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Differences in Mannose-Binding Lectin Gene Polymorphisms in Different Diseases

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Abstract: Mannose-Binding Lectin (MBL) is a member of the collectin family. It binds to various oligosaccharides and activates the classical pathway of complement independent from C1q. The aim of present study is to study the distribution of the alleles of MBL gene and promoter variants in intracellular, extracellular pathogens and autoimmune diseases. Our studies showed occurrence of the codon 54 mutation (allele B) of MBL was associated with the occurrence of the acute hepatitis C, this showed the low MBL level can intense progress of this infection, but in other intracellular infections, low expression MBL genotypes associated with protection against these infections and wild type alleles with high MBL production considered as a risk factor for these intracellular pathogens. In extracellular pathogens, there was contrary and wild types of genotype with high production of MBL were associated with protection against these infections and alleles with low MBL production considered as a risk factor for these pathogens. In autoimmune diseases our study and other studies demonstrated that low MBL was a risk factor for these diseases.

Key words: Mannose binding lectin, extracellular, autoimmune, intracellular

INTRODUCTION

Mannose-Binding Lectin (MBL) is a member of the collectin family of proteins that has been recognized as an important component of innate immunity (Presanis *et al*., 2003). It is a pattern recognition molecule for which the spacing and orientation of carbohydrate-recognition domains, define what ligands the protein can target (Jack and Turner, 2003). It is a multimeric molecule composed of up to six 96 kD subunits, each subunit consisting of three identical 32 kD polypeptide chains that associate at collagen-like domains to form a triple helix (Lu *et al*., 1990). The molecule can be seen by electron microscopy as a bunch of tulip (Malhotra *et al*., 1994). The MBL exists in serum as a mixture of oligomers with two to six 96 kD subunits but only the molecules with four or more subunits seem to activate complement (Garred *et al*., 1992a). It binds to mannose and N-acetylglucosamine residues while presented in the orientations and densities commonly found on microorganisms (Jack *et al*., 2001b; Maas *et al*., 1998), it has an important role in antibody-independent pathway (Ikeda *et al*., 1987). The MBL is structurally related to the complement C1 subcomponent, C1q and seems to activate the complement system through an associated serin protease known as MASP (Mannose binding lectin-associated serin protease 1 and 2) (Thiel *et al*., 1997) which is similar to C1r and C1s of the classical pathway. The MBL can bind to surface of a range of microorganisms including bacteria, parasites, viruses and yeasts (Turner, 1996).

Several studies have shown a direct interaction of MBL with phagocytic cells, resulting in enhanced phagocytosis and modification of cellular activation (Jack *et al*., 2001a; Jack and Turner, 2003). Thus, MBL plays an important role in the innate immunity of the immune system.

Human MBL is derived from a single gene on chromosome 10 at q11.2-q21 (Sastry *et al*., 1989), it contains four exons: Exon 1 encodes a part of collagene-like region which is a cystein rich region; exon 2 encodes the rest of the collagenous region; exon 3 encodes a neck region of MBL and exon 4 encodes carbohydrate binding region (Sastry *et al*., 1989). The normal structural MBL allele of exon 1 is named A while the common designation for the three 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 (Hegele *et al*., 1999; Neth *et al*., 2001). In general, individuals with a normal genotype (A/A) have MBL concentration in serum that are 6-8 time higher than those in individuals heterozygous for one of the variant alleles (A/O, A/B, A/C or A/D) while individuals with a defective genotypes (2 alleles B/B, C/C, D/D, B/C, B/D or C/D) have almost undetectable MBL serum levels (Garred *et al*., 1999; Graudal *et al*., 2000). Moreover, MBL

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expression is influenced by polymorphic sites in the upstream part of the MBL gene (Crosdale *et al*., 2001; Ip *et al*., 1998). The promoter region of the MBL gene has nucleotides substitution at position-550, -221 and +4 give rise to H/L, X/Y and P/Q, respectively, that makes different haplotypes while LX haplotype is associated with low MBL serum level (Santos *et al*., 2001; Soborg *et al*., 2003).

In this study, it was aimed to review the previous studies and other studies on the role of MBL gene and promoter polymorphisms in outcome of different diseases.

STUDY METHODS

Serum MBL level studies usually accompanied by genetic studies. Serum MBL level usually measuring by a sandwich enzyme-linked immunosorbent assay (sandwich Elisa) (Terai *et al*., 1993) or by time resolved immunoflurometric assay (Liu *et al*., 2001) while the second method is more common. Commercial monoclonal anti-MBL antibody is available for serum assays (Immunolex, Finland) (Hansen *et al*., 2003). The serum concentration of MBL in individuals from the general population shows a wide range.

In British mannose binding serum level was 1.630 ng mL^{-1} (Lipscombe *et al*., 1992), in Gambians it was 1.790 ng mL^{-1} (Garred *et al*., 1992a) and in Danish it was 1.234 ng mL^{-1} (Garred *et al*., 1992b). Serum MBL levels being lowest at birth but rising to adult levels during the first weeks of life (Thiel *et al*., 1995).

Genetic diversity of MBL can be studied by allele specific PCR (Asgharzadeh *et al*., 2007a, b). In this method specific primers for detecting presence of each allele and promoter regions of MBL in the human genome were used. In addition to PCR, B and C alleles should be detected by PCR-RFLP which usually perform by Ban I and Mbo II restriction enzyme digestion of the 320 bp product amplified by the allele P and Q primers. Ban I cleaves the A allele into two fragments (245 and 83 bp) and leaves the B allele undigested while Mbo II specifically cleaves the C allele into two fragments (266 and 62 bp) (Madsen *et al*., 1998). These methods can be confirmed by Southern blot analysis. Reverse transcription-polymerase chain reaction (RT-PCR) is a new method for detection MBL expression in the cell in which total RNA should be isolated from liver tissue by reagents like TRIzol and then should be reverse-transcribe, CDNA is subjected to PCR amplification using pairs of complementary oligonucleotide primers that represented MBL alleles and variants.

MBL IN INTRACELLULAR PATHOGEN

Intracellular pathogens are pathogens who complete the main cycle of their life is inside of cells. For the study the MBL gene and promoter polymorphisms in intracellular pathogens we studied its polymorphisms in hepatitis C infected patients and in patients with visceral leishmaniasis caused by Leishmania infantum. In hepatitis C virus infected patients study, we found codon 57 mutation of MBL as a risk factor (Somi *et al*., 2006). A study performed in 100 infected patients and 100 blood donors as the control group and genotyping method revealed A/A allele was more frequent among healthy donors while genotype A/O and O/O were significantly more frequent among patients with hepatitis C ($p<0.005$) and occurrence of the codon 54 mutation (allele B) was significantly higher in infected patients ($p<0.005$). Results of this study showed MBL variant alleles which are known to decrease the serum MBL levels, are associated with increased risk and severity of viral hepatitis. These genotypes have been shown to be associated with viral persistence in hepatitis B virus infection (Thio *et al*., 2005). Also in a similar study low MBL level was associated with occurrence of cirrhosis and hepatocellular carcinoma in progressed carriers (Chong *et al*., 2005), our study clearly showed accompany of allele B carriers be more prone to hepatitis C virus infection. In another study, we investigated the association of MBL gene and promoter polymorphism and outcome upon infection with *Leishmania infantum* as an intracellular parasite. Interestingly our study results showed genotypes with high MBL concentration were more frequent among healthy individuals in comparison with healthy controls ($p = 0.003$) (Asgharzadeh *et al*., 2007a; Asgharzadeh and Kafil, 2007).

In fact here we had contrary, with hepatitis C virus study results. Both of these infections are intracellular low concentration of MBL in hepatitis C virus was a risk factor and high MBL concentration was a risk factor for visceral leishmaniasis.

Several previous studies confirmed MBL deficiency in intracellular infections confers protection against these infections (Jack and Turner, 2003). A new study suggests a protective role for MBL deficiency against development of the most severe and multibacillary form of leprosy but not the tuberculoid form (Dornelles *et al*., 2006) or in tuberculosis has been demonstrated that heterozygosis for MBL variant allele (XA/O) which encodes low serum MBL level is associated with protection against clinical tuberculosis (Bellamy and Hill, 1998; Soborg *et al*., 2003),

in another study it was proved that lack of MBL enhances survival in a mouse model of acute septic peritonitis (Takahashi *et al*., 2002). In leishmania case studies, previous studies confirmed increasing concentration of MBL cause to increase the release of TNF-α and interleukin 6 from monocytes contaminated with parasite (Jack and Turner, 2003). The simplest way to explain it is MBL binds to parasite surface and most intense at the base of the flagella in many parasites on an area of the plasma membrane that is the major site for exocytosis for these cells and contains a high concentration of surface antigen (Pimenta *et al*., 1991). The MBL can promote the opsonization of microorganisms, thus intensify their attachment to phagocytic cells (Jack and Turner, 2003). Several hypotheses can explain the prevalence of MBL genes and promoters with high concentration in *Leishmania* infected patients, phagocytosis is essential for the disease establishment. The MBL is binding to *Leishmania* promastigotes could provide an additional uptake mechanism of the parasites by phagocytic cells, but on the contrary, our study in hepatitis C virus showed MBL have not the same role in all intracellular pathogens and in viral infections there is some differences. Also more recent reports indicate susceptibility to viral hepatitis B in low concentration of MBL (Thomas *et al*., 1996) also a study showed an association of human immunodeficiency virus (Garred *et al*., 1997) with MBL mutations.

The MBL has been shown to inhibit *in vitro* infection by human immunodeficiency virus (Ezekowitz *et al*., 1989) in fact MBL will activate complement after *in vitro* binding to the human immunodeficiency virus glycoproteins gp120 and gp110 (Haurum *et al*., 1993), it can be concluded that in patients with low MBL concentration, progress to acute hepatitis or other viral infections is more rapid than patients with wild type alleles. In other intracellular pathogens (Bacterial, parasite and fungi), it has been suggested that the variant alleles may be maintained at high frequency by heterozygote advantage, perhaps by conferring resistance to these infections. As above mentioned in tuberculosis or leprosies, it would be fascinating if MBL deficiency which is frequently described as the world's commonest immune deficiency, has been selected for by heterozygote resistance to intracellular pathogens like tuberculosis or leprosies.

Some new studies showed high MBL levels decrease the production of inflammatory cytokines, such as IL-6, IL-1β and TNF-α especially in response to meningococci by monocytes while low MBL concentration can enhance the production of IL-6 and IL-1 (Jack *et al*., 2001b) and give rise of inflammation and phagocytosis of pathogens.

MBL IN EXTRACELLULAR PATHOGENS

Studying the role of MBL gene polymorphisms in extracellular pathogens we studied patients which lost their kidney in the results of different extracellular pathogens like *Escherchia coli*, *Klebsiella*, *Entrobacter*, *Proteus* and *Pseudomonas*. We have shown that genotypes with low MBL concentration were more frequent among patients had kidney infection than healthy controls and genotypes with high MBL serum level were more frequent among healthy individuals in comparison with infected patients. In structural alleles of mannose binding lectin, allele B with low MBL concentration was more frequent in infected patients ($p = 0.0011$) and allele A with the highest concentration of MBL was more frequent in healthy controls ($p = 0.0912$). In promoter haplotypes, we had a same situation and Ly and Lx haplotypes with low MBL concentration were more frequent in infected patients. In this study, we found high-expression MBL genotypes can be associated with protection against infections cause to renal failure, as a first line immunity against these infections and defective alleles with low concentration as a risk factor for kidney infections (Asgharzadeh *et al*., 2007b).

Several other studies are in agreement of our finding; in aspergillus's codon 52 mutations was particularly common that demonstrated MBL low serum level as a risk factor for chronic necrotizing pulmonary aspergillosis (Crosdale *et al*., 2001). The MBL deficiency found to have an important influence on the febrile neutropenic episodes in children with malignancy (Neth *et al*., 2001). A study by Kakkanaiah *et al*. (1998) demonstrated that, as in children, low concentration of serum MBL can be associated with recurrent extracellular infections in adults and was consistent with a lifelong increased risk of infections in some patients with low levels or an absence of serum MBL. In studies, about MBL genotypes and risk of invasive pneumococcal disease, homozygote for MBL codon variants, could be at substantially increased risk of invasive pneumococcal disease (Roy *et al*., 2002), more new investigations confirmed the role of MBL deficiency with sever and lifelong risk of extracellular pathogens (Summerfield *et al*., 1995; Koch *et al*., 2001). Studies on role of MBL deficiency and recurrent volvovaginial candidiasis revealed possession of a polymorphism in codon 54 of the MBL gene were determined in 42 women with recurrent volvovaginial candidiasis (RVVC), this study showed reduced vaginal MBL levels accompanied with increased occurrence of RVVC in women (Babula *et al*., 2003).

Overall, in extracellular pathogens MBL deficiency confer a lifelong risk of infection (Summerfield *et al*.,

1995). The MBL act as a complement activator to kill gram-negative organisms directly via the membrane attack complex or to enhance, complement mediated phagocytosis through the increased deposition of opsonic C3 fragments (Jack *et al*., 2001a), the boundary lectin is capable of initiating opsonophagocytosis and bacterial lysis (Hartshorn *et al*., 1993). Therefore, low level production haplotypes have defects in their opsonic orders and phagocytosis of pathogens.

MBL IN AUTOIMMUNE DISEASES

As an autoimmune disease we investigated Systemic Lupus Erythematosus (SLE), this disease is a prototypical autoimmune disease characterized by the production of autoantibodies and the deposition of immune complexes in effected end organs (Sullivan *et al*., 2003; Kelsoe, 2003). There is an implied loss of both B-cell and T-cell tolerance. Several genetic factors such as hereditary complement deficiencies contribute to disease susceptibility and inherited homozygous deficiencies of C1, C2 and C4 have been reported to be associated with a high incidence of systemic lupus erythematosus (Lachmann *et al*., 1991; Walport, 1993). Among patients with systemic lupus erythematosus, there is a slightly increased frequency of variant MBL alleles resulting in lower circulating levels of the protein (Davies *et al*., 1995). Our study in MBL gene polymorphisms and susceptibility to renal dysfunction in systemic lupus erythematosus patients showed that presence of Lx haplotype which cause to low concentration of MBL can be determined as a risk factor for renal failure in these patients (Asgharzadeh *et al*., 2007c; Asgharzadeh *et al*., 2008), other previous studies have been reported low serum MBL levels associated with systemic lupus erythematosus (Ip *et al*., 1998; Senaldi *et al*., 1995). As MBL is an acute phase protein, such serum level measuring results may be difficult to interpret and genetic studies maybe more informative.

Garred *et al*. (1999) studied relation of MBL polymorphism and susceptibility to infections in systemic lupus erythematosus and found hemozygosity for MBL variants was strongly associated with infections in these patients. Senaldi *et al*. (1995) in an investigation demonstrated the association of codon 54 mutation (allele B) and systemic lupus erythematosus. Ip *et al*. (1998) have been showed the low producing promoter polymorphisms of the MBL gene were associated with systemic lupus erythematosus. Because MBL plays an important role in the clearance of immune complexes, this can be concluded that low levels of protein might be a slight risk factor for systemic lupus erythematosus (Davies *et al*., 1995).

In rheumatoid arthritis, MBL can be detected in the synovial fluid of these patients, where it may contribute to the inflammatory process by binding to agalactosyl antibodies and triggering complement activation (Malhotra *et al*., 1995). Graudal *et al*. (2000) studied association of variant MBL genotypes with radiographic outcome in rheumatoid arthritis, they found MBL genotypes giving rise to its insufficient level in serum are a highly significant risk factor for fast progression of radiographic joint destruction. New investigations showed patients with severe athrosclerosis had a reduced frequency of the MBLA allele and increased frequency of the B, C and D alleles compared with apparently healthy controls (Madsen *et al*., 1998; Hegele *et al*., 1999).

New investigations revealed relation of MBL gene polymorphism with more diseases. In a study in patients with glomerulonephritis, MBL showed as a risk factor for this disease (Lhotta *et al*., 1999), also another study revealed the role of MBL deficiency and glomerular immune deposition in IgA nephropathy (Gong *et al*., 2001).

CONCLUSION

Our observations in gene and promoter polymorphism in extracellular and intracellular pathogens and autoimmune diseases showed some differences, in hepatitis C virus infection, occurrence of the codon 54 mutation (allele B) of MBL was associated with the occurrence of the acute hepatitis C, this was a viral model and because of first line immunity role of MBL in viral infections, low MBL level can intense progress of infection, but in other intracellular infections low expression MBL genotypes associated with protection against these infections and wild type alleles with high MBL production considered as a risk factor for these intracellular pathogens.

In extracellular pathogens there was contrary and wild types of genotype with high production of MBL were associated with protection against these infections and alleles with low MBL production considered as a risk factor for these pathogens.

In autoimmune diseases our study and other studies demonstrated that low MBL was a risk factor for these diseases. These studies showed the importance and different roles of MBL in immunity against pathogens and diseases but more investigations are needed for revealing the exact role and mechanism of MBL interaction in these diseases, especially in autoimmune diseases.

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