International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2015): 78.96 | Impact Factor (2015): 6.391

Role of Mannose Binding Lectin and their associated Srine Protease in innate immunity

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Abstract: ***Mannose binding Lectin (MBL) is a key pattern recognition receptor molecule, found in invertebrates to higher vertebrates, MBL initiates various immune and immunomodulatory responses on binding with the pathogen associated molecular patterns (PAMPs). MBL recognizes a wide variety of viruses, bacteria, protozoa, fungi and cell debris opsonizing and clearing them either by opsonophagocytosis or activating complement pathway through MASP-1/2 mediated cleavage of complement components C4 and C2, thus generating the C3 convertase C4bC2b. A new insight on the responses, their mechanism and role of MBL associated serine proteases are discussed in the review.***

Keywords: Mannose binding Lectin, Complement pathway, Pentraxin, Lectin pathway, MASP

1. Introduction

The core function of the immune system are recognition and efficient removal of the pathogens with self-tolerance. The recognition of pathogen and self-tolerance are so crucial for the body that it has developed an array of receptors to monitor and control the immune responses. The innate system represents the first line of defence to an intruding pathogen. The response evolved is therefore rapid, and is unable to memorise the same said pathogen should the body be exposed to it in the future, also it evolved in such a way that it eliminates pathogens while limiting autoimmune response and excessive inflammation. The soluble proteins and phagocyte cells are major component of innate immunity and effector mechanisms. One of the groups of proteins involved in innate immune responses is collectins, family of proteins named so because they contain collagen-like domain and calcium-dependent lectin domains. Collectin is a family of conserved C-type lectins, and the major effectors proteins of innate immune responses; since, these can recognize pathogen-associated molecular patterns on foreign organisms through their carbohydrate recognition domain. The trimeric CRDs can recognize carbohydrate or charge patterns on microbes, allergens, and dying cells while the collagen region can interact with receptor molecules present on a variety of immune cells in order to initiate clearance mechanisms. Once bound with the foreign particle it elicitis appropriate responses by activation of multiple processes of innate immunity such as agglutination, complement activation, opsonization, direct microbicidal action, regulation of inflammation, orchestration of adaptive immunity, interaction with allergens and apoptotic clearance. The members of group includes mannan-binding lectin (MBL), lung surfactant protein A (SP-A), lung surfactant protein D (SP-D), conglutinin, collectin of 43 kDa (CL-43) and collection of 46 kDa (CL-4)(1).

2. Mannose Bindings Lectin

MBL belongs to c-type receptor family collectins. The MBL molecules built from 32kd polypeptide chains, encompassing four regions; C-terminal carbohydrate recognition domain (CRD), an alpha helical hydrophobic neck, a collagenous region with 19 glycine-X-Y repeats (where X,Y may be any amino acid) and cysteine rich N-terminal region(2,3). The tri-peptide monomer subunits are formed and stabilized by the hydrophobic bonds and inter chain disulphide linkage within the N-terminal cysteine rich region. MBL exist in oligomeric forms ranging from diamer to hexamers to form a tulip-like structure. Inter-subunit disulfide bond in N-terminal linker region have been shown to be responsible for the association of monomer subunits into oligomeric forms (2).

MBL binds with mannose moieties by its C-terminal CRD with low affinity, but the multiple binding of CRDs increase the affinity by several order of magnitude (4). The α-helical coiled domain (hub and swivel region) provides flexibility to the orientation of the CRD to recognize terminal hydroxyl group present in certain sugars like D-mannose and L-fucose (5–7)

Structural studies have demonstrated that three sugar binding site of one MBL subunit (*i.e.* the triple helix) are separated in a constant distance (45 in humans), offering a flat platform to recognize multiple sugar simultaneously (4,6). The clustering of triple helix (higher order oligomers) can further provides wider interface, permitting bindings of multiple CRDs to the array of sugar structures on microbial surface.

The serum MBL level is determined genetically by three point mutation in exon-1 of human MBL gene located at codon 52, 54 and 57 (referred as B, D and C respectively while the wild type is referred as A) (8). The mutation results in substitution of amino acids in collagen-like domain resulting in decrease of functional serum MBL concentration

(8). Additionally the structural and promoter polymorphism gave rise to combinations with variation in serum MBL level.

3. MBL Associated Serine Protease

MBL in the blood is complexed with (bound to) another proteins, i.e. serine proteases called MASP. There are three types of MASPs, 1, 2 and 3 having catalytic domain. Also there are sMAP (or MAp19) and MAp44 protins lacking the catalytic domain and thought to be the regulatory molecules of MASPs. MASP-1, MASP-3 and MAp44 are produced from the alternative splicing of *MASP1* gene (9–11). The protease circulates as pro-enzyme and is activated on MBL binding with suitable surfaces. Upon binding of MBL the pro-enzyme MASP get cleaved between CCP2 and serine protease domain leading to formation of active enzyme. MASP-1, MASP-2 and MASP-3 forms calcium dependent heterocomplex *in-vitro* , that may imped the mutual activation that would otherwise occurs between MASPs bound to MBL (12). Activated MASP 1 has various substrate like it cleaves C3, cause localized coagulation and a potent chemoattractant factor for neutrophils & fibroblasts (13). MASP-1 even have a factor D like activity and has a reactivity profile very similar to that of thrombin (14). MASP-1 appears to be 10-20 % as active as thrombin in fibrinogen cleavage which is a much faster clevage reaction than observed for C3, indicates that fibrinogen and factor 13 are significant substrates *in-vivo (15)*. MASP-1 is clearly an active enzyme which may initiate clevage of several substrates, some being member of the complement system but others belonging more traditionally to other physiological systems i.e. a thrombin like activity in cleaving fibrinogen, factor 13 and protease activated receptor 4 (PAR 4) (7,16,17). Fibrino peptide B generated by MASP-1 cleavage of fibrinogen has a chemotactic activity as potent as C5a and represent a biologically significant activity of MASP-1 (12). Map 19 ha a inhibitory effect on renal stone (oxalate crystal) and excreted in urine. MASP-3 has been reported to have an enzymatic activity towards insulin-like growth factor binding protein-5, the functional activity of MASP-3 and Map 44 has so far been described primarily to an inhibitory activity on the activation of lectin pathway (18). MASP-2 cleaves C4 and C2 thus generating C3 convertase C4bC2b.

4. The Complement Activation

The complement system is the most important effector mechanism in the immune defense which comprises at least thirty proteins and can be activated by classical, lectin and alternative pathways to neutralize the pathogens. The lectin pathway of complement activation is critical for innate immune response beacause certain infections like pneumococal infection could not be controled without lectin pathway although classical and alternative pathways could activate complement system (19).

The lectin pathway is initiated when, MBL in complex with the the three MASPs and Map binds to appropriate targets (20,21). The targets for MBL display patterns of adequately spaced terminal carbohydrates with horizontal 3- and 4-OH groups where as targets for the ficolins are carbohydrate with N-acetyl groups or indeed other compounds with a suitable pattern of acetyl groups (11). The MBL-MASP complex can activate complement in a similar manner to that of the C1 complex. MASP-1 get auto-activated when MBL bound to microbial carbohydrate (due to extension of CUB2-EGF domain MASP get activated) (22). Activated MASP-1 then activates MBL bound MASP-2 (28-30). MASP-1 can cleave complement C3 (weakly as compare to C3-convertase), complement factor D in mice (23) and appears to cleave complement C2 (20). The exact composition of the MBL/MASP complexes remains unsolved. But it is agreed that MASP-2 plays a most significant role in generation of C3 convertase, C4bC2a. MASP-2 fulfills a similar role to that of C1s, in that it cleaves and activate the complement protein C2 and C4 (24,25). In C1, two proteases, C1r amd C1s are needed to mediate the steps between C1q binding to target, and activation of C2 and C4. C1r auto-activates when C1q binds to a target, then the activated C1r in turn cleaves and activates C1s. C1s itself does not auto-activates, and does not bind to C1q unless C1r is present. It was assumed that MASP-2 binds directly to MBL, and auto-activates when MBL binds to a target, without the need for any other protease and alone is sufficient to activate C2 and C4, so enzymatic activity from MASP-1 or MASP-3 is not essential. But recent monospecific inhibitors based studies showed that MASP-2 activation strictly depends on MASP-1. MASP-1 can only activates MASP-2 and inhibition of MASP-1 prevents further activation of MASP-2 (23). It also been showed that human and rat recombinant MASP-2 can bind directly to MBL, and does not require the presence of MASP-1 and MAp19 for binding. However, studies also suggested that MASP-1 accelerates while MASP-3 and MAp44 inhibits the generation of C3 convertase (18,26,27). MASP-1 may play an important role both in activating MASP-2 and cleaving C2 (produces 60% of C2a) (28,29).

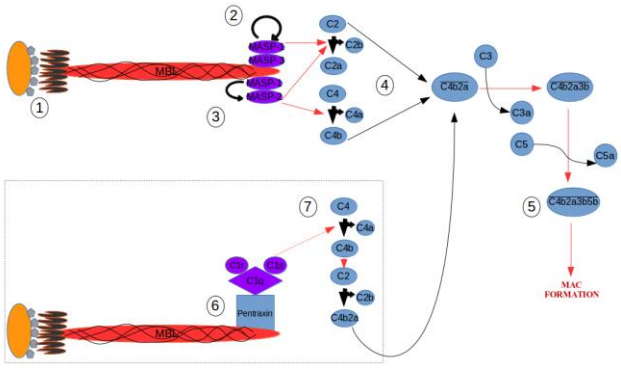

Figure 1: (1) the CRD binds with suitable PAMP (mannose at 45°A) (6) (2) which leads to conformational changes in MBL molecule that activate MASP-1; which further auto-activate and cleave MASP-2. The MASPs exists in heterocomplexes forms (12,30). Activation of MASP-2 strictly requires activated MASP-1 (23) (3). MASP-1 catalyze the C2→C2a conversion , where as MASP-2 can catalyze both C2→C2a & C4→C4b which combinly forms C3 convertase (C4b2a) (6) in inflammatory conditions pentraxin increases the complement activation by binding with MBL at MASP-3 site and recruit C1q molecules to initiate the cascade (31).

MBL enhances MASP-2 activity after binding of the MBL/MASP-2 complex to a cell substrate by the MBL moieties. MBL then incteases the rate of MASP-2 auto-

catalysis leading to cleavage of nearby covalently attached C4 and C2. It is not known whether MASP-1 required a similar process of MBL and substrate dependent activation *in-vivo*. However, recombinant MASP-1 is able to cleave pro-factor D (pro-Df) into mature factor D in the fluid phase *in-vitro* in absence of serum as a source of MBL or FCN (32). MASP-1 is 20 fold abundant than MASP-2 (27), making it plausible that MASP-2 could be a limiting factor in lectin pathway activation. Importantly, because it have been previously determined that MASP-1 may potentiate lectin pathway activation by auxiliary cleavage of C2 (33). Pentraxin is a recognition molecule that can also initiate complement activation. Recent findings suggests that it can interact with MBL molecule to amplify the complement pathway via MASP binding motif of the coolagen-like domain (MASP-3 and pentraxin competes for the same bonding site) (34).

5. Recognition of Microbes and Disease Associations

MBL can binds with a wide range of clinically relevent microbes, fungi and viruses (35,36). The binding of MBL leads to opsonization of the microorganisms and a more efficient clearance. MBL has an opsonic role, which is independent of its ability to activate complement. The mechanism of uptake has been variously described as direct opsonization or indirect opsonization (the enhancement of other phagocytic mechanism, namely the immunoglobulin and complement phagocytic pathways) (37). During this recognitionand response process, reactive oxygen species (ROS) and nitrogen oxide (NO) are produced that modulate the immune response signaling (38); also studies reveals that the recognition of glycans modulate not only innate immune response but immune cell homeostasis.

Table 1: Few micro-organism recognized by MBL leading to complement activation

Bacteria	Virus	Fungi
Staphylococcus aureus	Ebola virus (41)	*Candida albicans(45)*
Trypanosoma cruzi (39)	Flavivirus (42) Dengue virus (35)	*Aspergillus fumigatus (46)*
Neisseria gonorrhoeae (40)	Hepatitis B virus (43)	*Cryptococcus neoformans (47)*
Mycobacterium sp.	HIV (44)	

MBL deficient mice are highly susceptible to infection to provide formal proof that MBL is important in host defense *in-vivo*, Takahashi et. al (51) set out to create a mouse model of MBL-Aand MBL-C double knockout (MBL-null) mice and verified that the MBL- null mice lack MBL in serum and ,therefore have a nonfunction MBL complement pathway. Also found that MBL -null mice died 2 days after intravenous inoculation with S. a*ureus*, compared with 55% survival of wild-type mice. Pretreatment of the MBL -null mice with recombinant human MBL reversed the phenotype. In addition,the viscera of MBL null mice accumulated significantly more bacteria than did the viscera of wild-type mice 24 h after inoculation. Result indicated a decrease in phagocytosis of bacteria in blood and peritoneal cavity in MBL-null mice,thereby providing a mechanism for decreased clearance of bacteria in MBL-null nice in vivo.
MBL greatly modifies the receptor usage on dendritic cells by acting as opsonin. Evidence suggests that MBL deficiency leads to or is corelated with development of bacterial, fungal and viral infections. Becteremia or pneumonia after chemotherapy, candidasis, dysentery, respiratory tract infections are comman examples. Interestingly, collectins seems to favor phagocytosis of fungus without inducing the production of cytokines- an activity with ability to down regulate the inflammatory response to fungi. This results might explain the increased susceptibility to fungal infection of patients with defective MBL or MBL gene polymorphism (48).

The clinical manifestation of MBL deficiency seems to be of greater significance either when immune system is still immature as in infancy or when there is associated immunodeficiency (neutropenia) due to chemotherapy. The incidence and final outcome of severe infections are influenced by the levels and activity of mannose binding lectin. Since the structure of our immune system is redundant ,in many cases polymorphism of MBL-2 genes were not observed to influence susceptibility to infections.

High levels of MBL have also been considered deleterious to human health because its presence may favour some intracellular organisms which take the advantage of C3 opsonization and C3 receptor om monocytes /macrophages to entre their host. Patient suffering from visceral leishmaniasis had higher level of MBL than uninfected controls. Another African study suggested that codon 54 mutation afforded protection against both pulmonary and menineal M*ycobacterium tuberculosis* infection (49,50).

MBL is the initiating molecule that activates lectin pathway after myocardial infarction and repurfusion. MASP-1 resembels thrombin in terms of structural features and substrate specificity. Due to its interplay with several coagulationnfactors it has the ability to induce fibrin clot formation independent of usual coagulation pathway.Formation of this clot may lead to ischemic stroke or myocardial infarction. Role of MBL in animal model of human diosease has also been studied.Pavlov et al (55) have generated a novel human MBL expressing mouse that lacks murine MBL-1 and MBL-2 but expresses human MBL-2 (MBL2KI) and display lectin pathway activity similar to wild type mice.Anti MBL-2 (clone 3F8) monoclonal Ab) in the MBL-2 KI mouse significantly protects the ischemic /repurfusion murine myocardium from loss of myocardial function, decrease myocardial infarct size and prevent myocardial infarct size and prevent myocardial fibrin deposition and occlusive thrombogenesis in vivo. MASP and MAp44 levels are associated with cardiovascular risk events indicating that MASPs levels were found altered in cardiovascular diseases (52,53). A low MASP-2 levels increased the susceptibility to leprosy (54).

MBL replacment therapy in deficient patients has been proposed .MBL serum levels < 500 ng/ml or MBL activity < 200U/ml may be considered siginificantly deficient.(56).Recombinant human MBL use to supplement

MBL deficiency status has been investigated in phase I/II human studies (56).

6. Acknowledgements

The financial assistance from UGC as research grant

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