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Complement receptor 1 (CR1) and Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is the most common neurodegenerative disease and it poses an ever-increasing burden to an aging population. Several loci responsible for the rare, autosomal dominant form of AD have been identified (APP, PS1 and PS2), and these have facilitated the development of the amyloid cascade hypothesis of AD aetiology. The late onset form of the disease (LOAD) is poorly defined genetically, and up until recently the only known risk factor was the ε4 allele of *APOE*. Recent genome-wide association studies (GWAS) have identified common genetic variants that increase risk of LOAD. Two of the genes highlighted in these studies, *CLU* and *CR1*, suggest a role for the complement system in the aetiology of AD. In this review we analyse the evidence for an involvement of complement in AD. In particular we focus on one gene, *CR1*, and its role in the complement cascade. *CR1* is a receptor for the complement fragments C3b and C4b and is expressed on many different cell types, particularly in the circulatory system. We look at the evidence for genetic polymorphisms in the gene and the possible physiological effects of these well-documented changes. Finally, we discuss the possible impact of CR1 genetic polymorphisms in relation to the amyloid cascade hypothesis of AD and the way in which *CR1* may lead to AD pathogenesis.

Introduction

Alzheimer's disease (AD) is the most common form of dementia and according to the World Alzheimer's Report 2010 there are currently 35.6 million people worldwide living with the condition. This is estimated to rise to 65.7 million people by 2030 (Alzheimer's Disease International 2010). In the United Kingdom alone this presents a huge socioeconomic burden, with AD costing the UK economy £23 billion per year (Alzheimer's Research UK (ARUK) 2010).

AD typically involves memory degeneration and deterioration of other cognitive domains. Death of the patient typically occurs between 3 and 9 years after diagnosis (Querfurth and LaFerla 2010). Alzheimer's disease can be divided into early-onset AD (EOAD) and late-onset AD (LOAD), a classification that is usually distinguished by the presence of the first disease symptoms before or after the age of 65, respectively (Kowalska 2004). Familial EOAD is typically inherited in an autosomal dominant fashion and three genes have been found to harbor AD causative mutations: the amyloid precursor protein, *presenilin 1* and *presenilin 2* genes (Bekris et al. 2010). Until recently the genetics of LOAD were not well understood and the ε4 allele of Apolipoprotein E (*ApoE*) was the only confirmed risk factor (Chartier-Harlin et al. 1994). However, recent genome-wide association studies (GWAS) have indicated common genetic variations in *CLU*, *CR1*, *PICALM*, *ABCA7*, BIN1, *EPHA1*, *CD33*, *CD2AP* and the *MS4A* gene cluster as additional risk factors for the development of LOAD (Harold et al. 2009; Lambert et al. 2009; Hollingworth et al. 2011; Naj et al. 2011). The finding of complement receptor 1 (*CR1*) and *CLU* by GWAS suggests a central role for complement in AD pathogenesis. The purpose of this review is to discuss the potential role of CR1 in AD.

Complement activation in AD brain

The complement system is composed of 30 proteins that play a role in host defense and in the regulation of inflammation (Morgan and Gasque 1996). Complement activation occurs through three pathways; lectin, classical and alternative pathways which are triggered by different activators. However these converge to produce an enzyme, complement factor 3 (C3), which is responsible for the formation of the activation products that lead to opsonisation and lysis of pathogens, recruit phagocytes and peptide mediators of inflammation and activation of the membrane attack

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-beta; ApoE, apolipoprotein E; BBB, blood–brain barrier; CCP, complement-control proteins; CFH, complement factor H; C3, complement factor 3; CR1, complement receptor 1; CSF, cerebrospinal fluid; E-CR1, erythrocyte complement receptor 1; EOAD, early onset Alzheimer's disease; GWAS, genome-wide association studies; IFN-γ, interferon-gamma; LHR, long homologous repeats; LOAD, late-onset Alzheimer's disease; MAC, membrane attack complex; MBL, mannan-binding lectin; N-CR1, neutrophil CR1; PfEMP1, plasmodium falciparum erythrocyte membrane protein 1; SCR, short consensus repeats; SNP, single-nucleotide polymorphism.

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Table 1
The characteristics of the four different alleles of CR1. The information in this table is derived from (Wong et al. 1983; Krych-Goldberg et al. 2002; Birmingham et al. 2003).

CR1 allele	Protein size (non-reducing conditions) (kDa)	SCR/CCP number	LHR number	Frequency			
				Caucasian	African American	Mexican	Asian Indian
CR1-C	160	23	3	Infrequent			
CR1-A	190	30	4	0.87	0.82	0.89	0.916
CR1-B	220	37	5	0.11	0.11	0.11	0.084
CR1-D	250	44	6	Infrequent			

complex (MAC) (Murphy et al. 2008). Complement was known to be involved in AD prior to the discovery of recent genetic associations. Upregulation of the expression of complement factors of the classical pathway has been observed in AD affected brain regions (Eikelenboom and Stam 1982; Shen et al. 1997; Shen 1998; Van Beek et al. 2000; Veerhuis 2010). Neurons have been reported to be a source of complement in the brain (Terai et al. 1997), in addition to glial cells, where expression of complement receptors was demonstrated in astrocyte, microglia and oligodendroglial cell cultures and in astrocytoma cell lines (Gasque et al. 1993; Walker et al. 1995, 1998; Hosokawa et al. 2003). Complement proteins are present in high concentrations in blood plasma (Kang et al. 2009) and although the blood–brain barrier (BBB) would prevent this as a method of entry to the brain, the barrier can become compromised in a number of neurodegenerative diseases including AD (Alafuzoff et al. 1987; Gay and Esiri 1991; Claudio 1995; Fiala et al. 2002; Minagar and Alexander 2003). This model therefore proposes complement damage as a secondary effect of AD after initial processes have led to the breakdown of the BBB.

The antigen–antibody complex is the characteristic activator of the classical complement pathway however alternative complement activators are known (Yasojima et al. 1999). Specifically in the AD brain the presence of neuritic plaques and neurofibrillary tangles (Selkoe 1991) and material extracted from these has been shown to activate the complement system (McGeer et al. 1989; Shen et al. 2001). Amyloid-β (Aβ) plaques are capable of activating the classical complement pathway in the absence of an antibody in the AD brain (Rogers et al. 1992). The Aβ peptides that accumulate in the AD brain bind to a specific site within the collagen-like domain of C1q, the first component of the classical complement pathway (Jiang et al. 1994) to activate the complement pathway. Fibrillar Aβ has also been reported to interact with C1q through one of the three globular heads of C1q, ghB, resulting in activation of the classical and alternative complement pathways (Kishore et al. 2003). Tau, the major constituent of neurofibrillary tangles, was also found to be an activator of the classical complement pathway (Shen et al. 2001). This ability of plaques and tangles to activate the complement pathway may provide rationale for the chronic, low levels of inflammation observed throughout the course of the disease (Zotova et al. 2010).

C1q, which initiates the classical complement pathway through recognition of immune complexes, is known to be expressed in the AD brain (Eikelenboom and Stam 1982; Fischer et al. 1995; Afagh et al. 1996; Kishore and Reid 2000). Aβ deposits that are colocalized with C1q, appear at the time of cognitive decline in AD and Zhou et al. (2008), reported that C1q deficient mice display less neuropathology compared with C1q sufficient mice. The crossing of C1q deficient mice with a mouse model with the APP Swedish mutation, the latter of which displays an age dependent increase in Aβ deposition as well as dystrophic neuritis and activated glial cells, presented a decrease in Aβ plaque deposition compared with the AD mouse model (Fonseca et al. 2004). Additionally the C1q deficient mice displayed a reduced amount of synaptophysin and MAP-2 compared with the wild-type control suggesting that C1q has a damaging effect on neuronal integrity (Fonseca et al. 2004).

AD associated components have not only been linked with the activation of the complement pathway but have also been associated with the membrane attack complex (MAC). This complex, made from the components cleaved by the C3 convertase enzyme, forms a pore in the membrane allowing the influx of Ca^{2+} resulting in cell lysis (Kim et al. 1987). CD59 is a complement regulator normally expressed by cells that works to protect against cell lysis by preventing the complete assembly and insertion of the MAC into the membrane (Gordon et al. 1993). Yang et al. (2000), were able to demonstrate through ELISA assays that in the hippocampus and frontal cortex of the AD brain there is a significant deficit in CD59 expression compared with non-demented elderly brains. CD59 expression was found to be downregulated by Aβ at the mRNA level, which could account for the decreased levels of this complement regulator observed in AD brains (Yang et al. 2000). In the search for possible biomarkers of AD it was found that complement factor H (CFH), a critical component of the alternative complement pathway showed a significant positive correlation between plasma CFH and hippocampal volume (Thambisetty et al. 2008). While a negative correlation between hippocampal volume and CFH may have been expected, this result is analogous to the positive association found between levels of cerebrospinal fluid (CSF) phosphorylated tau and baseline hippocampal volume, considered the foremost biomarkers in AD (Hampel et al. 2005).

The complement receptor 1 gene

CR1 is found on chromosome 1 at the locus 1q32 in a genetic cluster of complement related proteins (Weis et al. 1987). The gene is present in four co-dominant alleles of different sizes and the variation is due to genetic duplications and deletions (Krych-Goldberg et al. 2002). This is a process thought to arise as a result of imprecise chromosome crossing over (Holers et al. 1987). These changes are pre-translational, rather than post-translational and this has been shown by observation of the same degree of variation in unglycosylated primary transcripts (Lublin et al. 1986). The different alleles are known by different names depending on the group studying them. The smaller alleles are known in ascending order of size as CR1-C or CR1-F' (160 kDa); CR1-A or CR1-F (190 kDa); CR1-B or CR1-S (220 kDa); and CR1-D (250 kDa).

The relative frequencies of the four alleles vary only slightly between populations (Wong 1990). The most frequent alleles are CR1-A/F and CR1-B/S. In Caucasians these alleles have frequencies of 0.87 and 0.11, respectively. This is different to 0.82 and 0.11 in African Americans, 0.89 and 0.11 in Mexicans (Moulds et al. 1996) and 0.916 and 0.084 in Asian Indians (Katyal et al. 2003). The remaining two alleles, CR1-C/F' and CR1-D are infrequent in all populations (Eikelenboom and Stam 1982; Wong et al. 1983; Moulds et al. 1996) (Table 1). The relative scarcity of the smallest and largest alleles is likely due to population selection effects which can confer a survival advantage, such as resistance to malaria (Noumsi et al. 2011).

Although the differences between these alleles seem large, the functional differences in the resultant proteins are apparently subtle. The increased number of LHR regions means that the larger alleles (CR1-B/S and CR1-D) have an additional C3b/C4b