Scientific background

Mannan-binding lectin (MBL; also called mannose-binding lectin or protein) is a key factor in innate immunity. MBL is a multimeric carbohydrate-binding protein produced in the liver and secreted into the blood. Here it defends the body against invading microorganisms, including bacteria, viruses, protozoa and fungi.

1. MBL activation of the complement system

Most microorganisms have carbohydrate chains on their surface which differ from the carbohaydrates on the host cell surfaces. On specific binding to microbial surface

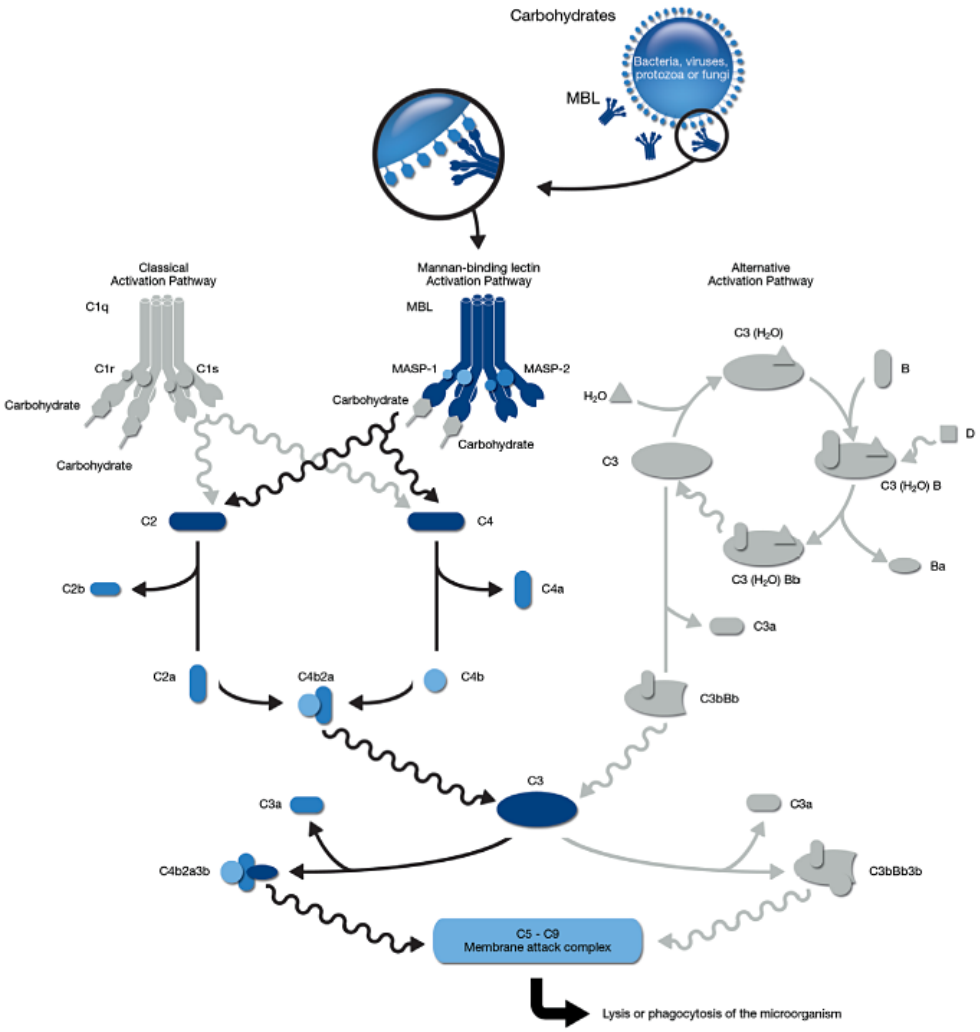

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Figure 1: Complement activation pathways with the mannan-binding lectin pathway in blue.

carbohydrates, MBL activates the complement system by means of its own lectin pathway, (Figure 1), which depends on activation of the MBL-associated serine proteases (MASPs).

The complement system consists of multiple plasma and membrane proteins designed to destroy invading microbes. Much of its early reaction sequence behaves like a biologic avalanche in which one component activates further components down the line by proteolysis and complex formation. This proteolytic cascade allows for a well regulated, rapid and powerful amplification system. Some proteolytic fragments promote the inflammatory response, while others facilitate phagocytosis.

Three activation pathways have been characterized in the complement system. The three pathways are triggered differently but merge at a critical, junctional step involving complement component C3. The result is the same for all pathways – an attack on the foreign microorganism.

Only the normally oligomerized forms of MBL (Figure 2) are capable of associating with the MASPs and binding efficiently to the microbial carbohydrates, thus activating complement via the MBL or lectin pathway.

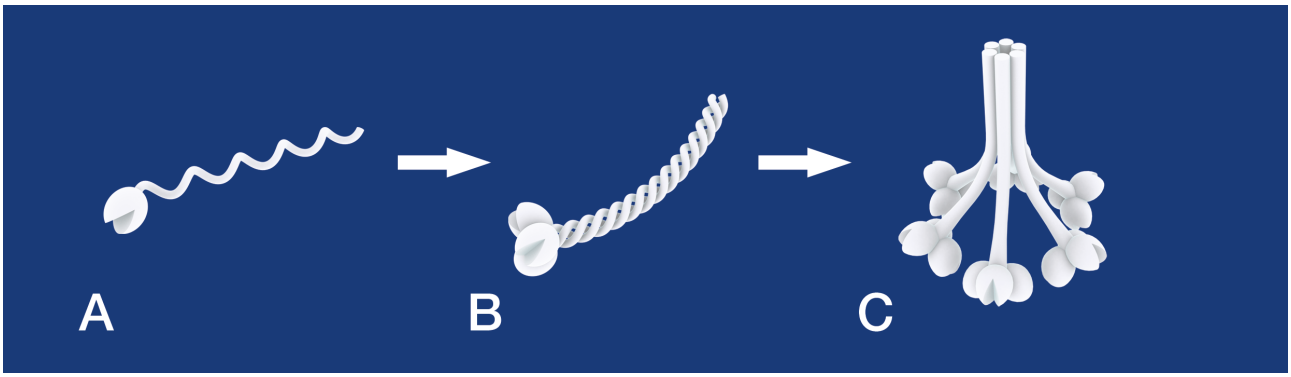

Figure 2: The MBL oligomer molecule.

The MBL oligomer consists of up to 18 MBL protein chains. 3 protein chains are joined in a spiral to form a subunit shaped like a three-petaled flower and up to 6 of these subunits are joined together to form the complete molecule.

2. Effect of genetic variants on MBL function and serum levels

MBL deficiency can be caused by allelic variants in the promoter (H/L, Y/X and P/Q variants) and/or structural region (A/B/C/D variants) of the MBL gene. Certain promoter alleles (L and X) are associated with lower serum concentrations of MBL, while the structural variants B, C or D impair both normal oligomerization of MBL and total chain synthesis (Figure 3).

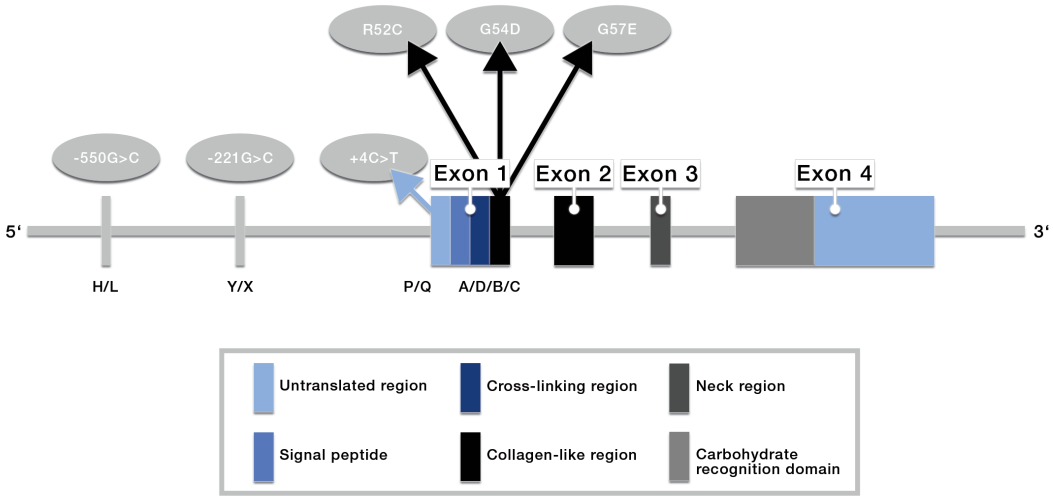

Figure 3: Schematic presentation of the MBL gene and promoter region. Points of mutation are indicated.

Subjects who are homozygous for a structural defect show very low levels of oligomerized MBL, while heterozygotes show low-intermediate levels. In 100 healthy Danish blood donors, serum MBL concentrations determined by an oligomer-selective immunoassay showed low values (<50 ng/ml) in 12 individuals (= 12%)[1]. These were due to a variety of combinations of structural and/or promoter alleles.

MBL concentrations in serum or plasma from healthy human donors as measured by the AntibodyShop MBL ELISA Kits and analogous assays range from 0 to 8000 ng/mL. Values below 100 ng/mL may be found in O/O structural genotypes (where O = B, C or D) regardless of

promoter genotype, or in A/O structural genotypes (where A = wild-type) in combination with HY/LX or LX/LY promoter genotypes, or in the LX/LX promoter genotype (Table 1).

Values between 100 ng/mL and 1000 ng/mL may be found in A/O structural genotypes or in LX/LY or LX/LX promoter genotypes. Values above 1000 ng/mL are associated with wild-type MBL (A/A), although A/D heterozygotes may occasionally reach this level. The HY/HY promoter genotype typically shows values above 1500 ng/mL for wild-type MBL, but such values are also shown by other promoter genotypes in the absence of O structural alleles.

Structural genotype	Promoter genotype					
	HY/HY	HY/LY	LY/LY	HY/LX	LX/LY	LX/LX
A/A	>1500	>1000	>1000	>1000	>600	0-250
A/O	600-800	200-1500	200-400	<50	<50	not found
O/O	≈50	<50	<50	not found	not found	not found

Table 1: Correlation between MBL genotype and serum MBL concentrations (ng/ml). MBL levels were determined by the MBL Oligomer ELISA, KIT 029[1].
O = B, C or D. Values in A/D genotypes are generally higher than in A/B or A/C genotypes.

Clinical studies have historically used cut-off values of 50 ng/mL or 100 ng/mL for defining severe MBL deficiency. But recent clinical studies have used higher cut-off levels to define relative MBL deficiency. For example, a value below 300 ng/mL is now used to qualify patients for entry to clinical studies of recombinant human MBL replacement therapy. In any case, values below these cutoffs have in certain individuals been reported to be associated with a history of increased susceptibility to infection.

3. Clinical significance

The determination of MBL concentrations in serum may be useful for the elucidation of suspected immune defects and as a prognostic indicator alerting to the need for heightened therapeutic or prophylactic measures for many patients.

Deficiency of functional MBL has been reported to be associated with increased susceptibility to infections in the following circumstances:

Immature adaptive immune system

- In early childhood[2,3,4,5]

Immunosuppression

- During cancer chemotherapy[6,7]
- After organ transplantation[8,9]

MBL deficiency is also associated with increased disease severity in:

Autoimmune diseases

- Systemic lupus erythematosus (SLE)[10,11,12]
- Rheumatoid arthritis[11,13]

Immunocompromised individuals

- Cystic fibrosis[14,15,16]
- Meningococcal disease[17,18,19]

Unexplained recurrent miscarriages[20,21,22]

- >70% of women who have had more than 4 miscarriages are MBL deficient.

4. References

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