Asthmatic population may show a clearer relationship between FcεRI promoter translocations and IgE binding.

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IDENTIFICATION OF Tapr (AN AIRWAY HYPERREACTIVITY REGULATORY LOCUS) AND THE LINKED Tim GENE FAMILY


Purpose of the Study. To identify a central asthma susceptibility gene in the large chromosome 5q23–35 region that has been linked to asthma and atopy, using mouse models of asthma.

Study Population. Congenic inbred mouse strains: 1) selected for genetic variance in only the chromosomal region homologous to the human chromosome 5q region (mouse chromosome 11), and 2) in which fundamental features of atopic asthma (eg, TH-2-mediated immune responses and enhanced bronchial hyperresponsiveness [BHR]) can be induced.

Methods. A positional cloning approach was taken to identify and map the genetic locus on mouse chromosome 11 that protected against the induction of TH-2 immune responsiveness and BHR. Using this information, the human homolog to the asthma susceptibility locus in mice was identified, as were genes in this region. The functional consequences of polymorphisms in these genes were then studied in the mouse models.

Results. A single gene locus in mouse chromosome 11 was associated with both TH-2 immune responsiveness and BHR. Called Tapr (T cell and airway phenotype regulator), the human homolog to this region was mapped to human chromosome 5q33.2 and found to contain a Tim gene (T cell membrane glycoproteins with conserved immunoglobulin variable domain and mucin domains) family of genes. Both TIM-1 and TIM-3 gene expression were strongly associated with TH-1/TH-2 differentiation and BHR. Additionally, the human homolog of TIM-1 is a cellular receptor for the hepatitis A virus (HAV).

Conclusions. Tim genes play an important role in allergic T cell responses, BHR, and asthma susceptibility.

Reviewer’s Comments. Genetic studies have discovered candidate genes for asthma susceptibility on chromosomes 5, 6, 11, 12, and 14. Chromosome 5q23–35 region has recently received the most attention because this region includes a large number of cytokine and control protein genes that have been associated with asthma, including the TH-2 cytokine cluster ( interleukin [IL]-4, IL-5, and IL-13), β-adrenergic receptor, IL-12p40 and IL-9. However, a single asthma susceptibility gene in this region has not yet been conclusively identified. This study identified a novel gene cluster of Tim genes in mouse and man, in which polymorphisms were associated with both TH-2 cytokine production and BHR in mouse asthma models. One particularly intriguing aspect of this finding is that human TIM-1 is the HAV receptor. Several recent studies in Italy and the United States by Maricardi and colleagues have associated serologic evidence of previous HAV infection with less allergen sensitization and asthma. The authors of this article postulate that an interaction of HAV with TIM-1 may reduce TH-2 differentiation and the subsequent risk of asthma and allergy. Studies of the immune-modulating effect of HAV via the TIM-1 gene in humans, and the influence of TIM-1 polymorphisms on this effect, are required to confirm this hypothesis. For more information, please see an editorial comment by Wills-Karp titled “Asthma Genetics: Not for the TIMid?” by on page 1095–1096 in the same issue of Nature Immunology, and a review article by Umetsu et al titled “Asthma: An Epidemic of Dysregulated Immunity” in Nature Immunology (2002;3: 715–720).

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MULTI-PRONGED INHIBITION OF AIRWAY HYPER-RESPONSIVENESS AND INFLAMMATION BY LIPOXIN A4


Purpose of the Study. To investigate the potential counterregulatory role of lipoxin A4 (LXA4) and lipoxin A4 receptors (ALX) in allergic pulmonary inflammation and bronchial hyperresponsiveness (BHR) in asthma.

Methods. In a murine model of allergic asthma, pulmonary inflammation and BHR with administration of a lipoxin A4 analog (LXA) was studied. Transgenic mice expressing human LXA4 receptors were also studied.

Results. LXA administered intravenously after allergen sensitization and before airways allergen exposure, significantly reduced both BHR and allergic pulmonary inflammation, including eosinophils, lymphocytes, interleukin (IL)-5, IL-13, eotaxin, and cysteinyl leukotrienes. Similar findings were observed in transgenic mice that constitutively expressed human LXA4 receptors.

Conclusions. Lipoxin A4 and its analog offer a novel therapeutic approach to the treatment of BHR and pulmonary inflammation in asthma.

Reviewer’s Comments. Lipoxins are endogenously produced eicosanoids with antiinflammatory actions. LXA4, the best-studied member of this family, has antiinflammatory activity in vitro and in vivo model systems. Its antiinflammatory actions include downregulation of proinflammatory cytokines and chemokines involved in neutrophil and eosinophil trafficking, inhibition of cysteinyl-stimulated metalloproteinase activity and cell proliferation, and stimulation of macrophage clearance of apoptotic cells from an inflammatory focus. LAX4 has recently been shown to interfere with cysteinyl leukotriene (cysLT) mediator inflammation by competitively binding the cysLT1 receptor. This and another recent study (Bonnas C, et al, Am J Respir Crit Care Med. 2002;165:1531–1535) reveal the therapeutic potential of LAX4 in asthma. Other potential applications of LAX4 are for topical use as an antiinflammatory agent for inflammatory skin conditions (Schottelius AJ, et al, J Immunol. 2002;169:7070–7076). Given the efficacy of the compound, LAX4 may be a compelling alternative to corticosteroids in certain clinical settings. A commentary on this study, titled “Good Lipids for Asthma” by Peters-Golden on pages 931–932 of the same issue, and an article titled “Lipoxins: Revelations on Resolution” by McMahon et al in Trends in Pharmacological Sciences (2001;22:391–395) are suggested for further review.

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