Complement C1q subcomponent subunit A

Anjana Chandrasekhar¹, Ashok Reddy Dinasarapu¹, Andrea J Tenner², Shankar Subramaniam¹

Complement C1q subcomponent subunit A (C1qA) is one of the three components of C1q molecule. Functional C1q is composed of eighteen polypeptide chains: six C1qA chains, six C1qB chains, and six C1qC chains, which are arranged as six heterotrimers of ABC: (ABC)₆. Each of the individual C1q polypeptide chain consists of a N-terminal region and a C-terminal globular region (gC1q), of ~135 residues. Each N-terminal consists of 2-11 amino acid segments containing a half-cysteine residue that is involved in formation of inter-chain disulphide bonds, followed by a collagen-like region (CLR) consisting of ~81 residues. The collagen-like regions in A, B and C chains of each heterotrimer come together to form a triple helical collagen like structure. Further, A and B chains in each heterotrimer are bound by a disulphide bond, while C chain forms a disulphide bond with a C chain from the adjoining heterotrimer. Therefore the sixteen subunits come together to form six globular heads (gC1q), which are clusters of 3 independently folded C-terminal domains of the A, B and C chain. These globular domains recognize an array of self, non-self and altered-self ligands. C1q associates with the proenzymes C1r and C1s (2 molecules of each, in the molar ratio of 1:2:2 in a calcium dependent manner) to yield an active C1 complex, the first component of the serum complement system. C1r, upon binding of gC1q to an inciting stimulus, autoactivates itself and catalyzes breakage of a C1s ester bond, resulting in C1s activation and subsequent cleavage of C2 and C4 into their respective “a” and “b” fragments. Recognition of ligands by C1q molecule also defines C1q as a pattern recognition molecule (PRM). C1q recognizes distinct structures either directly on microbial structures and apoptotic cells, or indirectly after their recognition by antibodies or C-reactive protein (CRP). C1q in turn binds to multiple receptors (such as cC1qR (calreticulin), integrin α₅β₁, or other molecules on the surface of specific cell types of either myeloid or endothelial cell origin) and shows regulated broad physiological functions beyond complement activation.

KEYWORDS
C1QA; Complement C1q subcomponent subunit A; Complement component 1, q subcomponent, A chain; Complement component 1, q subcomponent, alpha polypeptide; Complement component C1q, A chain

IDENTIFIERS
Molecule Page ID:A004228, Species:Human, NCBI Gene ID:712, Protein Accession:NP_057075.1, Gene Symbol:C1QA

PROTEIN FUNCTION
C1qA (C1qB and C1qC as well) has functions as part of the C1q or C1 complex. C1q complex is formed of six subunits each of C1qA, C1qB and C1qC. C1q in turn, with C1r and C1s to form the C1 enzyme complex (C1qC1rC1s₂).

Activation of classical complement pathway: Binding of C1q to immunoglobulins (Ig) or to other specific molecules generally associated with microbes, apoptotic cells or polyanionic structures such as DNA, activates C1q associated C1r and C1s, which are serine proteases. These proteases then cleave downstream complement proteins, C4 and C2, to result in C4a, C4b2a and C2b. C4b2a sequentially recruits and activates downstream complement proteins, while C4a and C2b can serve as anaphylotoxins.

Opsonization/phagocytosis: C1q interacts with immunoglobulin (IgG or IgM) bound targets, which could be either pathogens or host cells expressing altered self-ligands. Along with the C1q role in complement activation, C1q is also involved in clearance of apoptotic cells (Trouw et al. 2008). C1q can directly bind to some of the surface expressed macromolecules on apoptotic cells (such as DNA, lipids, newly exposed proteins) (Nauta et al. 2002; Navratil et al. 2001). C1q binding opsonizes the apoptotic cells and activates classical complement pathway (Zwart et al. 2004; Gaboriaud et al. 2011). Apoptotic cell clearance can be enhanced by C1q independent of the remaining complement components, but is further increased with classical pathway activation. Macrophages show reduced ability to take up apoptotic cells in individuals deficient in C1q, C4, C2 or C3 (Gullstrand et al. 2009). Apoptotic neuronal cells are also recognized by C1q, which again independently or engaging the other complement components (if present in the tissue) leads to opsonization, and facilitates receptor mediated phagocytosis by activated microglia (Fraser et al. 2010). Clearance of apoptotic cells requires interaction of C1q with its various receptors and has other effects on phagocyte cytokine production (see’ Interaction with ligands and other proteins’ section).

Mannose binding lectin 2 (MBL2), which activates the lectin pathway, is structurally similar to C1q and can therefore compete with C1q for binding to many altered self-ligands (Oroszlán et al. 2007; Agostinis et al. 2012). Both C1q and MBL2 enhance ingestion of modified low density lipoprotein (LDL) by monocytes and macrophages, and modulate monocyte activation and chemokine responses during the clearance of oxidized LDL (OxLDL) (cholesterol efflux) in OxLDL-loaded monocytes and macrophages (Fraser and Tenner 2010).

Inflammation: Complement activation that follows binding of C1q and cascade activation through cleavage of C5 leads to inflammation. However, inflammation is not always harmful, as it leads to host defense against pathogens and several other threats. For instance, C1q can bind to outer membrane proteins of Gram-negative bacteria and lead to complement susceptibility of the invading pathogen (Roumenina et al. 2008). On the other hand, C1q bound to “self-cargo” directly inhibits inflammasome activation, cleavage of caspase-1, and subsequent IL-1β processing in human monocyte derived

¹Department of Bioengineering, University of California, San Diego, CA 92093, US. ²University of California, Irvine, CA 92697, US. ³Department of Bioengineering, University of California at San Diego, CA 92939, US.

Correspondence should be addressed to Anjana Chandrasekhar: 4chandra@ucsd.edu

Published online: 9 Oct 2012 | doi:10.6072/H0.MP.A004228.01
Expression of cytokines and interleukins: Binding of C1q to immune cells generally results in suppression of pro-inflammatory cytokines and enhanced expression of anti-inflammatory cytokines. Interaction of C1q with human monocytes or dendritic cells results in the downregulation of proinflammatory cytokines upon toll-like receptor 4 (TLR4) stimulation by lipo-poly saccharide (LPS) (Fraser et al. 2006; Yamada et al. 2004). C1q bound apoptotic lymphocytes increase the expression of interleukin (IL)-33 which is a recently described member of the IL-1 family that can amplify M2 (alternative) polarization of macrophages induced by IL-13 (Benoit et al. 2012; Yoshi et al. 2010). C1q bound apoptotic lymphocytes increase the expression of IL-37 (IL-IF7) which is a natural suppressor of innate inflammatory responses (Benoit et al. 2012; Nold et al. 2010). C1q sequentially induces type I interferons, IL-27, and IL-10 secretion in LPS-stimulated human macrophages (Fraser et al. 2009; Fraser et al. 2006; Benoit et al. 2012).

Immune cell maturation: C1q influences the maturation and function of dendritic cells (DCs) (Cosmor et al. 2007; Castellano, et al. 2004; Baruah, et al. 2009). DCs cultured on immobilized C1q have a modulating effect on the T-cell production of interferon γ (IFNγ) and IL-17 in an mixed leukocyte reaction (MLR) reaction (Teh et al. 2011). Immature DCs are also good sources of C1q on their own (Cosmori et al. 2007; Castellano et al. 2007), and additionally express the C1q receptors, gC1qR (gC1qBP, p33) and cC1qR (calreticulin). DCs have been reported to migrate in response to soluble C1q with maximal cell movement observed at 0.01-0.05μM C1q. In contrast, mature DCs neither express C1qR nor do move to a gradient of soluble C1q (Vegh et al. 2006). DC-SIGN (CD209), a transmembrane C-type lectin, which has been shown to interact with both C1q and gC1qR, probably plays a role in DC maturation (Hosszu et al. 2012). C1q may also be involved in modulating T-cell and B-cell activity (Chen et al. 1994). C1q, by binding to platelets, modulates platelet aggregation, P-selectin production and thereby regulates platelet activation (Skoglund et al. 2010).

REGULATION OF ACTIVITY
Host cell factors: The modified apoptotic cell surface acquires C-reactive protein (CRP) and C1q together with factor H (FH) (Zipfel and Skerka 2009; Gershov et al. 2000) and C4bbinding protein (C4BP) (Trouw et al. 2007). CRP, which is a pentraxin, promotes binding of C1q to the cell surface, while FH and C4BP prevent C3b deposition and amplification by the alternative pathway. The levels of CRP, FH and C1q shift the balance either towards complement activation or limited activation that may facilitate ingestion without downstream inflammatory anaphalatoxins or membranolytic complex formation. Other pentraxins, such as PTX3 and serum amyloid P-component, also activate C1 by binding to C1q (Bottazzi et al. 1997; Nauta, et al. 2003) and reviewed in Bottazzi et al. 2010 and MBL can also play a role in targeting a pathogen for enhanced complement activation in conjunction with pentraxins and C1q in C1 (Ma et al. 2011). Inhibition of the C1 complex activity of can be useful in protecting against host cell damage. Formation of C1 complex can be inhibited by binding of C1q to surfactant associated protein A (SP-A) and chondroitin sulfate proteoglycan (CSPG4) (Watford et al. 2001; Kirschfink et al. 1997). C1q binding to IgG is inhibited by heme (Roumenina et al. 2011). Active C1q binds strongly to decorin and biglycan, which are leucine-rich proteoglycans involved in matrix assembly and bone mineralisation, respectively (Groeneveld et al. 2005). The binding of these extracellular matrix proteins hampers activation of complement cascade. Decorin and biglycan prevent C1q binding to human umbilical vein endothelial cells (HUVEC) and U937 cells, with biglycan further inhibiting C1q-mediated release of monocyte chemoattractant peptide-1 (MCP-1) and IL-8 from HUVEC (Groeneveld et al. 2005).

Pathogenic factors: The human astrovirus have special coat proteins that bind to C1q and inhibit the complement activation and hence evade the host immune response (Bonaparte et al. 2008; Hair et al. 2010). Trypanosoma cruzi calreticulin (TeCRT) prevents C1 complex formation, by interfering with the ability of the (C1r–C1s)_2 tetramer to bind C1q (Valck et al. 2010).

INTERACTIONS
C1qA chain binds to C1qB and C1q chains to form a heterotrimer. Six such heterotrimers come together to form a functional C1q molecule (Kishore and Reid 2000). C1q has an N-terminal collagen-like region (CLR), also known as collagen stem or tail region, and C-terminal globular heads. The 3-dimensional crystal structure of the C1q globular domain has been solved (Gaboriaud et al. 2003). Circulating C1q is bound in equilibrium with the tetramer of serine proteases C1r, C1s, as C1 complex (Ziccardi and Tschopp 1982). This interaction with C1r and C1s occurs at the collagen-like region of the C1q molecule (Philips et al. 2009; Bally et al. 2009; Roumenina et al. 2011). C1s cleaves C4 to C4a and C4b. C4b recruits C2 which is then cleaved by the active C1 complex resulting in active products, C4b2a and C2b (Rossi et al. 1998).

Binding to ligands: The serine proteases C1r and C1s of C1 become activated when two or more gC1q domains of C1q bind to its ligands. One such ligand is the aggregated IgG or IgM immune complexes. This binding is ionic in nature and the B chain module of the gC1q in particular is implicated in facilitating the binding of C1q to IgG (Schneider and Zacharias 2012; Zlatorova et al. 2006; Gadjeva et al. 2008; Kojuharova et al. 2010). Pentraxins, such as PTX3 and serum amyloid P-component (SAP) can also bind C1q and facilitate activation of the complement cascade (Bottazzi et al. 1997; Bristow and Boackle 1986; Roumenina et al. 2006). PTX3, which also binds to C4 binding protein (C4BP) and FH, plays an important role in innate immunity (Doni et al. 2012; Cieslik and Hrycek 2012). PTX3 has been shown to form a tri-complex with C1q and MBL on the surface of Candida albicans (Ma et al. 2011). Binding of C1q to β amyloid protein in β sheet fibrils (Ro et al. 1992; Jiang et al. 1994; Tacnet-Delorme et al. 2007) and biglycan, which bind to the collagen-like region, downregulate activity (Sjöberg et al. 2009; Groeneveld et al. 2005). The classical complement pathway is also activated in...
vascular injury which leads to inflammation. C1q interacts with platelets via gC1qR (gC1qBP, p33) binding the globular head of C1q (Ghebrehiwet et al. 1994; Ghebrehiwet et al. 2001). Adaptor molecules, such as C-reactive protein (CRP), a pentraxin, play a major role in augmenting the binding capacity of C1q to platelets (Peerschke et al. 2006; Peerschke et al. 2009).

It is the C1q globular domain that binds the apoptotic cell surface (Korb and Ahearn 1997; Navratil et al. 2007). C1q can enhance apoptotic cell phagocytosis in cooperation with other surface receptors such as CR1, FcR, CD91 (reviewed in Bohlson et al. 2007) and most recently RAGE, the multiligand receptor of Ig super family, (Ma et al. 2012). For example, C1q demonstrates more efficient phagocytosis in the presence of both RAGE and integrin α5β1 (CD11b/CD18), as compared to the individual presence of either of these proteins (Ma et al. 2012). CRP can also promote the binding of C1q to apoptotic cells, amplifying classical pathway activation while also recruiting IF, which inhibits alternative pathway amplification and C5 convertase formation, thereby protecting cells from necrotic lysis and the host from unwarranted inflammation (Gershov et al. 2000). Apoptotic cell surfaces expose ligands such as DNA, histones and amino groups of phospholipids. While C1q can directly bind to DNA and histones, there is currently a controversy as to whether C1q binds directly to phosphatidyl serine on apoptotic cells (Paidassi et al. 2008) or indirectly binds to phosphatidyl residues via annexins 2 and 5 or both, thus contributing to clearance by macrophages (Jiang et al. 1992, Martin et al. 2012).

C1q (or C1 complex) binds directly to a variety of altered-self ligands via gC1q domain (Gaboriaud et al. 2011). It can bind to oxidized and enzymatically modified forms of LDL (E-LDL) (Biró et al. 2007; Fraser and Tenner 2010), by recognizing unesterified cholesterol formed by cholesterol esterase (Biro et al. 2010). C1q can also bind to adiponectin (produced by adipose tissue) and when C1q is in the C1 complex activates the complement cascade (Peake et al. 2008; Nakatsuji et al. 2012). However, the binding is substantially increased by modification of adiponectin by metaperiodate, and thus the physiological role of this interaction remains to be determined. In rheumatoid arthritis condition, binding of C1q to histidine rich glycoprotein (HRG) aids in clearance of necrotic cells (Manderson et al. 2009). C1q has been reported to bind to decidual extracellular matrix, and may play a role in promoting trophoblast invasion of decidua (Agostinis et al. 2010).

C1q interacts with salivary scavenger and agglutinin (SALSA), which in turn binds to pathogens, leading to complement activation (Reichhardt et al. 2012; Boackle et al. 1993). Ligands from pathogenic microbes include Lipid-A of E.coli (Tan et al. 2011) and Klebsiella pneumoniae porin (OmpK36), both of which activate complement cascade and lead to destruction of the pathogen (Alberti et al. 1995; Alberti et al. 1996). C1q can bind to Human immunodeficiency virus (HIV) envelope proteins gp120 and gp41. In most cases, binding of gp120 and gp41 to C1q facilitates entry of the virus into CD4+ cells via complement receptors for C3 (Stoiber et al. 1994; Proházska et al. 1995; Thielens et al. 2002; Stoiber et al. 1995; Ebenbichler et al. 1991; Thieblemont et al. 1993a; Thieblemont et al. 1993b). In one report, binding of gp120 to C1q, in presence of fibronectin reduced infection in saliva (Su and Boackle 1991). In dendritic cells, C1q-gC1qR forms a trimolecular complex with DC-SIGN, a C-type lectin (Hosszu et al. 2012).

Binding to the receptors on host immune cells via collagen-like stem region (CLR):

CLR domain of C1q enhances phagocytosis of suboptimally opsonized immune complexes as well as apoptotic cells and cell debris. However, the cell surface receptors involved have not been definitively established, and likely involve complexes of surface molecules. cC1qR (Calreticulin or CRT) is a well-studied and most ubiquitous C1q receptor thought to be involved in mediating C1q effects on biological processes (Malhotra et al. 1990; Malhotra 1993; Nicholson-Wellner and Kickstein 1999). It is produced intracellularly, but is exposed on the cell surface of damaged cells. This protein facilitates binding of C1q to a receptor CD91(LRP1,A2MR), and was thereby proposed to promote phagocytosis of apoptotic cells (Ogden et al. 2001). In addition, a recent study has supported evidence for the possibility of CD91 directly recognizing C1q (Duus et al. 2010). However, genetic abrogation of the CD91 expression in mice did not reduce the C1q enhancement of uptake (Lillis et al. 2008), suggesting redundancy of receptors or compensatory mechanisms. CR1(CD35), yet another cell surface C1q binding molecule, also binds to other opsonins (C3b and C4b). This interaction favors cell adhesion and thereby apoptotic cell clearance (Tan et al. 1999; Klickstein et al. 1997). CD93, a protein expressed on myeloid lineage cells, endothelial cells, and platelets was originally considered the C1qR that mediated enhanced phagocytic activity (C1qRP)(Nepomuceno et al. 1997; Nepomuceno and Tenner, 1998; Fonseca et al. 2001) but genetic abrogation had no effect on in vitro C1q enhanced phagocytosis and thus is not necessary for this C1q function (similar to CD91). Its roles include angiogenic properties and involvement in endothelial cell migration and intercellular adhesion (Greenlee et al. 2008; Bohlson et al. 2007). The α2β1 integrin has also shown the ability to function as a C1q receptor (Edelson et al. 2006). This integrin is expressed on a variety of cell types including mast cells, and has been reported to bind to C1q, implying a role for this integrin in innate immunity (Zutter and Edelson 2007), but also as a C1q dependent mechanism for bacteria invasion (Xue et al. 2011). Interestingly, Trypanosoma cruzi calreticulin (TcCRT) binds to C1q and prevents C1 formation, by interfering with the ability of the (C1r–C1s), tetramer to bind C1q (Valck et al. 2010). Fibrinogen, a protein composed of α, β and γ chains, binds to C1q and may also facilitate phagocytosis (Entwistle and Furcht 1988).

PHENOTYPES

The A, B, and C chains of C1q are arranged in the order A-C-B on human chromosome 1 and are transcribed in a synchronized manner (Chen et al. 2011). An insertion polymorphism has been identified in the murine New Zealand Black (NZB) C1q gene that correlated with lower C1q levels in sera and production by macrophages in vitro (Miura-Shimura et al. 2002). While little more is known of the transcriptional control of C1q, some analysis of the gene locus has been provided (Lattin et al. 2009), with evidence that a deficiency in β- arrestin 2 abrogates C1q synthesis in murine bone marrow derived macrophages (Lattin et al. 2009).

C1QA alleles showing single nucleotide polymorphisms (SNP) have been documented (Racila et al. 2003; Namjou et al. 2009; Cao et al. 2012). There are two forms of C1q deficiency. One
form produces no C1q, and the other form produces a dysfunctional C1q (includes non-sense and mis-sense mutations) (Kirschfink et al. 1993; Petry et al. 1997; Hoekzema et al. 1985). Genetic analysis of the C1q-deficient patients has revealed mutations affecting each of its three chains (Petry et al. 1995; Mayilyan 2012; Namjou et al. 2012; Topaloglu et al. 2012). C1q deficiency, a rare autosomal recessive disorder, is known to result in an increased risk for bacterial infections, recurrent skin lesions, chronic infections, and autoimmune diseases such as, systemic lupus erythematosus (SLE) or SLE-like diseases and lupus nephritis (Petry 1998; Bowness et al. 1994; Carroll 1998; Tsao 1998; Stone et al. 2000; Pickering et al. 2000). Recent studies have shown SLE patients, with or without lupus nephritis, to express anti-C1q antibodies (Jourde-Chiche et al. 2012; Katsumata et al. 2011; Yin et al. 2012). Epitopes for anti-C1q antibodies in lupus nephritis patients have been reported (Vanhecke et al. 2012; Stoyanova et al. 2012). In patients with C1q deficiency, serum and cerebrospinal fluid levels of IFN-α and IFN-γ-inducible protein-10 levels were elevated and strongly correlated with Ro autoantibodies (Santer et al. 2010). A C1q homozygous mutation at GlyB63Ser, resulting in lupus condition, exhibits a normal C1q structure, and can bind to immunoglobulins and pentraxins. However, this mutation abrogates binding of C1r, implying that mere ligand recognition is not enough to prevent lupus condition (Roumenina et al. 2011) and/or this site may be involved with C1q interaction with and signaling of host cells to enhance uptake of apoptotic cells and suppress production of inflammatory mediators.

MAJOR SITES OF EXPRESSION

C1q is predominantly synthesized by peripheral tissue macrophages and dendritic cells in vivo (Petry et al. 1991; Castellano et al. 2010) and by macrophages, microglia and dendritic cells in vitro (Tenner and Volkin 1986; Castellano et al. 2004; Bensa et al. 1983). This local myeloid cell synthesis of C1q is hypothesized to be the major source of C1q for the rapid opsonization of dying cells in tissue, before recruitment of plasma-derived components such as C1r and C1s and subsequent activation of the complement cascade (Benoit et al. 2012). Induced synthesis of C1q has been detected in several injury models in vivo and in vitro, including in atherosclerotic lesions (Cao et al. 2003), suggesting that the induction of C1q synthesis in tissue may be a response to injury that promotes rapid clearance of apoptotic cells and concomitant suppression of inflammation (Dietzschold et al. 1995). A recent report has shown osteoclasts to produce C1q, which in turn leads to osteoclast development (Teo et al. 2012). Neurons can also be induced to produce C1q by injury or infection or during development (reviewed in Alexander et al. 2008).

SPlice VARIANTS

There are no known splice variants.

REGULATION OF CONCENTRATION

A recent method has estimated C1q concentration to be ~113 +/- 40 μg/ml in normal serum. However, previous studies have shown concentrations to range from 56 - 276 μg/ml (Ziccardi and Cooper 1978; Dillon et al. 2009). Ratio of C1q bound adiponectin to total adiponectin in blood has been reported to serve as a biomarker for cardiovascular risk (Nakatsuji et al. 2012).

ANTIBODIES

C1q monoclonal antibodies (mAbs) can be obtained from Quidel Corporation. This monoclonal antibody, raised against purified human C1q protein, is specific for the globular head domain (Stoltzner et al. 2000). Several monoclonal antibodies to human C1q were produced and characterized as to reactivity with the globular domain vs collagen like region by Kilchherr and colleagues (Kilchherr et al. 1985).
<table>
<thead>
<tr>
<th>STATE DESCRIPTION</th>
<th>LOCATION</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1QA/C1qB/C1qC</td>
<td>extracellular region</td>
<td>Kishore U and Reid KB 2000</td>
</tr>
<tr>
<td>C1q</td>
<td>extracellular region</td>
<td>Kishore U and Reid KB 2000</td>
</tr>
<tr>
<td>C1q/CRP</td>
<td>extracellular region</td>
<td>Volanakis JE and Narkates AJ 1981</td>
</tr>
<tr>
<td>C1q/PTX3</td>
<td>extracellular region</td>
<td>Bottazzi B et al. 1997</td>
</tr>
<tr>
<td>C1q/SAP</td>
<td>extracellular region</td>
<td>Bristow CL and Boackle RJ 1986</td>
</tr>
<tr>
<td>C1q/Fibrinogen</td>
<td>extracellular region</td>
<td>Binnie CG and Lord ST 1993; Entwistle RA and Furcht LT 1988; Guan EN et al. 1991; Mosesson MW et al.</td>
</tr>
<tr>
<td>C1q/Fibrin</td>
<td>extracellular region</td>
<td>Entwistle RA and Furcht LT 1988</td>
</tr>
<tr>
<td>C1q/Adiponectin</td>
<td>extracellular region</td>
<td>Nakatsuji H et al. 2013; Peake PW et al. 2008</td>
</tr>
<tr>
<td>C1q/a2B1</td>
<td>plasma membrane</td>
<td>Edelson BT et al. 2006</td>
</tr>
<tr>
<td>C1q/C1qR</td>
<td>plasma membrane</td>
<td>Malhotra R and Sim RB 1989; Malhotra R et al. 1990; Arvieux J et al. 1984</td>
</tr>
<tr>
<td>C1q/gC1qR</td>
<td>extracellular region</td>
<td>Ghebrehiwet B et al. 2001; Ghebrehiwet B et al. 1994</td>
</tr>
<tr>
<td>C1q/gC1qR/DC-SIGN</td>
<td>plasma membrane</td>
<td>Hosszu KK et al. 2012</td>
</tr>
<tr>
<td>C1q/ccC1qR</td>
<td>extracellular region</td>
<td>Csomor E et al. 2007; Nicholson-Weller A and Klickstein LB 1999; Ogden CA et al. 2001; Stuart GR et al. 1997</td>
</tr>
<tr>
<td>C1q/CD91</td>
<td>plasma membrane</td>
<td>Duus K et al. 2010</td>
</tr>
<tr>
<td>C1q/cC1qR/CD91</td>
<td>plasma membrane</td>
<td>Ogden CA et al. 2001</td>
</tr>
<tr>
<td>C1q/CRI</td>
<td>plasma membrane</td>
<td>Tas SW et al. 1999; Klickstein LB et al. 1997</td>
</tr>
<tr>
<td>C1q/APOA1</td>
<td>extracellular region</td>
<td>Zhou M et al. 2004</td>
</tr>
<tr>
<td>C1q/DC-SIGN</td>
<td>plasma membrane</td>
<td>Hosszu KK et al. 2012</td>
</tr>
<tr>
<td>C1q/CSGP4</td>
<td>extracellular matrix</td>
<td>Kirschfink M et al. 1997</td>
</tr>
<tr>
<td>C1q/SP-A</td>
<td>extracellular region</td>
<td>Watford WT et al. 2001</td>
</tr>
<tr>
<td>C1q/LDL</td>
<td>extracellular region</td>
<td>Biró A et al. 2007; Fraser DA and Tenner AJ 2010</td>
</tr>
<tr>
<td>C1q/DNA</td>
<td>extracellular region</td>
<td>Jiang H et al. 1992</td>
</tr>
<tr>
<td>C1q/RAGE</td>
<td>extracellular region</td>
<td>Ma W et al.</td>
</tr>
<tr>
<td>C1q/aMβ2</td>
<td>plasma membrane</td>
<td>Ma W et al.</td>
</tr>
<tr>
<td>C1q/aMβ2/RAGE</td>
<td>plasma membrane</td>
<td>Ma W et al.</td>
</tr>
<tr>
<td>C1q/SALSA</td>
<td>extracellular region</td>
<td>Boackle RJ et al. 1993; Reichhardt MP et al.</td>
</tr>
<tr>
<td>C1q/HRG</td>
<td>extracellular matrix</td>
<td>Manderson GA et al. 2009</td>
</tr>
<tr>
<td>C1q/SLRP</td>
<td>extracellular matrix</td>
<td>Sjöberg AP et al. 2009</td>
</tr>
<tr>
<td>C1q/Histone2[a,b]/Histone1</td>
<td>extracellular region</td>
<td>Martin M et al. 2012</td>
</tr>
<tr>
<td>C1q/OmpK36 (K. pneumoniae)</td>
<td>extracellular region</td>
<td>Alberti S et al. 1995; Alberti S et al. 1996</td>
</tr>
<tr>
<td>C1q/FKBP2</td>
<td>Unknown</td>
<td>Neye H and Verspohl EJ 2004</td>
</tr>
<tr>
<td>C1q/HIV-gp120 (HIV)</td>
<td>extracellular region</td>
<td>Prohászka Z et al. 1995; Su H and Boackle RJ 1991; Thiellens NM et al. 2002; Stoiber H et al. 1994</td>
</tr>
<tr>
<td>C1q/HIV-gp41 (HIV)</td>
<td>extracellular region</td>
<td>Ebenbichler CF et al. 1991; Stoiber H et al. 1995</td>
</tr>
<tr>
<td>C1q/Lipid A (E. coli)</td>
<td>extracellular region</td>
<td>Tan LA et al. 2011</td>
</tr>
<tr>
<td>C1q/TcCRT (T. cruzi)</td>
<td>extracellular region</td>
<td>Valck C et al. 2010</td>
</tr>
<tr>
<td>C1q/Heme</td>
<td>extracellular region</td>
<td>Roumenina LT et al. 2011</td>
</tr>
<tr>
<td>C1q/R2s2 (C1)</td>
<td>extracellular region</td>
<td>Gaboriaud C et al. 2004; Weiss V et al. 1986</td>
</tr>
<tr>
<td>C1/C4b</td>
<td>extracellular region</td>
<td>Rossi V et al. 1998</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENTS

The UCSD Signaling Gateway Molecule Pages (SGMP) is funded by NIH/NIGMS Grant 1 R01 GM078005-01. The authors thank Dr. John D. Lambris, University of Pennsylvania, Philadelphia, UCSD-SGMP editorial board member, for extensive discussions.

SUPPLEMENTARY

Supplementary information is available online.

REFERENCES


Boackle RJ, Connor MH, Vesely J (1993). High molecular weight non-immunoglobulin salivary agglutinins (NIA) bind C1q globular heads and have the potential to activate the first complement component. Mol Immunol, 30, 3.


Autoimmunity, 45, 2.


Hughes-Jones NC, Gardner B (1979). Reaction between the isolated


Nakatsuji H, Kobayashi H, Kishida K, Nakagawa T, Takahashi S,


chains. Biochemistry, 45, 13.


Stoiber H, Ebenbichler CF, Thielens NM, Arlaud GJ, Dierich MP (2004). The envelope glycoprotein of HIV-1 gp120 and human complement protein C1q bind to the same peptide derived from three different regions of gp120, the transmembrane glycoprotein of HIV-1, and share antigenic homology. Eur J Immunol, 24, 2.


Tan LA, Yang AC, Kishore U, Sim RB (2011). Interactions of complement components C1q and factor H with lipid A and Escherichia coli: further evidence that factor H regulates the classical complement pathway. Protein Cell, 2, 4.


Vanhecke D, Roumenina LT, Wan H, Osthoff M, Schaller M, Trendelenburg M (2012). Identification of a major linear C1q epitope...
allows detection of systemic lupus erythematosus anti-C1q antibodies by a specific peptide-based enzyme-linked immunosorbent assay. *Arthritis Rheum*, 64, 11.


This molecule exists in 46 states, has 47 transitions between these states and has 2 enzyme functions. (Please zoom in the pdf file to view details.)