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The Role of Complement Factors in Neurodegeneration, Neuroinflammation and Neuroprotection: Friend or Foe?

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Abstract

Complement is a major component of innate immune system involved in defending against all the foreign pathogens through complement fragments that participate in opsonization, chemotaxis, and activation of leukocytes and through cytolysis by C5b-9 membrane attack complex. The complement (C) system has been implicated as a factor in the causation or propagation of tissue injury in central and peripheral nervous system disorders. Complement factors play a predominant role in nerve injury, inflammation and repair, thus playing part in neurodegeneration, neuroinflammation and neuroprotection.

Keywords: Immunology; Neuroimmunology; Immunogenetics; Genetic neurology; Complement system.

Complement is a major component of innate immune system involved in defending against all the foreign pathogens through complement fragments that participate in opsonization, chemotaxis, and activation of leukocytes and through cytolysis by C5b-9 membrane attack complex.[1] The complement (C) system has been implicated as a factor in the causation or propagation of tissue injury in central and peripheral nervous system disorders.[2]

Complement opsonins (C1q, C3b, and iC3b) interact with surface complement receptors to promote phagocytosis, whereas complement anaphylatoxins C3a and C5a initiate local inflammatory responses by taking part in humoral and cellular immunity mechanisms of neurodegeneration and neuroprotection involved in cytolysis and immune/ inflammatory responses.[3]

Many studies had reported their role in central nervous system disorders like encephalomyelitis, multiple sclerosis, Alzheimer's disease.[4,5] Rus and Nicolescu[6] described the role of complement factors as; "Myelin and oligodendrocyte (OLG) activate the classical pathway of complement in vitro in the absence of antibodies. Sublytic C5b-9 in the absence of cell death induces proto-oncogenes, activates cell cycle, and enhances cell survival in OLG. In addition, C5b-9 reverses the differentiation phenotype in OLG and enhances cell survival. Beta amyloid protein is an activator of the complement system and neurons are susceptible to bystander complement mediated damage."

Astrocytes, ependymal cells, endothelial cells, microglia, and neurons synthesize various complement proteins or express complement receptors on their cell surfaces, and binding of proteolytic fragments derived from activation of complement by specific receptors leads to responses towards inflammation, opsonization, and B-cell activation.[7] A fine balance of C activation and regulation mediated the elimination of invading pathogens and the protection of the host from excessive C deposition on healthy tissues, and upon disruption of this delicate balance, the C system may cause injury and

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contribute to the pathogenesis of various diseases, including peripheral neuropathies.[8]

Complement cascade factors of classical (C1qa, C1qb, C1qc, C2 and C4) and alternative (C3, B and adipsin) pathways were known to play a critical role in myelin clearance after peripheral nerve injury.[9] The receptors located within the nerve fascicles are probably of glycoprotein nature and the receptors for C3b in peripheral nerve tissues may be of significance in the deposition of immune complexes, thus playing a role in acute polyradiculoneuritis.[10]

Furthermore, activation of complement by peripheral nerve myelin (PNM) *via* the alternative pathway was shown by cleavage of C3 in normal human serum (NHS) and of B in C2-deficient serum (C2d-HS). Increasing consumption of hemolytic activity of C3 in Mg-EGTA-treated NHS was also noted with increasing amounts of PNM as a consequence of a variety of pathologic conditions affecting the peripheral nervous system.[11]

RNA (RT-PCR and northern blot hybridization) and protein (western blot analysis and immunohistochemistry) studies confirmed high expression of classical pathway components, alternative pathway components and inhibitory components in sciatic nerve (first components of complement in axons, inhibitory components in perineurium) to protect the nerve from a complement attack.[12]

Complement factors play a predominant role in nerve injury, inflammation and repair.[13] Expression of complement and clusterin were prominent features of neural degeneration and regeneration and they provide useful insights into potentially new therapeutic approaches in neurodegenerative disorders.[14] Most of the studies were on experimental rodent models, and future clinical trials are needed to establish a bedside evidence to relate it into clinical practice.

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