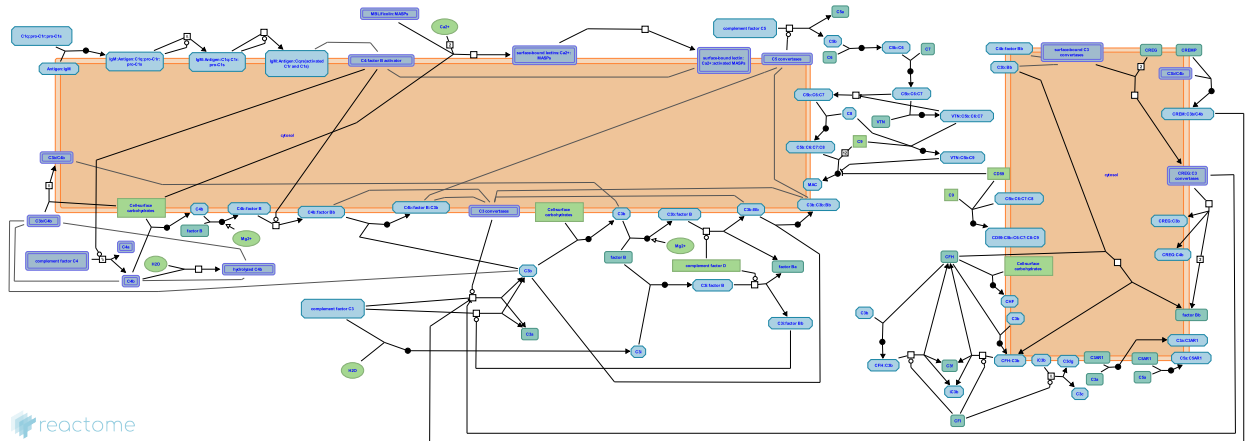


# Complement Cascade



D'Eustachio, P., Jupe, S., Shamovsky, V.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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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/).

25/04/2024

## 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

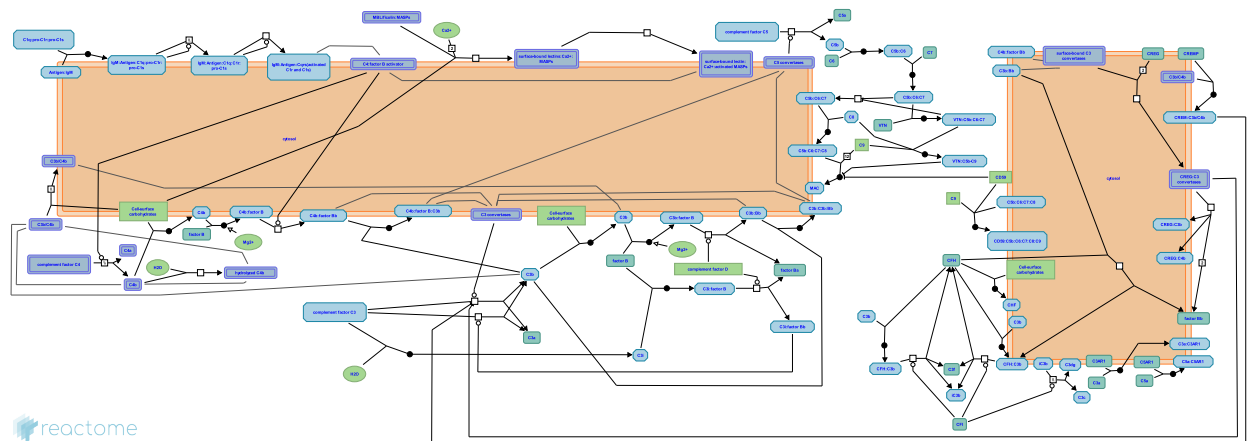
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Reactome database release: 88

This document contains 6 pathways and 6 reactions ([see Table of Contents](#))

## Complement Cascade ↗

Stable identifier: R-GGA-2132285



The complement system is the first line of defense against invading microbes. It consists of a large number of distinct proteins, which circulate in the blood stream in functionally inactive states. When activated, complement components assemble on the surface of a target cell. The activation of one component induces its proteolytic function that acts on the next component in the cascade, cleaving it into biologically active fragments. In mammals, the complement system is activated via three distinct pathways: the classical, lectin and alternative pathways. All three pathways merge at the proteolytic cleavage of component C3 to form the key molecule C3b. The activation of the complement system leads to four principal outcomes: (1) opsonization of target cells to enhance phagocytosis (2) lysis of target cells via an assembly of the membrane attack complex (MAC) on the pathogen surface (3) production of anaphylatoxins that are involved in the host inflammatory response (4) clearance of antibody-antigen complexes.

Avian species (chicken, turkey and duck) have been reported to induce functional complement pathways in response to immunization with sheep red blood cells (SRBC) [Ellis MG et al 1989; Koppenheffer TL et al 1999; Baelmans R et al 2005]. Complement activation in chicken was also shown to mediate host response against bacterial and viral infections [Skeeles JK et al 1979a, b; Ohta H et al 1983; Laursen SB and Nielsen OL 2000]. Immune competence of the distinct chicken ecotypes was assessed by measuring complement hemolytic activity after immunization with SRBC [Baelmans R et al 2004; Baelmans R et al 2005]. Both classical  $\text{Ca}^{2+}$  dependent complement pathway (CPW) and alternative calcium-independent complement pathway (APW), as well as total Ig (IgG and IgM antibody) responses were detected. However, the type and magnitude of immune response varied for individual chickens even within the same ecotype.

Analysis of genome data revealed that mammals and aves seem to share practically the same set of complement genes [Nonaka M and Kimura A 2006]. Indeed, most of the components of the classical and alternative complement pathways have been found in the chicken genome. However, an absence of some components such as chicken C9, factor D, properdin, MASP-1 has been also reported [Barta O and Hubbert NL 1978; Lynch et al 2005; Koch C 1986; Mikrou A and Zarkadis IK. 2010]. In this project we assume that antimicrobial functions of chicken complement are similar to those of human, although the mechanism of the chicken complement activation remains to be clarified.

This Reactome module refers to the larger complement fragments as "b" and the smaller "a", based on the nomenclature of the complement proteins .

### Literature references

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Baelmans, R., Demey, F., Parmentier, HK., Dorny, P., Berkvens, D., Nieuwland, MG. (2005). Haemolytic complement activity and humoral immune responses to sheep red blood cells in indigenous chickens and in eight German Dahlem Red chicken lines with different combinations of major genes (dwarf, naked neck and frizzled) of tropical interest. *Trop Anim Health Prod*, 37, 173-86. [↗](#)

Koch, C. (1986). The alternative complement pathway in chickens. Purification of factor B and production of a monospecific antibody against it. *Acta Pathol Microbiol Immunol Scand C*, 94, 253-9. [↗](#)

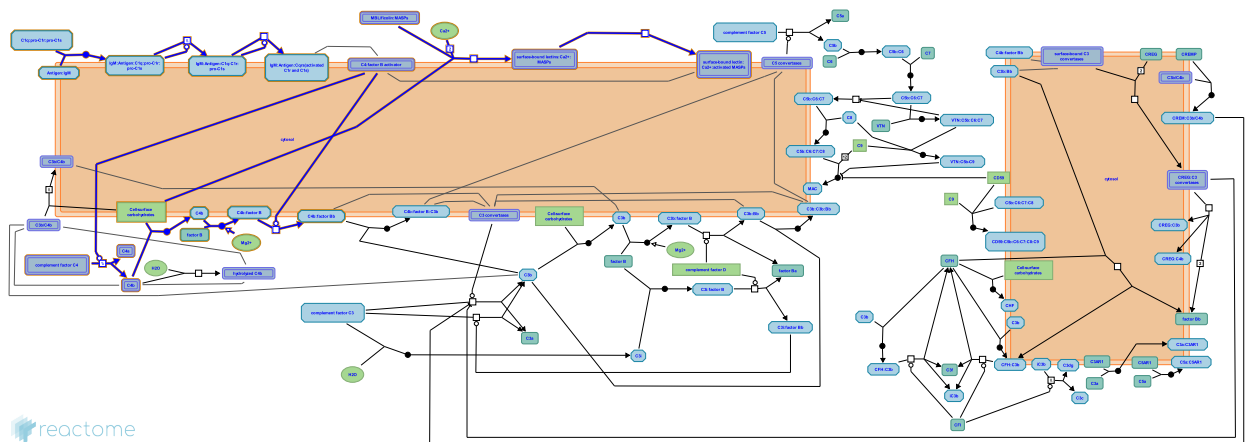
## **Editions**

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## Creation of classical C3 convertase ↗

**Location:** Complement Cascade

**Stable identifier:** R-GGA-2132263



The components of the classical and lectin pathways have been found in chickens (Barta O & Hubbert NL 1978; Lynch et al 2005). Complement activation results in the proteolytic cleavage of C3 to C3b and C3a, a reaction that is mediated by the C3 convertase. C3 convertase cleaves C3 component to generate a large amount of C3b, that binds to the target surface. The other cleavage product, anaphylatoxin C3a, initiates an inflammatory response. In mammals, in the classical and lectin-mediated pathways the C3 convertase is formed from the surface-bound C4b complexed with C2b (C4b:C2b). In the alternative pathway, factor B serves as the catalytic subunit of C3 convertase. In mammals, factor B and C2 share extensive amino acid homology; they have the same exon and intron organization and are located in tandem on the same chromosome within the mammalian MHC class III region (Carroll MC et al. 1984; Campbell RD & Bentley DR 1986; Cross SJ & Thomson W 1990; Salter-Cid L & Flajnik MF 1995; Nonaka M & Kimura A 2006). For these reasons, the two proteins are thought to have originated by gene duplication from an ancestral molecule. It remains unclear in which animal phyla the duplication event took place.

Chicken factor B-like protease (factor B) was found to be equally related to mammalian complement components B and C2A (Kjalke M. et al. 1993). In addition, a homologue for C2 was not found in chickens and factor B seemed to participate in both classical and alternative pathways of complement activation (Barta O & Hubbert NL 1978; Kjalke M. et al. 1993). It was assumed that the role of C2 may be fulfilled by the chicken factor B-like protease, an evolutionary remnant of a common C2/factor B ancestor (Kjalke M. et al. 1993).

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- Marston, D., Sandrini, SM., Stover, CM., Schwaeble, WJ., Presanis, JS., Khan, SU. et al. (2005). Composition of the lectin pathway of complement in *Gallus gallus*: absence of mannan-binding lectin-associated serine protease-1 in birds. *J Immunol*, 174, 4998-5006. ↗
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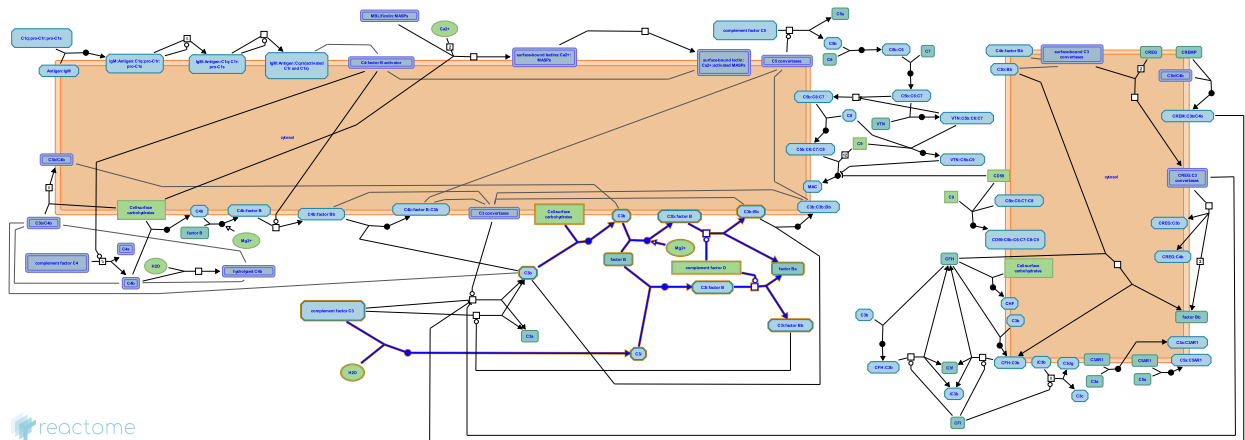
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## Creation of alternative pathway C3 convertase [↗](#)

**Location:** [Complement Cascade](#)

**Stable identifier:** R-GGA-2132287



In mammals, the alternative pathway is activated either by spontaneous hydrolysis of the internal thioester bond of C3 or by covalent attachment of C3b to target surfaces. Factor B binds to both hydrolyzed forms of C3 (or C3i) and surface-bound C3b. Factor B is subsequently cleaved by factor D to generate C3bBb or C3i:Bb, the alternative C3 convertases.

Antibody independent complement activity in chicken shows characteristics similar to those of the mammalian alternative complement pathway. Thus, hemolytic activity of chicken serum against horse erythrocytes (HRBC) required the presence of  $Mg^{2+}$ , but not  $Ca^{2+}$  ions. The lysis of HRBC remained unaffected by the treatment with carrageenan, which acts as a C1 inactivator via classical pathway [Otha H et al 1984]. Besides, normal chicken serum, which lacked viral-neutralizing antibody, was found to cause C3 deposition in Fowlpox virus-infected chicken embryonic cells. This C3 deposition occurred independently of  $Ca^{2+}$  ions [Otha H et al 1983].

The major proteins of the human alternative pathway are C3, factor B, factor D, properdin and regulatory factors I and H. Complement component C3 and factor B-like protease were purified and characterized in chicken [Laursen I and Koch C 1989; Mavrodis M et al 1995; Koch C 1986; Kjalke M et al 1993]. Predicted chicken factors H (CFH) and I (CFI) show 38% and 51% aminoacid sequence identity with their human counterparts respectively. Factor D and properdin are not found in the chicken genome, but the absence of factor D may reflect technical problems in identifying it due to its simple domain structure [Nonaka M and Kimura A 2006].

Here we assume that chicken processes of the alternative pathway might be occurring in a similar fashion to that in human, forming fluid-phase and surface-bound C3 convertases.

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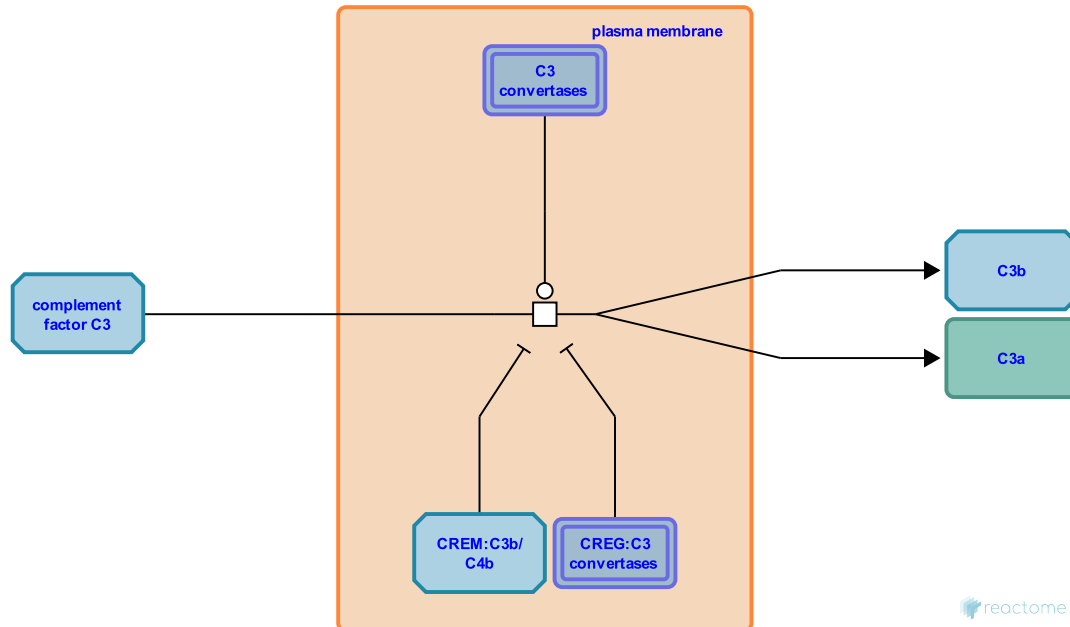
## Cleavage of C3 by surface-bound C3 convertases ↗

**Location:** [Complement Cascade](#)

**Stable identifier:** R-GGA-2132085

**Type:** transition

**Compartments:** plasma membrane, extracellular region



In mammals, three pathways of complement activation - alternative, classical and lectin - merge at the key event in complement activation, the cleavage of complement C3 to C3b and C3a. Proteolytic cleavage of C3 is mediated by surface-bound C3 convertase. A single molecule of C3 convertase can enzymatically cleave hundreds of molecules of C3. The smaller fragment, anaphylatoxin C3a, initiates local inflammatory responses while the larger cleavage product C3b binds covalently to the target surface for opsonization. Opsonized particles are recognized by receptors on macrophages, and upon attachment are cleared by phagocytosis. In addition, C3b can bind C3 convertases to produce C5 convertases, C4b:C2a:C3b or C3b:C3b:Bb, which cleave C5 into C5a and C5b. C5b is an active fragment which initiates membrane attack complex (MAC) formation (Janeway CA et al. 2001).

Chicken complement factor C3 has been isolated, mapped and characterized (Laursen I & Koch C 1989; Mavroidis M et al. 1995). Chicken C3 consists of 1652 amino acids and has 54% identity with its human and mouse counterparts. Like its mammalian orthologs, chicken C3 has a two-chain structure with an alpha chain (11kDa) and a beta-chain (70kDa). Upon complement activation chicken C3 is cleaved into fragments that resemble mammalian C3a and C3b (Laursen I & Koch C 1989).

**Followed by:** [Opsonization with C3b or C4b](#), [Formation of classical C5 convertase](#), [Formation of alternate C5 convertase](#)

### Literature references

Walport, MJ., Travers, P., Shlomchik, J., Janeway C, Jr. (2001). Innate Immunity, Immunobiology.

Laursen, I., Koch, C. (1989). Purification of chicken C3 and a structural and functional characterization. *Scand J Immunol*, 30, 529-38. ↗

Mavroidis, M., Lambris, JD., Sunyer, JO. (1995). Isolation, primary structure, and evolution of the third component of chicken complement and evidence for a new member of the alpha 2-macroglobulin family. *J Immunol*, 154, 2164-74. ↗



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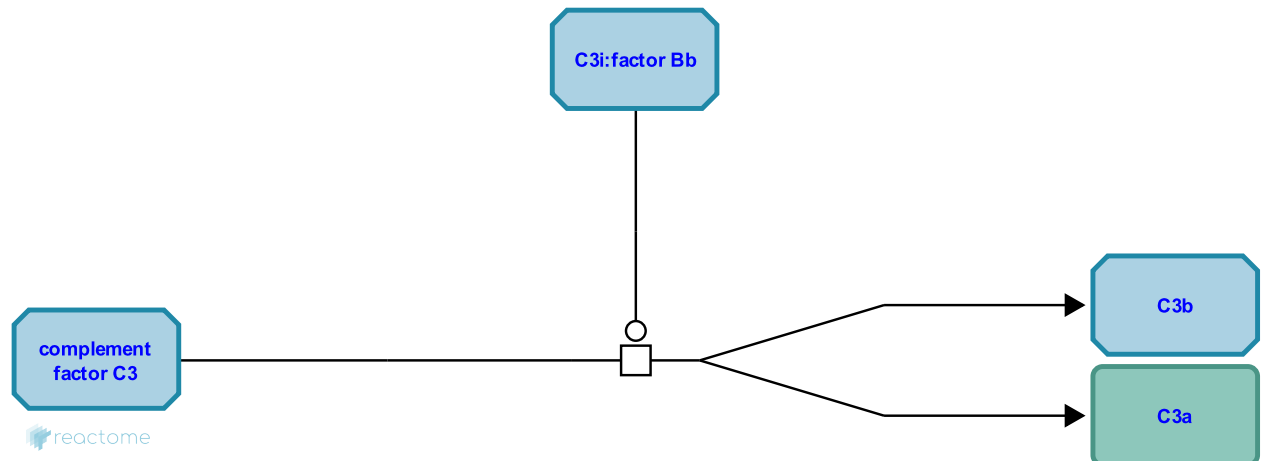
## Cleavage of C3 by fluid-phase C3i:factor B [↗](#)

**Location:** [Complement Cascade](#)

**Stable identifier:** R-GGA-2173323

**Type:** transition

**Compartments:** extracellular region



In mammals, three pathways of complement activation - alternative, classical and lectin - merge at the key event in complement activation, cleavage of complement C3 to C3b and C3a. The proteolytic cleavage of C3 is mediated by fluid-phase C3 convertase. A single molecule of C3 convertase can enzymatically cleave hundreds of molecules of C3. The smaller fragment, anaphylatoxin C3a, initiates local inflammatory responses while the larger cleavage product C3b binds covalently to the target surface for opsonization. Opsonized surfaces are recognized by receptors on macrophages, and upon attachment are cleared by phagocytosis. In addition, C3b can bind to C3 convertases to produce C5 convertases, C4b:C2a:C3b or C3b:C3b:Bb, which cleave C5 into C5a and C5b. C5b is an active fragment which initiates the membrane attack complex (MAC) formation (Janeway CA et al 2001).

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### Literature references

Laursen, I., Koch, C. (1989). Purification of chicken C3 and a structural and functional characterization. *Scand J Immunol*, 30, 529-38. [↗](#)

Mavroidis, M., Lambris, JD., Sunyer, JO. (1995). Isolation, primary structure, and evolution of the third component of chicken complement and evidence for a new member of the alpha 2-macroglobulin family. *J Immunol*, 154, 2164-74. [↗](#)

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## Formation of classical C5 convertase ↗

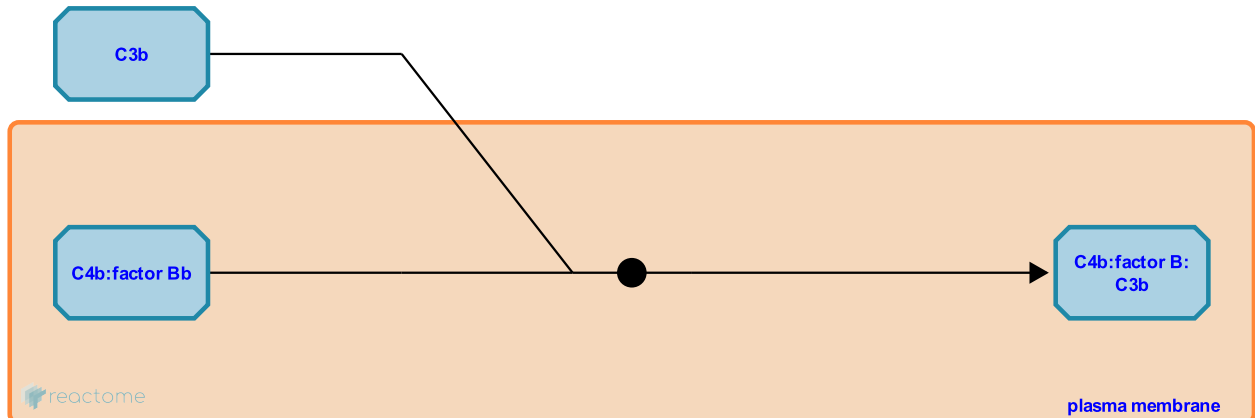
**Location:** [Complement Cascade](#)

**Stable identifier:** R-GGA-2132269

**Type:** binding

**Compartments:** plasma membrane, extracellular region

**Inferred from:** [Formation of classic pathway C5 convertase \(Homo sapiens\)](#)



In mammals, C3b binds covalently to a specific site on the C4b subunit of the C3 convertase resulting in the formation of the complex C4b:C2a:C3b, which functions as a C5 convertase. Here we assume that avian C5 convertase is formed in a similar way. A homologue for C2 was not found in chickens and factor B seemed to participate in both classical and alternative pathways of complement activation (Barta O & Hubbert NL 1978; Kjalke M. et al. 1993). It was assumed that the role of C2 may be fulfilled by the chicken factor B-like protease, an evolutionary remnant of a common C2/factor B ancestor (Kjalke M. et al. 1993).

**Preceded by:** [Cleavage of C3 by surface-bound C3 convertases](#)

**Followed by:** [Cleavage of C5 by C5 convertases](#)

## Literature references

Rawal, N., Pangburn, MK. (2003). Formation of high affinity C5 convertase of the classical pathway of complement. *J Biol Chem*, 278, 38476-83. ↗

## Editions

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## Formation of alternate C5 convertase ↗

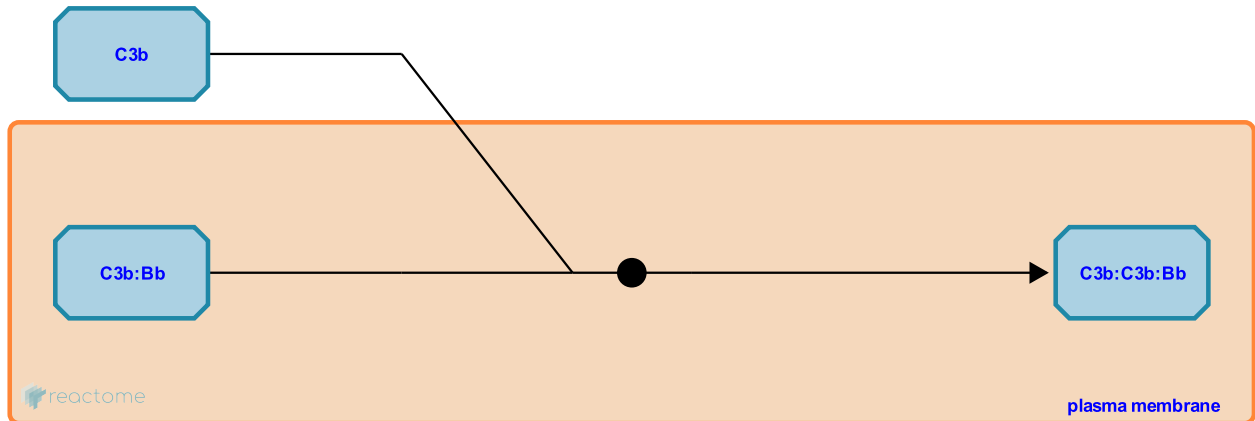
**Location:** [Complement Cascade](#)

**Stable identifier:** R-GGA-2132264

**Type:** binding

**Compartments:** plasma membrane, extracellular region

**Inferred from:** [Formation of alternative pathway C5 convertase \(Homo sapiens\)](#)



In mammals, C3b binds covalently to a specific site on the C3b subunit of the C3 convertase resulting in the formation of the complexes C3b:C3b:Bb, which function as an alternative C5 convertase. Here we assume that a similar mechanism exists in Gallus.

**Preceded by:** [Cleavage of C3 by surface-bound C3 convertases](#)

**Followed by:** [Cleavage of C5 by C5 convertases](#)

### Literature references

Rawal, N., Pangburn, MK. (2003). Formation of high affinity C5 convertase of the classical pathway of complement. *J Biol Chem*, 278, 38476-83. ↗

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## Cleavage of C5 by C5 convertases ↗

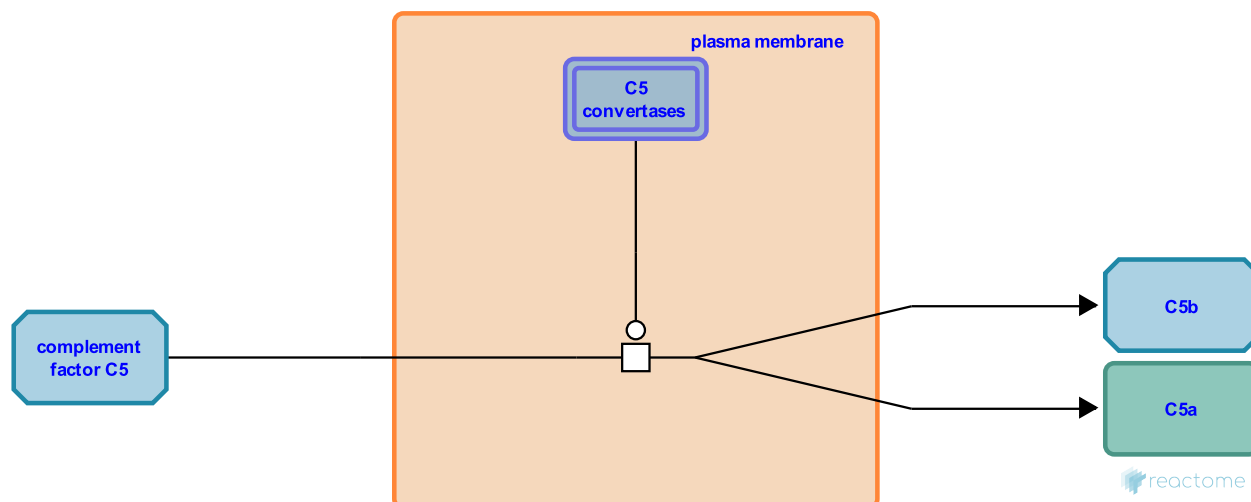
**Location:** [Complement Cascade](#)

**Stable identifier:** R-GGA-2132278

**Type:** transition

**Compartments:** plasma membrane, extracellular region

**Inferred from:** [Activation of C5 \(Homo sapiens\)](#)



C5 convertases are serine proteases that cleave complement C5 resulting in the formation of two biologically active fragments, C5a and C5b. Both fragments play vital roles in killing microorganisms. The smaller fragment C5a, which is a potent chemotactic agent and anaphylatoxin, mediates inflammatory responses. The larger fragment C5b initiates the formation of the membrane attack complex (MAC) which results in the lysis of the target cell.

**Preceded by:** [Formation of classical C5 convertase](#), [Formation of alternate C5 convertase](#)

### Literature references

Rawal, N., Pangburn, MK. (2003). Formation of high affinity C5 convertase of the classical pathway of complement. *J Biol Chem*, 278, 38476-83. ↗

Nonaka, M., Kimura, A. (2006). Genomic view of the evolution of the complement system. *Immunogenetics*, 58, 701-13 . ↗

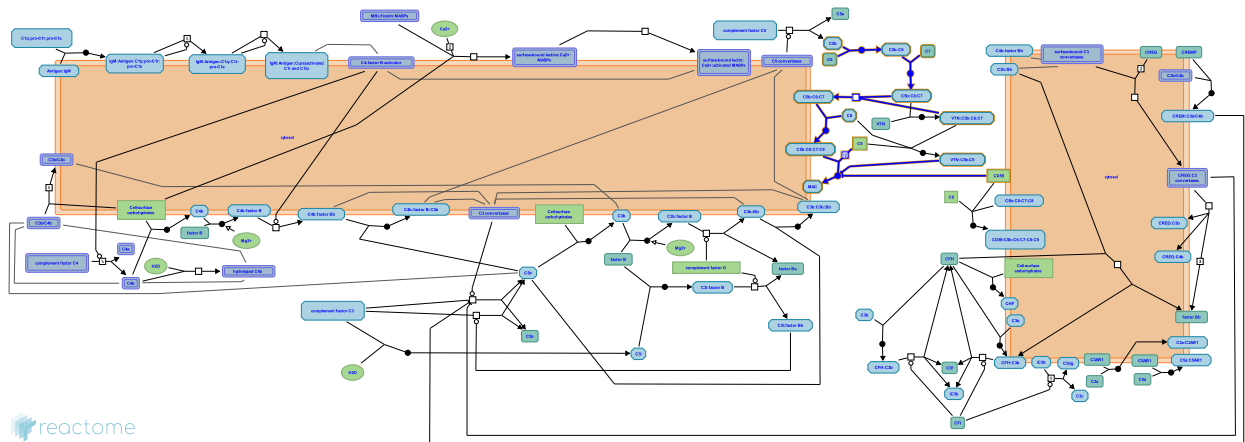
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# Formation of membrane attack complex (MAC) ↗

**Location:** [Complement Cascade](#)

**Stable identifier:** R-GGA-2132267



In mammals, reactions following C5b formation are common to the classical and alternative complement activation pathways, both lead to formation of the membrane attack complex (MAC), which forms pores in the target cell membrane resulting in cell lysis. Assembly of MAC is initiated by proteolytic cleavage of C5 by C5 convertases at the target cell surface, generating C5a and C5b. C5b has the transient ability to associate tightly with C6. The C5b:C6 complex subsequently interacts with C7, C8, and up to 18 molecules of C9 to create MAC.

All terminal complement component (TCC) genes are present in mammalian, avian, and amphibian genomic sequences, except for the avian C9 gene, which is not found in the draft chicken genome [Nonaka M and Kimura A 2006]. Chicken MAC structural (C6, C7 and C8 alpha, beta, gamma) and regulatory genes (CD59, vitronectin and clusterin) are expressed in a wide range of adult chicken tissues, most abundantly in the liver [Mikrou A and Zarkadis IK 2010].

## Literature references

Barta, O., Hubbert, NL. (1978). Testing of hemolytic complement components in domestic animals. *Am J Vet Res*, 39, 1303-8. ↗

Mikrou, A., Zarkadis, IK. (2010). Cloning of the sixth complement component and, spatial and temporal expression profile of MAC structural and regulatory genes in chicken. *Dev Comp Immunol*, 34, 485-90. ↗

Nonaka, M., Kimura, A. (2006). Genomic view of the evolution of the complement system. *Immunogenetics*, 58, 701-13. ↗

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## Opsonization with C3b or C4b ↗

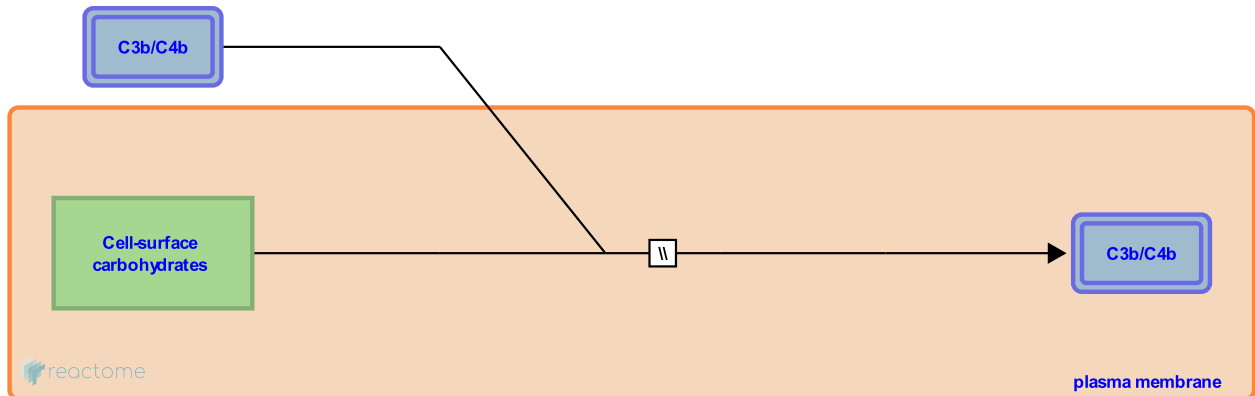
**Location:** [Complement Cascade](#)

**Stable identifier:** R-GGA-2132201

**Type:** omitted

**Compartments:** plasma membrane, extracellular region

**Inferred from:** [C4b binds to cell surface \(Homo sapiens\)](#), [C3b binds to cell surface \(Homo sapiens\)](#)



C4b and C3b are opsonins, which are able to bind covalently to glycoproteins on the target cell surface. Opsonization by C3b or C4b leads to engagement of complement receptors (CR1, CR3 or Cr4) on acceptor phagocytic cells, thus targeting foreign particles for phagocytosis [Bohnsack JF et al 1985].

C3b and C4b have been reported to facilitate a clearance of immune complexes (IC) which begins with covalent attachment of C3b or C4b to IC. C3b/C4b-coated immune complexes are loaded on erythrocytes via C1R and are transferred to phagocytes in the liver and spleen [Håkansson L et al 1982; Taylor RP et al 1991; Pascual M and Schifferli JA 1992; Emlen W et al 1992].

**Preceded by:** [Cleavage of C3 by surface-bound C3 convertases](#)

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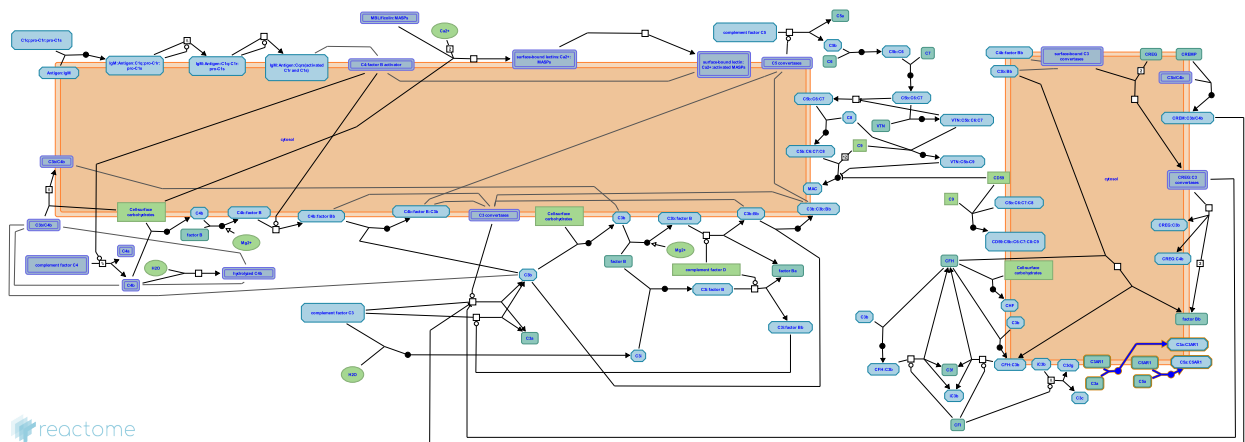
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# Anaphylatoxins initiate inflammatory responses ↗

**Location:** [Complement Cascade](#)

**Stable identifier:** R-GGA-2173345



Anaphylatoxic peptides C3a and C5a function as mediators of host inflammatory response in mammals. These molecules are generated during complement activation and bind to their specific G protein coupled receptors (GPCR), which are expressed on granulocytes, monocytes, mast cells and activated lymphocytes (Peng Q et al. 2009; Haas PJ and van Strijp J 2007).

Expression of both C3 and C5 as well as C3aR and C5aR was detected in chicken liver and eye tissues (Haynes T et al. 2013). Moreover, chicken C3a was shown to stimulate chick retina regeneration through MAPK-STAT3 activation in a C3aR-dependent manner (Haynes T et al. 2013). In addition, functionally active anaphylatoxins and their receptors were found in teleost fish and *Xenopus* (Rotlland J et al. 2004; Boshra H et al. 2004; Holland MC and Lambris JD 2004; Boshra H et al. 2005; Carmona-Fontaine C et al. 2011). The studies in those species suggested that the basic structure and function of anaphylatoxins and their receptors have been conserved for more than 300 million years (Sunyer JO et al. 2005). Taken together, the observations above suggest that the chicken complement signaling may release active fragments C3a and C5a, which associate with C3a and C5a receptors respectively.

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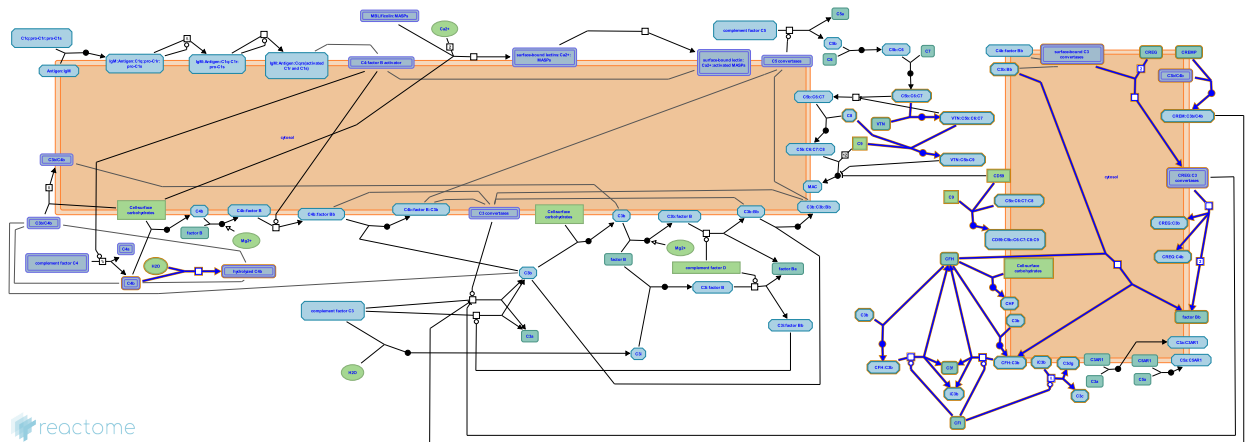
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# Regulation of complement cascades ↗

**Location:** Complement Cascade

**Stable identifier:** R-GGA-2132281



Complement activity is non-specific and requires the assembly of regulatory molecules to tune the cascade of enzymatic cleavage events to protect bystander cells. In human, several membrane-associated proteins, complement receptor 1 (CR1), CR2, decay-accelerating factor(DAF or CD55), membrane cofactor protein (MCP or CD46) and plasma proteins, factor H and C4b-binding protein(C4bp) have been identified as complement regulators. Genes of these regulators, except for factor H, are clustered in a region which is named the regulator of complement activation (RCA) gene locus [Carroll MC et al 1988]. Analysis of the chicken genome revealed that chicken possesses an RCA gene locus similar to the human RCA [Oshiumi H et al 2005]. Three genes encoding proteins with short consensus repeats (SCRs) were identified in this region - complement regulatory secretory protein of chicken (CRES), complement regulatory protein (CREM or Cremp) and complement regulatory GPI-anchored protein (CREG). Based on the structural and functional analysis of these SRC-containing chicken proteins the authors suggested that human and chicken RCA genes evolved from a common ancestral RCA locus.

Spatial and temporal expression profiles of chicken genes involved in membrane attack complex (MAC) formation showed that a wide range of adult chicken tissues express MAC regulatory genes - CD59, vitronectin (VTN) and clusterin (CLU), with the liver being the major source of their produced transcripts. MAC regulatory chicken genes are also expressed in all the developmental stages investigated [Mikrou A and Zarkadis IK 2010]. The chicken complement regulatory proteins remain to be structurally and functionally characterized so the chicken events annotated here are mostly inferred from the human complement cascade and should be considered as a suggestive model.

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