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Complement C5

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Complement C5 is a 189 kDa protein synthesized in liver as a single-chain precursor molecule. The precursor molecule is then cleaved to a disulfide linked two-chain glycoprotein consisting of a 115 kDa (C5α) and a 75 kDa N-terminal (C5β) chain. C5 is present in all the three known complement activation pathways: classical, alternative and lectin. C5α chain is cleaved by C5 convertases, which are formed during the complement activation process, to form C5a (74 a.a long) and C5α' chain (925 a.a long). C5α' chain and C5β chain (655 a.a. long) together form C5b. C5a is a major anaphylotoxin involved in chemotaxis of neutrophils and release of pro-inflammatory cytokines. These functions of C5a require binding to its receptor, C5aR. C5b sequentially recruits C6, C7, C8 and C9 in a non-enzymatic manner to form the terminal complement complex (TCC, also called membrane attack complex or MAC). TCC forms a lytic pore in the target membrane and kills the pathogen. While the functions of C5a and C5b aid in killing the pathogen, they can also be responsible for generating an excess inflammatory response, which can damage host cells. Therefore, C5 functions are tightly regulated by interaction with other proteins in host. The regulatory proteins can either be host generated or pathogenic factors. Unregulated C5 function can result in disease phenotypes. Therapeutic antibodies against C5 are being developed with a view to treat these conditions.

KEYWORDS
Anaphylatoxin C5a analog; C3 and PZP-like alpha-2-macroglobulin domain-containing protein 4; C5; Complement C5; Complement component 5; CPAMD4

IDENTIFIERS
Molecule Page ID:A004240, Species:Human, NCBI Gene ID: 727, Protein Accession:NP_001726.2, Gene Symbol:C5

PROTEIN FUNCTION
C5, a serum protein, is inactive in its native form. It is cleaved by different C5 convertases, formed during complement activation, into its active forms, C5a and C5b (see 'Regulation of Activity' section). The cleaved products of C5 and its various functions are detailed below:

Anaphylotoxin: C5a, derived from the C5α chain, is a small serum peptide and acts as an anaphylotoxin (Guo and Ward 2005) by binding to its receptor C5aR, present on a variety of leukocytes. Anaphylotoxin response involves recruitment of polymorphonuclear neutrophils (PMNs) and macrophages to the site of inflammation (Chenoweth and Hugli 1978; Fernandez *et al*. 1978; Nilsson *et al*. 1996; Ottonello *et al*. 1999). Neutrophil recruitment is followed by lipid mediator leukotriene C4 (LTC4) generation, and release of cytokines such as interleukin (IL)-17, IL-4 and IL-13 (Bosmann *et al*. 2011; Eglite *et al*. 2000). Infection with *Candida albicans* led peripheral blood mononuclear cells (PBMC) to generate C5a induced IL-6 and IL-1β (Cheng *et al*. 2012). C5a, again *via* binding to C5aR, promotes coagulation by inducing expression of tissue factor (TF) (Ritis *et al*. 2006) and plasminogen activator inhibitor 1 (PAI-1) (Wojta *et al*. 2002). Further, C5a can also initiate pro-survival signaling events (Buhl *et al*. 1995) (see 'phenotypes' section), which delay apoptosis of neutrophils during sepsis. Pro-survival signaling events mediated by C5a-C5aR have also been shown during neutrophil activation and recruitment (involving p38-MAPK, Erk and PI3K pathways) (Hao *et al*. 2012) and activation (as well as functional modulation) of monocyte-derived dendritic cells (Li *et al*. 2012). In contrast, C5a promotes apoptosis in lymphocytes, leading to immune suppression (Huber-Lang *et al*. 2012). C5a can also bind to a decoy receptor such as C5L2 (Okinaga *et al*. 2003) (see 'Interaction with ligands and other proteins' section).

C5a is cleaved at its carboxy terminal end by carboxypeptidase R (activated form is known as carboxypeptidase B2) (Campbell *et al*. 2001), which removes the arginine residue from C5a, to form $C5a^{desArg}$. Carboxypeptidase N (CPN) can also generate $C5a^{desArg}$, however in much lower amounts (Campbell *et al*. 2001). $C5a^{desArg}$ does bind to C5aR, but it is less potent than C5a in generating an inflammatory response. Specifically, it has been shown that $C5a^{desArg}$ cannot generate lipid mediator LTC4 (Eglite *et al*. 2000).

Terminal Complement Complex: C5b is the initiator protein of the terminal complement complex (TCC, also known as membrane attack complex), which ultimately forms lytic pores in the membrane of the pathogen, resulting in lysis and cell death. Though C5b is a serum protein, it is found deposited on the cell surface of pathogens. During complement activation C5b interacts with complement C6, C7, C8 and C9 in a sequential and non-catalyzed manner to result in the formation of TCC (see 'Interaction with ligands and other proteins' for more details). C5b-C6 complex is found in the serum (Yamamoto and Gewurz 1978). Binding of C7 to the C5b-C6 complex results in loose attachment to the target membrane, and subsequent addition of C8 and C9 firmly integrates the complex in the membrane and forms a pore (TCC) (Podack *et al*. 1978; Stewart *et al*. 1987; DiScipio 1992). TCC in sub-optimal concentrations promotes cell cycle (Badea *et al*. 2002) and in optimal amounts is responsible for lysis of the pathogenic cell by leakage of cell contents. C5b also has the ability to interact with other host and pathogenic factors to limit the formation of TCC.

REGULATION OF ACTIVITY
Activity of C5 is regulated at various levels both in a positive and negative manner. Each of the modes of regulation is discussed below.

Conversion of C5 to C5a and C5b: Conversion of native C5 to

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active products, C5a and C5b, is the last enzymatic step of the complement activation cascade. This conversion is catalyzed by the host enzyme complexes such as classical pathway C5 convertase (C4b2a3b) (Kozono *et al*. 1990; Pangburn and Rawal 2002; Rawal and Pangburn 2003) and alternative pathway C5 convertase (C3bBb3b). Bb is a cleaved product of complement factor B and addition of C3b (a complement C3 proteolytic fragment generated by the action of C3 convertase) to C3bBb (C3 convertase) results in C5 convertase with a high affinity for C5 as a substrate (Rawal and Pangburn 1998; Pangburn and Rawal 2002; Rawal *et al*. 2008). C5 convertases are generally formed when high quantity of C3b is available (after amplification of C3b generation). Coagulation factors such as thrombin (IIa), plasmin (from plasminogen), IXa, Xa, XIa and XIIa have been shown to cleave C5 into C5a, demonstrating a close nexus between the complement and coagulation system (Huber-Lang *et al*. 2006; Amara *et al*. 2010; Amara *et al*. 2008). In a recent study, thrombin has been shown to cleave C5 at a site other than C5 convertase to result in a C5b-like product ($C5b_T$), which can form effective TCC (Krisinger *et al*. 2012). Plasmin however has been demonstrated to degrade C5 and thereby prevent C5b depostion and TCC formation (Barthel *et al*. 2012). Human leukocyte elastase (HLE) can cleave C5 into C5a-like (Döring 1994) and C5b-like products in the presence of C6. This C5b-like product forms an active complex with C6 and goes on to form TCC. However, as C6 is hydrolysed by elastase, the yield of the complex is very low (Vogt 2000). Elastase, produced by neutrophils is generally present in higher amounts in pregnant women (Greer *et al*. 1989). Tissue injury sites produce proteases such as, cathepsin D and factor VII activating protease (FSAP), which generate C5a leading to pro-inflammatory signaling events (Huber-Lang *et al*. 2012; Kanse *et al*. 2012). Vitamin D binding protein (DBP), bound to leukocytes, is known to enhance the chemotactic response to C5a and $C5a^{desArg}$, possibly by binding to ligands such as CD44 and annexin A2 (DiMartino *et al*. 2001; McVoy and Kew 2005).

Inhibition of C5 activity: Prolonged activation of C5 can result in damage to host tissue, leading to sepsis (see 'Phenotypes' section). Thus, it is important for the host to down-regulate C5 activation when needed. Several host proteins inhibit C5 activation. Complement factor H (fH) binds to C3b and prevents further binding of C5 as a substrate for both alternative pathway and classical pathway C5 convertases (Isenman et al. 1980; Discipio et al. 1981). Factor H-related protein 1 (CFHR-1) inhibits C5 activity at two levels. It binds to C5 and prevents its cleavage by alternative pathway C5 convertase. Further, it can also bind to C5b-C6 complex and prevents its surface deposition and thereby TCC formation. This down-regulation of activity offers protection of host cells during hemolytic uremic syndrome (HUS) (Heinen *et al*. 2009). Likewise, thioredoxin-1 (Trx-1) can also regulate C5 activation by inhibiting both C5 convertase and depostion of C5b (King *et al*. 2012). Clusterin inhibits TCC at multiple levels by binding to C5b-C7, C5b-C8 or C5b-C9. Clusterin binding to each of the above complexes prevents the subsequent steps of TCC formation. For example, upon clusterin binding to C5b-C9, C9 polymerization is inhibited (Tschopp *et al*. 1993). Vitronectin, also known as human-S protein, can bind to soluble C5b-C7 (present in the serum) and prevents its attachment to the cell surface and thereby prevent TCC formation. Further, it can also prevent C9 polymerization in C5b-C9 complex (Dahlbäck and Podack 1985; Milis *et al*. 1993; Podack and Müller-Eberhard 1979). Membrane bound CD59 acts on TCC by preventing the insertion of C9 into the membrane. Thus, it can inhibit both the formation of C5b-C9 complex and also C9 polymerization to the C5b-C9 complex. As C9 insertion, followed by polymerization is required for TCC formation, CD59 effectively blocks TCC activity. This has also been shown by measuring the pore activity of C5b-C8 and C5b-C9 complexes in the presence of CD59. Results show that CD59 can block the ion channel activity of these complexes (Farkas *et al*. 2002; Meri *et al*. 1990; Edwards *et al*. 1991; Watts *et al*. 1990; Lehto and Meri 1993; Lockert *et al*. 1995). Not just activity of C5b, but also activity of C5a can be regulated. Active CPB2 (upon cleavage of pro carboxypeptidase R by thrombin) removes an arginine residue from the carboxy terminal end of C5a to generate $C5a^{desArg}$. $C5a^{desArg}$ is significantly less potent than C5a (Campbell *et al*. 2001; Campbell *et al*. 2002).

Not surprisingly, for the sake of survival, pathogens try to evade complement attack by inhibiting C5 activity. The following pathogenic factors are known to be involved in down-regulating C5 activity. Streptococcal peptidase inactivates C5a by cleaving seven residues ($C5a^{-7\ residues}$) at its carboxy terminal end (Cleary *et al*. 1992). Staphylococcal super antigen like protein (SSL7) is a staphylococcal super antigen which binds to C5 and inhibits C5 activity, most probably by blocking the conversion of C5 to C5a and C5b (Langley *et al*. 2005). Another protein, OmCI, produced by the tick parasite *Ornithodoros moubata*, also binds to C5 and inhibits C5 cleavage by convertases (Nunn *et al*. 2005). Leishmanial protein kinase 1 (LPK1) phosphorylates components of the complement system, including C5 at S719. This phosphorylation inactivates formation of TCC, most probably by rendering C5 resistant to cleavage by C5 convertase (Hermoso *et al*. 1991). Streptococcal inhibitor of complement (SIC) is secreted by *Streptococcus pyogenes* and can bind to C5b-7 and C5b-8 complexes to inhibit TCC formation. It can also weakly bind to C5b-9 complex (Fernie-King *et al*. 2001). Interestingly two pathogens involved in perodontitis, *Porphyromonas gingivalis* and *Tannerella forsythia*, produce proteases gingipain and karilysin respectively, which can degrade C5 to result in active C5a-like product but not C5b. As a result, these pathogens initiate an inflammatory response due to neutrophil recruitment by C5a action, and at the same time evade complement attack due to lack of C5b (Wingrove *et al*. 1992; Jusko *et al*. 2012).

INTERACTIONS

C5 interacts with several and diverse set of proteins, either in its native or cleaved forms. Below, we will list all the known interactions.

Host factors: C5, in its native form binds to very few proteins. Nevertheless, these interactions have physiological significance. C5 binds to target surface bound C3b, when C3b is part of the C5 convertase complex. Binding to C3b facilitates recognition of C5 by the enzyme for cleavage (Jokiranta *et al*. 2001; Vogt *et al*. 1978). The N-terminal region of CFHR-1 (consisting of 1 and 2 short consensus repeats (SCR) domains) binds to C5. This binding prevents recognition of C5 by alternative pathway C5 convertase. As a result, there is no activation of C5. CFHR-1 therefore down-regulates activity in a view to exclude complement attack on host cells (Heinen *et al*. 2009).

C5a and $C5a^{desArg}$ bind to their receptors C5aR and C5L2. C5aR, which is a G protein coupled receptor (GPCR) is the major surface receptor for C5a and has a 10-100 fold higher

binding affinity for C5a as compared to $C5a^{desArg}$. This lower affinity makes $C5a^{desArg}$ a less potent anaphylotoxin. C5a binds to C5aR (Hagemann *et al*. 2008) and ligand bound C5aR initiates Ca^{2+} mobilization and a series of signaling events through interaction with G- proteins and β-arrestin (Lee *et al*. 2008; Cain *et al*. 2001; Chen *et al*. 1998). In contrast, C5L2 is largely intracellular and does not initiate Ca^{2+} mobilization. Rather, it appears to down-regulate the signaling actions of C5aR. This receptor can bind to both $C5a^{desArg}$ and C5a with equal affinities (Cain and Monk 2002; Scola *et al*. 2007; Okinaga *et al*. 2003).

C5b interacts with a range of proteins. Mainly, C5b interacts with other complement proteins to form TCC. Soluble C5b in the plasma, *via* its α' chain binds to carboxy-terminal end of C6, to form soluble C5b-C6 complex (Aleshin *et al*. 2012; Haefliger *et al*. 1989). C5b-6, again *via* α' chain of C5b, interacts with the carboxy-terminal end of C7 and recruits it (DiScipio 1992; Podack *et al*. 1978). C5b-7 complex is initially soluble, but later attaches to the outside of the membrane (DiScipio *et al*. 1988). This complex then binds to C8 molecule. C8 is a heterotrimer of α, β and γ chains. It is believed that C8β binds to C5b, forming C5b-8 complex, loosely attached to the membrane. Meanwhile C8α firmly integrates into the membrane, and binds to C9 possibly *via* C8γ (Lovelace *et al*. 2011; Stewart *et al*. 1987; Hadders *et al*. 2007). Binding of C9 to form C5b-C9 complex, displays a sub-lytic pore like structure spanning the membrane. Further polymerization of C9 to this complex, generally 18-21 oligomers of C9, forms a lytic pore, leaks the cell contents and thereby kills the cell. Thus, C5b recruits the above complement proteins in a sequential non-catalyzed manner, either by direct interaction or through its interacting partners, to form a membrane integrated lytic pore, TCC (Tschopp 1984).

The formation of TCC is highly regulated by host proteins, to limit the complement attack exclusively to the infected cells and thereby protect undamaged host cells. This regulation can be achieved by binding to the following host factors. C5b-6 binds to N-terminal region of CFHR-1, which prevents target surface attachment of the C5b-6 complex (Heinen *et al*. 2009). C5b-7 and C5b-9 bind to vitronectin (the former more strongly). Binding to vitronectin prevents membrane attachment of C5b-7 (Dahlbäck and Podack 1985; Milis *et al*. 1993; Podack and Müller-Eberhard 1979). Clusterin can bind to C5b-7, C5b-8 and C5b-9, which prevents the formation of the next step of TCC. For example, upon clusterin binding to C5b-C9, C9 polymerization is inhibited (Tschopp *et al*. 1993). Binding of clusterin to different complexes suggests that clusterin binds to a structural motif common between C7, C8 and C9. Membrane bound C5b-8 binds to CD59, *via* C8 α chain, which blocks the sub-lytic pore and inhibits C5b-9 complex formation. Further, CD59 can also inhibit C9 polymerization (Farkas *et al*. 2002; Meri *et al*. 1990; Edwards *et al*. 1991; Watts *et al*. 1990; Lehto and Meri 1993; Lockert *et al*. 1995). Cancer cells express CD59 which prevents assembly of TCC and thereby protects the cell from complement-mediated lysis (Fishelson *et al*. 2003).

Pathogenic factors: Cleavage of C5 to C5a and C5b can also be inhibited by binding to SSL7, a staphylococcal secreted antigen. This binding facilitates evasion of complement attack by pathogens such as *Escherichia coli* (Langley *et al*. 2005). SIC, a streptococcal protein can bind to C5b-7 and prevent surface attachment. It can also bind to C5b-8 and C5b-9 complexes and inhibit further recruitment of proteins to form TCC (Fernie-King *et al*. 2001). OmCI, yet another C5 inhibitor, produced by *Ornithodoros moubata*, binds to C5 both *in vivo* and *in vitro* (Nunn *et al*. 2005; Hepburn *et al*. 2002). Crystal structure studies show that OmCI binds to C5 at a site distant to the cleavage site. However, this binding modifies the structure such that it renders C5 resistant to cleavage by convertases (Fredslund *et al*. 2008).

PHENOTYPES

As C5 is part of the complement network, involved in lysis of the target cells such as pathogens, C5 deficiency will reflect in impaired response to infection. Patients with C5 deficiency have been shown to be particularly susceptible to systemic infections by *Neisseria meningitidies* and *N. gonorrhoeae* (Hildenhagen and Bitter-Suermann 1985; Owen *et al*. 2012). Single nucleotide polymorphisms (SNPs) of C5 have been observed in periodontitis (Chai *et al*. 2010) and in male subjects showing increased cardiovascular risk (Hoke *et al*. 2012). Human genetic deficiencies reveal that C5 is required for induction of an oxidative burst, phagocytosis and killing of *E.coli*, and complement - CD14 cooperation (TLR-Crosstalk) (Lappegård *et al*. 2009).

C5a, promotes coagulation and inhibits fibrinolysis by inducing the expression of tissue factor, a key initiating component of the blood coagulation cascade (Ritis *et al*. 2006) and plasminogen-activator inhibitor 1 (Markiewski *et al*. 2007). C5a (and C3a) induce expression of vesicular endothelial growth factor (VEGF), which is required for angiogenesis and tissue repair after injury (Nozaki *et al*. 2006). In contrast, unregulated amounts of C5a can contribute to organ damage in combination with the cytokine storm in the later stages of sepsis (Ward 2004) and hemodialysis-associated thrombosis (Kourtzelis *et al*. 2010).

C5 in growth and cancer: Both C5a and C5b can be involved in growth regulation. C5a, upon binding to C5aR mediates diverse pro-survival and anti-apoptotic functions in a variety of cells by activating pathways such as p38-MAPK in macrophages (Rousseau *et al*. 2006), ERK1/2 in human intestinal epithelial cells and monocytes (Cao *et al*. 2012; Buhl *et al*. 1994), Akt, and JNK in monocytes (la Sala *et al*. 2005) and phosphatidylinositol 3-kinase (PI3-K) in mast cells (Venkatesha *et al*. 2005). C5a also promotes proliferation of undifferentiated human neuroblastoma cells, possibly by partial effects of protein kinase C (PKC) and NF-κB activation (O'Barr *et al*. 2001). Lung cancer cell lines show increased C5 deposition and C5a generation (Corrales *et al*. 2012). Further, tumor studies in mice showed that increased C5a production led to immune suppression upon binding to C5aR (Corrales *et al*. 2012).

Sublytic doses of the TCC (C5b-9) induce cell cycle activation and proliferation. These doses cause a rapid increase in intracellular free Ca^{2+} concentration before any other detectable biochemical changes in the cell (Morgan *et al*. 1986; Kim *et al*. 1987; Papadimitriou *et al*. 1994), and this increase in $[Ca^{2+}]$ can explain the proliferative effect of TCC. Studies have shown C5b-9 to activate PI3-K and the ERK1 pathway in a $G\alpha_i$ protein-dependent manner (Fosbrink *et al*. 2005), and enhance response gene to complement (RGC)-32 mRNA expression (Badea *et al*. 2002).

MAJOR SITES OF EXPRESSION

C5 has been shown to be expressed by monocytes/macrophages, polymorphonuclear cells, endothelial and epithelial cells in

tissues such as liver, lung, and brain (Schraufstatter *et al*. 2002; Langeggen *et al*. 2001; Ikeda *et al*. 1997; Foreman *et al*. 1994; Foreman *et al*. 1996). However, the major source of C5 is most likely the liver tissue as a study using a human hepatocyte-derived line, HEPG2, produces C5 (and C3) at a rate which is more or less proportional to C5 concentrations in serum (Perissutti and Tedesco 1994).

SPLICE VARIANTS

There are no known splice variants

REGULATION OF CONCENTRATION

The physiological concentration of C5a in plasma is a median of ~0.012 µg/ml (Soto *et al*. 2005). Several factors involving inflammation of tissues increase the local concentration of C5 active products. Few known examples are cited here: pregnant women suffering from pyelonephritis show increased C5a levels, with a median of 0.02 µg/ml (Soto *et al*. 2005), while patients with acute systemic lupus erythematosus have a concentration of 0.046 µg/ml (Belmont *et al*. 1986).

ANTIBODIES

Commercial antibodies against C5 are available from different companies such as Santa Cruz, R and D. Novus, Epitomics, CompTech etc. These include monoclonal, polyclonal, and are targeted against different epitopes, which can also help to distinguish C5a from C5b. Further, eculizumab, a therapeutic monoclonal antibody against C5 has been developed and approved for treatment of patients suffering from paroxysmal nocturnal haemoglobinuria (Parker 2009; Parker 2012; Alfinito *et al*. 2012). Eculizumab has also been shown to treat patients suffering from atypical hemolytic uremic syndrome (aHUS) (Zuber *et al*. 2012).

Table 1: Functional States

STATE DESCRIPTION	LOCATION	REFERENCES
C5	extracellular space	
C5/C3b	plasma membrane	DiScipio RG *et al.* 1981; Isenman DE *et al.* 1980; Jokiranta TS *et al.* 2001; Vogt W *et al.* 1978
C5/CHFR1	extracellular space	Heinen S *et al.* 2009
C5/Plasminogen	extracellular space	Barthel D *et al.* 2012
C5/SSL7 (S.aureus)	extracellular space	Langley R *et al.* 2005
C5/OmCI (O.moubata)	extracellular space	Nunn MA *et al.* 2005
C5P-S719	extracellular space	Hermoso T *et al.* 1991
C5a	extracellular space	Fernandez HN and Hugli TE 1978; Guo RF and Ward PA ; Hartmann K *et al.* 1997
C5a-7 residues	extracellular space	Brown CK *et al.* 2005; Cleary PP *et al.* 1992
C5adesArg	extracellular space	Eglite S *et al.* 2000; Cain SA and Monk PN 2002; Hugli TE *et al.* 1981
C5adesArg/C5aR	plasma membrane	Lee H *et al.* 2008; Cain SA *et al.* 2001
C5adesArg/C5L2	plasma membrane	Scola AM *et al.* 2007; Cain SA and Monk PN 2002
C5a/C5L2	intrinsic to membrane	Bamberg CE *et al.* 2010; Cain SA and Monk PN 2002; Chen NJ *et al.* 2007; Chenoweth DE *et al.* 1982; Johswich K *et al.* 2006; Lee H *et al.* 2008; Okinaga S *et al.* 2003
C5a/C5aR	intrinsic to membrane	Chenoweth DE and Hugli TE 1978; Huber-Lang MS *et al.* 2003; Lee H *et al.* 2008; Cain SA *et al.* 2001
C5b	extracellular space	Yamamoto KI and Gewurz G 1978; Podack ER *et al.* 1978
C5b/C6	extracellular space	Haefliger JA *et al.* 1989
C5b/C6/CFHR1	extracellular space	Heinen S *et al.* 2009
C5b-C7 (plasma)	extracellular space	DiScipio RG *et al.* 1992; Podack ER *et al.* 1978
C5b-C7 (membrane)	extrinsic to membrane	DiScipio RG *et al.* 1992; DiScipio RG *et al.* 1988
C5b-C7/Vitronectin	extracellular space	Podack ER and Müller-Eberhard HJ 1979; Dahlbäck B and Podack ER 1985; Milis L *et al.* 1993
C5b-C7/Clusterin	plasma membrane	Tschopp J *et al.* 1993
C5b-C7/SIC (S. pyogenes)	extrinsic to membrane	Lambris JD *et al.* 2008; Fernie-King BA *et al.* 2001
C5b-C8	plasma membrane	Hadders MA *et al.* 2007; Lovelace LL *et al.* 2011; Cole DS and Morgan BP 2003
C5b-C8/CD59	Unknown	Huang Y *et al.* 2005; Kozono H *et al.* 1990; Lockert DH *et al.* 1995; Farkas I *et al.* 2002; Meri S *et al.* 1996; Meri S *et al.* 1990; Rollins SA and Sims PJ 1990; Watts MJ *et al.* 1990
C5b-C8/Clusterin	plasma membrane	Tschopp J *et al.* 1993
C5b-C8/SIC (S. pyogenes)	Unknown	Fernie-King BA *et al.* 2001; Lambris JD *et al.* 2008
C5b-C9	plasma membrane	Lambris JD *et al.* 2008; Lovelace LL *et al.* 2011; Hadders MA *et al.* 2007; Tschopp J *et al.* 1984
C5b-C9/Vitronectin	plasma membrane	Dahlbäck B and Podack ER 1985; Milis L *et al.* 1993; Podack ER and Müller-Eberhard HJ 1979
C5b-C9/Clusterin	plasma membrane	Tschopp J *et al.* 1993
C5b-C9/CD59	plasma membrane	Lehto T and Meri S 1993
C5b-C9(18) TCC	plasma membrane	Lovelace LL *et al.* 2011; Hadders MA *et al.* 2007
C5b-C9/SIC (S. pyogenes)	Unknown	Lambris JD *et al.* 2008; Fernie-King BA *et al.* 2001

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SUPPLEMENTARY

Supplementary information is available online.

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This molecule exists in 32 states , has 49 transitions between these states and has 0 enzyme functions.(Please zoom in the pdf file to view details.)