Review paper

Complement – known and unknown facts

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Abstract

This paper presents the selected issues regarding the functioning of the complement system, namely its activation pathways and regulating mechanisms. It explains its role in innate immunity, as well as in adaptive immunity. This study gives examples of diseases associated with the dysfunctions of the complement system, and characterizes some mechanisms of pathogens that may inhibit complement activity.

Key words: *complement system, innate immunity, acquired immunity.*

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Introduction

The immune system of mammals is very complex and effective, owing to which it is possible to recognize non-self, potentially dangerous particles and self structures, and therefore to ensure macroorganism's protection against various microorganisms, including bacteria and viruses. At present, in immune system, its two basic components are recognized, namely natural – innate immunity, and acquired – adaptive immunity [1]. Innate immunity forms the first line of defence, while immune response is immediate and non-specific to the entering antigens. Owing to this, microorganisms are directly destroyed, yet this does not lead to the development of immunological memory [1]. In turn, acquired immunity is characterized with greater specificity of antigen recognition, ensuring the development of immunological memory and capacity of quicker responding to another contact with a specific pathogen [1]. An important role in the correct functioning of innate immunity is performed by the complement system, significantly contributing to pathogen recognition and destruction [1, 2]. Its function is principally related to opsonisation, chemotaxis, killing microorganisms' cells, elimination of immunological complexes, as well as initiation of local inflammation. It was, however, evidenced [3, 4] that complement is not just an element of innate immunity, but it also participates in the regulation of adaptive immunity.

Complement activation and regulation

The complement system comprises approximately 30 proteins that are present both in serum, and in tissues, in the form of inactive precursors [2, 5, 6]. In mammals, complement activation may have three separate pathways: classical, lectin and alternative pathway [2, 4, 5]. Each of those pathways leads to accumulation of the key enzyme of the complement cascade - C3 convertase, which cuts C3 protein into subunits C3a and C3b, which constitutes the main stage in complement activation [2, 4]. As a result of conformation changes of one component, proteolytic properties of another component are activated, or the capacity is achieved to bind to the next component in the activation chain [2, 4]. Activation of classical pathway takes place as a result of C1q protein binding to immunoglobulin present in the complex with antigen. C1 component of the complement, apart from C1q particle, also contains two subunits – C1r and C1s, which cause distribution of components C4 and C2, respectively, on C4a and C4b, as well as C2a and C2b [2, 4, 7]. As a result of such transformations, C4b2a complex is formed, with proteolytic properties, referred to as C3 convertase. It is the key protein complex necessary for formation of C3b component, and then C5 convertase, namely C4b2aC3b complex [2, 4, 8]. C5 convertase has the capacity of decomposing C5 factor, as a result of which C5b is formed, which binds, respectively, components C6, C7, C8 and C9. The created complex C5b6789 is defined as membrane attack complex (MAC), which creates a channel in the membrane of the target cell, leading to distortions to cell metabolism [2, 4]. Lectin pathway, referred to as "independent of antibodies", is activated by mannose-binding lectin (MBL) or a group of proteins called ficolins [2, 4, 7]. They have the capacity of binding

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to carbohydrates present on the surface of various pathogens, such as bacteria, viruses, fungi or protozoa. MBL and ficolins then bind to serine proteases MASP (MBL – associated serine proteases), which function in a manner similar to C1, namely decompose C4, C2 and C3, as a consequence leading to formation of convertase C3 (C4b2a) and C5 (C4b2aC3b) [2, 4, 9]. In turn, the alternative pathway involves the participation of properdin, formed by factor B (β-globulin), factor A (identical with fragment C3 of the complement), component D (convertase C3 of proactivator), component P (properdin) and factors H and I, belonging to regulator proteins of complement (RCA – regulator of complement activation) [1]. This pathway begins with binding factor B at the presence of Mg^{2+} with $C_3(H_2O)$ form of C3 protein, which allows factor D, principally occurring in the active form, for decomposition of factor B into Ba and Bb [2, 4]. As a result of such changes, complex $C_3(H_2O)Bb$ is formed, which is an initial form of C3 convertase. The form then transforms into active complex C3bBb, namely "final C3 convertase", affixed to the cell membrane and decomposing factor C3 into a and b subunits [2, 4]. C3bBb complex may also bind additional C3b fragments, thus becoming convertase C5 of alternative pathway (C3bBb3b). The enzyme is at the surface of the target membrane and is stabilised by properdin, which protects it against regulator factors, namely factor H and factor I [1, 2, 4].

Recent studies indicated that one may also differentiate additional two complement activation pathways [4, 10-13]. Hourcade [10] evidenced that component P of properdin may function as the main initiator of alternative pathway, namely may recognize and bind to the surface of pathogens, such as *Neisseria*, *E. coli* and yeast, as well as to component C3b. Next, C3bP binds to factor B, and the created complex C3bBP is transformed under the influence of factor D into an active form of convertase C3 (C3bBbP). This convertase, in turn, decomposes C3 with the generation of C3b component that also binds to the pathogen surface via the second place on properdin. The complex again cooperates with factors B and D, and then C3 is broken down to subunits, and convertase C5 and MAC are created [10]. The other "new" complement activation pathway comprises direct decomposition of complement's components under the influence of proteases participating in the blood coagulation cascade, such as kalikrein, plasmin or thrombin [13]. The studies revealed that in mice deprived of C3, where convertase C5 could not be formed, C5 component was activated by thrombin [11]. Furthermore, it was evidenced [12] that administration of thrombin and thromboplastin in rabbits induced complement activation. Complement activation could be, however, weakened by thrombocytopenia, which suggests that thrombocytes are also involved in this phenomenon [12].

Complement activity and its capacity of creating channels in cell membrane and lysis of pathogen cells must be regulated principally in order to prevent the damage of cells and tissues of macroorganism [4]. Basic regulators of complement activity include RCA proteins, among which one can differentiate membrane proteins and plasma proteins. Membrane proteins are represented CR1 (complement receptor type1), CD55 (DAF – decay – accelerating factor), CD46 (MCP – membrane cofactor protein), CD59 (protectin) and HRF (homologous restriction factor), while plasma proteins include i.a. factor I and factor H – elements of properdin, factor C4bp, and protein S (vitronectin) [2, 4]. The most "desired" regulation mechanism is the prevention of further transformations of C3 and C4 components owing to the initiation of their decomposition by factor I and co-factors, such as CD46 or CR1 [4, 14]. CD46 and CR1 move within the lipid two-layer towards C3b and C4b, which are present on the surface of the cell membrane, and bind to them, thus facilitating their decomposition by factor I. Similar mechanism of action is also observed for factors H and C4bp, which are also co-factors for factor I [4, 14]. If this mechanism is not effective enough, then convertases C3 and C5 may be formed, as well as MAC complex on the host's cells. And so, the creation of C3/C5 convertase is prevented by so-called regulators showing decay-accelerating activity (DAA), namely receptors CD55 and CR1, and factors H and C4bp [4, 15]. It is worth stressing that such proteins also have capacity to decompose the already formed convertases. In turn, generation of MAC complex is inhibited by CD59 and protein S [4, 15].

The role of complement in immunity

The complement system has always been associated with the mechanisms of innate immunity, although as early as in 1971, there were first reports on its role in acquired immunity, when it was evidenced [16] that C3 component can be bound on the surface of B cells. Further studies evidenced that as a result of C3 exhaustion, immune response related to humoral immunity is weakened, while the classical complement activation pathway is an important mechanism involved in successful capture of antigens and their keeping in lymphoid tissue, i.a. in splenic lymphoid nodules [17, 18]. Complement enhances immunity associated with B cells, principally owing to expression of receptors CR – CR1 (CD35) and CR2 (CD21) on their surface, as well as on the surface of follicular dendritic cells (FDC) [19, 20]. Receptor CR2 binds in the cell membrane to CD19 and CD81 particles, creating so-called co-receptor for B cells (CD21-CD19-CD81), while in the presence of antigens connected to complement components, it allows for cross-binding to the typical B-cell receptor (BCR) [4, 20]. Binding of CR2 and BCR leads to lowering of the B-cell activation threshold and over 1000-fold increase of such cells response to antigens [20]. Expression of co-receptor CD21-CD19-CD81 on B cells takes place already during their migration from the bone marrow to peripheral blood,

which contributes to elimination of auto-reactive B cells and positive selection of B1 cells, which are the main source of natural antibodies [21]. Moreover, cross-binding of the co-receptor with BCR increases B-cell activity also in later stages of their differentiation, principally towards memory B-cells and naive B-cells [20, 22]. The studies revealed that in mice deprived of CR1/2 and C3 component of the complement, clear reduction in the level of immunoglobulins IgM and IgG is observed, damage of IgM class switching to IgG, as well as decrease in capacity of antigen capture in a manner independent of T-cells [23, 24]. Similar results were obtained during the analysis of antigen capture in a manner dependent of T-cells, which referred both to bacteria (*Streptococcus pneumoniae*), and viruses (herpes virus, West Nile virus) [25-27]. At present, it was evidenced [4, 20] that the complement not only affects immune response related to B-cells, but also significantly contributes to regulation and functioning of T-cells. It was recorded that in mice with deficit of C3, infected with influenza virus or lymphocytic choriomeningitis virus (LCMV), significant decrease is observed in activity of T-cells with receptors $CD4^+$ and $CD8^+$ [28, 29]. On the basis of these studies, it was concluded that lack of C3 component leads to decrease in the capacity of antigen opsonisation and their capture, as well as reduced activity of T-cells. In turn, in mice with DAF deficit (CD55), increased complement activity was observed, which leads to enhancement of immune response dependent on T-cells, particularly Th1 cells. This was principally characterized with increased secretion of IFN-γ and IL-2, and inhibition of IL-10 secretion as a result of stimulation with antigens [30, 31]. DAF deficit in mice infected with LCMV also resulted in increase in activity of naive and helper T-cells $CD8^+$, yet this required the presence of C3 or C5aR [32]. Furthermore, it was evidenced that DAF may function as a co-stimulating particle on the surface of human T-cells $CD4^+$, inducing, together with CD3, proliferation of such cells [33]. Co-stimulating particles during activation of T-cells $CD4^+$ also includes CD46 receptor (MCP), which induces the synthesis of e.g. IFN-γ and IL-10. As a result of simultaneous activation of CD46, C3b and TCR receptor in the presence of IL-2, T regulator (Treg) cells develop, which secrete IL-10 and granzyme B [34]. It is suggested that Treg lymphocytes induced by the complement system weaken the response of effector T cells, which protects tissues against damage, as well as autoimmunological diseases [35]. The studies evidence that in mice deprived of receptors C3aR and C5aR, anafilatoxins C3a and C5a play the role of modulators in IL-12 production by APC cells, which is the regulator in the development of Th1 and Th2 cells [36]. In the case of lack of C5aR in mice infected with type A influenza virus, decrease in the number of specific T $CD8^+$ cells was also recorded [37].

It was also evidenced that pathogens may develop various mechanisms that inhibit activity of the complement, which results in their survival, and even replication in the host's organism [20]. The studies evidenced that bacteria may interfere with complement's action at almost every stage of its activation [38]. For example, *Staphylococcus aureus* produces membrane protein SpA (Staphylococcal protein A), which not only has the capacity of binding to Fc region of immunoglobulins IgG, which leads to inhibition of the phagocytosis process, but also limits the classic complement activation pathway by binding to C1q [39]. A similar role is played by protein G and protein L [38]. Moreover, *S. aureus* produces Staphylococcal Complement Inhibitor (SCIN), which blocks all pathways of its activation by effective inhibition of C3 convertases, as well as inhibits opsonisation and reduces the effectiveness of phagocytosis [40]. Bacteria may also inhibit MAC formation or reduce its cytolytic properties, principally owing to the presence of thick membrane wall in the case of Gram-negative bacteria [20]. It was evidenced that among MAC inhibitors, there is also surface protein with 80 kDa weight, present in *Borrelia burgdorferi*, which is similar to human CD59, which also acts as inhibitor of this complex [41]. Apart from this, pathogens may react with the host's regulator proteins, e.g. by binding H factor – element of properdin, which causes an increase to degradation of C3b component, and limitation to C3 convertase formation, and thus decrease in the complement's activity. This phenomenon was described in *Neisseria* (*N.*) *meningitidis* and *N. gonorrhoeae*, which avoid its own destruction owing to binding factor H [42]. Another mechanism related to this process involves inhibition of chemotaxis and inflow of leukocytes through pathogens, owing to reaction with receptors taking part in activation of such processes, principally with C5aR and FPR (formyl peptide receptor) [38]. Moreover, the process involves baterial proteins that inhibit chemotaxis, which include CHIPS (chemotaxis inhibitory protein of *S. aureus*) [43]. Some viruses aim at inhibition of complement system activity in order to increase their virulence, which was first described at the example of measles virus [44]. It was evidenced that as a result of influence of this virus, CD46 receptor is destroyed, and production of IL-12 by APC cells is reduced, which contributes to weakened functioning of the immune system [44]. It was also evidenced that CD46 receptor may also act as the role of receptor for bacteria, such as *N. meningitidis* and *N. gonorrhoeae* [45]. Moreover, many viruses from the *Picornaviridae* family, e.g. echovirus and Coxsackie virus, have the capacity of binding to DAF receptor, yet the places of their binding may differ, and additionally the participation of adhesive particles ICAM-1 is required in this process [46, 47].

Selected diseases related to dysfunction of complement system

Complement constitutes an important element of immune system, therefore dysfunctions in its activation and

regulation have a negative impact on the maintenance of homeostasis, which may contribute to the development of various diseases [4]. It was evidenced that deficiencies of various complement components have a negative impact on immunity in animals, including humans [20]. The important role of complement activation is visible in patients with C3 deficiency, in whom principally lack of capacity is observed to coat pathogens or immunological complexes, which results in the increased risk of various infections and diseases, including auto-immunological diseases [5, 6]. In the case of complete deficiencies in components of the classical pathway, increased susceptibility is observed to autoimmunological diseases, while deficiencies to C3 component or factors H and I – elements of properdin, result in increased risk of bacterial infections [6]. In the case of deficiencies of C3, principally increased susceptibility is recorded to infections caused by *Hemophilus influenzae*, *Streptococcus pneumoniae* and *Streptococcus pyogenes* [6]. Furthermore, deficiency of components C3, C1, C2 or C4 is related to the occurrence of suppurative infections, while deficiency of components C5-C9, MBL, as well as components of alternative pathway, namely factors B, D and P of properdin, results in increased risk of infections caused by *Neisseria* sp. [6, 48, 49]. Infections caused by *Neisseria meningitidis* may also be a result of defects in the functioning of MAC, or deficiency of components necessary to generate it [20]. In turn, MBL deficiency in children aged from 6 months to 2 years, therefore in the period between the loss of passively acquired mother's antibodies and the development of own immune system, cases pyrogenic diseases [20]. Furthermore, recurrent infections may be caused by mutations or deficiencies in the area of factors H, I and D of properdin, which cause the wear or deficiency of C3 [48, 49]. It is worth stressing that our improved knowledge on the role of the complement system in acquired immunity significantly contributes to better understanding of relations between the complement and autoimmunization [4]. In rheumatic diseases, such as SLE (systemic lupus erythematosus) or juvenile idiopathic arthritis (JIA), there are genetically conditioned deficiencies of complement components, which makes it difficult not only to eliminate immunological complexes, but also contributes to their deposition in tissues, and thus to sustaining the inflammatory processes [6]. The studies indicated that the deficit of components C1, C2, C4 or MBL is related to the development of SLE, yet according to other authors, deficiency of components to the lectin pathway, in particular MBL and C3, rather contributes to the development of circulatory system diseases or arteriosclerosis [50]. Deficiency of C1q or C2 components may lead to the development of other autoimmunological diseases, e.g. the focal form of lupus erythematosus, glomerulonephritis, dermatomyosytis, or scleroderma [6]. In the case of DAF receptor (CD55) deficiency in mice, increased morbidity with intestinal diseases was recorded [51]. At present, it is also believed that C3 component of complement is one of the main mediators in damage to tissues occurring as a result of reperfusion and implant rejection [4].

Conclusion

It must be stated that complement system is an evolutionally old and unusually complex element of immune system, which takes part in regulation of both innate and acquired immunity. Deficiencies of any of the complement components not only contribute to the development of bacterial, or viral infections, but are also related to some autoimmunological diseases, such as SLE or multiple sclerosis. Furthermore, studies also indicated correlation between the complement and damage to tissues, i.a. as a result of implant rejection. These facts make complement system interesting to researchers, both in the aspect of its regulation and participation in immunological processes, and in the aspect of its reaction with pathogens, which may significantly contribute to the development of not only effective treatment of many diseases, but also to their prophylaxis.

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