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Amyotrophic lateral sclerosis: The complement and inflammatory hypothesis

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a devastating, neurodegenerative motor neuron disease. The aetiology of ALS remains an enigma which hinders the design of an effective treatment to prevent, postpone, or reverse the pathophysiological changes occurring during the aggressive progression of this disease.

During the last decade, basic research within the innate immune system, and in particular the complement system, has revealed new, important roles of the innate immune system during development, homeostasis, and ageing within as well as outside the central nervous system. Several lines of evidence indicate that aberrant activation of the complement system locally in the central nervous system as well as systemically may be involved in the pathophysiology of ALS. This exciting new knowledge could point towards the innate immune system as a potential target of medical intervention in ALS. Recently, the historic perception of ALS as a central neurodegenerative disease has been challenged due to the significant amount of evidence of a dying-back mechanism causing the selective destruction of the motor neurons, indicating that disease onset occurs outside the borders of the blood-brain-barrier. This review addresses the function of the innate immune system during ALS. We emphasize the role of the complement system and specifically suggest the involvement of ficolin-3 from the lectin pathway in the pathophysiology of ALS.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a rare and devastating neurodegenerative disease with a poor prognosis indicated by a median survival time of 20–36 months from onset of the disease. (Chio et al., 2009) Even though the clinicopathological findings have been known for almost two centuries, the aetiology of ALS remains unknown, and no effective treatment exists. However, recent evidence points towards the innate immune system and, in particular, the complement system as a potential culprit and hence a future target for treatment. Numerous different factors have been suggested to contribute to the pathogenesis of ALS including aggregation of misfolded protein, impaired clearance of excitotoxins such as glutamate, mitochondrial dysfunction, oxidative stress, malfunction of the endoplasmatic reticulum, impaired axonal transportation mechanisms, dysregulation of intracellular calcium levels, detrimental environmental factors, and neuroinflammatory reactions during the destruction of the motor neurons. (Zufiria et al., 2016)

This review focuses on the potential role of the complement system in the pathogenesis of ALS. We describe how the complement system is involved in the development and homeostasis of the normal brain and conferring elimination of invading pathogens. Thereafter, we present two recent hypotheses, which speculate that inappropriate activation of the complement system may be central for the pathogenesis of ALS. If substantiated, this may facilitate the development of effective therapies against a disease that is currently perceived to be fatal.

2. ALS symptomatology, genetics, and pathophysiology

2.1. The ALS patient

ALS was first named by the French neurologist and anatomist, Jean Martin Charcot, who described the clinicopathology of the disease. (Charcot, 1874) *Amyotrophic* refers to the atrophy of muscles, *lateral* refers to the failure of the descending fibres in the lateral columns of the spinal cord and *sclerosis* to the hardening of the structure of the supportive tissue surrounding the motor neurons. (Goetz, 2000) The

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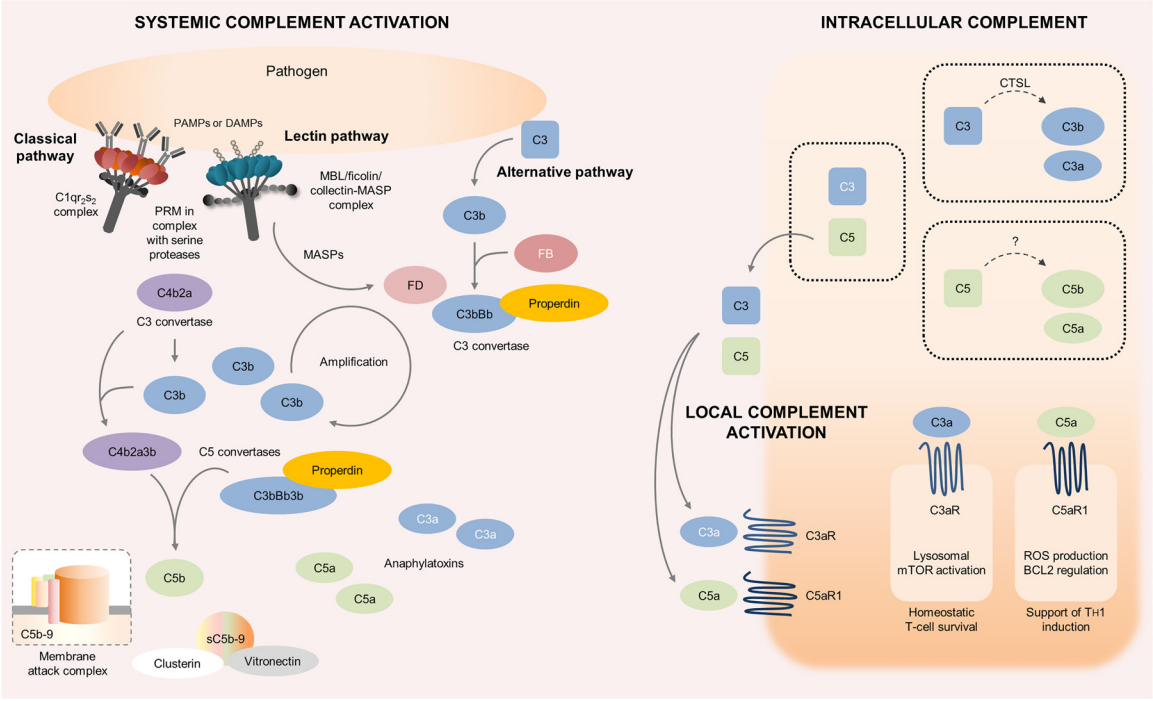

Fig. 1. The complement system. The complement system is activated through three different pathways: the classical pathway (CP), the lectin pathway (LP), and the alternative pathway (AP). The CP is activated by the PRM C1q in complex with the serine proteases C1r and C1s. The LP is activated by the PRMs MBL, ficolins (ficolin-1, -2, and -3), and collectins (collectin-10 and -11) in complex with the serine proteases MASP-1, MASP-2, and MASP-3. Activation of the CP or the LP leads to the formation of a C3 convertase (C4b2a). The C3 convertase cleaves C3 leading to the formation of the anaphylatoxin C3a and the opsonin C3b. Activation of C3 also leads to the formation of a C5 convertase (C4b2a3b), which cleaves C5 into the anaphylatoxin C5a and C5b. C5b binds C6 and C7 in the fluid phase, and then the C5b-7 complex binds to the cell membrane via sites in C6 and C7 and mediate the formation of the membrane attack complex (C5b-9) that causes direct cytolysis. C5b is also part of a soluble C5b-9 complex (sC5b-9), where the membrane binding site of C5b-7 is occupied by binding of vitronectin or clusterin, thus preventing insertion into a membrane. The AP is activated by spontaneous hydrolysis of C3. When C3 is activated, factor B (FB) binds to C3b and is cleaved by factor D (FD). This results in the formation of the alternative C3 convertase (C3bBb), which is stabilized by properdin. The AP functions as a potent amplification loop driven by C3, but also results in the formation of the AP C5 convertase (C3bBb3b). The LP serine protease MASP-3 can cleave the key enzyme of the AP pro-FD into FD and thereby cross activate the AP, thus MASP activation might be essential in the activation of the AP. The effector functions of the systemic complement system is the production of anaphylatoxins C3a and C5a, which activate other components of the innate and the adaptive immune system, C3b, which facilitates the recognition of pathogens by phagocytes, and C5b, which causes direct cytolysis by triggering formation of the membrane attack complex C5b-9. The activated extra-cellular cascades of the complement system thus represent a powerful first line of defence against infections. Local complement stimulation occurs when intracellular complement components C3 and C5 is secreted upon stimuli and activated extracellularly. The activation products C3a and C5a are then able to bind to their respective receptor on the cell surface and induce cellular responses. The view of the complement cascade as three separate pathways is oversimplified. The pathways are known to interact and recently discovered, autocrine, intracellular complement, termed the complosome, has been found. Intracellularly complement is activated in e.g. CD4+ T-cells when C3 is cleaved by the protease CTSL and C5 is cleaved by a currently unknown protease. This results in intracellularly formed C3a and C5a binding to their respective intracellular receptors C3aR and C5aR1. Intracellular complement has an important regulating role of normal cell physiology including vital metabolic pathways, and cell survival, proliferation, and death.

progressive loss of both upper and lower motor neurons leads to loss of control of skeletal muscle with muscular atrophy, hyperreflexia, fasciculations, and eventually paresis of both bulbar and extremity muscles. In the final stage the patient is unable to move, breathe and communicate.

Symptoms appear initially in the extremities in 70%, in bulbar muscle in 25%, and in the trunk with or without respiratory impairment in five per cent of ALS cases. (Zufiria et al., 2016) In up to 15%, frontotemporal dementia coexists with ALS. (Phukan et al., 2007) Diagnosis may be hampered by the absence of a definitive test; the diagnosis of ALS according to the El Escorial Revised criteria requires clinical, electrophysiological, or neuropathological evidence of progressive upper and lower motor neuron degeneration as well as the absence of electrophysiological, pathological or neuroimaging evidence of other diseases that might explain the findings. (Brooks et al., 2000)

As the El Escorial Revised criteria are usually applied (Brooks et al., 2000), there is some controversy regarding this classification system as it fails to describe the great interindividual diversity of the disease. (Al-Chalabi et al., 2016) The incidence of ALS in Europe is about 2/100000, and slightly higher in men than in women (3.0:2.4). (Logroscino et al., 2010) The most aggressive cases are seen after a bulbar onset. (Kiernan et al., 2011) Between 90 and 95% of ALS cases occur sporadically (sALS); five to ten per cent are of the familial type (fALS), which is genetically heterogenous, but usually has a Mendelian inheritance pattern. (Philips and Rothstein, 2015) Clinically, fALS and sALS are identical, although the average age of onset in familial cases is approximately ten years lower than in sporadic cases. One of the four major, known ALS gene mutations, the Cu/Zn superoxide dismutase 1 (*SOD1*) gene mutation, the *FUS* and *TARDBP* (both genes encoding for TDP-43), and repeat nucleotide expansions in the gene *C9ORF72* are present in 60–80 % of all fALS cases. (Zufiria et al., 2016)

2.2. The dying-back mechanism

ALS patients often complain of fatiguability during repetitive movements. Histological and electromyographical studies have found this symptom to be caused by dysfunctional neuromuscular junctions (NMJ). (Henderson and Daube, 2004; Maselli et al., 1993) In animal models of ALS, an early sign of pathology occurs at the NMJ prior to onset of symptoms (Bahia El Idrissi, 2016; Clark et al., 2016; Fischer