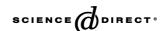


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## Mannose binding lectin: Genetics and autoimmune disease<sup>☆</sup>

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#### Abstract

Mannose binding lectin (MBL) is a serum protein with structure and functions similar to those of complement factor C1q, and is a key molecule in innate immunity. Interestingly, absence or extremely low concentration of serum MBL (MBL deficiency) seems to be a risk factor for occurrence of autoimmune diseases, in particular systemic lupus erythematosus. In addition, individuals with MBL deficiency are at risk of infection when in immunocompromised conditions. The concentration of serum MBL is greatly influenced by relatively common single nucleotide polymorphisms of the MBL gene. Therefore, typing of the MBL gene, or measurement of serum MBL may be valuable for determining the risk of infections in patients with systemic autoimmune diseases, who frequently undergo immunosuppressive therapies. MBL deficiency may also be a risk factor for atherosclerosis and arterial thrombosis, both being common complications of autoimmune diseases. On the other hand, MBL may be pathological in tissue injuries, and the precise roles of MBL in autoimmune diseases, and the value of MBL gene typing or serum MBL measurement in a clinical setting are yet to be clarified. Recently, presence of anti-MBL autoantibodies in sera of SLE patients has been reported. The significance of this autoantibody remains to be elucidated. © 2005 Elsevier B.V. All rights reserved.

Keywords: Mannose binding lectin; Single nucleotide polymorphisms; Innate immunity; Apoptosis; Anti-mannose binding lectin autoantibody

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#### 1. Introduction

Mannose binding lectin (MBL) is a serum protein produced in the liver, and is a key molecule in innate immunity. MBL, along with other molecules such as surfactant protein A (SP-A) and surfactant protein D (SP-D), is a member of the collectin family, the characteristic of which being possession of a carbohydrate recognition domain (CRD) and a collagenous domain [1].

MBL is a trimer protein composed of 3 identical polypeptides with a molecular weight of around 32 kD (228 amino acids), and 3 to 6 trimers further combine to make a huge bouquet-like structure similar to that of complement C1q [2] (Fig. 1-A). Each polypeptide consists of a CRD, a neck domain, a collagen domain and a cystein rich region. MBL binds to various organisms by its CRD, and excises an opsonin effect. The multimeric structure of MBL allows it to bind to various microorganisms including Gram positive and negative bacteria, mycobacterium, viruses and fungi. The binding of MBL leads to agglutination of these microorganisms and will help their clearance by phagocytes. In addition, MBL activates the complement pathway (the lectin pathway) through mannose binding lectin associated serine proteases (MASPs). Therefore, MBL is important in host defense, especially in infancy, when the acquired immunity has not fully developed. Individuals lacking this protein may develop severe episodes of bacterial infections from early life [3,4]. MBL is also important when the immune system of an individual is compromised, such as when a patient is under immunosuppressive therapy, or receiving chemotherapies or bone marrow transplant [5].

While MBL is an acute phase protein and its production is enhanced by inflammatory stimuli, polymorphisms of the MBL gene is known to greatly influence serum MBL concentration. The MBL gene, located on the long arm of chromosome 10 at 10q11.2–q21, contains 4 exons [2]. There are 5

known single nucleotide polymorphisms (SNPs) that affect serum MBL concentration [6-9] (Fig. 1-B). Codon 52 (+223), 54 (+230) and 57 (+239) polymorphisms are all on exon 1, and the minority alleles are designated allele D, B, C, respectively, while the majority allele is designated allele A. Presence of any of the minority alleles (collectively designated allele O) results in an amino acid substitution and significant reduction of serum MBL concentration. Furthermore, homozygosity or a combination of the minority alleles (genotype OO) results in almost complete deficiency of serum MBL [6,7]. This has been attributed to increased degradation of the mutated protein [7]. Frequencies of the minority alleles differ significantly among ethnicities, varying from around 1% to up to around 30%. In the promoter region of the MBL gene, polymorphisms are reported at positions -550, -221and +4, and these polymorphisms also influence the levels of serum MBL [9,10] (Table 1). Thus, some individuals with MBL genotype AO or even AA may have extremely low serum MBL concentration. In this review, however, we will focus on the SNPs in the coding region of the MBL gene.

## 2. Mannose binding lectin and autoimmune diseases

A number of studies have suggested that MBL deficiency, or low serum MBL levels caused by the SNPs described above may be associated with occurrence of SLE [11]. By a meta-analysis of 8 previous studies, it has been shown that presence of the minority alleles (B, C or D alleles) confer a 1.6 times overall increased risk of acquiring SLE [11]. In the same study, by observing their own patients, Garred et al. reported that the lag time from the appearance of the first lupus attributable symptom to the diagnosis of definite SLE was shorter in patients carrying at least one minority allele than in patients homozygous for the majority allele [11]. Two possible explanations for the association between MBL defi-

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