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SCIENCE DIRECT
Immunobiology 211 (2006) 283–293
Immunobiology
www.elsevier.de/imbio

REVIEW

Lectin complement system and pattern recognition

Yuichi Endo, Momoe Takahashi, Teizo Fujita*

Department of Immunology, Fukushima Medical University, Fukushima 960-1295, Japan

Received 1 December 2005; accepted 10 January 2006

Abstract

Living organisms have strong defense mechanisms against invading microorganisms as survival strategies. One of the defense mechanisms is the complement system, composed of more than 30 serum and cell surface components. This system collaborates in recognition and elimination of pathogens as a part of both the innate and acquired immune systems. The two collagenous lectins, mannose-binding lectin (MBL) and ficolins, are pattern recognition proteins acting in innate immunity and, upon recognition of the pathogens, they trigger the activation of the lectin complement pathway through attached serine proteases (MASPs). A similar lectin-based complement system, consisting of the lectin-protease complex and C3, is present in ascidians, our closest invertebrate relatives and in lamprey, the most primitive vertebrate. Furthermore, a lamprey *N*-acetylglucosamine (GlcNAc)-binding lectin was identified as the orthlogue of mammalian C1q, and lamprey MASP is suggested as the prototype of MASP-2/C1r/C1s, indicating that the classical complement pathway arose as a part of the innate immune system. Thus, the complement system is one of the most highly organized innate immune systems in invertebrates and jawless vertebrates, and this system has survived in vertebrates with its core components little changed for 600–700 million years.

Keywords: Complement; Ficolin; Lectin; MASP; MBL

Contents

*Corresponding author. Fax: +81 24 548 6760.
E-mail address: tfujita@fmu.ac.jp (T. Fujita).

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doi:10.1016/j.imbio.2006.01.003

Introduction

Immunity is comprised of innate and adaptive defense mechanisms. The innate immune system is an evolutionarily ancient form and crucial for the first line of defense (Hoffmann et al., 1999). Accumulating evidence indicates that adaptive immunity was established at an early stage of jawed vertebrate evolution. In invertebrates, therefore, the innate immune system is the only defense mechanism against infection. Innate immunity was formerly thought to be a non-specific immune response characterized by phagocytosis. However, innate immunity has considerable specificity and is capable of discriminating between pathogens and self as proposed in the concept of pattern recognition molecules of host. These molecules recognize conserved pathogen-associated molecular patterns shared by large groups of microorganisms, thereby successfully defending invertebrates and vertebrates against infection (Medzhitov and Janeway, 2000).

The complement system mediates a chain reaction of proteolysis and assembly of protein complexes, playing a major role in body defense as a part of both the innate and adaptive immune systems (Walport, 2001a, b). Complement was first described in the 1890s as a heat-labile protein in serum that 'complemented' heat-stable antibodies in the killing of bacteria. Now, the complement system consists of three activation pathways, classical, alternative and lectin pathways, which merge at the proteolytic activation step of C3, the central component of the complement system. C3 is equipped with a unique intra-molecular thioester bond which is exposed to the molecular surface upon activation and forms a covalent bond with invading microorganisms (Law et al., 1980). This covalent tagging of foreign molecules by C3 is considered to be one of the most important functions of the complement system; bound C3 activation products enhance the phagocytosis of pathogens through C3 receptors on phagocytes, and contribute to the activation of the late complement components, C5–C9, which form a cytolytic complex (the so-called membrane attack complex). The classical pathway is activated by antibody–antigen complexes and is a major effector of antibody-mediated immunity. The recently discovered lectin pathway (Fujita, 2002; Matsushita and Fujita, 1996) activates complement following the recognition of microbial carbohydrate patterns by either mannose-binding lectin (MBL) or ficolins, typical fluid phase pattern recognition molecules (Holmskov et al., 2003; Matsushita and Fujita, 2001, 2002), and the subsequent activation of associated unique enzymes, MBL-associated serine proteases (MASPs) (Matsushita et al., 1998; Schwaeble et al., 2002). The alternative pathway is initiated by the covalent binding of a small amount of C3 to hydroxyl or amine groups on cell surface molecules of microorganisms and does not involve specific recognition molecules. This pathway also functions to amplify C3 activation (amplification loop) (Walport, 2001a, b).

Most components of the classical pathway have their structural and functional counterparts in the alternative or lectin pathways, suggesting that gene duplications played an important role in establishing these three pathways. These duplications could be an epoch-making event, which enabled generation of the classical pathway, considered to be the most modern pathway contrary to its name, from the alternative and lectin pathways (Nonaka et al., 1998). Accumulating evidence indicates that the modern complement system seems to have been established by the emergence of jawed vertebrates, and that the complement system of bony and cartilaginous fish has basically the same set of components as the mammalian complement system (Fujita, 2002; Nonaka, 2001; Fujita et al., 2004a). The development of the complement system is illustrated in Fig. 1.

In addition, one of the outstanding advances in recent complement research is the discovery of the lectin pathway. In the lectin pathway, MBL and ficolin act as the recognition molecules and activate complement in association with MASPs, a C1r/C1s-like serine protease that is able to cleave the complement components C4, C2 and C3 (Fujita et al., 2004b). Recent biochemical identification of several components of the lectin pathway from a solitary ascidian, *Halocynthia roretzi*, revealed that the primitive complement system is one of the most highly organized innate immune systems in invertebrates. Furthermore, in lamprey, the most primitive vertebrate (jawless vertebrate) we found that C1q, the component of the classical pathway, has a lectin activity and acts as the pattern recognition molecule (Matsushita et al., 2004). In this review, we focus on typical pattern recognition proteins, MBL and ficolin, and associated serine protease, MASP in ascidian and lamprey, and further we would like to mention the architecture of the primitive complement system.

MBL is one of the typical pattern recognition proteins

MBL is a C-type lectin that plays a crucial role in the first line of host defense (Drickamer et al., 1986; Ezekowitz et al., 1988; Kawasaki et al., 1978; Turner, 1996). The importance of this molecule is underlined by a number of clinical studies linking MBL deficiency with increased susceptibility to a variety of infectious diseases (Jack et al., 2001; Neth et al., 2000; Summerfield et al., 1995; Super et al., 1989). MBL is an oligomer of structural subunits, each of which is composed of three identical 32-kDa polypeptide chains. One polypeptide chain contains an N-terminal region rich in cysteine, a