UCSD MOLECULE PAGES

doi:10.6072/H0.MP.A004235.01
Volume 1, Issue 2, 2012

Review Article Open Access

Complement C3

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Complement C3 is the central component of the human complement system. It is ~186 kDa in size, consisting of an α-chain (~110 kDa) and a β-chain (~75 kDa) that are connected by cysteine bridges. C3 in its native form is inactive. Cleavage of C3 into C3b (~177 kDa) and C3a (~9 kDa) is a crucial step in the complement activation cascade, which can be initiated by one or more of the three distinct pathways, called alternative, classical and lectin complement pathways. In the alternative pathway, hydrated C3 ($C3_{(H20)}$) recruits complement factor B (fB), which is then cleaved by complement factor D (fD) to result in formation of the minor form of C3-convertase ($C3_{(H20)}$Bb) that cleaves C3 into C3a and C3b. A small percent of the resulting C3b is rapidly deposited (opsonization through covalent bond) in the immediate vicinity of the site of activation (e.g. pathogen surface) and now forms the major form of C3-convertase (C3bBb), thereby creating an efficient cycle of C3 cleavage. Properdin, a positive regulator of the alternative pathway convertases, provides a hub for the assembly of C3bBb in addition to stabilization of the convertase. Classical and lectin pathways, when activated with recognition of pathogens or immune complexes use another C3-convertase (C4b2a) to cleave C3 into C3a and C3b. Although the three pathways are activated independently, they converge at C3 and use C3 as a substrate for their pathway specific C3-convertase: $C3_{(H20)}$Bb, C3bBb or C4b2a. Further, C3b undergoes successive proteolytic cleavages by the regulatory complement factor I (fI) in presence of cofactors and lead to generation of iC3b (~174 kDa), C3d/C3dg (~33 kDa), C3c (~142 kDa) and C3f (~2 kDa). C3a is an anaphylatoxin while C3b is involved in opsonization of pathogens or apoptotic cells. Covalently bound C3b on pathogen/apoptotic cell surface is recognized by host immune cells through phagocytic (or complement component) receptors and induce subsequent immune response or directly target pathogen for clearance. The C3a fragment functions as a chemokine, and thereby recruits phagocytic and granulocytic cells to the sites of inflammation and cause strong pro-inflammatory signaling through their G-protein coupled receptors (GPCRs). As pathogen or apoptotic cell surface bound C3-convertases (C3bBb or C4b2a) can induce the amplification of the alternative pathway, this pathway might contribute to the major part of the complement activation process, even when initially triggered by the classical pathway and/or lectin pathway. 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-convertases, $C3_{(H20)}$Bb3b, C3bBb3b and C4b2a3b). C5-convertase activates C5, which by series of additional steps, promotes killing of target cell (pathogen) by pore formation.

KEYWORDS
Acylation-stimulating protein cleavage product; AHUS5; ARMD9; ASP; C3; C3 and PZP-like alpha-2-macroglobulin domain-containing protein 1; Complement C3; Complement component 3; Complement component C3; CPAMD1

IDENTIFIERS
Molecule Page ID:A004235, Species:Human, NCBI Gene ID: 718, Protein Accession:NP_000055.2, Gene Symbol:C3

PROTEIN FUNCTION
The central component of the complement system is C3 molecule, consisting of a β-chain and an α-chain connected by cysteine bridges. Cleavage of C3 into C3b and C3a is a pivotal step in the complement activation cascade, which can be initiated by three distinct pathways — the classical (CP), the lectin (LP) and the alternative (AP) pathway. The AP is antibody independent and relies on native C3 undergoing minimal spontaneous hydrolysis of thioester bond, represented by $C3_{(H20)}$. Complement factor B (fB), when bound to $C3_{(H20)}$, is cleaved by complement factor D (fD) into Ba and Bb. $C3_{(H20)}$Bb, a fluid phase C3-convertase, is responsible for a constant low level of C3 cleavage into C3a and C3b (tick-over) (Nilsson *et al*. 2012). C3b can bind covalently, via its reactive thioester, to cell surface carbohydrates or immune aggregates (opsonization). When C3b binds to an appropriate surface then fB associates with C3b and is cleaved by fD to form C3bBb, which is a highly efficient C3-convertase. Classical and lectin complement pathways use complement components C4 and C2 for C3-convertase of form C4b2a (Müller-Eberhard *et al*. 1967). Upon binding to pathogen or apoptotic cell surface, C3-convertases (C3bBb and C4b2a) can induce amplification of the alternative pathway. Thus, the AP might account for up to 80-90% of total complement activation, even when initially triggered by the classical or lectin pathway (Harboe and Mollnes 2008). The prolonged activation of complement pathways results in addition of one more molecule of C3b to C3 convertases to form C5 convertases: $C3_{(H20)}$Bb3b, C3bBb3b and C4b2a3b (Rawal and Pangburn 2001; Rawal and Pangburn 2003). C3-convertases selectively cleave C3 at Arg-/-Ser bond in C3α-chain to form C3a and the α-chain portion of C3b (Nagasawa *et al*. 1985). Further, C3b undergoes successive proteolytic cleavages leading to inactive C3 products. These steps are mediated by complement factor I (fI) and lead to generation of iC3b, C3d/C3dg, C3c and C3f. Functions of C3 and each of its cleavage products are listed below:

C3a, an anaphylatoxin, binds to its receptor C3aR to mediate local inflammatory process (Hartmann *et al*. 1997; Bokisch *et al*. 1969). It thereby induces the contraction of smooth muscle, increases vascular permeability and causes histamine release from mast cells and basophilic leukocytes. C3a also suppresses B cell polyclonal responses by binding to C3aR (Fischer and Hugli 1997). C3a (and C5a) induce expression of vascular endothelial growth factor (VEGF) which is required for angiogenesis and tissue repair after injury (Nozaki *et al*. 2006). C3a and its desarginated (desArg) product $C3a^{desArg}$ are potent enhancers of C-X-C motif ligand-12 (CXCL12)-induced

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Published online: 5 Oct 2012 | doi:10.6072/H0.MP.A004235.01

chemotaxis of human hematopoietic stem/progenitors (HSPCs) and B lineage cells. The potentiating effect of C3a on CXCL12 is independent of the classical C3a receptor (C3aR) (Honczarenko *et al*. 2005).

$C3_{(H20)}$ is conformationally different from C3, and in fact similar to C3b because of which, $C3_{(H20)}Bb$ has similar catalytic specificity as C3bBb but the kinetics are different. The hydrolyzed form may produce a more open structure in the C3d region (Winters *et al*. 2005). The convertase activity of C3bBb was approximately twice that of $C3_{H2O}Bb$, as observed by the generation of C3a (Pangburn *et al*. 1986). C3b as detailed above, functions both as an opsonin and as an integral part of C3 and C5 convertases. iC3b is formed by the release of C3f fragment from C3b. This degradation is aided by fI and its cofactors (Alcorlo *et al*. 2011; Becherer and Lambris 1988; Ross *et al*. 1982; Blom *et al*. 2003). iC3b is further degraded slowly (possibly by fI) to form C3c, which is released into solution, and C3dg, which remains bound to the target. Such degradation is thought to play an important role in limiting activation of the pathway.

Overall, C3 functions include opsonization and phagocytosis of pathogens/apoptotic cells, clearance of immune complexes and chemotaxis (mobilization of HSPCs, during infection or injury). All these functions are through the cooperative action of pattern recognition molecules (PRMs), opsonins and receptors (Lutz 2012; Trouw *et al*. 2008). More specific functions upon interaction with other proteins, is detailed in the 'Interactions with Ligands and Other Proteins' section.

REGULATION OF ACTIVITY

In addition to C3-convertases, mannose-binding lectin serine protease 1 (MASP-1) (Matsushita *et al*. 2000; Rossi *et al*. 2001), gingipain proteinase (from *Porphyromonas gingivalis*) (Wingrove *et al*. 1992), fibrin (Amara *et al*. 2008) and coagulation factors IIa (thrombin), IXa, Xa and XIa (Amara et al. 2010; Amara *et al*. 2008), cleave C3 into C3a and C3b. Coagulation factor XIIIa may cross-link C3 to clot components such as fibrin (Nikolajsen *et al*. 2012). Properdin (fP), a positive regulator of alternative pathway convertases, stabilizes C3bfB (as C3bfBfP) and provides a focal point for the formation of C3-convertase, C3bBb (Hourcade 2006; Fearon and Austen 1975). C3b is an opsonin that binds to pathogens or apoptotic cells, and is recognized by receptors present on phagocytes. Complement activation, which has high amplification potential due to action of alternative C3-convertase, is favored on foreign surfaces to result in the quick elimination of pathogens, but is inhibited and controlled tightly on the surface of host cells to prevent self-damage. The complement regulators, involving about a dozen host proteins, are present as soluble factors, cell surface attached fluid phase regulators or as integral membrane proteins to prevent C3b deposition on healthy cells (Zipfel and Skerka 2009). Complement factor I (fI) is a serine protease that inactivates C3b (and C4b) in the presence of cofactors complement factor H (fH), membrane cofactor protein (MCP), C4b-binding protein (C4BP), or complement receptor type 1 (CR1) (Hourcade *et al*. 1989). fH and its splice variant, FHL-1, are crucial regulators of complement activation, both in the fluid phase and on the cell surface. fH mainly regulates alternative pathway (AP) by destabilizing alternative C3 (C3bBb) and C5 (C3bBb3b) convertases, and degrading C3b (and also C4b) (Zipfel *et al*. 1999). MCP (CD46) is a widely expressed, intrinsically acting regulator of the complement system (Seya *et al*. 1986; Oglesby *et al*. 1992). MCP, a cofactor for fI-mediated cleavage of C3b (Oglesby *et al*. 1992), can also act as a cofactor for C4b cleavage. MCP's cofactor activity is sufficient to restrict complement activation in the alternative pathway (Barilla-LaBarca *et al*. 2002). C4BP is a multimeric glycoprotein composed of seven identical α-chains (C4BPα) and a β-chain (C4BPβ) and is an essential cofactor in the proteolysis of C4b, which regulates classical pathway associated C3/C5-convertases (C4b2a and C4b2a3b) (Fujita *et al*. 1978; Barnum 1991). CR1 (CD35) is a monomeric single-pass type I membrane glycoprotein found on erythrocytes, leukocytes, glomerular podocytes, and splenic follicular dendritic cells (Rothman *et al*. 1975; Ahearn and Fearon 1989). CR1, a cofactor for fI, also acts as a decay accelerator by facilitating dissociation (decay acceleration) of C3-convertases (Hourcade *et al*. 1989).

Plasma protease C1 inhibitor (C1INH) or serpin peptidase inhibitor, clade G, member 1 (SERPING-1) is a member of the serine protease inhibitor, which binds to activated sub-components (C1r and C1s) of the C1 complex (C1q-r2s2) and shuts down their proteolytic activity. C1 complex is activated by antigen-antibody complexes, which cleaves C4 and C2 before it is deactivated by C1INH. C1INH also interacts with C3b to inhibit binding of fB to C3b, and is shown to be a down-regulator of the alternative pathway convertase at physiological concentrations (Jiang *et al*. 2001). Complement decay-accelerating factor (DAF, CD55) is a membrane glycoprotein found on various cells such as erythrocytes, platelets, neutrophils, monocytes, B- and T- lymphocytes, and endothelial cells that are in contact with complement. It inhibits the formation of C3-convertases (Kinoshita *et al*. 1986) as well as deactivates C3-convertases by accelerating the spontaneous dissociation (decay acceleration) (Kuttner-Kondo *et al*. 2003; Hourcade *et al*. 1989), in both the classical (C4b2a) and alternative (C3bBb) pathways. V-set and immunoglobulin domain-containing protein 4 (VSIG4) or complement receptor of the immunoglobulin superfamily (CRIg) is a phagocytic receptor expressed exclusively on tissue resident macrophages and binds C3b, iC3b and C3c opsonized pathogens, apoptotic cells or cell remnants (Helmy *et al*. 2006; Weismann *et al*. 2006). It regulates the C3b-containing C3 and C5-convertases. Further, CRIg is a potent inhibitor of the alternative pathway convertases (Weismann *et al*. 2006). Carboxypeptidase-N or Carboxypeptidase-R rapidly converts C3a anaphylatoxin (also C5a) to its desarginated ($C3a^{desArg}$) form. This cleavage impairs signaling through the primary receptors C3aR (C5aR for C5a) and also shifts the signaling pattern. The C3a/C5a desArg forms can trigger important functions such as HSPC mobilization (Ratajczak *et al*. 2006; Jalili *et al*. 2010) and lipid metabolism (Amara *et al*. 2008).

Many pathogens (bacteria, viruses, fungi and parasites) have been shown to counter the complement attack at the level of C3, by protease mediated inactivation/depletion of complement components, recruitment of complement regulators to the pathogen surface or secretion of regulator mimics and molecular inhibition of convertase activity (Lambris *et al*. 2008; Kraiczy and Würzner 2006). For example, Staphylococcal superantigen-like (SSL5) binds to C3aR and inhibits neutrophil stimulation induced by C3a anaphylatoxin (Bestebroer *et al*. 2009). Leishmanial protein kinase 1 (LPK-1) phosphorylates components of the complement system, including C3. This phosphorylation renders C3 resistant to cleavage by C3-convertase (Hermoso *et al*. 1991). Some pathogens take advantage of the complement system to enter cells by binding

cell-bound complement receptors and regulators, either through pathogen-expressed surface proteins or by 'voluntary opsonization' with complement fragments (Olivia *et al*. 2009; Wang *et al*. 2007; Ricklin *et al*. 2010). See 'Interactions with Ligands and Other Proteins' section for more details.

INTERACTIONS

C3, $C3_{(H20)}$ and their degradation products bind to a variety of host and pathogen proteins or ligands.

Host factors: C3 directly binds to immunoglobulin M (IgM) (Zhou *et al*. 2004) and to low-density lipoprotein-receptor-related protein 1/α2-macroglobulin receptor (LRP-1/α2MR), a receptor protein responsible for the clearance of α2-macroglobulin-protease complexes (Meilinger *et al*. 1999). Compstatin is a 13-residue synthetic peptide that binds to C3, its fragments C3b and C3c, and inhibits activation of the complement system (Sahu *et al*. 1996; Magotti *et al*. 2009). $C3_{H2O}$ was found to bind efficiently to solid-phase laminin (a basement membrane protein) while native C3 from fresh plasma did not bind to laminin (Leivo and Engvall 1986). Likewise C3b and C3d, but not C3c, bind via laminin to basement membranes of glomerulus and trophoblast (Leivo and Engvall 1986).

Anaphylotoxin C3a binds to C3a receptor(C3aR) which is expressed on neutrophils and monocytes (Martin *et al*. 1997). C3a has a moderate affinity for C5a anaphylatoxin chemotactic receptor, C5L2 (GPR77). However, this interaction may not contribute significantly to C3a's function as an anaphylotoxin, as cross-competition studies suggest that C3a binds to a distinct site from C5a and further, C3a binding to C5L2 may induce anti-inflammatory signaling in lipopolysaccharide (LPS) induced sepsis (Klos *et al*. 2009; Hajishengallis and Lambris 2010). C3a-CXCL12 interaction is independent of C3aR, which may provide a mechanism to modulate the function of CXCL12 in the bone marrow (BM) microenvironment (Honczarenko *et al*. 2005). C3a-mediated enhancement of CXCL12-induced chemotaxis of hemopoietic cells is also achieved by $C3a^{desArg}$-CXCL12 (Honczarenko *et al*. 2005).

C3b, by its reactive thioester moiety, covalently attaches with amino or hydroxyl groups on the target surface, before degradation to iC3b and C3c. The reactivity of the thioester moiety to specific carbohydrates might lead to preferential opsonization of foreign particles and represent a basic pattern recognition mechanism (Pangburn *et al*. 2008; Sahu *et al*. 1994). Properdin (fP) forms complexes with C3b, as C3bfP and C3bfBfP, and stabilizes and provides a focal point for the assembly of C3bBb, a C3 convertase (Hourcade 2006; Fearon and Austen 1975). C3b interacts with C3 convertases of both alternative and classical pathway (C3bBb and C4b2a respectively) to form efficient C5 convertases: C3bBb3b, C4b2a3b (Rawal and Panburn 2001; Rawal and Panburn 2003; Rawal *et al*. 2008). C3b opsonization is quickly amplified on foreign cells but is instantly regulated on host cells by interaction with complement receptor type 1 (CR1), membrane cofactor protein (MCP), complement factor B (fB), complement factor H (fH), and complement decay-accelerating factor (DAF) (Farries *et al*. 1990; Harris *et al*. 2005; Kinoshita *et al*. 1986). The presence of multiple binding sites on fH for C3 suggests a multi-point interaction between fH and C3b (Jokiranta *et al*. 2000; Sharma and Pangburn 1996). The bound fH sterically interferes with fB or Bb binding site and provides a binding site for complement factor I (fI), which cleaves C3b (fH dependent cleavage of C3b by fI) (Farries *et al*. 1990; Jokiranta *et al*. 2000; Wu *et al*. 2009). fH also binds to C3d (Lambris *et al*. 1988). Like fH, complement factor H-related 1 (CFHR-1), CFHR-3, CFHR-4 and CFHR-5, can bind to C3b/C3d and host cells (Heinen *et al*. 2009; Hellwage *et al*. 1999; McRae *et al*. 2001). CR1 binds to C3b, iC3b, and C3c but not to C3d (Becherer and Lambris 1988).

iC3b binds to the apolipoprotein A-I (APOA-1) portion of lipoprotein-a. The sialic acid residues on APOA-1 are necessary for the APOA1-iC3b interaction (Seifert *et al*. 1992). iC3b also interacts with CR1 (Gordon *et al*. 1987), CR2 (Ross *et al*. 1983), CR3 (Gordon *et al*. 1987; Lecoanet-Henchoz *et al*. 1995), CR4 (Lecoanet-Henchoz *et al*. 1995; Shelly *et al*. 2002) and CRIg (Helmy *et al*. 2006) receptors. While interaction of iC3b with CR1 and CRIg leads to further degradation (Hourcade, *et al*. 1989; Wiesmann *et al*. 2006), binding to CR3 and probably to CR4 receptors expressed on monocyte-derived dendritic cells leads to significantly enhanced T-cell proliferation (Török *et al*. 2012). C3c and C3dg are cleavage products of iC3b by fI/CR1 (Ross *et al*. 1982) or plasmin (Lachmann *et al*. 1982). Human plasma fibronectin interacts with native C3 of human sera and with isolated C3c and C3d fragments of C3 (Hautanen and Keski-Oja 1983). Low levels of C3dg are observed in normal human plasma, and higher levels are seen in disorders associated with increased complement consumption (Nydegger *et al*. 1977). On B cells, binding of C3d or C3dg to the CR2 (CD21) promotes interaction with CD19 to form a tripartite complex, which plays a role in innate immune recognition of microbial antigens by the complement system and B-cell maturation (Carroll 2008; Fearon and Carroll 2000). Other interactions of C3 with host proteins include myeloperoxidase (MPO) (Segelmark *et al*. 1997) and RAD1, a subunit of the cohesin complex (Panigrahi *et al*. 2012). However, the physiological significance of these interactions is yet to be determined.

Pathogenic factors: Vaccinia complement control protein (VCP) binds to C3b to inhibit both the classical and alternative pathways of complement activation (Sahu *et al*. 1998; Smith *et al*. 2003; McKenzie *et al*. 1992; Rosengard *et al*. 1999). SPICE (a variola virus complement regulator) has been shown to be much more potent in inactivating human complement than the VCP, although they differ only in 11 amino acid residues. SPICE was the most potent regulator of human complement and attached to cells *via* glycosaminoglycans (Liszewski *et al*. 2009; Yadav *et al*. 2008; Rosengard *et al*. 2002). C3b can also interact with Kaposica, encoded within the viral genome of *Kaposi's sarcoma-associated human herpesvirus* (KSHV) and complement control protein homolog (CCPH) of *Herpesvirus saimiri* (HVS), both of which are potent regulators of the complement system (Mullick *et al*. 2003; Mark *et al*. 2004; Singh *et al*. 2006).

Staphylococcus aureus has developed a sophisticated and effective complement evasion approach with potent inhibitory proteins. fH binds to Sbi (*Staphylococcus aureus* binder of IgG) in combination with C3b (or C3d), and forms the tripartite Sbi:C3b:fH complex. The type of C3 fragment influences the stability of the complex. Surface plasmon resonance studies revealed a higher stability of C3d in complex with Sbi, as compared to C3b. Sbi, by recruiting fH and C3b, acts as a potent complement inhibitor, and inhibits alternative pathway (Haupt *et al*. 2008). Extracellular fibrinogen-binding protein (Efb or fib), also a staphylococcal protein, forms a specific

high-affinity complex with the C3d domain of C3 (Hammel *et al*. 2007b; Lee *et al*. 2004a; Lee *et al*. 2004b), iC3b (Lee *et al*. 2004b) and C3d (Haspel *et al*. 2008), and inhibits complement activation and blocks opsonophagocytosis. Efb homologous protein (Ehp) potently inhibits C3b deposition onto alerted surfaces by the alternative complement activation pathway. This inhibition was directly related to Ehp/C3d binding and was more potent than that seen for Efb (Hammel *et al*. 2007a). Ehp binds specifically to all C3 fragments that include the thioester-containing C3d domain, such as native C3, $C3_{H2O}$, C3b, C3dg, and C3d (Hammel *et al*. 2007a; Ricklin *et al*. 2008). Staphylococcal complement inhibitor (SCIN) binds and stabilizes C3 convertases, interfering with additional C3b deposition through the classical, lectin and alternative complement pathways. This led to a substantial decrease in phagocytosis and killing of *Staphylococcus aureus* by human neutrophils (Rooijakkers *et al*. 2005; Ricklin *et al*. 2009; Garcia *et al*. 2009; Garcia *et al*. 2010). SCIN reduces the efficiency of fI and fH mediated degradation of C3b to iC3b by directly interacting with C3b. SCIN also shown to interacts C3c (Garcia *et al*. 2010).

C3 interacts with choline binding protein A (CbpA) of *Streptococcus pneumoniae* (Smith and Hostetter 2000; Rosenow *et al*. 1997; Cheng *et al*. 2000). HbhA of *Mycobacterium tuberculosis* is a multifunctional binding protein, binding to both sulfated sugars such as heparin and to C3. HbhA may therefore interact with host molecules and/or host cells during *M. tuberculosis* infection and play a role in the pathogenesis of this bacterium. Another *M. tuberculosis* C3-binding protein, similar in size to HbhA was identified as HupB, but the role of HupB as a C3-binding protein in intact organisms remains to be determined (Mueller-Ortiz *et al*. 2002). C3b and iC3b interact with specific sites in HIV-gp120 and HIV-gp41, the envelope proteins of *Human immunodeficiency virus* (HIV-1) (Süsal *et al*. 1996; Stoiber *et al*. 1995; Sadlon *et al*. 1994). Glycoprotein C (gC) of both *Herpes simplex virus* type 1 (HSV-1) and HSV-2 interacts with complement C3, C3b and C3c and protects the virus from complement-mediated neutralization (Kostavasili *et al*. 1997).

PHENOTYPES

Hereditary complement C3 deficiency (C3D) is a rare defect of the complement pathways. Patients develop recurrent, severe, pyogenic infections because of ineffective opsonization of pathogens (Reis *et al*. 2006; Singer *et al*. 1994; Santos-Valente *et al*. 2012). C3 deficiency is associated with impaired chemotactic activity, slow response of neutrophils to infectious agents, development of immune complex disease, systemic lupus erythematosus, and membrane proliferative glomerulonephritis. Further, C3 deficiency can also influence antibody and T cell responses. Genetic variation in C3 is associated with susceptibility to age-related macular degeneration and susceptibility to atypical hemolytic uremic syndrome (aHUS) (Roumenina *et al*. 2012; Maga *et al*. 2010; Frémeaux-Bacchi *et al*. 2008). C3 has also been described as a marker of pathological conditions such as insulin resistance in an elderly population (Muscari *et al*. 2007), metabolic risk syndrome (Philips *et al*. 2012), renal arteriolosclerosis (Kojima *et al*. 2012) and heart transplant induced infection (Sarmiento *et al*. 2012). C3b in complex with cartilage oligomeric matrix protein (COMP) is found in elavated levels in serum of rheumatoid arthritis patients (Happonen *et al*. 2012). C3f has been recently described as a blood based bio-marker for detection of autism spectrum disorders (Momeni *et al*. 2012).

C3a (and also C5a) increases the activity of several mitogenic signaling pathways, such as Erk1/2 (Schraufstatter *et al*. 2002; Monsinjon *et al*. 2003), Akt (Venkatesha *et al*. 2005) and PI3-K (Venkatesha *et al*. 2005). On the other hand, cancer cells evade complement-mediated lysis by expressing membrane cofactor protein (MCP), decay-accelerating factor (DAF) and complement receptor type 1 (CR1), all of which facilitate inactivation of the C3-convertase (Fishelson *et al*. 2003).

MAJOR SITES OF EXPRESSION

Liver is the main source for C3 production. Although 90% of C3 synthesis is in the liver, its synthesis in monocytes, astrocytes, B lymphocytes and several tumor cell lines of different origins has been described. C3 levels in adipocytes substantially increases after exposure to insulin or dietary lipid. HIV-1 induces the upregulation of C3 in astrocytes and neurons through signaling pathways that involve protein kinase C and adenylate cyclase activation, which is an effect that may contribute to the pathogenesis of acquired immunodeficiency syndrome (AIDS) in the brain (Speth *et al*. 2002). Local production of inflammatory mediators could induce C3 synthesis in the kidney (Welch *et al*. 1993). This is further supported by data showing expression in renal tubular epithelial cells (Oren *et al*. 1995; Sacks *et al*. 1993b) and in the glomerular mesangial cells (Sacks *et al*. 1993a).

SPLICE VARIANTS

There are no known splice variants.

REGULATION OF CONCENTRATION

C3 is the most abundant protein of the complement system with a concentration of ~1.3 mg/ml in plasma. C3c is present in the range of 2.12 - 4.92 µg/ml in the plasma, with a mean of 3.47 µg/ml (Palarasah *et al*. 2010). A low level of C3dg is observed in normal human plasma, and higher levels are seen in disorders associated with increased complement consumption (Nydegger *et al*. 1977). During pregnancy, C3dg exists as a complex with angiotensin (AGT) and the proform of proteoglycan 2 (PRG2). Further, C3 expression is regulated by interferon (IFN; Hill *et al*. 1993; van den Dobbelsteen *et al*. 1994), interleukin-1 (IL-1; van den Dobbelsteen *et al*. 1994), tumor necrosis factor (TNF; Hoie *et al*. 2004), estrogen (in uterus; Sundstrom *et al*. 1989) and Vitamin D (in osteoblasts; Hong*et al*. 1991).

ANTIBODIES

Antibodies that selectively recognize C3b were developed (Katschke *et al*. 2009). Hycult Biotech provides monoclonal antibodies against human C3/C3b, C3/C3a, C3a/C3a des-Arg, C3/C3a (C-terminus) and activated C3, C3d. Quidel Corporation provides monoclonal antibody to an epitope in the C3d domain of C3. Others include, Acris Antibodies GmbH (C3b), Abnova Taiwan Corp (C3), Scipac Ltd. (C3), Novus Biologicals, Abcam, Complement Technology (C3 and C3a) and Abbiotec.

Table 1: Functional States

STATE DESCRIPTION	LOCATION	REFERENCES
C3	extracellular region	Carroll MC *et al.* 2004; Janssen BJ *et al.* 2005; Lambris JD *et al.* 1988; Leivo I and Engvall E 1986; Walport MJ *et al.* 2001; Walport MJ *et al.* 2001
C3-P	extracellular region	Ekdahl KN and Nilsson B 1999; Ekdahl KN and Nilsson B 1995; Forsberg PO *et al.* 1990; Nilsson Ekdahl K and Nilsson B 1997
C3-S71	extracellular region	Hermoso T *et al.* 1991
C3-DSC	extracellular region	Nikolajsen CL *et al.* 2012
C3 (degradation)	Unknown	Morgan EL *et al.* ; Seya T *et al.* 1985; Thoman ML *et al.* 1984; Wingrove JA *et al.* 1992
C3/Compstatin	Unknown	Janssen BJ *et al.* 2007; Magotti P *et al.* Nov-Dec; Sahu A *et al.* 1996; Soulika AM *et al.* 2006
C3/Fibronectin	extracellular region	Hautanen A and Keski-Oja J 1983
C3/IGHM	plasma membrane	Zhou M *et al.* 2004
C3/LRP1	Unknown	Meilinger M *et al.* 1999
C3/MPO	Unknown	Segelmark M *et al.* 1997
C3/fib (S. aureus)	extracellular region	Hammel M *et al.* 2007
C3/EhP (S. aureus)	extracellular region	Hammel M *et al.* 2007; Ricklin D *et al.* 2008
C3/CbpA (S. pneumoniae)	extracellular region	Rosenow C *et al.* 1997; Cheng Q *et al.* 2000; Smith BL and Hostetter MK 2000
C3/HbhA (M. tuberculosis)	extracellular region	Mueller-Ortiz SL *et al.* 2002
C3/HupB (M. tuberculosis)	extracellular region	Mueller-Ortiz SL *et al.* 2002
C3/HSV-gC (Human herpesvirus)	extracellular region	Kostavasili I *et al.* 1997
C3(H2O)	extracellular region	Pangburn MK and Müller-Eberhard HJ 1980; Winters MS *et al.* 2005
C3(H20)fB	extracellular region	Ricklin D *et al.* 2010; Pangburn MK and Müller-Eberhard HJ 1980
C3(H2O)Bb (C3-Convertase)	extracellular region	Sahu A and Lambris JD 2001; Pangburn MK *et al.* 1981
C3(H20)/Laminin	extracellular region	Leivo I and Engvall E 1986
C3(H20)/fib (S. aureus)	extracellular space	Hammel M *et al.* 2007; Lee LY *et al.* 2004
C3(H2O)/Ehp (S. aureus)	extracellular space	Ricklin D *et al.* 2008; Hammel M *et al.* 2007
C3(H20)/VCP (Vaccinia)	extracellular space	McKenzie R *et al.* 1992; Sahu A *et al.* 1998
C3a	extracellular region	Harrison RA and Lachmann PJ 1980; Hartmann K *et al.* 1997; Huber R *et al.* 1980; Bokisch VA *et al.* 1969
C3a/C3aR	plasma membrane	Martin U *et al.* 1997; Werfel T *et al.* 2000
C3a/C5aR	intrinsic to membrane	Ames RS *et al.* 1996; Gerard NP and Gerard C 1991; Nataf S *et al.* 1999
C3a/C5L2	plasma membrane	Johswich K *et al.* 2006; Kalant D *et al.* 2003; Cain SA and Monk PN 2002; Klos A *et al.* 2009
C3a/CXCL12	extracellular region	Honczarenko M *et al.* 2005
C3adesArg	extracellular region	Bokisch VA *et al.* 1969; Gerard C and Hugli TE 1981
C3adesArg/C5L2	plasma membrane	Johswich K *et al.* 2006; Kalant D *et al.* 2003
C3adesArg/CXCL12	extracellular region	Honczarenko M *et al.* 2005
C3b	extracellular region	Pangburn MK *et al.* 2008; Sahu A *et al.* 1994
C3b/fH	extracellular region	Farries TC *et al.* ; Jokiranta TS *et al.* 2000; DiScipio RG *et al.* 1981; Kühn S *et al.* 1995; Sharma AK and Pangburn MK 1996; Soames CJ and Sim RB 1997; Wu J *et al.* 2009
C3b/MCP	plasma membrane	Cole JL *et al.* 1985; Farries TC *et al.*
C3b/Laminin	basement membrane	Leivo I and Engvall E 1986
C3b/fB (pro-C3-Convertase)	extracellular region	Farries TC *et al.* ; DiScipio RG *et al.* 1981; Forneris F *et al.* 2010; Lambris JD and Müller-Eberhard HJ 1984; Torreira E *et al.* 2009
C3b/fP	extracellular region	DiScipio RG *et al.* 1981; Hourcade DE *et al.* 2006
C3b/fB/fP	extracellular region	Hourcade DE *et al.* 2006
C3bBb (Alternative C3-Convertase)	extracellular region	Pangburn MK and Müller-Eberhard HJ 1986; Ricklin D *et al.* 2012
C3bBb/fP	extracellular space	DiScipio RG *et al.* 1981; Fearon DT and Austen KF 1975; Fearon DT and Austen KF 1975; Hourcade DE *et al.* 2006; Medicus RG *et al.* 1976
C3bBb/SCIN (S. aureus)	extracellular region	Rooijakkers SH *et al.* 2005
C3bBb3b (Alternative C5-Convertase)	extracellular region	Pangburn MK and Rawal N 2002; Rawal N and Pangburn MK 1998
C3bBb3b/fP	extracellular region	
C3b/CR1	plasma membrane	Ahearn JM and Fearon DT ; Arnaout MA *et al.* 1981; Becherer JD and Lambris JD 1988; Dobson NJ *et al.* 1981; Farries TC *et al.* ; Fearon DT *et al.* 1980; Gordon DL *et al.* 1987; Krych M *et al.* 1994; Krych M *et al.* 1991; Ross GD *et al.* 1983; Ross GD and Polley MJ 1975
C3b/CR2	plasma membrane	Ahearn JM and Fearon DT ; Farries TC *et al.*
C3b/DAF	plasma membrane	Kinoshita T *et al.* 1986; Nicholson-Weller A *et al.* 1982

C3b/sbi (S. aureus)	extracellular region	Haupt K *et al.* 2008
C3b/sbi/fH (S. aureus)	extracellular region	Haupt K *et al.* 2008
C3b/fib (S. aureus)	extracellular region	Lee LY *et al.* 2004; Hammel M *et al.* 2007; Lee LY *et al.* 2004
C3b/Ehp (S. aureus)	extracellular region	Hammel M *et al.* 2007
C3b/SCIN (S. aureus)	extracellular region	Garcia BL *et al.* 2010; Garcia BL *et al.* 2012; Garcia BL *et al.* 2009
C3b/Opa (N. gonorrhoeae)	extracellular region	Lewis LA *et al.* 2008
C3b/VCP (Vaccinia)	extracellular region	Bernet J *et al.* 2004; Liszewski MK *et al.* 2009; McKenzie R *et al.* 1992; Mullick J *et al.* 2005; Rosengard AM *et al.* 1999; Sahu A *et al.* 1998; Yadav VN *et al.* 2012
C3b/SPICE (Vaccinia, VCP homolog)	extracellular region	Rosengard AM *et al.* 2002; Sfyroera G *et al.* 2005; Yadav VN *et al.* 2008; Liszewski MK *et al.* 2009
C3b/HSV-gC (Human herpesvirus)	extracellular region	Kostavasili I *et al.* 1997
C3b/HIV-gp120 (HIV)	extracellular region	Sadlon TA *et al.* 1994; Stoiber H *et al.* 1995
C3b/C1INH	extracellular region	Davis AE *et al.* 2008; Jiang H *et al.* 2001
C3b/Compstatin	Unknown	Magotti P *et al.* Nov-Dec; Sahu A *et al.* 1996; Sahu A *et al.* 2000
C3b/C4b	extracellular region	Kim YU *et al.* 1992; Lambris JD *et al.* 1988
C3b/CRIg	plasma membrane	Helmy KY *et al.* 2006; Wiesmann C *et al.* 2006
C3b/CFHR1	extracellular space	Gordon DL *et al.* 1995; Kühn S *et al.* 1995
C3b/CFHR3	extracellular region	Hellwage J *et al.* 1999
C3b/CFHR4	extracellular region	Hellwage J *et al.* 1999
C3b/CFHR5	extracellular region	McRae JL *et al.* 2001
C3b/fH/C3b	extracellular region	Jokiranta TS *et al.* 2000
C3b/C5	extrinsic to plasma membrane	Jokiranta TS *et al.* 2001; Vogt W *et al.* 1978
C4b2a3b (Classical C5-Convertase)	extracellular region	Kozono H *et al.* 1990
iC3b	extracellular region	Alcorlo M *et al.* 2011; Becherer JD and Lambris JD 1988
iC3b/APOA1	extracellular region	Seifert PS *et al.* 1992
iC3b/CR1	plasma membrane	Gordon DL *et al.* 1987
iC3b/CR2	plasma membrane	Ross GD *et al.* 1983
iC3b/αMβ2	plasma membrane	Gordon DL *et al.* 1987; Micklem KJ and Sim RB 1985; Taniguchi-Sidle A and Isenman DE 1994
iC3b/αXβ2	plasma membrane	Lecoanet-Henchoz S *et al.* 1995; Shelley CS *et al.* 2002
iC3b/CRIg	plasma membrane	Helmy KY *et al.* 2006; Roozendaal R and Carroll MC 2006
iC3b/fib (S.aureus)	extracellular region	Lee LY *et al.* 2004
iC3b/Ehp (S.aureus)	extracellular region	Hammel M *et al.* 2007
iC3b/SCIN (S. aureus)	extracellular region	Ricklin D *et al.* 2009
iC3b/HIV-gp120 (HIV)	extracellular region	Sadlon TA *et al.* 1994
C3c	extracellular region	Harrison RA and Lachmann PJ 1980
C3c/Fibronectin	extracellular region	Hautanen A and Keski-Oja J 1983
C3c/Compstatin	Unknown	Magotti P *et al.* Nov-Dec; Sahu A *et al.* 2000
C3c/CR1	plasma membrane	Becherer JD and Lambris JD 1988; Ross GD *et al.* 1983
C3c/CRIg	plasma membrane	Wiesmann C *et al.* 2006
C3c/HSV-gC (Human herpesvirus)	extracellular region	Kostavasili I *et al.* 1997
C3c/SCIN (S. aureus)	extracellular region	Garcia BL *et al.* 2010
C3d	extracellular region	Harrison RA and Lachmann PJ 1980; Gilbert HE *et al.* 2005; Nagar B *et al.* 1998
C3d/fH	extracellular space	Lambris JD *et al.* 1988; Wu J *et al.* 2009
C3d/Fibronectin	extracellular space	Hautanen A and Keski-Oja J 1983
C3d/MPO	Unknown	Segelmark M *et al.* 1997
C3d/CFHR1	extracellular region	Lesher A and Song WC 2009; Heinen S *et al.* 2009
C3d/Laminin	basement membrane	Leivo I and Engvall E 1986
C3d/(CR2-CD19)	plasma membrane	Dempsey PW *et al.* 1996; Fearon DT and Carroll MC
C3d/CR2	plasma membrane	Ross GD *et al.* 1983; Szakonyi G *et al.* 2001; van den Elsen JM and Isenman DE 2011
C3d/Ehp (S. aureus)	extracellular space	Hammel M *et al.* 2007; Ricklin D *et al.* 2008
C3d/sbi/fH (S. aureus)	extracellular space	Haupt K *et al.* 2008
C3d/fib (S. aureus)	extracellular space	Chen H *et al.* 2008; Hammel M *et al.* 2007; Haspel N *et al.* 2008; Lee LY *et al.* 2004
C3d/sbi (S. aureus)	extracellular space	Haupt K *et al.* 2008
C3dg	extracellular region	Harrison RA and Lachmann PJ 1980; Nydegger UE *et al.* 1977
C3dg/CR2	plasma membrane	Carroll MC *et al.* 2008; Fearon DT and Carroll MC
C3f	extracellular region	Ganu VS *et al.* 1989; Soames CJ and Sim RB 1997

C3g	extracellular region	Lachmann PJ *et al.* 1982; Chaplin H *et al.* 1983; Mollnes TE and Lachmann PJ 1987

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 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 101 states , has 131 transitions between these states and has 4 enzyme functions.(Please zoom in the pdf file to view details.)