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Therapeutic targeting of complement to modify disease course and improve outcomes in neurological conditions

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ABSTRACT

The recognition that complement proteins are abundantly present and can have pathological roles in neurological conditions offers broad scope for therapeutic intervention. Accordingly, an increasing number of experimental investigations have explored the potential of harnessing the unique activation pathways, proteases, receptors, complexes, and natural inhibitors of complement, to mitigate pathology in acute neurotrauma and chronic neurodegenerative diseases. Here, we review mechanisms of complement activation in the central nervous system (CNS), and explore the effects of complement inhibition in cerebral ischemic-reperfusion injury, traumatic brain injury, spinal cord injury, Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease and Huntington's disease. We consider the challenges and opportunities arising from these studies. As complement therapies approach clinical translation, we provide perspectives on how promising complement-targeted therapeutics could become part of novel and effective future treatment options to improve outcomes in the initiation and progression stages of these debilitating CNS disorders.

Contents

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; BBB, blood-brain barrier; BSB, blood-spinal cord barrier; C1-Inh/C1-INH, C1 complex inhibitor; CNS, central nervous system; CR1, complement receptor 1; CR2, complement receptor 2; CVF, cobra venom factor; DAF, decay accelerating factor; GFAP, glial fibrillary acidic protein; HD, Huntington's disease; Iba1, ionised calcium binding adapter protein 1; ICH, intracerebral haemorrhage; MAC, membrane attack complex; MASP, MBL-associated serine proteins; MBL, mannose-binding lectin; MCAO, middle cerebral artery occlusion; MCP, membrane cofactor protein; PD, Parkinson's disease; SCI, spinal cord injury; SOD1, superoxide dismutase 1; TBI, traumatic brain injury; VCP, vaccinia virus complement control protein.

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1. Introduction

Neurological disorders represent a significant global health and economic burden, and they are increasingly becoming a priority health issue as their prevalence increases with an aging population [1]. A common feature of all major disorders affecting the central nervous system (CNS) is inflammation, with chronic non-resolving inflammation generally being thought of as contributing to disease progression and/or worsened outcomes [2]. Activation of the innate immune complement system involves many membrane-associated proteins, receptors and regulators that interact in a cascade manner to generate a number of biologically active products that normally protect the host against pathogens [3]. This same system, however, is thought to play a major role in (secondary) immune-mediated pathology in neurological disease. Complement precursor proteins are predominantly synthesized by hepatocytes and then released into the bloodstream, primed for activation [4] via the classical, alternative, lectin or extrinsic protease pathways, all of which culminate in the formation of the cytolytic membrane attack complex (MAC) [3]. In neurological diseases involving complement system activation, these host-protective factors can mediate neuronal loss, axonal damage, demyelination, and blood-brain barrier (BBB)/blood-spinal cord barrier (BSB) dysfunction [5]. Fig. 1 summarises these processes. The following section will explore how the various pathways of complement can be activated in the absence of microbes and evoke neuropathology in acquired, sterile CNS injury and chronic neurodegenerative diseases.

2. Mechanisms of complement activation and complement-mediated pathology in the CNS

Physical damage to neural tissue and various genetic and environmental factors, particularly ageing, increases mitochondrial dysfunction, oxidative stress and protein damage, reduces basal autophagy, and promotes BBB/BSB dysfunction. These processes expose intracellular CNS antigens to (circulating) complement proteins such as C1q, a multimeric pattern recognition receptor [5]. C1q binds to apoptotic cells, necrotic cells, and blebs of degenerated neurons via its globular head domains [6]. The opsonization of exposed intracellular antigens such as DNA and phosphatidylserine [7] by C1q significantly enhances their recognition and engulfment by immune cells bearing complement receptor 1 (CR1) and the phagocytic receptor cC1qR$_P$ [8]. This process is critical for rapid clearance of otherwise toxic cellular debris [6,9]. C1q can also activate complement by binding to the F_c portion of surface-bound antibodies and immune complexes, which is of clinical relevance for patient populations that have autoantibodies targeting CNS self-antigens, which may include myelin-associated glycoprotein, GM-1 gangliosides, glial fibrillary acidic protein, AMPA and NMDA glutamate receptors, β-III-tubulin, and nuclear antigens [10,11]. The deposition of such autoantibodies in CNS tissue has been shown to cause neurological symptoms, neuronal and axonal pathology as well as demyelination via activation of the classical pathway [12]. Additional (indirect) mechanisms for C1q-mediated pathology may include the production of reactive oxygen species (ROS) [13], and leukocyte chemotaxis [14]. Membrane-bound C1q is much more stable than fluid-phase C1q, which activates the zymogen proteases C1r and C1s [15]. The stable C1qrs complex inducts the *classical complement pathway* by sequentially cleaving C4 and C4b-bound C2 substrates, enabling formation of the classical C3 convertase (C4bC2a) [16].

Once formed, the classical C3 convertase cleaves C3, which is the central and most abundant circulating component of the complement cascade, into the small C3a peptide and a larger C3b fragment [3]. C3a signals through the G protein-coupled receptor C3aR that is expressed on most myeloid cells. The immune-modulatory actions of this axis include regulation of oxidative burst in macrophages and pro-inflammatory cytokine production, although other physiological roles of C3aR stimulation are becoming increasingly recognised [17]. Comparably, the much larger C3b fragment serves as a major opsonin of cellular debris. C3b-dependent opsonization is normally critical for clearing pathogens and abnormal host cells. Neuropathological roles have, however, also been uncovered for C3b in relation to immunological demyelination and neurodegeneration [18]. The C3b fragment is also essential for production of the alternative pathway C3 convertase (C3bBb) on the surface of cellular membranes, and for generating downstream convertases that have high affinity for and cleave C5 [19].

The *alternative pathway of complement* is initiated through spontaneous hydrolysis of C3 in plasma, leading to the formation of C3(H_2O). When bound to factor B, the enzymatic action of factor D subsequently generates another C3 convertase, C3(H_2O)Bb. This steady 'tick-over' of C3 assists normal immunosurveillance, but is dramatically increased when an activating surface is encountered [3]. Although this route may not be a major initiating pathway for complement activation in CNS diseases in the absence of substantial and long-term hemorrhage, *in vitro* experiments have demonstrated that up to 80% of the complement activation products that are generated following classical pathway activation can be the result of alternative pathway amplification [20], suggesting that a functional alternative pathway is required for maximal complement-dependent damage *in vivo*.

The *lectin pathway for complement activation* begins when pattern recognition molecules known as mannose-binding lectins (MBLs) recognise carbohydrate moieties and Ig-coated antigens. MBLs can opsonize exposed carbohydrates on apoptotic cells and antibody-bound surfaces, promoting their phagocytosis by mononuclear cells [21]. In a manner akin to C1q-dependent activation of C1r and C1s, surface-bound MBL activates MBL-associated serine proteins (MASPs), which cleave circulating complement factors to produce a C3 convertase (C4bC2a). Deposited C4b molecules are more likely to form a functional convertase through the lectin pathway than the classical pathway [22], and MBL can also directly engage C3 and activate complement in C2 and C4 deficient sera via the alternative pathway [23]. It is therefore possible that the lectin pathway may be a prominent source of pro-inflammatory complement products in severe neurotrauma and advanced stages of CNS diseases, but this requires further investigation.

The C5a peptide, which is generated following the proteolytic cleavage of C5 downstream of C3 activation, is also integrally linked to CNS disease. C5a signals through interaction with C5aR1 (also known as CD88), another member of the rhodopsin family of G-protein-coupled receptors, which is expressed by most cells of myeloid lineage as well as microglia, astrocytes and certain populations of neurons in the CNS [24]. C5aR1 signaling promotes inflammatory processes that can be detrimental to the CNS, including phagocytosis, oxidative burst, pro-inflammatory cytokine production, increasing integrin expression required for leukocyte adhesion/extravasation, and recruitment of most leukocyte subsets toward the inflammatory stimulus [25]. Whist there is some evidence of neuroprotective and physiological actions of C5a [26,27], C5aR1 activation, at least in the acute phase of neurotrauma, promotes neuronal death [28,29], demyelination [30], and BBB dysfunction [31]; C5aR1 appears similarly deleterious in chronic neurodegenerative diseases [32–35]. It should be noted that C5a has a second receptor, namely C5aR2 (formerly known as C5L2), although the role and distribution of this protein in the brain and during neuroinflammation remains largely unknown [36]. Deposition of the larger cleavage product generated from the parental C5 protein, i.e. C5b, initiates the terminal pathway of complement, in which C6, C7 and numerous hydrophobic C9