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Review

The role of ficolins in the lectin pathway of innate immunity

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ABSTRACT

Ficolins are a family of oligomeric proteins consisting of an N-terminal collagen-like domain and a C-terminal globular fibrinogen-like domain. They are novel lectins that employ the fibrinogen-like domain as a functional domain. Ficolins specifically recognize N-acetyl compounds such as N-acetylglucosamine, components of bacterial and fungal cell walls, and certain bacteria. Like mannose-binding lectin (MBL), ficolins circulate in complexes with MBL-associated serine proteases (MASPs). MASP complexes form with ficolins and MBL, thereby activating the complement through the lectin pathway. Upon binding of ficolins and MBL to carbohydrates on pathogens, MASPs convert to active forms, and subsequently activate the complement. The activated complements lead to pathogen phagocytosis, aggregation and lysis. In humans, three ficolins (L-, M- and H-ficolins) have been identified, which exhibit differences in tissue expression, protein location site, ligand-binding and bacteria-recognition, suggesting a specific role of each ficolin. In addition, these ficolins form complexes with three MASPs (MASP-1, MASP-2 and MASP-3) and two nonenzymatic proteins (sMAP and MAP-1), suggesting a highly sophisticated organization and regulated activation of the ficolin-dependent lectin pathway. This review provides an overview of our current knowledge of ficolins, especially human ficolins and their mouse homologues. We also discuss their possible physiological roles in innate immunity, especially their defensive role against bacterial infection.

Contents

1. Introduction

The molecular basis of innate immunity critically relies on the discrimination of infectious agents by first-line host defense molecules. Lectin occupies a crucial position in this system by recognizing pathogen-associated molecular patterns (PAMPs) on the surfaces of a variety of microbes. Lectin is the general term for carbohydrate-binding proteins with multivalent sites, which are involved in recognition and aggregation of oligosaccharide and polysaccharide compounds. Among the lectins, ficolins (FCNs) and mannose-binding lectin (MBL) have a unique property in forming complexes with MBL-associated serine proteases (MASPs) in the circulation, consequently leading to complement activation (Matsushita and Fujita, 1992; Matsushita et al., 2000a, 2002). This pathway is called the lectin pathway and is the third pathway of complement activation (Matsushita and Fujita, 1996; Fujita, 2002;

Abbreviations: FCN, ficolin; MBL, mannose-binding lectin; MASPs, MBL-associated serine proteases; sMAP, small MBL-associated protein; GlcNAc, N-acetylglucosamine.

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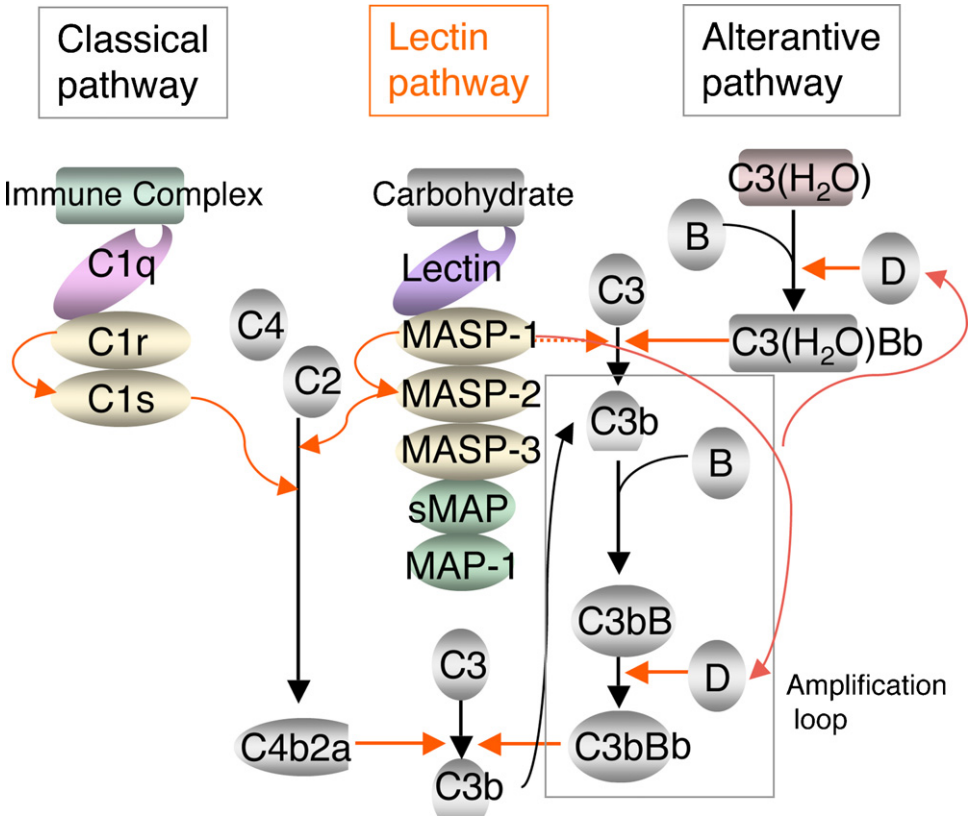

Fig. 1. A schematic representation of the three pathways of complement activation: the classical, alternative and lectin pathways. In the first step of the classical pathway, C1q recognizes the immune complexes, while in the lectin pathway, lectins such as ficolin and MBL recognize carbohydrates on invading pathogens. Such recognition activates the associated serine proteases of the MASP/C1r/C1s family, and in turn the activated MASPs and C1s trigger the complement activation. The alternative pathway is activated on the surface of targets without the involvement of recognition molecules, and also acts as an amplifier of the classical and lectin pathways, by amplifying C3 cleavage (amplification loop). Red arrows depict the activation reactions.

Fujita et al., 2004), in addition to the classical and the alternative pathways.

In the classical pathway, C1q, a subcomponent of complement C1, recognizes immune complexes and thereby activates the associated serine protease C1r (Fig. 1). Activated C1r then activates C1s, which in turn cleaves C4 and C2 to generate C3 convertase C4b2a. This consequently leads to the activation of the central component of complement C3. The generated C3b opsonizes pathogens to facilitate their elimination by phagocytosis, and the generated convertases C4b2a and C3bBb activate C5 on pathogens, inducing the lytic pathway *via* the late components of complement, C5 to C9. It is generally accepted that the alternative pathway is activated on the surface of pathogens without the involvement of specific recognition molecule. The alternative pathway also acts as an amplification pathway for the classical and lectin pathways by enhancing the generation of C3 convertase, C3bBb. Thus, the classical and alternative pathways are involved in adaptive immunity and innate immunity, respectively.

In the lectin pathway, MBL and ficolins serve as recognition molecules against pathogens. While activated MASP-2, which is one of three human MASPs (MASP-1, MASP-2 and MASP-3) and a main effecter of the lectin pathway, activates C4 and C2 to generate C3 convertase C4b2a, like C1s in the classical pathway (Matsushita et al., 2000b; Rossi et al., 2001) (Fig. 1). It was reported that MASP-1 activates MASP-2 (Takahashi et al., 2008). MASP-1 also activates factor D, which is an early component of the alternative pathway, suggesting that MASP-1 is an initiator of the alternative pathway (Takahashi et al., 2010). MASPs, C1r and C1s are each members of the MASP/C1r/C1s family, a subfamily of the serine protease superfamily (Endo et al., 1998, 2003).

Ficolin was first identified as a thermolabile β2-macroprotein, which precipitates autoantibody in the sera from patients with systemic lupus erythematosus (Epstein and Tan, 1973; Yae et al., 1991). This protein was termed “Hakata antigen” and later described as “H-ficolin” or “ficolin-3” (Table 1). Another ficolin was identified as a transforming growth protein on the cell membranes of a porcine uterus (Ichijo et al., 1993). The human homologue was isolated from the plasma as an elastin-binding protein (Harumiya et al., 1995), a corticosteroid-binding protein (Edgar, 1995) and an opsonin P35 (Matsushita et al., 1996). This human protein was later renamed L-ficolin or ficolin-2. The third ficolin was identified in humans (Endo et al., 1996; Lu et al., 1996) and was initially designated as a P35-related protein before being described as M-ficolin or ficolin-1. In 1996, we first reported that L-ficolin (opsonin P35) is a kind of lectin specific for N-acetylglucosamine (GlcNAc) (Matsushita et al., 1996). Ficolins are a family of oligomeric protein consisting of an N-terminal collagen-like domain and a C-terminal fibrinogen-like domain, which are similar to MBL and C1q, in that each has a N-terminal collagen-like stalk. Ficolins are novel lectins that employ the C-terminal fibrinogen-like domain as a functional domain (Garlatti et al., 2007a, 2007b; Tanio et al., 2007). So far, it has been demonstrated that almost all ficolins identified recognize GlcNAc. The terminal GlcNAc residue is widely present on a variety of pathogens but not in human cells. We also demonstrated that all three human ficolins can associate with MASPs and small MBL-associated protein (sMAP), suggesting they play a role in the complement activation through the lectin pathway (Matsushita et al., 2000a, 2002; Liu et al., 2005a).

To date, the ficolin homologues have been isolated from non-human vertebrate species such as mice (Fujimori et al., 1998; Ohashi and Erickson, 1998), hedgehog (Omori-Satoh et al., 2000)