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Feature Article

The Role of Mannose-Binding Lectin in Health and Disease

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Abstract Mannose-binding lectin (MBL) is an important constituent of the innate immune defence system. The protein binds to the sugars decorating many microbial surfaces and subsequently activates the complement system through a specific protease called MASP-2. A comparison of the importance of the capsule and lipopolysaccharide (LPS) structures of selected Gram-negative organisms for the binding of MBL suggests that the LPS structure is of primary importance. For several clinically relevant organisms MBL binding leads to activation of C4 suggesting that this is a major pathway for oposonophagocytosis. MBL deficiency mainly results from three mutations in exon 1 of the gene and is associated with both increased susceptibility to infections and autoimmune disease. Recent evidence indicates that the protein also modulates disease severity, possibly through a dose dependent influence on cytokine production.

Key words Complement activation; Innate immune defence; Mannose-binding lectin

Introduction

MBL (mannose-binding lectin, also referred to as mannan-binding lectin and mannose-binding protein) belongs to a family of proteins called the collectins[1] in which lectin (carbohydrate recognition) domains are found in association with collagenous structures. In man, three such proteins are recognised, namely MBL, lung surfactant protein A (SP-A) and lung surfactant protein D (SP-D). Each of these proteins is believed to be of importance in innate immune defence but MBL is of particular interest because it is able to activate the complement system.

MBL Structure

MBL has a bouquet-like structure similar to C1q. However, various oligomeric structures have been visualised (dimers, trimers, tetramers, hexamers), and full functional activity, including both binding to microbial surfaces and the activation of complement, requires higher order structures such as tetramers.[2]

All higher order oligomers of MBL are based on subunits which comprise three identical peptide chains of 32 kDa (see Figure 1). Each chain is characterised by a lectin domain, a coiled-coil hydrophobic neck region, a collagenous region and, a cysteine-rich N-terminal region.[3,4] Three such chains interact to give a classical collagenous triple helix.[5]

MBL is a calcium-dependent (or C-type) lectin that makes co-ordination bonds with the 3- and 4-hydroxyl groups of various sugars, including N-acetyl-D-glucosamine, mannose, N-acetyl-mannosamine, fucose and glucose.[6]

The repeating arrays or patterns of sugar groups decorating microbial surfaces make appropriate targets for MBL binding since the three sugar binding sites of one subunit array offer a flat platform with a constant distance between the sites (45 Å for human MBL).[7] Such simultaneous multiple binding is critical because the Kd of each separate MBL-sugar interaction is relatively low (10^{-3} M).[8] All of these features facilitate interactions with non-self microbial surfaces but make self recognition less likely.

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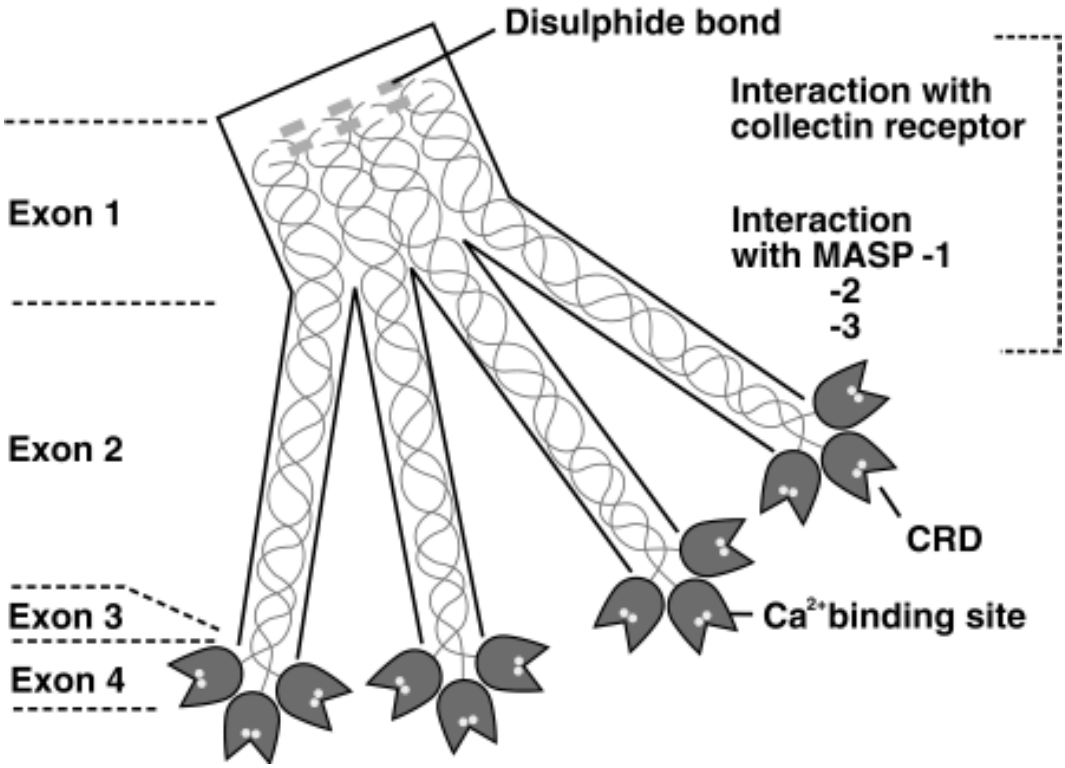

Figure 1 Structure of tetrameric human mannose-binding lectin (MBL). In each of the four subunits shown there are three identical 32 kDa peptide chains associated to give a collagenous triple helix and a cluster of three lectin domains. The four subunits are linked by disulphide bridges in the N-terminal region. The protein regions encoded by the four exons of the human MBL gene are indicated on the left.

MBL Function

The activation of complement by MBL represents a third pathway independent of both the classical and alternative pathways, but with similarities to the classical pathway. In the circulation MBL is found in association with four structurally related proteins. These are the MBL-associated serine proteases (MASP)-1, 2 and 3[9-11] and a truncated version of MASP-2 called MAp 19.[12,13] In serum there is a 20-fold excess of MASP-1 over MBL,[14] but MASP-2, which is present at much lower concentrations, appears to be the more important in complement activation.[10] The available evidence suggests that MBL-MASP-2 complexes become activated when bound to appropriate sugar arrays on microbial surfaces.[15] The enzyme activity expressed by the MASP-2 is apparently identical to that of Cl esterase and results in the sequential cleavage of C4 and C2. The C4b fragments generated bind covalently to the microbial surface and act as a focus for C2 binding/activation. The resultant C4b2a complex has C3 convertase activity and cleaves C3 in a similar manner to the C3 convertases of both the classical and alternative pathways of complement activation (see Figure 2).

There is also evidence to suggest that MBL is able to interact directly with cell surface receptors and promote opsonophagocytosis and other immune processes (Figure 2). A number of putative MBL-binding proteins/receptors have been proposed, including cClqR/calreticulin,[16] $ClqR_p$[17] and CR1.[18,19] However, it is unclear whether MBL is acting as a direct opsonin for microorganisms[20] or enhancing well established pathways of complement and/or immunoglobulin receptor-mediated phagocytosis.[21]

MBL Genetics and Polymorphisms

The human collectin genes are clustered on chromosome 10 in the region 10q 21-24.[22] There is a single functional MBL gene comprising four exons (see Figure 3). Exon 1 encodes the signal peptide, a cysteine rich-region and part

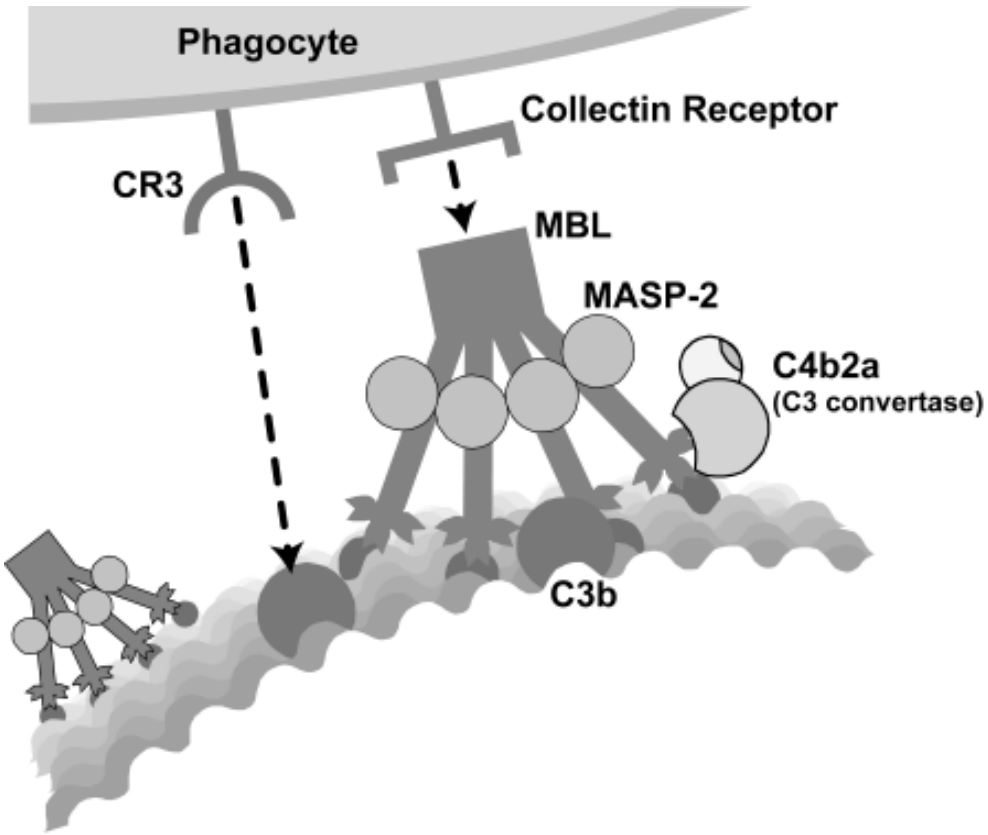

Figure 2 Biological functions of MBL. MBL is a multifunctional molecule which mimics many of the characteristics of antibodies. When the protein, with its associated MASP-2, binds to sugar groups on microbial surfaces the MASP-2 becomes activated and is able to cleave sequentially C4 and C2, thereby generating a C3 convertase enzyme. Subsequent cleavage of C3 molecules creates C3b opsonic fragments which become covalently bound to the microbial surface. Phagocytic cells are able to interact with the C3b through CR3 (and CR4) receptors whilst a poorly defined collectin receptor is believed to bind directly to the MBL collagenous region.

of the glycine-rich collagen-like region. Exon 2 encodes the remainder of the collagenous region, whilst exon 3 encodes for the "neck" region with an α-helical coiled-coil structure. The fourth exon encodes the C-terminal lectin domain. Upstream of the MBL gene are a number of regulatory, promoter elements which are believed to enhance MBL transcription during the acute-phase response.[3,4]

MBL deficiency is one of the most common immunodeficiencies. Three single point gene mutations in codons 52, 54 and 57 of exon 1 of the MBL gene have been described[23] and are referred to as the D, B and C variants, with A indicating wild type. The B variant mutation occurs in approximately 26% of Caucasians and 22% of the southern Chinese whereas the C variant mutation is characteristic of sub-Saharan African populations in whom it may reach frequencies of 50-60%. The frequencies of the B, C and D variant alleles in selected populations are shown in Table 1. Both the B and C mutations result in the substitution of a dicarboxylic acid for an axial glycine and it is believed that this impairs correct oligomerisation.[24] In addition to the above structural gene mutations, several polymorphisms exist within the promoter region of the MBL gene. These polymorphisms, which were identified by Madsen et al.,[25] are the H/L, X/Y and P/Q loci at positions -550, -221 and +4 of the MBL gene. Four promoter haplotypes (LXP, LYP, LYQ and HYP) are commonly found and of these the HYP haplotype is associated with

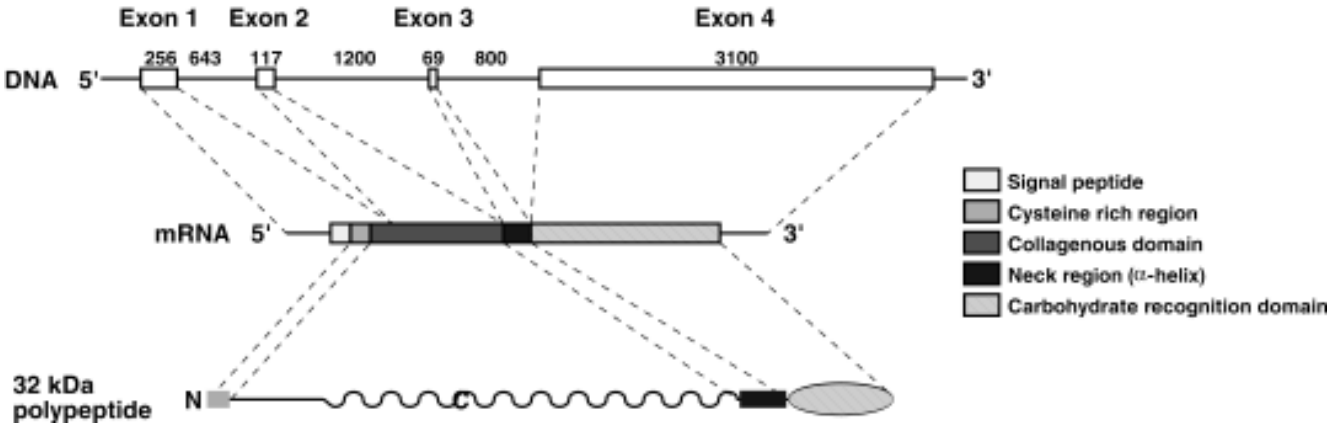

Figure 3 Structure of the human MBL gene with the corresponding mRNA and protein domains. The lengths of the four exons and three introns are indicated by the number of base pairs at the top of the figure. The mRNA encodes for the various protein domains shown at the bottom of the figure.

Table 1 Frequencies in selected populations of three structural gene mutations in exon 1 of the human MBL gene

	Observed frequency		
Population	**B allele**	**C allele**	**D allele**
Hong Kong Chinese	0.11	0.00	0.01
UK	0.14	0.02	0.07
Mid-West USA	0.12	0.01	0.07
Gambia	0.00	0.29	0.02
Indigenous Australians	0.00	0.00	0.00

Data from Turner et al. (2000),[27] Babovic-Vuksanovich et al. (1999),[61] Mead et al. (1997)[62], Lipscombe et al. (1996)[63]

high MBL levels whereas the LXP haplotype is found in association with low levels of the protein.[26] In approximately 12% of the Caucasian population the combined effects of the exon 1 mutations and the LXP promoter polymorphisms result in profoundly reduced MBL levels (< 500 ng/ml).

The three structural gene mutations are in linkage disequilibrium with the promoter polymorphisms and every individual expresses two of the following seven possible haplotypes – HYPA, LYQA, LYPA, LXPA, LYPB, LYQC and HYPD. The frequencies of these haplotypes differ markedly between different population groups [25] (see Figure 4). Our original observations on the distribution of the B and C alleles in African and non-African populations led us to suggest that the two mutations had probably arisen independently after the migration of hominids out of Africa some l00,000-150,000 years ago.[24] A later study of indigenous Australian populations showed that none of the three structural gene mutations was introduced into Australia at the time of first settlement (50,000 years ago)[27] whereas the B mutation was introduced into North America at the time of the last glaciation (~20,000 years ago). This suggests that the B mutation may have arisen 20,000-50,000 years ago on the LYP background.[27]

MBL Binding to Microorganisms

MBL deficiency has been implicated in susceptibility to viral, bacterial, fungal and protozoal infections.[28-32] We have developed a simple flow cytometric method for measuring MBL attachment to microorganisms and have used this procedure to survey a variety of microbial groups and some individual pathogens.

We have studied MBL binding to a range of clinically relevant pathogens isolated from immunocompromised children and found large differences.[33] Some organisms such as *Candida albicans, β-haemolytic Group A Streptococci* and *Staphylococcus aureus* consistently

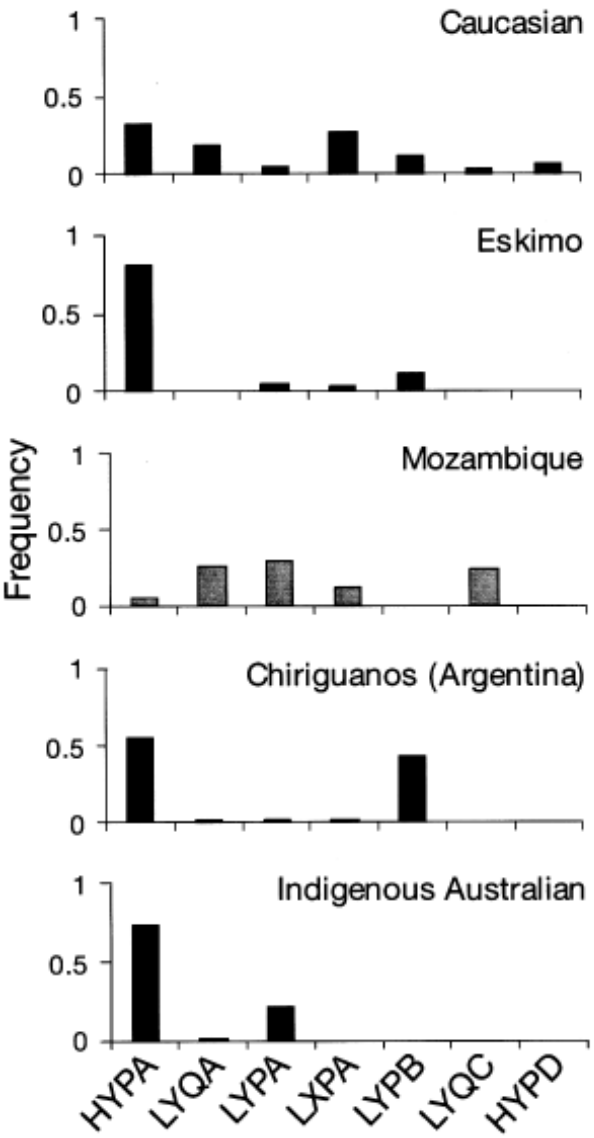

Figure 4 MBL haplotype frequencies in selected populations. Four promoter haplotypes are characteristic of A variant (wild type) exon 1 sequences ie HYPA, LYQA, LYPA and LXPA. The three exon 1 mutations (B, C and D alleles) are each in linkage disequilibrium with a different promoter haplotype (LYPB, LYQC and HYPD). There is, to date, no published data for any Chinese population but the frequency profile may be similar to that of the Caucasian population but with lower frequencies of LYPB, LYQC and HYPD.

exhibited high binding whereas others such as Clostridium sp., *Pseudomonas aeruginosa Staphylococcus epidermidis, β-haemolytic Streptococcus Group B* and *Streptococcus pneumoniae* apparently did not bind the protein. Between these extremes we observed other organisms with more variable patterns of binding e.g. *Klebsiella species* and *Escherichia coli*. Such heterogeneity has prompted us to explore in more detail the determinants of MBL binding to bacteria.

We have studied the effect of LPS structure on MBL attachment to both *Salmonella enterica* serovar Typhimurium[34] and the human pathogen *Neisseria gonorrhoeae*[34] and *N. meningitidis* (serogroups B and C).[35,36] In particular, we have examined the relative importance of LPS structure and capsule in determining MBL binding to the serogroup B meningococcus.

We found that the absence of sialic acid from the LOS of *Neisseria meningitidis* serogroup B,[35] serogroup C[36] and *Neisseria gonorrhoeae*[34] allowed MBL to bind to each of these organisms. MBL appeared to bind very poorly, or not at all, to organisms with sialylated LOS. In the case of Salmonella species, organisms of the rough chemotype (not expressing the O-antigen) showed MBL binding whereas organisms having the smooth chemotype and expressing the O-antigen exhibited little or no MBL binding.[34] The results obtained lead us to conclude that LPS structure exerts a major influence on MBL attachment to bacteria.

MBL-disease Associations

Initially, the immunological significance of MBL was established in studies of children with MBL deficiency,[37] but there are now numerous studies indicating a role for the lectin in later life and supporting the notion that it should be considered as an ante-antibody, a humoral factor playing a critical role in first line defence before the production of antibodies.[38]

Increasingly there is evidence that the role of MBL in disease is a complex issue. At present it is convenient to consider the topic under the following separate headings: (a) MBL and disease susceptibility (b) MBL and disease severity and (c) inappropriate activation of the MBL-MASP pathway. These categories are summarised in Table 2.

Table 2 MBL - Disease Associations

MBL deficiency and increased susceptibility to disease:

- Infectious diseases (esp. extracellular pathogens)
- Autoimmune disease (e.g. SLE)

MBL deficiency and protection against disease:

- Infectious disease (e.g. intracellular parasites, e.g. Leishmania)

MBL and modulation of disease severity

- Infectious disease
  e.g. HIV
  Pulmonary disease in cystic fibrosis
  Hepatitis B and C in Asians
- Autoimmune disease
  e.g. Rheumatoid arthritis

Inappropriate activation of MBL-MASP pathway

- Lectin pathway activation in renal disease
  e.g. Lupus nephropathy
  Membranoproliferative glomerulonephritis
  Post-streptococcal glomerulonephritis
  Henoch-Schonlein Purpura Nephritis
- Lectin pathway activation on vascular endothelium following oxidative stress
  e.g. Myocardial reperfusion injury

MBL and Disease Susceptibility

Several studies have presented evidence that deficiency of MBL increases the generalised susceptibility of an individual to infectious disease[30,39] but a particularly striking association is that with acute respiratory tract infections during early childhood.[40] Many MBL deficient children benefit form the prophylatic use of antibiotics suggesting that many of the infections are bacterial. Other studies have identified an increased susceptibility to infection by specific pathogens in MBL-deficient individuals, including human immunodeficiency virus[28,41] *Plasmodium falciparum*,[31] *Cryptosporidium parvum*[32] and *N. meningitidis*.[29] However, there are some striking exceptions to these reports, and in the case of intracellular parasites (e.g. *Leishmania*) it seems that MBL deficiency may actually protect against disease. It is suggested that since such parasites use C3 opsonisation and C3 receptors to enter cells, any reduction in the complement-activating function of the host may help to reduce the probability of parasitisation. The most persuasive evidence to date of such a mechanism is a study of patients with visceral leishmaniasis in Brazil.[42] The median MBL level of these patients was significantly higher than that of healthy individuals and, as expected, MBL mutations were significantly more common in the healthy controls.

In addition to the above reports of associations with infectious disease, there have been numerous investigations focusing on possible associations between MBL deficiency and susceptibility to autoimmune disease. There is strong evidence of such an association in the case of systemic lupus erythematosus (SLE). Cohorts of British,[43] Hong Kong Chinese,[44] American Black[45] and Spanish[46] SLE patients have all shown evidence of an increased frequency of mutant MBL alleles or deficiency of the protein. These observations are similar to earlier work on components of the classical complement pathway and suggest that impaired mechanisms for removal of immune complexes may be the common underlying aetiological link.

MBL and Disease Severity

In addition to the studies showing that MBL deficiency influences susceptibility to disease there are several reports suggesting that the protein can also modulate disease severity. There have been several studies of Asian patients with hepatitis which strongly suggests that MBL may have a modulatory role in this disease. One investigation of 93 Japanese patients with chronic hepatitis C found that those patients responding poorly to interferon therapy had a significantly higher frequency of homozygosity for the B variant allele.[47] Subsequently, the same group found that both the LYPB haplotype and the low promoter LXPA haplotype were more common in the interferon resistant patients.[48] On the basis of these observations the authors suggested that determination of the MBL haplotype of patients with hepatitis C will help to identify those most likely to benefit from interferon treatment.

MBL levels and exon 1 mutations have also been investigated in a cohort of 190 Chinese patients who were chronic carriers of hepatitis B or C.[49] The authors found an increased frequency of the B variant allele in patients with symptomatic hepatitis B cirrhosis and in patients with spontaneous bacterial peritonitis (SBP). The authors suggested that the screening of Asian hepatitis B carriers for MBL variant alleles would identify those individuals at risk of developing symptomatic cirrhosis and spontaneous bacterial peritonitis. Moreover, it was argued that patients with symptomatic cirrhosis and the B variant allele should be offered prophylactic antibiotic therapy.

In the field of autoimmunity there is particularly persuasive evidence of a modulatory role for MBL. Recent

studies from two centres have indicated that MBL variant alleles are associated with both severity and early onset of disease in patients with rheumatoid arthritis.[50-53] The mechanism by which MBL exerts such effects is unclear but extrapolating from our recent studies on *Neisseria meningitidis*[54] we would suggest that one possible pathway is cytokine modulation. We found that when *N. meningitidis* was incubated with increasing concentrations of MBL and added to whole blood the release of the cytokines TNF-α, IL-1β and IL-6 from monocytes was enhanced at lower MBL concentrations (<4 μg/ml) but reduced at higher concentrations (>4 μg/ml).

Inappropriate Activation of the Lectin Pathway

Pathology associated with unregulated or inappropriate activation of the classical/alternative pathways of complement is well documented and it is to be expected that similar reports involving the MBL-MASP pathway will appear. To date these fall into two areas, namely renal disease and reperfusion injury.

Endo and colleagues concluded that MBL-MASP activation contributed to the glomerular damage observed in a significant number of patients with IgA nephropathy.[55] However, in another study of renal biopsies from several patients with different forms of glomerulonephitis Lhotta and co-workers concluded that the MBL deposition observed was of minor importance.[56] Subsequent studies have described MBL deposition in the glomeruli of a patient with post-streptococcal glomerulonephritis[57] and in ten patients with Henoch-Schonlein Purpura Nephritis.[58] Further work is required to evaluate the role of the MBL-MASP system in these disorders.

In a recent report MBL depletion and anti-human MBL monoclonal antibodies were used to establish a role for the MBL-MASP pathway in initiating the complement activation which occurs following hypoxia-reoxygenation of human endothelial cells.[59] In a follow up study from the same group the MBL-MASP pathway was shown to be activated in rats following myocardial ischaemia-reperfusion suggesting that it is implicated in the subsequent tissue injury.[60] Blockade of the lectin pathway with inhibitory monoclonal antibodies protected the heart from ischaemia-reperfusion, and may represent a promising therapeutic approach for this common surgical complication.

Conclusions

MBL is one of several pattern recognition molecules involved in innate immune defence. Like IgG and IgM of the adaptive immune system the major effector function of MBL is complement activation. Whilst many clinically relevant organisms bind MBL, others avoid recognition by LOS sialylation e.g. *Neisseria*. In contrast, some intracellular parasites such as *Leishmania* may actively seek recognition in order to facilitate pathogenicity. Although MBL deficiency is associated with an increased susceptibility to infections involving extracellular pathogens, there is also increasing evidence of a role for MBL in modulating disease severity through pro-inflammatory cytokines. Further dissection of both these roles is required in a range of diseases.

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References

1. Holmskov U, Malhotra R, Sim RB, Jensenius JC. Collectins: collagenous C-type lectins of the innate immune defense system. Immunol Today 1994;15:67-74.
2. Yokota Y, Arai T, Kawasaki T. Oligomeric structures required for complement activation of serum mannan-binding proteins. J Biochem (Toyko) 1995;117:414-9.
3. Sastry K, Herman GA, Day L, et al. The human mannose-binding protein gene. Exon structure reveals its evolutionary relationship to a human pulmonary surfactant gene and localization to chromosome 10. J Exp Med 1989;170:1175-89.
4. Taylor ME, Brickell PM, Craig RK, Summerfield JA. Structure and evolutionary origin of the gene encoding a human serum mannose-binding protein. Biochem J 1989;262:763-71.
5. Weis WI, Drickamer K. Trimeric structure of a C-type mannose-binding protein. Structure 1994;2:1227-40.

6. Weis WI, Drickamer K, Hendrickson WA. Structure of a C-type mannose-binding protein complexed with an oligosaccharide. Nature 1992;360:127-34.
7. Sheriff S, Chang CY, Ezekowitz RA. Human mannose-binding protein carbohydrate recognition domain trimerizes through a triple alpha-helical coiled-coil. Nat Struct Biol 1994;1:789-94.
8. Iobst ST, Wormald MR, Weis WI, Dwek RA, Drickamer K. Binding of sugar ligands to Ca(2+)-dependent animal lectins. I. Analysis of mannose binding by site-directed mutagenesis and NMR. J Biol Chem 1994;269:15505-11.
9. Matsushita M, Fujita T. Activation of the classical complement pathway by mannose- binding protein in association with a novel C1s-like serine protease. J Exp Med 1992;176:1497-502.
10. Thiel S, Vorup-Jensen T, Stover CM, et al. A second serine protease associated with mannan-binding lectin that activates complement. Nature 1997;386:506-10.
11. Dahl MR, Thiel S, Willis AC, et al. Mannan-binding lectin associated serine protease 3 (MASP-3) – A new component of the lectin pathway of complement activation. Immunopharm 2000;49:79-79.
12. Stover CM, Thiel S, Thelen M, et al. Two constituents of the initiation complex of the mannan-binding lectin activation pathway of complement are encoded by a single structural gene. J Immunol 1999;162:3481-90.
13. Takahashi M, Endo Y, Fujita T, Matsushita M. A truncated form of mannose-binding lectin-associated serine protease (MASP)-2 expressed by alternative polyadenylation is a component of the lectin complement pathway. Int Immunol 1999;11:859-63.
14. Terai I, Kobayashi K, Matsushita M, Fujita T. Human serum mannose-binding lectin (MBL)-associated serine protease-1 (MASP-1): determination of levels in body fluids and identification of two forms in serum. Clin Exp Immunol 1997; 110:317-23.
15. Thiel S, Petersen SV, Vorup-Jensen T, et al. Interaction of C1q and mannan-binding lectin (MBL) with C1r, C1s, MBL-associated serine proteases 1 and 2, and the MBL-associated protein MAp19. J Immunol 2000;165:878-87.
16. Malhotra R, Thiel S, Reid KB, Sim RB. Human leukocyte C1q receptor binds other soluble proteins with collagen domains. J Exp Med 1990;172:955-9.
17. Tenner AJ, Robinson SL, Ezekowitz RA. Mannose binding protein (MBP) enhances mononuclear phagocyte function via a receptor that contains the 126,000 M(r) component of the C1q receptor. Immunity 1995;3:485-93.
18. Klickstein LB, Barbashov SF, Liu T, Jack RM, Nicholson-Weller A. Complement receptor type 1 (CR1, CD35) is a receptor for C1q. Immunity 1997;7:345-55.
19. Ghiran I, Barbashov SF, Klickstein LB, Tas SW, Jensenius JC, Nicholson-Weller A. Complement receptor 1/CD35 is a receptor for mannan-binding lectin. J Exp Med 2000;192:1797-807.
20. Kuhlman M, Joiner K, Ezekowitz RA. The human mannose-binding protein functions as an opsonin. J Exp Med 1989;169: 1733-45.
21. Kitz DJ, Stahl PD, Little JR. The effect of a mannose binding-protein on macrophage interactions with Candida albicans. Cell Mol Biol 1992;38:407-12.
22. Hansen S, Holmskov U. Structural aspects of collectins and receptors for collectins. Immunobiology 1998;199:165-89.
23. Turner MW. Mannose-binding lectin: the pluripotent molecule of the innate immune system. Immunol Today 1996;17:532-40.
24. Lipscombe RJ, Sumiya M, Hill AV, et al. High frequencies in African and non-African populations of independent mutations in the mannose binding protein gene. Hum Mol Genet 1992;1: 709-15.
25. Madsen HO, Garred P, Thiel S, et al. Interplay between promoter and structural gene variants control basal serum level of mannan-binding protein. J Immunol 1995;155:3013-20.
26 Madsen HO, Satz ML, Hogh B, Svejgaard A, Garred P. Different molecular events result in low protein levels of mannan-binding lectin in populations from southeast Africa and South America. J Immunol 1998;161:3169-75.
27. Turner MW, Dinan L, Heatley S, et al. Restricted polymorphism of the mannose-binding lectin gene of indigenous Australians. Hum Mol Genet 2000; 9:1481-6.
28. Garred P, Madsen HO, Balslev U, et al. Susceptibility to HIV infection and progression of AIDS in relation to variant alleles of mannose-binding lectin. Lancet 1997;349:236-40.
29. Hibberd ML, Sumiya M, Summerfield JA, Booy R, Levin M. Association of variants of the gene for mannose-binding lectin with susceptibility to meningococcal disease. Lancet 1999;353: 1049-53.
30. Summerfield JA, Sumiya M, Levin M, Turner MW. Association of mutations in mannose binding protein gene with childhood infection in consecutive hospital series. BMJ 1997;314:1229-32.
31. Luty AJ, Kun JF, Kremsner PG. Mannose-binding lectin plasma levels and gene polymorphisms in Plasmodium falciparum malaria. J Infect Dis 1998;178:1221-4.
32. Kelly P, Jack DL, Naeem A, et al. Mannose-binding lectin is a component of innate mucosal defense against Cryptosporidium parvum in AIDS. Gastroenterology 2000;119:1236-42.
33. Neth O, Jack DL, Dodds AW, Holzel H, Klein NJ, Turner MW. Mannose-binding lectin binds to a range of clinically relevant microorganisms and promotes complement deposition. Infect Immun 2000;68:688-93.
34. Devyatyarova-Johnson M, Rees IH, Robertson BD, Turner MW, Klein NJ, Jack DL. The lipopolysaccharide structures of Salmonella enterica serovar Typhimurium and Neisseria gonorrhoeae determine the attachment of human mannose-binding lectin to intact organisms. Infect Immun 2000;68:3894-9.
35. Jack DL, Dodds AW, Anwar N, et al. Activation of complement by mannose-binding lectin on isogenic mutants of Neisseria meningitidis serogroup B. J Immunol 1998;160:1346-53.
36. Jack DL, Jarvis GA, Booth CL, Turner MW, Klein NJ. Mannose-binding lectin accelerates complement activation and increases serum killing of Neisseria meningitidis serogroup C. J Infect Dis 2001;184:836-45.
37. Super M, Thiel S, Lu J, Levinsky RJ, Turner MW. Association of low levels of mannan-binding protein with a common defect of opsonisation. Lancet 1989;2:1236-9.
38. Ezekowitz RAB. Ante-antibody immunity. Curr Opin Immunol 1991;1:60-2.
39. Garred P, Madsen HO, Hofmann B, Svejgaard A. Increased frequency of homozygosity of abnormal mannan-binding-protein alleles in patients with suspected immunodeficiency. Lancet 1995;346:941-3.
40. Koch A, Melbye M, Sorensen P, et al. Acute respiratory tract infections and mannose-binding lectin insufficiency during early childhood. JAMA 2001;285:1316-21.
41. Nielsen SL, Andersen PL, Koch C, Jensenius JC, Thiel S. The level of the serum opsonin, mannan-binding protein in HIV-1

antibody-positive patients. Clin Exp Immunol 1995;100:219-22.
42. Santos IK, Costa CH, Krieger H, et al. Mannan-binding lectin enhances susceptibility to visceral leishmaniasis. Infect Immun 2001;69:5212-5.
43. Davies EJ, Snowden N, Hillarby MC, et al. Mannose-binding protein gene polymorphism in systemic lupus erythematosus. Arthritis Rheum 1995;38:110-4.
44. Lau YL, Lau CS, Chan SY, Karlberg J, Turner MW. Mannose-binding protein in Chinese patients with systemic lupus erythematosus. Arthritis Rheum 1996;39:706-8.
45. Sullivan KE, Wooten C, Goldman D, Petri M. Mannose-binding protein genetic polymorphisms in black patients with systemic lupus erythematosus. Arthritis Rheum 1996;39:2046-51.
46. Davies EJ, Teh LS, Ordi-Ros J, et al. A dysfunctional allele of the mannose binding protein gene associates with systemic lupus erythematosus in a Spanish population. J Rheumatol 1997;24: 485-8.
47. Matsushita M, Hijikata M, Ohta Y, et al. Hepatitis C virus infection and mutations of mannose-binding lectin gene MBL. Arch Virol 1998;143:645-51.
48. Matsushita M, Hijikata M, Matsushita M, Ohta Y, Mishiro S. Association of mannose-binding lectin gene haplotype LXPA and LYPB with interferon-resistant hepatitis C virus infection in Japanese patients. J Hepatol 1998;29:695-700.
49. Yuen MF, Lau CS, Lau YL, Wong WM, Cheng CC, Lai CL. Mannose binding lectin gene mutations are associated with progression of liver disease in chronic hepatitis B infection. Hepatology 1999;29:1248-51.
50. Garred P, Madsen HO, Marquart H, et al. Two edged role of mannose binding lectin in rheumatoid arthritis: a cross sectional study. J Rheumatol 2000;27:26-34.
51. Graudal NA, Homann C, Madsen HO, et al. Mannan binding lectin in rheumatoid arthritis. A longitudinal study. J Rheumatol 1998;25:629-35.
52. Graudal NA, Madsen HO, Tarp U, et al. The association of variant mannose-binding lectin genotypes with radiographic outcome in rheumatoid arthritis. Arthritis Rheum 2000;43:515-21.
53. Ip WK, Lau YL, Chan SY, et al. Mannose-binding lectin and rheumatoid arthritis in southern Chinese. Arthritis Rheum 2000; 43:1679-87.
54. Jack DL, Read RC, Tenner AJ, Frosch M, Turner MW, Klein NJ. Mannose-binding lectin regulates the inflammatory response of human professional phagocytes to Neisseria meningitidis serogroup B. J Infect Dis 2001;184:1152-62.
55. Endo M, Ohi H, Ohsawa I, Fujita T, Matsushita M, Fujita T. Glomerular deposition of mannose-binding lectin (MBL) indicates a novel mechanism of complement activation in IgA nephropathy. Nephrol Dial Transplantat 1998;13:1984-90.
56. Lhotta K, Wurzner R, Konig P. Glomerular deposition of mannose-binding lectin in human glomerulonephritis. Nephrol Dial Transplant 1999;14:881-6.
57. Ohsawa I, Ohi H, Endo M, Fujita T, Matsushita M, Fujita T. Evidence of lectin complement pathway activation in poststreptococcal glomerulonephritis. Kidney Int 1999;56: 1158-9.
58. Endo M, Ohi H, Ohsawa I, Fujita T, Matsushita M. Complement activation through the lectin pathway in patients with Henoch-Schonlein purpura nephritis. Am J Kidney Dis 2000;35: 401-7.
59. Collard CD, Vakeva A, Morrisey MA, et al. Complement activation after oxidative stress: role of the lectin complement pathway. Am J Pathol 2000;156:1549-56.
60. Jordan JE, Montalto MC, Stahl G. Inhibition of mannose-binding lectin reduces postischemic myocardial reperfusion injury. Circulation 2001;104:1413-8.
61. Babovic-Vuksanovic D, Snow K, Ten RM. Mannose-binding lectin (MBL) deficiency. Variant alleles in a midwestern population of the United States. Ann Allergy Asthma Immunol 1999;82:134-43.
62. Mead R, Jack D, Pembrey M, Tyfield L, Turner M. Mannose-binding lectin alleles in a prospectively recruited UK population. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. Lancet 1997;349:1669-70.
63. Lipscombe RJ, Beatty DW, Ganczakowski M, et al. Mutations in the human mannose-binding protein gene: frequencies in several population groups. Eur J Hum Genet 1996;4:13-9.