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Review

Mechanisms of complement lectin pathway activation and resistance by trypanosomatid parasites

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ABSTRACT

Studies in the past decade have demonstrated a crucial role for the complement lectin pathway in host defence against protozoan microbes. Recognition of pathogen surface molecules by mannan-binding lectin and ficolins revealed new mechanisms of innate immune defence and a diversity of parasite strategies of immune evasion. In the present review, we will discuss the current knowledge of: (1) the molecular mechanism of lectin pathway activation by trypanosomes; (2) the mechanisms of complement evasion by trypanosomes; and (3) host genetic deficiencies of complement lectin pathway factors that contribute to infection susceptibility and disease progression. This review will focus on trypanosomatids, the parasites that cause Chagas disease, leishmaniasis and sleeping sickness (African trypanosomiasis).

1. Introduction

Advances in complement research have revealed important mechanisms of both host innate immune defence and pathogen immune evasion strategies, in particular: (1) the role of the lectin pathway (discovered in the late 90s) in pathogen recognition through pathogen-associated molecular patterns (PAMPs); (2) the discovery of new complement regulators and pathogen's immune evasion strategies; and (3) the identification of genetic deficiency in genes coding for mannan-binding lectin and ficolins causing susceptibility to infection.

Trypanosoma cruzi, *Trypanosoma brucei* and *Leishmania* sp. are unicellular, uniflagellated protozoan parasites responsible for causing Chagas disease, sleeping sickness and leishmaniasis, respectively. They are transmitted to human (or other mammalian hosts) by an insect vector, and together they affect more than half a million people worldwide (WHO, 2011). During the infection, these parasites migrate through the host bloodstream, where they have to evade the host innate immune response and, in the case of *T. cruzi* and *Leishmania* sp., infect host cells (see Buscaglia et al., 2006 for review). The complement system is one of the first mechanisms of host defence against these parasites, and their success in infecting the host is dependent on their capacity to resist the complement attack, either by inhibiting the complement cascade or by escaping its activation.

In this review, we will discuss the molecular mechanisms of complement lectin pathway activation, mechanisms of resistance to complement-mediated lysis and studies on the host genetic deficiencies of the lectin pathway associated with susceptibility to infection and disease progression focusing on trypanosomatid parasites.

2. Complement lectin pathway activation

The lectin pathway represents one of the first innate immune responses to a pathogen (Lambris et al., 2008). It can be activated through the binding of mannan-binding lectin (MBL), L-ficolin, H-ficolin or M-ficolin to carbohydrates on the pathogen coat (Fig. 1). MBL and ficolins are members of the collectin family of proteins. They possess collagenous and lectin domains and their main function are to recognize PAMPs on microbial surfaces (Fig. 2).

Activation of the lectin pathway does not depend on a specific antibody response (such as in the classical pathway), but is

Abbreviations: MAC, membrane attack complex; MASP, mannan-binding lectin-associated serine protease; MBL, mannan-binding lectin; PAMP, pathogen-associated molecular patterns.

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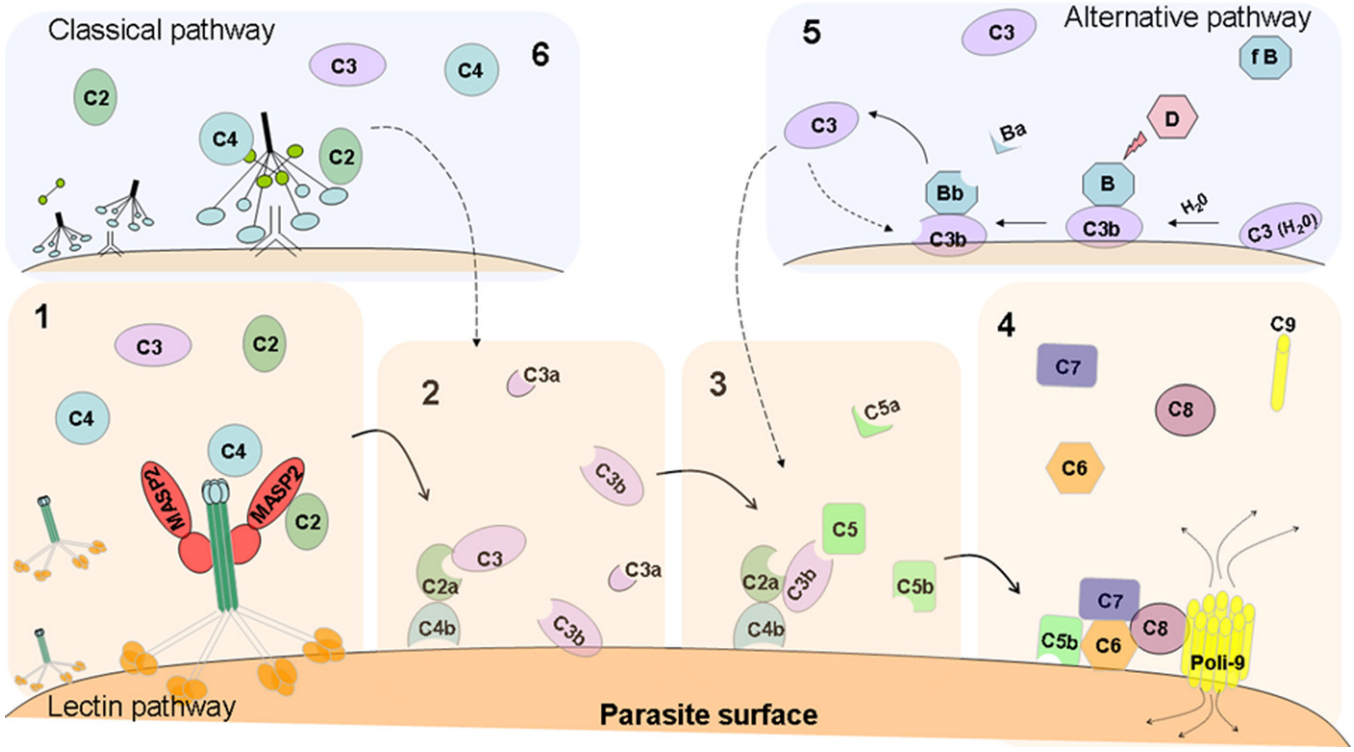

Fig. 1. Complement system activation. There are three pathways that activate the complement system: lectin, classical and alternative pathways. The *lectin pathway* (in **1**) is activated when MBL or ficolins recognize carbohydrate-containing molecules on pathogen surface. They form a complex with MASPs (MASP2 is shown in the diagram) which cleave C2 and C4 resulting in the C3 convertase formation C4b2a (in **2**). The C3 convertase can cleave C3 into C3a and C3b, the latter associates with the C3 convertase (C4b2a or C3bBb, in **3** only shown C4b2a) forming the C5 convertase C4b2a3b (in **3**). The C5 convertase cleaves C5 into C5a and C5b. The fragment C5b attach to the pathogen surface forming an anchor that together with C6, C7 and C8 will hold the MAC, which is formed by several C9 molecules (in **4**). The MAC is a pore that will lyse the pathogen allowing the flux of electrolytes and water. Activation of the complement system by the *classical pathway* is mainly dependent on an antibody response against the pathogen. It occurs by binding of the C1 complex ($C1q\text{-}r_2s_2$) to antibodies that recognizes the pathogen (in **6**). Once bound to the pathogen surface the C1 complex is activated and cleaves C2 and C4 to generate the C3 convertase C4b2a (similar to the lectin pathway). The *alternative pathway* (in **5**) activation is primarily dependent on C3b, which can be formed by spontaneous hydrolysis of C3(H_2O) or by the C3b generate by activation of the classical and lectin pathways (from the C3 convertase activity). In the alternative pathway, once C3b is deposited on the pathogen surface the molecule factor B binds to C3b. The factor B is then cleaved by a soluble molecule called factor D generating the fragments Ba and Bb. The C3bBb formed on the pathogen surface is the C3 convertase of the alternative pathway (which is different from the classical pathway, C4b2a). This C3 convertase also cleaves C3 similarly to the other two pathways. Once the C3 convertase is formed all the subsequent steps are common for all the three pathways.

triggered by PAMPs composed of surface carbohydrates present on several microbes (Runza et al., 2008). Weis et al. (1992) showed that MBL has a high specificity for mannan on glycosylated proteins, and its interaction with pathogen surface carbohydrates is Ca^{2+}-dependent. L-ficolin and H-ficolin bind preferentially to acetylated and neutral carbohydrates such as N-acetylglucosamine (GlcNAc) and galactose, respectively (Garlatti et al., 2007; Krarup et al., 2008; Matsushita et al., 2002). Pathogen recognition by MBL and ficolins results in activation of the complement system, which can lead to pathogen lysis through the membrane attack complex (MAC) formation. Initially, MBL or ficolins bind to the pathogen surface and associate with MBL-associated serine proteases (MASPs), thereby forming a protein complex that activates the complement cascade (Matsushita and Fujita, 1992). There are three MASP enzymes; MASP1, MASP2 and MASP3 (Matsushita and Fujita, 2001; Thiel et al., 1997), that together with a truncated version of MASP2

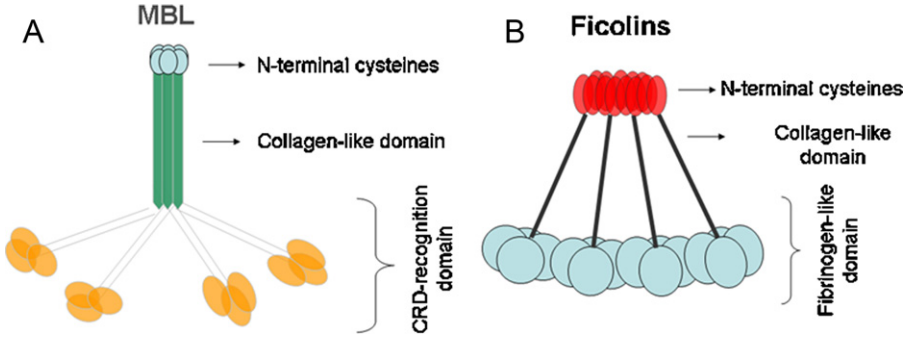

Fig. 2. MBL and ficolins schematic structure. (A) MBL oligomers has a "bouquet"-like structure composed by monomeric subunits of 32 kDa. It contains a cysteine-rich region at the N-terminal and a collagen-like domain that are necessary to assemble the oligomeric form. At the C-terminal there is a carbohydrate recognition domain (CRD) which binds to carbohydrates (such as mannose and GlcNAc) on pathogen surface molecules. (B) Ficolin proteins are composed of a short N-terminal region with one or two cysteine residues followed by a collagen-like domain, a short link region, and a fibrinogen-like domain. Ficolin proteins form trimeric subunits through the binding of the collagen-like domain. These subunits assemble into active oligomers through the binding of four subunits via disulfide bridges at the N-terminal regions. Ficolins recognizes acetylated carbohydrates through the C-terminal fibrinogen-like domain.