

EDITORIAL



Asthma and Chitinases

Miriam F. Moffatt, D.Phil., and William O.C.M. Cookson, M.D., D.Phil.

Asthma is a complex and heterogeneous syndrome in which the airway mucosa is abnormal and inflamed. Although its causes are unknown, there are strong clues: it runs in families, and many, but by no means all, patients with asthma have signs and symptoms of IgE responses to common allergens. Asthma has an incomplete association with the phenomenon of nonspecific bronchial hyperresponsiveness to a variety of stimuli. The mechanism of bronchial hyperresponsiveness is itself mysterious. A childhood in an environment rich in microbes protects against the development of asthma in many parts of the world.

In this issue of the *Journal*, Ober et al.¹ contribute to the understanding of the asthma conundrum with their report on the genetic influences on asthma and a chitinase-like protein known as YKL-40 (in which YKL refers to the terminal sequence of the 40 amino acids of the protein). The Human Genome Organization Gene Nomenclature Committee now refers to the gene encoding YKL-40 as *CHI3L1* (for chitinase 3-like 1).

The level of expression of YKL-40 has previously been shown to be genetically regulated.² The minor allele of the single-nucleotide polymorphism (SNP) rs4950928, -131C→G, disrupts binding of transcription factors in the *CHI3L1* promoter and is known to be associated with reduced levels of the protein. Ober et al. now show that the serum YKL-40 level is highly heritable in Hutterite families and that rs4950928 accounts for 9.4% of its variance.

Some members of the collaborative group including Ober previously established that YKL-40 levels were increased in the lung and circulation of patients with severe asthma, and they reasoned that YKL-40 could either cause or be a marker for asthma.³ The results of the current study by Ober

et al. support a causal role of YKL-40, suggesting that the protein directly influences the asthmatic process.

Ober et al. found that, among Hutterites, serum levels of YKL-40 were 15% higher in those with asthma, and 10% higher in those with bronchial hyperresponsiveness, than in controls. Two copies of the wild-type -131C allele (ensuring an intact *CHI3L1* promoter) were found to be associated with susceptibility to asthma, indicating that -131C acts recessively. The authors also found associations with asthma of the same recessive CC genotype in children approximately 10 years of age from Freiburg, Germany, and in adults and children from Chicago. Although the significance of the association in the Hutterite and Chicago populations was limited by the small numbers of participants, overall the results are consistent and convincing. These findings may be valuable in understanding the mechanisms of asthma and in determining the risk of asthma in various clinical and epidemiologic contexts.

YKL-40 binds chitin but has no chitinase activity.⁴ It is produced at sites of inflammation in many cells and is secreted from vascular smooth-muscle cells and macrophages.⁴ It is strongly up-regulated in the airway epithelium and alveolar macrophages of patients with asthma.³ It has also been implicated in diverse disease processes, including rheumatoid arthritis, inflammatory bowel disease, schizophrenia, and type 2 diabetes. It has previously been shown that another chitinase, CHIA (acidic chitinase; also known as AMCase) influences cellular infiltration in an ovalbumin-induced murine model of airway inflammation.⁵ Moreover, SNPs in the *CHIA* gene have been associated with asthma in German children.⁶

It is therefore clear that chitinases have a role

in the pathogenesis of asthma and other inflammatory diseases in humans. However, it is difficult to understand exactly what this role is. Mammalian cells do not make chitin, and fungal or parasitic infection was not a common characteristic of asthma in the subjects studied by Ober et al. YKL-40 alters the handling of bacteria by colonic epithelial cells⁷; it may have a similar effect in the airway mucosa. The lack of knowledge about the true functions of chitinases in patients with asthma or other diseases reflects the fact that most forms of life on earth do not have an adaptive immune system and that possibly only a fraction of innate immune mechanisms in humans have yet to be discovered or understood.

From the epidemiologic point of view, the results of Ober et al. suggest that they have identified an important genetic risk factor for asthma but, as with all genetic findings, this impression needs to be confirmed through larger surveys. The SNP conferring this risk also seems to increase susceptibility to bronchial hyperresponsiveness in the Hutterites, but given the small numbers of persons analyzed, this association cannot be separated from the association with asthma. The authors did not find a significant association between the diagnosis of asthma by the age of 6 years and serum YKL-40 levels or the rs4950928 SNP (–131C→G) in a birth cohort of children from Wisconsin in the Childhood Origins of Asthma (COAST) study. This may suggest that some mechanisms of asthma differ between children younger than 6 years of age and older children and adults.

The authors also did not find a significant association between the *CHI3L1* SNPs and atopy, a finding shared with SNPs that regulate another gene of unknown function (*ORMDL3*) associated with asthma.⁸ The disjunction between atopy and disease is even stronger in children with atopic dermatitis, in whom mutations in genes encoding the barrier proteins *SPINK5*⁹ and *FLG*¹⁰ indicate that atopy is a secondary process. The relations of atopy with asthma and atopic dermatitis vary geographically,^{11,12} implying that atopy does not drive the underlying disease processes (although the presence of atopy clearly can lead to symptoms that may be responsive to treatment).

This is an exciting time to be studying the genetics of asthma, with large-scale, collaborative, whole-genome association studies under way in the United States and Europe. These are expected to yield results within the next year, and epidemiologists may quickly be able to translate genetic associations into a better classification of the disease. The study by Ober et al. identifies the next challenge: understanding how each implicated gene contributes to asthma.

No potential conflict of interest relevant to this article was reported.

From the National Heart and Lung Institute, Imperial College, London.

This article (10.1056/NEJMe0802072) was published at www.nejm.org on April 9, 2008.

1. Ober C, Tan Z, Sun Y, et al. Effect of variation in *CHI3L1* on serum YKL-40 level, risk of asthma, and lung function. *N Engl J Med* 2008;358:1682-91.
2. Zhao X, Tang R, Gao B, et al. Functional variants in the promoter region of Chitinase 3-like 1 (*CHI3L1*) and susceptibility to schizophrenia. *Am J Hum Genet* 2007;80:12-8.
3. Chupp GL, Lee CG, Jarjour N, et al. A chitinase-like protein in the lung and circulation of patients with severe asthma. *N Engl J Med* 2007;357:2016-27.
4. Rathcke CN, Johansen JS, Vestergaard H. YKL-40, a biomarker of inflammation, is elevated in patients with type 2 diabetes and is related to insulin resistance. *Inflamm Res* 2006;55:53-9.
5. Zhu Z, Zheng T, Homer RJ, et al. Acidic mammalian chitinase in asthmatic Th2 inflammation and IL-13 pathway activation. *Science* 2004;304:1678-82.
6. Bierbaum S, Nickel R, Koch A, et al. Polymorphisms and haplotypes of acid mammalian chitinase are associated with bronchial asthma. *Am J Respir Crit Care Med* 2005;172:1505-9.
7. Mizoguchi E. Chitinase 3-like-1 exacerbates intestinal inflammation by enhancing bacterial adhesion and invasion in colonic epithelial cells. *Gastroenterology* 2006;130:398-411.
8. Moffatt MF, Kabisch M, Liang L, et al. Genetic variants regulating *ORMDL3* expression contribute to the risk of childhood asthma. *Nature* 2007;448:470-3.
9. Walley AJ, Chavanas S, Moffatt MF, et al. Gene polymorphism in Netherton and common atopic disease. *Nat Genet* 2001;29:175-8.
10. Palmer CN, Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006;38:441-6.
11. Weinmayr G, Weiland SK, Björkstén B, et al. Atopic sensitization and the international variation of asthma symptom prevalence in children. *Am J Respir Crit Care Med* 2007;176:565-74.
12. Flohr C, Weiland SK, Weinmayr G, et al. The role of atopic sensitization in flexural eczema: findings from the International Study of Asthma and Allergies in Childhood Phase Two. *J Allergy Clin Immunol* 2008;121(1):141.e4-147.e4.

Copyright © 2008 Massachusetts Medical Society.