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REVIEW

Paths reunited: Initiation of the classical and lectin pathways of complement activation

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Abstract

Understanding the structural organisation and mode of action of the initiating complex of the classical pathway of complement activation (C1) has been a central goal in complement biology since its isolation almost 50 years ago. Nevertheless, knowledge is still incomplete, especially with regard to the interactions between its subcomponents C1q, C1r and C1s that trigger activation upon binding to a microbial target. Recent studies have provided new insights into these interactions, and have revealed unexpected parallels with initiating complexes of the lectin pathway of complement: MBL–MASP and ficolin–MASP. Here, we develop and expand these concepts and delineate their implications towards the key aspects of complement activation via the classical and lectin pathways.

Keywords: Complement; Innate immunity; Classical pathway; Lectin pathway

Contents

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Introduction

The classical and lectin pathways of complement activation are central combatants in the fight against disease. Both are able to lyse pathogens directly via antibody-independent mechanisms thereby providing an immediate response against invasion (Fujita et al., 2004; Schwaeble et al., 2002). They also stimulate key cellular and humoral interactions, including chemotaxis, phagocytosis and cell adhesion. Crucially, complement activation promotes B-cell differentiation and maintenance of immune tolerance to build vital bridges with adaptive immunity (Carroll, 2004), and subsequent activation on antibody–antigen complexes and other host-derived proteins (Arnold et al., 2006) further facilitates directed killing once an immune response is established (Porter and Reid, 1978). Recently it has emerged that complement components not only target non-self but also altered-self structures, and that early complement components are key players in tissue homeostasis through clearance of apoptotic and necrotic cells (Botto, 1998; Stuart et al., 2005; Taylor et al., 2000).

As expected from their important biological roles, deficiencies in complement components are associated with increased risk of acute, severe infections (Summerfield, 2003). For example, lack of C1q increases susceptibility to encapsulated bacteria such as *Streptococcus pneumoniae* (Colten and Rosen, 1992). It is also linked with defective clearance of immune complexes and cellular debris, leading to glomerulonephritis (Botto et al., 1998), and increased risk of autoimmune diseases such as systemic lupus erythematosus (Lewis and Botto, 2006). Whilst normally protective, complement can inadvertently contribute to disease pathogenesis. For example, C1q is involved in the pathology of several amyloid diseases, such as Alzheimer's disease and readily binds to prion proteins to initiate complement activation (Sim et al., 2007) and exacerbate disease progression (Yasojima et al., 1999). In addition, reperfusion of tissues following ischemia triggers lectin pathway-mediated host damage in conditions such as myocardial infarction and in kidney disease. Thus, specific inhibitors of complement have considerable therapeutic potential (Møller-Kristensen et al., 2003; Mollnes et al., 2002), and understanding the molecular interactions triggering complement activation is of great interest from biochemical, immunological and medical perspectives and will form the basis for rational drug design.

Befitting its biological importance, the study of the composition and structure of the C1 complex has a long history. In the early 1960s it was shown to comprise three subcomponent proteins: C1q, C1r and C1s (Lepow et al., 1963). It is now well established that C1q functions as the recognition subcomponent of the complex by binding to a wide variety of targets including microorganisms, immune complexes, apoptotic and necrotic cells and amyloids to initiate the stepwise activation of the associated serine proteases, C1r and C1s. C1q is a hexamer of subunits, each assembled from three different polypeptide chains, A, B and C (Reid and Porter, 1976) (Fig. 1). N-terminal collagenous tails (subsequently referred to as stalks) splay apart at an interruption in this domain called the kink, and terminate in C-terminal globular heads to form bouquet-like structures (~530 kDa) (Strang et al., 1982). The protease subcomponents C1r and C1s are homologous modular proteins, each consisting of two CUB domains separated by an EGF-like domain, followed by two CCP modules and a serine protease domain (SP) (Schwaeble et al., 2002; Sim and Tsiftsoglou, 2004). C1r dimerizes through interactions between the SP domain of one polypeptide and the CCP

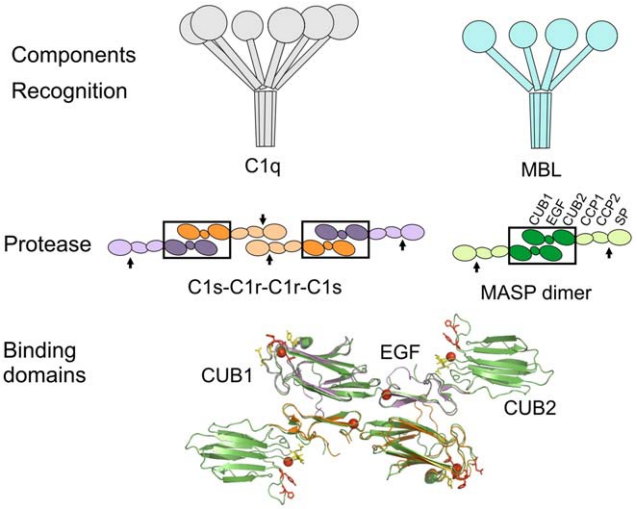

Fig. 1. Schematic representations of components of the initiating complexes of lectin and classical complement pathways. Top, C1q, MBL and ficolins (not shown) resemble bouquets, comprising N-terminal collagen-like domains linked to C-terminal target-recognition domains (carbohydrate-recognition, antibody-binding and fibrinogen-like, respectively). *Middle*, domain organisations of C1rs heterotetramers and MASP homodimers. C1r–C1s and MASP–MASP interactions are conserved (*black boxes*), so that the C1rs tetramer is effectively equivalent to two MASP dimers linked through their CCP–SP domains. *Bottom*, crystal structures of MASP-1 CUB1–EGF–CUB2 (*green*; PDB: 3DEM (Teillet et al., 2008)) and C1s CUB1-EGF fragments (*orange* and *purple*; PDB: 1NZI (Gregory et al., 2003)). Each EGF domain binds a Ca^{2+} ion (*red sphere*) aiding binding to the CUB1 domain of its partner. Additional Ca^{2+} ions (*red spheres*) are co-ordinated within the CUB domains and organize the loops that form the binding sites for the MBL/C1q stalks. Putative binding residues are coloured *red* and *yellow* for large and lesser effects on binding, respectively. *In vivo*, C1s does not form homodimers, but instead each chain binds to a C1r polypeptide through homologous interactions.