Editorial

Are mannose-binding lectin gene 2 (MBL2) polymorphisms and MBL deficiency associated with infections?

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Mannose-binding lectin (MBL) is an important element of the innate immune system. MBL binding leads to activation and cleavage of C3 and C4, suggesting the role of the MBL pathway for opsonization and/phagocytosis. The role of adaptive immune response in the development of pathogenic autoantibodies in various autoimmune diseases is well understood. The link between innate and acquired immunity is helpful for understanding the immunopathogenesis of autoimmune diseases. Evidence that the innate immune system could lead to autoimmunity is growing with the major recent concept that autoimmune disease pathogenesis is related to impaired apoptotic cell clearance. MBL has been demonstrated to facilitate clearance of apoptotic cells *in vivo* and *in vitro*. Low MBL serum levels resulting in impaired apoptotic clearance have shown to enhance the risk for infection and high MBL serum levels and high MBL activity have been associated with inflammatory autoimmune diseases like systemic lupus erythematosus (SLE), which, in turn, results in tissue damage and, finally, leads to organ damage. Serum MBL levels fluctuate during the course of SLE disease activity, and MBL genotypes have been found to be useful in assessing the risk of infection during the immunosuppressive treatment that the majority of the SLE patients receive.[1]

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In this issue, Demirhan *et al*. presented the first report that describes the association of MBL-2 polymorphisms with infection in children with Down syndrome (DS) from Turkey. This study gives a distribution of MBL-2 exon 1 genotypes (Codon 54 and 57) in a large number of DS patients and normal healthy individuals. Demirhan *et al*.'s study provides an evidence that a homozygote or heterozygote for a different MBL-2 allele is not associated with infections in patients with DS and do not influence the incidence of infections.[2] The gene encoding MBL, MBL2 (MBL1 is a pseudogene), is located on chromosome 10q11.2-q21 and contains four exons. A number of single-nucleotide polymorphisms (SNPs) have been characterized in the gene. Exon 1 harbors three missense SNPs giving rise to amino acid exchanges in the first part of the collagenous region. Two of these (Gly54Asp, named "B" and Gly57Glu, "C") exchange glycine with an acetic amino acid. The third (Arg52Cys, "D") introduces a cysteine in the collagen region (the residue numbers includes the leader sequence of 20 residues). The wild type is denoted "A." The three variant structural alleles are associated with decreased MBL levels. The promoter region shows a number of SNPs as well, some of which influence the expression of MBL, like the polymorphisms at −550 (termed H/L), −221 (termed Y/X) and −66 (termed P/Q). Because of linkage disequilibrium, only seven haplotypes are found; HYPA, LYPA, LYQA, LXPA, HYPD, LYPB and LYQC, giving a total of 28 possible genotypes (e.g., the MBL-deficient genotype: LXPA/LYPB). Individuals homozygous for A show MBL levels above 1 ng/ml, except some of those homozygous for LXPA. Heterozygous people with A on

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one gene and B, C or D on the other mostly have MBL levels between 0.5 and 1 ng/ml, while those with variant structural allotypes on both genes (genotypes often denoted 0/0) show MBL levels below 50 ng/ml. Such low levels are also found in individuals with LXPA on one gene and B, C or D on the other. The frequency of the haplotypes differs between ethnic groups, with, e.g., LYPB being the common variant haplotype in Caucasians (12%) and Asians (22%), but very rare in Africans. In contrast, LYQC is the common variant haplotype in Africans (24%) but is rarely found in Caucasian and Asian people. It is not always realized that the LXPA haplotype, with a gene frequency of 24%, is the most common cause of MBL deficiency in Caucasians, either presented as homozygous LXPA individuals (where the concentration is somewhat unpredictable) or in concert with a variant haplotype, always resulting in very low levels.[3]

Most subjects who are MBL-deficient appear to remain healthy. However, low serum MBL levels and their cognate haplotypes have been associated with a range of bacterial infections in both children and adults. The wide variety of pathogens involved in these infections is typical of an immunodeficiency. However, the fact that most MBL-deficient people do not get infections had led to speculation that a second immune defect needs to be present for susceptibility to infection, leading to several primary and secondary immunodeficiency syndromes.[4-8]

Immunodeficiency and Low Mannose-Binding Lectin Levels

Common variable immunodeficiency (CVID) is a heterogeneous syndrome characterized by failure of B cell differentiation and defective immunoglobulin (Ig) production, leading to recurrent bacterial infections, particularly in the respiratory tract. Although reduced Ig secretion from B cells is the hallmark of CVID, other immunological abnormalities such as T cell dysfunction and monocyte/macrophage hyperactivity are seen in a considerable proportion of patients. These abnormalities may be important for both the B cell deficiency as well as for some of the clinical manifestations in these patients, such as increased frequency of autoimmune disorders, granulomatous inflammation and malignant and nonmalignant lymphoid hyperplasia.[2,8,9] In syndromes as diverse as CVID, human immunodeficiency virus/acquired immunodeficiency syndrome and chemotherapy-induced neutropenia, the presence of variant MBL alleles is associated with earlier, more frequent and more severe infection. Presumably, the co-existence of MBL deficiency increases infection susceptibility, allowing further rapidly progressive lung and liver disease. Thus, MBL deficiency may affect susceptibility to a disease (e.g., meningococcal disease) or alter the natural history of a disease, such as cystic fibrosis, CVID and chronic granulomatous disease.[5,10,11]

DS is associated with a significant health burden, which is particularly apparent in young children who will frequently present with cardiac and respiratory problems. Children with DS have a high prevalence of respiratory infections. Such infections are more often seen in children who have congenital heart disease and pulmonary artery hypertension. Otitis media also has been noted more often in children with DS. Demirhan *et al*. have provided valuable information about the low expression of heterozygosity, which is not a major risk factor for infections in this study, suggesting that it may be associated with protection against infections. As there are some conflicting evidences of MBL deficiency and associated infections,[12,13] we feel that additional data on the types of infections in DS patients, MBL promoter region polymoprhisms, namely -550 H/L (G→C), -221 Y/X (G→C), +4 P/Q (C→T), and serum MBL levels should support these findings. Such data should be evaluated by statistical analysis. Still, we feel that Demirhan *et al*. have made a beginning in this area as this is an indexed study that gives an insight for further studies in DS patients from other parts of the world to understand the associated risk of MBL deficiency and MBL genotypes with infections. Such studies may further throw some light on the possible correlation between high-expression MBL-2 genotypes and the associated biological functions of MBL.

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