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Review Article

THE COMPLEMENT SYSTEM: A KEY TO OVERALL HEALTH

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ABSTRACT

The complement system is a part of the immune system that enhances the ability of antibodies and phagocytic cells to clear pathogens from an organism. It is part of the innate immune system which is not adaptable and does not change over the course of an individual's lifetime. However, it can be recruited and brought into action by the adaptive immune system. The complement system is one of the major mechanisms by which pathogen recognition is converted into an effective host defense against initial infection. The activity of complement components is modulated by a system of regulatory proteins that prevent tissue damage as a result of inadvertent binding of activated complement components to host cells or spontaneous activation of complement components in plasma.

Keywords: Complement System, Host Defense, Immune System, Regulatory Proteins.

INTRODUCTION

The term 'Complement' was originally applied by Ehrlich to describe the activity in serum which could 'Complement' the ability of specific antibody to cause lyses of bacteria. The discovery of this heat labile activity in serum is usually attributed to Border (1985), although Nuttal had described a similar activity some years earlier. In 1908, Ferrata demonstrated that complement could be separated into two components by dialysis of serum against acidified water. This yielded a euglobulin precipitate and a water soluble albumin fraction^{1,2}. Complement activity could only be demonstrated in the presence of both of these fractions, which he called mid piece (C1) and end piece (C2). Subsequently, Sachs and Omorokow showed that cobra venom inactivated another component (C3), and Gordan found that a further component was destroyed by ammonia (C4).

WHAT IS COMPLEMENT?

The complement system is the major effector of the humoral branch of the immune system and complement is a collective term for a series of complex protein in normal serum. These complement proteins mainly consist of β 2 globulins. They exist as proenzymes and circulate as inactive forms. On activation, they become active, acquire enzymatic or esterase activity, react in a particular sequence and cause damage to neighboring cells. However, it is assured in the complement system that the active sites formed periodically on activation are inactivated by inactivators of complement called regulatory proteins.

It is also assured in the system that once the active sites are inactivated by the regulatory proteins, they cannot further generated. Such a process of activation and inactivation or regulation of complement system is a unique phenomenon. The byproducts of these phenomena also assure biologically significant. Certain consequences of complement action like inflammation, coagulation, defense against infective agents and control of neoplastic cells.

COMPLEMENT COMPONENTS:

The basic work on the nature of complement and the nomenclature proposed for its components proteins is primarily based on an immune hemolysis that has been recognized over the years as an indicator system for in vitro complement fixation test. In this, the complement proteins that exist as proenzymes undergo a chain reaction on activation³.

However, the nomenclature of the complement components can broadly be described under three main headings: Complement proteins, regulatory proteins and associated proteins. Associated proteins are those that react with the intermediate complexes formed on activation and during the chain reaction of the complement system.

There are two pathways for complement activation and they are named as classical pathway and alternate pathway. The former is called classical, because of activation of this was described first; whereas the latter is referred as alternative, because it was later on found that complement system can also activated by means other primitive for defense against infection.

COMPLEMENT PROTEINS:

Complement proteins are those serum components that take part in a particular sequence on activation both in classical and alternative pathways.

Proteins of the classical pathway:

There are at least fifteen complements proteins designated as C1 to C15, of which C1 to C9 are involved in a specific sequence to cause cell lyses and perform some other biologically significant function. The complement protein C1 to C9 are arranged on the basis of their action in a specific sequence, such as C1, C4, C2, C5, C6, C7, C8 and C9. Component C4 acts as second in sequence and still retains the position only because of the fact that the number was given prior to the complete sequence was known which thus becomes a part of the history.

Complement components cleaved proteolytically during activation into fragments are denoted by lower case letter. The smaller fragment of the split of a component is being designated by letter “a” and the larger fragment by letter “b” such as C3a and C3b as a result of activation of C3 or 5a and 5b as a result of activation of C5. The C3b can further be fragmented designated as “c” and “d”, whereas the subcomponents but enzymatic products of C1 are designated by postscript q, r and s, such as C1q, C1r and C1s. the C1q is the recognition unit of the complement that follows C1r and C1r in sequence.

Proteins of the alternative pathway:

The protein of the alternative pathway is designated by factor B, D, P, H and I. The serum concentration of these factors varies from 3 to 1500 µg/ml and molecular weight from 25 to 180 KD. In this, C3 retains its numerical notation as central component of the complement system that pass through C5 to C9. the nomenclature proposed for the factors in the alternative pathway does not specify a preceding reaction in sequence as in classical pathway.

Moreover, the factor P designated for Properdin, is a glycoprotein which once was thought to be an activating agent in classical pathway. It is now shown that factor P helps in binding Bb to C3 and stabilizing C3b, Bb complex. Complexes between two or more proteins, for instance, C3b and Bb are represented by enumerating the proteins with an intervening comma, as in C3b, Bb. A postscript “i” represents the inactive form of previously active state as a result of alteration in the primary polypeptide structure and dissociation

from C3b, such as Bbi, whereas prescript “i” represents a protein when it loses its defined activity as a result of hydrolysis.

Complement activation:

It refers to an interaction between complement components and activating substances resulting to the expression of a new biological activity. It means, once the complement system is activated by the activating agents, it acquires a unique property:

- a. Bind on to biological membrane
- b. Generate enzyme function.
- c. Activate the next protein in order to participate in a chain reaction.

Some of the proteins of the chain reaction become bound to the initiating or activating agent that bring about alteration in the structural configuration of the molecule and functional properties of the cell membrane which may be red cells or microbial cells.

Some of the proteins with enzymatic action that remain free in solution be inactivated by specific inactivators or inhibitors that remain free in solution be inactivated by specific inactivators or inhibitors that ensures the protection of neighboring cells from potentially enzymatic action.

A short half life of these proteins and the mechanism involves in series of reaction further ensures that enzymatic activity generated during the process is confined to the immediate vicinity of the activating sensitized cells.

As mentioned earlier that there are two pathways for activation of the complement system; Classical and Alternate. Each one of these passes through 2 distinct phases, activating phase and lytic phase. Activating agents involve in these two pathways are different.

However an activation of complement components that participate in a chain reaction involves :

- a. Interaction of recognition unit of the complement with activating agent.
- b. C3 and C5 convertase.
- c. Cleavage of C3 and C5 component and
- d. Assembly of lytic components for membrane attack and lyses of cell.

However, cleavage of C3 into C3a and C3b or C5 into C5a and C5b is a significant and a number of cells are shown to express receptor for C3a and C3b.

Activating agents of Classical and Alternate pathways:

Classical pathway	Alternate pathway
<ul style="list-style-type: none"> • Antigen – antibody complexes • Gram – ve bacteria (rough strain) • Animal viruses 	<ul style="list-style-type: none"> • Aggravated IgC or IgA • Lipopolysaccharide or bacterial endotoxin • Yeast

Classical and Alternate pathway:

Activating phase of classical pathway:

- Activation of classical pathway is initiated by antigen – antibody complexes.
- The substances other than Ag – Ab complexes that are being shown to act as activating agents and carry receptor for C1 in classical pathway are certain rough strain of gram – ve bacteria and animal viruses that interact

directly with the first component of the complement and result in killing such micro organism.

- Interaction with classical pathway starts at recognition unit C1 level and ends at C9 in sequence.
- Activation occurs in CH2 domain of the Fc region of the antibody (A) molecule complexed with erythrocytes (E) on which C1 acquires a receptor or attachment site.

- C1 component is a trimolecular complex that is 3 subcomponents, C1q, C1r and C1s and held together by calcium ions.
- The activation of C1 component starts on EA by interactions with C1q subcomponent which has six valencies for immunoglobulin.
- C1q subunits bind to IgM and sub classes of IgG, such as IgG1 and IgG3 in man.
- The inability of IgA, IgD and IgE to activate complement system is considered to be due to lack of complementary receptor site on the Ig molecules.
- C1q lacks enzymatic activity, but can be acquired on interaction with C1r and C1s.
- C1s acts on C4 and split into C4a and C4b. C4b, free in solution or bound on the membrane, interacts reversibly with C2 in the presence of magnesium ions and split C 2 into C2a and C2b.
- C4b complexed with C2a form C4b, C2a and acquires classical pathway C3 convertase activity which splits C3 into C3a and C3b.
- Some of the C3b thus formed can be deposited on the membrane where it serves as an attachment site for polymorphs and macrophages.
- Some of the C3b remains associated with C2a and C4b to contribute to the formation of C5 convertase in the classical pathway, and some of the C3b combines with factor B to form C3 convertase in the alternative pathway and some can be inactivated into C3c and C3d by the action of C3b inactivator.
- C3 and C5 convertase are immunological enzymes that respectively.
 - a. C3 into C3a and C3b
 - b. C5 into C5a and C5b
- The C3 convertase activity can also be acquired by non – immunological enzymes like thrombin that is involved in coagulation.
- The cleavage of C3 can also be induced by peptide bond breakage not only naturally during the fixation of complement but also artificially by the use of enzyme like trypsin.
- Any deficiency of C1 inhibitor in man therefore leads to hereditary angioneurotic edema as a result of extensive retention of C1 and the introduction of pharmacologically active substances.

Activating phase of alternative pathway:

Activation of alternative pathway is initiated by non – antigen antibody complex. The substances that are being shown to act as activating agents and carry receptor for C3 in alternative pathway are bacterial polysaccharides and endotoxins derived from smooth strains of gram – ve bacteria, yeast cell zymogen and inulin, and aggravated Igs of human IgG or IgA class.

Although there are many controversies on the details of this pathway, it is now believed that C3 conversion ‘ticks over’ under normal circumstances is non – specifically stabilized by cell membrane. It means, the reaction is independent of the participation of Fc region of the Ig and C2 is a recognition unit in the process of reaction that ends at C9 indicating that the activation of alternate pathway may play an important role

in preventing recurrent infection in patients with antibody deficiency syndrome.

The alternate pathway C3 convertase is otherwise formed by the action of enzyme factor D (analogous to C1s in the classical pathway) on C3b and factor B. Interaction between C3b and factor B form a weak C3b B complex in the presence of magnesium ions. The factor B in C3b B can be stabilized or retarded from dissociation by the action of factor P (Properidin) and cleaved by the action of enzyme factor D to form active C3b Bb as these complexes may be dissociated into inactive Bi and free C3b. In other words, an increased C3 cleavage and breakdown products can lead to a positive feed back loop. The formation of some of these can however be prevented by the action of C3b inactivator by homeostatic mechanism.

It may be worthwhile to mention that there is a serum factor in patients with hypocomplementic chronic nephritis. This factor is non – Ig 7s gamma globulin in nature and capable of activating complement via alternative pathway exclusively leading to the formation of cytolytic complex and production of anaphylotoxin.

Lytic phase of classical and alternative pathways:

Lytic phase in classical and alternative pathways is similar. It starts at C5 and ends at C9. Assembly of lytic components is initiated by attraction of C5 and split into C5a and C5b through enzyme reaction or C5 convertase activity. C5a similar to C3a acquires anaphylotoxic activity which acts on mast or basophil cells and promote inflammatory responses ; whereas C5b binds C6 and C7 initiates the assembly to form C567 complex to attract C8 for cytolytic activity.

Although one molecule of C8 is enough to make a functional hole on the cell membrane and cause erythrocyte lyses, the cytolytic activity of C8 is enhanced by participation of six molecules of C9. the membrane damage was thought to be due to phospholipase activity, but it is now believed to be due to ionophore effect. Reactive lysis is used for a condition, in which certain innocent cells are lysed by fixation of a proportion of free C567 complex in association with C89 components of the complement.

Classical and alternate pathways overlap^{2,3}:

It has been shown that antibodies and antigen – antibody complexes may activate the alternative pathway and agents like Cardiolipin, C – reactive protein and bacterial surface antigens may directly activate classical pathway, indicating that these two pathways are not separated as to the activation of complement. It further indicates that one can substitute to some extent for other. As a result, deficiency of one or two of the 25 components cannot affect the overall functional or biological activity of the complement in defense against infections.

Regulatory proteins:

Regulatory proteins are mainly inhibitors or activators of the individual steps of complement activation. Since spontaneous activation of complement may occur and lead to auto – cytolyses, the main aim of these proteins is to keep the process under control. Some are regulators of early components and some are regulators of components that participate in subsequent steps of the complement activation pathways.

There are ten to fifteen regulatory proteins that are chemically and functionally characterized. Some are free in the fluid phase to inactivate and some are bound to the cell membrane like erythrocytes, platelets and leukocytes that take part in the regulation of classical, alternate and terminal pathways.

Associated proteins:

Associated proteins are those that are known to react with the intermediate complexes and play role as agglutinating agents or slitting enzymes, such as conglutinin, immuno conglutinin, cobra venom factor, C3 splitting enzyme and so on.

- **Conglutinin** : Conglutinin K is a non antibody naturally occurring β_2 bovine serum protein. It has attachment site on bound C3 complex of a number of a mammalian species.
- **Immuno – conglutinin** is an auto – antibody (γ globulin) to fixed C3 and C4, found in sera of subjects frequently after microbial infections or following immunization with infecting agents. It also plays a role in agglutinating small complexes with bound C3 and makes them susceptible to phagocytic cells.
- **Cobra venom factor** is a snake C3b in a mammalian serum, which can activate alternative pathway in presence of factor B. Cobra venom factor may act as C3 convertase.
- **C3 splitting enzyme:** In addition to C3 convertase produced during complement activation, the fragments of C3 component can also produced artificially by peptide bond cleavage using number of non immunological enzymes such as plasmin, trypsin and lysosomal enzymes which play role in many other biological systems.

Biology of Complement:

Complement in vitro has been shown to promote chemotaxis, enhance phagocytosis and cause lyses of microbial cells or cells of erythro myelo – lymphoid series. It has thus been assumed that complement is the principle humoral effector system. An activation of components of the complement amplifies inflammatory response and can give rise to protective function against microbial infections. C3 is the central component of the complement system and its concentration in the serum is highest of all complement proteins. C3a and C5a are usually unifunctional in the sense as these products can mainly interact with effector cells bearing complement receptors.

Whereas C1q, C3b and C4b are bifunctional in the sense as these products can interact with the target of complement activation as well as with effector cells bearing complement receptors.

Complement deficiencies:

A deficiency of all components of the complement in a host does not exist, but a single component deficiency is not uncommon both in animal and man. Such a deficiency may be due to hyper catabolism or inadequate synthesis or defective gene or its association with other diseases. Complement may thus be grouped under inherited deficiency and acquired deficiency.

Inherited complement deficiency:

Deficiency of C1 and C2 which are essential for in vitro red cell lyses by classical pathway are known in man. An unopposed C1 esterase activity occurs in individuals with late adolescence with C1 inhibitor deficiency, causing severe non – inflammatory reaction in the skin, upper respiratory tract and GIT, known as hereditary angioneurotic edema. Persons with this C1 inhibitor are heterozygous and a deficiency is inherited as an autosomal dominant trait⁵.

CONCLUSION

The complement system is an ancient part of the innate immune system that acts as the first line of defence in the fight against infection. It is composed of at least 30 proteins, mostly synthesised in the liver, which typically circulate as inactive precursors. Then inactive state of the protease elements is maintained by the presence of several inhibitors. When the complement system is triggered a proteolysis based activation cascade proceeds causing an increased local immune responses and formation of a membrane attack complexes.

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