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Review

Complement and spinal cord injury: Traditional and non-traditional aspects of complement cascade function in the injured spinal cord microenvironment

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ABSTRACT

The pathology associated with spinal cord injury (SCI) is caused not only by primary mechanical trauma, but also by secondary responses of the injured CNS. The inflammatory response to SCI is robust and plays an important but complex role in the progression of many secondary injury-associated pathways. Although recent studies have begun to dissect the beneficial and detrimental roles for inflammatory cells and proteins after SCI, many of these neuroimmune interactions are debated, not well understood, or completely unexplored. In this regard, the complement cascade is a key component of the inflammatory response to SCI, but is largely underappreciated, and our understanding of its diverse interactions and effects in this pathological environment is limited. In this review, we discuss complement in the context of SCI, first in relation to traditional functions for complement cascade activation, and then in relation to novel roles for complement proteins in a variety of models.

Contents

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Introduction

Complement proteins are important effectors of the host immune response to pathogens, but are also present and active after tissue injury, including CNS trauma and specifically spinal cord injury (SCI). While some experiments have investigated the effect of the complement cascade as a whole after SCI, others have begun to dissect individual roles for complement proteins and effector arms in a host of functions relevant to SCI in variety of animal models. We begin our review by summarizing the complement cascade in the standard context of inflammation, followed by a focused discussion of complement sources and activation following SCI. Next, we outline putative roles for complement proteins in SCI, and highlight examples of nontraditional roles for complement proteins in cellular functions highly relevant for SCI-related pathophysiology. These functions have been described in a variety of SCI and non-SCI models, and include tissue regeneration, cell migration, proliferation, differentiation, survival, synaptic remodeling, and axon growth. We conclude with a discussion of the influence of several key variables on nontraditional functions for complement after SCI.

Traditional roles for complement cascade function

Complement in host defense from pathogens

Overview of pathways leading to complement activation

The complement system is an enzymatic cascade consisting of over 40 proteins that participate in host defense against pathogens by recruiting inflammatory cells, marking pathogens for removal, and initiating pathogen cell lysis directly (reviewed in: (Bohana-Kashtan et al., 2004; Ehrnthaller et al., 2011; Janeway, 2001; Ricklin et al., 2010)). There are several pathways for complement activation (Fig. 1). Complement initiating proteins recognize unique molecular patterns directly on pathogen membranes or host proteins produced in response to infection or injury.

The classical complement pathway is activated when complement protein C1q binds to IgM or IgG antibody:antigen complexes, the surface of a pathogen, or acute phase proteins (e.g. C-reactive protein (CRP) and pentraxin-3) (Gadjeva et al., 2008; McGrath et al., 2006; Nauta et al., 2003; Roumenina et al., 2006). This interaction results in a conformational change that induces autocatalytic cleavage in the first of two associated zymogen pairs, C1r and C1s. C1s is a substrate for C1r, with serine protease activity that cleaves both C4, and C2 if bound to C4b. Cleavage of C4 and C2 release soluble C4a (and C2a) anaphylatoxin, and create a membrane bound C3 convertase (C4b, C2b) capable of cleaving C3 into soluble C3a and membrane bound C3b. C3b can combine with C4b,C2b to form a C5 convertase (C4b,C2b, C3b), which cleaves C5 into soluble anaphylatoxin C5a and membrane-associating C5b. Further, C5b associates with C6 and C7, anchors to the membrane, and binds C8, which penetrates the lipid bilayer. Complement C9 then binds and polymerizes, resulting in creation of a transmembrane pore (Stanley et al., 1986; Whitlow et al., 1985). This pore disrupts or attacks the integrity of the cell membrane, leading to cell lysis when a sufficient number of transmembrane pores are inserted (Edwards et al., 1983; Muller-Eberhard, 1985). Therefore, C5b-9 or terminal complement complex (TCC) is commonly called the membrane attack complex (MAC).

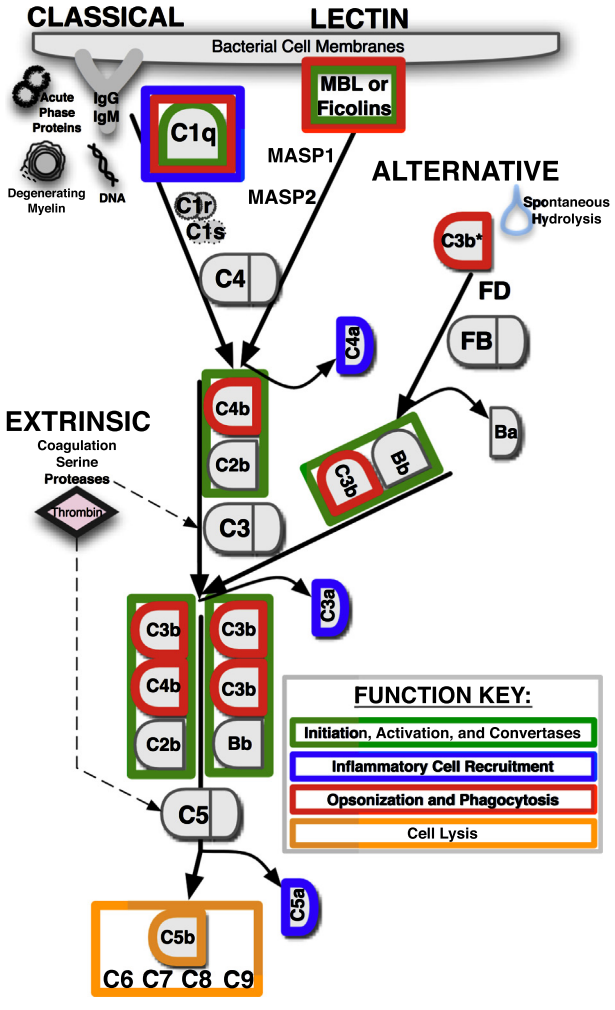

Fig. 1. Summary diagram of the traditional description of the complement cascade in inflammatory response to pathogens and to injury. Each pathway of the complement cascade (classical, lectin, alternative, and extrinsic) can be activated in the spinal cord following injury, and are likely triggered by bacterial cell membranes, antibody, acute phase proteins, degenerating myelin, DNA, coagulation cascade enzymes, and spontaneous hydrolysis. In addition to recognition/initiation, activation, and convertase-mediated cleavage by proteins outlined in green, the traditional effector functions for complement activation products are inflammatory cell recruitment (blue), opsonization (red), and direct cell lysis by the MAC (orange). C3b* of the alternative pathway denotes either C3b generated from the other pathways or C3b(H_2O) created upon hydrolysis, which is functionally similar to C3b.