tative 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-biased 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 (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 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.

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 cysteiny1 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.

Reviewers’ Comments. Lipoxins are endogenously produced eicosanoids with antiinflammatory actions. LXA4, the best-studied member of this family, has antiinflammatory activities 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 leukotriene-stimulated metalloproteinase activity and cell proliferation, and stimulation of macrophage clearance of apoptotic cells from an inflammatory focus. LXA4 has recently been shown to interfere with cysteiny1 leukotriene (cysLT)-mediated inflammation by competitively binding the cysLT1 receptor. This and another recent study (Bonnas C, et al, Am J Respir Crit Care Med. 2002;165:7063–7070). Given the efficacy of the compound, LXA4 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 931–952 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.
MULTI-PRONGED INHIBITION OF AIRWAY HYPER-RESPONSIVENESS AND INFLAMMATION BY LIPOXIN A4

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