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The molecular switches controlling the interaction between complement proteases of the classical and lectin pathways and their substrates

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Complement represents a major bridge between the innate and adaptive immune systems of the body. It plays a vital role in host defences against pathogens, but has also been implicated in numerous inflammatory diseases. The system has been the subject of intensive research in recent times with a number of key structural insights into the functioning of the system. Here, we will give an overview of the activation of each pathway, following which recent developments in our understanding of the mechanisms governing the interaction between enzymes and substrates in the classical and lectin pathways in particular will be discussed.

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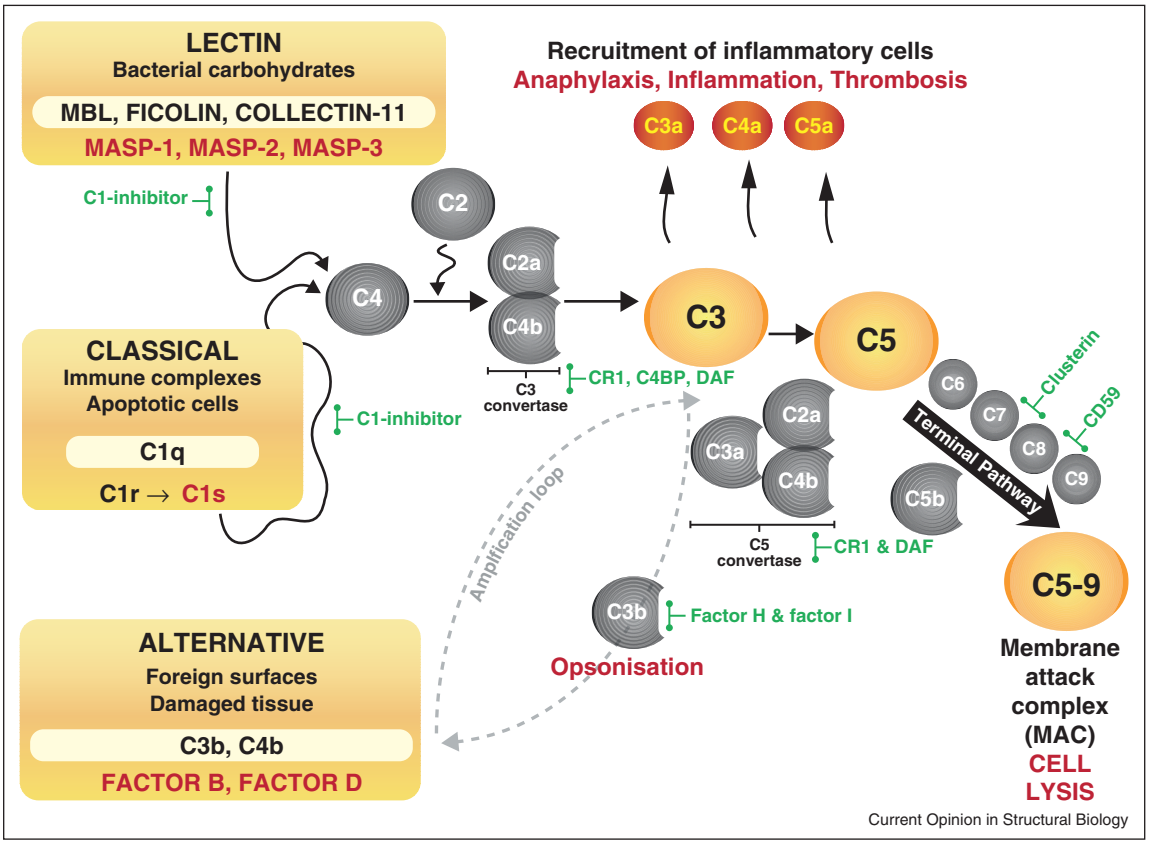
Introduction

The complement system is an ancient defense system for the body that plays key functions in immune reactions against pathogens and diseased (e.g. cancerous) self-cells. The system can be activated by three different pathways: the classical, lectin and alternative pathways.

The classical pathway is activated when the first component, C1, binds to ligands such as an immunoglobulin molecule in complex with an antigen. The binding occurs through the globular heads located on the C1q component of C1. It is theorised that binding to the six heads of the C1q transmits changes through the collagenous arms of the component to the associated C1r and C1s serine proteases arranged in a heterotetramer, comprising two molecules of each protease (Figure 1) [1,2]. Binding of C1q to its ligands thus causes activation of C1r through an autocatalytic mechanism [3]. Activated C1r in turn cleaves and activates C1s, which can then cleave the C4 and C2 complement components into the C4b and C2a fragments that assemble into the so-called C3 convertase [4]. The C3 convertase cleaves C3 to yield C3a and C3b, with C3b joining the C4b2a complex to give rise to the C5 convertase complex, which in turn cleaves C5 to yield C5a and C5b. The C3a, C4a and C5a peptides, are potent pro-inflammatory peptides that activate the immune system by acting as chemotaxins and opsonins for white blood cells. The C5b molecule acts as a scaffold for the assembly of the membrane attack complex (MAC), which punches holes in the membranes of cells targeted by the initiation complex. Finally, molecules such as C3b coating the surface of targeted cells act as opsonins to cause white blood cells to attack and engulf the cells labelled by the complement system.

The lectin pathway of complement is activated in a similar fashion to the classical pathway apart from the molecules comprising the initiating complexes. The lectin pathway is initiated by the binding of lectin recognition molecules, such as mannose binding lectin (MBL), ficolins or the CL-11 collectin, which bind to carbohydrate arrays on the surface of pathogens or damaged cells [5–7]. It is likely that a large spectrum of the lectin recognition complexes exist to allow recognition of the range of different microorganisms encountered in the life of an organism — given this thought, it is likely that many more lectin recognition molecules or variants of the currently known ones will be identified in coming years. There are 5 proteins associated with the lectin recognition molecules, encoded by the *MASP1* and *MASP2* genes. The *MASP1* gene gives rise to three proteins through alternative splicing: MBL-associated serine protease-1 (MASP-1), MASP-3 and MAP44 [8]. The MASP-1 and MASP-3 proteins have common domain architecture except for the C-terminal serine protease (SP) domain, which differs significantly between the two proteins [9–11]. MAP44 has the same 5 N-terminal domains as MASP-1 and MASP-3, but apart from a small 17 amino acid extension of the CCP2 domain, it has no SP domain [12]. The *MASP2* gene gives rise to the MASP-2 and SMAP proteins, with SMAP consisting of the first 5 domains of MASP-2 and lacking the SP domain [13–15]. It has been shown that MASP-1 autoactivates when the associated lectin recognition molecule binds to a ligand. While MASP-2 is also capable of autoactivating, convincing evidence now exists to show that MASP-1 is required to activate MASP-2 [16••]. MASP-2 carries out the same function as C1s to cleave C4 and C2 and thus propagate the activation of the complement system [17].

Figure 1



Schematic diagram of complement activation and regulation. Complement can be activated through three pathways: the classical, lectin and alternative pathways. The lectin pathway is activated by binding of lectins (MBL, ficolins and collectin-11) to carbohydrate arrays on pathogens not found on 'self' cells. The classical pathway is activated primarily by the interaction of C1q with immune complexes of antibody with antigen, but can also occur after interaction of C1q with non-immune molecules. The alternative pathway is activated on the surface of targets without the involvement of recognition molecules and also acts to amplify the classical and lectin pathways (amplification loop). All three pathways culminate in the formation of the C3 and C5 convertases that, in turn, generate the anaphylatoxins C3a, C4a and C5a, the membrane-attack complex (MAC; C5b–C9) and the opsonin C3b. These effectors function as chemokines, chemoattractants and activators of immunocompetent cells (C3a, C4a and C5a), mediate direct lysis of target cells (C5b–C9) or induce immune adherence and phagocytosis of the pathogen (C3b). Complement activation is regulated at multiple steps by various regulatory proteins, as indicated by the characteristic inhibitory symbols (green). C4BP, C4b-binding protein; CR1; complement receptor 1; DAF, decay accelerating factor.

The alternative pathway activates when the C3 complement component binds to surfaces and spontaneously activates a unique thioester bond within its structure to allow binding to be stabilised. Lack of clearance of the bound C3 results in further activation of the system, culminating in assembly of the terminal components of complement and the formation of the membrane attack complex, which results in cell lysis. The bound C3 attracts further alternative pathway factors, such as factors D and B, which assemble into the C3 and C5 convertase complexes with C3. The structure and function of these fascinating complexes have been elucidated in series of outstanding publications [18,19]. Normal mammalian cells are protected from alternative pathway activation by so-called decay factors and other protective proteins that essentially remove the bound C3 before it can activate the rest of the system. It is now widely accepted that the alternative pathway acts as an amplification loop for the entire complement system, acting from the point where C3 is cleaved to form C3b [20].

The functions of the initiating proteases of the classical and lectin pathways

The five initiating proteases of the classical and lectin pathways, C1r, C1s and MASPs1–3, all share similar domain architecture. Each has a CUB-EGF-CUB segment that is thought to play crucial roles in dimerising the proteases and allowing them to bind the recognition molecules. The CCP1-CCP2-SP segment is the catalytic unit that is able to interact with substrates and inhibitors.

The roles of C1r and C1s of the classical pathway appear to be clear, with C1r capable of autoactivation and subsequent cleavage of C1s, while C1s is required for

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