Mannose-Binding Lectin: Ancient Molecule, Interesting Future

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(See the article by Eisen et al. on pages 510–6)

Five hundred sixty-five million years ago, when the world was empty and barren because animal life had not colonized land yet, a common ancestor that we share with sea squirts (Ascidians) inhabited the seas. One of the genes that we still share with sea squirts today is a gene for mannose-binding lectin (MBL), signifying that this gene has existed for $>565$ million years [1,2] and, thus, has been highly conserved throughout animal evolution. Surely, this must indicate that MBL, the molecule encoded by the gene $MBL2$ in humans, is crucial for survival of all kinds of species; otherwise, the gene would have quickly been lost as a result of natural selection.

But do humans really need it? There is a large body of data that indicate that low serum MBL concentration or $MBL2$-variant alleles that confer to low serum concentration are associated with an increased risk of infectious diseases, a more severe course of infection, and an increased risk of autoimmune diseases, cardiovascular diseases, and cancer. Conversely, a large population-based prospective study of MBL deficiency in $>9000$ adults from Scandinavia failed to reveal an effect of MBL deficiency on the morbidity and mortality associated with infectious diseases [3]. Moreover, recent evolutionary evidence indicates that the high worldwide prevalence of $MBL2$ deficiency or low-producing alleles is caused exclusively by human migration and genetic drift, indicating that $MBL2$ variation does not have strong effects on population fitness [4]. These findings suggest that MBL is largely redundant in innate defence against infection and that the effects of MBL on susceptibility to or the course of infectious diseases are small, evident only in combination with other immunodeficiencies, or merely present in the context of specific or rare infections. Consequently, studies that address the role of MBL in infectious diseases should either include large groups or focus on patients with specific conditions. Unfortunately, few studies of MBL have been performed with a large sample size; therefore, conflicting results have been reported.

In this issue of Clinical Infectious Diseases, Eisen et al. [5] present a reanalysis of risk of death due to MBL deficiency from 6 previous studies with a total of 477 patients who had diverse infections, ranging from well-defined pneumococcal disease to undefined intensive care unit–acquired septic shock. The authors defined MBL deficiency as a serum MBL concentration $<0.5 \, \mu g/mL$; this cutoff value was based on reassessment of data from 4 studies with a total of 1642 control subjects. To our knowledge, this is the largest study to date to address these questions. The authors revealed that a serum MBL concentration $<0.5 \, \mu g/mL$ (obtained $<48$ h after hospital admission) was associated with an increased likelihood of death in patients with severe bacterial infections (OR, 2.11; 95% CI, 1.30–3.43), especially in the (largest) subcohort of patients with pneumococcal infection (OR, 2.65; 95% CI, 1.03–6.81) in the univariate analysis.

These are convincing results and are especially important because they were found in a large group of relatively unselected patients. The findings might have important implications for the current understanding of the role of MBL deficiency and therapeutic options in severe infections, and they raise some interesting questions.

First, what explains the higher mortality among patients with serum MBL concentration $<0.5 \, \mu g/mL$? Is this related to more severe initial infection caused by MBL deficiency, and do MBL-deficient patients have higher disease severity scores and a higher incidence of bacteremia [6]? Is the increased mortality not attributable to the primary insult but rather caused by...
increased infectious complications in the ward during recovery [7]? Or because MBL binds to apoptotic and necrotic cell debris, is the increased mortality caused by impaired reparation mechanisms during recovery a result of infection [8]?

Second, is the effect on mortality stronger in patients with lower serum MBL concentrations? It would be interesting to know the mortality rates among patients completely deficient of MBL or with serum MBL concentrations <0.1 μg/mL, although the sample size might have been too small for this analysis. Because these patients are expected to have more severe immunodeficiency, the effect may be more significant in these groups. On the other hand, they also might have less severe (complement dependent) inflammation and, thus, be protected from severe systemic inflammatory response syndrome, which has been suggested for patients with meningococcal sepsis and a terminal complement deficiency [9]. The latter hypothesis needs to be answered before clinical trials of MBL supplementation for severe sepsis are performed.

Third, do these results mean that we should treat MBL-deficient patients who have severe pneumococcal infections with MBL supplementation? Because mortality associated with sepsis was 25% among the MBL-deficient group and 12% among the MBL-replete group, there might be a significant benefit from such a therapy. It needs to be stressed that supplementation must be started as soon in the diseases process as possible; therefore, MBL deficiency should be assessed quickly.

The study by Eisen et al. [5] also has some pressing caveats. The most important problem is that it cannot be ruled out that the low MBL concentrations that the authors found in patients who died were caused, at least in part, by capillary leak, fluid resuscitation, or consumption of MBL caused by severe disease. According to this phenomenon, low MBL level would not be related causally to death but would be only a mere bystander of severe disease. A second concern is the definition of clinically relevant MBL deficiency. The cutoff value is high as only includes most individuals with YO/YO and XA/YO genotypes, but it also includes >50% of patients with YA/YO genotypes and >25% of patients with XA/XA genotypes. Although such a high cutoff level may be very specific, it is overinclusive. This means that it a large proportion of patients treated with MBL supplementation on the basis of these criteria probably will not benefit.

The authors of the study should be applauded for their efforts to reanalyze these various previously performed studies. Analysis of the effect of MBL on morbidity and mortality associated with different infectious diseases requires large groups of patients and, thus, necessitates a combination of data from different studies. It is disappointing that some data files, containing data on a large number of patients, remained unavailable to the authors, because availability of these data would certainly have strengthened their results and would have made some interesting subgroup analyses possible. Large studies such as the study by Eisen et al. [5] are essential to fully detail the role of MBL in infectious and other diseases, and we appeal to the scientific community to fully cooperate with these kinds of studies.

Acknowledgments


References