Review Article

Mannose-Binding Lectin: Biologic Characteristics and Role in the Susceptibility to Infections and Ischemia-Reperfusion Related Injury in Critically Ill Neonates

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The mannose-binding lectin (MBL) is a member of the collectin family, belonging to the innate immunity system. Genetic, biologic, and clinical properties of MBL have been widely investigated throughout the last decades, although some interesting aspects of its potential clinical relevance are still poorly understood. Low circulating concentrations of MBL have been associated with increased risk of infection and poor neurologic outcome in neonates. On the other hand, an excessive and uncontrolled inflammatory response by the neonatal intestine after the exposure to luminal bacteria, leading to an increased production of MBL, may be involved in the onset of necrotizing enterocolitis. The purpose of the present review is to summarize the current knowledge about genetic and biologic characteristics of MBL and its role in the susceptibility to infections and to ischemia-reperfusion related tissue injuries to better explore its clinical relevance during the perinatal period and the possible future therapeutic applications.

1. Introduction

The mannose-binding lectin (MBL) is a protein of the innate immune system, belonging to the collectin family, able to deploy a variety of antimicrobial activities. It recognizes and binds various pathogens (including bacteria, viruses, fungi, and parasites), providing protection against the microbial invasion of the host [1]. Although the clinical impact of MBL deficiency and its association to a wide variety of diseases has been extensively studied, the clinical significance of low MBL serum levels in healthy subjects is still debated. The image is that of a mosaic, as studies suggest a detrimental or beneficial or no impact of low or high MBL serum levels on the susceptibility to different diseases. In early life MBL insufficiency seems to have clinical relevance in the presence of immunodeficiency and whenever the immune system is particularly challenged [2]. Consecutively, MBL could play a critical role in the first line defence during the neonatal period, when the maternal-derived antibodies disappear and the child’s own immune system is immature [3, 4]. In the same period of life, MBL seems also to play a role in contact guidance of neuronal migration, interneuronal recognition, myelinization, and tightening of the ependymal cell barrier [5].

While low MBL serum levels have been associated to an increased risk of nosocomial sepsis [6, 7] and of neurological risks [8] in neonates, recent studies performed in rodents support the role of MBL in the exacerbation of tissue damage (myocardial, gastrointestinal, cerebral, and renal tissues) in the course of ischemia-reperfusion injuries, by the activation
of the lectin pathway of the complement. According to these data, we found that MBL-2 genotypes associated with high MBL serum levels represent a risk factor for necrotizing enterocolitis (NEC) in preterm neonates [9].

In conclusion the role of MBL, the exact clinical significance of the different MBL haplotypes and, consecutively, the associated serum MBL levels, is still poorly understood and needs to be further elucidated. Furthermore, it is still unclear if the exogenous administration of MBL may have protective or rather harmful effects on the host’s organism [10].

The purpose of the present review is to summarize the current knowledge on the clinical role of MBL, especially during the perinatal period, and address controversial issues, discussing at the end on its possible future therapeutic applications.

2. MBL: Protein and Biologic Properties

The human MBL2 gene product is a 24 kDa polypeptide characterized by a 248-amino-acid sequence, with four distinct regions, a cysteine-rich N-terminal region, a collagenous domain, a short α-helical coiled-coil domain, the so-called neck region, and a carbohydrate-recognition domain, and forms the prominent globular head of the molecule. Three polypeptide chains form a triple helix through the collagenous region, stabilized by hydrophobic interaction and interchain disulphide bonds within the N-terminal cysteine-rich region. This trimeric form is the basic structural subunit of all circulating forms of MBL. Larger molecules can be obtained by the oligomerization of these homotrimetric subunits [11, 12] (Figure 1). The highly ordered oligomeric structure, the spacing, and orientation of the carbohydrate-recognition domains define what ligands MBL can target and are essential for its function. Through the carbohydrate-recognition domain MBL binds to specific carbohydrates such as mannose or N-acetylglucosamine that are exposed on the surface of a number of pathogens such as bacteria, viruses, parasites, and fungi [13–15]. For this reason, MBL belongs to the group of the so-called “pattern recognition molecules” [16] that mediate the precocious activation of the immune response. MBL is produced by the liver [15, 17–19] and released in the serum under stress conditions [20, 21] as a calcium-dependent acute phase protein. Significantly increased circulating levels have been reported in response to infections. During inflammatory conditions MBL can also leave the blood stream due to vascular leakage and can be detected in the mucus of the middle ear, in upper airway secretions, in inflamed synovial fluid, and in the normal amnion fluid [22, 23]. MBL activates macrophages [24], enhances phagocytosis [25, 26], and plays a role in complement activation by inducing the antibody-independent lectin pathway [1, 13, 16, 27–31]. In particular, MBL, in cooperation with three MBL-associated serine proteases (MASPs 1, 2, and 3), is able to initiate the lectin pathway of complement activation, the release of cytokines, and coagulation factors. A single MASP entity was initially identified and characterized as a protease with the ability to cleave complement proteins C4, C2, and C3 [31, 32]. MASP was indeed a mixture of two related but distinct proteases, MASP-1 and MASP-2 [30]. A third protease, MASP-3, is also shown to be associated with MBL [33]. It is generally believed that MASP-2 is the initiator of the lectin-complement pathway, while the role of the other MASPs is still uncertain [34]. MASPs additionally form active complexes with Ficolin-1 (M-Ficolin), Ficolin-2 (L-Ficolin), and Ficolin-3 (H-Ficolin), which are also defence collagens [35–37].

In the case of tissue damage after ischemia-reperfusion, MBL rapidly deposits on target cells and forms an IgM-MBL complex as soon as a specific autoreactive IgM binds to exposed tissue antigens and triggers the downstream complement activation in the acute phase, enhancing the cleavage of C3 [38]. Small amounts of MBL are also produced in organs other than the liver such as brain [39], kidney [40, 41], spleen [42], tonsil [43], thymus, small intestine [44], testis [42, 44], ovary [41], and vagina [45], suggesting that local expression of MBL may be relevant in local immune defence.
The structural differences due to the variant alleles. 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. In the wild type, the correct repetition of Gly-Xaa-Yaa permits the association of three identical polypeptide chains generating the structural subunit. This subunit is stabilized through disulphide bonds in the collagen-like region, with a high-order MBL oligomer formation. The mutations in exon 1 generate three amino acid substitutions in the collagen-like region; two of these substitutions disrupt the Gly-X-Y repeats by exchanging a glycine residue with aspartic acid (variant B) or with glutamine (variant C). A third substitutes a cysteine for an arginine (variant D). These amino acid substitutions disrupt the assembly of the MBL molecule, generating a nonfunctional low-order oligomer formation [15, 46].

3. MBL: Genetics

In 1989, the gene structure of MBL and the protein were identified by Taylor and Sastry [48, 49]. The human MBL gene (MBL2) was cloned and sequenced and has been located in the chromosome 10q11.1–q21. Comparison of the genomic nucleotide sequence of MBL2 with the cDNA sequence revealed that the protein-coding region consists of four exons interrupted by three introns of 600, 1350, and 800 base pairs in size, respectively. Exon 1 encodes the signal peptide, a cysteine-rich domain, and seven copies of a repeated glycine-Xaa-Yaa motif typical for the triple helix formation of collagen structures (Xaa and Yaa indicate any amino acid). This pattern is continued by additional 12 glycine-Xaa-Yaa repeats in exon 2. Exon 3 encodes a neck region and exon 4 a carbohydrate-binding domain. The resulting protein consists of oligomers each with three identical polypeptide chains of 32kDa as evaluated on Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE). The liver synthesizes the protein as structures consisting of three–six oligomers [50] (Figure 1).

3.1. MBL2 Gene Polymorphisms. The presence of variant alleles of the MBL2 gene encoding three different structural variants of the MBL polypeptide is strongly associated with MBL deficiency. Five single nucleotide polymorphisms (SNPs) in the MBL2 gene lead to variations in quantity or function of MBL in serum. Two SNPs are localized in the promoter region, at positions −550 (H/L variant) and −221 (X/Y variant), and one is localized in the 5′ untranslated region at position +4 (P/Q variant) [51, 52] (Figure 1). They affect the expression of the MBL2 gene. The haplotypes HY, LX, and LY correlate with high, medium, and low promoter activity, in agreement with the serum measurements [49]. The other three functional SNPs are situated in exon 1, exactly in codon 52 (allele D) [51], in codon 54 (allele B) [2], and in codon 57 (allele C) [53], and result in the disruption of the repeated Gly-Xaa-Yaa structure of the collagenous triple helix by substituting the essential glycine residue with cysteine, aspartic acid, and glutamic acid, respectively [54]. All three variants prevent the assembly of MBL subunits into the basic trimer structure, thereby reducing the amount of MBL protein (Figure 2).

The variant alleles are very frequent in normal, healthy populations, where they are present in 20 to 50% of the individuals, with the highest frequencies found in Africans. The B allele is common in Caucasians, Chinese, and Eskimos with gene frequencies of 0.11 to 0.17%, while the C allele is almost exclusively present in Africans, where it is highly frequent (0.23 to 0.29%). The D allele is present in both Caucasians and Africans, although with a lower frequency (0.05% in both) [14]. All population studies have shown a significant dominant effect of the B, C, and D alleles [51].

MBL serum levels are genetically determined, as described by Sorensen, who estimated the heritability of serum MBL levels and MASP-2 activity in an elegant study on adult twins, underlining the contribution of common genes affecting both traits. The data of this study indicate...
Ischemic Ag IgM MBL MASPs C3a C3 C4 C2 C5 C9 C7 C6 C8 C3b Carbohydrates MASP-2 C2a C4b C3b Pathogen membrane

**Figure 3:** A model illustrates the activation of the lectin pathway by natural IgM in I/R injury. IgM binds to the neoepitope in self-Ag and activates the lectin pathway of complement. The downstream events include the releasing of proinflammatory factors C3a and C5a, deposition of the membrane attack complexes C5–C9, recruitment of inflammatory cells, and leading to direct cell damage [38].

**Figure 4:** A model illustrates the activation of the lectin pathway by infective agents. MBL recognizes specific carbohydrates such as D-mannose, L-fucose, and N-acetylglucosamine that are represented on the surface of a wide variety of infectious agents. Engagement of ligand by MBL activates MASPs, which then cleaves the C2C4 convertase and results in the cleavage of C3 and the generation of C3b. It has also been proposed that MASPI can directly cleave C3 [47].

There is a strong genetic influence for the serum levels of MBL and for MASPs activity, with a significant genetic correlation between the two traits. In fact, twin-twin correlations were higher in monzygotic than in dizygotic twins for both traits, which seem to be influenced, although in part, by the same genes. The genetic correlation may also represent a casual relation between the phenotypes [55].

The genetic variability of both the promoter and the exon domains of MBL gene influences the subsequent stability and serum concentrations of the functionally active protein, leading to defect in opsonization and susceptibility to infections [1].

### 4. MBL: Role in the Activation of Complement in Ischemia/Reperfusion Tissue Injury

Many studies have shown a determinant role of the complement system in ischemia/reperfusion (I/R) injury in human and animals. Indeed, during the ischemia and in the following reperfusion, the classical pathway has a pivotal role, but the lectin pathways are also involved. Natural circulating IgM (specific to self-antigens) may bind to antigens exposed by ischemia. Antigen interaction initiates the classical pathway, followed by the activation of C1 and downstream components (C4, C3, and C2). The interaction between IgM and ischemic antigen leads to the exposure of binding for the MBL through the carbohydrate pattern on IgM, and activates the MASPs. The activated MASPs further cleave relevant substrate activating the lectin pathway (Figure 3). Activated MASP-2 very efficiently cleaves the complement factors C4 and C2 to the fragments C4b and C4a and C2b and C2a, respectively, and C4b and C2b join to form a C3 convertase 2 [30, 56]. MASP-1 can cleave C4b-bound C2, but not C4 [47]. Therefore the lectin pathway activation route is deficient in the absence of MASP-2. MASP-1 can augment MASP-2 functional activity by cleaving C2 and possibly enhancing complement activation by conversion of MASP-2 into the enzymatic active form, but it cannot compensate for the loss of MASP-2 functional activity [57, 58].

This way to the complement activation has been implicated in the pathophysiology of myocardial infarction [59], gastrointestinal ischemia [60], and kidney I/R [61]. A recent study shows the benefits of C1 inhibitor administration in a murine model of cerebral I/R and suggests that MBL is involved in this effect [62].

### 5. MBL: Clinical Significance

#### 5.1. MBL and Susceptibility to Infections

MBL recognizes and binds to sugar moieties on the surface of bacteria, viruses, fungi, and parasites. MBL binding causes these microorganisms to agglutinate and allows phagocytic clearance of pathogens as well as lectin-complement pathway activation, through MBL-associated proteases [63] (Figure 4). Since mounting evidence has supported a crucial role of the MBL in the innate immune response during the last years, several studies focused on the association between MBL expression and/or concentrations in the body fluids and the clinical presentation. Likewise to proteins of the acute phase of inflammation, MBL blood levels increase in response to infections. Healthy adult individuals usually have MBL concentrations above 1000 ng/mL, and these levels seem to be not affected by the age, circadian cycle, and physical exercise. During inflammation, MBL levels increase within the 3-4 fold compared to the baseline level [64]. MBL deficiency in adults has been defined as plasmatic concentrations lower
than 500 ng/mL or as an MBL function below 0.2 U/μLC4 deposition [65]. MBL levels may rise under stress to sufficient levels, in individuals who are usually deficient. A positive acute phase response was generally observed in individuals with wild-type MBL2 genes [64].

MBL-deficient adults are characterized by a higher risk, severity, and frequency of infections in a number of clinical settings, although the exact impact of this kind of innate immunodeficiency on the clinical outcome is still poorly understood [66, 67]. Moreover, the risk of developing infections due to low MBL levels seems to be particularly accentuated if associated to other conditions such as cystic fibrosis [68, 69], or after chemotherapy [70–72] and transplantation [73–77].

Nevertheless, despite these results suggesting a protective role of MBL, an excess of MBL activation might be also harmful, due to an unbalanced proinflammatory response leading to additional tissue damage. High MBL activity has been associated with inflammatory autoimmune diseases such as the Systemic Lupus Erythematosus, resulting in organ injury [78]. Furthermore, increased MBL serum concentrations and activity have also been associated with other disorders including transplant rejection [79–84], diabetic nephropathy [85–89], enhanced uptake of mycobacteria [90–93] and Leishmania [94–99], and primary biliary cirrhosis [10, 100, 101].

As for the adult population, low MBL levels seem to represent a risk factor also for the development of neonatal infections [6, 7, 102–104]. Particularly low MBL levels have been detected among preterm neonates [64, 105] and a genetically determined MBL deficiency has been described [106, 107], leading to a significant interindividual variability of serum MBL concentrations in the neonatal period.

Low MBL concentrations already in the cord blood were found to correlate with a higher incidence of gram-negative sepsis [4]. Low MBL serum levels on admission to the Neonatal Intensive Care Unit are associated with an increased risk of nosocomial sepsis, independently on gestational age (GA) [6]. Since such low serum MBL concentrations have been reported among septic neonates, a possible role of MBL as biomarker for the early identification of neonates at risk for infection has been suggested [6, 7, 108, 109]. A prospective observational study performed at our institution, which included 365 critically ill neonates, demonstrated that median MBL serum levels were significantly lower among the infected than among the uninfected neonates. Furthermore, low MBL concentrations on admission represented a risk factor for the subsequent development of infection, independently from GA and invasive procedures. Nevertheless, the MBL levels on admission and the peak levels during infection were not associated with death [7].

Schlapbach et al. found a trend towards an increased incidence rate of severe respiratory symptoms in infants with low MBL concentrations, although this association was not as strong as expected [110]. Other authors found that neonates with MASP-2 deficiency had a shorter mean GA, a higher incidence of prematurity, and lower birth weight (BW). Moreover, a trend towards higher MASP-2 concentrations was found among infected neonates [111].

With reference to the correlation between MBL2 genotypes and serum MBL levels on admission in Neonatal Intensive Care Unit, we observed that only 13.8% of our preterm patients carried a genetically deficient MBL2 haplotype, while 43.1% of babies had deficient MBL levels (<700 ng/mL) on admission to the unit. The finding of a discrepancy between MBL genotypes and serum MBL levels in neonates supports the role of immaturity in causing low MBL levels in neonates. Therefore, in preterm neonates MBL deficiency at birth and in the first month of life seems to be described better by serum concentrations than by MBL genotype [109, 112].

5.2. MBL and Adverse Neurological Outcome in Preterm Infants. Robust epidemiological studies, performed in preterm and term-born neonates, suggest a strong association between fetal infection, inflammation (e.g., chorioamnionitis), perinatal brain damage, and neurological disability in term-born infants. Infection and hypoxia-ischemia, despite being very different types of injuries, can individually trigger the fetal inflammatory response, by activation of the fetal immune system, contributing to preterm brain injury, including periventricular white matter injury [9].

In mice or rats with brain insult induced at 5 days of life by ibotenate administration, after systemic injection of IL-1β, IL-6, TNFα, or IL-9 between first and fifth day of life, a different brain response has been seen, with up to twice the level of brain damage observed in these rodents compared with that observed in nonsensitized animals [113, 114]. Furthermore, in neonates developing later cerebral palsy, an increase of IL-9 plasma level was found without an increase of proinflammatory cytokines. The brain sensitization could be induced by the trigger of neural H1 and H2 receptor, due to release of histamine secondary to the mast cell activation. Also TLR pathway activation (TLR4, TLR3, and adaptor molecule TRIF), leading to cytokines production, seems to be implicated in inflammatory brain sensitization to hypoxia-ischemia insult. The cytokine response due to activation of a common inflammatory pathway could explain the correlation observed between cerebral palsy and the blood cytokine levels of newborn infants born at term [115]. Although a role for neonatal immunity and sepsis has been demonstrated in neonatal encephalopathy, few studies have explored the role of fetal and maternal genetics in predicting the neurological outcome in neonates and whether genetic characteristics of some innate immunity factors may constitute a biomarker of fragility in neonates. In a group of very preterm infants at 24 months of corrected age, we observed that the homozygosity of SNPs of exon 1 of the MBL2 gene was associated with an adverse neurological outcome. Moreover, all the patients with genotype OO had at least one episode of infection during hospitalization and showed an increased risk for intraventricular hemorrhage (IVH) [70]. So, the effect of MBL2 SNPs on neurological development could be indirect in these infants, perhaps mediated by the infection, and the brain damage induced by MBL deficiency may be partially independent of complement cascade, less active in such preterm infants than in more mature babies and in adults. Other MBL mediated mechanisms, related to the marked...
brain immaturity of neonates, may have a role in the genesis of the neurological damage [8].

In a model of traumatic brain injuries in mice, Yager et al. found that MBL deficiency exacerbates acute CA3 (Cornu Ammonis) cells death and cognitive dysfunction, independently of complement activation. This suggests a neuroprotective role for MBL and a functional linkage between innate immunity and neurological outcome after traumatic brain injuries [116]. Yager et al. studied MBL2 genotype in mice and in 135 stroke adult patients (mean age >70 years). At three months of follow-up, they concluded that genetically defined MBL deficiency was associated with a better outcome after acute stroke, without an increased risk of infections in MBL-deficient patients. Moreover, patients with MBL low genotypes disclosed lower serum levels of C3 and C4 than patients with MBL sufficient genotypes [116]. Recently, Cervera et al. confirmed in murine model of middle cerebral artery occlusion the neuroprotective effects of genetic MBL deletion in the acute post-stroke but did not find improvements in either infarct volume or neurological function at 7-day examination [117]. These results are in conflict with each other. If MBL has a protective or harmful role in the physiopathology of the ischemia-reperfusion brain damage is still unclear. According to the studies by Zanetta, we can speculate that MBL may play a protective role in brain development [5]. Mannose rich glycoproteins markedly accumulate during the second and the third postnatal weeks compared with other monosaccharides and are thereafter degraded. They are concentrated at the surface of axons, especially at the surface of parallel fibers (axons of the granule cells, the quantitatively major neuronal cell type in the cerebellum). In premature babies, MBL could promote the contact guidance of neuronal migration, interneuronal recognition, formation of bridges between migrating neurons and radial astrocytes fibers, myelinization, and tightening of the ependymal cell barrier, during the ontogenic development of the brain. A single gene mutation could easily suppress these functions increasing the susceptibility of the brain tissue to various pathogenic insults, as infections and hemorrhages [9].

5.3. MBL and Necrotizing Enterocolitis (NEC). As for adult population, not only MBL deficiency but also MBL hyperproduction seems to have potentially harmful effects. The host immune defence depends on maintaining an appropriate balance between proinflammatory processes and apoptosis. Immaturity of the inflammatory pathways could increase susceptibility to apoptotic activation, upsetting this balance, and result in increased apoptotic tissue damage during bacterial infection. The onset of an excessive and uncontrolled inflammatory response by the neonatal intestine after the exposure to luminal bacteria may trigger the onset of necrotizing enterocolitis. Polymorphisms of the MBL2 gene associated with high expression of active serum and tissue proteins may predispose perterm neonates to develop NEC and generate the pathophysiology of NEC, which contributes to the disease progression [9].

MBL is expressed by hepatocytes, but Sastry et al. observed low extrahepatic levels of MBL-2 mRNA, predominantly in small intestine [49]. Prencipe et al. detected the expression of MBL protein in the diseased guts of preterm infants with NEC: MBL was strongly expressed in enterocytes, in endothelial cells, and in histiocytes of the small intestine and colon. Moreover, they observed a positive staining for MBL also in enterocytes of intestinal tissues from healthy infants. The −221 promoter MBL-2 variant allele Y, associated with higher serum MBL levels, was shown to be significantly more common in neonates with NEC than in control neonates. Moreover, a significant association of the −221 YY promoter genotype and of the combined exon 1/promoter −221YA/YA genotype, both causing high MBL protein levels, with a higher risk of developing NEC, independently GA, was observed. MBL-2 genotypes related to low MBL levels were shown to be associated with a decreased mortality among neonates with severe NEC, suggesting that MBL levels may affect the outcome of NEC and further supporting the hypothesis of a role of high MBL levels in contributing to intestinal damage [9].

6. MBL: Future Perspectives

The observation that low MBL levels represent a risk factor for infection development and severity suggested that the external administration of MBL may be beneficial. Therefore, MBL replacement treatments in critically ill neonates with severe infections are currently discussed, although still far to be applied in clinical practice. However, considering the increased risk of some disorders which have been associated with an uncontrolled production of the MBL (as described above in the text), the potential prophylactic/therapeutic MBL administration should be carefully investigated prior to embarking upon potentially dangerous strategies [12, 118]. Despite the large number of studies investigating the role of MBL, the exact clinical significance of the different MBL haplotypes and, consecutively, the associated serum MBL levels is still poorly understood and needs to be further elucidated, especially in neonates, in which such pathways are not fully developed and functionally mature. In particular, it is still unclear if the response to infection could be blunted or rather exaggerated by the early administration of MBL before the infection development. Population studies have revealed unexpectedly high frequencies of structural MBL gene mutations. It has been suggested that this may reflect a selection advantage for reduced activities of MBL-associated immune mechanisms, such that, for example, individuals with lower levels of MBL might be protected against the complement-mediated damage associated with inflammatory diseases.

The possibility to understand the genetic contribution of specific responses to immunomodulatory agents is a challenge of the current research on infections and inflammatory illness. SNPs of the MBL2 gene could predict the susceptibility to specific pathogens or complications of infections, allowing us to implement unconventional strategies of prophylaxis and therapy.

In addition, the importance to know the MBL involvement in brain injury, participating in the activation of the inflammatory response, could be important because the
induced brain damage due to a first insult makes the developing brain more susceptible to a second insult. Understanding the role of MBL in brain insult and whether the MBL levels could be correlated with neurological outcome could be a possible end point for new study, that is, in newborn with hypoxic/ischemic encephalopathy treated with whole body hypothermia.

**Abbreviations**

CRD: Carbohydrate-recognition domain  
GA: Gestational age  
I/R: Ischemia/reperfusion  
IVH: Intraventricular hemorrhage  
MASPs: MBL-associated serine proteases  
MBL: Mannose-binding lectin  
NEC: Necrotizing enterocolitis  
SNPs: Single nucleotide polymorphisms.

**Competing Interests**

The authors declare that there is no conflict of interests regarding the publication of this article.

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