition of leukotriene synthesis or blockade of leukotriene receptors. In that context it has been reported that the *LTC4S* allele is associated with a better response to leukotriene receptor antagonists,¹³ and a favorable response to such drugs was found in asthmatic children who had increased levels of urinary leukotriene E₄.¹⁴

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