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ScienceDirect
Immunobiology 212 (2007) 301–311
Immunobiology
www.elsevier.de/imbio

New perspectives on mannan-binding lectin-mediated complement activation

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Received 10 August 2006; received in revised form 24 November 2006; accepted 5 December 2006

Abstract

The complement system is an important part of the innate immune system, mediating several major effector functions and modulating adaptive immune responses. Three complement activation pathways exist: the classical pathway (CP), the alternative pathway (AP), and the lectin pathway (LP). The LP is the most recently discovered, and least characterized. The CP and the LP are generally viewed as working through the generation of the C3 convertase, C4bC2b, and are here referred to as the "standard" pathways. In addition to the standard CP and LP, so-called bypass pathways have also been reported, allowing C3 activation in the absence of components otherwise believed critical. The classical bypass pathways are dependent on C1 and components of the AP. A recent study has shown the existence also of a lectin bypass pathway dependent on mannan-binding lectin (MBL) and AP components. The emerging picture of the complement system is more that of a small "scale-free" network where C3 acts as the main hub, than that of three linear pathways converging in a common terminal pathway.

Keywords: C3 convertase; Lectin pathway; MBL; Complement bypass pathway

Introduction

The complement system is a defense mechanism comprising around 30 different soluble and membrane-bound proteins. It is part of the innate immune system and proceeds via controlled limited proteolysis and conformational changes of constituent proteins through three activation pathways, the classical pathway (CP), the alternative pathway (AP) and the lectin pathway (LP), which converge in a common lytic cascade. The CP is initiated by recognition of immune complexes containing IgG or IgM, and C-reactive protein, as well as some pathogen-associated molecular patterns (PAMPs), by the pattern recognition molecule (PRM) C1q. Activation of the LP occurs through recognition of PAMPs by either mannan-binding lectin (MBL) or ficolins. Finally, activation of the AP occurs constitutively by spontaneous hydrolysis of the thioester bond in C3, and specificity is achieved through inhibition on non-activating self-surfaces, and lack of inhibition on non-self (e.g., bacteria) and altered self (e.g., cancer cells). The AP also serves as an amplification loop for

Abbreviations: AP, alternative pathway; CP, classical pathway; CRD, carbohydrate-recognition domain; FBG, fibrinogen-like domain; IGFBP-5, insulin-like growth factor-binding protein 5 ; LP, lectin pathway; MAC, membrane attack complex; MASP, MBL-associated serine protease; MBL, mannan-binding lectin ; PAMP, pathogen-associated molecular pattern; PRM, pattern-recognition molecule; SIGN-R1, specific intercellular adhesion molecule-3 grabbing nonintegrin-related 1; SP, serine protease

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doi:10.1016/j.imbio.2006.12.004

the other two activation pathways (Harboe et al., 2004; Brouwer et al., 2006). All three activation pathways converge in the common lytic cascade, which terminates in the formation of the membrane attack complex (MAC), also known as the terminal complement complex (TCC). The MAC inserts into cell membranes and forms pores leading to osmotic lysis of the target cells. An overview of the three activation pathways is given in Fig. 1. The CP is believed to be the most recent of the activation pathways, having evolved around the same time as the adaptive immune system (Fujita, 2002), approximately 500 million years ago. The interaction between the CP and the adaptive immune system creates an interesting and important cross-bridge between the innate and the adaptive defense systems. The LP has features in common with the CP but is evolutionarily much older (Fujita, 2002; Dodds, 2002). The AP is believed to be as old as the LP, possibly having appeared first as an amplification mechanism of this, and later evolved into an independent pathway (Dodds, 2002). Although the LP is a primordial defense mechanism, it is the most recently discovered of the three activation pathways, and thus also the least characterized. This review will give an overview of the LP, as well as describe the recently discovered lectin bypass pathway in the context of the classical bypass pathways.

The standard LP of complement activation

Activation of the LP occurs through recognition of PAMPs by either MBL or ficolins in association with MBL-associated serine proteases (MASPs). Upon binding to the target, the MASPs are activated allowing them to generate the C3 convertase, C4bC2b. MBL, the better-known PRM of the LP, is a plasma protein of hepatic origin, belonging to a family of proteins known as the collectins. Collectins are oligomers of polypeptide chains containing a C-type lectin carbohydrate-recognition domain (CRD) attached to a collagen-like region. In the case of MBL, three identical polypeptide chains assemble to form each structural subunit, which then associate into higher oligomeric forms, ranging from dimers to hexamers and even higher oligomers (Dahl et al., 2001). The overall structure of MBL resembles that of C1q, being sertiform (Holmskov et al., 2003). The PAMPs recognized by MBL comprise various

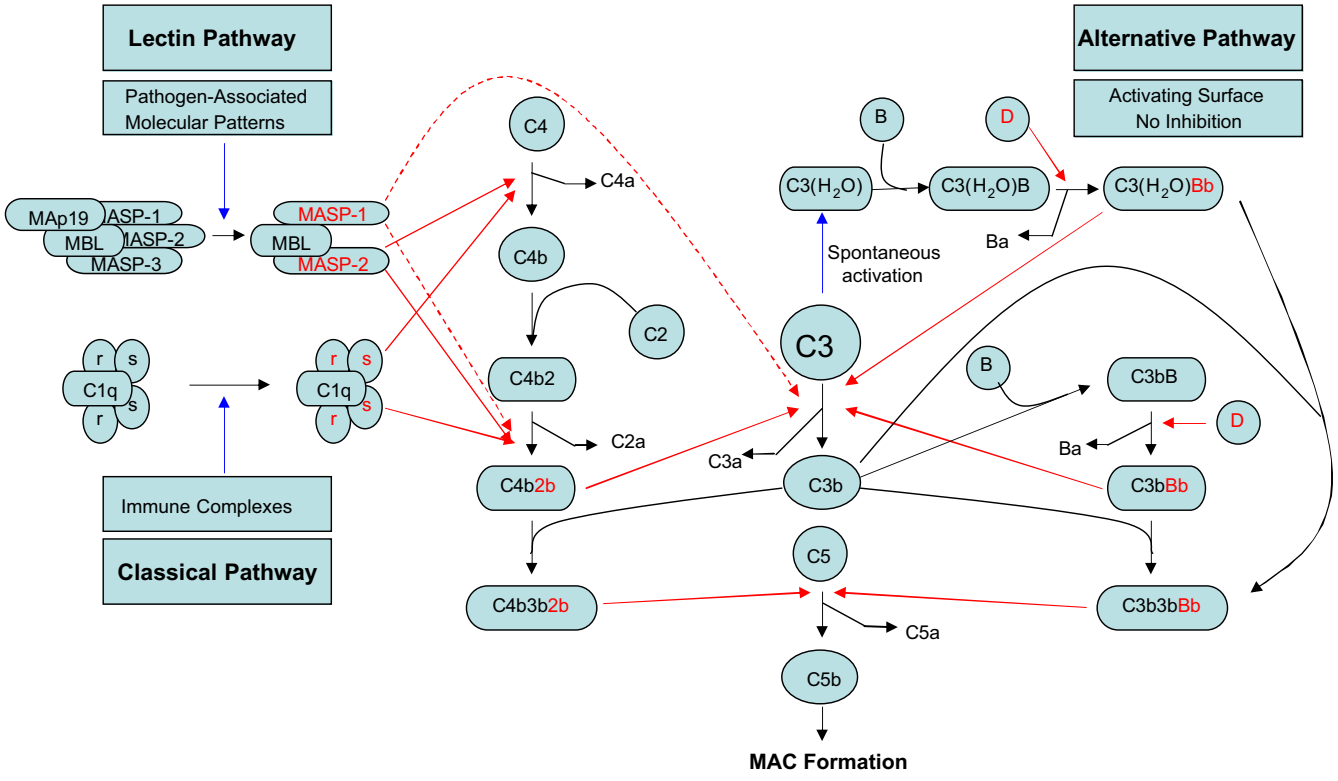

Fig. 1. The three activation pathways of the complement system. The names of the pathways and their main activators are shown in square boxes, proteins of the pathways in rounded boxes, and released fragments as plain text. Blue arrows denote the initiating events. Red letters denote the active serine proteases of the pathways, and red arrows the cleavages they mediate. The dashed arrows progressing from MASP-1 indicate activities on which there is not yet consensus. Curved black arrows indicate associations, broken black arrows dissociations, and straight black arrows progression to subsequent steps. The ficolin/MASPs can initiate the lectin pathway in a manner similar to MBL/MASPs.