Mannose Binding Lectin (MBL) in Autoimmunity and its Role in Systemic Lupus Erythematosus (SLE)

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Abstract
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 MBL pathway for opsonization and phagocytosis. The role of adaptive immune response in 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 innate immune system could lead to autoimmunity is growing with the major recent concept of autoimmune disease pathogenesis is related to impaired apoptotic cell clearance. MBL have 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) that in turn results in to 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 immunosuppressive treatment the majority of the SLE patients receive. This review focuses on the genetic and molecular characteristics of MBL and discusses MBL disease association in autoimmunity with special emphasis on SLE.

Introduction
Autoimmunity is the failure of an organism to recognize its own constituents parts as its self, which result in an immune response against its own tissues and cells. Autoimmune diseases are the disorders in which the body’s immune system reacts against its own tissues and form autoantibodies which attack its own antigens. Paul Ehrlich at the beginning of the twentieth century had proposed the concept of “horror autotoxicus”, in which a normal body does not recognize an immune response against its own tissues. Inherited genes, viruses, ultraviolet light and certain medication may play some role in etiopathogenesis of autoimmune disorders. Genetic factors increase the tendency of developing autoimmune diseases. Systemic Lupus Erythematosus (SLE) is a prototype autoimmune disease containing chronic and acute inflammation of various tissues in the body. It is a disorder of generalized autoimmunity with unknown etiology, characterized by autoantibody production and immune complex (IC). Patients with SLE produce abnormal antibodies in their blood that target tissues within their own body rather than foreign infectious agents, these antibodies and accompanying cells of inflammation can affect tissues anywhere in the body, thus SLE has potential to affect a variety of area causing disease of skin, lungs, kidney, joints and nervous system.1,2

Patients with SLE are more susceptible to infections because they have altered immune systems, and also because many patients are on treatment (steroids and cytotoxics) that suppresses immune system function, leaving them more prone to infections. Lupus patients who get infection frequently show worse clinical signs and require longer treatment than non lupus patients. Most of the opportunistic infections are fungal, parasitic or protozoan. The most common bacterial infections seen in lupus are related to respiratory tract and urinary tract.3

Mannose Binding Lectin (MBL)
Mannose Binding Lectin (MBL) is an important element of innate immune defense system. The protein binds to the sugars present on many microbial surfaces and subsequently activates the complement system through a family of specific proteases called the MASP (MBL Associated Serine Proteases). MBL has an oligomeric structure (400-700 kDa), built of subunits that contain three identical peptide chains of 32 kDa each. MBL has a bouquet-like structure with many similarities to C1q. Each is characterized by a lectin domain, an α-helical coiled-coil hydrophobic neck region, a collagenous region and a cysteine-rich N-terminal region. Three such chains interact to give a collagenous triple helix, but separate at the neck region to give three independent carbohydrate recognition domains.4

MBL belongs to the class of collectins in the C-type lectin superfamily, whose function appears to be pattern recognition in the first line of defense in the pre-immune host. MBL recognizes carbohydrate patterns, found on the surface of a large number of pathogenic micro-organisms, including bacteria, viruses, protozoa and fungi. To activate the complement, MBL in the blood complexes binds to another known as serine proteases called MASPs. The MASP protein function like a convertase to clip C3 into C3a and C3b. C3b combines with other complement proteins to make a Membrane Attack Complex (MAC), which causes lysis of pathogens and cells. C3b can also bind to complement receptors on phagocytes causing opsonization of pathogens. The MBL pathway involves the MBL proteins, MASP-1, MASP-2, C4, and C2. MASP acts as a C3 convertase, creating a C3b fragment from C3. C3b attaches to the pathogen surface and binds to receptors on phagocytes leading to opsonization. C3b can also combine with other proteins on the pathogen surface and form a membrane attack complex.5,6
However, enhanced complement activation may also induce and plays a central role in the host defense against microbes. The normal structural MBL alleles is named A, while the common designation for the 3 variant structural allele B (mutation in codon 54, Gly to Asp), C (mutation in codon 57, Gly to Glu) and D (mutation in codon 52, Arg to Cys) are O. MBL expression is influenced by polymorphic sites in the upstream part of the MBL gene nucleotides substitutions at positions -550, -221 and +4 which give rise to H/L, Y/X and P/Q respectively and causes different haplotypes, while LX haplotypes is associated with low MBL plasma levels. MBL enhances the opsonization and activates complement. Dysfunctional alleles of MBL have been associated with low plasma concentrations of MBL and increased risk of SLE, thus case control studies of MBL polymorphism are performed in different Ethnic groups. MBL genotyping in SLE shows that the MBL functional variants are associated with SLE.7

Homozgyosity for MBL variant alleles leads to increased risk of complicating infections in SLE patients. Codon 52, 54, 57 polymorphism are all on exon 1 of the MBL gene, and the presence of any of the minority alleles significantly reduces serum MBL concentration. The incidence rates of SLE in individuals with C1q and C4 are reported to be around 90% and 75% respectively. Patients with C2 deficiency develop SLE with lesser frequency (around 15%). MBL deficiency is linked with frequent pyogenic infection including pneumococcal infection in infants and young children, severe pneumococcal disease is also reported in patients with MAS2 deficiency. MBL deficiency is 2–3 times as common in patients in with SLE as in the general population.8

During an active phase of renal involvement in SLE, the C1q levels are decreased because of activation of the classical pathway of complement activation, triggered by the interaction of C1q with immune complexes. A second cause of reduced C1q levels is the presence of anti-C1q. Genetic deficiency of C1q is strongly correlated with the development of SLE. Association of reduced MBL levels (as a consequence of gene polymorphism) with SLE has been reported previously. Anti-MBL, similarly to anti C1q, could be a cause of low MBL levels in SLE patients. Higher MBL levels were found in sera of SLE patients. Anti-MBL autoantibody levels were higher in patients with high MBL concentration.9,10

Thus complement system, consisting of more than 30 proteins, represents an important component of the innate immune system and plays a central role in the host defense against microbes. However, enhanced complement activation may also induce tissue damage and inflammation. Accordingly, a dysregulated complement system has been associated both with increased susceptibility to infections and autoimmune disease. Mannose-binding lectin (MBL), being another important part of innate immunity, is a key component of the lectin pathway of the complement system. Serum levels of MBL are closely correlated to polymorphism in promoter regions as well as mutations in the MBL gene. Children with recurrent pulmonary infection have low MBL, but low MBL do not seem to increase mortality or the occurrence of infectious disease in an adult population. Altered MBL level have been associated with persistent inflammation and tissue destruction. High serum MBL concentrations in some cases enhance the risk of infection. As an opsonizing factor, it favors a penetration of some intracellular pathogens such as mycobacteria into their target cells.11-15

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 in several primary and secondary immunodeficiency syndromes.12,14,16-18

### 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 cells dysfunction and monocyte/macrophages hyperactivity are seen in a considerable proportion of patients. These abnormalities may be importance for both the B cells 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.13,19,20

In syndromes as diverse as common Variable Immuno Deficiency (CVID), HIV/AIDS 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.5,14,19

### References


3. Gupta K, Gupta RK and Hajela K. Disease association of mannose


