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doi:10.6072/H0.MP.A004234.01
Volume 2, Issue 2, 2013

Review Article Open Access

Complement C2

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Complement C2 is a single chain serum glycoprotein (110 kDa), which serves as the catalytic subunit of C3 and C5 convertases in the classical and lectin pathways. During complement activation, C2 is cleaved by classical (C1s) or lectin (MBL-associated serine protease-2; MASP-2) proteases into two fragments: C2b and C2a. C2a, a serine protease, in complex with C4b fragment of complement factor C4, generates the C3 (C4b2a) or C5 (C4b2a3b) convertase. C3 convertase is very short-lived and cleaves complement C3 into C3a and C3b fragments (selective cleavage of Arg-|-Ser bond in C3 alpha-chain). C3 convertase requires the presence of magnesium and decays over time at physiologic temperatures. However, continuous activation of complement pathways shifts the substrate preference from C3 to C5 by formation of C5 convertase (formed by addition of C3b fragment to C3 convertase i.e. C4b2a3b). C5 convertase cleaves complement C5 to become activated into C5a and C5b fragments (selective cleavage of Arg-|-Xaa bond in C5 alpha-chain) and by a series of additional steps, promotes lysis of bacteria and damaged cells by pore or membrane attack complex (MAC) formation. Deficiency of C2 has been reported to be associated with certain autoimmune diseases. Single nucleotide polymorphisms (SNPs) in the C2 gene have been associated with altered susceptibility to age-related macular degeneration.

KEYWORDS
C2; C3/C5 convertase; CO2; Complement C2; Complement component 2; Complement component C2

IDENTIFIERS
Molecule Page ID:A004234, Species:Human, NCBI Gene ID: 717, Protein Accession:NP_000054.2, Gene Symbol:C2

PROTEIN FUNCTION
The human complement system is activated by three pathways: the classical, lectin, and alternative pathways, resulting in generation of opsonins and subsequent destruction of pathogens or in the clearance of antigen (Ag)–antibody (Ab) complexes from the bloodstream (Ricklin and Lambris 2013; Ricklin *et al*. 2010). Complement C2, a serine protease, is highly homologous to complement factor B, showing 39% identity at the amino acid level, and plays an important role in the classical and lectin pathways by formation of C3 (C4b2a) and C5 (C4b2a3b) convertases. Alternative pathway C3 (C3bBb) and C5 (C3b3bBb) convertases, which are C2 independent, use complement factor B to cleave C3 and C5 (Pangburn *et al*. 1986; McGreal and Gasque 2002; Rawal and Pangburn 1998).

Classical complement pathway: The classical pathway is activated normally by Abs such as immunoglobulin (Ig)G or IgM of Ag-Ab complexes (or bacterial surface) and results in assembly of the C1 enzyme complex on target surfaces (Miletic and Frank 1995). This complex is calcium-dependent and is composed of one C1q and two molecules each of C1r and C1s (C1qr2s2) (Sim and Reid 1991). Further, C1q is composed of eighteen polypeptide chains: six C1qA chains, six C1qB chains, and six C1qC chains (McGreal and Gasque 2002; Kishore *et al*. 2004). Once an antibody is bound to C1q, the C1q molecule undergoes structural changes, causing autocatalytic activation of C1r, a serine protease. Activated C1r then cleaves a bond in C1s to activate C1s, (formerly called ‘C1 esterase’) which in turn cleaves C4 (C1s bound C4) into C4a and C4b (C1s bound C4b). C4b, the major cleavage fragment, binds to bacterial membrane (if present) and recruits C2. C1s further cleaves C2 in a C4b-C2 complex (Nagasawa and Stroud 1977). The smaller C2b (30 kDa N-terminal of C2) fragment is released while the larger C2a (63 kDa C-terminal fragment) is a serine protease and forms C4b2a (C3 convertase). However, the classical pathway can also be activated by mechanisms independent of Ab. Heparin (a polyanionic anticoagulant) and protamine (a polycation that is used to block heparin), when present in equimolar concentrations, can activate the classical pathway (Sahu and Pangburn 1993). Various other polyanions (eg, DNA and RNA) or C-reactive protein (CRP) are thought to be able to react directly with C1q to activate the classical pathway activation without the presence of Abs (Volanakis *et al*. 1991; Jiang *et al*. 1992).

In addition, C1 independent pathways have also been described, which do not use components of the classical pathway but result in C3 cleavage. One of these has been characterized as the mannose-binding lectin (MBL)/Lectin pathway.

Lectin complement pathway: The lectin pathway of complement activation, initiated through MBL-MASP or ficolin-MASP cascades, is Ab- and C1 (or C1q)- independent (Fujita 2002). MBL or ficolins bind to specific carbohydrate structures found on the surface of a range of microorganisms in association with MASPs such as MASP-1, MASP-2, and MASP-3 and activates the complement system. On binding to appropriate targets, the MASP-1 activated MASP-2 (both the MASPs are in the MBL-MASP complex) sequentially cleaves complement factors C4 and C2 leading to the formation of C4b2a (C3 convertase) (Héja *et al*. 2012a; Héja *et al*. 2012b).

REGULATION OF ACTIVITY
The classical pathway (CP) is regulated by C1 esterase inhibitor (C1INH), which binds stoichiometrically (1:1) to C1r and C1s proteins to result in permanent inactivation. C1INH also binds stoichiometrically to plasmin, kallikrein and activated coagulation factors XI and XII (Schreiber *et al*. 1973). Factor J is a cationic glycoprotein that also inhibits C1 activity (Lopez-Trascasa *et al*. 1989; González-Rubio *et al*. 1996). C4-binding protein (C4BP) disassembles the C4b2a complex (C3 convertase), allowing complement factor I to inactivate C4b (Gigli *et al*. 1979; Scharfstein *et al*. 1978). The alkaline protease

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Published online: 10 Dec 2013 | doi:10.6072/H0.MP.A004234.01

(AprA) of *Pseudomonas aeruginosa* interferes with classical and lectin pathway-mediated complement activation via degradation (by cleavage) of C2 (Laarman *et al*. 2012).

INTERACTIONS

Both C2 and C2a interact with C4b (fragment of complement factor C4). C2a in complex with C4b sequentially generates the C3 (C4b2a) and C5 (C4b2a3b) convertases (see 'Protein Functions' section). Heparin, which is a clinical anticoagulant and primarily an intracellular polysaccharide localized in the granules of mast cells (Rabenstein 2002; Casu and Lindahl 2001) can interact with C2 (Sahu and Pangburn 1993). A trispanning orphan receptor (TOR), now known to be tetraspanning, has been described in *Schistosoma haematobium* and *Schistosoma mansoni* (Lochmatter *et al*. 2009; Inal 1999; Inal and Sim 2000), which interacts with C2a via its N-terminal extracellular domain. This interaction results in inhibition of the classical and lectin pathway of complement activation, probably due to interference with binding of C2 to C4b such that C3 convertase cannot be formed. This leads to resistance against complement-mediated cell lysis, allowing parasite survival and infection. The C2-binding (and complement inhibiting) domain of Sm-TOR, as well as inhibiting immune complex-stimulated inflammation in the Reversed Passive Arthus Reaction (Inal *et al*. 2003) and complement-mediated lysis of the intracellular parasite *Trypanosoma cruzi* (Cestari *et al*. 2009) has recently shown promise as a vaccine candidate, in a model of Schistosoma infection (Lochmatter *et al*. 2012).

CMAP, a complement database, documents the biochemical methods used to identify these interactions (Yang *et al*. 2013).

PHENOTYPES

Complement C2 deficiency (C2D), ~1:20,000 in individuals of Caucasian ancestry, is an autosomal recessive disorder that is characterized by a reduced serum C2 levels and an increased susceptibility to infections (Pickering *et al*. 2000; Jönsson *et al*. 2005). Deficient individuals have an increased incidence of systemic lupus erythematosus (SLE) and lupus-like syndrome, glomerulonephritis, vasculitis, polymyositis susceptibility and pyogenic infections (Newman *et al*. 1978; Jersild *et al*. 1976). The deficiency is, in the majority of cases, caused by homozygosity for C2 genes having deletions in exon 6, resulting in complete absence of C2, or in some cases caused by other C2 gene mutations (Truedsson *et al*. 1993). In addition, HL-A analysis revealed evidence for close linkage between the C2 defect and the histocompatibility HL-A loci (Fu *et al*. 2004) and C2 polymorphisms with anterior uveitis are observed (Yang *et al*. 2012). Two distinct molecular mechanisms shown to cause C2D were identified (Johnson *et al*. 1992b). Type I C2 deficiency is characterized by a complete loss of the protein (Wang *et al*. 1998; Johnson *et al*. 1992a) while type II C2 deficiency is characterized by a defective C2 secretion (Wetsel *et al*. 1996).

Type I Human Complement C2 Deficiency: In type I C2D, a 28 base pair (bp) deletion (9 bp of the 3′ end of exon 6 and 19 bp of the 5′ end of the adjacent intron) in C2 gene was observed. This deletion promotes skipping of exon 6 during RNA splicing, resulting in generation of a premature termination codon (no C2 protein translation) such that no protein is detected in blood or within cells. Type I C2D is in strong linkage disequilibrium with the MHC haplotype HLA-A25, B18, C2Q0, BfS, C4A4, C4B2, Drw2. This extended haplotype occurs in >90% of C2D individuals (Johnson *et al*. 1992a; Awdeh *et al*. 1981).

Type II Human Complement C2 Deficiency: Type II C2 deficiency may be caused by a defective protein folding due to missense mutations of amino acid residues (Ser189→Phe and Gly444→Arg substitutions) (Wetsel *et al*. 1996) or different, as yet uncharacterized, molecular genetic defect (Johnson *et al*. 1992a). Individuals with type II C2D are rare, representing about 7% of all cases of C2D, and are characterized by a defective C2 secretion, leading to the retention of a full-length C2 polypeptide in the intracellular compartment (Johnson *et al*. 1992b).

MAJOR SITES OF EXPRESSION

C2 is produced by liver hepatocytes, monocytes/macrophages (Lappin *et al*. 1990; Cole *et al*. 1985), fibroblasts, kidney (Song *et al*. 1998) and astrocytes. Incubation of different astrocytic cell lines and primary astrocytes with HIV-1 induced a marked upregulation of the expression of the complement factors C2 and C3 (Speth *et al*. 2001).

SPLICE VARIANTS

Complement C2 gene (with 18 exons) localizes within the major histocompatibility complex (MHC) class III region on the short arm of chromosome 6 (6p21.33)(Bentley *et al*. 1984; Dunham *et al*. 1987; Raum *et al*. 1979). 6p21 also includes the complement factor B (CFB) region (Bentley 1986). CFB and C2 loci are close to each other (such that no recombination was observed) and the 2 loci are 3 to 5 centimorgans from the HLA-A and HLA-B loci on chromosome 6p (Raum *et al*. 1976). Previous studies have demonstrated the presence of at least six C2 mRNA species in liver and a variety of cell lines (Cheng and Volanakis 1994), which are apparently derived through differential splicing of pre-mRNA from the single C2 gene.

REGULATION OF CONCENTRATION

C2 is a single chain glycoprotein present in normal human serum at a concentration of 30 µg/ml (Glovsky *et al*. 2004). C2 deficiency, the most common complement deficiency, is associated with systemic lupus erythematosus (SLE, see Phenotypes section). In one study, the serum concentration of C2 was 37.8 +/- 5.0 (s.d) µg/ml in healthy controls (n = 133) and in patients with SLE, the values were below normal (Ueda *et al*. 1983). In another study, the normal range of C2 concentration was 11–35 µg/ml in 32 healthy individuals (Oglesby *et al*. 1988).

ANTIBODIES

Antibodies are available from Thermo Fisher Scientific Inc. (based on the PA5-21659 immunogen, is a recombinant fragment corresponding to a region within amino acids 265 and 642 of C2), Sino Biological Inc. and Abcam (immunogen is based on amino acids 180-229 of human C2).

Table 1: Functional States

STATE DESCRIPTION	LOCATION	REFERENCES
C2	extracellular space	Bentley DR and Porter RR 1984; Horiuchi T *et al.* 1989
C2/Heparin	extracellular region	Sahu A and Pangburn MK 1993
C2/C4b	extracellular region	Wallis R *et al.* 2007
C2a/TORE (Schistosoma)	extracellular region	Inal JM and Sim RB 2000; Inal JM *et al.* 1999
C4b2a (Classical/Lectin, C3 Convertase)	extracellular region	Kerr MA *et al.* 1980; Kondo M *et al.* 1972
C4b2a3b (Classical C5 convertase)	extrinsic to membrane	Pangburn MK and Rawal N 2002; Rawal N and Pangburn MK 2003; Kozono H *et al.* 1990
C2b	extracellular region	Krishnan V *et al.* 2009
C4b2a/SCIN (S. aureus)	extracellular region	Rooijakkers SH *et al.* 2005

ACKNOWLEDGEMENTS

The UCSD Signaling Gateway Molecule Pages (SGMP) is funded by NIH/NIGMS Grant 1 R01 GM078005-01. J. Inal was supported internally by the School of Human Sciences and by the NHS (Queen's Hospital, Essex). The authors thank Dr. John D. Lambris, University of Pennsylvania School of Medicine, Philadelphia, UCSD-SGMP editorial board member, for extensive discussions.

SUPPLEMENTARY

Supplementary information is available online.

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This molecule exists in 8 states , has 10 transitions between these states and has 2 enzyme functions.(Please zoom in the pdf file to view details.)