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EDITORIAL

Mannose-binding lectin and maladies of the bowel and liver

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Abstract

Mannose-binding lectin (MBL) is a pattern-recognition molecule that binds to characteristic carbohydrate motifs present on the surface of many different pathogens. MBL binding stimulates the immune system *via* the lectin pathway of complement activation. In certain clinical situations, often characterized by pre-existing immune compromise, MBL deficiency increases the risk of infectious and other disease-specific complications. Many of the key pathogenic processes inherent to common gastroenterological diseases, such as infection, immunological damage, and carcinogenesis, have been linked to MBL. This editorial reviews the biology of MBL, outlines key disease associations to document the breadth of influence of MBL, and finally, highlights the relevance of MBL to both gastroenterological health and disease.

Key words: Mannose-binding lectin; Collectins; Innate immunity; Polymorphism; Infection

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INTRODUCTION

Mannose-binding lectin (MBL) is an important component of the innate immune system. MBL is primarily produced by the liver, circulates throughout the body, and is able to recognize a wide array of common pathogens through repeating carbohydrate sequences present on microbial surfaces. MBL binding of pathogens initiates complement activation via the lectin pathway. There have been a large number of studies addressing the influence of MBL deficiency on infection, autoimmunity, and carcinogenesis, all critical processes in the pathogenesis of gastrointestinal disease. Genetically determined MBL deficiency increases the risk and manifestations of a wide range of diseases, particularly when the immune system is already compromised. This editorial provides an introduction to the structure, function and regulation of MBL and explores its clinical relevance, placing it in the context of common medical and, in particular, gastrointestinal conditions.

THE BIOLOGY OF MANNOSE-BINDING LECTIN

The MBL2 Gene

The capacity of MBL to recognize and eradicate pathogens is extremely variable. Within any given population there are individuals that have varying functional levels of circulating MBL. The relative sufficiency of MBL function for any given individual is largely determined by polymorphisms within the *MBL2* gene, on chromosome 10. Three missense mutations within the first exon of *MBL2* significantly effect MBL function (codon 54 '*B*', codon 57 '*C*', and codon 52 '*D*') (Figure 1). These coding mutations are collectively designated '*O*', and the wild-type, sufficient allele is represented by '*A*'. An Australian study of healthy blood donors found that the prevalence of *MBL2* wild-type coding genotype *A/A* was 57.6%, coding mutation heterozygosity *(A/O)* was 34.8% (*A/D* 11%, *A/B* 19.9%, *A/C* 3.8%), and coding mutation homozygosity *(O/O)* was 7.6% (*B/B* 2.1%, *B/C* 2.1%, *B/D* 2.5%, *D/D* 0.9%)[1]. These frequencies are consistent with other Caucasoid populations[2-4]. In Asian communities, the most common mutation is also the *'B'* allele, but the '*D*' allele is virtually absent[5].

Further variability of MBL function is due, at least in part, to other polymorphisms within the promoter (position -550, G to C substitution, alleles '*H*' and '*L*' and position -221, G to C substitution, alleles '*X*' and '*Y*'); and 5'-untranslated (position +4, C to T, alleles '*P*' and '*Q*') regions of the gene (Figure 1). When inherited in the context of a normal coding allele (*A*), the promoter region haplotypes

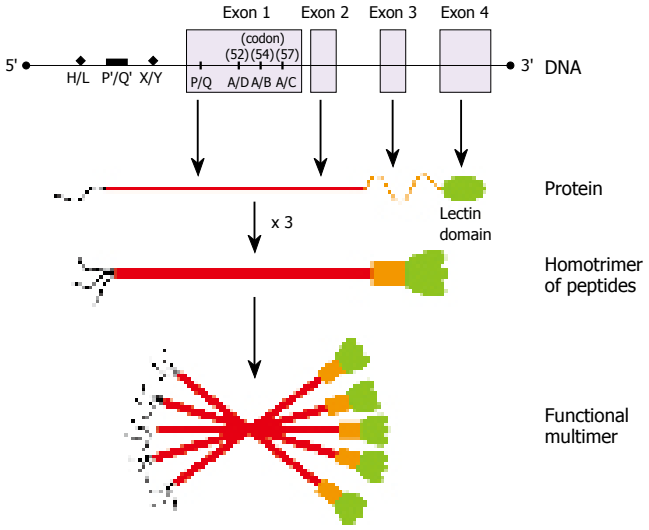

Figure 1 Schematic representation of the four exons of the *MBL2* gene, with the important polymorphisms identified. The peptides self associates into a homotrimer (structural subunit). Each peptide contains a lectin domain (green) to bind the specific, microbial carbohydrate motifs. Functional MBL circulates in higher-order multimers.

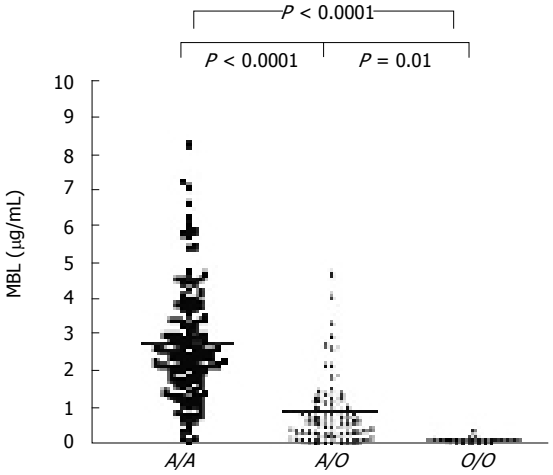

Figure 2 Distribution of plasma MBL levels within a normal population, stratified by *MBL2* genotype (Figure reproduced from Worthley *et al*[82] with permission). The *O/O* genotype is associated with the most extreme deficit in circulating MBL level (shown) and activity.

HY, *LY*, and *LX* are associated with high, intermediate, and low serum MBL concentrations, respectively. The genotypes *O/O, A/O* and *LXA/LXA*, are all associated with low antigenic and functional levels of MBL (compared to *A/A*). The *O/O* genotype is correlated with the most extreme MBL deficit (Figure 2). Low levels of MBL associated with the common polymorphic variants appear to result from impaired oligomerization of the MBL triple helix (see below) into functional higher order multimers[6], as well as increased susceptibility to degradation by metalloproteinases[7].

The MBL Protein

The basic structural subunit of MBL is a homotrimer of MBL peptides, entwined in a triple helix (Figure 1). Each peptide contains a lectin domain to bind the specific oligosaccharide motifs present on the surface of many different microorganisms[8]. Functional MBL circulates as a higher-order multimer (tetramers, pentamers and hexamers) of the basic MBL subunit. This oligomerization allows high-affinity interaction between MBL and the microorganism. Binding of MBL to pathogens causes a conformational change in the MBL multimer, and activation of associated molecules, the MBL-associated serine proteases (MASPs), that initiate the lectin-complement pathway.

The lectin-complement pathway

The enzymatic cascade of complement activation is a vital aspect of innate immunity. Complement-derived opsonization also provides an effective means of articulation with adaptive immunity through subsequent phagocytosis and antigen processing. The classical complement pathway is initiated by the binding of the C1 complex (C1q, r and s) to bound antibody on pathogen surfaces and the alternative pathway by binding of C3b to hydroxyl or amino groups on cell-surface molecules, as a result of spontaneous C3 turnover[9]. The lectin-complement pathway is the third arm of complement activation. Higher order MBL multimers circulate in a functional complex with three serine proteases MASP-1, MASP-2, MASP-3 and one non-protease molecule, MAp19[8]. This complex is analogous to the C1 complex that initiates the classical complement pathway, except that MBL binds to pathogens independently of antibody. Once activated, MASP-2, like its classical-pathway counterpart C1s, cleaves C4 to C4b, producing C4b2a, the C3 convertase. Subsequent production of C3b, also a key opsonin, generates the C5 convertase, which in turn produces the chemoattractant C5a, and, through C5b, the formation of the membrane-attack complex, C5b-C9 (Figure 3).

Recently, an additional mechanism of lectin-mediated complement activation, which bypasses the classical pathway proteins, has been described. Selander *et al*[10] demonstrated that an MBL-dependent alternative pathway mediated C3 deposition in C2 deficient serum. This bypass pathway may be of particular significance in the presence of complement deficiencies[11].

THE CLINICAL RELEVANCE OF MANNOSE-BINDING LECTIN

MBL binds a broad range of bacteria, viruses, fungi and protozoa (Table 1). Its affinity for Gram-negative and Gram-positive bacteria is mediated through cell surface components, such as lipopolysaccharide (endotoxin) and lipoteichoic acid, respectively. MBL deficiency increases *in vivo* susceptibility to many common bacterial infections, including *Neisseria meningitidis*[12], *Streptococcus pneumoniae*[13], and *Staphylococcus aureus*[14]. MBL deficiency may also increase the risk of several viral infections and some of the most compelling data in this area have been conducted in viral hepatitides, discussed below.

The balance of evidence suggests that MBL deficiency is most relevant when immunity is already compromised as a consequence of immunological immaturity, for example

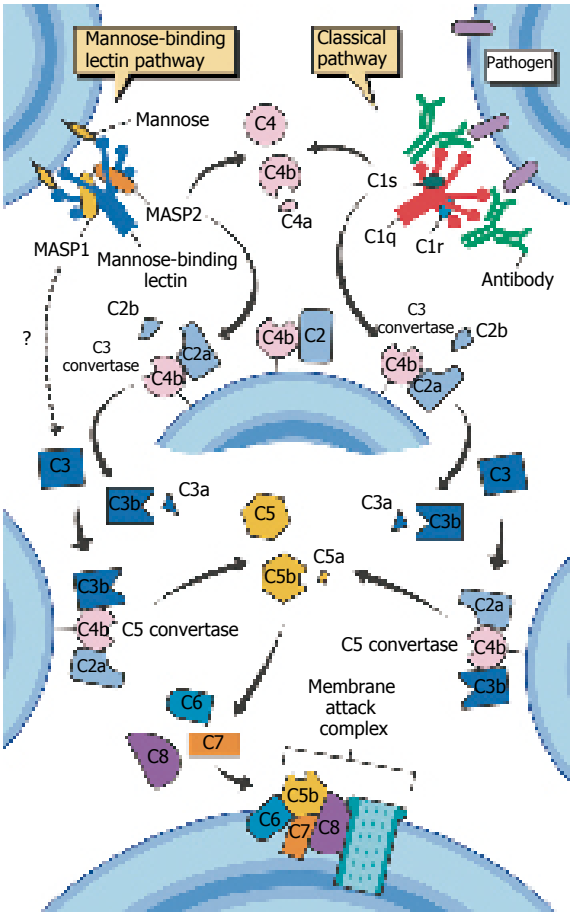

Figure 3 The lectin and classical complement pathways (Figure reproduced from Worthley *et al*[82] with permission).

Table 1 Some clinically relevant microorganisms recognized by MBL

Bacteria	Viruses	Fungi	Protozoa
Staphylococcus aureus	HIV-1 and 2	*Aspergillus fumigatus*	*Plasmodium falciparum*
Streptococcus pneumoniae	Herpes simplex 2	*Candida albicans*	*Cryptosporidium parvum*
Streptococcus pyogenes	Influenza A	*Cryptococcus neoformans*	*Trypanosoma cruzi*
Enterococcus spp.	Hepatitis B virus	*Saccharomyces cerevisiae*	
Listeria monocytogenes	Hepatits C virus		
Haemophilus influenzae			
Neisseria meningitidis			
Neisseria gonorrhoeae			
Escherichia coli			
Klebsiella spp.			
Pseudomonas aeruginosa			
Salmonella montevideo			
Salmonella typhimurium			
H pylori			
Chlamydia trachomatis			
Chlamydia pneumonia			
Proprionibacterium acnes			
Mycobacterium avium			
Mycobacterium tuberculosis			
Mycobacterium leprae			
Leishmania chagasi			

in young children[15], or is impaired by comorbidity or medical therapy, such as in cystic fibrosis[16], after chemotherapy[17,18], or following transplantation[19,20]. In the pediatric population, MBL exerts greatest influence during an immunological "window of vulnerability", between the decline in maternal passive immunity but before the development of a fully mature adaptive immune system. There is a strong association between MBL deficiency and childhood infection, which has been found for both milder respiratory tract infections managed within the community[21], as well as more severe infections requiring hospitalization[15]. In cystic fibrosis (CF), innate immunity is compromised in part by impaired mucociliary clearance and bronchiectasis. In one series of CF patients, those with mutant *MBL2* alleles had worse pulmonary function and shorter survival to end-stage CF[16]. The same investigators reported successful MBL replacement in the management of one patient with rapidly progressive CF[22]. Several studies have shown an association between MBL deficiency and risk or severity of infection following chemotherapy[17,18].

A number of autoimmune disorders are associated with MBL. This may in part relate to the role of MBL in removing pathogens and apoptotic bodies, thus minimizing the emergence of cross-reactivity or auto-immunogenic epitopes[23]. Inherited deficiencies within the classical complement pathway predispose to systemic lupus erythematosus (SLE), thus it was logical to evaluate the role of MBL in this condition. A recent meta-analysis concluded that deficient *MBL2* genotypes increase the risk of developing SLE[24]. Other studies have shown that MBL deficiency increases the risk of SLE-related complications, such as arterial thrombosis[25]. The effect of variant MBL and risk of vascular complications extend beyond patients with SLE. Several studies have now demonstrated an association between *MBL2* mutations and risk of coronary artery disease[26-28]. These results have been supported by a population-based study from Denmark, that genotyped 9 245 individuals for *MBL2* coding mutations[29]. Although MBL deficiency did not greatly increase the rate of morbidity or mortality within the population, those with biallelic mutations had a significantly greater risk of hospitalization for cardiovascular disease compared to those without deficient alleles [RR = 1.2 (1.0-1.4), $P = 0.02$][29].

To this point, all of the disease associations presented have identified the wild-type (*A*/*A*) *MBL2* gene as advantageous. The global preservation of *MBL2* -deficient haplotypes, however, hints at a selective advantage, at least under certain circumstances, of the deficient state. The concept of heterosis, whereby a heterozygous trait may demonstrate a selective advantage, has many well known examples, such as the ΔF508 mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene and resistance to cholera toxin[30]. MBL-facilitated opsonization and phagocytosis could theoretically enhance the infectivity of some intracellular pathogens. The dichotomous nature of MBL deficiency is supported by several clinical

studies that show it to be protective against several obligate intracellular organisms, including *Mycobacterium leprae*[31], *M. tuberculosis*[32], and *Leishmania chagasi*[33].

Both plasma-derived as well as recombinant MBL are now available for therapeutic use, albeit that the indications for replacement are still evolving. The results from the first phase I trial conducted in healthy, MBL-deficient individuals, has been published[34]. This study confirmed that MBL replacement is a technically viable option. Phase II trials are eagerly awaited.

MALADIES OF THE BOWEL AND LIVER

Innate immunity has developed multiple strategies for protecting us against microbiological threats. Pattern-recognition molecules, such as toll-like receptors (TLR), *NOD2/CARD15*, and MBL, are particularly important in the alimentary tract, characterized by its large surface area and intimate relationship to the bowel contents, particularly the extreme microbial burden found within the colonic lumen. In addition to initiating inflammation, the capacity for immune tolerance is critical for normal bowel function. Although it is clear that the liver is the chief contributor to plasma MBL, mucosal MBL production may be relevant in localized immune defence, particularly within the alimentary tract[35]. The following examples present some of the better developed areas of gastroenterological MBL research, including inflammatory bowel disease, carcinogenesis, gastrointestinal and hepatotropic infection, and chronic liver disease.

MBL and inflammatory bowel disease

Inflammatory bowel disease (IBD) is a pathological spectrum encompassing ulcerative colitis (UC), Crohn's disease (CD), and indeterminate colitis. The resultant IBD phenotype is the consequence of multiple interactions between environmental factors, particularly enteric flora, and the host response to this environment, determined by immunogenetic, epithelial, and other non-immune genetic factors[36]. MBL, as an important component of innate immunity, has engendered considerable research interest. In an early study of 340 unrelated patients with IBD genotyped for *MBL2* exon 1 coding mutations, the frequency of deficient alleles was significantly lower in patients with UC than either the control group ($P = 0.02$), or those with CD ($P = 0.01$)[37]. This study suggests that MBL deficiency could be protective against UC; alternatively, it could be interpreted that MBL deficiency, in individuals otherwise predisposed to IBD, may skew the phenotype away from the UC spectrum of disease towards CD. This concept is supported by another study that genotyped *MBL2* in patients with CD, UC, or healthy controls[38]. In this study the allele frequency of coding mutations was approximately 30% in patients with CD, 8% in UC, and 16% in healthy controls. In addition, the frequency of homozygosity or compound heterozygosity for coding mutations (i.e. *O/O MBL2* genotype) within the IBD group was significantly higher than in the healthy control population and the association was strengthened if the small number of UC patients were excluded from the analysis (16% *vs* 0%; $P = 0.05$)[38]. The study also assessed anti-*Saccharomyces cerevisiae* antibody (ASCA) and MBL levels within the same subsets of patients, albeit slightly different numbers within each group[38]. CD patients with MBL deficiency were significantly more likely to be positive for ASCA and for their lymphocytes to proliferate in response to mannan. Thus, it appears that MBL deficiency could impair normal processing of mannan-expressing microbial antigens, such as those found on the cell surface of many common microorganisms. The accumulated antigens could then stimulate the immune system, and contribute to the production of ASCA and possibly the pathogenesis of Crohn's disease[38]. ASCA is a well established phenotypic marker of IBD, tending to aggregate with Crohn's rather than the ulcerative colitis phenotype, and within CD the presence of ASCA is particularly associated with the fibrostenosing phenotype and ileal inflammation[39]. Thus, MBL deficiency might act primarily to influence IBD-specific phenotype in these patients. It should be noted, however, that a follow-up study, testing a larger cohort of CD patients ($n = 241$), failed to confirm the significant association between variant MBL genotypes and ASCA positivity[40]. The observed trend, however, did show that the frequency of ASCA positivity was proportional to the relative deficiency of the coding genotype, with 54% ASCA positivity for *A/A,* 58% for *A/O,* and 67% for *O/O*[40]. Nevertheless, further studies into the role of MBL as a marker or regulator of IBD phenotype are warranted. Finally, the contribution of *M. avium* subspecies *paratuberculosis* to the pathogenesis of Crohn's disease is controversial[41]. Nevertheless, it would be interesting to investigate whether, in a fashion analogous to *M. tuberculosis,* MBL might predispose to Crohn's disease by facilitating the infectivity of this obligate intracellular pathogen.

MBL and coeliac disease

Coeliac disease is an important autoimmune disorder involving the alimentary tract[42]. The majority of patients with coeliac disease express the major histocompatability complex (MHC) molecule DQ2 and the remainder usually carry DQ8[42]. But HLA genes convey only about 40% of the genetic risk, and although 30%-40% of Caucasians carry DQ2 or DQ8, less than 3% of these will develop coeliac disease[42]. In one study, 117 patients with histologically and serologically confirmed coeliac disease were genotyped for *MBL2* exon 1 mutations, and compared to a healthy blood donor population. There was a significant difference in the frequency of the *O/O* genotype between those with coeliac disease (13%) and the control group (5%) ($P = 0.04$)[43]. A follow-up study included a detailed assessment of the coeliac disease patients' MHC[23]. HLA susceptibility alleles and *MBL2* exon 1 coding mutations were genotyped in 147 healthy controls and 149 patients with coeliac disease, enriched with 29 coeliac disease patients known to be negative for DQ2 and DQ8, which is extremely rare[23]. As in their first study, patients with coeliac disease had a greater frequency of the *O/O* genotype than healthy controls, but in addition, the association between coeliac disease and MBL deficiency was even stronger in the small number of patients negative for DQ2 and DQ8.

It is likely that in those rare cases of coeliac disease that are negative for DQ2 and DQ8, the non-HLA susceptibility genotypes would exert a greater effect. Their study also analyzed apoptosis within small intestinal biopsy specimens, and showed that MBL tended to aggregate to areas of apoptosis within the epithelium. MBL has been implicated in the normal clearance of apoptotic bodies[44,45]. The authors postulated that the association between MBL and coeliac disease, and indeed other autoimmune conditions, could relate to impaired apoptosis, whereby MBL deficiency impairs the normal removal and clearance of apoptotic cells, that may subsequently reveal previously hidden self-antigen, causing loss of self-tolerance, and spreading of autoimmunity[23]. The association between variant *MBL2* alleles and coeliac disease has also been confirmed within the Finnish population[46].

MBL and colorectal cancer

Experimentally there is the suggestion that MBL (both wild-type and the mutant *B* allele) may possess anti-colorectal cancer tumour activity[47]. *In vitro* MBL binds specifically to oligosaccharide moieties on colorectal cancer cell line SW1116[47]. The investigators transplanted SW1116 cells subcutaneously in nude mice, resulting in palpable tumor masses at three weeks. In order to evaluate the *in vivo* anti-tumoral activity of MBL, the mice were administered one of four different intra-tumoral injections. The first group received an injection with vaccinia virus carrying the wild-type (*'A'*) *MBL2* allele, the second group with the variant *'B'* allele and the two control groups received vaccinia virus alone, or saline alone. Intra-tumoral administration of the recombinant vaccinia virus carrying a *MBL2* gene (either the *'A'* or *'B'* allele) significantly reduced tumor size as compared with the two control groups ($P < 0.005$), and also prolonged survival[47]. These laboratory results have not, however, been reflected in clinical trials. In fact, patients with colorectal cancer have increased activation of the lectin-complement pathway and increased levels of serum MBL[48]. In patients undergoing surgery for colorectal cancer, however, low preoperative levels of serum MBL has been linked to an increased risk of developing post-colectomy pneumonia[49]. Most recently, increased preoperative serum levels of MASP2 predicted adverse outcome following colorectal cancer surgery, both in terms of disease recurrence ($P = 0.03$; HR = 1.4, 1.0-2.0) and survival ($P = 0.0005$; HR = 1.4, 1.2-1.7)[50]. There are several possible explanations for these results. A preoperative elevation in acute phase markers, such as CRP, is known to predict worse outcome[51], and the elevation in MASP2 may simply reflect a heightened inflammatory state. Alternatively, MASP2 may meaningfully influence tumor progression. Further studies are required to clarify the role of the lectin-complement pathway in cancer.

MBL and gastrointestinal infection

Despite the well-established role of MBL in innate immunity, there have been relatively few studies detailing the clinical effect of MBL deficiency in enteric infections. One notable exception analyzed the association between MBL deficiency and risk of *Cryptosporidium parvum* enteritis. This study included 72 African patients with acquired immunodeficiency syndrome (AIDS) and diarrhea. They were genotyped for exon 1 *MBL2* mutations and had their duodenal aspirates tested for MBL. Patients with biallelic coding mutations (*O/O)* had a significantly greater chance of cryptosporidiosis compared to those who were either wild-type or heterozygous for *MBL2* mutation (*A/A or A/O,* respectively) (OR = 8.2; 95% CI: 1.5-42; $P = 0.02$)[52]. This study places MBL's anti-microbial function back in the context of the 'window of vulnerability' hypothesis. Of further interest from this study was the detection of MBL within some of the duodenal aspirates. The presence of albumin in the intestinal lumen led the authors to postulate that MBL entered the bowel through mucosal leakage of serum; however, local intestinal production could not be excluded. The association between MBL deficiency and cryptosporidiosis was recently confirmed in a second case-control study, this time in young (< 3 year) Haitian children. Mean serum MBL levels were significantly lower in the cases (1110 *vs* 2395 ng/mL, $P = 0.002$), and 37% of the cases compared to only 10% of the healthy controls were found to be deficient in MBL (level $\leqslant$ 70 ng/mL) ($P = 0.005$)[53]. Unlike the earlier study, *MBL2* genotyping was not performed, and thus MBL deficiency secondary to enteric protein loss, as a consequence of cryptosporidiosis, could not be excluded. When considered together, however, these two studies present compelling evidence for the role of MBL in the host defense against *Cryptosporidium spp.* infection.

Another study analyzed serum MBL levels in a pediatric population presenting with *Escherichia coli* 0157: H7 colitis. MBL levels were measured in patients with uncomplicated *E. coli* 0157:H7 colitis, patients in whom the colitis was complicated by haemolytic uraemic syndrome (HUS), and in normal and disease (rotavirus enteritis) control groups[54]. MBL deficiency was not associated with an increased risk of either infection nor the complication of HUS, albeit that without analysis of *MBL2* genotype, overall MBL status may be more difficult to assess.

H pylori is one of the most common human bacterial infections, affecting approximately 50% of humans, although only 10%-20% of those affected will develop a clinical disorder[55]. Several immunogenetic polymorphisms are associated with clinical outcomes in *H pylori* infection[56], as well as with the risk of infection itself[57,58]. *H pylori* activates MBL *in vitro*[59], and a recent study demonstrated that *H pylori*-related chronic gastritis causes an increase in gastric mucosal MBL expression, but no association was found between *MBL2* genotype and risk of chronic gastritis[60]. A recent study was performed to investigate whether MBL deficiency increased the risk of *H pylori* infection[61]. Two normal populations (166 blood donors and 108 stem cell donors) were included in the analysis. All individuals were genotyped for *MBL2,* had their peripheral MBL activity characterized by level and functional assays, and were tested for serological evidence of *H pylori* infection. In this study, MBL deficiency did not increase the risk of *H pylori* infection, and in one population greater MBL activity actually increased the risk of infection.

It is worth noting that MBL has been implicated in

mediating gastrointestinal ischemia/reperfusion injury in mice[62]. MBL-null mice (deficient in the two murine genes encoding MBL) developed only minor gut injury after induced ischemia/reperfusion insult compared to the wild-type mice. MBL has been implicated as a mediator of ischemia/reperfusion injury in both the myocardium[63] and the kidney[64] and thus clinical correlation of MBL status and risk or outcome following mesenteric ischemia may yield interesting results.

MBL and viral hepatitides

MBL was first isolated from hepatocytes[65], and the liver produces most if not all of the circulating MBL[20]. There is obviously considerable functional reserve in hepatic MBL production, because in the setting of cirrhosis, unlike many other hepatic proteins, MBL production appears to be increased[66]. The viral hepatitides have stimulated considerable MBL-related research. In one study of chronic hepatitis B virus (HBV) infection, MBL codon 54 (*B*) mutations were significantly associated with risk of developing both symptomatic cirrhosis and spontaneous bacterial peritonitis (SBP)[67]. The increased risk of SBP in patients with MBL deficiency is biologically plausible, given that low levels of ascitic fluid opsonins are important in the pathogenesis of SBP, and MBL deficiency would be likely to compound this deficit[68]. A second study by the same investigators recently confirmed the association, extending the results from their previous study, to include the low expression haplotype *XA* as a risk factor, as well as the '*B*' allele. The odds ratio for developing cirrhosis and hepatocellular carcinoma was 1.97 for patients with *XA* and 1.90 for those with *YB* ($P = 0.002$)[69]. A study from the U.S. confirmed these findings, which is important given that the age and route of acquisition of HBV may vary between different countries[70]. It is likely that MBL plays an important role in the pathogenesis of HBV-related chronic disease, even though some small studies have failed to confirm the association[71,72]. It will be interesting to examine the influence of MBL status upon the rate or type of drug resistance that emerges in individuals during long-term antiviral therapy.

Many of the studies analyzing MBL in chronic hepatitis C virus (HCV) infection have investigated the role of MBL mutations on rate of sustained viral response following interferon alpha (IFN-α) monotherapy. Two studies, from the same Japanese group, reported that patients who failed to eradicate HCV following IFN monotherapy were more likely to have variant *MBL2* alleles, either the '*B*' coding mutation[73,74] or the '*LXPA*' haplotype[73]. A third Japanese study addressed whether MBL deficiency altered the course of HCV chronic liver disease[75]. In their cross-sectional study, 52 patients with chronic HCV and 50 controls were genotyped for the '*B*' coding mutation in exon 1 of *MBL2*. All patients with HCV had the stage and activity of their liver disease categorized as "chronic inactive hepatitis", "chronic active hepatitis" (CAH), or cirrhosis. No significant differences in the frequency of mutations was found between the patients and the controls, but within the HCV-infected group, all of the patients with heterozygous or homozygous codon 54 mutations had either CAH or cirrhosis, whilst none of those in the "chronic inactive hepatitis" group had mutations. This represented a significantly higher frequency of mutation in the advanced (CAH plus cirrhosis) liver disease group ($P = 0.0405$)[75]. A final study from Scotland sought to test the Japanese findings in a Caucasoid population[76]. This study failed to find an association between MBL deficiency and either progression of liver disease or response to IFN-α therapy. This study, however, did not perform *MBL2* genotyping, but stratified MBL concentrations into four groupings for comparison. On balance, there appears to be an association between MBL status and HCV in terms of both disease progression and response to monotherapy, at least in the Japanese population. The development of newer anti-viral treatment regimens, including pegylated-IFN in combination with ribavirin treatment, makes it necessary to re-evaluate immunogenetic influences, at least, any which are hoped to inform therapy.

MBL and liver transplantation

One of the more exciting recent reports regarding MBL and hepatobiliary disease, addressed the role of MBL deficiency following orthotopic liver transplantation (OLT)[20]. OLT provides the unique opportunity not only to evaluate the role of MBL in post-transplant infection, but also to assess the contribution of hepatic and extra-hepatic MBL production, because in many recipients the *MBL2* genotype will be different in the liver. The study reported the clinical results from 49 transplants, in which 49 of the donors were genotyped for *MBL2*, 25 of the recipients were genotyped, and serum samples were collected from 25 of the recipients to evaluate the change in serum MBL concentration post-transplant. There was an impressive correlation between the risk of post-transplant clinically significant infection and the relative deficiency of the donor *MBL2* genotype, with infection occurring in 12% receiving a wild-type *A/A* liver, 39% of those receiving an *A/O* liver, and in 67% of those receiving an *O/O* donor liver ($P = 0.01$)[20]. In addition, the post-transplantation serum MBL level was predicted by the hepatic, not the extra-hepatic, genotype. Nevertheless, as only 25 of the recipients, and thus only 25 extra-hepatic genotypes were analyzed, this study was too small to detect more subtle changes in the risk of infection, conferred through local, extra-hepatic MBL production[77].

MBL and hepatic synthesis

The site of MBL production has been a contentious area. Undoubtedly, the liver produces the majority of MBL and most if not all of the circulating MBL within peripheral blood. This view is supported by the liver transplantation study above, as well as a report documenting that successful allo-SCT failed to correct peripheral blood MBL deficiency[20,78]. Nevertheless, MBL mRNA is expressed in extra-hepatic tissue[35,79,80] possibly including haemopoietic lineages[35], and there have now been two allo-SCT studies that support a contribution from donor (i.e. hematopoietic) *MBL2* genotype, and risk of post-transplant infection[4,81]. The most important issue is not whether extra-hepatic MBL production significantly influences peripheral

blood MBL levels, but whether it contributes in a clinically meaningful way to local, tissue-specific immunity.

CONCLUSION

MBL has stimulated a great deal of basic and clinical gastroenterological research and has provided new insights to the pathogenesis of infectious and immune disorders within the bowel and liver. The possibility of a local, mucosal effect of MBL as suggested by gene expression[35,79,80], as well as clinical studies[23,60] is an exciting discovery. Further work is needed to clarify whether mucosal production occurs, and if so whether it contributes to local immune surveillance in health, or under certain situations, even exacerbates alimentary tract disease.

Despite the promise of replacement therapy and the value of MBL in predicting the risk of disease and disease-specific complications, for now investigation of MBL status remains primarily a research tool. Future studies more rigorously examining MBL status by both measurement of MBL levels and *MBL2* genotyping in large patient cohorts will help clarify the most important disease associations and identify those clinical settings in which MBL replacement therapy is most likely to be beneficial. Now that MBL replacement has been shown to be feasible, the first trials of MBL replacement therapy in several clinical settings, including recurrent infection, severe sepsis, and liver transplantation, are likely to be reported in the next few years. This prospect of MBL replacement therapy represents the culmination of several decades of basic and translational research and is an exciting advance in the field of innate immunity.

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