

The mannose-binding lectin gene in atopic dermatitis: lessons from genetics

Atopic dermatitis (AD) is a common, chronic inflammatory skin condition that has been increasing in prevalence during the last several decades.¹ Currently, AD affects up to 20% of children worldwide and can persist into adulthood.² The underlying cause is not clear, although the pathogenesis has been associated with IgE-bearing Langerhans cells, atopic keratinocytes, lymphocytes, monocytes and macrophages, eosinophils, and mast cells.³ Clinically, AD is characterized by unremitting pruritus, damaged skin barrier from repetitive mechanical trauma, and frequent bacterial and viral skin infections, presumably from increased rates of skin colonization.⁴ In fact, children with AD are 3 to 10 times more likely to have long-term colonization of *Staphylococcus aureus* on nonlesional skin when compared with healthy controls.^{5,6} This increased infection susceptibility in conjunction with an early age of presentation suggests a role for an innate immune defect. A protein of emerging interest in innate immunity is mannose-binding lectin (MBL). The report by Carréra et al, in the current issue of the *Annals*, examined the frequencies of variant alleles in the *MBL2* gene in 131 children with AD and 165 individuals without AD.⁷

There are 3 common polymorphisms in exon 1 of the *MBL2* gene that alter the ability of the MBL protein to oligomerize; they are at codons 52, 54, and 57 and are termed the D, B, and C alleles, respectively.⁸ In addition, there are 2 polymorphisms in the promoter region, termed H/L and Y/X, that determine serum levels by regulating protein expression. When describing *MBL2* gene variants, the nomenclature A/A refers to individuals homozygous for the wild-type gene, A/O to heterozygotes, and O/O to variant homozygosity. In wild-type individuals, those with HYA haplotype produce the highest levels of MBL, whereas those with LXA produce the lowest levels.⁹ In this study, the authors found that children with AD had a significantly higher frequency of the 2 variant alleles (A/O and O/O vs A/A) when compared with healthy children.⁷ Furthermore, because these genotypes are associated with reduced MBL expression, the authors contend that the association with AD is through diminished MBL production in children with AD.

MBL is a C-type serum lectin produced by the liver as an acute-phase reactant. It belongs to a family of circulating pattern recognition receptors termed *collectins* and is composed of multimers of identical 32-kDa polypeptide chains that possess carbohydrate recognition domains. These domains are responsible for binding highly conserved polysaccharide structures presented by a wide array of pathogens, including *S aureus*. Binding of MBL to target structures on pathogens has a 2-fold function: it activates the lectin pathway of complement activation, and it acts as an opsonin, inducing phagocytosis of the bound pathogen.

MBL deficiency was first associated with clinical disease in 1968, when a serum-dependent phagocytic defect was identified in a patient with profound dermatitis and diarrhea.¹⁰ This defect was eventually linked to the complement system when it was shown that incubated serum samples from affected patients had lower amounts of C3b/iC3b deposited on yeast surfaces.¹¹ Since then, MBL deficiency has been associated with severe infection in children undergoing chemotherapy, those with invasive meningococcal and pneumococcal disease, those with increased human immunodeficiency virus susceptibility, and those with fungal infections, but MBL deficiency has never been directly linked with AD.⁸

Interestingly, the frequency of the variant alleles in the individuals without AD from the current report is remarkably similar to a report from more than a decade ago looking at healthy, nonatopic individuals.¹² This new report provides additional supportive evidence for the association of increased frequency of these alleles in AD patients, although at least 1 report from Japan failed to show any associations between MBL polymorphisms and AD.¹³

Overall, this study highlights that AD is a genetically complex disease and that the constituents of the innate immune response may play a more central role than formerly thought; however, the results of this study need to be viewed critically. In particular, the frequency of polymorphisms reported is greater than would be predicted by the principles of the Hardy-Weinberg equilibrium. This suggests that allelic and promoter variants may have been driven by a selective advantage of low MBL levels.⁸ It has been reported that different combinations of *MBL2* polymorphisms result in a wide range of serum levels in healthy individuals.¹⁴ So, although the authors have shown an increased frequency of variant alleles in children with AD, they have not addressed whether the serum levels and/or function of MBL was deficient. Nonetheless, this study clearly highlights the potential

Disclosures: Dr Grayson has received research grants from Genentech and the National Institutes of Health.

© 2010 American College of Allergy, Asthma & Immunology.

Published by Elsevier Inc. All rights reserved.

doi:10.1016/j.anai.2010.05.001

role for innate immune molecules in AD, and we should expect further studies in the near future that better clarify the role of MBL in the pathogenesis of AD.

EBRAHIM M. SHAKIR, MD
MITCHELL H. GRAYSON, MD

Section of Allergy and Immunology
Department of Pediatrics
Medical College of Wisconsin
Milwaukee, Wisconsin
wheeze@allergist.com

REFERENCES

1. Kay AB. Allergy and allergic diseases: first of two parts. *N Engl J Med*. 2001;344:30–37.
2. Leung DY, Boguniewicz M, Howell MD, Nomura I, Hamid QA. New insights into atopic dermatitis. *J Clin Invest*. 2004;113:651.
3. Leung DY, Nicklas RA, Li JT, et al. Disease management of atopic dermatitis: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2004;93:S1–S17.
4. McGirt LY, Beck LA. Innate immune defects in atopic dermatitis. *J Allergy Clin Immunol*. 2006;118:202–208.
5. Gong JQ, Lin L, Lin T, et al. Skin colonization by *Staphylococcus aureus* in patients with eczema and atopic dermatitis and relevant combined topical therapy: a double-blind multicentre randomized controlled trial. *Br J Dermatol*. 2006;155:680–687.
6. Breuer K, Häussler S, Kapp A, Werfel T. *Staphylococcus aureus*: colonizing features and influence of an antibacterial treatment in adults with atopic dermatitis. *Br J Dermatol*. 2002;147:55–61.
7. Carréra MC, Moura P, Crovella S, Eleutério de Souza PR, Arraes de Alencar LC, Sarinho E. High polymorphism of the *MBL2* gene in patients with atopic dermatitis. *Ann Allergy Asthma Immunol*. 2010;105:39–42.
8. Eisen DP, Minchinton RM. Impact of mannose-binding lectin on susceptibility to infectious diseases. *Clin Infect Dis*. 2003;37:1496–1505.
9. Madsen HO, Garred P, Thiel S, et al. Interplay between promoter and structural gene variants control basal serum level of mannan-binding protein. *J Immunol*. 1995;155:3013–3020.
10. Miller ME, Seals J, Kaye R, Levitsky LC. A familial, plasma associated defect of phagocytosis: new cause of recurrent bacterial infection. *Lancet*. 1968;2:60–63.
11. Turner MW, Mowbray JF, Robertson DR. A study of C3b deposition on yeast surfaces by sera of known opsonic potential. *Clin Exp Immunol*. 1981;46:412–419.
12. Babovic-Vuksanovic D, Snow K, Ten RM. Mannose-binding lectin (MBL) deficiency: variant alleles in a Midwestern population of the United States. *Ann Allergy Asthma Immunol*. 1999;82:134–138, 141–143.
13. Hashimoto S, Nakamura K, Oyama N, et al. Mannose-binding lectin (MBL) single nucleotide polymorphism is not associated with atopic dermatitis in Japanese patients. *J Dermatol*. 2005;32:1038–1040.
14. Ip WK, Takahashi K, Ezekowitz RA, Stuart LM. Mannose-binding lectin and innate immunity. *Immunol Rev*. 2009;230:9–21.