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 a 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 (C3bbBb) 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 (C1rq2s2) (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. C2s 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 I 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
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).

(442x812)
| 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      | extracellular region| Kerr MA et al. 1980; Kondo M et al. 1972                                 |
| Convertase)                      |                     |                                                                           |
| 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.)