REVIEW ARTICLE

Mannose-binding lectin in innate immunity: past, present and future

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Abstract

The human collectin, mannose-binding lectin (MBL), is an important protein of the humoral innate immune system. With multiple carbohydrate-recognition domains, it is able to bind to sugar groups displayed on the surfaces of a wide range of microorganisms and thereby provide first-line defence. Importantly, it also activates the complement system through a distinctive third pathway, independent of both antibody and the C1 complex. Three single point mutations in exon 1 of the expressed human *MBL-2* gene appear to impair the generation of functional oligomers. Such deficiencies of functional protein are common in certain populations, e.g. in sub-Saharan Africa, but virtually absent in others, e.g. indigenous Australians. MBL disease association studies have been a fruitful area of research and implicate a role for MBL in infective, inflammatory and autoimmune disease processes. Overall, there appears to be a genetic balance in which individuals generally benefit from high levels of the protein. However, in certain situations, reduced levels of circulating MBL may be beneficial to the host and this may explain the persistence of the deleterious gene polymorphisms in many population groups.

Introduction

It is now 60 years since the Australian Nobel prize winner Sir Frank Macfarlane Burnet, together with John McCrea, identified three inhibitors in serum (called α, β and γ), which were able to inactivate influenza virus (1). We now know that the β inhibitor was, in fact, a protein called mannose-binding lectin (MBL), a component of the innate immune system (2). During the past 30 years, our understanding of this protein has steadily increased as a result of extensive research activity in three main areas: (a) bio/immunochemistry (including molecular genetics), (b) microbiology and (c) immunodeficiency. Work in these areas initially proceeded independently as evidence for both an inexplicable biological function and a clinical deficiency state emerged. The isolation and characterization of the protein were necessary in order to illuminate the observations of the so-called RaRf bactericidal activity (3, 4) in the microbiology area and the opsonic deficiency reported in many paediatric populations. Some of the main developments are summarized in Table 1. This review briefly addresses issues relating to the early history of MBL, its structure, function, genetics and disease associations. Finally, future developments including the potential use of both plasma-derived and recombinant MBL are discussed.

The existence of mammalian serum lectins was first predicted in 1975 by Robinson et al. (5), and the protein was first isolated in 1978 from cytosolic fractions of rabbit liver by Kawasaki et al. (6). Subsequently, Wild et al. (7) were able to isolate MBL from both human and rat liver. More recently, extrahepatic transcription of MBL has been reported and this may have implications regarding its role in localized host defence (8).

MBL belongs to a family of proteins called the collectins, which possess both collagenous regions and lectin domains. The other major human collectins, surfactant protein A and surfactant protein D, possess structural characteristics similar to those of MBL and are found predominantly in the lung and other mucosal sites (9).

Table 1 Major discoveries in MBL-related research

	Biochemistry/immunochemistry	Microbiology	Immunodeficiency
1946		Identification of β inhibitors of heat-labile components of influenza virus in normal serum with both virus-neutralizing activity and haemaglutination-inhibiting activity (1)	
1968			Plasma-associated phagocytic defect (28)
1975	Existence of mammalian serum 'lectin-like proteins specific for mannose' predicted (5)		
1976			Association of opsonic defect with frequent infections in infancy, but deficiency also present in 5% of the general population (29)
1978	MBL isolated from rabbit liver (6)		
1980			Opsonic deficiency in infants with chronic diarrhoea (30)
1981			Association of yeast opsonization defect with suboptimal C3b deposition (31)
1982		Description of mouse RaRF: a complement-activating bactericidal protein (3)	
1983	Human MBL isolated from liver (7); human serum MBL isolated (121)		Prospective study of opsonic deficiency in infancy (122)
1984		RaRF activity present in vertebrate classes (4)	
1985	Bovine serum MBL described (123)		Opsonic defect linked to absence of an unidentified co-factor of the complement system (124)
1987	MBL activation of classical complement pathway (18)		
1988	Rat serum MBL A and C described (125); description of C-type CRD (126)		
1989	Gene for human MBL cloned (33, 34); human MBL has bactericidal activity (127); opsonic nature of MBL demonstrated (35)	MBL inhibits *in vitro* infection by HIV (85)	Correlation of opsonic defect with low serum MBL levels (32)
1990		Bovine and mouse serum β inhibitors of influenza A virus identified as MBL (2)	Correlation of MBL levels with classical complement pathway activation at low serum concentrations (128)
1991	Mouse MBL A and C described (129)		Opsonic deficiency and low MBL levels linked to single point mutation in codon 54 (variant B) (50)
1992	Human MBL levels in acute-phase responses (59); crystallography of MBL CRD (130); novel protease (MASP-1) and complement activation by MBL (19)	Human RaRF identical to MBL-MASP (131)	Low MBL levels in Africans linked to codon 57 (variant C) mutation in the MBL gene (51)
1994			Third MBL mutation in codon 52 (variant D) described (52)
1995			Polymorphisms found in promoter region of MBL gene (55)
1997	Second MASP found to activate complement (20)		MBL mutations are an important risk factor for infections in children (132)
1998			Reconstitution of opsonizing activity by infusion of purified MBL into MBL-deficient humans (112)
1999	Truncated form of MASP-2 – MAp19 (21)		
2000	Complement-activating complex of ficolins and MASP (133)	MBL shown to bind to clinically relevant organisms (15)	

2001	MASP-3 described (23)	Binding to capsulated bacteria (134); MBL regulates the inflammatory response to bacteria (42)	MBL deficiency associated with infectious morbidity in patients with cancer (81, 82)
2002	Activation of lectin pathway by H-ficolin (135)		
2003			Inherited deficiency of MASP-2 (116); association of MBL polymorphisms with sepsis and fatal outcome in patients with SIRS (102, 103)
2004		Increased mortality in MBL knockout mice with *Staphylococcus aureus* (84)	
2005	Human M-ficolin activates lectin pathway (26)		Association of MBL deficiency with risk of mycoplasma infection (72)

CRD, carbohydrate-recognition domain; MASP, MBL-associated serine proteases; MBL, mannose-binding lectin; SIRS, systemic inflammatory response syndrome.

Structural aspects of MBL

The protein structure of MBL has been studied extensively, and aspects are presented in Figures 1 and 2. The protein consists of multimers of an identical polypeptide chain of 32 kDa. Each chain comprises four distinct regions encoded by different exons of the *MBL-2* gene, as will be discussed in more detail later.

Each chain has a C-terminal, calcium-dependent carbohydrate-recognition domain (CRD); a short, α-helical, hydrophobic neck region (in the so-called coiled-coil configuration); a collagenous region containing 19 Gly-Xaa-Xaa triplets and a cysteine-rich N-terminal region. Three polypeptide chains form a triple helix within the collagenous region, stabilized by hydrophobic interactions
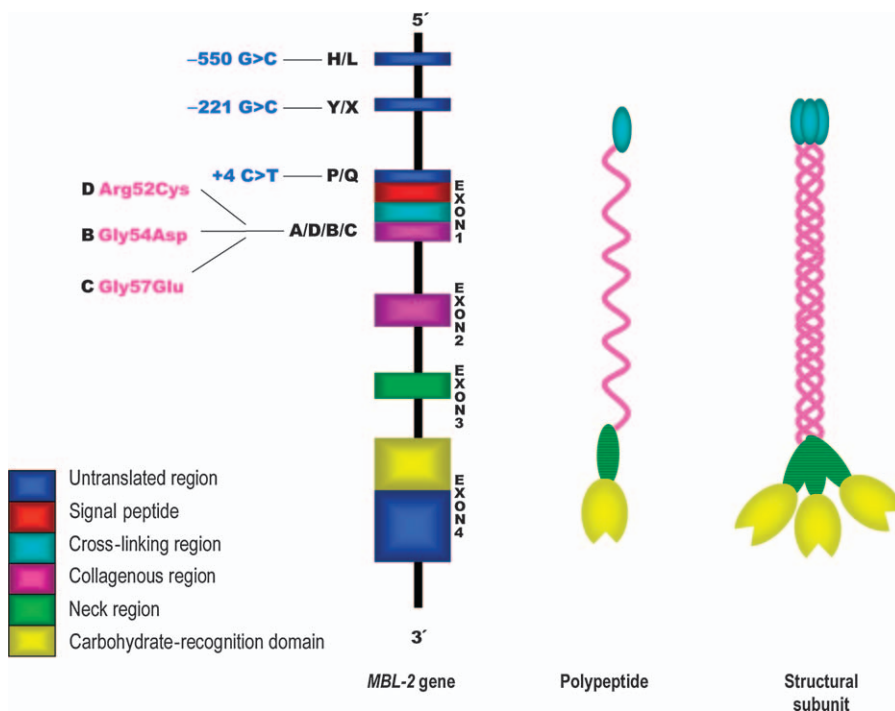

Figure 1 Structure of the human *MBL-2* gene and the encoded protein product. Positions of the exon 1 and promoter polymorphisms are shown. Different regions of the polypeptide are encoded by different exons of the MBL gene. Three identical 32-kDa polypeptides form a structural subunit, based on formation of a collagenous triple helix. Oligomerization of the structural subunit results in MBL molecules of differing size, but the tetrameric form shown in Figure 2 is probably the most common. MBL, mannose-binding lectin.
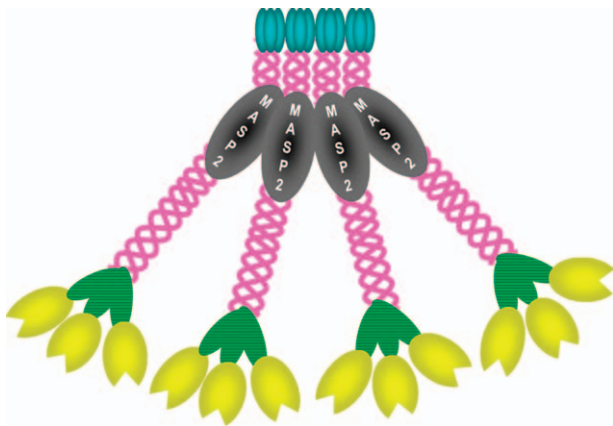
Figure 2 Tetramer of human MBL structural subunits (Figure 1). The subunits are cross-linked by disulphide bonds in the N-terminal regions. Each MASP-2 molecule is believed to bind close to the hinge point of the collagenous region. The number of MASPs able to bind to a given MBL tetramer is not definitively known, but the arrangement shown would be consistent with the model for rat MBL proposed by Feinberg *et al.* (24). The details of MASP-1, MASP-3 and MAp19 binding to MBL remain unclear. MBL, mannose-binding lectin; MASP, MBL-associated serine proteases; MASP-1, MBL-associated serine protease-2; MASP-2, MBL-associated serine protease-2; MASP-3, MBL-associated serine protease-3.

and interchain disulphide bonds within the N-terminal cysteine-rich region. This is the basic building block of all circulating molecular forms of MBL. In serum, MBL consists of oligomers ranging from dimers to hexamers, and X-ray crystallographic studies/electron micrographs have revealed that these oligomers have a sertiform or a bouquet-like structure due to an interruption in the collagenous region, giving rise to a kink/hinge. The ability of the protein to bind effectively to microorganisms and activate complement appears to depend on the presence of higher order oligomers (tetramers and above).

Work by Drickamer and colleagues (10, 11) and also by Ezekowitz and colleagues (12) has provided an insight into the structure of the CRD. Each CRD binds a calcium ion, enabling it to form co-ordination bonds with the 3- and 4-hydroxyl groups of specific sugars including mannose, *N*-acetyl-d-glucosamine, *N*-acetyl-mannosamine, fucose and glucose. The three CRDs in each structural subunit are separated by a constant 45-Å distance (12). Clustering of the structural subunits provides a flat platform, permitting binding of MBL to the arrays of repeating sugar groups on microbial surfaces. Although the binding affinity of each individual CRD–sugar interaction is relatively low at 10^{-3} M (13), the formation of higher order oligomers provides multiple CRDs, which are able to bind simultaneously with high avidity.

MBL is a major pattern-recognition molecule of the innate immune system. It primarily recognizes specific

sugar groups (as above) on the surface of microorganisms, enabling it to distinguish self from non-self. It can also bind to phospholipids, nucleic acids (14) and non-glycosylated proteins. MBL has been shown to bind promiscuously to a wide range of bacteria, viruses, fungi and protozoa and some selected examples are listed in Table 2.

Neth et al. used flow cytometry to demonstrate MBL binding to clinically relevant bacterial isolates from immunocompromised children and noted differences in binding within some species such that one isolate might show strong binding, whereas another was much weaker (15). The role of specific structural features of microorganisms (e.g. the capsule), which permit or prevent binding to MBL, has been explored in several studies. The earliest work was probably by Kawakami et al. on the so-called RaRf complex (which was later identified as MBL)

Table 2 Selected microorganisms that have been shown to bind MBL

	Reference
Bacteria	
Actinomyces israelii	Townsend et al. (136)
Bifidobacterium bifidum	Townsend et al. (136)
Burkholderia cepacia	Davies et al. (137)
Chlamydia pneumoniae	Swanson et al. (138)
Escherichia coli	van Emmerik et al. (139)
Haemophilus influenzae	Neth et al. (15), van Emmerik et al. (139)
Klebsiella aerogenes	Neth et al. (15)
Leptotrichia buccalis	Townsend et al. (136)
Listeria monocytogenes	van Emmerik et al. (139)
Mycobacterium avium	Polotsky et al. (140)
Mycoplasma pneumoniae	Hamvas et al. (72)
Neisseria meningitidis	Neth et al. (15), van Emmerik et al. (139)
Proprionibacterium acnes	Townsend et al. (136)
Pseudomonas aeruginosa	Davies et al. (137)
Salmonella montevideo	Kuhlman et al. (35)
Staphylococcus aureus	Neth et al. (15)
Streptococcus pneumoniae	Neth et al. (15)
Viruses	
Influenza A	Saifuddin et al. (141), Hart et al. (142), Ji et al. (143)
HIV	Saifuddin et al. (141), Hart et al. (142), Ji et al. (143)
Herpes simplex 2	Fischer et al. (144), Gadjeva et al. (145)
SARS-CoV	Ip et al. (75)
Fungi	
Aspergillus fumigatus	Neth et al. (15)
Candida albicans	Neth et al. (15), Tabona et al. (146)
Cryptococcus neoformans	Schelenz et al. (147)
Protozoa	
Cryptosporidium parvum	Kelly et al. (148)
Plasmodium falciparum	Klabunde et al. (149)
Trypanosoma cruzi	Kahn et al. (150)

HIV, human immunodeficiency virus; MBL, mannose-binding lectin; SARS-CoV, severe acute respiratory syndrome–coronavirus.

and its interaction with *Salmonella enterica* serovar *Typhimurium* (3). This suggested that the structure and composition of lipopolysaccharide play a crucial role in MBL binding and function. Other mechanisms that enable microorganisms to avoid recognition and killing by MBL include lipooligosaccharide sialyation (16, 17). Despite much progress in this area, many puzzles remain to be addressed, mostly related to the exact disposition of sugars on microbial surfaces.

Functional aspects of MBL

Our understanding of MBL function has grown rapidly over the past three decades. It is now recognized to have a role in processes as diverse as complement activation, promotion of complement-independent opsonophagocytosis, modulation of inflammation, recognition of altered self-structures and apoptotic cell clearance.

MBL and complement activation

A role for MBL in host defence was first proposed in 1987 when Ikeda et al. observed that the protein was able to activate the classical pathway of complement (18). However, it is now clear that MBL activates a novel third pathway of complement, often termed the MBL pathway, in an antibody- and C1-independent fashion as illustrated in Figure 3.

This functional activity reflects the fact that MBL circulates in association with a group of MBL-associated serine proteases (the so-called MASPs). In 1992, Matsushita and Fujita demonstrated the presence of a novel complement enzyme in serum, which was thought to generate the C3 convertase (C4bC2a), associated with classical pathway activation (19). However, this activity was later found to be mediated by MASP-2 (20), and the original enzyme is now known as MASP-1 and may activate C3 directly. Subsequently, a small separately synthesized fragment of MASP-2 termed sMAP or Map19 was identified (21, 22) and a third MASP (MASP-3) with no known function was also described (23).

Current understanding suggests that on binding to microorganisms, autoactivation of MASP-2 occurs, permitting cleavage of C4 and C2 to form a C3 convertase, which is indistinguishable in specificity from the convertases found in the other two activation pathways of complement (24).

It should be noted that the so-called MBL pathway is also activated by another family of proteins called ficolins. The ficolins are structurally similar to collectins, with collagenous domains linked to fibrinogen-like domains having sugar-binding properties. L- and H-ficolins are humoral factors synthesized by hepatocytes, although H-ficolin has also been observed in bronchial/alveolar fluid and in
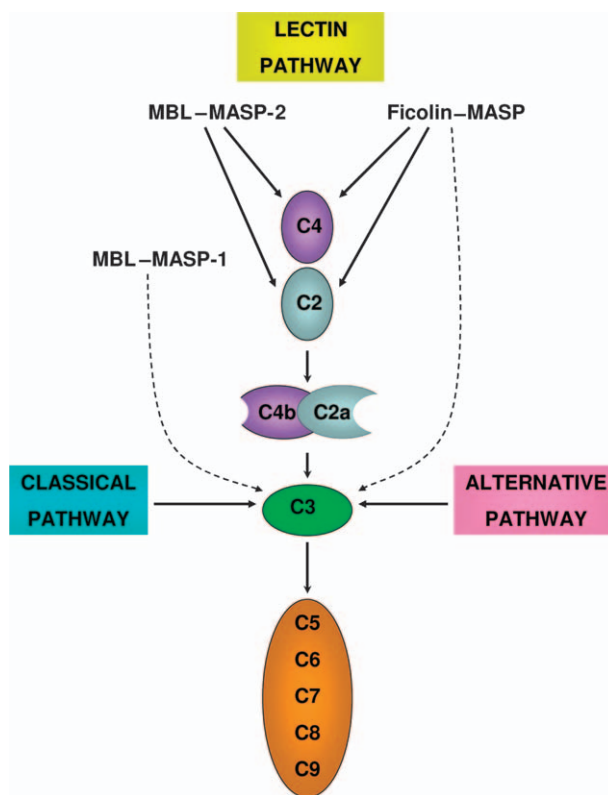

Figure 3 Complement activation pathway. The lectin pathway of complement is activated by MBL and ficolins. On binding to appropriate targets, MBL–MASP-2 complexes cleave C4 and C2 to form C3 convertase (C4bC2a). MBL–MASP-1 complexes may activate C3 directly. Ficolins also work in combination with the MASPs. The classical and alternative pathways also generate C3 convertase enzymes, which cleave C3. The lytic pathway (C5–C9) is common to all three routes of C3 cleavage. MBL, mannose-binding lectin; MASP, MBL-associated serine proteases; MASP-1, MBL-associated serine protease-2; MASP-2, MBL-associated serine protease-2.

bile (25). In contrast, M-ficolin is found on peripheral blood mononuclear cells, polymorphonuclear cells and type II lung epithelial cells (26). Ficolins are also found in complexes with the MASPs and are considered to have different binding specificities compared with MBL (27).

Opsonophagocytosis

In 1968, Miller et al. reported a plasma-associated defect of phagocytosis in a child with severe recurrent infections, failure to thrive and diarrhoea (28). *In vitro* work revealed a failure of the child's plasma to opsonize heat-killed bakers yeast (*Saccharomyces cerevisiae*). This defect was later detected in the sera of children with recurrent unexplained infections (29) and chronic diarrhoea of infancy (30), but, interestingly, studies in the general population also revealed a relatively high frequency of the defect (~5%). In 1981, studies linked this opsonic deficiency to the complement

system by demonstrating that sera with the deficiency deposited less C3b on yeast surfaces (31). However, it was not until 1989 that the common opsonic defect was found to be associated with low levels of the mannose-binding protein, which we now refer to as MBL (32). In that same year, the gene for MBL was cloned (33, 34) (*Genetics of Human MBL*).

Cell receptors for MBL

In a study of MBL-coated *Salmonella montevideo*, Kuhlman et al. reported that MBL was able to interact directly with cell surface receptors and promote opsonophagocytosis (35). Subsequently, a number of putative MBL-binding proteins/receptors have been proposed including cC1qR/calreticulin (36), C1qRp (37) and CR1 (38, 39). However, it is unclear whether MBL is acting as a direct opsonin or is merely enhancing other complement pathways and/or antibody-mediated phagocytosis.

MBL in inflammation

The role of MBL as a modulator of inflammation appears to be complex and, accordingly, its mechanism of action remains unexplained. One possible explanation is that MBL is able to trigger proinflammatory cytokine release from monocytes (40, 41). This concept was addressed in studies by Jack et al. using *Neisseria meningitidis* incubated with increasing concentrations of MBL before being added to MBL-deficient whole blood. Release of tumour necrosis factor α, interleukin (IL)-1β and IL-6 from monocytes was enhanced at MBL concentrations below 4 μg/ml but suppressed at higher concentrations (42). Clinical studies in this area are discussed later.

The role of MBL in the recognition of altered self and apoptosis

A role for MBL in the clearance of apoptotic cells was first proposed by Ogden et al. in 2001 (43). MBL was found to bind directly to apoptotic cells that expose terminal sugars of cytoskeletal proteins, thereby permitting their recognition and directly facilitating their phagocytosis by macrophages. Defects in the clearance of apoptotic cells have been implicated in the pathogenesis of certain autoimmune conditions, although the precise role of MBL, if any, remains elusive. For example, in 2005, Stuart et al. reported that although MBL-deficient mice displayed defective apoptotic cell clearance, they did not develop autoimmune diseases (44).

In animal studies, MBL has been implicated in the pathophysiology of ischaemia reperfusion injury due to its ability to recognize altered self-structures. Stahl and colleagues have proposed the lectin pathway as a mediator of this process in certain organs, and the absence of

MBL/MASP pathway activation appears to afford protection in these disease models (45, 46). However, the relevance of these findings to human health needs to be established.

Changes in cell surface structures during oncogenic transformation appear to promote binding of MBL to cancer cells (47) where the protein can mediate cytotoxic effects including MBL-dependent cell mediated cytotoxicity (48, 49). The relative importance of such mechanisms in tumour immunology is, at present, unknown.

Genetics of human MBL

There are two human MBL genes, but *MBL-1* is a pseudogene and only *MBL-2* encodes a protein product. The functional *MBL-2* gene is located on chromosome 10 (q11.2-q21) and comprises four exons as illustrated in Figure 1. Exon 1 encodes the signal peptide, a cysteine-rich region and part of the glycine-rich collagenous region. Exon 2 encodes the remainder of the collagenous region and exon 3 encodes an α-helical coiled-coil structure, which is known as the 'neck' region. Exon 4 encodes the CRD, which adopts a globular configuration. The promoter region of the MBL gene contains a number of regulatory elements, which affect transcription of the protein.

In 1991, the complete nucleotide sequence of all four exons of the human *MBL-2* gene was determined by Sumiya et al. in two British children with recurrent infections and low MBL levels (50). In both individuals, a point mutation was observed in codon 54, changing the codon sequence from GGC to GAC and substituting aspartic acid for glycine in the translated protein. Familial studies confirmed that the defect was inherited in an autosomal dominant fashion. In 1992, Lipscombe et al. identified a second exon 1 mutation in codon 57 (Gly → Glu), when studying a sub-Saharan African population (51), and in 1994, Madsen et al. reported a mutation in codon 52 (Arg → Cys) (52). These point mutations are now commonly referred to as variants B, C and D respectively, with variant A indicating the wild type. The B variant mutation occurs at a gene frequency of approximately 25% in Eurasian populations. In contrast, the C variant is rare in Eurasians but is commonly seen in sub-Saharan African populations, with frequencies of 50%–60%. Population studies suggest that the B variant mutation may have arisen between 50,000 and 20,000 years ago (53) since no structural gene mutations have been identified in studies of indigenous Australian populations who arrived on the continent approximately 50,000 years ago, whereas the B variant mutation was probably introduced into both North and South America at the time of the last glaciation approximately 20,000 years ago.

The effect of these exon 1 mutations on the protein product continues to be the focus of study. They are believed to impair oligomerization and lead to a functional deficiency. The B and C mutations result in the replacement of

critical axial glycines in the triple helix by dicarboxylic acids, resulting in distortion of this important part of the protein (50). In contrast, the D mutation results in the replacement of arginine with cysteine. This extra cysteine has been proposed to cause formation of adventitious disulphide bonds that hinder higher oligomer formation (54).

Several polymorphisms have also been reported in the promoter region of the gene. Studies by Madsen et al. investigating the large interindividual variation in serum MBL levels revealed three polymorphisms, H/L, X/Y and P/Q at positions -550, -221 and $+4$ of the MBL gene (55, 56). Subsequently, four common haplotypes were identified, namely LXP, LYP, LYQ and HYP. Of these, HYP, which is associated with medium to high levels of MBL and LXP, which is associated with low levels of the protein, appear to be most important. These promoter haplotypes are in strong linkage disequilibrium with the exon 1 mutations, resulting in seven common extended haplotypes, namely HYPA, LYPA, LYQA, LXPA, HYPD, LYPB and LYQC. Other rare haplotypes have also been described (57). Figure 4 illustrates the frequency of these various haplotypes in selected populations and highlights the degree of ethnic variation.

The combination of structural gene and promoter polymorphisms results in a dramatic variation in MBL concentration in apparently healthy individuals of up to 1000-fold (Caucasian: range <20–10,000 ng/ml). In addition, Ezekowitz and colleagues presented evidence in 1988 that MBL was an acute-phase reactant (58). In these investigations, RNA was isolated from a 'normal' liver taken as part of a staging biopsy for Hodgkins disease and was compared with RNA isolated from a fresh post-mortem liver of a victim with severe trauma. The authors found that MBL messenger RNA transcripts were barely detectable in normal liver but that induction was seen in liver exposed to acute stress. Subsequent studies have shown that MBL levels can increase between 1.5 and threefold during the acute phase, but this response is variable between individuals (59). It should also be noted that even during an acute-phase response, individuals heterozygous or homozygous for MBL mutations appear unable to achieve the protein levels of those possessing a wild-type genotype. Approximately one-third of the Caucasian population possess genotypes conferring low levels of MBL, with approximately 5% having very low levels. No absolute level of MBL deficiency has been defined. Genotype and phenotype show a relatively strong correlation and studies often use just one measure to infer deficiency. However, there is 'added value' in performing both measures and we would strongly advocate this approach whenever possible.

MBL gene evolution

MBL occurs in two distinct forms in rodents and rhesus monkeys (60), but only one form is found in humans and chickens. As discussed previously, there are two human MBL genes, which are most likely due to a gene duplication event (61). However, *MBL-1* is a pseudogene and the potential mechanisms responsible for silencing the *MBL-1*
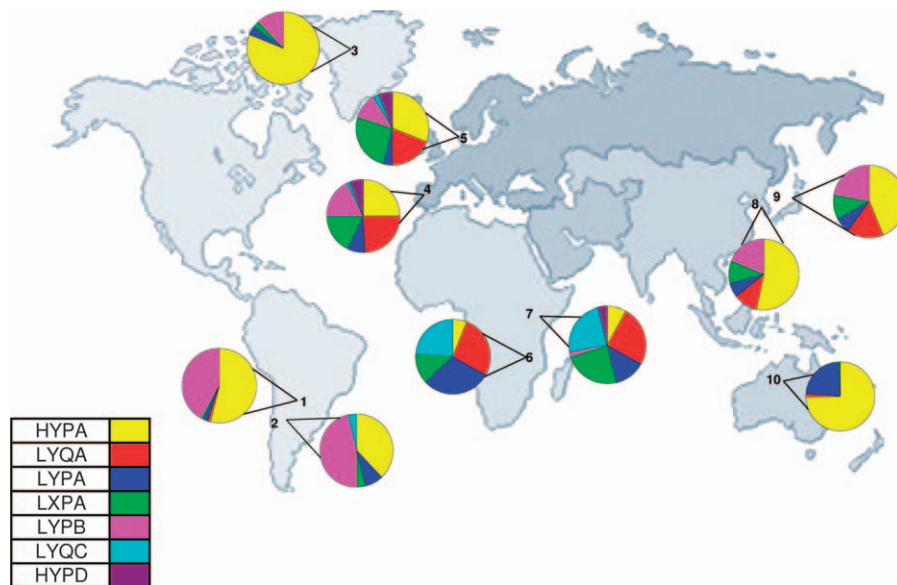

Figure 4 MBL haplotype frequencies have been shown to differ in various populations. Variant A (wild type) is found in association with four different promoter haplotypes, HYPA, LYQA, LYPA and LXPA. The B, C and D variant exon 1 alleles are in linkage disequilibrium with three different promoter haplotypes, LYPB, LYQC and HYPD. Haplotype frequency data are taken from published population studies. 1, Chiriguanos, Argentina (56); 2, Mapuche, Argentina (56); 3, Eskimos, Greenland (56); 4, Caucasians, Spain (151); 5, Caucasians, Denmark (56); 6, Mozambique (56); 7, Kenya (56); 8, Korea (152); 9, Japan (153); 10, Warlpiri, Australia (53). MBL, mannose-binding lectin.

gene are under debate. In 1998, Guo et al. described an intron 1 splicing defect and two stop codons in exons 3 and 4 of the *MBL-1* gene (62). More recently, Seyfarth et al. identified glycine substitutions in codon 53 of the *MBL-1* gene, which bear a close resemblance to those found in codon 54 of the *MBL-2* gene (63). Such substitutions were also found in other higher primates including chimpanzees and gorillas but not in more distant primates such as the rhesus monkey. The authors concluded that both the *MBL-1* and the *MBL-2* genes have been selectively silenced by the same molecular mechanisms, but skewed in time resulting in overall downregulation of MBL levels in the present human population.

The MBL paradox

The high frequency of variant alleles observed in certain populations was initially puzzling since it suggests that functional MBL deficiency may well be advantageous. Similarities have been proposed between the MBL genetic system and the role of the sickle cell gene in protection against malaria as occurs in carriers of the sickle cell haemoglobin allele (64). The argument runs as follows: certain intracellular parasites use C3 opsonization and C3 receptors on monocytes/macrophages to enter their host. Therefore, any reduction in complement-activating function of the host may reduce the probability of parasitization. In support of this notion is a study on patients with visceral leishmaniasis, which revealed that such patients are more likely to have high MBL levels than uninfected controls (65). A small study of Ethiopian patients with lepromatous or borderline lepromatous leprosy also found that their MBL levels were significantly higher than those of healthy blood donors (66). An alternative explanation of the unexpectedly high frequency of low MBL phenotype individuals found in many tropical regions is that excessive complement activation can result in immunopathologically mediated host damage; therefore, any mechanism that reduces complement activation may be beneficial (51).

Disease association studies

The identification of MBL deficiency as the cause of the so-called common opsonic defect has been followed by a plethora of disease association studies aimed at defining the precise role of this protein. A number of the early studies concentrated on paediatric populations and MBL was suggested to provide substitute 'antibody'-like activity during the 'window of vulnerability' (approximately 6–24 months), when maternal immunoglobulin G (IgG) antibody levels have waned but the infant's own adaptive immune response is still immature (32). Nevertheless, studies in adults suggested that there might be a role for MBL throughout life (67). Notwithstanding these reports, the majority of individuals possessing a variant MBL allele apparently suffer no ill effects and remain essentially healthy. In a study that apparently confirms this, Dahl et al. monitored 9245 adults in a Danish Caucasian population and found no evidence for significant differences in infectious disease or mortality in MBL-deficient individuals compared with controls (68). Similar findings were reported by Tacx et al. in unselected adults admitted to hospital with infections (69). Nevertheless, these studies should not be regarded as proof that MBL levels have no clinical relevance. Many groups have undertaken case–control studies, which do indeed suggest that MBL is an important immunological modulator. In some cases, there is evidence that the significance of MBL deficiency is more readily appreciated when there is another co-existing defect (70), as we first proposed in 1991 (71).

Space does not permit a comprehensive review of all the MBL clinical studies that have been undertaken to date, and the topics covered below have been selected in order to illustrate examples of possible roles for MBL in a variety of clinical situations.

MBL and infectious diseases: susceptibility and severity

Most studies have explored the role of MBL in relation to the acquisition of an infectious organism (susceptibility) and the nature of the associated clinical course (severity). In clinical practice, this distinction can be difficult. However, for the purposes of this review, we will highlight examples of infections in which MBL appears to have an influence on one or other of these two aspects of infectious diseases.

Infections in which MBL appears to have a predominant role in susceptibility to disease

Hamvas et al. have recently shown a role for MBL in mycoplasma infection (72). They studied cases of infection in patients with primary antibody deficiencies (PAD) that are known to be particularly susceptible to such organisms and compared them with a control population. More than two-thirds of PAD patients with mycoplasma infections were MBL deficient (in possession of an exon 1 variant allele) compared with one-third of the control group. In the same study, they were able to demonstrate binding of MBL to three strains of *Mycoplasma* using flow cytometry and proposed a role for MBL in prevention of invasive disease.

In 2003, severe acute respiratory syndrome (SARS) emerged as a highly infectious disease caused by a novel coronavirus (SARS-CoV). It provided a new challenge to previously unexposed individuals predominantly in Asia. Specific antibodies to SARS-CoV could be detected ≥10 days after the onset of symptoms, making sufferers reliant on innate immune mechanisms during the early phase of

infection. Since the structure of the virus was rapidly established (73, 74), it also became clear that this novel infectious agent was rich in the sugars known to be targeted by MBL and it was hypothesized that this lectin might well be involved in first-line defence against this infection. Subsequent studies found significant differences in the distribution of MBL-deficient genotypes in patients with SARS compared with those in controls (75, 76). These studies suggested that MBL plays a role in susceptibility to the infection but does not influence subsequent severity. In their investigations, Ip et al. were also able to demonstrate binding of MBL to the virus and its ability to inhibit infection (75).

Infections in which MBL exerts its effects on both susceptibility and severity

Hepatitis

A number of studies have addressed the role of MBL in both hepatitis B and hepatitis C infection. Yuen et al. investigated chronic carriers of hepatitis B and hepatitis C in China (77). The B variant allele was found more commonly in patients with symptomatic hepatitis B cirrhosis and in those with spontaneous bacterial peritonitis. It was also noted that MBL levels were lower in this patient cohort with chronic infection. Screening for MBL mutations in such patients was suggested in order to enable identification of those at increased risk of complications who may benefit from prophylactic antibiotic treatment. In 2005, Chong et al. also reported that MBL genotypes correlating with low protein levels were associated with the occurrence of cirrhosis and also hepatocellular carcinoma in hepatitis B carriers (78). They also demonstrated that MBL is able to bind hepatitis B surface antigen. In the same year, Thio et al. published the results of a nested case–control study of 527 patients who had either naturally recovered from hepatitis B ($n = 338$) or had persistent infection ($n = 189$). They found that MBL genotypes correlating with high serum levels were associated with recovery from infection, whereas those correlating with lower levels were associated with persistence of the virus (79). It should be noted that approximately half of the subjects were also infected with human immunodeficiency virus (HIV), but the authors concluded that this did not influence the results obtained. Matsushita et al. investigated the influence of MBL mutations in hepatitis C infection and found that sufferers who were homozygous for B variant alleles were less likely to respond to interferon treatment (80). Further work would be warranted in order to define the role of MBL in the pathogenesis of hepatitis infection.

Neutropenia

Secondary immunodeficiencies due to disease or treatment have provided interesting patient populations within which to study the role of MBL. One such group comprises those receiving chemotherapy for malignancy. These patients are rendered neutropenic by their treatment (or underlying disease process) and are subsequently at increased risk of infectious complications. In 2001, two studies were published reporting an effect of MBL deficiency in such patients. Neth et al. studied 100 children and measured MBL levels and genotype. Children in possession of MBL variant alleles spent twice as many days in hospital with febrile neutropenia during the first 6 months of their treatment compared with wild-type individuals (81). In the other study, Peterslund et al. followed 54 adults undergoing chemotherapy for various haematological malignancies and found that those who developed 'significant' infections (bacteraemia, pneumonia or both) in the 3-week periods post-treatment had significantly lower levels of MBL compared with those without significant infections (82). Subsequent studies have shown differing results, but drawing comparisons between them is inherently difficult. These patients are a highly heterogeneous population, with different underlying disease processes, undergoing treatment regimens of differing intensity, resulting in various degrees of immunosuppression. In one contrasting study, Bergmann et al. followed 80 adults undergoing therapy for acute myeloid leukaemia, which involves intense highly myelosuppressive treatment. They found no effect of MBL deficiency on frequency, severity or duration of fever and suggested that the nature of the treatment overwhelmed any potential influence of MBL (83). Further clinical studies in such patients are required in order to delineate the exact role of MBL.

An MBL double-knockout mouse model has been used to explore the above clinical conundrum. In 2004, Shi et al. demonstrated that MBL null mice were highly susceptible to intravenous inoculation with *Staphylococcus aureus*, all dying within 48 h, compared with 55% survival of MBL wild-type mice. However, when the mice were inoculated via the intraperitoneal route and rendered neutropenic (using cyclophosphamide), neutropenic MBL null mice were found to have higher accumulations of bacteria in the blood and organs compared with neutropenic wild-type mice. By day 8 post-infection, the neutropenic wild-type mice had cleared their blood, but the neutropenic MBL null mice had persistent bacteraemia. The authors were able to reverse the phenotype by treating the MBL null mice with recombinant MBL (84).

MBL and human immunodeficiency virus

To date, nearly 40 million humans have been infected with HIV. The clinical consequences of viral exposure are variable. Some individuals can be repeatedly exposed to the virus but remain free from infection. Others can be infected but remain free from clinical disease. While numerous viral

and host factors will determine the fate of an individual exposed to HIV, there are data to indicate that MBL can influence both susceptibility and severity of HIV infection.

The likely target for HIV binding is the heavily glycosylated glycoprotein, gp120. While MBL can be readily demonstrated to bind to purified gp120 (85), the capacity of MBL to neutralize primary HIV isolates is less convincing. Recent data indicate the MBL can opsonize HIV but does not induce neutralization at the levels at which it is normally present in serum. However, binding and opsonization of HIV by MBL may alter virus trafficking and viral antigen presentation during HIV infection. MBL may influence uptake by dendritic cells (DC), which express a cell surface lectin called 'DC-specific intracellular adhesion molecule 3-grabbing non-integrin' (DC-SIGN). DC-SIGN has been shown to mediate a type of infection called 'trans'-infection, where DC bind HIV and efficiently transfer the virus to T cells. Preincubation of HIV strains with MBL prevents DC-SIGN-mediated trans-infection of T cells and indicates that at least *in vitro*, MBL may inhibit DC-SIGN-mediated uptake and spread of HIV (86).

Whatever the mechanism of MBL interactions with HIV, a number of clinical studies have suggested that deficiency of MBL is a risk factor for acquiring HIV infection.

MBL deficiency appears to increase the acquisition of HIV infection by between three- and eightfold (87–90). There is also an increased risk of vertical transmission from infected mothers to their offspring (91). However, these findings have not been replicated in all populations, with some studies failing to demonstrate a role for MBL in HIV infection (92–94). There is even less clarity with regard to the role of MBL in HIV disease progression. Garred et al. (87) demonstrated that men with MBL variant alleles had a shorter survival time following the onset of acquired immune deficiency syndrome (AIDS) than did patients with wild-type MBL alleles. However, in a well-characterized cohort of homosexual men, variant MBL alleles had an insignificant effect on survival following the diagnosis of AIDS (95). In this latter study, there appeared to be a protective effect of MBL variant alleles, with a delay in the development of AIDS from the time of HIV seroconversion. Patients with MBL variant alleles had lower CD4 counts at the time of developing AIDS, indicating that MBL deficiency may influence the onset of AIDS for any given CD4 count. Furthermore, MBL mutations appeared to protect against the development of Kaposi sarcoma, a finding that was difficult to explain (95). In another study, Prohaszka et al. (90) found that MBL levels were lower in asymptomatic HIV-positive individuals compared with HIV-negative controls. However, the protective effect of MBL was lost in patients with an AIDS diagnosis; patients with high MBL levels had significantly lower numbers of CD4 cells. A possible explanation is that enhanced proinflammatory cytokine production in advanced HIV disease acts to increase MBL synthesis (96), elevating levels in patients with late-stage disease. Indeed, a recent study has shown *in vitro* that MBL can enhance proinflammatory cytokine production and viral replication (97). In the light of studies indicating a role for MBL in inflammatory modulation, it is tempting to suggest that under some circumstances, MBL may act to promote inflammatory cell activation, thereby accelerating the rate of CD4+ T-cell depletion.

Few studies have assessed the impact of MBL in the context of effective antiviral therapy. However, one study has attempted to relate MBL status and HIV-infected long-term non-progressors (LTNPs) (98). MBL levels were consistent with a wild-type genotype in the six LTNPs studied. Amoroso and colleagues had also suggested such an effect in a study showing that children with rapidly progressing disease were more likely to have MBL variant alleles (codon 54) than slower progressors (99).

MBL in infection susceptibility and modulation of inflammation

MBL and cystic fibrosis

Cystic fibrosis provides an example of a clinical condition where MBL appears to be exerting its role as an infection susceptibility gene and inflammatory modulator. Garred et al. were the first group to report that patients with MBL variant alleles have significantly impaired lung function and decreased life expectancy in comparison with wild-type individuals (100). The effect of MBL deficiency on the severity of lung disease was most apparent in patients with chronic *Pseudomonas aeruginosa* infection and it was also found that *Burkholderia cepacia* infection was more common in patients with MBL deficiency. In 2004, Davies et al. reported that an effect of MBL was only seen in adults homozygous for MBL mutations. These patients had significantly reduced lung function, more frequent hospital admissions and raised systemic inflammatory markers. However, there was no evidence of increased susceptibility to *Burkholderia cepacia* and *Pseudomonas aeruginosa* (101). Whether MBL has an effect on early colonization with *Burkholderia cepacia* and *Pseudomonas aeruginosa* or subsequent secondary viral infections or whether there is an (anti)inflammatory effect on subsequent lung damage remains unclear.

Systemic inflammatory response syndrome and myocardial infarction

Clinical studies of critically ill patients requiring intensive care management have shown that individuals who are MBL deficient are more likely to develop the systemic inflammatory response syndrome (SIRS) (Figure 5) and progress to septic shock and death (102, 103), findings which may well relate to the proinflammatory cytokine response.
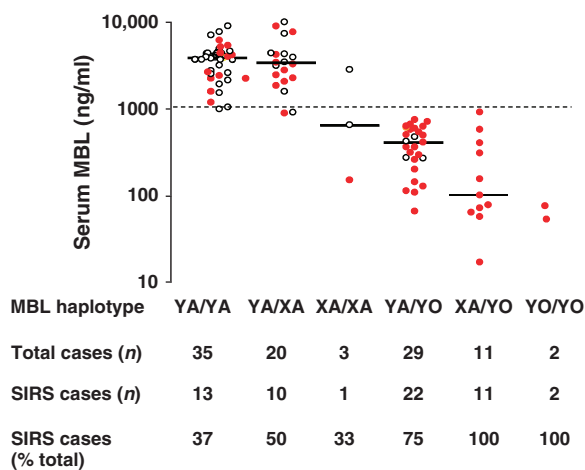
MBL haplotype	YA/YA	YA/XA	XA/XA	YA/YO	XA/YO	YO/YO
Total cases (*n*)	35	20	3	29	11	2
SIRS cases (*n*)	13	10	1	22	11	2
SIRS cases (% total)	37	50	33	75	100	100

Figure 5 Serum MBL levels, MBL haplotype and development of SIRS. Serum MBL level is plotted against MBL haplotype (exon 1 and X/Y promoter polymorphisms, where O indicates the presence of B, C or D variants). Haplotypes are grouped from those associated with the highest serum levels (YA/YA), to those associated with the lowest levels (YO/YO). Red circles show cases that developed SIRS; open circles, cases that did not develop SIRS [Adapted from Fidler et al. (103)]. MBL, mannose-binding lectin; SIRS, systemic inflammatory response syndrome.

It should also be noted that chronic inflammation is now increasingly accepted to be a risk factor for myocardial infarction (MI), and a recent study by Saevarsdottir et al. has found that patients with high MBL levels have a decreased likelihood of suffering a MI – again suggesting a potential role for MBL in modulating the inflammatory response (104).

MBL and autoimmune disease

As a component of the complement system with similarities to C1q, but also as a player in infectious and inflammatory processes, the structure and function of MBL have prompted studies exploring a possible role in autoimmune conditions. Systemic lupus erythematosus (SLE) has been the focus of a number of MBL genotyping studies, but the results have been somewhat inconsistent. Nevertheless, a recent meta-analysis has reviewed studies in this area and found that MBL variant alleles are indeed SLE risk factors (105). As with infectious disease, there is some evidence that the risk of pathology increases if there is another co-existing immune defect. For example, in a cohort of Spanish patients, the odds ratio for developing SLE was 2.4 for individuals with MBL deficiency, but this increased to 3.2 when there was also a co-existing partial C4 deficiency (106). Studies in patients with SLE have reported that MBL deficiency also influences their risk of developing certain complications, which include arterial thromboses (107) and respiratory tract infections (108, 109).

A role for MBL in the pathogenesis of rheumatoid arthritis has also been suggested. Malhotra et al. reported that changes in IgG glycosylation secondary to the underlying disease results in MBL-associated complement activation (110). Such complement activation then contributes to chronic inflammation of the synovial membrane. However, Graudal et al. found that patients with lower MBL levels experienced earlier, more severe, symptoms and had more rapid joint destruction as visualized radiologically (111).

MBL – the future

Several recent research publications suggest the directions in which future work on this collectin and its associated molecules may proceed. These include therapeutic interventions, functional assays and the evaluation of the importance of MBL in disease. These are considered briefly below.

Therapeutic potential of MBL

MBL replacement was first attempted (without any knowledge of the deficiency) when fresh frozen plasma was given to patients and found to correct the opsonic defect (28, 29). Since then, affinity-purified, plasma-derived MBL has been safely given to many patients, resulting in normalization of enzyme-linked immunosorbent assay detectable MBL and complement-mediated opsonic activity (112). A phase 1 study showed the half-life of the protein to range between 18 and 115 h (113). The development of recombinant MBL is also at the phase 1 trial stage and such developments provide exciting prospects for the future exploration of the therapeutic potential of MBL. Exactly who would benefit from replacement therapy is under debate and the importance of targeting well-defined patient groups will be vital to its success.

Functional investigations of the MBL and ficolin-lectin pathways

The discovery of other components of the lectin pathway including the ficolins and the MASPs indicates that this limb of the immune system is complex and extends beyond MBL and MASP-2 alone. This knowledge enables us to question the impact of these molecules either in isolation or in combination. Functional assessment of the lectin pathway may be a far more accurate and clinically relevant measurement than MBL level and/or genotype alone. A number of different assays have been reported, which assess activity at different stages of the functional pathway; therefore, the results must be interpreted accordingly (114, 115).

The impact of deficiencies of the various adjunctive components is also the subject of much current research.

In 2003, Stengaard-Pedersen et al. reported the first identified case of MASP-2 deficiency (116). Functional analysis of the ability of MBL to activate the lectin pathway, estimating C4b deposition on a mannan surface, was performed on a group of patients with suspected immuno-deficiency. One patient was found to have deficient pathway activity despite having sufficient MBL. No MASP-2 or Map19 was found in the plasma, and genetic analysis indicated that the patient was homozygous for a point mutation in exon 3 of the gene (D105G). Clinically, the patient suffered from recurrent infections and autoimmune symptoms. Subsequently, the frequency of this mutation has been assessed in a small number of populations and values range from 1.3% to 6.3% (117). As discussed previously, the contribution of MASP-1 and MASP-3 in the pathway remains unexplained.

The role of ficolins is now beginning to be addressed in clinical studies. Like MBL, no absolute levels of deficiency have yet been defined. Atkinson et al. studied more than 300 children with recurrent respiratory tract infections and measured L-ficolin levels (118). An association with MBL deficiency in the same patient cohort had already been reported (119). In this study, low levels of L-ficolin were more common in patients than in controls and most common in patients with co-existing atopic disorders, suggesting a role for L-ficolin in protection from micro-organisms complicating allergic disease. Polymorphisms in the ficolins have been identified, although their clinical significance is as yet unknown.

How important is MBL in human disease?

MBL is an ancient molecule, which has probably been subject to a large number of evolutionary pressures. The last 50,000 years of human evolution have been associated with major changes as hominids moved from an essentially nomadic lifestyle to increasingly crowded living arrange-ments in large settled communities. Associated with these changes, the spectrum of common infectious diseases would also have changed. More recently, the introduction of antibiotics, the emergence of novel infections and increasing use of immunosuppressive therapies have provided new challenges to our innate host defence system. Despite all these changing evolutionary pressures, MBL gene poly-morphisms persist at high frequencies, suggesting that they offer potential advantages to the host. Thus, there exists a balance in which certain individuals benefit from the expression of high levels of the protein, whereas others (living in differing environments, eg. the tropics) may benefit from reduced levels of circulating MBL (Figure 6).

MBL status may also be either advantageous or disadvantageous when considered from the viewpoint of the severity of a particular illness. Thus, it is known that those with higher levels of MBL are better able to modulate inflammation, probably through an effect on cytokine responses. In contrast, those deficient in MBL appear to be at risk of sepsis and SIRS. For these reasons, we believe that analyses of the relevance of MBL (120) should be extended beyond its role in infectious disease and include clinical areas such as autoimmunity and inflammatory disorders.
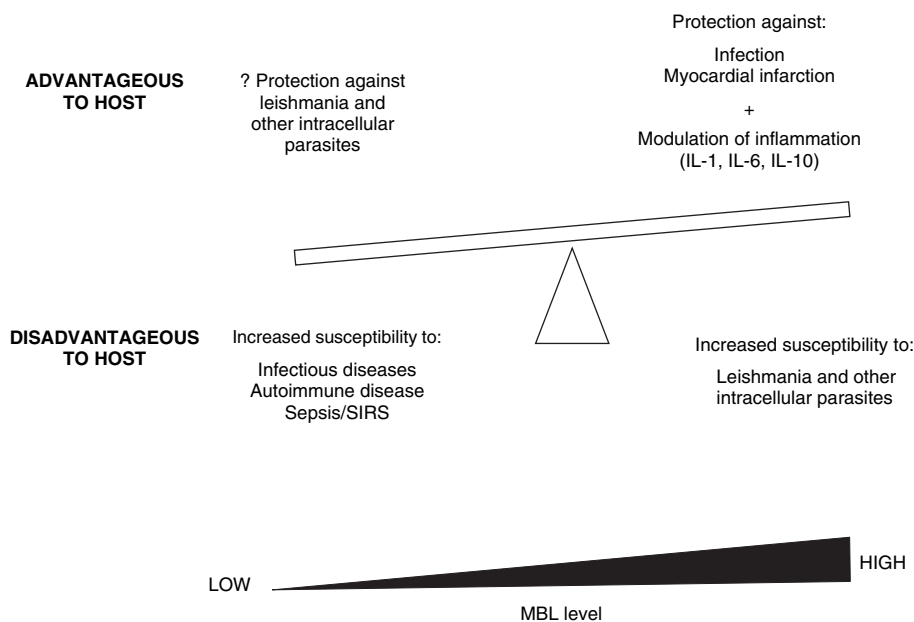

Figure 6 Schematic representation illustrating how both high and low serum MBL levels may impact the health of a given host. IL, interleukin; MBL, mannose-binding lectin.

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