Complement

An Overview for the Clinician

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KEYWORDS

• Complement system • Complement activation • Complement regulation
• Complement function • Inflammation • Immune response

KEY POINTS

- The complement system is composed of over 50 interacting serum and membrane-bound proteins that provides an effective immune surveillance.
- Complement can be activated via 3 different pathways: the classical, lectin, and alternative pathways, which converge at the cleavage and activation of C3 with the subsequent generation of various biological effector molecules.
- Strict regulation of the complement system is mediated by a number of soluble and membrane-bound proteins to prevent damage to self.
- Complement plays a key role in a number of biological processes, including host defense, removal of injured cells and debris, modulation of metabolic and regenerative processes, and the regulation of adaptive immunity.
- Inappropriate complement activation and impaired regulation can lead to self-directed attack and contributes to various diseases and disease-related conditions.

The complement system is a major component of the innate immune system and it provides a powerful and effective mechanism to protect the host from pathogens. It was first described in the late 19th century as a heat-labile component of serum that "complemented" the effects of antibodies in the lysis of bacteria and red blood cells.[1–4] The term *complement* was coined by Paul Ehrlich in 1899.[5,6] We now know that the complement system is made up of some 50 serum and membrane proteins with tightly regulated proteolytic activation cascades that culminate in the production of effector molecules with multiple biological functions.[4–9] It has long been known that complement provides host surveillance and protection from microbes, and it is now

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clear that complement also plays important and diverse roles in several other physiologic and homeostatic functions, such as the clearance of dead and dying cells, developmental and regenerative processes, and the modulation of humoral and cell-mediated immune responses.[10] Furthermore, disruption of the balance between complement activation and complement regulation is involved in the pathogenesis of several diseases and disease states, ranging from traumatic injury and ischemia-related conditions, to autoimmune disease, to alloreactivity and transplant rejection. Complement is also implicated in tumor immune surveillance, and recently tumor-promoting functions of complement have also been described.[11,12]

Soluble complement proteins are synthesized primarily by hepatocytes, although significant amounts are also synthesized by monocytes, macrophages, and some epithelial cells in the gastrointestinal and urinary tracts.[5] Activation of complement is normally achieved via 3 different pathways: the classical, alternative, and lectin pathways. Each of these pathways is initiated by different stimuli (**Table 1**), but all lead to the cleavage and activation of the central complement protein C3, with the subsequent cleavage of C5 and generation of biological effector molecules. In addition to the 3 well-defined pathways of activation, there are also bypass mechanisms of activation, such as the direct proteolytic cleavage of C5.[13]

ACTIVATION OF THE COMPLEMENT SYSTEM

The Classical Pathway

The classical pathway is triggered by antibody-antigen immune complexes via C1q recognition of Fc domains in conformationally altered immunoglobulin (Ig)M or clustered IgG (**Fig. 1**). The interaction of C1q with Fc causes a conformational change within the C1q molecule and the subsequent cleavage and activation of the associated C1r and C1s serine proteases. Activated C1s then cleaves C4 and C2 into 2 large active fragments (C4b and C2a) and 2 small soluble inactive fragments (C4a and C2b). Cleavage of C4 exposes a reactive thioester within the C4b fragment, which results in covalent attachment of C4b to the activating surface. The binding of C2 to C4b and the subsequent cleavage of C2 result in the covalently attached classical pathway C3 convertase, C4bC2a (note that there is discrepancy in the literature in the designation of C2a vs C2b). This complex cleaves C3 into C3b (large) and C3a (small). Similar to C4b, C3b contains a reactive thioester that can become bound covalently to the activating surface, and that can initiate activation of the alternative pathway. If C3b binds to the C4bC2a complex, it forms to classical pathway C5 convertase (C4bC2aC3b) that cleaves C5 into C5b and C5a, with initiation of the terminal complement pathway.

Table 1
Activation of the complement system

Pathway	Trigger for Activation
Classical	Antibodies bound to bacteria, fungi, viruses, or tumor cells Immune complexes Apoptotic cells C-reactive protein Activated Factor XII
Alternative	Continuous hydrolysis of complement protein C3
Lectin	Microbes with terminal mannose groups
Other activators of complement	Thrombin Kallikrein