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Review

MBL-associated serine proteases (MASPs) and infectious diseases

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ABSTRACT

The lectin pathway of the complement system has a pivotal role in the defense against infectious organisms. After binding of mannan-binding lectin (MBL), ficolins or collectin 11 to carbohydrates or acetylated residues on pathogen surfaces, dimers of MBL-associated serine proteases 1 and 2 (MASP-1 and MASP-2) activate a proteolytic cascade, which culminates in the formation of the membrane attack complex and pathogen lysis. Alternative splicing of the pre-mRNA encoding MASP-1 results in two other products, MASP-3 and MAp44, which regulate activation of the cascade. A similar mechanism allows the gene encoding MASP-2 to produce the truncated MAp19 protein. Polymorphisms in *MASP1* and *MASP2* genes are associated with protein serum levels and functional activity. Since the first report of a MASP deficiency in 2003, deficiencies in lectin pathway proteins have been associated with recurrent infections and several polymorphisms were associated with the susceptibility or protection to infectious diseases. In this review, we summarize the findings on the role of MASP polymorphisms and serum levels in bacterial, viral and protozoan infectious diseases.

1. Introduction

The complement system is one of the major effectors of the innate immune system and an important bridge between innate and adaptative immunity (Ricklin et al., 2010; Walport, 2001). Complement clears immune complexes and cell debris and elicits immediate, highly efficient and tightly regulated inflammatory and cytolytic immune responses to infectious organisms including bacteria, viruses and protozoan parasites (Dunkelberger and Song, 2010). The complement system comprises more than 50 plasma and membrane-associated proteins (Kjaer et al., 2013). Complement activation leads to a proteolytic cascade that culminates with the recruitment of inflammatory cells, phagocytosis and cell lysis (Kjaer et al., 2013). It produces anaphylatoxins (C3a, C4a, C5a), which are potent proinflammatory mediators, and opsonins (C3b and C4b), which cover the pathogen's surface, mediating phagocytosis. The cascade culminates with assembly of the membrane attack complex (MAC) on the cell membrane, forming pores that lead to cell lysis (Dunkelberger and Song, 2010).

Complement can be activated through the classical, alternative and lectin pathways (Fig. 1). Independently of the initiation pathway, proteolytic cascades converge towards activation of the major component C3, with subsequent assembly of MAC (Chen et al., 2010). Activation of the classical pathway is initiated on immune complexes by the binding of the C1 complex mainly to IgM or IgG, but also to apoptotic cells, pentraxins and pathogens. On the other hand, the activation of the alternative pathway occurs by spontaneous hydrolysis of C3 in plasma. The lectin pathway is initiated by the binding of pattern recognition molecules (PRMs) to carbohydrates or acetylated residues present on the surface of microorganisms (known as PAMPs or pathogen-associated molecular patterns) or on aberrant glycocalyx patterns of apoptotic, necrotic or malignant cells (known as DAMPs or damage-associated molecular patterns) (Ricklin et al., 2010).

2. Lectin pathway

The lectin pathway was discovered by Matsushita and Fujita in 1992, a landmark report on the mechanism of the lectin pathway activation by MBL and MASPs (Matsushita and Fujita, 1992). In fact, different PRMs activate the lectin pathway: oligomers of mannose-binding lectin (MBL), heteromers of collectins 10 and 11 (COLEC10, alias collectin liver 1 or CL-L1 and COLEC11, alias collectin kidney 1 or CL-K1) and oligomers of either Ficolin-1, 2 or 3 (also called M-, L- and H-ficolin, respectively) (Henriksen et al., 2013; Holmskov et al., 2003; Ma et al., 2013). They recognize PAMPs, highly conserved structures present in several microorganisms, such as lipoteichoic

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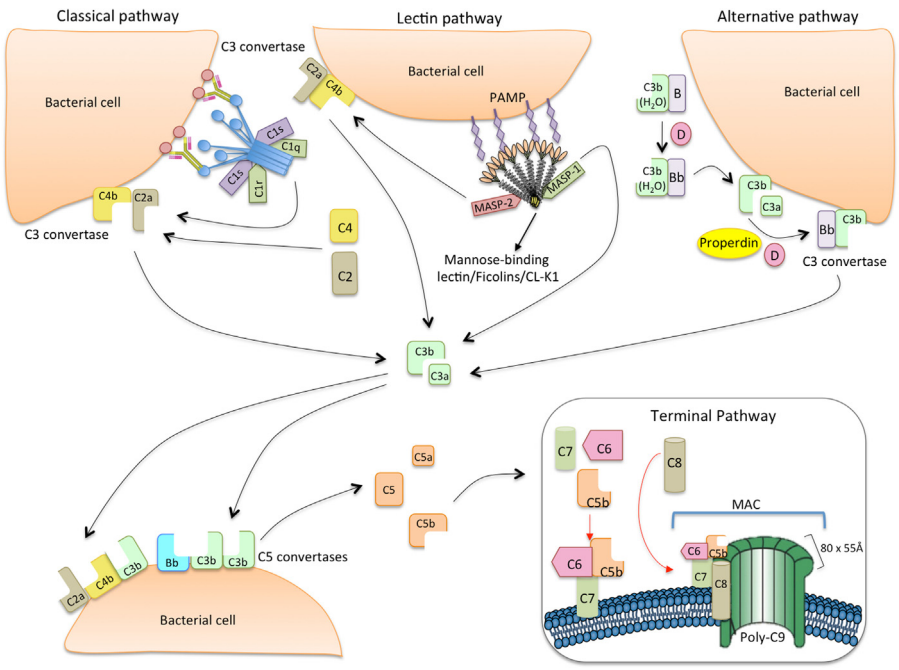

Fig. 1. The classical, lectin and alternative pathways of complement activation. The classical pathway is initiated via binding of C1 complex (which consists of C1q, C1r and C1s molecules) through its recognition molecule C1q to target molecules on the surface of pathogens. Subsequently, C1s cleaves C4, which binds covalently to the pathogen surface, and then cleaves C2, leading to the formation of C4b2a complex, the C3 convertase of the classical pathway. Activation of the lectin pathway occurs through binding of mannose-binding lectin (MBL) oligomers, ficolin oligomers or collectin heteromers (CL-K1 + CL-L1), complexed with MBL-associated serine proteases 1 and 2 homodimers (MASP-1 and MASP-2, respectively), to various carbohydrates or acetylated groups on the surface of pathogens (PAMPs: pathogen associated molecular patterns). Like C1s, MASP-2 leads to the formation of the C3 convertase, C4b2a, but its activation is dependent on MASP-1. MASP-1 also cleaves C2. Activation of the alternative pathway depends on spontaneous low-grade hydrolysis of C3 in plasma leading to the formation of C3b. This C3b binds Factor B (homologous to C2) to form a C3bB complex. The cleavage of Factor B by Factor D form the alternative pathway C3 convertase, C3bBb. Properdin stabilizes this complex. The C3 convertases cleave C3 to C3b, which bind covalently next to the site of complement activation (opsonization). This amplifies the cascade and mediates phagocytosis, as well as adaptive immune responses. The addition of additional C3b molecules to the C3 convertase forms C5 convertases (C3bBbC3b for the alternative pathway or C4bC2aC3b for both classical and lectin pathways). This C3b acts as a binding site for C5 and initiate the assembly of the membrane-attack complex (MAC) by cleavage of C5–C5a and C5b. Whereas C5a acts as a potent anaphylatoxin, C5b forms a complex with C6 and C7, which is inserted in the cell membrane. Thereafter, C8 and 10 – 18 C9 molecules (80 × 55 Å each) bind to this complex, resulting in a fully functional MAC (C5b-9). The three pathways converge to this common terminal pathway, culminating with cell lysis and death (Abbas et al., 2012).

acid of Gram-positive bacteria, endotoxin or lipopolysaccharide of Gram-negative bacteria, β-glucan of fungi (Zhu et al., 2005), glycoproteins of viruses (Tarr et al., 2012), protozoa and multicellular parasites (reviewed by (Messias-Reason and Boldt, 2008). They also bind DAMPs, altered carbohydrate patterns on the surface of apoptotic, necrotic and malignant cells (Ren et al., 2014). The dimers, trimers and/or higher oligomers of trimeric structural subunits of these PRMs form complexes with homodimers of serine proteases (known as "MBL-associated" serine proteases or MASPs), which are initially in the form of proenzymes (zymogens) (Kjaer et al., 2013). After binding of these PRMs to their targets, MASPs are cleaved and activated (Dahl et al., 2001; Degn et al., 2009; Héja et al., 2012b). Although MASP-2 autoactivates, being long thought to be the central activator of the lectin pathway (Ambrus et al., 2003; Gál et al., 2005; Matsushita et al., 2000), different authors provided recent evidence that MASP-1, which also autoactivates, has a significant role in activating MASP-2 (Degn et al., 2012; Héja et al., 2012b; Kjaer et al., 2013).

Activation was initially supposed to occur through conformational changes similar to those undergone by the C1 complex of the classical pathway (Gingras et al., 2011). More recently, the proteolytic cascade was proposed to initiate through MASP-1–MASP-2 cross-activation. This occurs with comparable efficiency within co-complexes comprised of a MASP-1 homodimer, a MASP-2 homodimer and a pentamer or higher-order oligomer of PRMs, or by clustering and juxtaposition of PRM/MASP-1 and PRM/MASP-2 complexes on ligand surfaces, where the PRMs may not be identical (MBL and FCNs, for example) (Degn et al., 2014). Although MASP heterodimerization (e.g. MASP-1 + MASP-2, MASP-1 + MASP-3) is possible *in vitro*, its physiological importance is uncertain (Degn et al., 2013; Paréj et al., 2014). The observation that around 70% of MBL circulate in blood as trimers of trimeric subunits ($MBL_{3\times3}$) associated with MASP-1 or MAp19, or as tetramers of trimeric subunits ($MBL_{4\times3}$) associated with MASP-2 or MASP-3 (Dahl et al., 2001) implies a major role for intercomplex cross-activation in the initiation of the complement cascade. This is also supported by images of 450 kDa MBL/MASP-1 complexes obtained with small-angle X-ray scattering and electron microscopy (Kjaer et al., 2015). Non-active complexes may be formed with the truncated proteins MAp44 (also called MAP-1) (Degn et al., 2009; Skjoedt et al., 2010a) and MAp19 (also known as sMAP) (Stover et al., 1999a,b; Takahashi et al., 1999), which lack the serine protease domain and thus functional activity. Once associated with MBL, MASP-1 and 2 seem not to exchange, nor are they competitively replaced by MASP-3 and MAp19 (Laursen et al., 2012). Nevertheless, they can be displaced by MAp44 (Degn et al., 2013).

Proteolytic activity is acquired by cleavage of the MASP Arg Ile bond of the activation peptide, also called "linker peptide". This cleavage generates two chains covalently linked by a disulfide bond: a heavy chain (alias "A chain") and a light chain (alias "B chain") (Sato et al., 1994). The heavy chain comprises the linker and the CUB1-EGF-CUB2-CCP1-CCP2 regulatory domains, i.e. the *N*-terminal CUB (C1r/C1s, Uegf and bone morphogenetic protein-1) domain of about 110 amino acid residues (CUB1), followed by an epidermal growth factor (EGF)-like domain of the Ca^{2+}-binding type, of approximately 50 amino acid residues, a second CUB domain (CUB2) and two contiguous complement control protein modules (CCP1 and CCP2). The light chain constitutes