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Review

Complement in autoimmune diseases

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ABSTRACT

The complement system is an ancient and evolutionary conserved element of the innate immune mechanism. It comprises of more than 20 serum proteins most of which are synthesized in the liver. These proteins are synthesized as inactive precursor proteins which are activated by appropriate stimuli. The activated forms of these proteins act as proteases and cleave other components successively in amplification pathways leading to exponential generation of final effectors. Three major pathways of complement pathways have been described, namely the classical, alternative and lectin pathways which are activated by different stimuli. However, all the 3 pathways converge on Complement C3. Cleavage of C3 and C5 successively leads to the production of the membrane attack complex which is final common effector.

Excessive and uncontrolled activation of the complement has been implicated in the host of autoimmune diseases. But the complement has also been bemusedly described as the proverbial "double edged sword". On one hand, complement is the final effector of tissue injury in autoimmune diseases and on the other, deficiencies of some components of the complement can result in autoimmune diseases.

Currently available tools such as enzyme based immunoassays for functional assessment of complement pathways, flow cytometry, next generation sequencing and proteomics-based approaches provide an exciting opportunity to study this ancient yet mysterious element of innate immunity.

Contents

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1. Introduction

The complement system is a part of the innate immunological armamentarium that comprises of effector molecules and receptors that help in both fighting against the invasion of pathogens and regulation of the immune system. Paul Ehrlich, in the year 1899, introduced the term 'complements' for heat labile substances in sera that were responsible for antimicrobial immunity in addition to antibodies [1,2]. Ever since its first description, a number of complement components were subsequently discovered and were numbered according to the order of discovery. Extensive research has been done till date to understand various aspects and functions of the complement system and its role in the pathogenesis of autoimmune diseases. One of the most important reasons for tissue insults and end organ damage in autoimmune diseases is the excessive activation of the complement pathway [3,4]. Paradoxically, deficiencies of certain components of complement pathways also result in manifestations of autoimmune diseases such as systemic lupus erythematosus (SLE) [3,4]. This topical review focuses on the role of complement system in the pathogenesis of various systemic autoimmune disorders and its therapeutic implications. (See Fig. 1.) (See Table 1.)

2. Mechanism of complement system activation and its functions

Activation of complement pathway can occur by three different mechanisms. All the three mechanisms converge at the activation of C3 and C5, and finally result in the formation of the membrane attack complex (MAC). MAC disrupts the cell membrane, by forming pores on the cell membrane, and causing osmotic cell lysis [2].

The first mechanism is the activation of classical pathway by immune complex deposits (IgG or IgM). The complement binding site in the Fc portion of the antibody gets exposed during formation of antigen-antibody complexes. C1q, a component of C1 complex will attach to the antibody site and this initiates a conformational change in the C1 complex. This, in turn, leads to the activation of C1r and then C1s which are the serine protease units. Activated C1s subsequently activates C4 and then C2 to form C3 convertase (C4b2a). C3 convertase furthers forms activated C3 (C3a) and leads to the formation of C5 convertase (C3bBbC3b) that finally leads to the formation of membrane attack complex (MAC) [5].

The second mechanism is an antibody-independent pathway termed as 'alternative pathway' that involves proteins such as factor B, factor D, factor H, and properdin. A 'tick over' process that involves spontaneous hydrolysis of C3 in the circulation to form C3(H2O) initiates the process. Factor B binds to C3(H2O), which on further activation by factor D forms a labile C3 convertase (C3(H2O)Bb) which in turn initiates cleavage of C3. The short-lived C3 convertase (C3(H2O)Bb) is stabilized by properdin to form a C5 convertase (C3bBbP), which activates C5 to form C5a and helps in the formation of MAC [6].

The third mechanism, also called 'lectin pathway', is activated by recognition of specific carbohydrate moieties in the microbes by the mannose-binding lectin (MBL) or ficolin. With the help of MBL-associated serine proteases, activation of C2 and C4 would occur, which further initiates the cascade for MAC formation [5].

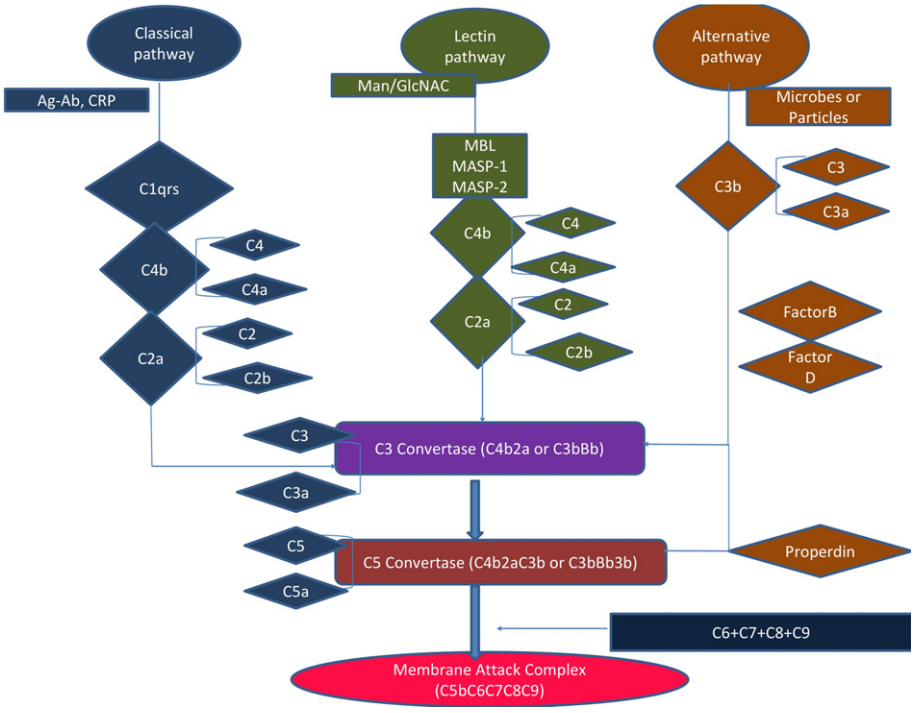

Fig. 1. Flowchart of the complement activation by classical, alternative and lectin pathways. In the classical pathway upon antigen-antibody binding, C1 gets activated and cleaves C4 and C2 complement components. The active components bind on the cell surface forming classical pathway C3 convertase (C4b2a). Lectin pathway has Mannose binding lectin (MBL) and ficolin instead of C1q. MBL associated serine proteases (MASP) cleave C4 and C2 to form C4b2a (C3 convertase). C3 convertase cleaves C3 into C3a and C3b, and forms C5 convertase (C4b2a3b). C5 convertase cleaves C5 into C5a and C5b which combines with the other terminal components to form membrane attack complex. Alternative pathway depends on the spontaneous hydrolysis of C3 to C3b. C3b binds to factor B to form C3bBb that act as C3 convertase. C3bBbC3b forms C5 convertase which is stabilized by properdin. C5b finally then forms a complex with 1 molecule of C6, C7, C8 forming C5b.6.7.8 complex (membrane attack complex). *Ag-Ab: Antigen antibody complex; CRP-C reactive protein; Man: Mannose; GlcNAC: N-acetylglucosamine.