Impact of Mannose-Binding Lectin on Susceptibility to Infectious Diseases

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When the adaptive immune response is either immature or compromised, the innate immune system constitutes the principle defense against infection. Mannose-binding lectin (MBL) is a C-type serum lectin that plays a central role in the innate immune response. MBL binds microbial surface carbohydrates and mediates opsonophagocytosis directly and by activation of the lectin complement pathway. A wide variety of clinical isolates of bacteria, fungi, viruses, and parasites are bound by MBL. Three polymorphisms in the structural gene \(^1\)MBL2\(^1\) and 2 promoter gene polymorphisms are commonly found that result in production of low serum levels of MBL. Clinical studies have shown that MBL insufficiency is associated with bacterial infection in patients with neutropenia and meningococcal sepsis. Low MBL levels appear to predispose persons to HIV infection. Numerous other potential infectious disease associations have been described. Therapy to supplement low MBL levels is being explored using either plasma-derived or recombinant material.

Five hundred fifty million years ago, key elements of the innate immune system, including mannose-binding lectin (MBL), were developing in early invertebrates, such as tunicates, sponges, and sea urchins \([1]\). In humans, innate immune system recognition depends on detection of repeating patterns of common molecules, such as lipopolysaccharide, mannans, glycans and double-stranded RNA, which are displayed by a wide range of pathogens but not by self. Innate immune system cells and proteins must then demonstrate rapid response kinetics to effect the elimination of the pathogen \([2]\). The modern, adaptive immune system, which synthesizes a highly specific and sophisticated response to invading pathogens, did not begin to emerge until 90 million years later, in the primitive ancestors of vertebrates, which were the ectothermic, cartilaginous sharks, skates, and rays \([3]\). Comparative immunologists believe that the switch from a general-purpose, immediate effector response to the sophisticated, time-delayed, adaptive immune response was driven by the need to better discriminate self from infectious nonself in increasingly complex organisms \([2, 3]\). Nevertheless, whenever the modern, adaptive immune response is either immature or compromised, the elements of the innate immune system emerge into prominence as the principle defense against infection.

MBL is a central player in the innate immune response \([4]\). It is a C-type serum lectin produced by the liver, and it responds as an acute-phase reactant \([5]\). MBL binds microbial surface carbohydrates and mediates opsonophagocytosis directly and by activation of the lectin complement pathway. A wide variety of clinical isolates of bacteria, fungi, viruses, and parasites are bound by MBL \([6–9]\). MBL deficiency is common and appears to predispose to serious infection \([10]\).

In a recent Australian study involving 236 healthy blood donors, 30% were found to be heterozygous for structural gene mutations, and an additional 8% were homozygous or had double mutations of the structural genes \([11]\). Low serum levels of MBL are found in the presence of single nucleotide polymorphisms in the structural gene–coding region and with particular pro-
moter gene polymorphisms. Three polymorphisms in the structural gene MBL2, at codons 52, 54, and 57, encode for variant alleles referred to as D, B, and C, respectively; the wild-type gene is A [12–14]. Promoter gene polymorphisms at positions −550 and −221 of the 5′ flanking region of the MBL2 gene encode for alleles H/L and X/Y and influence the MBL level in individuals with wild-type genes and in individuals heterozygous for structural gene mutations [11]. The HYA haplotype produces high MBL levels, LYA produces intermediate levels, and LXA produces low levels [15]. When describing MBL2 structural gene variants, many studies and this review adopt the nomenclature A/A for individuals homozygous for the wild-type gene, A/O for heterozygotes, and O/O for homozygotes and compound heterozygotes. The terms “B haplotype” and “H haplotype” refer to individuals carrying, respectively, variant structural and promoter MBL alleles.

MBL genetics provides support for hypotheses about the initial migration of hominoids out of Africa [16]. The evolution from the original haplotype, which produced high MBL levels, to structural gene mutations and promoter gene variants may have been driven by advantages conferred by low MBL levels. Wild-type MBL2 genes providing abundant circulating MBL contribute to efficient opsonization of parasites and mycobacteria, which potentially enhances hematogenous spread and intracellular uptake of these organisms [17]—that is, individuals who have reduced MBL levels may be at an advantage, compared with those who have normal MBL and who are more susceptible to disease due to Mycobacterium tuberculosis. Moderately low levels of MBL conferred by a heterozygous MBL2 exon 1 structural gene mutation might mitigate excessive complement-mediated damage found in conditions with inflammation that causes tissue destruction, such as rheumatoid arthritis and meningococcemia [14]. Hypotheses explaining the selective advantage of MBL2 polymorphisms arose from population group studies describing a higher frequency of MBL structural gene mutations in geographic areas where mycobacterial infections are endemic. For example, the B allele has an observed frequency of 42%–46% in South American Chiriguano and Mapuches [18]; in Danish, American midwestern, and Greenland Eskimo population groups, the B allele frequency is 11%–13% [13, 17, 19]. The C allele is more common in sub-Saharan African populations than in white populations; it is 23%–29% in Gambians and Kenyans [13, 14, 16], compared with 6% in white populations [11]. The D allele is uncommon in all groups studied [13], and it is interesting to consider that individuals with A/D alleles have significantly higher MBL levels and function than do individuals with A/B and A/C alleles [11].

The primary 32-kDa subunit of MBL consists of an N-terminal cross-linking region, a collagen-like domain, and a C-terminal carbohydrate-recognition domain. These identical subunits combine to form an MBL structural unit stabilized by N-terminal disulphide bonds (figure 1) [10]. Oligomers of the structural units most efficiently activate the lectin comple-

Figure 1. Manose-binding lectin (MBL) subunit features and assembly into structural unit and high-order, functional MBL oligomers
Figure 2. Mannose-binding lectin (MBL) and MBL-associated serine protease 2 (MASP-2) forming a complex that binds to sugar groups on microbial structures. Complement activation through the lectin pathway is initiated by C4 deposition and results in C3b formation and damage to microorganisms.
ment pathway (figure 2). The structural gene polymorphisms described above are found in the collagenous domain and interfere with the formation of MBL oligomers. The resulting variant monomers have poor complement fixation capability and may have higher turnover (figure 3) [20].

Pediatric patients with infections [21] and with suspected immunodeficiency [22] have increased frequencies of MBL variant alleles. Adult patients with recurrent infections are also more likely to have insufficient MBL levels than are control patients [23]. This review describes the associations between MBL insufficiency and specific infectious diseases, comments on the pathophysiology of the association, and assesses the possibility of MBL replacement therapy.

MBL INSUFFICIENCY AND ASSOCIATIONS WITH INFECTIOUS DISEASES

Bacterial Infection

Severe infection associated with treatment of hematological malignancy. In patients who are immunosuppressed as a result of cytotoxic chemotherapy or myeloablative bone marrow transplantation conditioning regimens, innate immunodeficiency would be predicted to pose additional infective risks (tables 1 and 2). Bacteremia and pneumonia were significantly associated with decreased MBL levels (<500 μg/L) in chemotherapy-treated Danish hematology patients [42]. In English children with cancer (hematological malignancy, in most cases), an association between both A/O and O/O MBL alleles and the number of days, but not the number of episodes, of febrile neutropenia was noted. Children with wild-type genes had elevated MBL levels (which peaked on day 7) throughout the period of febrile neutropenia. By contrast, patients with variant MBL alleles had reduced levels of MBL throughout the febrile period [43]. Similar associations have been found in patients after allogeneic stem cell transplantation, with invasive bacte-

Figure 3. Variant alleles of mannose-binding lectin (MBL). Variant alleles of MBL have altered collagenous regions and only form nonfunctional, low-order oligomers.
In vitro observations of interactions between mannose-binding lectin (MBL) infective pathogens.

<table>
<thead>
<tr>
<th>Observation</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-level binding for <em>Staphylococcus aureus</em>, <em>Candida albicans</em>, <em>Aspergillus fumigatus</em>, and <em>Streptococcus pneumoniae</em>; moderate-level binding for <em>Escherichia coli</em>, <em>Haemophilus influenzae</em>, <em>Klebsiella species</em>, and <em>Cryptococcus neoformans</em>; and no binding for <em>Streptococcus pneumoniae</em>, <em>Enterococcus species</em>, and <em>Pseudomonas aeruginosa</em></td>
<td>[6, 24]</td>
</tr>
<tr>
<td>High-level binding for <em>Listeria monocytogenes</em> and nonencapsulated <em>Neisseria meningitidis</em>; intermediate-level binding for <em>S. pneumoniae</em></td>
<td>[9]</td>
</tr>
<tr>
<td>Binding to and killing by MBL is maximal in <em>N. meningitidis</em> serogroup C strains with nonsialylated lipooligosaccharides</td>
<td>[45]</td>
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<tr>
<td>MBL increases phagocytosis of <em>N. meningitidis</em> serogroup B isolates, with down-regulation of inflammatory cytokines</td>
<td>[37]</td>
</tr>
<tr>
<td>MBL binding to mannose homopolymers of gram-negative lipopolysaccharide-activating complement</td>
<td>[60]</td>
</tr>
<tr>
<td>MBL induces C4 deposition after binding to <em>S. aureus</em>, resulting in increased neutrophil phagocytosis</td>
<td>[8]</td>
</tr>
<tr>
<td>MBL binds to gp120 and HIV-infected cells, inhibiting reverse-transcriptase activity</td>
<td>[65]</td>
</tr>
<tr>
<td>MBL binds to gp120/gp41 of primary isolates of HIV</td>
<td>[66]</td>
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<tr>
<td>MBL opsonizes influenza A viruses and inhibits hemagglutinin activity</td>
<td>[59]</td>
</tr>
<tr>
<td>MBL/surfactant protein D chimera increased anti-hemagglutinin and opsonization effect against influenza A viruses</td>
<td>[24]</td>
</tr>
<tr>
<td>Increased binding of <em>C. neoformans</em> by PBMCs, neutrophils, and macrophages</td>
<td>[58]</td>
</tr>
<tr>
<td>MBL induces TNF release from PBMCs incubated with cryptococcal mannoprotein</td>
<td>[73]</td>
</tr>
<tr>
<td>Binding to unencapsulated <em>C. neoformans</em> induces TNF and GM-CSF, increasing phagocytosis of encapsulated <em>C. neoformans</em></td>
<td>[28]</td>
</tr>
<tr>
<td>MBL levels decreased in transgenic mice infected with <em>C. albicans</em>, then levels rebounded over the course of 72 h, indicating binding to organism; mannose-specific IgG levels increased later</td>
<td>[29]</td>
</tr>
<tr>
<td>MBL increased TNF production by <em>C. albicans</em>-stimulated monocytes</td>
<td>[30]</td>
</tr>
<tr>
<td>MBL bound <em>Plasmodium falciparum</em> glycoproteins but did not inhibit parasite growth in culture</td>
<td>[31]</td>
</tr>
</tbody>
</table>

**NOTE.** GM, granulocyte macrophage.
*a* MBL binding ratio on flow cytometry.
*b* Ratio of MBL binding compared with zymosan.

(median age, 16 years), which supports the theory that MBL has an important protective role in early childhood [39].

**Invasive pneumococcal infection and mycobacterial infection.** Studies of mice with complement pathway deficiencies have shown that the classical pathway is the most significant mediator of innate immunity against *Streptococcus pneumoniae* [47]. Available results of tests of in vitro binding of MBL to *S. pneumoniae* are conflicting: they indicate intermediate binding [9] or no binding [6]. A higher proportion of patients from Oxfordshire, England, with invasive pneumococcal infection were homozygous for MBL variant alleles (all possible combinations of MBL alleles) than were race-matched control subjects [48]. Using the same study design, a higher proportion of homozygotes (B/B, B/D, C/D, and D/D) was found among Danish patients than among control subjects; however, this was not statistically significant [49]. Neither study show an association between heterozygous MBL states and promoter polymorphisms. These 2 studies are highly comparable: they included only white subjects with invasive pneumococcal infection. Combination of the results confirms that this disease was strongly associated with the homozygous MBL variant state (OR, 2.56; 95% CI, 1.47–4.47; *P* < 0.0003). No association with heterozygous states was shown in this combined analysis.

Intracellular infections, including *M. tuberculosis* [50] and *Mycobacterium leprae* infection [40], occur more frequently in patients with increased MBL levels, potentially through complement-mediated enhancement of phagocytosis. In a study involving a black South African population, the B allele was associated with protection from tuberculous meningitis and pulmonary disease [41]. Similarly, in The Gambia, where the D variant allele is the most prevalent, patients with tuberculosis were found to be less likely to carry this mutant MBL gene [51].

**Summary.** There are multiple studies showing robust associations between MBL insufficiency and severe infection in patients undergoing chemotherapy. A single large cohort study has indicated a probable association between MBL insufficiency and meningococcal infection [25]. However, this finding is supported by extensive reports of biological interactions between MBL and *N. meningitidis*. There appears to be an association between pneumococcal pneumonia and MBL insufficiency that is strengthened when the 2 studies are considered together [48, 49]. Paradoxically, normal levels of MBL appear to predispose persons to severe tuberculosis, but this finding is potentially explained by increased opsonization and phagocytosis of this intracellular pathogen.
Table 2. Clinical associations between mannose-binding lectin (MBL) and malignancy-associated neutropenia, susceptibility to meningococcal infection, and invasive pneumococcal infection.

<table>
<thead>
<tr>
<th>Clinical event</th>
<th>Observation</th>
<th>OR</th>
<th>P</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignancy-associated neutropenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invasive bacterial infection after chemotherapy</td>
<td>MBL level of &lt;1000 μg/mL was associated with invasive infection</td>
<td>...</td>
<td>.0001</td>
<td>[42]</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>Median duration of episodes was 20.5 and 10.0 days for A/O\textsuperscript{a} and A/A\textsuperscript{b}, respectively</td>
<td>...</td>
<td>.014</td>
<td>[43]</td>
</tr>
<tr>
<td>Infection after allogeneic hematopoietic stem cell transplantation</td>
<td>Infective episodes increased among A/O recipients (76%), compared with A/A recipients (44%)</td>
<td>4.1</td>
<td>.002</td>
<td>[44]</td>
</tr>
<tr>
<td></td>
<td>Rate of infection was 41% when HYA promoter haplotype was present and 81% when it was absent</td>
<td>0.16</td>
<td>.0001</td>
<td>[44]</td>
</tr>
<tr>
<td>Susceptibility to meningococcal infection</td>
<td>In a hospital-based study, 7.7% of Q/O patients\textsuperscript{c} were susceptible to infection, compared with 1.5% of control subjects</td>
<td>6.5</td>
<td>.0006</td>
<td>[26]</td>
</tr>
<tr>
<td></td>
<td>In a community-based study, 8.3% of Q/O patients were susceptible to infection, compared with 2.7% of control subjects</td>
<td>4.5</td>
<td>.06</td>
<td>[26]</td>
</tr>
<tr>
<td>Invasive pneumococcal infection</td>
<td>12% of 229 patients were homozygous for MBL variants, compared with 5% of 353 controls</td>
<td>2.59</td>
<td>.002</td>
<td>[48]</td>
</tr>
<tr>
<td></td>
<td>7% of 140 patients were homozygous for MBL variants, compared with 3% of 250 controls</td>
<td>...</td>
<td>NS</td>
<td>[49]</td>
</tr>
</tbody>
</table>

**NOTE.** NS, not significant.
\textsuperscript{a} MBL variant allele heterozygote.
\textsuperscript{b} Wild-type MBL.
\textsuperscript{c} MBL variant allele homozygote, compound heterozygote.

Viral Infection

**HIV susceptibility and disease progression.** MBL binds to the gp120 surface glycoprotein of cell line-derived isolates [65] and primary isolates [66] of HIV and has been shown to inhibit HIV infection of human T cells in vitro (tables 1 and 3) [65]. It appears that MBL insufficiency predisposes to susceptibility to HIV infection, but data on its influence on disease progression are conflicting. A prospective cohort study of Danish HIV-infected adults revealed infection and disease susceptibility associations with MBL variant alleles and low serum levels. HIV-infected patients were more likely to be homozygous for variant alleles than were homosexuals who were healthy or who engaged in high-risk behavior. The presence of variant alleles in HIV-infected patients was associated with a reduced median duration of survival, and a low serum MBL level at the time of AIDS diagnosis predicted death, independent of the CD4 cell count [50]. African HIV-infected patients were similarly shown to have undetectable MBL more frequently than did control subjects [62]. In Italian children with perinatally acquired HIV infection, the H promoter allele (associated with high MBL levels) appeared to protect against HIV infection [27], although no difference in susceptibility to infection based on the MBL B allele was shown in HIV-positive or -negative children of HIV-positive mothers [67]. In the same study population, children who had rapidly progressing disease were more likely to have MBL B alleles [67], in addition to the HH promoter genotype that correlates with high MBL levels [27].

Neither of these studies [27, 67] reported MBL levels, and one of these studies [67] did not assess promoter haplotype. The L promoter phenotype (low MBL levels) protected against rapid progression [27]. The potential association between high MBL levels and rapid progression of HIV infection may be explained, as for *M. tuberculosis* infection, by complement-mediated enhancement of uptake of HIV by macrophages. MBL levels are higher in HIV-infected patients at all stages of HIV infection than in control subjects [50, 53], particularly in HIV-infected patients with wild-type MBL genes [50]. A prospective Dutch cohort study of HIV-infected adults showed more-rapid progression to AIDS in patients with MBL variant alleles, but this finding did not achieve statistical significance [52]. Other cohort studies have found no correlation between MBL insufficiency and progression to AIDS [54, 68] or incidence of opportunistic infection [54]. The lack of association with progression in at least 1 of these studies [54] may be explained by the short follow-up period (median duration of follow-up, 16 months).

**Chronic viral hepatitis associations.** Both MBL B [69] and D [70] alleles have been shown to be associated with chronic hepatitis B virus (HBV) infection. However, a German study failed to confirm an increase of either of these mutant alleles among HBV-infected patients [71]. The rate of survival after fulminant hepatic failure due to HBV infection among Japanese patients was reduced among those with the MBL B allele, and it was increased in the presence of the H promoter.
Table 3. Clinical associations between mannose-binding lectin (MBL) and viral, parasitic, and fungal infection.

<table>
<thead>
<tr>
<th>Clinical condition or outcome</th>
<th>Observation</th>
<th>P</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td>Susceptibility was 8% among HIV-infected O/O patients, vs. 0.8% among healthy control subjects and 0% among high-risk control subjects.</td>
<td>.005, .05</td>
<td>[50]</td>
</tr>
<tr>
<td></td>
<td>H promoter allele frequency was 0.48 among HIV-uninfected subjects who were perinatally exposed to HIV and 0.31 for HIV-infected patients.</td>
<td>.0214</td>
<td>[27]</td>
</tr>
<tr>
<td></td>
<td>MBL was undetectable in 12.1% HIV-infected patients, compared with 3.5% of HIV-uninfected subjects.</td>
<td>.009</td>
<td>[62]</td>
</tr>
<tr>
<td>Disease progression</td>
<td>Duration of survival for patients with variant alleles and those with wild-type alleles, 11 vs. 18 months.</td>
<td>.007</td>
<td>[50]</td>
</tr>
<tr>
<td></td>
<td>B variant alleles were present in 52% of children with rapidly progressing disease, compared with 18.5% of those with slow progression.</td>
<td>.011a</td>
<td>[67]</td>
</tr>
<tr>
<td></td>
<td>HH promoter allele (high MBL) was present in 23% of patients with rapidly progressing disease, compared with 5% of those with slow progression.</td>
<td>.0194</td>
<td>[27]</td>
</tr>
<tr>
<td>Chronic hepatitis B</td>
<td>D variant allele was present in 27% of white patients with hepatitis B and in 4% of healthy uninfected controls.</td>
<td>.0004</td>
<td>[70]</td>
</tr>
<tr>
<td></td>
<td>B variant allele was present in 44% of Chinese patients with cirrhosis and in 23% of healthy uninfected controls.</td>
<td>.007</td>
<td>[69]</td>
</tr>
<tr>
<td>Outcome of fulminant hepatic failure</td>
<td>B variant allele was present in 40% of nonsurvivors and in 13% of survivors.</td>
<td>.043</td>
<td>[56]</td>
</tr>
<tr>
<td></td>
<td>H promoter allele was present in 39.5% of nonsurvivors and in 70% of survivors.</td>
<td>.0005</td>
<td>[56]</td>
</tr>
<tr>
<td>Chronic hepatitis C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFN responsiveness</td>
<td>LX promoter or B variant allele was present in 60.7% of unresponsive patients and in 38.5% of responsive patients.</td>
<td>.008</td>
<td>[72]</td>
</tr>
<tr>
<td>Disease status</td>
<td>B variant allele was present in all patients with progressive disease and in 76% of those with wild-type MBL alleles.</td>
<td>.04</td>
<td>[55]</td>
</tr>
<tr>
<td>Herpes simplex virus–associated Mollaret meningitis</td>
<td>D variant allele was present in 20% of patients and in 6.8% of control subjects.</td>
<td>.04</td>
<td>[57]</td>
</tr>
<tr>
<td>Parasitic infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasmodium falciparum</td>
<td>B and C variant alleles were more common in patients from Gabon with severe malaria.</td>
<td>.04</td>
<td>[34]</td>
</tr>
<tr>
<td>Susceptibility to Cryptosporidium parvum infection</td>
<td>C variant allele was not associated with malaria in patients from The Gambia.</td>
<td>...</td>
<td>[51]</td>
</tr>
<tr>
<td>Fungal infection: chronic necrotizing pulmonary aspergillosis</td>
<td>MBL variant alleles were more common among HIV-infected patients.</td>
<td>.02</td>
<td>[64]</td>
</tr>
</tbody>
</table>

* Relative risk, 3.68.

** OR, 8.2.

haplotype. No MBL C or D alleles were found in this population [56]. Japanese patients with chronic, active hepatitis C virus (HCV) infection and cirrhosis were found to be more likely to have the MBL B allele than were patients with chronic, inactive HCV infection. That study used aminotransferase levels, which are notoriously inaccurate markers of the activity of chronic viral hepatitis, to distinguish between chronic, inactive HCV infection and chronic, active HCV infection [55]. IFN-non-responsive HCV was significantly associated with the presence of “low” promoter and MBL B allele mutations (the XB genotype) in Japanese patients. This association was independent of HCV genotype [72].

Other viral pathogens. Mollaret meningitis due to recurrent herpes simplex virus infection has been associated with the D type variant MBL allele [57]. No association with IFN-γ receptor polymorphisms was shown. MBL and other collectins bind to influenza A viruses (IAVs), inhibiting hemagglutinin activity and reducing their infectivity [59]. IAVs are also opsonized and phagocytosed by MBL. Chimeric forms of MBL and surfactant protein D have increased binding to IAVs [58].

**Summary.** Multiple studies have reported increased susceptibility to HIV infection in patients with MBL insufficiency or protection from HIV in those with high MBL levels. Conflicting results are available with regard to progression of HIV disease. Progression of chronic hepatitis B and C disease has been found to be associated with MBL insufficiency, particularly in studies involving Asian patients.

**Fungal Infection**

Mannan is a major component of fungal cell walls, and MBL binds with high avidity to Candida albicans and Aspergillus
**Proteozoon Parasitic Infection**

Hospitalized Gabonese children with severe malaria had more MBL structural gene mutations and more low-promoter haplotypes associated with significantly lower admission MBL levels, compared with children who had mild malaria (tables 1 and 3) [34]. As has been shown elsewhere [5], patients with wild-type MBL structural genes had high MBL levels during severe malaria. A larger study of children in The Gambia showed no overall increase in variant MBL alleles in patients with severe malaria. There was an increase in \( O/O \) patients (\( C/C \) and \( B/C \)) among those with cerebral malaria, but the increase was not statistically significant [51]. MBL was subsequently shown to bind \( Plasmodium falciparum \)-derived proteins, but it did not inhibit parasite growth [31]. MBL binds to sporozoites of \( Cryptosporidium parvum \) and activates complement. Among Zambian HIV-infected patients, those who were homozygous MBL structural gene mutations were significantly more likely to have cryptosporidiosis. (There was no association with isosporiasis or microsporidiosis.) MBL could be detected in intestinal aspirates from some of these patients, which was probably a result of increased small-bowel permeability [64]. The XX MBL promoter polymorphism is associated with resistance to filariasis [61]. Therefore, it may be that MBL insufficiency is associated with severe malaria, as was shown in one study, with a trend detected in another [34, 51].

**MBL Replacement Therapy**

Two MBL-deficient Icelandic patients have received infusions of plasma-derived MBL. One was an adult patient without recurrent infection; the other was a 2-year-old child who had 45 separate documented infections. Opsonic activity was restored, and the MBL infusions were well tolerated, with an estimated half-life of 5–7 days. No anti-MBL antibodies were formed. There was a dramatic reduction in the number of infective episodes in the child after receipt of 6 MBL infusions over 10 days. This may have been coincident with the natural history of resolution of her illness [35]. Another adult patient with cystic fibrosis received infusions of plasma-derived MBL on 30 occasions during a 3-month period, without side effects. In this patient, the infused MBL half-life was 2 days [63]. Recombinant MBL with correct folding and oligomerization has been produced in human embryonic kidney cells [75]. This recombinant MBL has the same molecular weight as native MBL, and it has replicated the C4 activation capability of native MBL.

**Conclusions**

An increasing body of data supports the importance of MBL as a component of the innate immune system. States of MBL deficiency are common and appear to predispose persons to a broad range of infectious diseases. Strong associations with severe bacterial infection in neutropenic patients and patients with meningococcal meningitis have been presented. Susceptibility to HIV infection, invasive fungal infection, and severe malaria may also be associated with MBL insufficiency, although data regarding its effect on progression of HIV infection are conflicting. The potential effect of MBL insufficiency is particularly well characterized in meningococcal disease, for which the most invasive strains of \( N. meningitidis \) are those with nonsialylated lipoooligosaccharides that are optimally bound by MBL. Similar evidence of MBL’s binding to surface glycoproteins of HIV and fungi explain the increased susceptibility to infection when MBL levels are low. Therapy to supplement low MBL levels using either plasma-derived or recombinant material is being explored. The potential uses for such a novel therapeutic agent appear great but require careful clinical study. Patients with hematological malignancies who have brief periods of chemotherapy-induced neutropenia would appear to be the most appropriate group to investigate first (for protection from a broad variety of infections), by supplementation with this pluripotent innate immune system member.
References

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