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Review

Role and mechanism of action of complement in regulating T cell immunity

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ABSTRACT

Complement is a part of the innate immune system that contributes to first-line host defense. It is also implicated in a number of human inflammatory conditions and has attracted interest as a potential therapeutic target. Understanding the basic biology of complement and its mechanism(s) of action is imperative for developing complement-based treatments for infectious and autoimmune diseases. One of the exciting new developments in this regard is the revelation that complement plays an important role in T cell immunity. In this review, we highlight recent published studies implicating complement in models of CD4+ and CD8+ T cell immune responses, and discuss its potential mechanism(s) action in these processes. We also comment on issues that may impact data interpretation and draw attention to their consideration in future studies.

1. Complement and the innate immune response

The mammalian immune system provides defense against pathogenic invasion by way of detection, prosecution, and clearance of those entities which threaten host viability. Immune processes have traditionally been divided into two broad subsystems, innate and adaptive immunity. The former is composed of immunological effectors that provide robust, immediate, and relatively non-specific immune responses and constitutes the 'front-line' of host defense (Medzhitov and Janeway, 2000). The adaptive immune system is an evolutionarily younger and far more tailored system organized around two classes of specialized cell types, B and T cells. These cells display an extremely diverse repertoire of antigen-specific recognition receptors that enable specific identification and elimination of pathogens and generation of long-lived immunological memory which serves to curtail re-infection by the same pathogen (Janeway et al., 2005). Despite the intellectual distinction between these arms of immunity, over the past decades it has become increasingly clear that successful elimination of most pathogens requires concerted efforts on the part of the various immune responses and that crosstalk between innate and adaptive immunity plays a vital role in efficient host defense.

Complement is a part of innate immunity that was identified more than a century ago on the basis of its ability to 'complement' the lysis of bacteria by antibodies (Bordet, 1895). It is a significant protein component of serum, amounting to more than 3 g/L and constituting more than 15% of the globular fraction of plasma. Activation of complement can occur through three distinct pathways termed the classical, lectin, and alternative pathways (Walport, 2001a; Walport, 2001b; Dunkelberger and Song, 2010). Like other components of innate immunity, such as the Toll-like receptors (TLRs), retinoic acid-inducible gene (RIG)-I-like receptors (RLR) and nucleotide-binding oligomerization domain (NOD) receptors (Takeuchi and Akira, 2010), complement can recognize non-self through common and evolutionarily conserved pathogen-associated molecular patterns (PAMPs) and therefore provide immediate responses to common pathogenic surfaces. The classical and lectin pathways activate complement through recognition of PAMPs by natural (complement-fixing; generally IgM or IgG_1) antibodies and lectins (e.g. mannose-binding lectin, MBL), respectively (Walport, 2001a; Walport, 2001b) . In contrast, the alternative pathway (AP) is constitutively active by virtue of low-level, hydrolytic 'tick-over' of C3 and differentiation between self and non-self by the AP is thought to be achieved by membrane and plasma complement regulators functioning on the host cell but not foreign surfaces (Walport, 2001a; Walport, 2001b; Zipfel and Skerka, 2009; Dunkelberger and Song, 2010). It should be noted however that this 'textbook' view of AP activation is currently being expanded with evidence showing that properdin, a component of AP complement, may function as a pattern-recognition molecule for certain PAMPs such as lipopolysacharride (LPS), lipooligosacharride (LOS), zymosan and viral double-stranded RNAs to direct AP activation (Spitzer et al., 2007; Kimura et al., 2008; Kemper et al., 2010; Zhang et al., 2010).

Complement activation initiates a cascade of proteolytic reactions involving more than 30 proteins in the serum and on cell

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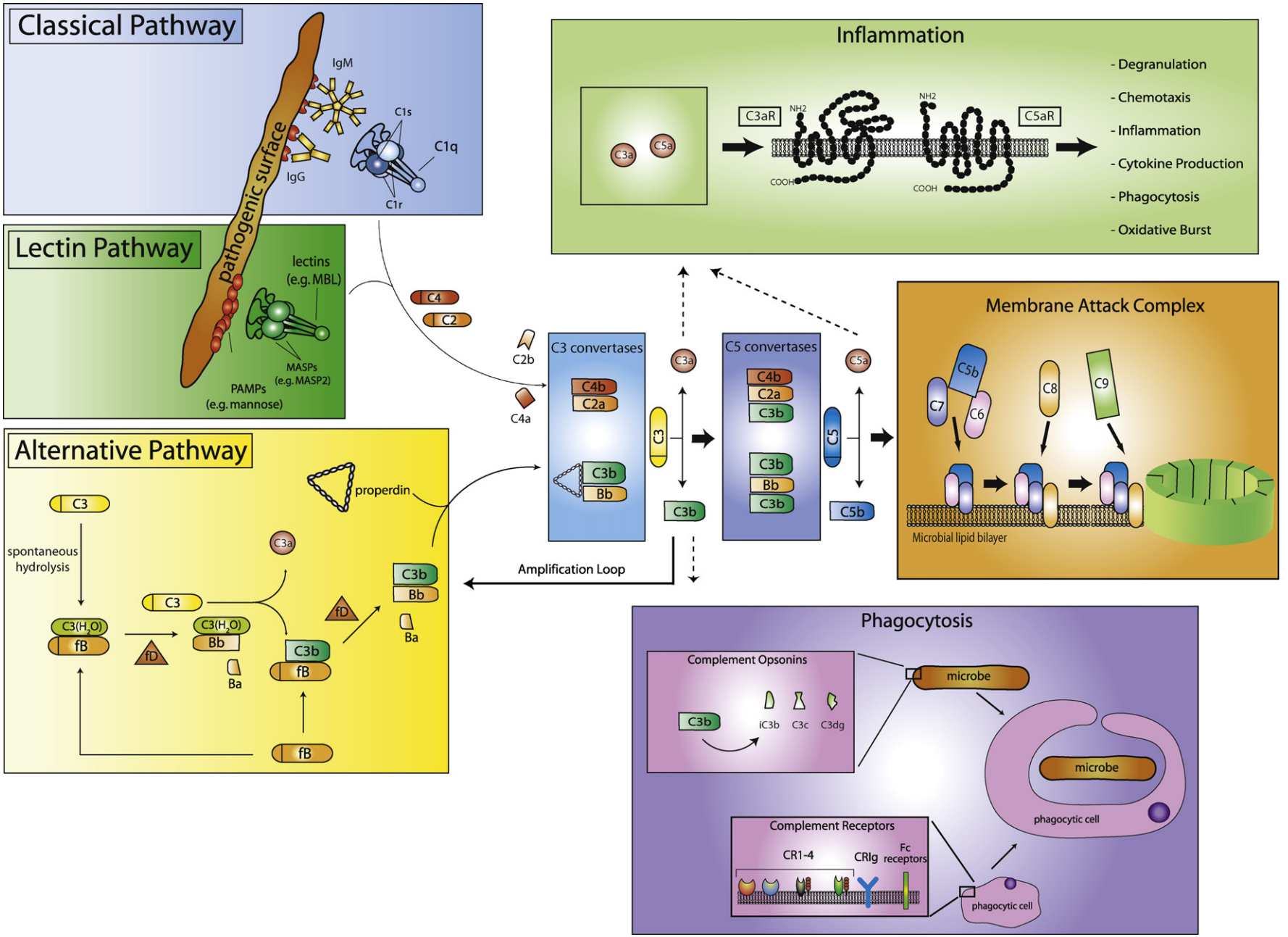

Fig. 1. Complement activation cascade. The complement system can be activated by the classical, lectin or alternative pathway; activated complement fulfills three types of effector function: inflammation, target opsonization and ingestion, and cell lysis. MBL, mannose-binding lectin; PAMP, pathogen-associated molecular pattern; MASP, mannose-binding lectin-associated serine protease; C3aR, C3a receptor; C5aR, C5a receptor; CR, complement receptor(s); CRIg, complement receptor of the immunoglobulin superfamily.