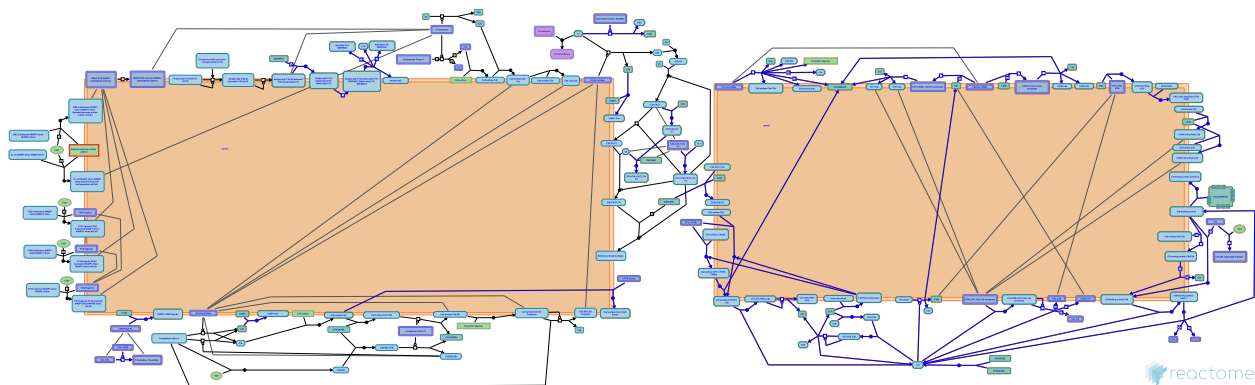


# Regulation of Complement cascade



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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the [Reactome Textbook](https://reactome.org/textbook/).

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## Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

## Literature references

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- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. [↗](#)
- Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res*, 46, D649-D655. [↗](#)
- Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

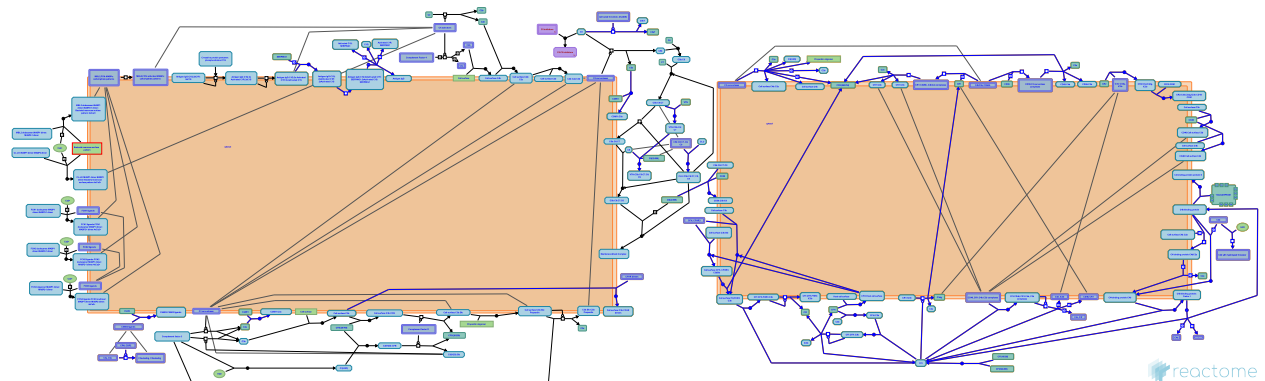
Reactome database release: 88

This document contains 1 pathway and 42 reactions ([see Table of Contents](#))

## Regulation of Complement cascade ↗

**Stable identifier:** R-HSA-977606

**Compartments:** plasma membrane, extracellular region



Two inherent features of complement activation make its regulation very important:

1. There is an inherent positive feedback loop because the product of C3 activation forms part of an enzyme that causes more C3 activation.
2. There is continuous low-level activation of the alternative pathway (see Spontaneous hydrolysis of C3 thioester).

Complement cascade activation is regulated by a family of related proteins termed the regulators of complement activation (RCA). These are expressed on healthy host cells. Most pathogens do not express RCA proteins on their surface, but many have found ways to evade the complement system by stably binding the RCA that circulates in human plasma (Lambris et al. 2008); trapping RCA is by far the most widely employed strategy for avoiding the complement response. RCA recruitment is common in bacteria such as *E. coli* and streptococci (Kraiczy & Wurzner 2006) and has also been described for viruses, fungi and parasites. RCA deposition and the complement system also have an important role in tissue homeostasis, clearing dead cells and debris, and preventing damage from oxidative stress (Weismann et al. 2011).

RCA proteins control complement activation in two different ways; by promoting the irreversible dissociation (decay acceleration) of complement convertases and by acting as cofactors for Complement factor I (CFI)-mediated cleavage of C3b and C4b.

Decay accelerating factor (DAF, CD55), Complement factor H (FH), Membrane Cofactor Protein (MCP) and Complement receptor 1 (CR1) are composed of arrays of tandem globular domains termed CCPs (complement control protein repeats) or SCRs (short consensus repeats). CR1, MCP and FH are cofactors for the CFI-mediated cleavage of C3b, generating iC3b. CR1 and MCP are also cofactors for C4b cleavage.

C4BP is an additional cofactor for the CFI-mediated cleavage of C4b.

### Literature references

Skerka, C., Zipfel, PF. (2009). Complement regulators and inhibitory proteins. *Nat Rev Immunol*, 9, 729-40. ↗

Gasque, P. (2004). Complement: a unique innate immune sensor for danger signals. *Mol Immunol*, 41, 1089-98. ↗

Yang, K., Lambris, JD., Hajishengallis, G., Ricklin, D. (2010). Complement: a key system for immune surveillance and homeostasis. *Nat Immunol*, 11, 785-97. ↗

Kimball, JW. (n.d.). The Complement System. Retrieved from <http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/C/Complement.html>

### Editions

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|------------|----------|----------------------------|
| 2010-10-26 | Authored | Jupe, S.                   |
| 2010-11-01 | Edited   | Jupe, S.                   |
| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |

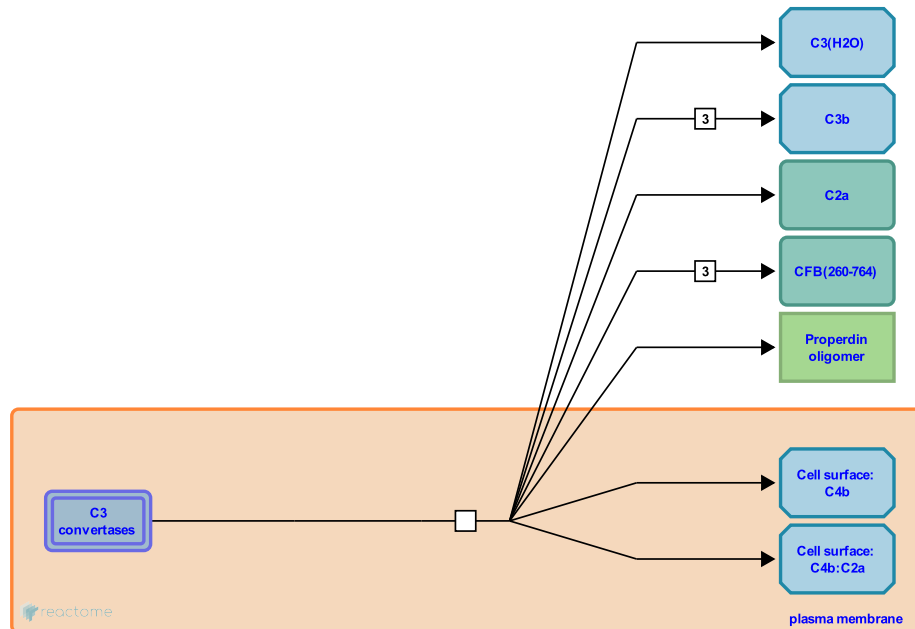
## C3 convertases spontaneously dissociate ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-981621

**Type:** transition

**Compartments:** plasma membrane, extracellular region



C3b:Bb is naturally labile with a half-life of ~90 s. unless bound to properdin on the cell surface (Medicus et al. 1976). C4bC2a is also unstable, lasting at best a few minutes (Kerr et al. 1980). Decay is associated with the release of the Bb or C2a fragments respectively into the fluid phase. The liberated C3b/C4b is able to re-bind Bb/C2a if Factor B/C2 are present.

### Literature references

Medicus, RG., Muller-Eberhard, HJ., Gotze, O. (1976). Alternative pathway of complement: recruitment of precursor properdin by the labile C3/C5 convertase and the potentiation of the pathway. *J Exp Med*, 144, 1076-1093. ↗

Kerr, MA. (1980). The human complement system: assembly of the classical pathway C3 convertase. *Biochem J*, 189, 173-81. ↗

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| 2010-11-01 | Edited   | Jupe, S.                   |
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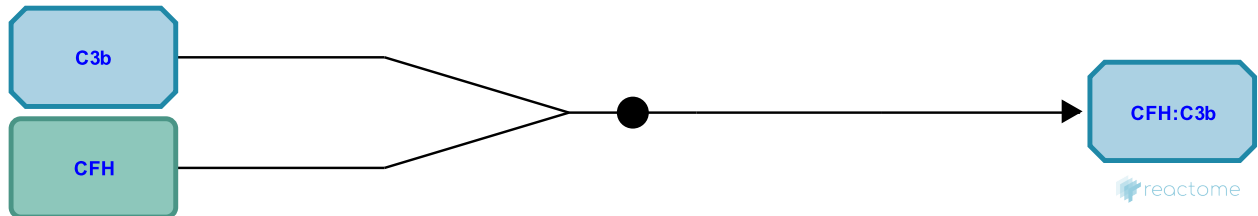
## Factor H binds to C3b [↗](#)

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-976768

**Type:** binding

**Compartments:** extracellular region



Factor H (CFH) regulates the alternative pathway C3 convertase C3bBb and its C3b component both in plasma and at host cell surfaces. FH binds to plasma C3b, making it unavailable, and acts as a cofactor for the factor I-mediated proteolytic inactivation of C3b to iC3b.

**Followed by:** [Complement factor I binds to extracellular Factor H:C3b](#)

## Literature references

Weiler, JM., Fearon, DT., Daha, MR., Austen, KF. (1976). Control of the amplification convertase of complement by the plasma protein beta1H. *Proc Natl Acad Sci U S A*, 73, 3268-72. [↗](#)

Schreiber, RD., Pangburn, MK., Muller-Eberhard, HJ. (1977). Human complement C3b inactivator: isolation, characterization, and demonstration of an absolute requirement for the serum protein beta1H for cleavage of C3b and C4b in solution. *J Exp Med*, 146, 257-70. [↗](#)

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| 2010-10-26 | Authored | Jupe, S.                   |
| 2010-11-01 | Edited   | Jupe, S.                   |
| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |

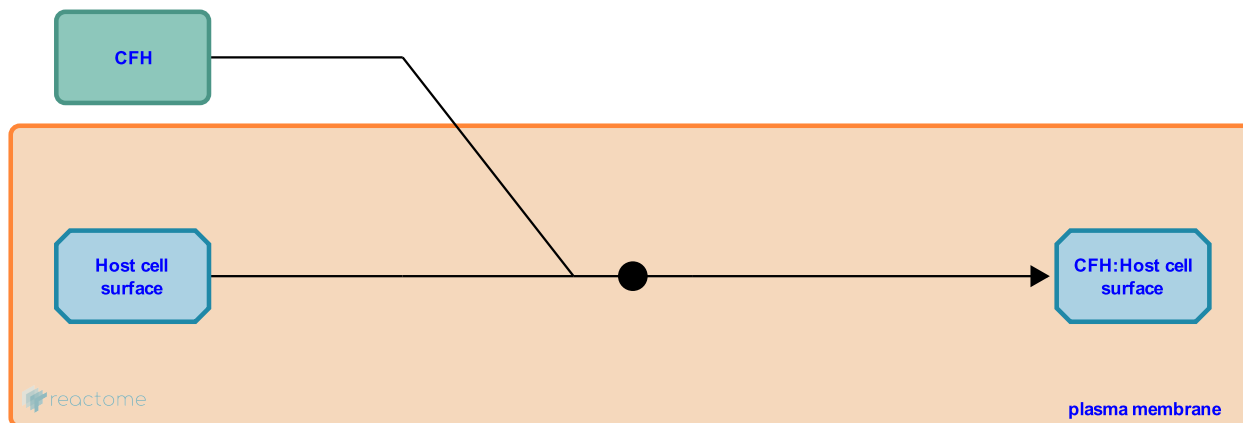
## Factor H binds host cell surface markers ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-1006169

**Type:** binding

**Compartments:** plasma membrane, extracellular region



Factor H (CFH) preferentially binds to host cells and surfaces that have negatively charged cell surface polyanions such as heparin and sialic acid commonly found on host cells (Kazatchkine et al. 1979, Meri & Pangburn 1990). This mediates protection of plasma-exposed host structures.

**Followed by:** [Factor H binds to membrane-associated C3b](#)

## Literature references

Remuzzi, G., Jòzsi, M., Seeberger, H., Gordon, DL., Noris, M., Cheng, ZZ. et al. (2005). Binding of complement factor H to endothelial cells is mediated by the carboxy-terminal glycosaminoglycan binding site. *Am J Pathol*, 167, 1173-81. ↗

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| 2010-11-09 | Authored, Edited | Jupe, S.                   |
| 2012-02-13 | Reviewed         | Bradley, DT., Fraczek, LA. |

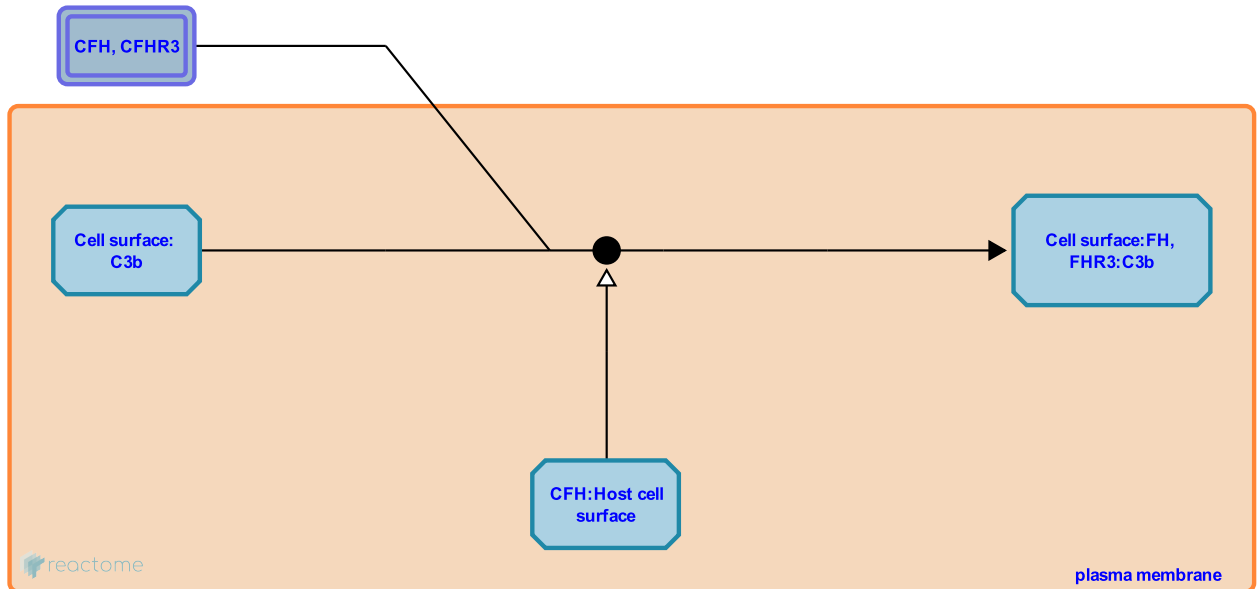
## Factor H binds to membrane-associated C3b ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-981728

**Type:** binding

**Compartments:** plasma membrane, extracellular region



Factor H (CFH) regulates the alternative pathway C3 convertase C3bBb and its C3b component both in plasma and at host cell surfaces. CFH binds to membrane-associated C3b, competing with Factor B and thereby preventing formation of the active C3 convertase C3bBb. In addition, it acts as a cofactor for the Factor I-mediated proteolytic inactivation of C3b to iC3b.

**Preceded by:** [Factor H binds host cell surface markers](#)

**Followed by:** [Complement factor I binds to membrane-associated Factor H:C3b](#)

### Literature references

Weiler, JM., Fearon, DT., Daha, MR., Austen, KF. (1976). Control of the amplification convertase of complement by the plasma protein beta1H. *Proc Natl Acad Sci U S A*, 73, 3268-72. ↗

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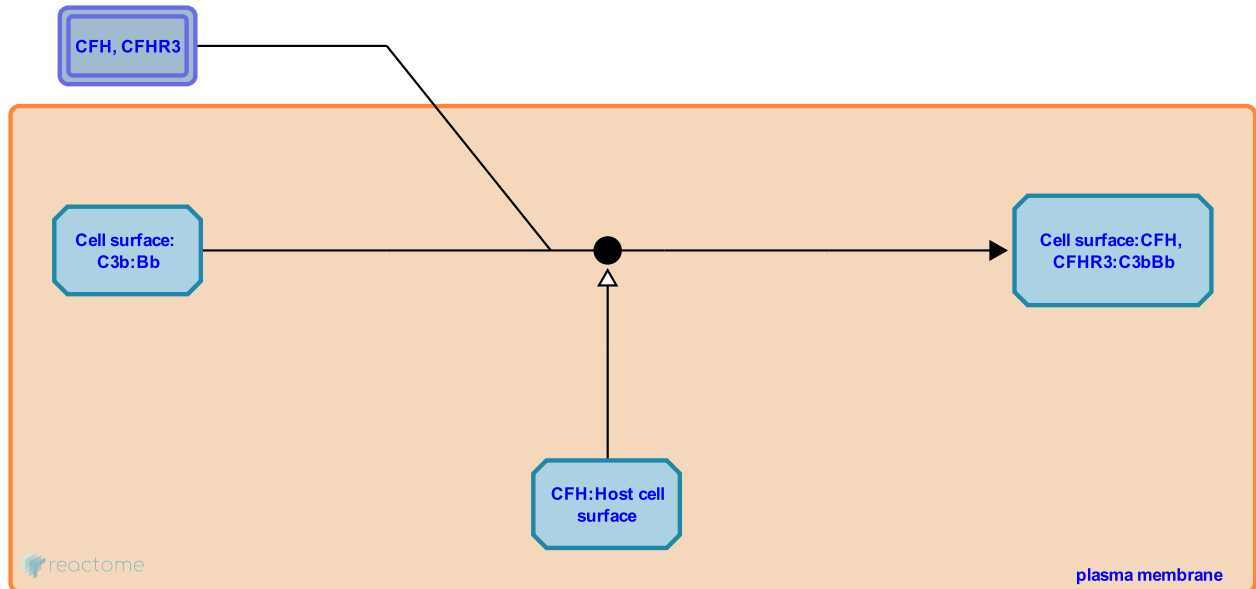
## Factor H binds to C3bBb ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-977363

**Type:** binding

**Compartments:** plasma membrane, extracellular region



Factor H (CFH) binds to C3bBb, leading to displacement of Bb. Complement factor H-related protein 3 (FHR3) has also been reported to bind C3Bb leading to inhibition of C3Bb C3 convertase activity (Fritsche et al. 2010). CFH also acts as a cofactor for the factor I-mediated proteolytic inactivation of C3b to iC3b.

**Followed by:** [Factor H displaces Bb](#)

## Literature references

Weiler, JM., Fearon, DT., Daha, MR., Austen, KF. (1976). Control of the amplification convertase of complement by the plasma protein beta1H. *Proc Natl Acad Sci U S A*, 73, 3268-72. ↗

Schreiber, RD., Pangburn, MK., Muller-Eberhard, HJ. (1977). Human complement C3b inactivator: isolation, characterization, and demonstration of an absolute requirement for the serum protein beta1H for cleavage of C3b and C4b in solution. *J Exp Med*, 146, 257-70. ↗

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| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |



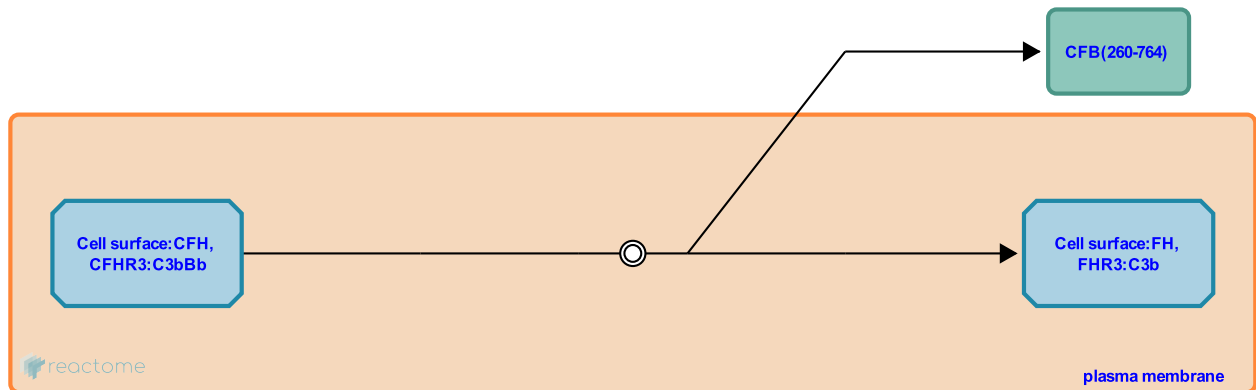
## Factor H displaces Bb ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-977605

**Type:** dissociation

**Compartments:** plasma membrane, extracellular region



Factor H (CFH) greatly accelerates the displacement (decay) of Complement factor Bb from C3b.

**Preceded by:** [Factor H binds to C3bBb](#)

## Literature references

Weiler, JM., Fearon, DT., Daha, MR., Austen, KF. (1976). Control of the amplification convertase of complement by the plasma protein beta1H. *Proc Natl Acad Sci U S A*, 73, 3268-72. ↗

## Editions

|            |          |                            |
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| 2010-10-26 | Authored | Jupe, S.                   |
| 2010-11-01 | Edited   | Jupe, S.                   |
| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |

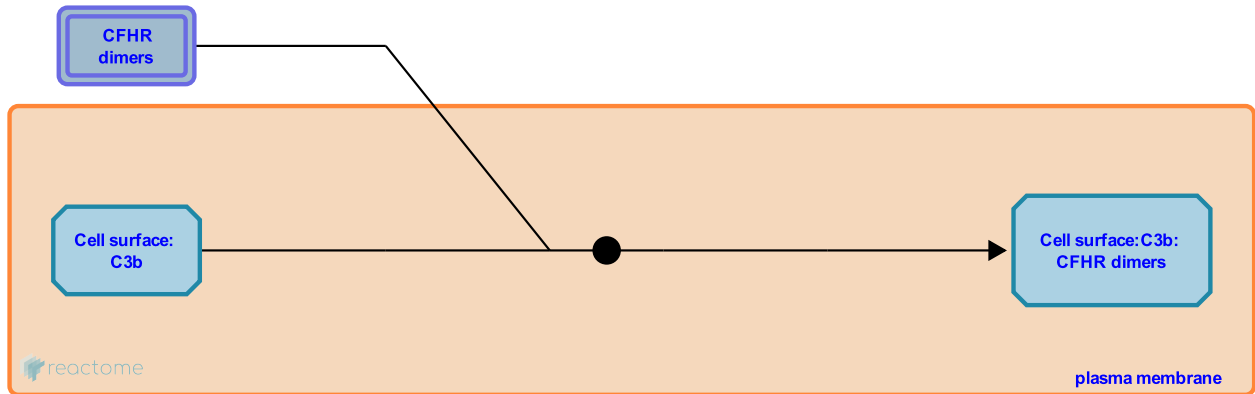
## CFHR dimers bind C3b ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-8851436

**Type:** binding

**Compartments:** plasma membrane



CFHR dimers bind C3b, acting as competitive antagonists of Factor H (CFH) binding (de Jorge et al. 2013, Tortajada et al. 2013). CFHR1, CFHR2, and CFHR5 have a dimerization motif within their amino-terminal domains that enables formation of three homodimers (CFHR1:CFHR1, CFHR2:CFHR2, CFHR5:CFHR5) and three heterodimers (CFHR1:CFHR2, CFHR1:CFHR5, and CFHR2:CFHR5). Multiple binding interactions and avidity enable these dimers to out-compete CFH at physiologically relevant concentrations. CFHR2 homodimers bind C3b while allowing C3 convertase formation, but the CFHR2 bound convertases does not cleave C3 (Eberhardt et al. 2013).

CFHR3 and CFHR4 do not contain the dimerization motif seen in CFHR1, 2 and 5 but compete with factor H for binding to C3b (Hellwage et al. 1999, Fritsche et al. 2010). CFHR4 exists predominantly as a dimer in plasma (Hellwage et al. 1999).

As the main function of CFH is down-regulation of C3 activation through the alternative pathway amplification loop, CFHR dimers interfere with the C3b inhibitory actions of CFH, a process termed deregulation (de Jorge et al. 2013, Tortajada et al. 2013).

### Literature references

Morgan, BP., Pickering, MC., Malik, TH., Caesar, JJ., Lea, SM., Johnson, S. et al. (2013). Dimerization of complement factor H-related proteins modulates complement activation in vivo. *Proc. Natl. Acad. Sci. U.S.A.*, 110, 4685-90. ↗

### Editions

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| 2016-01-06 | Authored | Jupe, S.  |
| 2017-02-01 | Reviewed | Bulla, R. |
| 2017-02-01 | Edited   | Jupe, S.  |

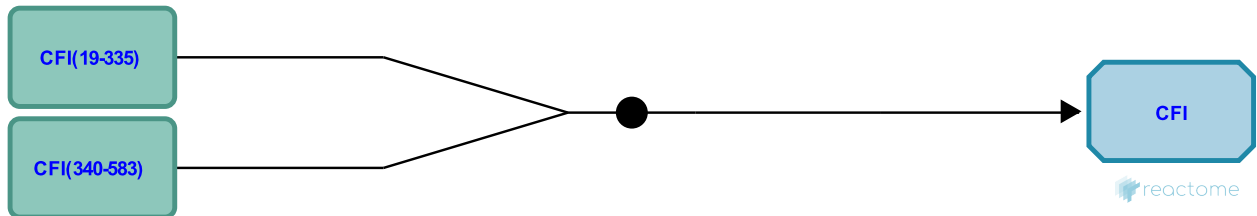
## Complement factor I complex formation [↗](#)

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-976801

**Type:** binding

**Compartments:** extracellular region



Complement factor I (CFI) is a complex of one heavy and one light chain, both cleaved from the same precursor peptide. It inactivates complement subcomponents C3b, iC3b and C4b by proteolytic cleavage of the alpha chains of C4b and C3b in the presence of cofactors such as Factor H, C4b binding protein, Complement receptor 1 (CR1) or MCP (CD46).

**Followed by:** [Complement factor I binds to extracellular Factor H:C3b](#), [Complement factor I binds to membrane-associated Factor H:C3b](#)

### Literature references

Rits, M., Goldberger, G., Kwiatkowski, DJ., Bruns, GA., Edge, MD. (1987). Human complement factor I: analysis of cDNA-derived primary structure and assignment of its gene to chromosome 4. *J Biol Chem*, 262, 10065-71. [↗](#)

Schreiber, RD., Pangburn, MK., Muller-Eberhard, HJ. (1977). Human complement C3b inactivator: isolation, characterization, and demonstration of an absolute requirement for the serum protein beta1H for cleavage of C3b and C4b in solution. *J Exp Med*, 146, 257-70. [↗](#)

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| 2010-11-01 | Edited   | Jupe, S.                   |
| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |

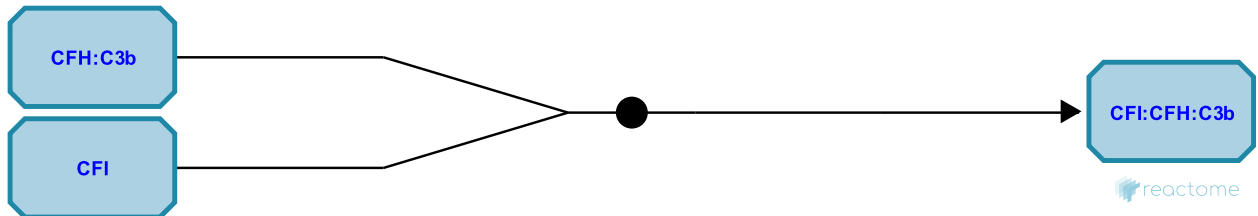
## Complement factor I binds to extracellular Factor H:C3b ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-976810

**Type:** binding

**Compartments:** extracellular region



Complement factor I (CFI) binds the factor H:C3b (CFH:C3b) complex.

**Preceded by:** [Complement factor I complex formation](#), [Factor H binds to C3b](#)

**Followed by:** [Factor I inactivates plasma Factor H-bound C3b](#)

### Literature references

Pangburn, MK., Muller-Eberhard, HJ. (1983). Kinetic and thermodynamic analysis of the control of C3b by the complement regulatory proteins factors H and I. *Biochemistry*, 22, 178-85. ↗

### Editions

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| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |

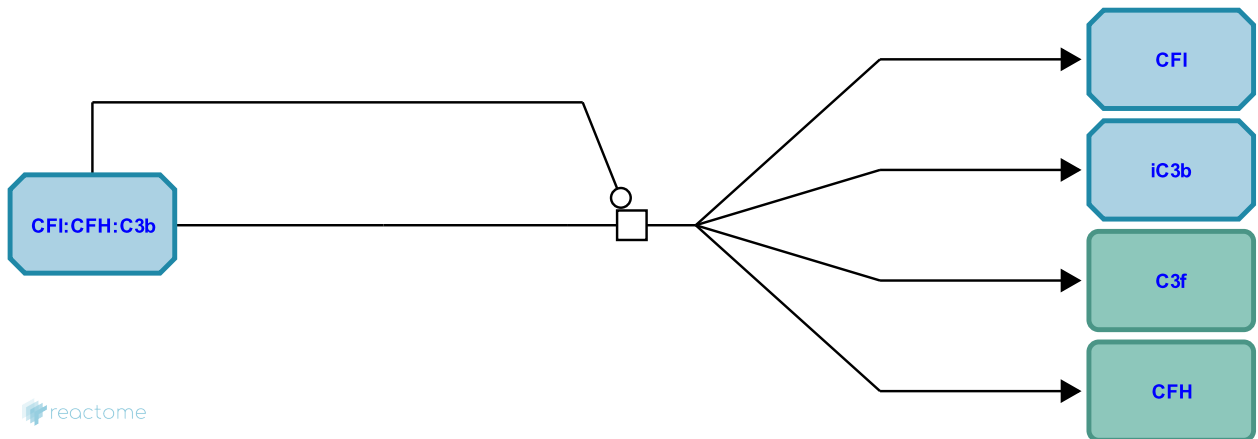
## Factor I inactivates plasma Factor H-bound C3b ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-976743

**Type:** transition

**Compartments:** extracellular region



Complement factor I (CFI) cleaves the alpha chain of C3b at two positions, generating inactivated C3b (iC3b) and a small fragment C3f, which is released. The majority of the alpha chain is retained as two fragments which are tethered by disulphide bonds. iC3b is proteolytically inactive.

**Preceded by:** [Complement factor I binds to extracellular Factor H:C3b](#)

### Literature references

Pangburn, MK., Muller-Eberhard, HJ. (1983). Kinetic and thermodynamic analysis of the control of C3b by the complement regulatory proteins factors H and I. *Biochemistry*, 22, 178-85. ↗

### Editions

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| 2010-10-26 | Authored | Jupe, S.                   |
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| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |

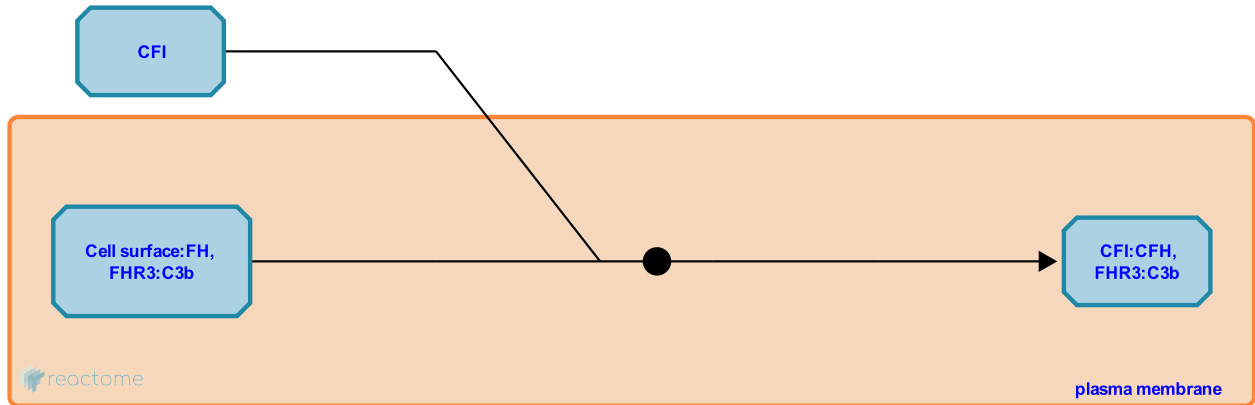
## Complement factor I binds to membrane-associated Factor H:C3b ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-977359

**Type:** binding

**Compartments:** plasma membrane, extracellular region



Complement factor I (CFI) binds to the membrane-associated Factor H:C3b complex.

**Preceded by:** [Complement factor I complex formation](#), [Factor H binds to membrane-associated C3b](#)

**Followed by:** [Factor I inactivates Factor H-bound C3b](#)

### Literature references

Medof, ME., Mold, C. (1985). C3 nephritic factor protects bound C3bBb from cleavage by factor I and human erythrocytes. *Mol Immunol*, 22, 507-12. ↗

### Editions

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| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |

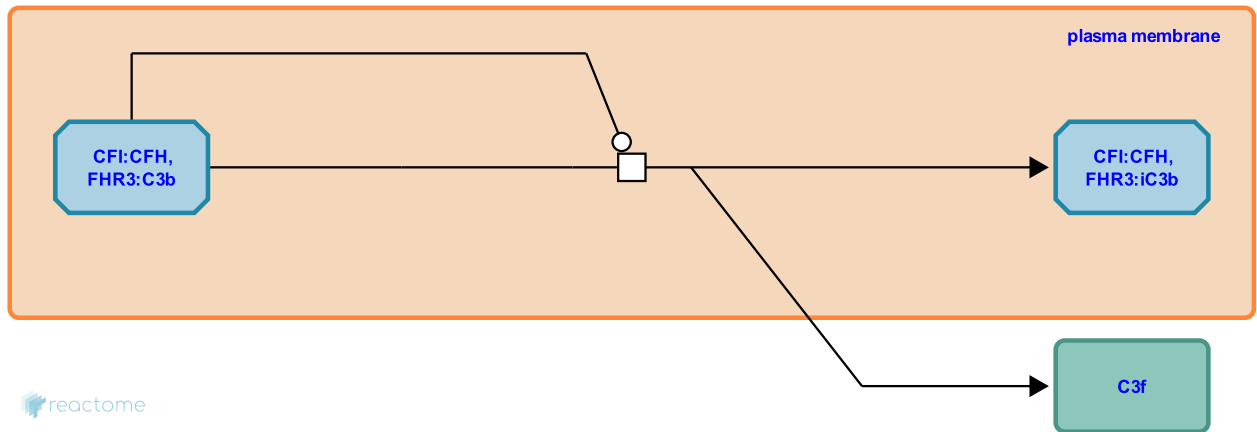
## Factor I inactivates Factor H-bound C3b ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-977371

**Type:** transition

**Compartments:** plasma membrane, extracellular region



reactome

Following the displacement of Bb from C3bBb, Factor I (CFI) cleaves Factor H-bound C3b producing iC3b, which remains bound to the membrane. The majority of the C3b alpha chain is retained as two fragments which are tethered to the beta chain by disulphide bonds. iC3b is proteolytically inactive and cannot contribute to the complement cascade process, though it still contributes to opsonization.

**Preceded by:** [Complement factor I binds to membrane-associated Factor H:C3b](#)

### Literature references

Medof, ME., Mold, C. (1985). C3 nephritic factor protects bound C3bBb from cleavage by factor I and human erythrocytes. *Mol Immunol*, 22, 507-12. ↗

Pangburn, MK., Muller-Eberhard, HJ. (1983). Kinetic and thermodynamic analysis of the control of C3b by the complement regulatory proteins factors H and I. *Biochemistry*, 22, 178-85. ↗

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| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |

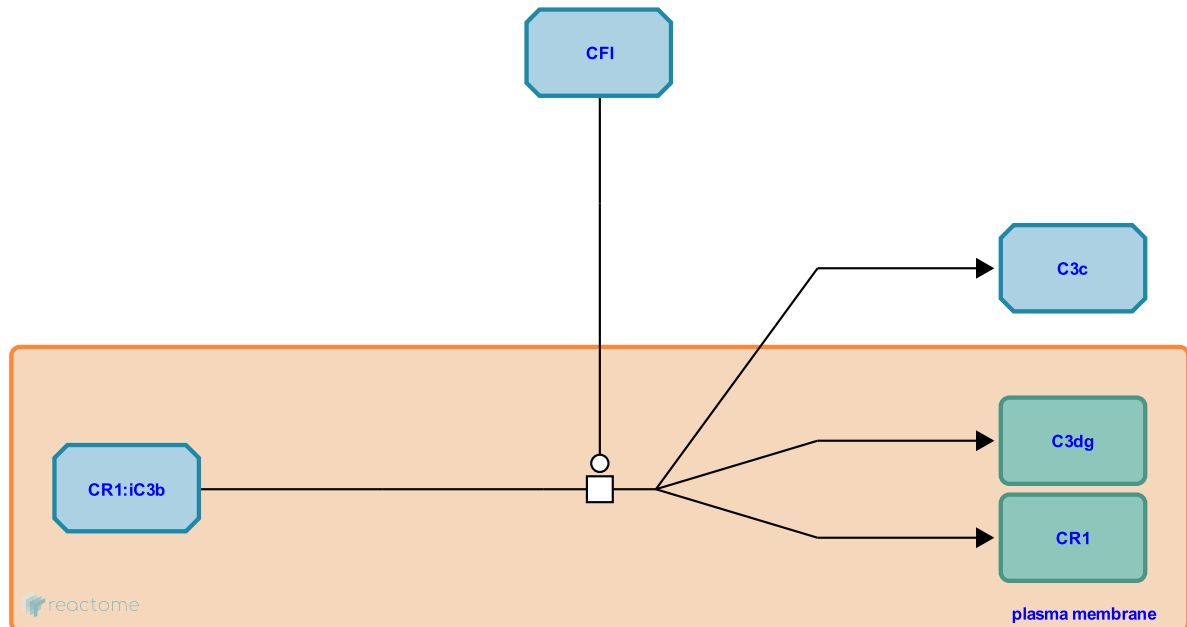
## Factor I cleaves iC3b ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-326657

**Type:** transition

**Compartments:** plasma membrane, extracellular region



Factor I (CFI) cleaves iC3b into two molecules, C3c, which is released into solution, and C3dg, which remains attached to the membrane. This cleavage requires Complement receptor type 1 (CR1), which serves a cofactor for CFI (Medof et al. 1982). iC3b and C3dg can bind CR2 (CD21) to enhance B-cell immunity (Tuveson et al.1991, Sarrias et al. 2001).

**Preceded by:** [Factor I inactivates MCP/CR1-bound C4b/C3b](#)

## Literature references

- Lambris, JD., Becherer, JD. (1988). Identification of the C3b receptor-binding domain in third component of complement. *J. Biol. Chem.*, 263, 14586-91. ↗
- Harrison, RA., Davis, AE., Lachmann, PJ. (1984). Physiologic inactivation of fluid phase C3b: isolation and structural analysis of C3c, C3d,g (alpha 2D), and C3g. *J. Immunol.*, 132, 1960-6. ↗
- de Córdoba, SR., Fernández, FJ., Round, A., Alcorlo, M., Martínez-Barricarte, R., Llorca, O. et al. (2011). Unique structure of iC3b resolved at a resolution of 24 Å by 3D-electron microscopy. *Proc. Natl. Acad. Sci. U.S.A.*, 108, 13236-40. ↗

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| 2012-02-13 | Reviewed | Bradley, DT.  |
| 2012-10-17 | Authored | Shamovsky, V. |
| 2013-05-23 | Reviewed | Shamovsky, V. |
| 2013-05-24 | Edited   | Shamovsky, V. |



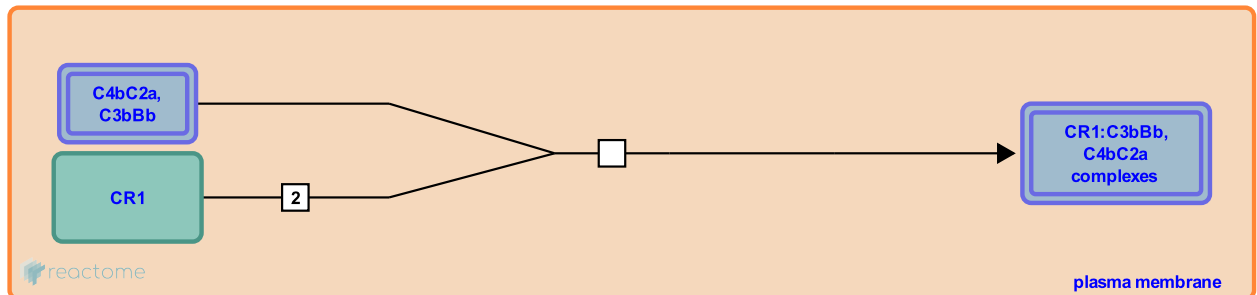
## CR1 binds C3bBb/C4bC2a ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-977375

**Type:** transition

**Compartments:** plasma membrane



Complement Receptor 1 (CR1) is a widely distributed cell surface protein that is a decay accelerating factor for the conventional (C4bC2a) and alternative (C3bBb) C3 convertases (Coico & Sunshine 2009).

**Followed by:** [Displacement of C2a/Bb by CR1](#)

## Literature references

Fearon, DT. (1979). Regulation of the amplification C3 convertase of human complement by an inhibitory protein isolated from human erythrocyte membrane. *Proc Natl Acad Sci U S A*, 76, 5867-71. ↗

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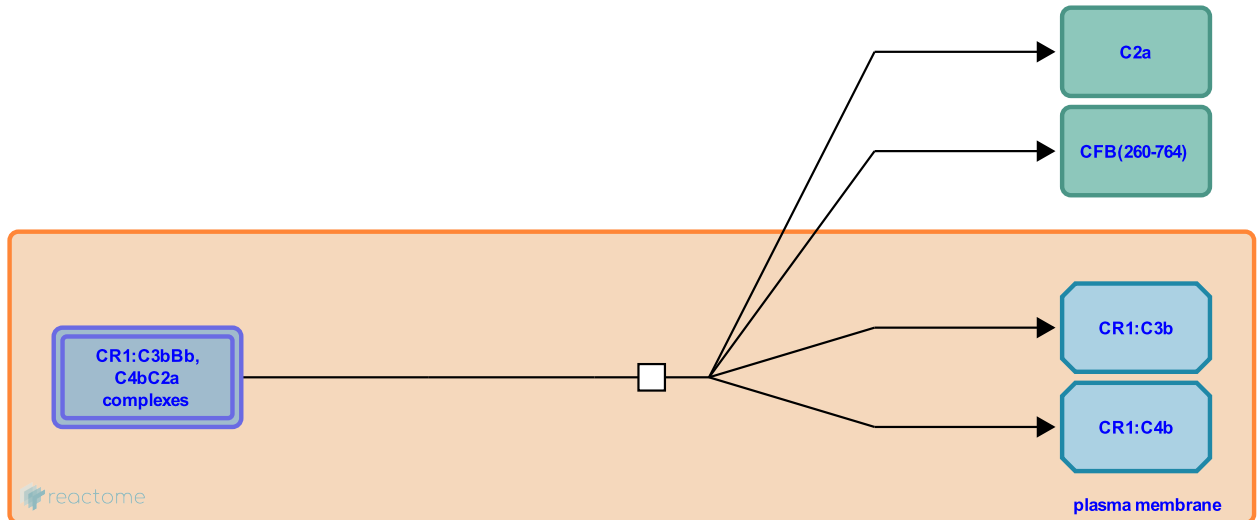
## Displacement of C2a/Bb by CR1 ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-977629

**Type:** transition

**Compartments:** plasma membrane, extracellular region



Complement Receptor 1 (CR1) displaces the activated enzyme components Bb and C2a from the conventional and alternative C3 convertases C4bC2a and C3bBb, respectively.

**Preceded by:** [CR1 binds C3bBb/C4bC2a](#)

**Followed by:** [Complement factor I binds to MCP, CR1:C4b, C3b](#)

### Literature references

Atkinson, JP., Hauhart, RE., Subramanian, VB., Krych-Goldberg, M., Crimmins, DL., Hourcade, DE. et al. (1999). Decay accelerating activity of complement receptor type 1 (CD35). Two active sites are required for dissociating C5 convertases. *J Biol Chem*, 274, 31160-8. ↗

Atkinson, JP., Kuttner-Kondo, LA., Medof, ME., Mitchell, L., Hourcade, DE. (2002). Decay-accelerating factor (DAF), complement receptor 1 (CR1), and factor H dissociate the complement AP C3 convertase (C3bBb) via sites on the type A domain of Bb. *J Biol Chem*, 277, 1107-12. ↗

Fearon, DT. (1979). Regulation of the amplification C3 convertase of human complement by an inhibitory protein isolated from human erythrocyte membrane. *Proc Natl Acad Sci U S A*, 76, 5867-71. ↗

### Editions

|            |          |                            |
|------------|----------|----------------------------|
| 2010-10-26 | Authored | Jupe, S.                   |
| 2010-11-01 | Edited   | Jupe, S.                   |
| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |

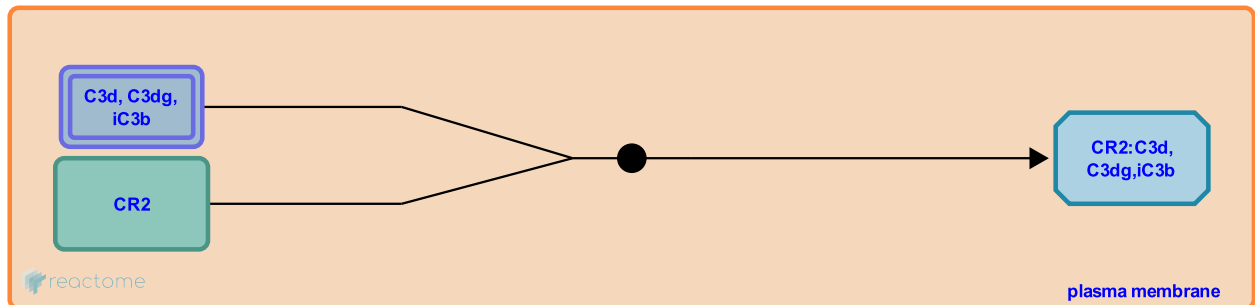
## CR2 binds C3d, C3dg, iC3b ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-8852874

**Type:** binding

**Compartments:** plasma membrane



Complement receptor CR2 (CD21) is predominantly expressed on the surface of B-cells and follicular dendritic cells (FDCs). It binds the C3 fragments C3dg, C3d, and with lower affinity, inactive C3b (iC3b) on the antigen surface, where it forms the B cell co-receptor complex with CD19 and CD81 (Matsumoto et al. 1993). Co-ligation of receptors due to C3dg opsonisation lowers the threshold for B cell activation by 1000 to 10,000 times (Dempsey et al. 1996, Mongini et al. 1997); the C3d:CR2 complex induces an increase of B cell receptor (BCR) signaling in the presence of C3d-opsonized antigen on the B cell surface (Cherukuri et al. 2001). C3 is required for the induction and maintenance of B-cell lineage memory cells in germinal centers (GCs), where B cells encounter antigen-antibody-C3 fragment complexes on the surface of FDCs (Klaus & Humphrey 1986). C3d-opsonized antigen binds to CR2 on FDCs, which can present the antigen and induce effector and memory B cells (Fang et al. 1998).

Complement fragments, iC3b and C3dg, are produced *in vivo* due to the actions of the complement serine protease, factor I. This enzyme cleaves C3b in the presence of cofactors (factor H, MCP/CD46, complement receptor 1/CR1/CD35) to generate iC3b. CR1 acts as a cofactor for further factor I-mediated cleavage to C3dg.

### Literature references

Tedder, TF., Weis, JJ., Fearon, DT. (1984). Identification of a 145,000 Mr membrane protein as the C3d receptor (CR2) of human B lymphocytes. *Proc. Natl. Acad. Sci. U.S.A.*, 81, 881-5. ↗

### Editions

|            |          |           |
|------------|----------|-----------|
| 2016-01-06 | Authored | Jupe, S.  |
| 2017-02-01 | Reviewed | Bulla, R. |
| 2017-02-01 | Edited   | Jupe, S.  |

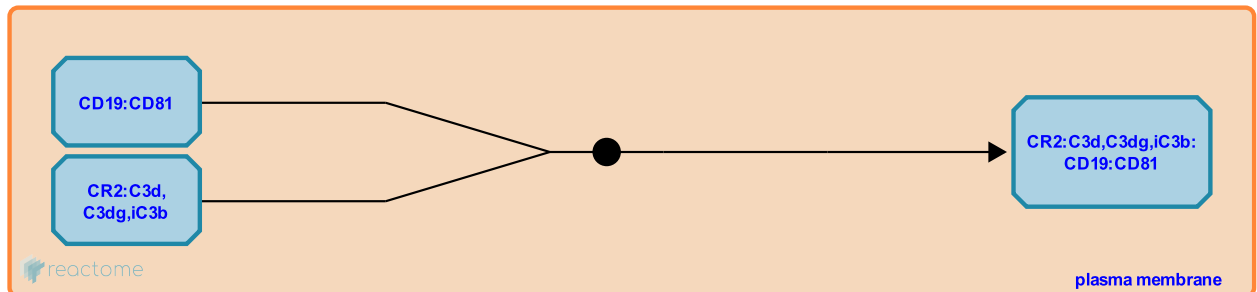
## CR2:C3d,C3dg,iC3b binds CD19:CD81 [↗](#)

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-8853252

**Type:** binding

**Compartments:** plasma membrane



Complement receptor CR2 (CD21), having bound to C3d, Cdg or 1C3b, forms the B cell co-receptor complex with CD19 and CD81 (Matsumoto et al. 1993).

### Literature references

Carter, RH., Martin, DR., Ahearn, JM., Matsumoto, AK., Klickstein, LB., Fearon, DT. (1993). Functional dissection of the CD21/CD19/TAPA-1/Leu-13 complex of B lymphocytes. *J. Exp. Med.*, 178, 1407-17. [↗](#)

### Editions

|            |          |           |
|------------|----------|-----------|
| 2016-01-06 | Authored | Jupe, S.  |
| 2017-02-01 | Reviewed | Bulla, R. |
| 2017-02-01 | Edited   | Jupe, S.  |

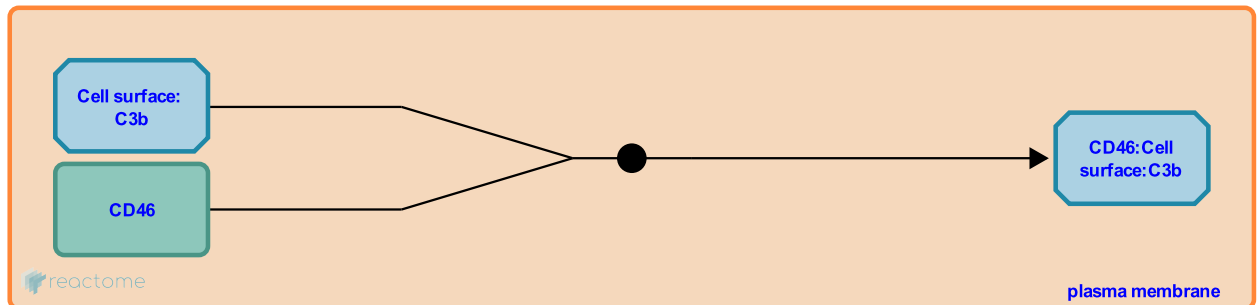
## CD46 binds C3b [↗](#)

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-1006143

**Type:** binding

**Compartments:** plasma membrane



Membrane cofactor protein (MCP; CD46) is a widely distributed C3b/C4b-binding cell surface glycoprotein which is a cofactor for Complement factor I.

**Followed by:** [Complement factor I binds to MCP, CR1:C4b, C3b](#)

### Literature references

Atkinson, JP., Barilla-LaBarca, ML., Lambris, JD., Liszewski, MK., Hourcade, D. (2002). Role of membrane cofactor protein (CD46) in regulation of C4b and C3b deposited on cells. *J Immunol*, 168, 6298-304. [↗](#)

Atkinson, JP., Seya, T. (1989). Functional properties of membrane cofactor protein of complement. *Biochem J*, 264, 581-8. [↗](#)

### Editions

|            |                  |                            |
|------------|------------------|----------------------------|
| 2010-11-09 | Authored, Edited | Jupe, S.                   |
| 2012-02-13 | Reviewed         | Bradley, DT., Fraczek, LA. |

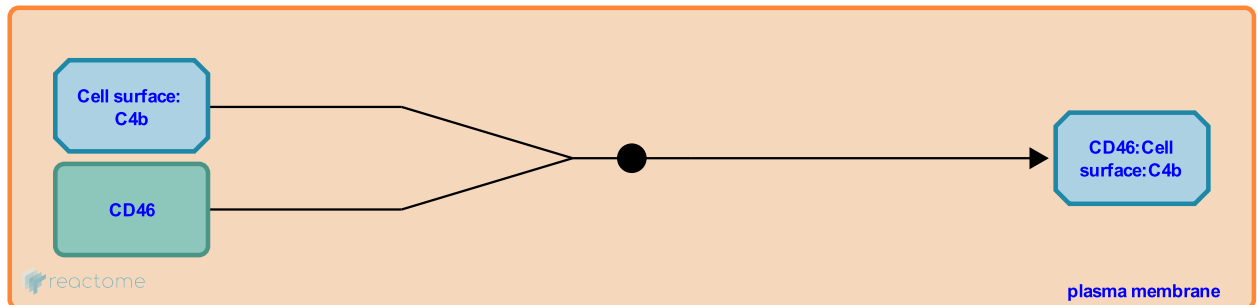
## CD46 binds C4b [↗](#)

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-8951486

**Type:** binding

**Compartments:** plasma membrane



Membrane cofactor protein (MCP; CD46) is a widely distributed cell surface glycoprotein that can bind C3b and C4b, which are cofactors for Complement factor I.

### Literature references

Atkinson, JP., Barilla-LaBarca, ML., Lambris, JD., Liszewski, MK., Hourcade, D. (2002). Role of membrane cofactor protein (CD46) in regulation of C4b and C3b deposited on cells. *J Immunol*, 168, 6298-304. [↗](#)

Atkinson, JP., Seya, T. (1989). Functional properties of membrane cofactor protein of complement. *Biochem J*, 264, 581-8. [↗](#)

### Editions

|            |          |                            |
|------------|----------|----------------------------|
| 2010-11-09 | Authored | Jupe, S.                   |
| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |
| 2016-12-07 | Edited   | Jupe, S.                   |

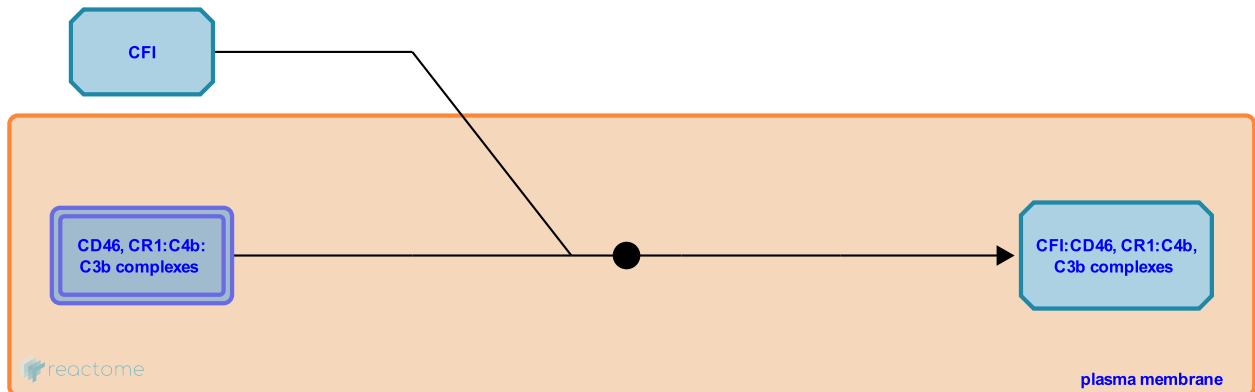
## Complement factor I binds to MCP, CR1:C4b, C3b ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-977602

**Type:** binding

**Compartments:** plasma membrane, extracellular region



Membrane cofactor protein (MCP, CD46) and Complement Receptor 1 (CR1) act as cofactors for the protease activity of complement factor I (CFI) which binds MCP or CR1 complexes with C3b or C4b, inactivating C3b/C4b.

**Preceded by:** [Displacement of C2a/Bb by CR1, CD46 binds C3b](#)

**Followed by:** [Factor I inactivates MCP/CR1-bound C4b/C3b](#)

### Literature references

Matsumoto, M., Yasuda, R., Nakanishi, I., Seya, T., Masaki, T. (1992). Factor I-dependent inactivation of human complement C4b of the classical pathway by C3b/C4b receptor (CR1, CD35) and membrane cofactor protein (MCP, CD46). *J Biochem*, 111, 573-8. ↗

Ross, GD., Newman, SL., Lambris, JD., Cain, JA. (1982). Generation of three different fragments of bound C3 with purified factor I or serum. I. Requirements for factor H vs CR1 cofactor activity. *J Immunol*, 129, 2051-60. ↗

### Editions

|            |          |                            |
|------------|----------|----------------------------|
| 2010-10-26 | Authored | Jupe, S.                   |
| 2010-11-01 | Edited   | Jupe, S.                   |
| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |

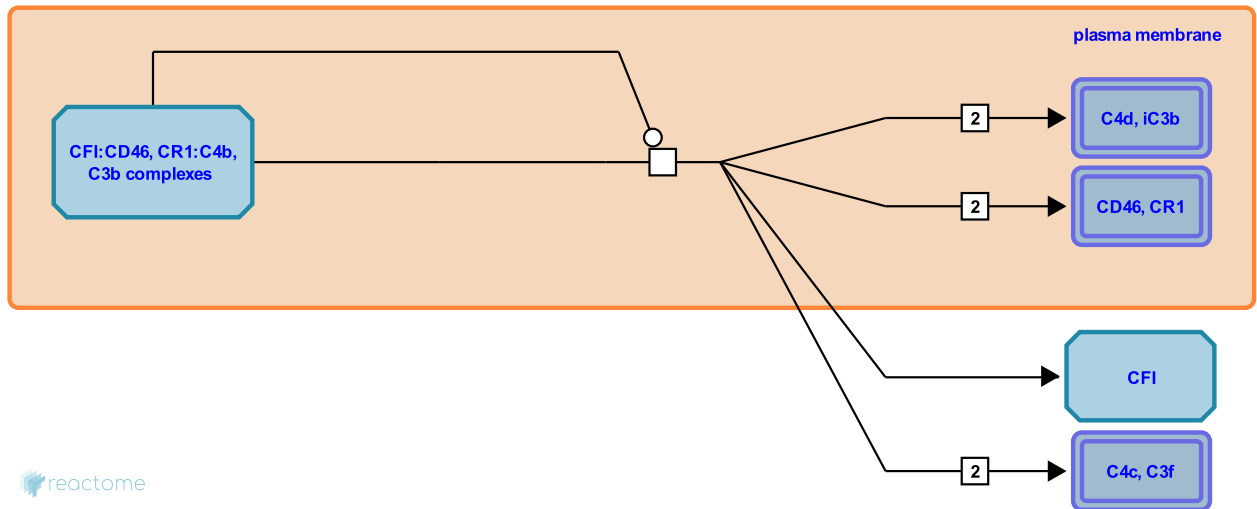
## Factor I inactivates MCP/CR1-bound C4b/C3b ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-977615

**Type:** transition

**Compartments:** plasma membrane, extracellular region



Factor I (CFI) cleaves the truncated alpha (a') chain of C4b between Arg-1336 and Asn-1337 and then again between Arg-956 and Thr-957, producing a 16 kDa fragment known as alpha4, derived from the C terminus of the a' chain, followed by a 27 kDa alpha3 fragment. The remaining alpha 2 (C4d) fragment stays covalently bound to the cell membrane while the complex of disulfide-linked alpha3, alpha4, beta chain and gamma chain are released (C4c) into the fluid phase (Fujita et al. 1978).

**Preceded by:** [Complement factor I binds to MCP, CR1:C4b, C3b](#)

**Followed by:** [Factor I cleaves iC3b](#)

### Literature references

Matsumoto, M., Yasuda, R., Nakanishi, I., Seya, T., Masaki, T. (1992). Factor I-dependent inactivation of human complement C4b of the classical pathway by C3b/C4b receptor (CR1, CD35) and membrane cofactor protein (MCP, CD46). *J Biochem*, 111, 573-8. ↗

Ross, GD., Newman, SL., Lambris, JD., Cain, JA. (1982). Generation of three different fragments of bound C3 with purified factor I or serum. I. Requirements for factor H vs CR1 cofactor activity. *J Immunol*, 129, 2051-60. ↗

Ichihara, C., Stroud, RM., Nagasawa, S. (1980). Cleavage of C4b by C3b inactivator: production of a nicked form of C4b, C4b', as an intermediate cleavage product of C4b by C3b inactivator. *J Immunol*, 125, 578-82. ↗

### Editions

|            |          |                            |
|------------|----------|----------------------------|
| 2010-10-26 | Authored | Jupe, S.                   |
| 2010-11-01 | Edited   | Jupe, S.                   |
| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |



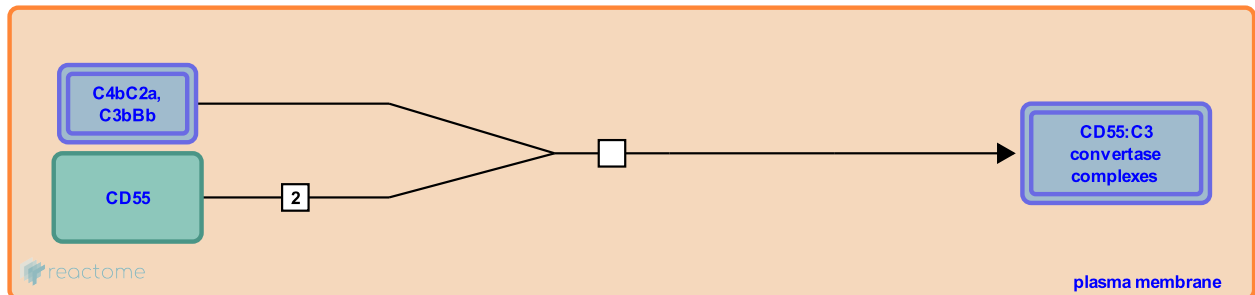
## CD55 (DAF) binds C3bBb, C4bC2a ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-981535

**Type:** transition

**Compartments:** plasma membrane



Decay-accelerating-factor (DAF, CD55) is a membrane-bound complement regulatory protein that inhibits autologous complement cascade activation. It is expressed on all cells that are in close contact with serum complement proteins, but also on cells outside the vascular space and on tumour cells. DAF binds to C3bBb and C4bC2a on cell surfaces, accelerating their dissociation and thereby inhibiting the amplification of complement. DAF can bind C3b and Bb, and must bind both for efficient decay acceleration. Although it can bind the inactive proenzymes C3b and C4b, the regulatory function of DAF is believed to be inhibition of activated C3 convertase enzymes (Harris et al. 2007).

**Followed by:** [CD55 \(DAF\) promotes C3bBb/C4bC2a dissociation](#)

### Literature references

Lea, SM., Pettigrew, DM., Morgan, BP., Harris, CL. (2007). Decay-accelerating factor must bind both components of the complement alternative pathway C3 convertase to mediate efficient decay. *J Immunol*, 178, 352-9. ↗

Atkinson, JP., Kuttner-Kondo, LA., Medof, ME., Mitchell, L., Hourcade, DE. (2002). Decay-accelerating factor (DAF), complement receptor 1 (CR1), and factor H dissociate the complement AP C3 convertase (C3bBb) via sites on the type A domain of Bb. *J Biol Chem*, 277, 1107-12. ↗

Kinoshita, T., Medof, ME., Nussenzweig, V. (1986). Endogenous association of decay-accelerating factor (DAF) with C4b and C3b on cell membranes. *J Immunol*, 136, 3390-5. ↗

### Editions

|            |          |                            |
|------------|----------|----------------------------|
| 2010-10-26 | Authored | Jupe, S.                   |
| 2010-11-01 | Edited   | Jupe, S.                   |
| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |

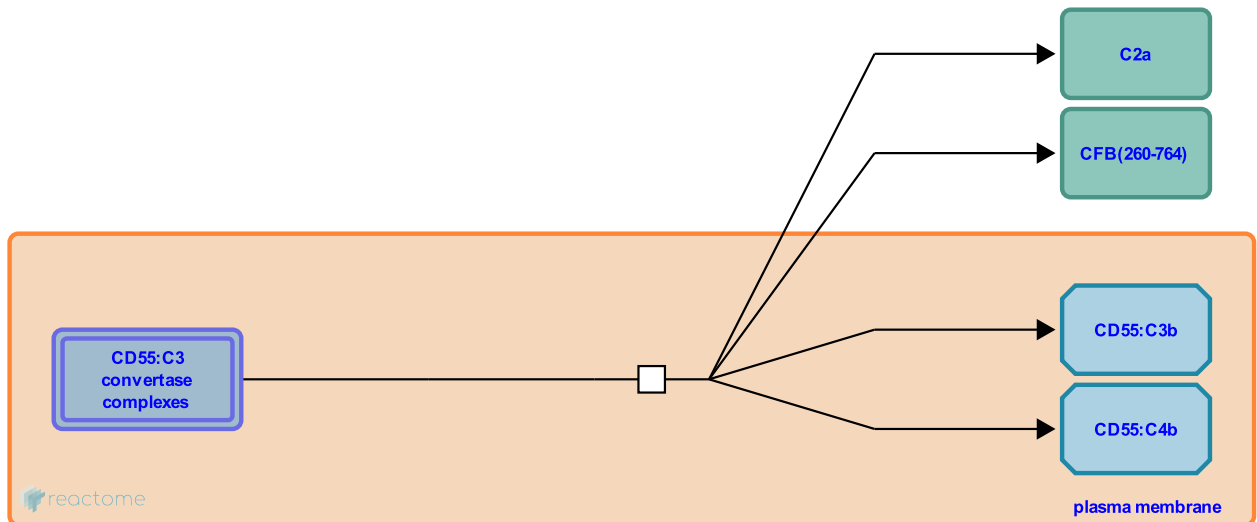
## CD55 (DAF) promotes C3bBb/C4bC2a dissociation ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-977619

**Type:** transition

**Compartments:** plasma membrane, extracellular region



Decay accelerating factor (DAF, CD55) is a widely distributed membrane protein. It accelerates the dissociation of C3bBb and C4bC2a, thereby inhibiting the amplification of complement. DAF can bind C3b and Bb but must bind both for efficient decay acceleration. The regulatory function of DAF is believed to be inhibition of activated C3 convertase enzymes rather than binding of inactive proenzymes (Harris et al. 2007).

**Preceded by:** [CD55 \(DAF\) binds C3bBb, C4bC2a](#)

### Literature references

Kinoshita, T., Medof, ME., Nussenzweig, V. (1984). Inhibition of complement activation on the surface of cells after incorporation of decay-accelerating factor (DAF) into their membranes. *J Exp Med*, 160, 1558-78. ↗

Brodbeck, WG., Medof, ME., Mold, C., Sperry, J., Liu, D. (1996). Localization of classical and alternative pathway regulatory activity within the decay-accelerating factor. *J Immunol*, 156, 2528-33. ↗

### Editions

|            |          |                            |
|------------|----------|----------------------------|
| 2010-10-26 | Authored | Jupe, S.                   |
| 2010-11-01 | Edited   | Jupe, S.                   |
| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |

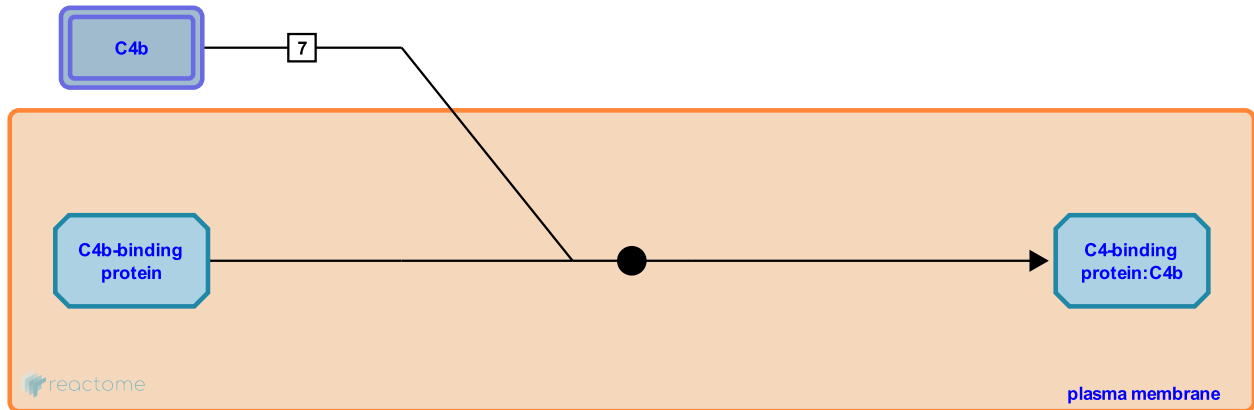
## C4b-binding protein binds C4b ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-977626

**Type:** binding

**Compartments:** plasma membrane, extracellular region



The most abundant form of C4b-binding protein (C4BP) consists of seven alpha-chains (70kDa) and one beta-chain (45kDa) all linked by disulphide bonds to form a native protein with a molecular weight of 570kDa (Hilarp et al. 1989). Each alpha chain can bind C4b; it is not known whether full occupancy is necessary for subsequent events. The beta chain binds and inactivates Protein S, a component of the coagulation system. C4BP down-regulates complement activity in several ways: It binds to C4b thus inhibiting the formation of the classical pathway C3 convertase C4bC2a; it acts as a decay accelerating factor for existing convertases, probably by promoting dissociation of C2a; it is a cofactor in Factor I mediated C4b proteolysis.

**Followed by:** [Complement factor I binds C4BP](#)

### Literature references

Dahlback, B., Muller-Eberhard, HJ., Smith, CA. (1983). Visualization of human C4b-binding protein and its complexes with vitamin K-dependent protein S and complement protein C4b. *Proc Natl Acad Sci U S A*, 80, 3461-5. ↗

Gigli, I., Ferreira, A., Scharfstein, J., Nussenzweig, V. (1978). Human C4-binding protein. I. Isolation and characterization. *J Exp Med*, 148, 207-22. ↗

Dahlback, B., Ziccardi, RJ., Muller-Eberhard, HJ. (1984). Characterization of the interaction of human C4b-binding protein with physiological ligands. *J Biol Chem*, 259, 13674-9. ↗

### Editions

|            |          |                            |
|------------|----------|----------------------------|
| 2010-10-26 | Authored | Jupe, S.                   |
| 2010-11-01 | Edited   | Jupe, S.                   |
| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |

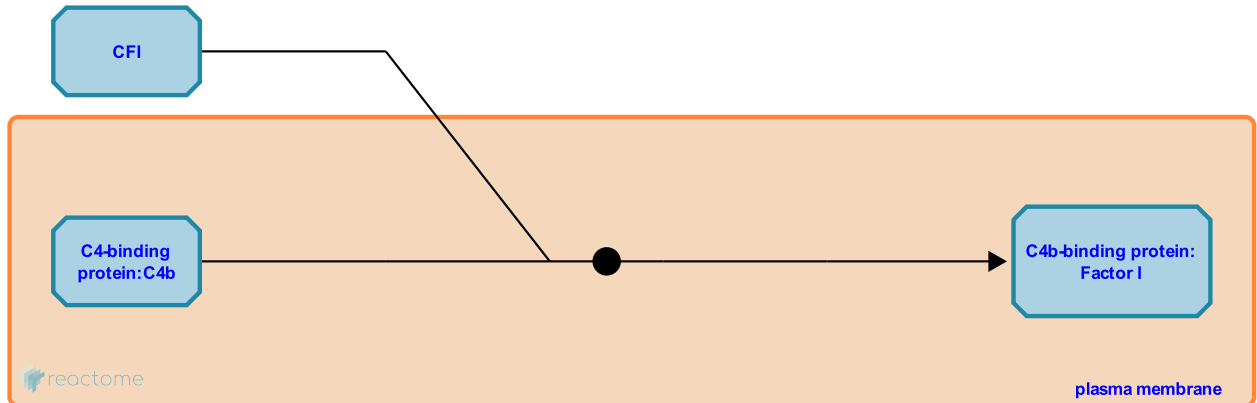
## Complement factor I binds C4BP ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-981658

**Type:** binding

**Compartments:** plasma membrane, extracellular region



C4b-binding protein is a cofactor for Complement Factor I (CFI), allowing it to bind and thereby mediating C4b proteolysis.

**Preceded by:** [C4b-binding protein binds C4b](#)

**Followed by:** [Complement factor I inactivates C4BP-bound C4b](#)

### Literature references

Gigli, I., Fujita, T., Nussenzweig, V. (1979). Modulation of the classical pathway C3 convertase by plasma proteins C4 binding protein and C3b inactivator. *Proc Natl Acad Sci U S A*, 76, 6596-600. ↗

Gigli, I., Fujita, T., Nussenzweig, V. (1978). Human C4-binding protein. II. Role in proteolysis of C4b by C3b-inactivator. *J Exp Med*, 148, 1044-51. ↗

### Editions

|            |          |                            |
|------------|----------|----------------------------|
| 2010-10-26 | Authored | Jupe, S.                   |
| 2010-11-01 | Edited   | Jupe, S.                   |
| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |

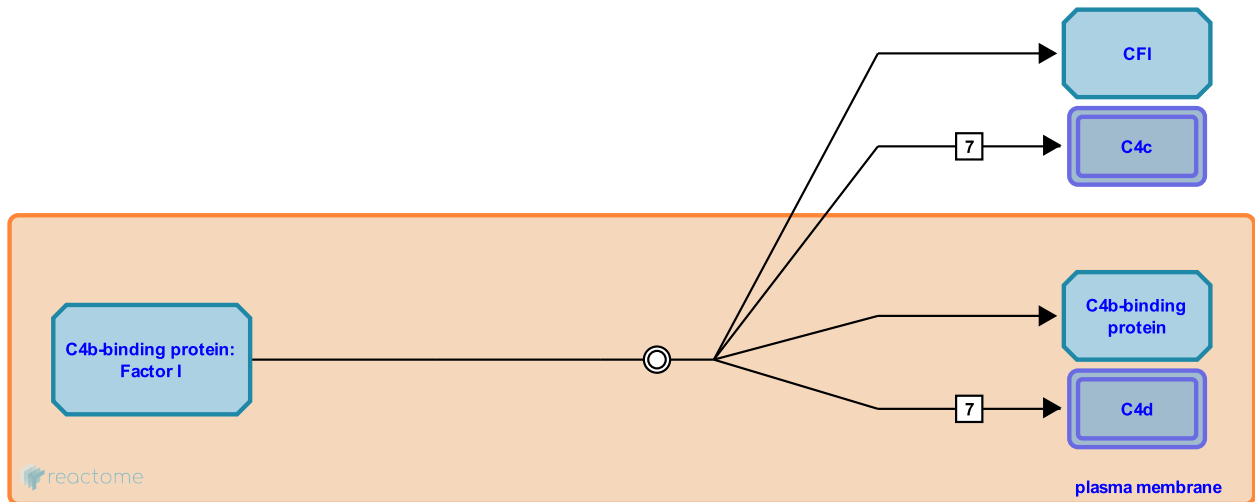
## Complement factor I inactivates C4BP-bound C4b ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-981637

**Type:** dissociation

**Compartments:** plasma membrane, extracellular region



C4b-binding protein is a cofactor in Factor I mediated C4b proteolysis. C4b is cleaved, releasing C4c, leaving C4d bound to the cell surface.

**Preceded by:** [Complement factor I binds C4BP](#)

### Literature references

Matsumoto, M., Yasuda, R., Nakanishi, I., Seya, T., Masaki, T. (1992). Factor I-dependent inactivation of human complement C4b of the classical pathway by C3b/C4b receptor (CR1, CD35) and membrane cofactor protein (MCP, CD46). *J Biochem*, 111, 573-8. ↗

### Editions

|            |          |                            |
|------------|----------|----------------------------|
| 2010-10-26 | Authored | Jupe, S.                   |
| 2010-11-01 | Edited   | Jupe, S.                   |
| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |

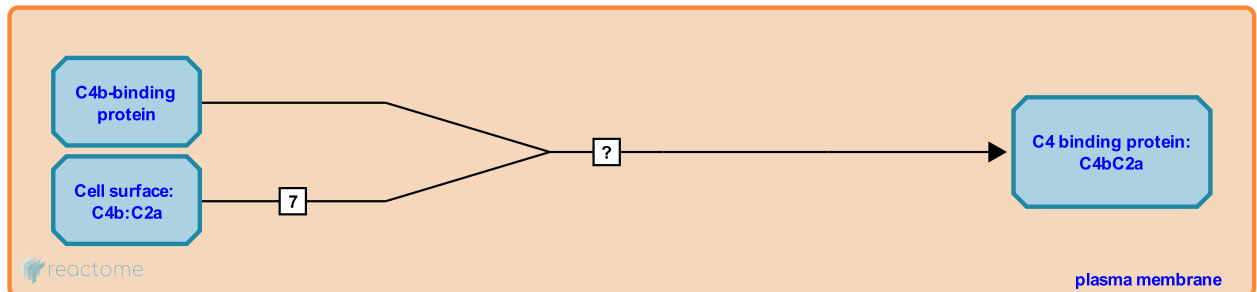
## C4b binding protein binds C4bC2a ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-981648

**Type:** uncertain

**Compartments:** plasma membrane



C4 binding protein accelerates the decay of C4bC2a in a dose-dependent fashion, without causing degradation of C4b, and is presumed to bind to the convertase to mediate this effect.

**Followed by:** [C4b binding protein displaces C2a](#)

### Literature references

Gigli, I., Fujita, T., Nussenzweig, V. (1979). Modulation of the classical pathway C3 convertase by plasma proteins C4 binding protein and C3b inactivator. *Proc Natl Acad Sci U S A*, 76, 6596-600. ↗

### Editions

|            |          |                            |
|------------|----------|----------------------------|
| 2010-10-26 | Authored | Jupe, S.                   |
| 2010-11-01 | Edited   | Jupe, S.                   |
| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |

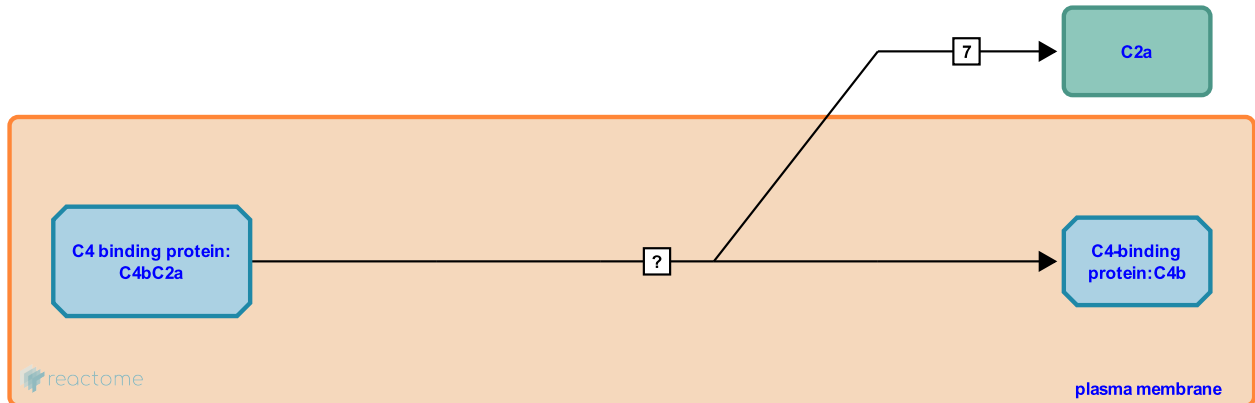
## C4b binding protein displaces C2a ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-981680

**Type:** uncertain

**Compartments:** plasma membrane, extracellular region



C4 binding protein accelerates the decay of C4bC2a in a dose-dependent fashion. The mechanism of this is poorly understood, but is distinct from Factor I mediated degradation of C4b and believed to represent the displacement of C2a from specific binding sites on C4b (Gigli et al. 1979).

**Preceded by:** [C4b binding protein binds C4bC2a](#)

### Literature references

Gigli, I., Fujita, T., Nussenzweig, V. (1979). Modulation of the classical pathway C3 convertase by plasma proteins C4 binding protein and C3b inactivator. *Proc Natl Acad Sci U S A*, 76, 6596-600. ↗

### Editions

|            |          |                            |
|------------|----------|----------------------------|
| 2010-10-26 | Authored | Jupe, S.                   |
| 2010-11-01 | Edited   | Jupe, S.                   |
| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |

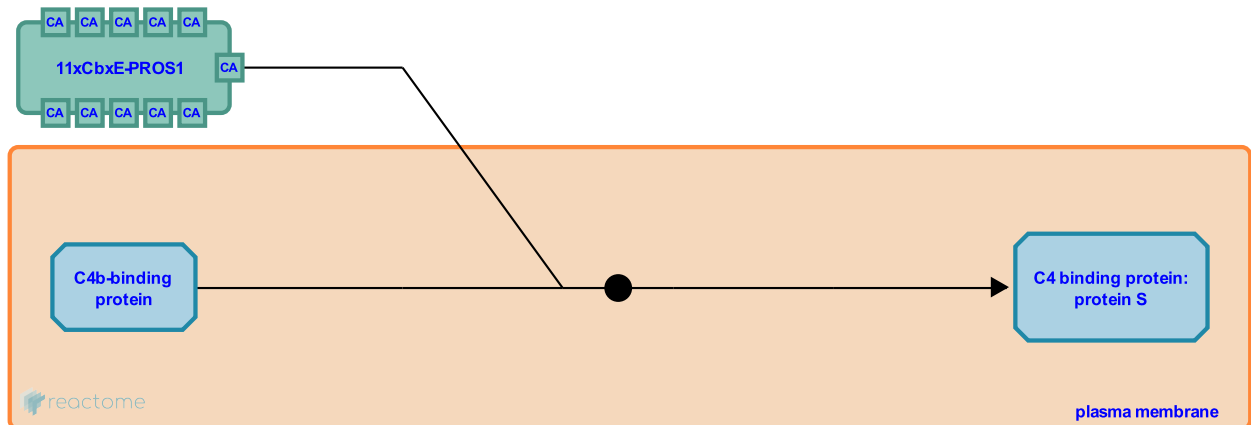
## C4b binding protein binds Protein S ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-981665

**Type:** binding

**Compartments:** plasma membrane, extracellular region



The beta subunit of C4b binding protein binds and inactivates Protein S, a vitamin K dependent anticoagulation factor. This may represent part of a mechanism for fine-tuning the process of phagocytosis (Kask et al. 2004).

### Literature references

Dahlback, B., Stenflo, J. (1981). High molecular weight complex in human plasma between vitamin K-dependent protein S and complement component C4b-binding protein. *Proc Natl Acad Sci U S A*, 78, 2512-6. ↗

### Editions

|            |          |                            |
|------------|----------|----------------------------|
| 2010-10-26 | Authored | Jupe, S.                   |
| 2010-11-01 | Edited   | Jupe, S.                   |
| 2012-02-13 | Reviewed | Bradley, DT., Fraczek, LA. |



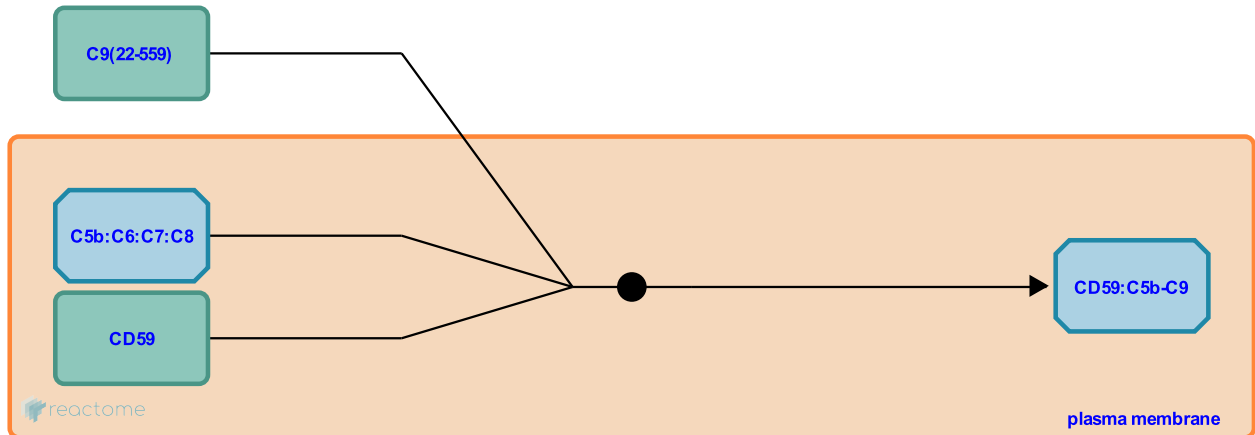
## CD59 inhibits MAC formation ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-2530445

**Type:** binding

**Compartments:** plasma membrane, extracellular region



CD59, the major inhibitor of the complement membrane attack complex, is an 18–20 kDa glycoprotein, linked to the membrane via a glycosylphosphatidylinositol (GPI)-anchor. It interacts with complement components C8 and C9 during assembly of the membrane attack complex (MAC) and inhibits C9 polymerization, thus preventing the formation of MAC [Lehto T and Meri S. 1993;Rollins SA et al 1991]

### Literature references

Christmas, SE., de la Mata Espinosa, CT., Halliday, D., Johnson, PM., Cummerson, JA., Buxton, CA. (2006). Levels of expression of complement regulatory proteins CD46, CD55 and CD59 on resting and activated human peripheral blood leucocytes. *Immunology*, 119, 522-8. ↗

Morgan, BP., Meri, S., Lehto, T. (1997). Binding of human and rat CD59 to the terminal complement complexes. *Immunology*, 90, 121-8. ↗

Abagyan, R., Morgan, BP., Tomlinson, S., Smith, CA., Song, H., Huang, Y. (2005). Insights into the human CD59 complement binding interface toward engineering new therapeutics. *J. Biol. Chem.*, 280, 34073-9. ↗

Lehto, T., Meri, S. (1993). Interactions of soluble CD59 with the terminal complement complexes. CD59 and C9 compete for a nascent epitope on C8. *J Immunol*, 151, 4941-9. ↗

Fedarovich, A., Davies, C., Tomlinson, S., Huang, Y. (2007). Crystal structure of CD59: implications for molecular recognition of the complement proteins C8 and C9 in the membrane-attack complex. *Acta Crystallogr D Biol Crystallogr*, 63, 714-21. ↗

### Editions

|            |          |               |
|------------|----------|---------------|
| 2012-10-17 | Authored | Shamovsky, V. |
| 2013-05-28 | Reviewed | Bradley, DT.  |
| 2013-05-28 | Edited   | Shamovsky, V. |

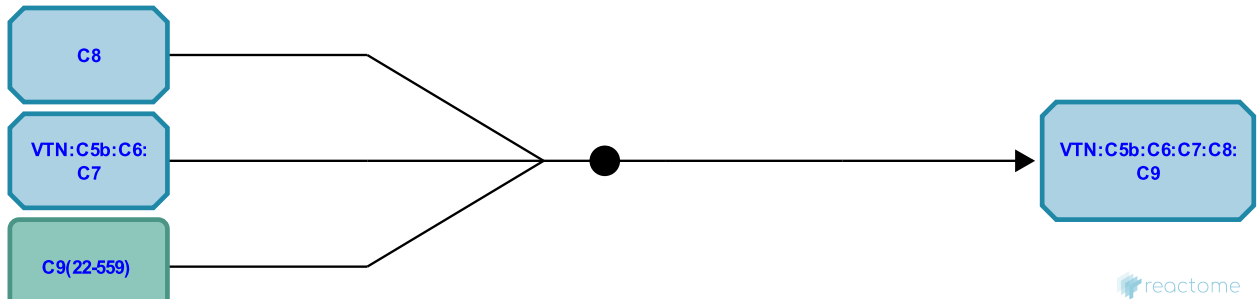
## Formation of soluble VTN:C5b-C9 ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-2530429

**Type:** binding

**Compartments:** extracellular region



Complement proteins C8 and C9 can bind to VTN:C5b:C6:C7 to form soluble C5b-C9 complex in plasma. The vitronectin binding to C5b-C9 complex prevents C9 polymerization by rendering it water-soluble and lytic inactive.

### Literature references

Charlesworth, JA., Morris, CA., Sheehan, M., Pussell, BA. (1995). Complement inhibition by human vitronectin involves non-heparin binding domains. *Clin. Exp. Immunol.*, 101, 136-41. ↗

Halstensen, TS., Hugo, F., Preissner, KT., Käflein, R., Mollnes, TE., Bhakdi, S. (1988). Complement S-protein (vitronectin) is associated with cytolytic membrane-bound C5b-9 complexes. *Clin. Exp. Immunol.*, 74, 459-64. ↗

Podack, ER., Müller-Eberhard, HJ., Preissner, KP. (1989). SC5b-7, SC5b-8 and SC5b-9 complexes of complement: ultrastructure and localization of the S-protein (vitronectin) within the macromolecules. *Eur. J. Immunol.*, 19, 69-75. ↗

### Editions

|            |          |               |
|------------|----------|---------------|
| 2012-10-17 | Authored | Shamovsky, V. |
| 2013-05-28 | Reviewed | Bradley, DT.  |
| 2013-05-28 | Edited   | Shamovsky, V. |

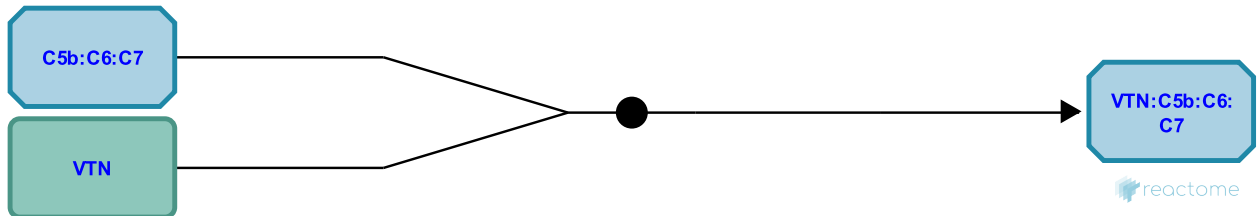
## Vitronectin (VTN) binds to C5b:C6:C7 [↗](#)

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-2530453

**Type:** binding

**Compartments:** extracellular region



Vitronectin interacts with C5b:C6:C7 complex preventing it from the binding with the cell membrane

### Literature references

Charlesworth, JA., Morris, CA., Sheehan, M., Pussell, BA. (1995). Complement inhibition by human vitronectin involves non-heparin binding domains. *Clin. Exp. Immunol.*, 101, 136-41. [↗](#)

Halstensen, TS., Hugo, F., Preissner, KT., Käflein, R., Mollnes, TE., Bhakdi, S. (1988). Complement S-protein (vitronectin) is associated with cytolytic membrane-bound C5b-9 complexes. *Clin. Exp. Immunol.*, 74, 459-64. [↗](#)

Podack, ER., Müller-Eberhard, HJ., Preissner, KP. (1989). SC5b-7, SC5b-8 and SC5b-9 complexes of complement: ultrastructure and localization of the S-protein (vitronectin) within the macromolecules. *Eur. J. Immunol.*, 19, 69-75. [↗](#)

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|            |          |               |
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| 2012-10-17 | Authored | Shamovsky, V. |
| 2013-05-28 | Reviewed | Bradley, DT.  |
| 2013-05-28 | Edited   | Shamovsky, V. |

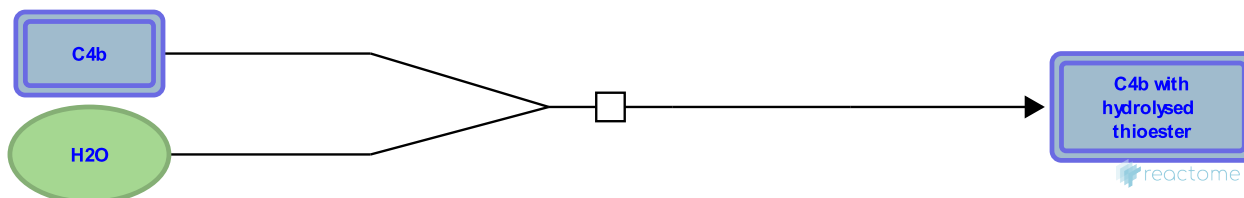
## Hydrolysis of internal thioester in C4b ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-2855047

**Type:** transition

**Compartments:** extracellular region



Cleavage of C4 exposes a highly reactive thioester bond on the C4b molecule. The thioester bond is rapidly inactivated by hydrolysis if C4b does not bind to the target cell surface [Sepp A et al 1993].

### Literature references

Campbell, RD., Sepp, A., Law, SK., Anderson, MJ., Willis, AC., Dodds, AW. (1993). Covalent binding properties of the human complement protein C4 and hydrolysis rate of the internal thioester upon activation. *Protein Sci*, 2, 706-16.

↗

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|            |          |               |
|------------|----------|---------------|
| 2012-10-17 | Authored | Shamovsky, V. |
| 2013-05-28 | Reviewed | Bradley, DT.  |
| 2013-05-28 | Edited   | Shamovsky, V. |

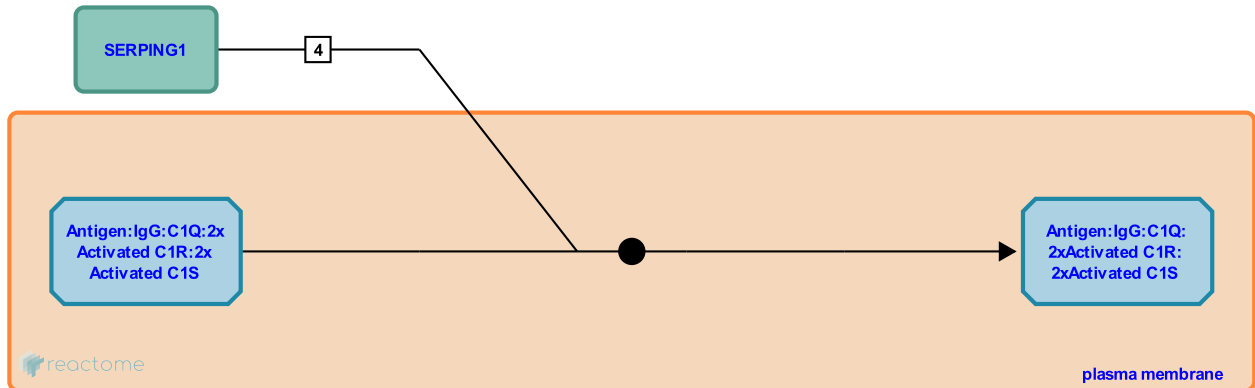
## C1-Inh binds Antigen: antibody: C1 complex activated C1r, C1s ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-8852266

**Type:** binding

**Compartments:** plasma membrane, extracellular region



The plasma protease C1 inhibitor (C1Inh, SERPING1) can bind the activated C1r and C1s proteases in the activated C1 complex, rendering them proteolytically inactive (Sim et al. 1979a) and leading to the disassembly of the C1 complex, releasing inactive C1r:C1Inh and C1s:C1Inh complexes (Arlaud et al. 1979, Sim et al. 1979b, Ziccardi & Cooper 1979). C1Inh also inhibits and controls certain non-antibody-induced as well as spontaneous C1 activation. Thus C1Inh plays an important role in regulating nonspecific complement activation (Ziccardi et al. 1983). C1Inh is also a major physiological inhibitor of kallikrein (Ratnoff et al. 1969), coagulation factors XIa and XIIa (Forbes et al. 1970), and the enzymatically active fragments derived from factor XIIa (factor XII<sub>f</sub>) (Schreiber et al. 1973).

**Followed by:** [C1-Inh binds and inactivates C1r, C1s](#)

### Literature references

Sim, RB., Arlaud, GJ., Reboul, A., Villiers, CL., Colomb, MG. (1979). Interaction of 125I-labelled complement sub-components C-1r and C-1s with protease inhibitors in plasma. *FEBS Lett.*, 97, 111-5. ↗

### Editions

|            |          |           |
|------------|----------|-----------|
| 2016-01-06 | Authored | Jupe, S.  |
| 2017-02-01 | Reviewed | Bulla, R. |
| 2017-02-01 | Edited   | Jupe, S.  |

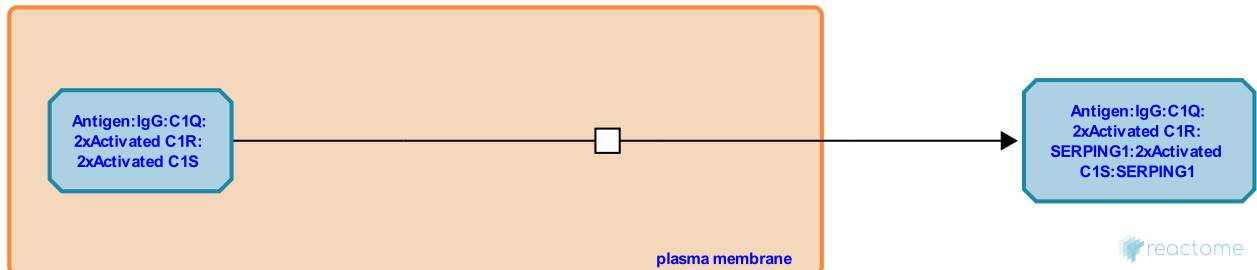
## C1-Inh binds and inactivates C1r, C1s ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-9021306

**Type:** transition

**Compartments:** plasma membrane, extracellular region



The plasma protease C1 inhibitor (C1Inh, SERPING1) forms proteolytically inactive stoichiometric covalent complexes with the C1r and C1s proteases (Sim et al. 1979a). This effectively disassembles the C1 complex, releasing inactive C1r:C1Inh and C1s:C1Inh complexes (Arlaud et al. 1979, Sim et al. 1979b, Ziccardi & Cooper 1979). C1Inh also inhibits and controls certain non-antibody-induced as well as spontaneous C1 activation. Thus C1Inh plays an important role in regulating nonspecific complement activation (Ziccardi et al. 1983). C1Inh is also a major physiological inhibitor of kallikrein (Ratnoff et al. 1969), coagulation factors XIa and XIIa (Forbes et al. 1970), and the enzymatically active fragments derived from factor XIIa (factor XII<sub>f</sub>) (Schreiber et al. 1973).

**Preceded by:** [C1-Inh binds Antigen: antibody: C1 complex activated C1r, C1s](#)

**Followed by:** [Antigen:IgG:C1Q:2xActivated C1R:SERPING1:2xActivated C1S:SERPING1 dissociates](#)

### Literature references

Sim, RB., Arlaud, GJ., Reboul, A., Villiers, CL., Colomb, MG. (1979). Interaction of 125I-labelled complement sub-components C-1r and C-1s with protease inhibitors in plasma. *FEBS Lett.*, 97, 111-5. ↗

### Editions

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| 2017-02-01 | Reviewed | Bulla, R. |
| 2017-02-01 | Edited   | Jupe, S.  |

# Antigen:IgG:C1Q:2xActivated C1R:SERPING1:2xActivated C1S:SERPING1 dissociates

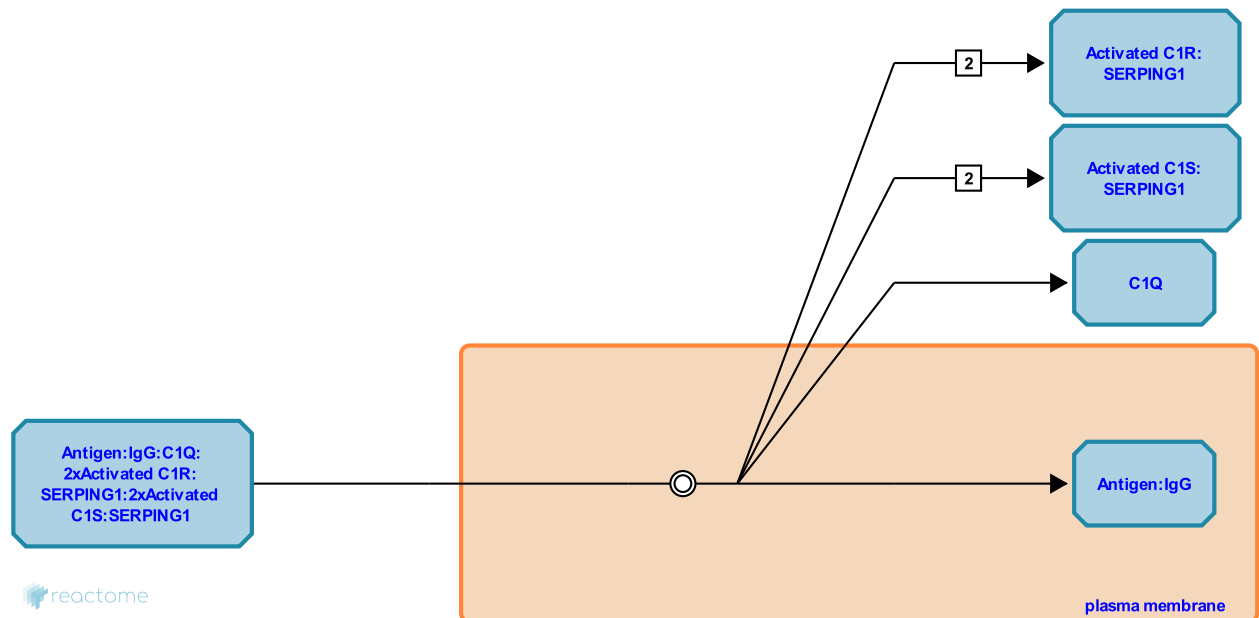


**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-8852481

**Type:** dissociation

**Compartments:** plasma membrane, extracellular region



Binding of the plasma protease C1 inhibitor (C1Inh, SERPING1) to the C1s and C1r subunits of the C1 complex leads to C1 disassembly, releasing inactive C1r:C1Inh and C1s:C1Inh complexes (Arlaud et al. 1979, Sim et al. 1979, Ziccardi & Cooper 1979). Thus C1Inh plays an important role in regulating nonspecific complement activation (Ziccardi et al. 1983).

**Preceded by:** [C1-Inh binds and inactivates C1r, C1s](#)

## Literature references

Sim, RB., Arlaud, GJ., Reboul, A., Colomb, MG. (1979). Interaction of C1-inhibitor with the C1r and C1s subcomponents in human C1. *Biochim. Biophys. Acta*, 576, 151-62. [↗](#)

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| 2016-01-06 | Authored | Jupe, S.  |
| 2017-02-01 | Reviewed | Bulla, R. |
| 2017-02-01 | Edited   | Jupe, S.  |

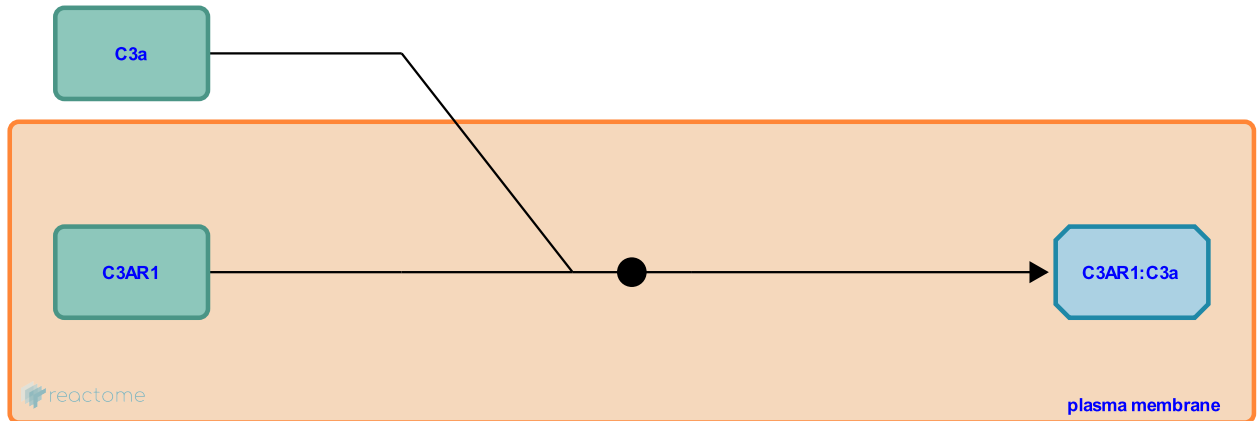
## C3a receptor binds anaphylatoxin C3a ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-444647

**Type:** binding

**Compartments:** plasma membrane, extracellular region



The complement component 3a receptor (C3AR) binds C3a, a 77-amino acid anaphylatoxin generated after proteolytic cleavage of C3 and C5 in response to complement activation. C3a is involved in a variety of inflammatory responses including chemotaxis and activation of granulocytes, mast cells and macrophages (Peng et al. 200, Klos et al. 2009).

### Literature references

Zeng, Z., Jurewicz, AJ., Hertzberg, RP., Nuthulaganti, P., Li, Y., Sarau, HM. et al. (1996). Molecular cloning and characterization of the human anaphylatoxin C3a receptor. *J Biol Chem*, 271, 20231-4. ↗

### Editions

|            |          |                 |
|------------|----------|-----------------|
| 2009-10-23 | Authored | Jupe, S.        |
| 2009-12-12 | Reviewed | D'Eustachio, P. |
| 2010-03-01 | Edited   | Jupe, S.        |



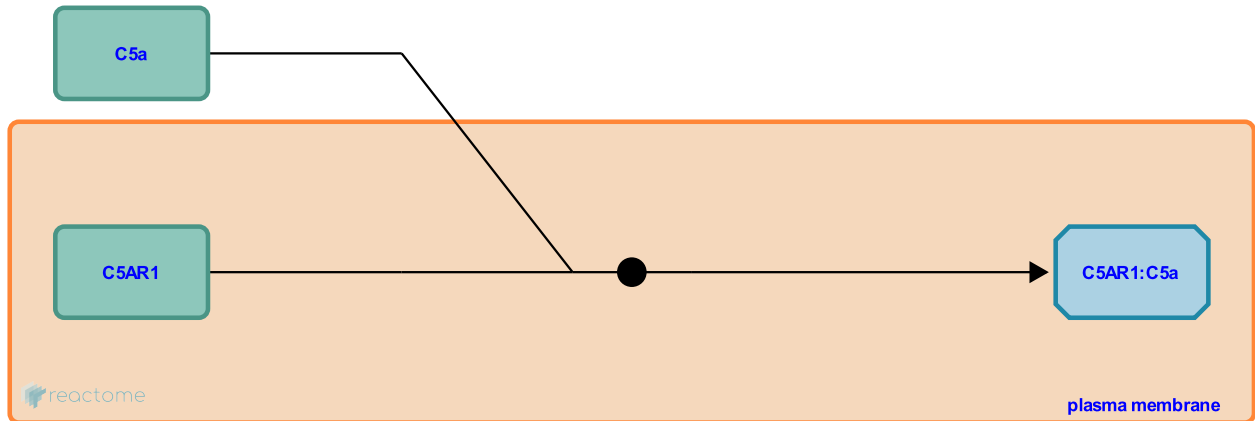
## C5a receptor binds C5a anaphylatoxin [↗](#)

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-375395

**Type:** binding

**Compartments:** plasma membrane, extracellular region



C5a (Fernandez HN and Hugli TE, 1978) is a protein fragment released from complement component C5. C5a is a potent anaphylatoxin, causing the release of histamine from mast cells and also being an effective leukocyte attractant. The C5a receptor (complement component 5a receptor 1, C5AR1; Cluster of Differentiation 88, CD88) (Gerard NP and Gerard C, 1991) mediates the pro-inflammatory and chemotactic actions of C5a.

### Literature references

Gerard, C., Gerard, NP. (1991). The chemotactic receptor for human C5a anaphylatoxin. *Nature*, 349, 614-7. [↗](#)

### Editions

|            |          |                 |
|------------|----------|-----------------|
| 2008-08-21 | Authored | Jassal, B.      |
| 2008-09-01 | Reviewed | Bockaert, J.    |
| 2008-09-01 | Edited   | D'Eustachio, P. |

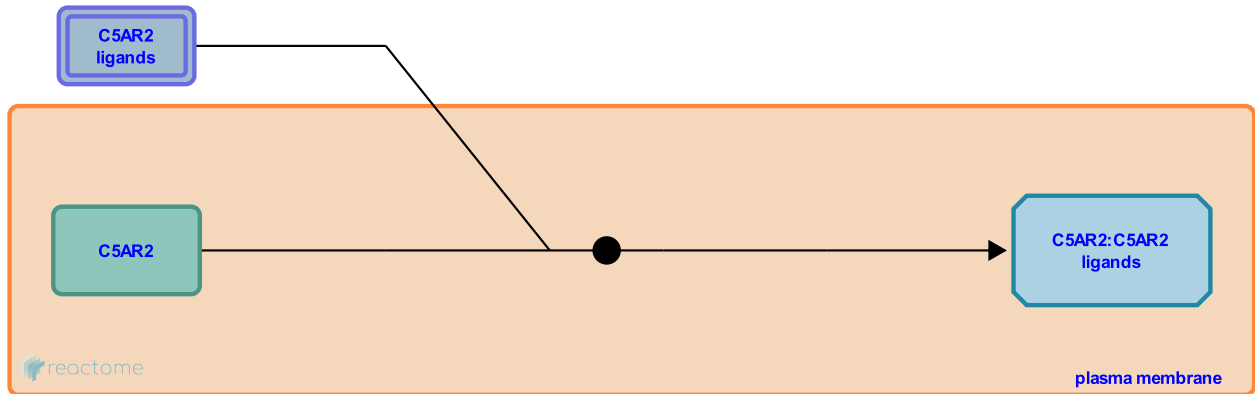
## C5AR2 binds anaphylatoxins and their desArginated derivatives ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-964811

**Type:** binding

**Compartments:** plasma membrane, extracellular region



C5AR2 (GPR77, C5L2) has been described as a receptor for the chemotactic and inflammatory peptides anaphylatoxin C5a, C4a and C3a and even their des-arginated derivatives. Highest binding affinity was for C3a-desArg, also called Acylation Stimulating Protein (ASP), produced from C3a following arginine removal by carboxypeptidases. Binding of C3a and its derivatives has been disputed (Johswich et al. 2006) leading to suggestions that this receptor may be a C5a scavenger. It is weakly coupled to G(i)-mediated signaling pathways and believed to function primarily as a decoy receptor though it can interact with beta arrestin (Van Lith et al. 2009).

### Literature references

Cain, SA., Monk, PN. (2002). The orphan receptor C5L2 has high affinity binding sites for complement fragments C5a and C5a des-Arg(74). *J Biol Chem*, 277, 7165-9. ↗

Cain, SA., Sniderman, AD., Maslowska, M., Monk, PN., Kalant, D., Cianflone, K. (2003). The chemoattractant receptor-like protein C5L2 binds the C3a des-Arg77/acylation-stimulating protein. *J Biol Chem*, 278, 11123-9. ↗

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| 2010-09-10 | Authored, Edited | Jupe, S.   |
| 2010-10-01 | Reviewed         | Jassal, B. |

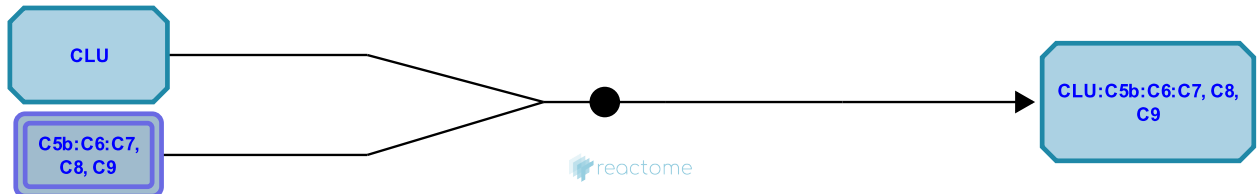
## Clusterin binds C5b-C7, C8, C9 ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-8852580

**Type:** binding

**Compartments:** extracellular region



Clusterin is a dimer of two fragments of the same translation product, which are disulfide bonded by five cysteines on each peptide (Tobe et al. 1991). It is able to modulate the terminal complement cascade in vitro and prevent cellular lysis by the membrane attack complex (MAC), C5b-9. Clusterin forms complexes with C5b:C6:C7, or C5b:C6:C7:C8 or C5b:C6:C7:C8:C9, as the proteins assemble into the amphiphilic MAC. Clusterin binding renders the complexes soluble and lytically inactive (Jenne & Tschopp 1989, Choi et al. 1989, Murphy et al. 1989, Tschopp et al. 1993).

### Literature references

Chonn, A., Hertig, S., French, LE., Tschopp, J. (1993). Clusterin, the human apolipoprotein and complement inhibitor, binds to complement C7, C8 beta, and the b domain of C9. *J. Immunol.*, 151, 2159-65. ↗

### Editions

|            |          |           |
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| 2016-01-06 | Authored | Jupe, S.  |
| 2017-02-01 | Reviewed | Bulla, R. |
| 2017-02-01 | Edited   | Jupe, S.  |

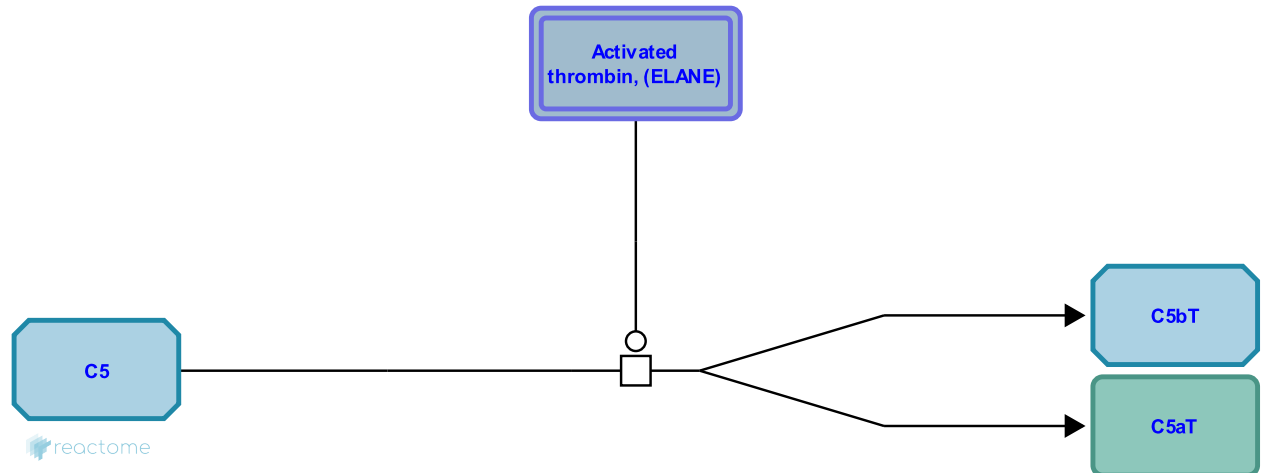
## Thrombin, ELANE cleave C5 ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-8852716

**Type:** transition

**Compartments:** extracellular region



Thrombin, coagulation factors XIa, Xa, IXa and plasmin (Amara et al. 2010) can cleave C3 and C5 to generate C3a and C5a. Neutrophil elastase (ELANE) can cleave C5 generating an active C5a-like fragment (Vogt 2000).

Under normal conditions, thrombin cleavage of C5 may not be a physiologically significant reaction (Bagic et al. 2015) but the combined action of thrombin and convertases appears to enhance the efficiency of the lytic pathway (Krisinger et al. 2012). Clotting-induced production of thrombin leads to cleavage of C5 at the atypical site R947 in the CUB domain. C5a can be released from the atypical C5a fragment (termed C5aT) by conventional C5 convertases; the truncated C5b fragment, termed C5bT, can form a C5bT-9 membrane attack complex that has significantly increased lytic activity (Krisinger et al. 2012).

### Literature references

Krisinger, MJ., Conway, EM., Goebeler, V., Lu, Z., Pryzdial, EL., Myles, T. et al. (2012). Thrombin generates previously unidentified C5 products that support the terminal complement activation pathway. *Blood*, 120, 1717-25. ↗

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| 2016-01-06 | Authored | Jupe, S.  |
| 2017-02-01 | Reviewed | Bulla, R. |
| 2017-02-01 | Edited   | Jupe, S.  |

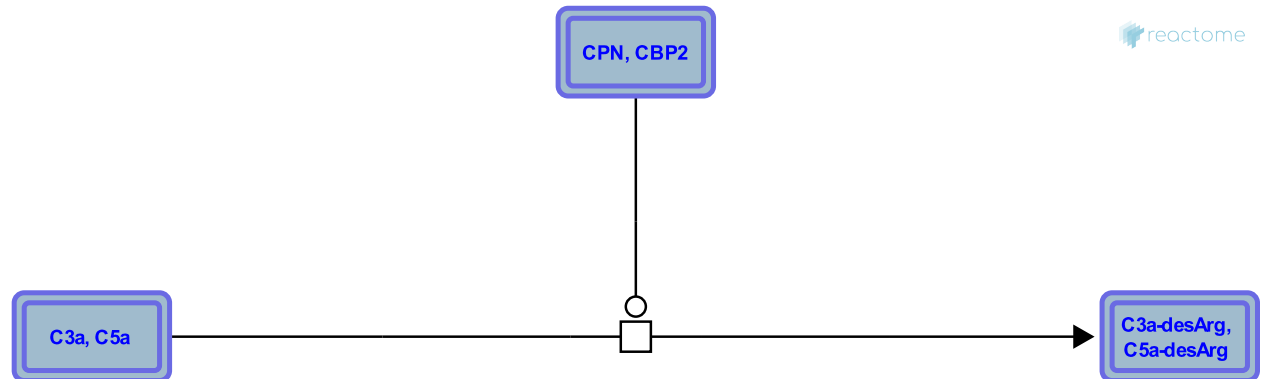
## CPN, CPB2 cleave C3a, C5a ↗

**Location:** [Regulation of Complement cascade](#)

**Stable identifier:** R-HSA-8852809

**Type:** transition

**Compartments:** extracellular region



Carboxypeptidase N (CPN) is able to inactivate the complement anaphylatoxins C3a, C4a, and C5a (Bokisch & Müller-Eberhard 1970), 74-77 amino acid peptides that are released during complement activation. They mediate smooth muscle contraction, vasodilation, release of histamine from mast cells, and chemotaxis of selective bone marrow derived myeloid cells. C3a and C5a mediate their activities by binding the C3a receptor (C3AR1) and C5a receptor (C5AR1), respectively. CPN regulates these anaphylatoxins by removing their carboxy-terminal arginines, which reduces their biological activities 10-100-fold (Ember et al. 1998).

Carboxypeptidase B2 (Plasma carboxypeptidase B, Thrombin-activable fibrinolysis inhibitor, TAF1, CPB2) also can convert C3a and C5a to C3a-desArg and C5a-desArg (Campbell et al. 2002). C3a-desArg cannot bind C3AR1, and C5a-desArg has a 90% decrease in pro-inflammatory activity compared to C5a (Sayah et al. 2003).

CPN is a tetramer comprised of two heterodimers each consisting of a CPN1 and CPN2 subunit (Levin et al. 1982, Keil et al. 2007). The catalytic CPN1 subunit ranges in size from 48 kDa to 55 kDa. This reflects processing by trypsin or plasmin, which can remove a C-terminal segment to produce the 48 kDa form, and cleave at Arg218-Arg219 to produce two peptide chains held together in an active conformation by non-covalent bonds (Levin et al. 1982, Quagraine et al. 2005). This step increases the catalytic activity of CPN towards chromogenic substrates.

### Literature references

- Müller-Eberhard, HJ., Bokisch, VA. (1970). Anaphylatoxin inactivator of human plasma: its isolation and characterization as a carboxypeptidase. *J. Clin. Invest.*, 49, 2427-36. ↗
- Okada, H., Okada, N., Campbell, WD., Lazoura, E. (2002). Inactivation of C3a and C5a octapeptides by carboxypeptidase R and carboxypeptidase N. *Microbiol. Immunol.*, 46, 131-4. ↗

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|            |          |           |
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| 2016-01-06 | Authored | Jupe, S.  |
| 2016-08-04 | Edited   | Jupe, S.  |
| 2017-02-01 | Reviewed | Bulla, R. |

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