



Review Article

Evasion and interactions of the humoral innate immune response in pathogen invasion, autoimmune disease, and cancer☆



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ABSTRACT

The humoral innate immune system is composed of three major branches, complement, coagulation, and natural antibodies. To persist in the host, pathogens, such as bacteria, viruses, and cancers must evade parts of the innate humoral immune system. Disruptions in the humoral innate immune system also play a role in the development of autoimmune diseases. This review will examine how Gram positive bacteria, viruses, cancer, and the autoimmune conditions systemic lupus erythematosus and anti-phospholipid syndrome, interact with these immune system components. Through examining evasion techniques it becomes clear that an interplay between these three systems exists. By exploring the interplay and the evasion/disruption of the humoral innate immune system, we can develop a better understanding of pathogenic infections, cancer, and autoimmune disease development.

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Abbreviations: Ab, antibody/antibodies; MBL, mannose binding lectin/s; Ag, antigen/s; FH, Factor H; FI, Factor I; MAC, membrane attack complex; mAb, monoclonal antibody/ies; TF, tissue factor; HF, hemorrhagic fever; APLS, anti-phospholipid syndrome; aPL, anti-phospholipid; SLE, systemic lupus erythematosus; WNV, West Nile virus; NAb, natural antibody.

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1. The role of complement evasion in disease

The complement system serves as a first line of defense, by directly lysing abnormal cells and pathogens, and recruiting other immune cells such as macrophages and neutrophils. Complement activation occurs by three distinct, but connected pathways: classical, lectin, and alternative. C1q and mannose binding lectin (MBL) initiate the classical and lectin pathways, respectively. Both pathways cleave C4 and C2 to form the C3 convertase C2aC4b. The alternative initiation pathway follows constitutive C3 hydrolysis to C3b which, after interaction with Factors B, D and P form the stable C3 convertase, C3bBb [1,2]. Both C3 convertases cleave C3 into C3a and C3b. C3b binds the C3 convertases to form the C5 convertase to cleave C5. C3a and C5a are anaphylatoxins which stimulate inflammation. C5b initiates the formation of the membrane attack complex (MAC or C5b-9) which leads to cytolysis and cell or pathogen death [3] (Fig. 1). Regulatory factors including CD55, CD46 and complement receptor 1 interact with co-factor, Factor I to control the convertases [4]. In addition, Factor H (FH) with the Factor I (FI) degrades the alternative C3 convertase.

1.1. Complement and Gram positive bacteria

Bacteria use three main methods of evading complement that include binding host inhibitors to the pathogen surface, using bacterial enzymes to cleave active complement components, and degrading surface bound proteins to prevent further activation of the complement cascade.

The ability to bind host inhibitors is prevalent among many different bacterial species, though this paper will focus only on Gram positive bacteria. Species such as *Haemophilus influenzae*, *Bordetella pertussis*, and the Gram positive *Streptococcus pneumoniae* use a conserved

“superevasion” site to bind FH which results in degradation of C3b bound to the bacterial surface [5]. Both the streptococcal family and *Staphylococcus aureus* also use multiple, and sometimes redundant, proteins to bind FH to facilitate the formation of FH:C3b complexes which inhibit complement activation and increase bacterial survival [6–10]. *S. aureus* proteins not only recruit FH to the bacterial surface but also recruit FI which together inactivates C3b to form iC3b [8]. *S. pneumoniae* uses multiple proteins to bind and sequester C1q, as well as modulate complement FH, C4bp, and the C3 convertase [9,11]. Members of the microbial surface components recognizing adhesive matrix molecules protein family commonly expressed on *S. aureus*, *Streptococcus equi*, and *Streptococcus mutans* also bind C1q [12]. Finally, bacterial spores utilize similar survival strategies as *Bacillus anthracis* spores recruit FH, Factor H related protein 1, C1 inhibitor, and C4bp to their cell surfaces [13]. Thus, both spore forming and non-spore forming, Gram positive bacteria evade destruction by recruiting natural host complement inhibitors or sequestering pathway initiators to prevent complement activation.

While recruiting complement pathway inhibitors to the bacterial surface is a common method of immune evasion, bacteria also use their own proteins to cleave active members of the complement pathway, preventing the cascade from proceeding. The most common target of Gram positive bacterial enzymes is C3b. For example, *S. aureus* uses at least three proteins to degrade C3b and yet another protein to inhibit the formation of the C3 convertase [8,14–16]. *S. aureus* also degrades C3 by activating plasminogen, a member of the coagulation pathway [8,14,17]. Other bacteria also bind fibronectin (streptococcal family) or interact with plasminogen (*B. anthracis*) to decrease the amount of C3b deposited on the bacteria [7,13].

Other targets for complement evasion include direct inhibition of the common complement pathway and formation of convertases that lead to this step. Proteins expressed on the *S. aureus* bacterial surface

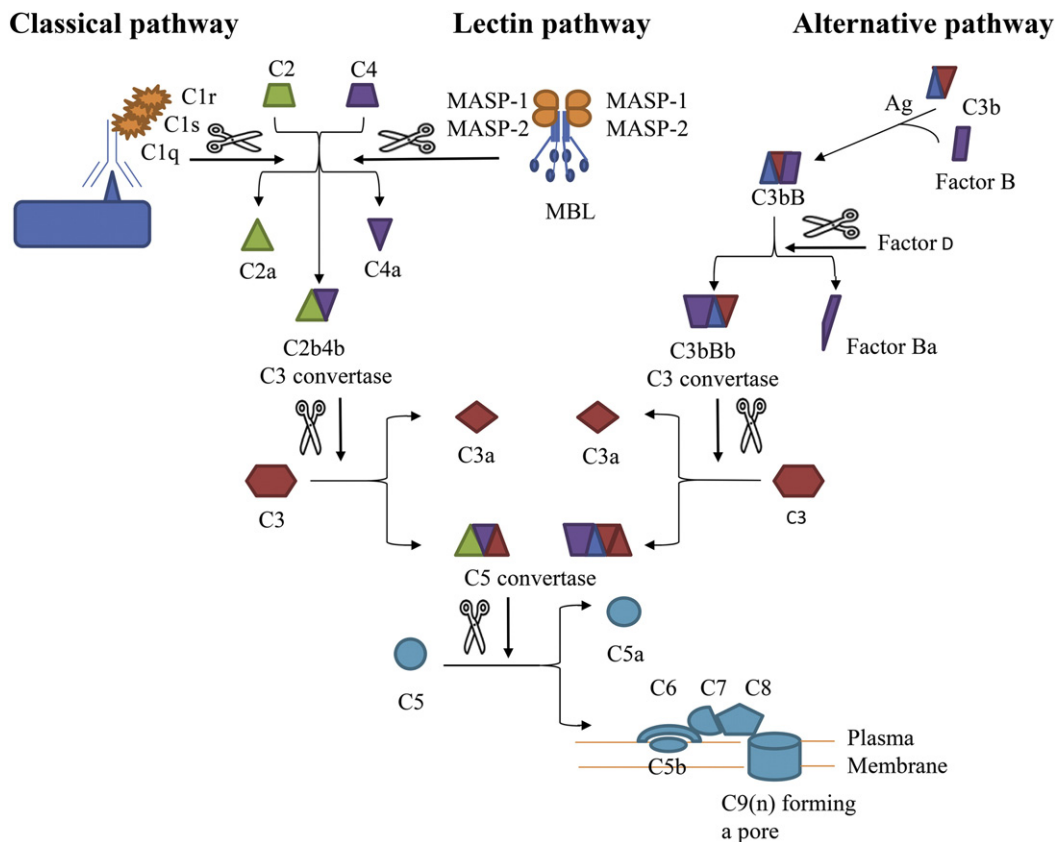


Fig. 1. Schematic representation of the complement cascade. Upon recognition of a foreign or damage cell surface, one or more complement pathways are activated. The classical and lectin pathways differ in their initiation. The alternative pathway is distinct from the other two pathways but all three pathways converge toward the formation of a C5 convertase, which is necessary for the MAC formation. The scissors indicates a cleavage. Ag, antigen; MAC, membrane attack complex.

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