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Mannose Binding Lectin (MBL) and Its Clinical Significance

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ABSTRACT

BACKGROUND AND OBJECTIVE: Mannose Binding Lectin (MBL) is a key molecule in innate immunity, this acute phase protein, synthesized in the liver, binds to various microorganisms and damaged cells and destroys them by opsonization of aggressive agents and activation of the complement by relevant serine associated proteases.

METHODS: In this review study, we investigated the literature from Scopus, Pubmed and Google Scholar databases using the following keywords: Genetic, Molecular Epidemiology Mannose Binding Lectin, Immunity, and Infectious disease.

FINDINGS: There are significant differences in serum levels of MBL and its genetic stability and this is due to genetic polymorphism of MBL and because of alteration of structural gene and the promoter region.

CONCLUSION: Homozygous or heterozygous individuals with compound structural MBL gene are susceptible to some malignancies, infectious and autoimmune diseases. Administration of plasma-free or recombinant MBL, may be helpful to treat certain patients have limited amount of it.

KEY WORDS: Mannose Binding Lectin(MBL), gene polymorphism, Immune system, infectious diseases.

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Introduction

Vertebrates with acquired immune system represent very good defensive mechanisms so that with unlimited number of antibodies possess a strong immune system against antigens, but unfortunately this defense system has two major limitations. First, there is a 1-4 week delay, from exposure to antigen and production of antibody. Second, before the host's response, the antigen must be swallowed by antigen presenting cells to be digested into smaller fragments that can be presented to immune system. In order to develop the immunity, in advance, stimulation of swallowing the antigen by presenting cells is essential to produce sufficient specific antibody. Meanwhile, other protective mechanisms act in the absence of antibody (1) and the innate immune system plays this role for mentioned needs from the birth (2).

Innate immunity system is the first line of defense and helps the acquired immune system to distinguish between structures of aliens by identification of the molecular patterns of pathogens (3). Complement system is known as an important component of innate immunity and it is composed of more than fifty types of proteins (4), and co-works with both innate and acquired immune systems and abridges between these two systems (5). The complement is activated via three routes: 1) classic pathway, 2) alternative and 3) lectin. Each pathway uses the specific identifying molecules in order to detect some of the indicators in pathogen surface (6). Activation of the complement is done in cascade form and leads to a series of immunological actions such as increased phagocytosis, inflammatory cell recruitment and creation of holes in the cell membrane (7). Mannose-binding (MBL) lectin is one of most important activators of complement-lectin pathways. MBL, which is known as a pattern recognition molecule (PRM) in innate immunity, (8) binds through the repeated exclusive oligosaccharides on the surface of microorganisms and attaches to them (9) and it destroys the microorganisms via opsonization of these agents and phagocytosis of them, and also activation of the complement lectin pathway (10).

MBL deficiency leads to severe infections, especially in neonates (11) as well as cancer patients undergoing chemotherapy (12). It also plays a critical role in moderation of MBL during production of cytokines, (13) inflammation and tissue damage, and it is essential for maintaining the homeostasis. The MBL impairment leads to immunological damages and autoimmune diseases (14). In this review, we assessed the structure and function of MBL, its genetics and serum levels and epidemiologic issues. Besides, we discussed the role of MBL in infectious and autoimmune diseases, malignancies and also effectiveness of the replacement therapy with MBL was investigated.

Structure and function of MBL: MBL is an acute phase protein, calcium dependent (15) and it is mainly produced in the liver (16), but it is possible to be generated by other tissues because of elevation of its serum level during liver cirrhosis. So, it is hypothesized that MBL also is produced by vaginal epithelial cells (17) and dendritic cells derived from monocytes (18). MBL has a macromolecular structure and it is similar to the bouquet like C1q (19) and it is a member of co-lectin family (Collagen + lectin) and a multi-form molecule which is composed of 2-6 subunits, each subunit is composed of three identical polypeptide chains of 25 kDa (fig 1) (20). Each chain contains 298 amino acids and its N-terminal includes a rich region of cysteine, followed by a flexible collagenous and neck regions and finally a C-terminal lectin domain. The N-terminal bonds between disulfide chains and subunits and causes their improved stability (21) and the C-terminal lectin domain is carbohydrate identifier and so called carbohydrate recognition domain (CRD), which has calcium-binding site (22). MBL has a pre-antibody defensive role in the delayed phase of infection, when proliferation of microbes is commenced, but no antibody is already produced (23).

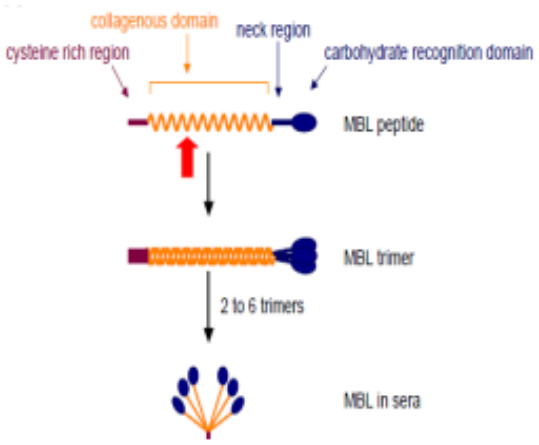

Figure 1. Multi-Mer structure of MBL molecule and its subunit that contains three identical polypeptide chain is shown in (20)

MBL by CRD identifies sugars mannose, N acetyl glucosamine, fucose and glucose on surface of various microorganisms such as bacteria, viruses, fungi,

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parasites and fits (24) but it cannot detect the terminal sugars of galactose and sialic acid on the surface of normal cells (25). In addition, MBL binds to modified oligosaccharides on the surface of apoptotic cells, necrotic and damaged tissues (26), and leads to the activation of MBL-associated serine proteases (MASPs) (20). MASP-1 and MASP-2 are activated by enzymatic activity of semi S1 esterase and thereby they result in separation of the C2 and C4 (27) and composition of C4b2a complex with C3 convertase activity (28). C3 convertase causes the formation of membrane-attack complex and leads to lysis of the organism or whole cell (29) and also production of C3b and iC3b that they act as opsonin to making the host phagocytic cells to devour the microorganisms (30). Through the collagen region, they can bind to phagocytic cells, leading to phagocytosis via receptors on the cell surface (10). So it can be said that MBL, as one of the key components of innate immunity system, has four different functions: 1) activation of the complement, 2) the complement-free phagocytosis, 3) modulatory for inflammation and 4) stimulating the apoptosis.

Genetic of MBL: Human MBL encoding-gene is located on chromosome 10 and there are two genes for MBL. MBL1 is a pseudogene and only MBL2 encodes the protein. MBL2 has 4 exons and 3 introns with the sizes of 600, 1350 and 800 bp sets (31). Each exon encodes a different functional part of the molecule; exon 1 encodes a signal peptide, a cysteine-enriched region and the glycine-enriched part, of which is essential for formation of triple helix in collagen structure. Exon 2 encodes the remnants of collagen region which has junction of MASPs. Finally exon 3 and exon 4 encode the neck region and carbohydrate identifier domain, respectively (32).

There are six mono nucleotide polymorphisms known in MBL2 gene associated with changes in quantity and function of MBL. Structural mutations are observed in exon 1; so that point mutation in codon number 52 result in replacement of cysteine instead of arginine (allele D), mutation at codon number 54 result in the placement of aspartic acid on glycine (allele B), and mutations at codon number 57 cause the placement of glutamic acid on glycine (allele C) (33). Alleles B, C and D also are known as allele O, whereas allele A is the common type of MBL2 gene (34), the alleles B, C and D reduce the stability in the collagen region of this protein. These variants are decompositionedand outcome of allele C cannot activate the complement system and the protein of allele B has dramatically lower power to activate the complement pathway (35). Mononucleotide replacement at the promoter region of MBL2 gene in positions of -550 (polymorphism H/L), -221 (polymorphism X/Y) and +4 (polymorphism P/Q) in 5 untranslated regions can affect serum levels of MBL (33). Promoter variants are associated with strong linkage disequilibrium with variations of the encoder, therefore the specific combination of genetic polymorphisms of MBL occurs non-randomly. Among 32 possible haplotypes, following seven haplotypes are commonly observed: HYPA, LYQA, LYPA, LXPA, LYPB, LYQC and HYPD (36). H variant is fitted to the allele B, and X variant only exists in LXPA type (33). In addition, another haplotypes may be existed in some ethnic groups. For example haplotype LYPD in Czechs (37), HXPA in a Negro in Morocco and one LYQB haplotype and three HYPB haplotypes in children in the Netherlands have been identified (38).

Serum levels of MBL: MBL serum levels are extremely variable and in healthy subjects ranges from 0 to over 5 µg/ml (22). Serum levels of MBL is highly dependent on the various genotypes of MBL2 (39). The structural gene arrangements and polymorphisms of the promoter can change the concentration of MBL up to thousand fold (40). As serum levels of MBL in people with genotype O/O is very low or as low as unmeasurable (41). Those with HYPA/HYPA genotype possess high serum levels of MBL. Also, the MBL is affected by polymorphism of promoter region, as the HY, LY and LX haplotypes cause high, medium and low amounts of MBL, respectively (42). Generally, four haplotypes, including LYPB, LYQC, HYPD and LXPA, lead to low levels of MBL in serum (43). Besides, some non-genetic factors such as age, hormones and activation of immune system can affect the amount of MBL. The amount of MBL increases by aging so its amount is lower in preterm infants (44). The rate of MBL increases during the first months after birth and it would reach to adult range in age of 12 (45) and after 49 year-old it decreases and its amount in women is higher than men (46).

Thyroid hormones (T3, T4) and growth hormone increase the synthesis of MBL (47). MBL, as an acute-phase protein, is doubled or tripled in inflammatory or infectious conditions (48). There are individuals with normal genotype (containing allele A) that their serum levels are very low, as no normal range cannot be accurately estimated for MBL, probably due to effect of external factors involved in regulation of gene

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transcription of MBL. In general, in can be concluded: 1) the amount of MBL would be more than 300 ng/ml in A/A homozygotes with HY or LY (49); if the promoter is LX, the MBL rate will be less than 300 ng/ml, 2) in homozygotes or heterozygotes with compound allele O, the MBL serum levels are very low and in most cases, it is unmeasurable; while B and D variants present the highest and lowest effects, respectively, compared to the rest of structural alleles (39).

Molecular epidemiology of MBL: Apart from rare exceptions, most of MBL haplotypes exist worldwide, but with varied frequencies in different populations (50). Hence, the frequency of LYPB haplotype observed in Iranians living in East Azerbaijan, the Koreans, the Japanese and northern Spaniards, Chinese, Brazilians living in Rio de Janeiro, Eskimos, Chiriguanos of Argentina and native Danish were 13.2% (51), 18.6% (46), 22% (52), 14% (53), 6.7% (34), 12% (54), 12 %, 42% (43) and 11% (43), respectively; while within population of sub-Sahara of Africa, Mozambique and Kenya, the LYQC haplotype was observed 24% (43) and in native Australians at Warlpiri region, no case of abovementioned haplotypes is found (table 1). Lack of observation of LYQC and LYPB haplotypes in native Australians, would be because migration to Australia has been occurred before mutation of B in exon 1 of MBL2 gene that took placed about 50,000 years ago and the existence of LYPB haplotype in Eskimos and the people of South America represents that the migration to America has been occurred via Bering Strait in eastern Siberia about 30,000 to 20,000 years ago and after emigrating to Australia (55). Variations of MBL which produce low volume of MBL exist noticeably in most populations and races, for example, high rates of the B allele in Americans and C allele in sub-Sahara Africans can be seen (43). This indicates that probably low concentrations of MBL could be useful; for example deficiency of MBL helps to protect the host against certain intracellular pathogens (56), so the natural selection effect might be responsible for some variations in certain populations (19). **Role of MBL in infectious diseases:** MBL as a pattern recognition molecule plays an important role in host's defense, especially during 6-17-months infancy period when immunity has not fully developed and the infants have hypogammaglobulinemia (11). Several studies have shown that people with MBL deficiency or the alleles produce very low levels of MBL, are especially more sensitive to some protozoan, viral, bacterial and fungal infections. (24) In addition, they are prone to Meningococcal infections (1), urinary tract infections (57), sepsis (59, 58), recurrent infections (60), respiratory tract infections in childhood (61), otitis media (62) and pneumococcal infections (63). MBL deficiency is important in increased susceptibility to viral infections as MBL recognizes the influenza virus A and binds to hemagglutinin of virus and neutralizes glycoprotein neuraminidase enzyme; MBL blocks the attachment of influenza A virus to host cells and prohibits distribution of virus-infected cells to adjacent non-infected cells (64). The role of MBL in HIV, has been more studied, and it is shown that the MBL deficiency have three consequences in HIV: a) increased post-exposure susceptibility to HIV infection (65), b) impact on duration of the disease, and c) more secondary infections in HIV-infected patients (66).

Table 1. The frequency MBL haplotypes in different populations around the world

Ethnics	No	HYPA	LYQA	LYPA	LXPA	LYPB	LYQC	HYPD	Rare Hyplotypes
East	144	0.329	0.233	0.017	0.21	0.132	0.21	0.055	0.003
Rio de Janeiro (Barazil)	294	0.28	0.22	0.11	0.15	0.012	0.08	0.04	-
Australia	190	0.747	0.013	0.229	0.008	-	-	0.003	-
Argentina	43	0.54	0.1	0.02	0.01	0.42	-	-	0.14
Koream	129	0.531	0.109	0.066	0.105	0.186	-	-	0.003
North Spaniard	441	0.44	0.16	0.07	0.11	0.22	-	-	-
Eskimo	72	0.81	-	0.04	0.03	0.12	-	-	0.03
Danish	250	0.31	0.19	0.04	0.26	0.11	0.03	0.06	0.03
Mozambique	154	0.06	0.27	0.30	0.13	-	0.24	-	0.06
Kenya	61	0.08	0.25	0.13	0.24	0.02	0.24	0.04	0.13
Chinese	105	0.695	-	0.138	0.024	0.67	-	-	0.076
Japanese	218	0.44	0.16	0.07	0.11	0.22	-	-	-

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In individuals with allele B, hepatic disease induced by hepatitis B infection, progresses more rapidly and they are more prone to fulminant hepatic failure (67). Also hepatitis C infection develop more commonly within cases with B allele (68) and they show more resistant to treatment with interferon (52). Allele-B owners more commonly suffer from recurrent candidiasis and vulvovaginitis (69). Besides, it is observed that alleles B and C, produce low amount of MBL and are risk factors for severe malaria infection in children, who possess under-developed acquired-immune-response system (70).

MBL deficiency is clinically more important when is associate with other deficits in immune response; for instance the children with deficiency of MBL, more commonly have defects in chemotoxy (71) or lack of some IgG subclasses (72). MBL protects the body by activating the complement system against infection, but in some intracellular microorganisms, MBL acts reversely. Possession of alleles that produce a low concentration of MBL, protects the subjects against intracellular organisms such as Mycobacterium tuberculosis (73):

First, binding of MBL to some microorganisms in some circumstances leads to uncontrolled activation of the complement and inflammatory response, second when there is high level of MBL, production of C3b increases and deposits on surface of micro-organisms and subsequently increases the removal of microorganisms by C3 receptors (74).

Also, phagocytosis is essential for tuberculosis stability, so MBL binding runs an additional uptake mechanism by phagocytic cells (24). The studies have shown that the alleles, causing lower levels of MBL, derive a protective effect against visceral leishmaniasis (75). While in extracellular infections, generally high level of MBL plays a protective role (77, 76)

MBL and autoimmunity diseases: One of the challenges in internal medicine is understanding pathophysiology of autoimmune diseases (78) and in these health problems such as systemic lupus erythematous (SLE), rheumatoid arthritis, and vitiligo,the main agent or the trigger of the disease is still unknown. But there are evidences for involvement of genetic, immunological and environmental factors; that show the innate immunity might play a role in pathophysiology of autoimmune diseases and it is effective through priming and increasing the immune responses in these diseases (79). Since in autoimmune diseases, the clearance of apoptotic cells is not achieved (80) and also MBL is effective in removal of apoptotic cells (26) and pathogen microorganisms (81), it is possible that MBL deficiency predisposes patients to autoimmune diseases such as SLE and rheumatoid arthritis. The literature shows that low level of MBL is considered as a risk factor for SLE (83, 82) and rheumatoid arthritis (84). In patients with SLE who have MBL deficiency, risk of renal dysfunction (85), infection rate (86) and arterialthrombosis (87) is higher than others. In SLE patients with low levels of MBL, the volume of autoantibodies increases against the molecules found in apoptotic cells, such as C1q and cardiolipin (88). In patients with rheumatoid arthritis, MBL deficiency is associated with increased rheumatoid factor (IgM), wear of joints and inflammation (86).

Cancer and MBL: Cancer is one of life-threatening diseases happening in different ages (89). The immune system prevents excessive growth and proliferation of malignant cells. This uncontrolled proliferation is associated with changes in cells. Aberrant glycosylation is shown as one of changes in cell membrane structures that can influence on degree of invasion and distance metastasis (90). The complement system as a part of the immune system has an inhibitory effect against cancer progression, by lysis and opsonization of malignant cells (7). MBL plays a role through opsonization and activation of the complement system. MBL attaches to malignant cells and causes deposition of C3 and C4, and eventually leads to cell death (91). Also, MBL identifies the changes in glycosylation structures of surface of cancer cells, leads to elimination of the necrotic and apoptotic cells by macrophages through macropinocytosis (26).

Various studies have reported association of risk of developing cancer and MBL2 polymorphisms; that reduces the amount of MBL in serum. It is shown that specific alleles which reduce MBL in serum, are related with breast cancer (92), gastric cancer (94, 93), glioma (95), acute lymphoblastic cancer in children (96) and ovarian cancer (98, 97). MBL deficiency is more indicative in cancer patients after chemotherapy, as severe infections during chemotherapy happen in these patients (12), also febrile neutropenia during chemotherapy lasts longer (99, 100). In some studies no significant relationship have been found between low MBL levels and cancer (102, 101) and in one study it was reported that subjects with lung cancer and low MBL in serum survived longer (103). Inconsistent results may be due to heterogeneity of the studied

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populations, difference in number of patients, chemotherapy regimens, duration of treatment, varied follow-up durations, and different definitions for MBL deficiency; certain results can be achieved through multi-centric studies on different populations. It seems MBL deficiency is likely to cause increased susceptibility to infection with pathogens such as Helicobacter pylori, HPV, hepatitis B and C, and so increase the risk of cancer.

Replacement therapy with MBL: Since it is determined that MBL deficiency can cause serious infections, especially in infants and cancer patients after chemotherapy, MBL replacement therapy is proposed. The treatment outcome have been acceptable with no toxicity and side effect (104,105). In one study, administration of MBL, decreased the intensity and number of infections during chemotherapy (106). In another study, twelve neutropenic children with MBL deficiency during the chemotherapy received MBL and no complications was observed; antibodies did not produce against MBL and phagocytosis increased after opsonization (107).

Studies have shown that administration of MBL would be useful in patients with cystic fibrosis (104), women who have had recurrent abortions (108), recurrent infections in children (61), hepatitis C infection (109) and Dengue virus. MBL neutralizes four serotypes of Dengue virus infection, as it is directly related to the concentration of MBL in serum (110). It seems that in recipients of hematopoietic stem cells that have mutations in MBL gene (111), and in MBL deficient groups such as: 1) cancer patients undergo chemotherapy (112), 2) recipients of liver transplant and faced with threatening infections (114 and 113) and 3) patients with dermal skin diseases, replacement therapy with MBL, for removal of apoptotic cells and immune complexes, is beneficial (116, 115). Since MBL activates the complement in leishmaniasis (76), tuberculosis (73), Ebola virus infection (117), leprosis (118) and cardiac transplantation (119), replacement therapy with MBL may be harmful, while MBL therapy is effective in healing of radiotherapy-induced chronic wounds in patients with breast cancer after mastectomy (120). Currently, two types of derived plasma MBL (122 and 121) and recombinant MBL (123 and 106) are used without complications; plasma derived MBL is a natural product and has a normal distribution of oligomers and also contains other factors involved in innate immunity system (124).

While the benefits of recombinant MBL include: long-term producing, lack of contamination with viruses and prions and prolonged biologic half-life, but its disadvantages are: different characteristics with natural form in case of oligomerization (different distribution of oligomers) and weaknessin connectivity to mannan and activation of the complement. But this type is useful in infection after kidney transplantation, which it is harmful to activate the complement for these patients, and aim solely is to eliminate the pathogens from the body (35). Generally speaking, MBL replacement therapy reduces infection in susceptible individuals and it can be used when conventional treatments are not effective in treatment of the patients in particular health conditions.

Discustion

It can be concluded that MBL, as a pattern identifier molecule, plays amodulatory role in infectious diseases and inflammation, so the lack of MBL would lead to increased susceptibility to infections in infants and patients with underlying diseases. Therefore, it is supposed that the determination of the type of genotype and its amount in the susceptible individuals is recommended. And if necessary, these people should be vaccinated against infectious diseases such as meningococcal and pneumococcal infections. Finally, replacement therapy with MBL is appropriate for MBL deficient, chemotherapy-treated, liver or bone marrow transplanted patients, or those with HIV and Dengue infections, in order to strengthen the innate immune system.

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