Review paper

The lectin pathway of complement activation. The role of complement in pathological processes and possible strategies of its activity modulation in therapy of some diseases

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Abstract

Complement activation pathways with particular attention to lectin pathway were reminded. The current trend is that detailed knowledge of activation triggers and substrates may pave the way to clinical interventions, i.e. inhibition of undesirable excessive activation of complement. Cellular receptors, possible inhibitors of complement cascade, and a list of diseases in which inhibition of complement is needed were shown. C1-inhibitor has its established value in the treatment of hereditary angioedema, but several other inhibitors, like soluble complement receptors, anti-C3 (-C3a), anti-C5 (-C5a) are proposed as therapeutic agents. These inhibitors may be useful in decreasing tissue lesions in such dangerous diseases as eg. Ischemic stroke, myocardial infarct, and septicemia (septic shock).Recently, also mannan binding lectins may be used in therapeutic interventions.

Key words: *lectin pathway of complement, disease consequences of of complement activation, complement inhibitors*

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Introduction

Various disorders of the immune system function reflect innate, genetically determined defects in synthesis of acute phase proteins, components of complement system or aberrations in immune cells differentiation as well as maturation. That leads to temporary or permanent impairment or even lack of immunity [1]. Innate or acquired defects of complement (C') components are also the reasons for autoimmunological processes. Besides classical and alternative C' activation pathways, the lectin pathway (LP) is intensively investigated.

More than 30 years ago, a girl suffering from atopic dermatitis and recurrent bacterial infections was described. The increased susceptibility to infections resulted from the defect of phagocytosis which reflected lack of a serum factor able to opsonize *Saccharomyces cerevisiae* yeast [2, reviewed in 3]. Similar defect was found several years later in children with recurrent abscesses [3, 4]. At the same time, first reports concerning mannose residues binding protein, present in plasma and liver of mammals, were published [3, 5, 6]. This protein was further investigated and characterized as mannan-binding lectin (MBL). MBL is considered to be an important factor of innate immunity, which deficiency (being believed to be commonest human immunodeficiency) may be a reason for increased susceptibility to numerous infectious and parasitic diseases [7]. In this paper we review the lectin pathway activation and possible modulation of complement activity in certain diseases.

The lectin pathway

The complement lectin pathway factors have been found in *Protochordata and Chordata*. Similarly to alternative

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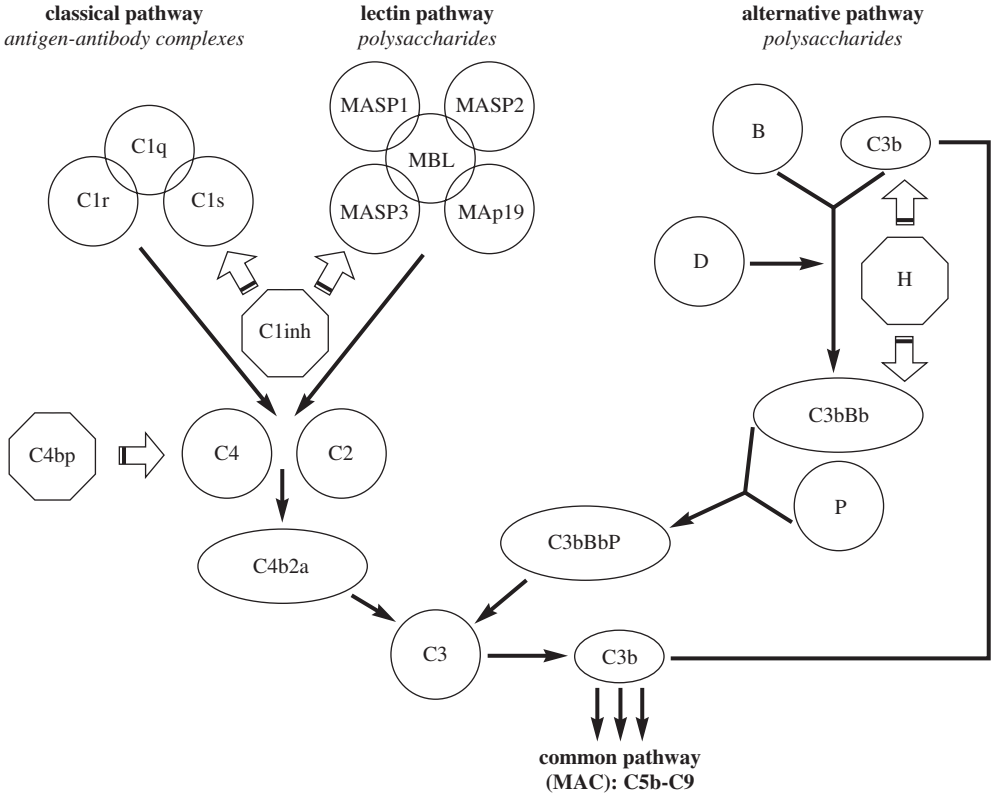

Fig. 1. Three pathways of complement activaction-initiating factors, principal components and resulting functions. It should be noted that C1-inhibitor acts both on C1r-C1s of the classical and MASP-1 and MASP-2 of the lectin pathway. Factor H is the inhibitor of the early phase of alternative pathway.

pathway, it is activated by microbial surface polysaccharides. Three pathways of complement activaction, according to the present views, are depicted on the Figure 1. On the other hand, like classical pathway, it consumes C4 and C2, however does not depend on either C1q, serine proteases C1r and C1s or antibodies. The factor initiating LP activation is mannan-binding lectin, interacting with MBL-associated serine proteases (MASP-1, 2, 3) and MBL-associated protein 19 (MAp19).

Mannan-binding lectin, MBL

MBL belongs to the collectin family: a group of oligomeric, Ca^{2+}-dependent animal lectins. This serum protein may be transported to places where the inflammatory processes develop (MBL presence has been demonstrated in amniotic fluid from women with spontaneous miscarriages, in exudate from children with otitis media, in synovial fluid from patients suffering from rheumatoid arthritis). MBL is synthesized in hepatocytes and secreted to the blood in a form of oligomer built up from two to eight subunits, consisting of three identical, 32-kD polypeptide chains (molecular mass of an oligomer: 200-800 kDa). It is an acute phase protein, however its concentration in serum during inflammation increases 2-3-fold only [7-9]. Similarly to Toll-like and mannose receptors, MBL represents factors recognizing pathogen-associated molecular pattern (PAMP), structurally-related microbial surface components [10]. C-terminal, carbohydrate recognition domain (CRD) binds rich in mannose, glucosamine and fucose microbial surface polysaccharides, lipopolysaccharides and glycoproteins. MBL protects the organism from infection via direct lysis of invading microorganisms as a result of LP activation. Anaphylatoxins released during this process contribute to the limitation of infection spreading thanks to chemotactic effect. Parallelly, MBL may enhance the phagocytosis acting as opsonin recognized by phagocytic cells' receptors (i.e. C1q (126kDa)). The opsonic activity is also the feature of activated LP factors, C4b and C3b [11, 12]. Aittoniemi demonstrated MBL level to increase rapidly after delivery, reaching maximum during the first month of life. Next, the lectin concentration systematically decreases. At the age of 12 it equals to the level characteristic for a mature organism [13]. MBL deficiences, accordingly to high frequency of point mutations in *mbl* gene (located at chromosome 10), are considered to be commonest immunodisorders [7, 9, 14]. These mutations lead to defects in synthesis and oligomerization, shorter half-life time of the protein and impair ability to interact with MASPs which results in weakened complement activity. Beside exon 1 mutation, polymorphisms of promoter region were described. These

influence the gene expression level and, in consequence, the serum concentration of the protein [14-20].

MBL-associated serine proteases, MASP

Initially, it was believed that MBL interacts with serine proteases known to be the components of classical complement pathway (C1r, C1s). However, it was demonstrated that this lectin co-operates with unique enzymes: MASP-1, MASP-2, MASP-3 and Map19 protein [21-23]. MASPs are structurally related with C1r and C1s and, similarly to them, exist in not activated form (zymogene), as single polypeptide chains. During the activation process they are converted to two-chain forms, connected via disulphide bonds. Over 95% serum MASP-1, MASP-2 and Map19 molecules are not complexed with MBL. The majority of MASP-1 is engaged in complexes with Map19, while MASP-2, probably with MASP-3. Each of the mentioned proteins binds to MBL on Ca^{2+}-dependent way [22, 23].

MASP-1 and MASP-3

The biological role of MASP-1 is not precisely determined. It has the ability to cleave C2 and C3 components with low efficiency [21, 24]. The investigation employing recombinant protease showed this activity to be physiologically insignificant [25]. Takahashi et al. [26] suggested that MASP-1 may initiate LP cascade due to MASP-2 activation. Recently, Hajela et al. [27] demonstrated that MASP-1 activates factor XIII (plasma transglutaminase) and fibrinogen (with activity equal to 10-20% of that of thrombin). This property may be important for elimination of infection, due to immobilization of bacteria. Moreover, fibrinopeptide B being liberated is a chemotactic factor for neutrophils [27]. The activity of the enzyme is regulated by C1-inhibitor (C1-inh) and α_2-macroglobulin [23].

MASP-3 synthesis is the effect of alternative splicing of the MASP-1 mRNA [28]. The described protease, together with MASP-2, interacts with higher, while MASP-1 and Map 19 - with lower oligomerized MBL molecules. Dahl et al. [28] suggested that MASP-3 regulates LP via inhibition of C4 and C2 activation by MASP-2.

MASP-2 and MAp19

MASP-2 cleaves C4 and C2 components [24, 25]. It was demonstrated that its lytic activity towards C2, and particularly - C4 is much higher than that of corresponding factor of the classical pathway, C1s (in the case of C4 - 40-fold higher) [23, 25]. The enzyme is inhibited by C1-inh, but not by α_2-macroglobulin. Vorup-Jensen et al. reported MBL-MASP-2 complex to be sufficient for the lectin pathway activation [29].

Map 19 synthesis is the result of MASP-2 mRNA alternative splicing. The protein does not contain serine protease domain, so has no ability to cleave C2, C3 and C4. Its role is not determined. Probably, due to competition with MASP-2 for binding site in MBL molecule, Map 19 regulates LP activation [23, 30, 31].

The lectin pathway activation

The lectin pathway is considered to be one of the key mechanisms of acute phase response against infection. LP activation is initiated by binding of MBL-MASP complex to mannose-, glucosamine- or fucose-rich microbial surface structures [12, 22]. Conformation changes occurring in MBL molecule lead to the activation of serine proteases. Activated MASP-2 cleaves C4 component, releasing C4a and C4b fragments. In C4b molecules, the thioester groups are exposed. They may bind to hydroxyl or amide groups in the microbial surface. Next, in the process of C2 cleavage, C2b fragment is released, while C2a binds to C4b. Formed thus C4bC2a convertase activates C3 which results in liberation of C3a (anaphylatoxin) and binding of C3b to the microbial surface via thioester groups. That leads to the formation of C4b2a3b convertase, which cleaves C5 component. C5a anaphylatoxin is released, while C5b, after binding to C3b may bind other C' cascade factors (common pathway), which allows to form membrane attack complex (MAC) and, in consequence, to lyse the microbial cell [12, 32, 33].

The role of MBL in immunity

MBL is particularly important for the protection against infection in 5-18 month children whose immune system is not able to produce specific immunoglobulins at sufficient level, while maternal antibodies have been metabolized ("window of vulnerability"). Therefore, MBL is called "ante-antibody", playing the role of widely specific "antibody" [7, 8].

MBL deficit/dysfunction are connected with an increased susceptibility to numerous infectious diseases (childhood diarrhoea, pneumococcal and fungal pulmonary infections, meningitis, otitis media, HIV, HBV and HCV infections) [3, 9, 34-38]. An association between MBL deficiency and shortened life span in cystic fibrosis (CF) patients was reported, which is thought to be connected with severity of pulmonary infections [39, 40]. MBL defects are involved also in pathogenesis of post-infection severe atherosclerosis, ischaemia-reperfusion injury, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), atopic dermatitis and recurrent miscarriages [38, 40-46]. They are also a disadvantageous factor in cancer patients undergoing chemotherapy. In these persons, the innate lectin deficit is accompanied by acquired immunodisorders due to treatment with cytotoxic agents [47, 48].

On the other hand, high MBL serum concentration may in some cases enhance the risk of infection. As an opsonizing factor, it favours a penetration of some intracellular pathogens such as mycobacteria into their target cells [49, 50]. The lectin pathway activation is believed to be connected with IgA nephropathy, since in renal glomeruli of patients, MBL-MASP complexes have been found [51]. Recently, Takahashi et al. demonstrated (in murine model) the contribution of MBL and LP activation in septic shock pathogenesis [52].

Table 1. Membrane receptors of complement

Ligand	receptor	localisation
C3b, C4b	CD35 (CR1) CD46 (MCP)	neutrophils, monocytes, erythrocytes, B lymphocytes, podocytes
C3d	CD21 (CR2)	B lymphocytes
C3dg	CR3, CR4	monocytes, macrophages, leukocytes
C4b2a, C4bBb	CD55 (DAF)	leukocytes, macrophages
C8+C9	CD59 (HRF, protectin)	leukocytes, macrophages

Table 2. Pathologic conditions associated with exessive complement activation

1) Hereditary and acquired angioedema
2) Alzheimer' disease
3) Asthma
4) Adult respiratory distress syndrome
5) Arthus reaction
6) Bullous pemphigoid
7) Burn injuries
8) Crohn' disease
9) Experimental allergic neuritis
10) Forssman shock
11) Septic shock
12) Glomerulonephritis; end stage renal disease
13) Haemolytic anemia
14) Ischemia and reperfusion: **heart infarct and stroke**
15) IC-induced vasculitis
16) Multiple sclerosis
17) Myasthenia gravis
18) Post 'by-pass' inflammation
19) Psoriasis
20) Rheumatoid arthritis and SLE
21) Vascular leak syndrome
22) Allo- and xeno- transplantation

Complement receptors

On the surface of various cells, specific receptors for complement factors and regulatory proteins are present, among them: CR1 (CD35), CR2 (CD21), CR3 (CD11b/18), CR4, C1qR, HR and C5aR [53]. The basic informations concerning their cell distribution and biological significance are listed in Table 1.

The activation of central complement system component - C3 leads to the formation of C3a and C3b fragments. The larger one, C3b, after binding to cell surface contributes to the formation of C5-C9 complex, and, on the other hand, acts as CR1 receptor (present among others on erythrocytes) ligand. Both mentioned activities are inhibited by factor I, cleaving C3b into iC3b and C3f. Next, iC3b fragment is degraded to C3c and C3dg. The latter is then cleaved by serum proteases giving C3d molecule. The iC3b, C3dg and C3d fragments bound to the cell surface may be recognized by leucocyte receptors (CR2, CR3, CR4). C3d, as well as generated on the similar way C4d, may circulate in a bloodstream. Their high concentration in serum, being a symptom of the immune complexes presence, can be detected with the help of specific antibodies. That is useful for the evaluation of complexemia in children with parasitic diseases [54].

The biological consequences of complement activation and possibilities of its modulation

Main biological functions of the complement [55-57]:
1) enhancement of immunological response,
2) participation in elimination of microorganisms via direct lysis or opsonization,
3) solubilization and elimination of the complexes formed in the course of infection,
4) participation in elimination of autoreactive B cells,
5) participation in elimination of endotoxins.

Despite these well known activities, the significance of complement in processes of cartilage and bone development, fertilization, tissue regeneration and hematopoesis is considered [58].

In the some cases, however, the complement activation may be unfavourable for the host. Diseases and pathological processes connected with C' hyperactivity are listed in Table 2.

Hereditary or acquired C1-inhibitor deficiency in angioedema is the reason of plasma transudation into extracellular compartment leading to the sudden, difficult to treat clinical symptoms [59].

A shock which may be a consequence of Gram-negative bacteriemia is connected with complement activation by endotoxin (LPS). That leads to the liberation of anaphylatoxins: C3a and C5a. C3a component activates mainly eosinophils and mastocytes, while C5a is an activating factor for eosinophils, neutrophils, basophils, monocytes/macrophages and microgliocytes [56]. Anaphylatoxins enhance blood vessels' permeability. The aggregation of neutrophils causes intravascular coagulation and formation of microclots in pulmonary circulation. Various mediators being secreted may contribute to interstitial pulmonary oedema, exudation of neutrophils to pulmonary alveoli and to hypoxaemia [60, 61].

Complement activation being the result of blood circulation via heart-lung apparatus (cardiopulmonary bypass) or passing

through cuprofan membranes causes temporary leucopenia, probably due to leucocytes' aggregation in lungs [55].

Tissue damage during ischaemic necrosis leads to complement activation and deposition of common pathway complexes. It was demonstrated with the help of experimental model of myocardial infarction that C' inhibition by soluble form of CR1 receptor relieved tissue damage. The treatment of angioedema with C1-inh was one of the first attempts of complement activity inhibition in therapy [55, 62]. Recently, it was demonstrated that MBL-specific antibodies administration led to the reduction of C3 binding to myocardial cells, diminishion of infarct size, tissue injury, infiltration of neutrophils and proinflammatory genes expression level in rats [63].

It is well known that complement system contributes to tissue lesion in immune complexes-dependent diseases. Such complexes are formed during acute infection, in result of C' activation as well as T-cell dependent cytotoxicity. The lack of elimination, chronic circulation and deposition of complexes cause the pathological reactions.

Immune complexes take part in enhancement of autoimmunity also. Activation of inflammatory process depends on 2 mechanisms:

(1) Attraction of activated leucocytes by locally formed anaphylatoxins to the places where immune complexes are being deposited, and their binding to C3b and C4b in these complexes,

(2) Membrane injury by MAC, and then stimulation of the prostaglandins synthesis from arachidonic acid [55].

Chronic complement activation takes place in Goodpasture's syndrome, in which basement membrane of renal glomerules and lungs is an autoantigen [64]. It occurs also in certain infectious diseases, such as *Helicobacter sp.,* HBV, HCV infections, bacterial endocarditis.

Therapeutic strategies

The mentioned above data are being exploited for the creation of treatment strategies in certain diseases by inhibition of C' activation with the help of various factors (soluble forms of receptors/monoclonal antibodies/immunoglobulins/blocking peptides). The most natural drug is C1-inhibitor, which deficiency in angioedema patients is a reason for severe clinical symptoms. Therapy with C1-inh in such cases occurred to be efficient and diminished the mortality. Initially, a preparation from blood donors' pooled plasma was being used, that was replaced by a recombinant protein. The administration of C1-inh separated from transgenic animals' milk is considered. Moreover, anabolic and anti-fibrinolytic drugs are used in chronic states treatment. What is important, C1-inh seems to be a promissing therapeutic agent in septicaemia, extravasation syndrome and myocardial infarct [56].

Therapeutic strategies being currently considered, commonly concern the C' activity inhibition at the stage of C3 or later (common pathway). One of the important inhibitors is protectin (CD59), which structure, and biological properties was described elsewhere [65]. It inhibits the cell lysis via blocking of MAC. Most of proposed therapeutic procedures is focused on classiscal or lectin pathways, while only few - alternative one [66]. The inhibitors of complement activation being currently used or potential medicines are shown in Table 3.

Table 3. Inhibitors of complement cascade - already used or tested for clinical use

Target protein	Inhibitor
◗ C1 (r,s)	C1-inh
◗ C3b, C4b; C3bBb	rCD35, rCD55, rCD46, rCD46-CD55, rCD55-CD59 rCD59
◗ C3, C3a	Anti-C3, anti-C3a; compstatin
◗ C5, C5a	Anti-C5, anti-C5a
◗ C5aR	Mutants C5a
◗ Factor D	BCX-1470, FUT-175 (peptides)

According to [56]; with modification

Possible use of MBL preparations in therapy

Immune defects may be treated by substitution therapy. Valdimarsson et al. reported the case of 2-years old girl, who was often being hospitalized for the reason of numerous bacterial and viral infections, including septicaemia [67]. The examination carried out showed her to be MBL-deficient and to have lower IgA level. Infusion of MBL prepared from the plasma Cohn fraction III protected from infections and did not cause either side effects or production of anti-MBL antibodies [67]. Recently, the phase I trial has been carried out. The plasma-derived product occured to be safe, its half-life was approximately 2-3 days [68].

The results presented by Ma et al. [69] and Muto et al. [70] may suggest the potential role of MBL preparation in antitumor therapy. MBL binds to human colon adenocarcinoma cells, showing a cytotoxic activity. This effect, however is not connected with complement activation. These studies were performed with the use of cell lines/animal model [69, 70]. The substitution treatment with MBL might be potentially useful in rheumatoid arthritis, cystic fibrosis, viral hepatitis C type, recurrent miscarriages and recurrent infections in children [3]. Both plasma-derived and recombinant products can be taken into consideration. The first mentioned ensure natural oligomerization of the molecule. The presence of MASP in a complex makes possible the complement activation. On the other hand, recombination products are free from the risk associated with blood preparations. They have cytotoxic activity against certain cancer cells and bind to influenza A virus. Moreover, although the complement system is essential for the host defence, its activation may be disadvantageous in some cases [3, 38, 71].

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