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REVIEW

Complementopathies

Andrea C. Baines, Robert A. Brodsky *

Division of Hematology, Department of Medicine, Johns Hopkins School of Medicine, Baltimore, MD 21205, USA

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ABSTRACT

The complement system is an essential part of the innate immune system that requires careful regulation to ensure responses are appropriately directed against harmful pathogens, while preventing collateral damage to normal host cells and tissues. While deficiency in some components of the complement pathway is associated with increased susceptibility to certain infections, it has also become clear that inappropriate activation of complement is an important contributor to human disease. A number of hematologic disorders are driven by complement, and these disorders may be termed "complementopathies". This includes paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), cold agglutinin disease (CAD) and other related disorders, which will be the focus of this review. A better understanding of the central role of the complement system in the pathophysiology of these disorders may allow for application of therapies directed at blocking the complement cascade.

1. Introduction

The complement system is a key component of the innate immune system that provides host defense against a variety of pathogens, including bacteria, fungi and viruses. A wealth of research in complement biology has taken place since the term "complement" was first coined in the late 19th century [1,2], and we now recognize that complement has diverse roles in a variety of cellular processes, including bridging the innate and adaptive immune responses, maintaining homeostasis and preventing autoimmunity [3,4]. An overview of the normal functions of the complement system will be presented first to provide the reader with a basic context for understanding how dysregulated complement underlies the hematologic disorders that are the focus of this review, including PNH, aHUS and CAD.

2. Role of complement in innate immunity and homeostasis

An effective system for immune surveillance requires mechanisms for detecting harmful pathogens or abnormal cells, while distinguishing them from healthy host cells and tissues. This ability to differentiate between self and non-self (or damaged/altered self) is a hallmark feature of the complement system. As a general paradigm, this is primarily accomplished through pattern recognition – host pattern recognition receptors (PRRs) bind to components unique to microbial surfaces (often consisting of specific carbohydrate structures that are not found on host surfaces), termed pathogen-associated molecular patterns (PAMPs). Interactions between PRRs and PAMPs lead to complement activation and destruction of invading microorganisms. Similarly, host PRRs are also able to recognize abnormal glycosylation patterns on the surface of dead or dying host cells (termed damage-associated molecular patterns, or DAMPs) and immune complexes, activating complement mechanisms that lead to their clearance.

3. Link to inflammation and adaptive immunity

Activation and amplification of complement leads to destruction of pathogens or abnormal host cells through opsonization – a process by which complement ligands coat surfaces, targeting them for phagocytosis – or by lysis induced upon formation of the membrane attack complex (MAC), also referred to as the terminal complement complex (TCC). Other intermediaries generated during this process promote the inflammatory response and modulate the adaptive immune response. Complement components C3a and C5a (known as "anaphylatoxins"), released upon activation of the complement cascade, serve as potent chemotactic agents, leading to recruitment and activation of immune mediators, including neutrophils, macrophages, monocytes and mast cells. Through interactions with B cells and T cells, products of the complement cascade also have an important role in modulating aspects of humoral and cell-mediated immunity.

4. Complement cascade

The complement cascade is a complex network of over 40 soluble and membrane proteins [5], that can be activated by one of three

* Corresponding author at: 720 Rutland Avenue, Ross Research Building, Room 1021, Baltimore, MD 21205-2196, USA.
E-mail addresses: abaines2@jhmi.edu (A.C. Baines), brodsro@jhmi.edu (R.A. Brodsky).

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primary pathways: (1) the lectin pathway; (2) the classical pathway; and (3) the alternative pathway (Fig. 1). Although the lectin, classical, and alternative pathways are sometimes depicted as three separate pathways, they actually constitute different modes of activation (Table 1) for an interconnected downstream complement cascade. Additionally, there are routes of activation through the coagulation and fibrinolytic systems that bypass these initial activation pathways [6].

Table 1
Complement pathways and activators.

Pathway	Activator(s)
Lectin pathway (LP)	MBL, ficolins (via binding to carbohydrates on pathogens)
Classical pathway (CP)	IgG and IgM immune complexes
Alternative pathway (AP)	Slow spontaneous hydrolysis of C3

4.1. Complement activation via the lectin pathway (LP)

The lectin pathway (LP) is activated when host PRRs, such as mannose-binding lectin (MBL) or ficolins, recognize unique carbohydrate structures (PAMPs) present on the surface of pathogens or altered glycosylation patterns (DAMPs) on abnormal host cells. This results in activation of C2 and C4 by the mannose-binding lectin-associated serine proteases (MASPs) and subsequent formation of the C3 convertase (C4b·C2a).

4.2. Complement activation via the classical pathway (CP)

Typically, the classical pathway (CP) is initiated by immune complexes through binding of complement protein C1q, a PRR, to immune complexes containing IgM or IgG, in solution or bound to antigens on the cell surface. The CP can also be activated by direct binding of C1q to PAMPs on microbial surfaces. Upon binding, the C1 complex undergoes a conformational change, activating the C1r and C1s protease subunits, which leads to cleavage of C2 and C4 and formation of the C3 convertase (C4b·C2a).

4.3. Complement activation via the alternative pathway (AP)

The alternative pathway (AP) of complement is unique among the three primary activation pathways in that it is constitutively active, allowing it to be primed for surveillance and rapidly activated when pathogens are encountered. This is accomplished through the slow spontaneous hydrolysis of complement component C3, referred to as "tick-over."

4.4. Complement activation via the coagulation cascade and fibrinolytic system

Extensive interplay exists between the complement system and coagulation/fibrinolytic systems. In light of their shared evolutionary origins and homeostatic functions, it follows that coordinate activation of coagulation and complement occurs in response to injury and infection. Indeed, it has been shown that certain activated factors in the coagulation and fibrinolytic cascades and complement components can cleave and activate one another [6–10]. These connections also explain why many complement driven diseases (e.g. PNH and aHUS) include pathologic thrombosis as a hallmark clinical manifestation. Under normal

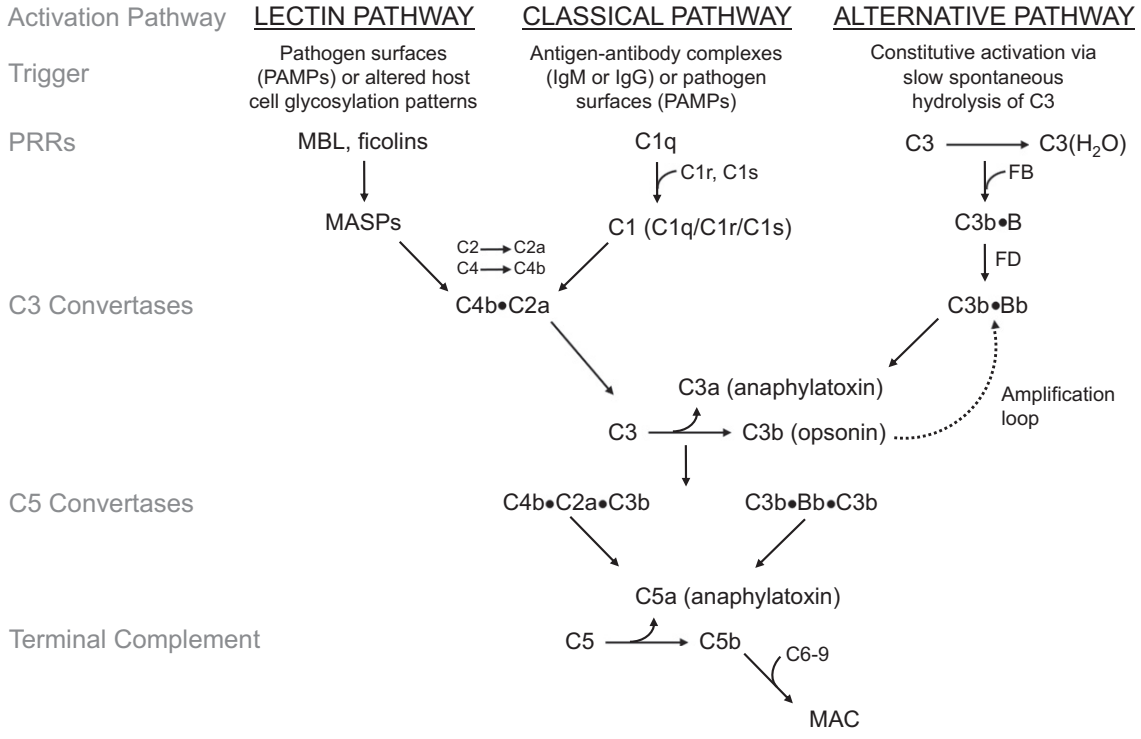

Fig. 1. Schematic of the complement cascade. The three primary routes for activation of complement are: (1) the lectin pathway (LP), (2) the classical pathway (CP), and (3) the alternative pathway (AP). The LP and CP are activated when specific triggers are recognized by host pattern-recognition receptors (PRRs). The AP is constitutively active. Initial activation through the LP or CP generates a shared C3 convertase (C4b·C2a). In the AP, C3b pairs with factor B (FB) to form the AP proconvertase (C3b·B), which is processed by factor D (FD) to form the AP C3 convertase (C3b·Bb). Both types of C3 convertases cleave C3 to generate C3a and C3b. C3a is an anaphylatoxin, a substance that promotes an inflammatory response. C3b that lands on the surface of a healthy host cell is quickly inactivated; C3b that attaches to the surface of a pathogen or altered host cell triggers a rapid amplification loop to generate more C3b, resulting in opsonization. C3b also complexes with the C3 convertases to form the C5 convertases (C4b·C2a·C3b and C3b·Bb·C3b). In the terminal complement cascade, C5 convertases cleave C5 into C5a (an anaphylatoxin) and C5b. C5b combines with C6-9 to form the membrane attack complex (MAC), also referred to as the terminal complement complex (TCC). Regulatory factors (Table 2) act at various stages of the cascade to control complement activation via their decay accelerating activity and/or cofactor activity. Additional abbreviations: PAMPs = pathogen-associated molecular patterns; MBL = mannose-binding lectin; MASPs = mannose-binding lectin-associated serine proteases.