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Review

The complement system in the peripheral nerve: Friend or foe?

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ABSTRACT

The complement (C) system plays a central role in innate immunity and bridges innate and adaptive immune responses. A fine balance of C activation and regulation mediates the elimination of invading pathogens and the protection of the host from excessive C deposition on healthy tissues. If this delicate balance is disrupted, the C system may cause injury and contribute to the pathogenesis of various diseases, including neuropathies. Here we review evidence indicating that C factors and regulators are locally synthesized in the peripheral nerve and we discuss the evidence supporting the protective or detrimental role of C activation in health, injury and disease of the peripheral nerve.

1. Introduction

Complement was discovered in the 1890s (von Fodor, 1887; Nuttall, 1888; Buchner, 1889) as a heat-sensitive serum factor capable of lysing bacteria in the presence of the heat-stable antibody (Bordet, 1895). Molecular biology profoundly transformed our understanding of the complement system and from its original description as "complement" to humoral immunity (Ehrlich and Morgenroth, 1899) today it represents a key component of the innate immune system, defending the host against infections, bridging innate and adaptive immunity and disposing of immune complexes and apoptotic cells (Walport, 2001a,b). Paradoxically, the same system responsible for such beneficial effects can be deleterious to the host. To prevent complement-mediated tissue injury, over 30 soluble and membrane-bound complement proteins are engaged in a fine coordination of activation and regulation. However, if the regulatory machinery fails, the complement system can contribute to tissue injury and the pathogenesis of various diseases.

The local synthesis of factors and regulators of the complement cascade in the peripheral nerve has been established (de Jonge et al., 2004) but its role in peripheral nerve health, injury and disease remains controversial. Local production of complement factors including regulators of complement activity in the peripheral nerve could protect the healthy nerve from infections. On the other hand, it could erroneously target self tissues. It could facilitate regeneration of injured axons by assisting in the efficient clearance of myelin debris, thought to be inhibitory for axon growth, but it could also exacerbate tissue damage during degeneration hampering the correct regeneration of the nerve. In addition, like it has been proposed for other diseases, complement could contribute to the pathogenesis and progression of neuropathies. Here we will review the evidence supporting the protective and detrimental role of the complement system in the peripheral nerve.

2. A fine balance of activation and regulation

Activation of the complement system is rapid and efficient. Soluble complement components are present in the blood, body fluids and tissues to readily trigger a defense reaction against external (i.e. pathogens) or internal (i.e. autoimmunity) danger signals (Kohl, 2006). Complement activation can occur via three routes: the classical, the lectin and the alternative pathway. The classical pathway is activated by the recognition of an antigen–antibody complex by C1q. Upon binding, C1r cleaves C1s which in turn cleaves C2 and C4 into a small (C2b, C4a) and a large fragment (C2a, C4b). C2a and C4b together form the C3 convertase. The lectin pathway is triggered by binding of mannose-binding lectins MBLs to certain carbohydrates expressed on the pathogen surface. This activates the MBL-associated serine protease (MASP) 2, cleaving C4 and C2 (Fujita, 2002). The alternative pathway starts by

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spontaneous low-rate hydrolysis of C3 generating C3(H_2O) which binds to factor B, permitting cleavage by factor D to form the fluid-phase C3 convertase C3(H_2O)Bb. This enzyme cleaves C3 and deposits C3b on surfaces where, in the absence of C inhibitors such as factor H, it binds and catalyses cleavage of factor B to form surface bound C3 convertase C3bBb (Nauta et al., 2004). Irrespective of the pathway involved, activation of the complement system leads to the cleavage of C3 and C5, generating the potent chemo-attractants C3a and C5a as well as the C3b and C5b fragments. The latter initiates the assembly of the C5b-9 membrane attack complex (MAC), a lipophilic complex which forms pores in cell membranes, leading to cell lysis (Nauta et al., 2004).

Recently, additional venues of complement activation have been identified. The so-called "C2 bypass" pathway consists of the direct cleavage of C3 by MASP-2 (Atkinson and Frank, 2006) and the "extrinsic protease" pathway involves the direct cleavage of C3 and C5 by non-complement proteins such as lysosomal enzymes, kallikrein or trombin (Markiewski and Lambris, 2007). Lastly, properdin stabilizes the C3 convertase on the pathogen surface (Hourcade, 2006; Spitzer et al., 2007) (Fig. 1a).

A sophisticated regulatory mechanism allows the complement system to rapidly attack invading pathogens while protecting host cells from its detrimental effects. This is achieved by the coordination of time, location and molecular interactions (Soares and Barlow, 2005). Regulatory complement components either induce an accelerated decay of the convertase or act as cofactor for Factor I to degrade activated complement fragments. Decay accelerating factor (DAF/CD55) and C4-binding protein (C4BP) accelerate decay of the convertase; membrane cofactor protein (MCP/CD46) acts together with Factor I to degrade C3b to its inactive form iC3b; complement receptor 1 (CR1/CD35) and Factor H can do both. In addition, CD59 prevents formation of the MAC by inserting between the C8 and C9 subunits of the C5b-9 polymer (Soares and Barlow, 2005) (Fig. 1b).

3. Complement as friend

For over 700 million years, the complement system has provided protection against microbial infections (Sunyer et al., 1998), yet its function extends beyond a simple defense mechanism. Today it is clear that the complement system is a key regulator of various stages of an inflammatory reaction. These events are mediated by the potent complement anaphylatoxins C3a and C5a which propagate the immune reaction by binding to their receptors (C3aR, C5aR, C5L2) on the host cell (reviewed by van Lookeren et al., 2007).

Complement is also involved in the disposal of immune complexes, necrotic and apoptotic cells which are usually generated during an inflammatory reaction (Walport, 2001a). The clearance of immune complexes is facilitated by maintaining their solubility through the binding of the C1 complex, C4 and C3 to the antigen. This prevents an increase in the size of the opsonized complex which is easily recognized by phagocytes and readily removed. This is a key process in the maintenance of tissue homeostasis and normally does not require complement binding. However, during overwhelming apoptosis or impaired phagocytosis complement initiation factors can bind dying cells to ensure proper disposal of self-antigens (Trouw et al., 2008), avoiding the generation of an autoimmune reaction against the host.

Although the physiological function of the complement system in the healthy peripheral nerve is probably immune surveillance, an alternative function in the regulation of fatty acid homeostasis has been proposed (Chrast et al., 2004). Adipocytes, which constitute a large portion of the epineurial compartment of the nerve, express and secrete factors of the alternative complement pathway (FB, C3 and fD also known as adipsin) (Choy et al., 1992). These factors are sufficient to cleave C3 into C3a and C3b. Further, the N-terminal arginine of C3a can be cleaved by the carboxypeptidase B (CBP), an enzyme present in the endoneurial compartment of the nerve (Chrast et al., 2004). The resulting C3adesArg, also called acylation stimulating protein (ASP), is a potent stimulator of triglyceride synthesis in adipocytes (Cianflone et al., 1999). Locally produced triglycerides may represent a readily available energy source for peripheral axons which elongate far from their cell body, making energy supply from the soma difficult. Altogether, complement factors are suggested as possible regulators of energy metabolism crass-talk between various compartments of the nerve but more work aimed to elucidate this mechanism is ongoing.

4. Complement as foe

Disruption of the delicate balance between complement activation and regulation is implicated in the pathogenesis, propagation and exacerbation of numerous diseases. Excessive complement activation results from the propagation of an inflammatory reaction or from alterations in the expression and function of complement regulatory proteins.

Complement activation, especially C5a production, plays a major role in the pathogenesis of inflammatory disorders including ischemia/reperfusion injury, sepsis, acute lung injury, allergy and asthma (Guo and Ward, 2005). It is also involved in a number of neurodegenerative disorders, including Alzheimer's, Huntington's, Parkinson's, Creutzfeld–Jacob disease and amyotrophic lateral sclerosis (ALS) (reviewed in Morgan and Gasque, 1996, 1997; Bonifati and Kishore, 2007) and neuroinflammatory diseases such as multiple sclerosis (MS) (Ffrench-Constant, 1994).

Evidence accumulated over the past two decades suggests that inflammation may contribute to AD pathogenesis and implicates complement as a potential mediator of the inflammatory response (Eikelenboom et al., 1991; Emmerling et al., 2000). Complement transcripts and proteins are upregulated in AD brains (Yasojima et al., 1999) and localized in close association with tangles and plaques. MAC deposits have been found on dystrophic neuritis (McGeer and McGeer, 2002) whereas the expression of the complement regulatory protein CD59 is strongly decreased in AD brains (Price et al., 2002). The role of complement in AD remains, however, controversial. Some groups proposed that complement activation mediates neuronal injury via MAC-induced neurite disintegration (Yang et al., 2000) and increase in the level of reactive oxygen species (Luo et al., 2003). Others suggested a possible neuroprotective role of complement in AD pathology, by reducing the accumulation and promoting the clearance of amyloid and degenerating neurons (Wyss-Coray et al., 2002; Pasinetti, 1996). Deposits of complement components and activated microglia have been reported in the substantia nigra of patients with sporadic (Yamada et al., 1992) and familial (Yamada et al., 1993) Parkinson's disease. The striatum, neurons, myelin and astrocytes of Huntington's disease patients and the extracellular deposits of the prion protein in Creutzfeld–Jacob disease are marked by deposits of activated complement fragments (Singhrao et al., 1999; Kovacs et al., 2004). Gene array analysis of motor neurons from mice with a mutation in the superoxide-dismutase 1 (SOD1) gene, modeling the familial form of ALS, identified the induction of components of the classical pathway of complement (Lobsiger et al., 2007; Ferraiuolo et al., 2007) but the question of whether the complement system plays a detrimental or neuroprotective role still remains open. Complement activation also occurs in the brain of MS patients (Yam et al., 1980; Storch et al., 1998) and a pathological role has been shown