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C1q as a Regulator of Brain Development: Implications for Autism Spectrum Disorders

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Abstract

Autism spectrum disorders (ASDs) represents a heterogeneous group of neurodevelopmental disorders with similar core features of social and communication impairments, restricted interests and repetitive behaviors. Early synaptic dysfunction due to neuroinflammatory insults may underpin the pathogenesis of abnormal brain development in some of individuals with ASDs. As a critical component of the innate immune response, the complement system comprises both directly acting factors and factors that augment other components of the immune system. Beyond its involvement with innate immune responses in the brain, the complement system also plays important roles in neurodevelopment. Recent studies suggest involvement of complement component C1q in fundamental neurodevelopmental pathways and in maintenance and elimination of dendrites and synapses. The impact of aberrant complement system activity during critical windows of brain development may not only affect the local immune response but lead to atypical brain development. This review summarizes and critically analyzes the evidence of a role for the complement system in the pathogenesis of ASDs.

Keywords: Complement C1q; Neurodevelopment; Membrane attack complex; CD14; C3/CR3; CNTNAP2 and RELN; Wnt; CNS; C1qA; C1qB; C1qC; dLGN; LGN

Abbreviations:

ASD: Autism spectrum disorder; ASDs: Autism spectrum disorders; C1q: Complement C1q; CNS: Central Nervous System; MAC: Membrane Attack Complex

Introduction

Background: Of the neurodevelopmental disorders, autism spectrum disorders (ASDs) are the most prevalent [1]. This heterogeneous group of developmental disorders share common core features of social and interpersonal communication deficits, restricted interests and repetitive behaviors, as well as varying degrees of intellectual impairment [2]. Prior investigations into potential disease mechanisms point to genetic mutations as a major risk factor in so called genetic ASDs. Now hundreds of genes have been found to be associated with ASDs; including those involved with synapse formation, function, elimination, and plasticity [3]. Despite this a majority of individuals with ASD have no identifiable genetic mutation associated with risk for ASDs. Studies of identical twins with ASD report a twin-twin concordance rate between 70-90%; albeit a high rate, this implicates the involvement of other unknown factors such as *de novo* mutations, epigenetic and environmental factors [4].

Environmental risk factors may alter neurodevelopment during critical windows of brain development; likely prior, during and after birth. Adverse *in utero* and perinatal environments caused by maternal immune activation during infection have also been implicated [5]. Essential to innate immune capabilities, complement component C1q appears to play key roles in neurodevelopment [6]. In this review, our purpose is to explore the current knowledge of the role of C1q in neurodevelopment and ASDs.

C1q Structure and Functions

Complement protein C1 is a macromolecular protein complex. It is composed of a C1q molecule and 2 each of C1r and C1s molecules (C1r2s2). C1q is the largest component of the complement system with a molecular weight of about 460 kD. C1q is composed of 6 of each A, B, and C chains. Each of the 18 chains comprising C1q contains 2 functional regions: a C-terminal globular head region and a collagen-like tail (or stalk) region. One each of A, B, and C chains form heterotrimeric strands and the combined globular regions and collagen-like regions are termed gC1q and cC1q respectively. Within the stalk regions of the heterotrimeric strands, A, B, and C chains form triple helical structures. Disulfide-bonds between individual C chains of each strand form a doublet of 2 strands, in turn 3 doublets non-covalently bind to form a single C1q hexameric glycoprotein [7].

The binding of C1 to a given activator such as antigen-antibody immune complexes initiates the classical complement pathway. Upon activation, such as by the binding of C1q with the Fc region of either IgM or IgG complexes, C1-inhibitor activity is overcome leading to the induction of conformational changes in C1r subunits of C1r2s2 by C1q thereby allowing proteolytic activation of all 4 subunits of C1r2s2. Activated C1s subunits in turn cleave C4 into C4a and C4b. C4b binds to C2 enhancing its proteolysis into C2a and C2b also by C1s. Next C2a and C4b complex into C4b2a thereby catalyzing C3 hydrolysis into C3a and C3b. C3b has multiple functions, in the classical

complement pathway it complexes with C4b2a to convert C5 into C5a and C5b. Next C5b, C6, C7, C8 lead to the polymerization of the channel C9 (membrane attack complex; MAC) functioning to span the target membrane leading to free movement of intra- and extracellular molecules and generally cell death by cell lysis or loss of ability to function.

The "canonical" C1q receptors are the receptor for the globular heads of C1q (gC1qR) and the receptor for the collagen-like stalk of complement component C1q (cC1qR); also known as calreticulin. The gC1qR is critical to the infection and inflammatory reactions in the body [8]. It is a highly acidic protein in almost all mammalian cells, except for red blood cells. In addition to binding to C1q, gC1qR can bind to many viral and bacterial proteins as well. In the ER, cC1qR is present and its function was considered as a molecular chaperone of the neogenic protein in the endoplasmic reticulum and regulation of the intracellular Ca^{2+} homeostasis. Aggregation of cC1qR is present in the blebs of apoptotic cells; pointing towards C1q's contribution to the phagocytosis of apoptotic cells [9].

Macrophages can produce large amounts of C1q, which help to reduce the accumulation of endogenic material, such as the debris of apoptotic cells. The rapid clearance of apoptotic cells can prevent the leakage of cell contents, maintaining a properly regulated immune response. C1q can directly promote the engulfment of apoptotic cells by macrophages [10] and interdigitating dendritic cells without inducing other inflammatory response, so it could help to maintain self-tolerance [11,12]. C1q can directly bind to apoptotic cells. The calreticulins are usually expressed on the endoplasmic reticulum in normal cells. When cells are undergoing apoptosis, the calreticulins are transferred to the cell surface and are bonded by C1q. Next, C1q promotes the phagocytosis of apoptotic cells through the C1q receptor on the dendritic cells (DCs) surface. The activation of the classical complement pathway does not occur in this process. C1q can also mediate phagocytosis of apoptotic cells by producing the C3 opsonin. C1q binds to IgM on the apoptotic cells and activates the classical pathway. A large number of C3 fragments are produced during the activation of the classical pathway, such as C3a and iC3b. C3a can guide DCs to the location of the apoptotic cell [9]. The iC3b fragment can directly bind to apoptotic cells and promote DC engulfment. The binding of iC3b to CR3 on DCs can suppress the expression of interleukin 12 (IL-12), tumor necrosis factor-α (TNF-α), cluster of differentiation 80 (CD80) and CD40 [13]. The phagocytosis mediated by complement receptor 3 (CR3) contributes to the maintenance of DC tolerance. Thus C1q may play a dual role in inflammatory responses through the C3 fragment; that of promotion of phagocytosis as well as inhibition of inflammatory reactions. The lectin pathway is similar to the classical pathway. Only the initiation of lectin pathway is not the binding of C1q to antibodies, it initiates with the binding of mannose-binding lectin (MBL) to mannose, glucose or other sugars of microorganisms. In contrast, the alternative pathway starts with spontaneous C3 hydrolysis. All three pathways converge with C3 hydrolysis culminating in the formation of the MAC.

The Role of C1Q in Normal Synaptic Pruning and Brain Development

During normal brain development, there are a series of overlapping phases, such as mitosis of neural progenitor cells, migration of neurons, dendritic outgrowth, neuron apoptosis, synaptic overproduction, synaptic pruning and myelination. Synaptic pruning is a process involving elimination of cell processes such as axons and dendrites, providing for a lower density but more efficient synaptic connections. The majority of synaptic pruning occurs during the 16th fetal week through young adulthood [14]. Depending on region, synapse density peaks between 3 months and 3.5 years [15-17]. Following this initial burst of synaptic development, pruning eliminates approximately 40% of original peak numbers of synapses [18,19], although somewhat smaller losses are observed when neuron density is taken into account [16].

It has been reported that the components of the immune system contribute to brain development [20]. Although the brain is protected by the blood brain barrier, the complement cascade proteins are found in the normal developing brain [21,22]. They are locally synthesized by resident neurons and glial cells; mainly microglia and astrocytes [23-26]. The retinal ganglion cells (RGCs) axons end at different non-overlapping eye-specific domains of the dorsal lateral geniculate nucleus (dLGN). Most of eye-specific segregation happens before the vision onset postnatally. However, the synaptic pruning lasts 2 weeks after the eyes open. By the end of the third week after birth, the dLGN neuron only receives stable inputs from one or two RGC axons [27]. In the developing brain, the expression of genes of complement components are regulated by cytokine signaling pathways just as they are in the immune system. Astrocytes are the main source of cytokines to regulate the complement genes in brain [28-31]. They can upregulate C1q genes in RGCs. C1q is localized to synapses during synaptic pruning in the developing retina [32]. The activation of the classical complement cascade mediates normal developmental synapse pruning during postnatal CNS development (Figure 1) [32].

The developing CNS neurons do not express high level of transmembrane complement inhibitor. They can bind the complement C1q and induce the classical complement activation cascade [33]. The initial complement protein C1q can activate C3 to produce the C3b and iC3b. C3b and iC3b opsonize cells or debris triggering their elimination via phagocytosis by glial cells.. It had been found that the complement proteins opsonize CNS synapses during postnatal development. The elimination of synapses in the developing retinogeniculate pathway requires the complement protein C1q and C3 [32]. In C1q knockout mice, failure of synaptic pruning leads to the appearance of markedly higher density, longer and thinner dendritic spines.

The initiation of complement-mediated synaptic elimination requires the complement protein C1q [34]. C1q interacts with lipoproteins and other receptors that are expressed on the surface of neuron and glial cells and activates the classic complement cascade. Then the activated C3b and iC3b opsonize the weak synapses. The C3/CR3 signal can activate microglia. Further, downstream cascade that activates the membrane attack complex is not presented due to high levels expression of downstream complement inhibitor CD59 in neurons [35]. The last stage of complement-dependent synaptic pruning is the engulfment of retinogeniculate synapses by microglia [36]. Microglia can be activated by C3/CR3 signaling because it is the only known cell type of brain that expresses C3 receptors [37].

C1q can facilitate engulfment by binding receptors, such as C1qRP and gC1qbp [38-40]. It can also bind opsonins, such as long pentrexin PTX3, short pentraxins serum amyloid protein (SAP) and C-reactive protein (CRP). Binding of C1q to these molecules leads to the activation of complement cascade, which promotes phagocytosis [41,42]. CRP is one of the pentraxin family proteins. It is expressed at high levels in the nervous system [43]. CRP has the important carboxy-terminal domain, which has been reported to bind C1q. They

can attach to membranes directly or oligomeric co-assembly with neuronal activity-regulated pentraxin (NARP), which is a membrane-bound pentraxin [43]. Pentraxins can also provide a synaptic binding site to C1q and help to localize its signaling ability.

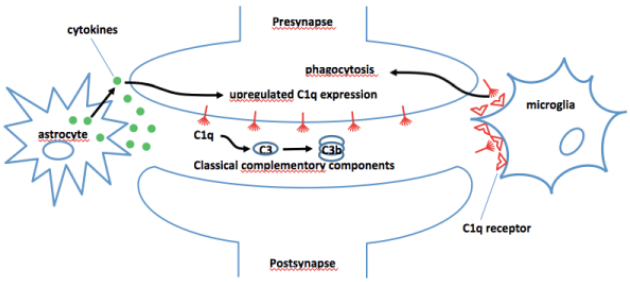

Figure 1: The activation of the classical complement cascade mediates normal synaptic pruning during neurodevelopment.. The engulfment of synapses by microglia can be activated by C3/CR3 signal or by directly binding of C1q.

Sentence should read: Some detrimental changes in synapses can trigger C1q activation and elimination by a complement-mediated pathway. For example, the stimulation of N-methyl-D-aspartate (NMDA) receptor can transiently induce long-term depression and activate caspase-3 in dendrites locally [44,45]. Caspase activation cascades provide apoptotic signals; and apoptotic dendrites bind and activate C1q by calreticulin that was transferred to the dendrite surface. There are some C1q-like proteins that also play a role in synaptic plasticity [46], such as C1ql1-4 (belongs to the complement component 1, q subcomponent-like 1 subfamily of the C1q family) and Cbln1-4 (belongs to Cbln1 family). Cbln1 (a member of the C1q tumor necrosis factor superfamily) and glutamate receptor δ2 (GluRδ2) can interact to affect synapse formation [47,48].

Complement Involvement in ASDs

ASDs are a heterogeneous group of complex neurodevelopmental disorders. They are typically characterized by impairments in verbal and non-verbal communication, deficits in social interactions and restricted stereotypical behaviors [49]. ASDs are usually diagnosed before three years of age during a dynamic period of synaptic development in the human brain [16]. 10-30% of the patients with autism display macrocephaly [50-52] in the first 4 years of life [53,54]. The macrocephaly suggests that there are excess neurons, glial cells, synapses or larger cells [55]. Bourgeron [55] suggests that abnormal synaptic growth and imbalance between inhibitory and excitatory synaptic currents could cause ASDs. Further evidence is that 10-30% ASD patients diagnosed in the past with autism have epilepsy [56]. Interestingly, in the C1q knockout model of epilepsy, failure to eliminate excessive excitatory synapses leads to the increased branching and alterations in spine type and density, which likely contribute to epileptogenesis [57]. This evidence considered together suggests that C1q-dysfunction may induce ASDs due to the failure of synaptic pruning.

Paradoxically, increased C1q expression has been observed in the peripheral serum of ASD patients [58]. It is not known whether these elevations represent an effort by the immue system to overcome a relative C1q deficiency possibly caused by genetic, epigenetic factors or through environmental exposures leading to higher levels of C1q inhibiting factors.

Some researchers suggest that neuroinflammation occurs in the brain of ASD patients [59-61]. The disruption of the blood-brain barrier could lead to the increased immune components in the brain, such as antibodies and complement proteins [62]. Compared with normal individuals, children with ASDs have a higher level of C-reactive protein (CRP) [63]. CRP can bind to the C1q in classical complement pathway [64] and mediate inflammatory responses [65,66].

Neuroinflammation during perinatal infections, which includes the activities of complement system and promotes the release of complement components [67], could contribute to autism pathogenesis [68]. In Mice, a study that used maternal influenza administration showed similar behavioral changes in the offspring as ASD patients, such as decreased social behavior and increased markers of anxiety [69]. Morphology features of autism, such as decreased Purkinje cell size, number and density in hippocampal and cerebellar regions, are observed in the prenatal influenza-infected mouse models [70-73].

Summary and Future Directions

Complement protein C1q is well known as the initiatory protein in the classical activation of the complement system. It has been found to play a role in microglia-mediated synaptic pruning in a typical developing human brain. C1q can activate the complement cascade and produce C3/CR3 signaling. The C3/CR3 signaling further activates and promotes microglia phagocytosis. There is another way that C1q is involved in synaptic pruning. C1q also binds directly to receptors on microglia [74-76]. In the C1q knockout mouse, there are significant defects in synaptic pruning. However, a large level of synaptic elimination still transpires in these mice [32] suggesting that C1q likely regulates normal synaptic development together with other pathways [77].

C1q-deficiency-induced failure of synaptic pruning is a potential mechanism in the pathogenesis of sub-sets of individuals with ASDs. Although increased C1q has been reported in peripheral serum of individuals with ASD it is not known whether this may represent a compensatory increase due to defects in C1q function and it is also not known whether this reflects conditions in CNS tissues. Further inflammatory insults resulting in chronic elevations in C1q may consequently result in elevations of C1q inhibiting factors leading to relative C1q dysfunction.

Competing Interests

The authors declare that they have no competing interests.

Authors Contribution

CF researched the literature, drafted, reviewed and edited the manuscript the manuscript. DFO researched the literature, assisted in drafted, reviewed and edited the manuscript. All authors read and approved the final manuscript.

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