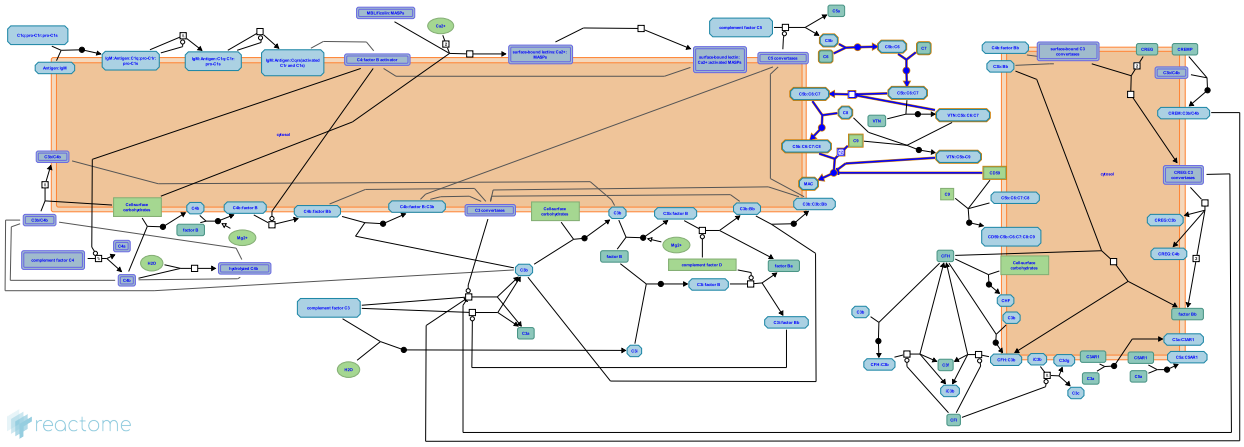
Formation of membrane attack complex (MAC)



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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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

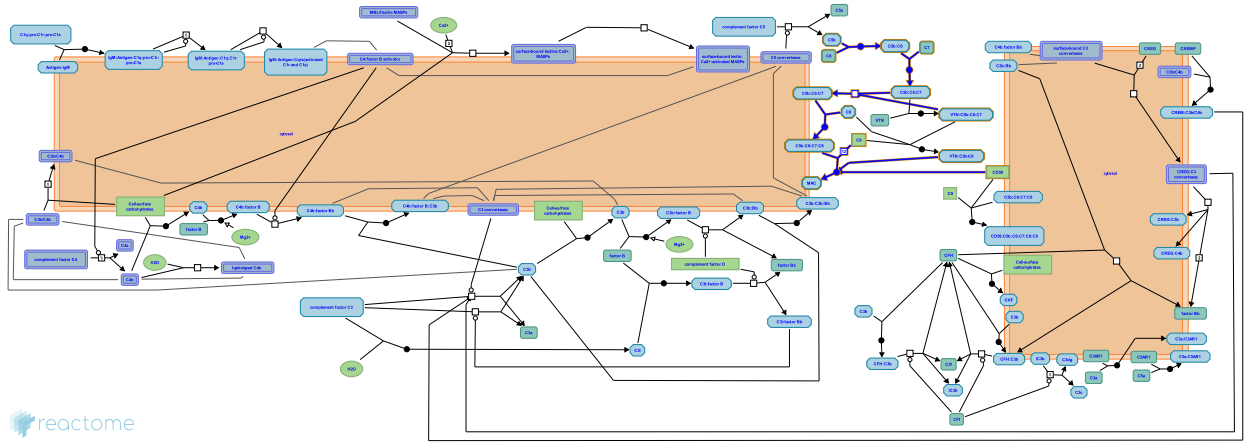
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Formation of membrane attack complex (MAC) ↗

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 . ↗

Editions

2012-11-07	Reviewed	D'Eustachio, P.
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Formation of C5b:C6 ↗

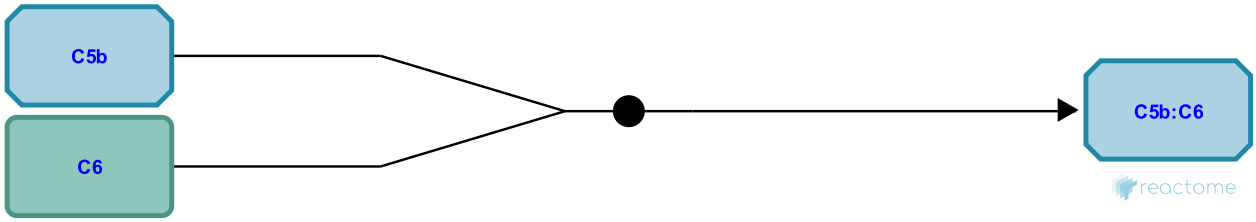
Location: Formation of membrane attack complex (MAC)

Stable identifier: R-GGA-2132284

Type: binding

Compartments: extracellular region

Inferred from: C5b binds C6 (Homo sapiens)



In mammals, C6 interacts with C5b through a metastable binding site to form a soluble C5b:C6 dimer.

Chicken complement component C6 was cloned and characterized [Mikrou A and Zarkadis IK 2010]. It shows 81% of amino acid identity to the predicted sequence of zebra finch C6, followed by human, frog and trout counterparts with 58%, 56%, and 44% identity, respectively. Chicken C6 contains the same structural motifs as those found in mammalian terminal complement components (TSP1, LDLa, MACPF, EGF). In addition, like mammalian C6/C7 components, chicken C6 contains two complement control protein (CCP) motifs. Chicken C6 carries two copies of the FIMAC domain, which has been implicated in the interaction of mammalian C6/C7 proteins with C5.

Chicken C6 mRNA expression was detected in various tissues - liver, brain, heart, kidney [Mikrou A and Zarkadis IK 2010].

Followed by: Formation of C5b:C6:C7

Literature references

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. ↗

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Formation of C5b:C6:C7 ↗

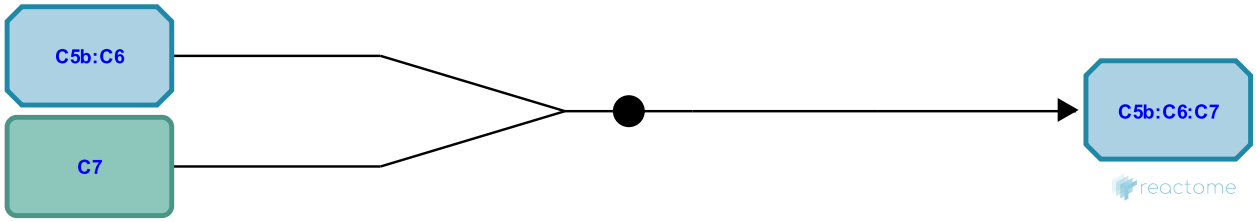
Location: Formation of membrane attack complex (MAC)

Stable identifier: R-GGA-2132060

Type: binding

Compartments: extracellular region

Inferred from: C7 binds C5b:C6 (Homo sapiens)



Complement C7 binds C5b:C6 to form the C5b:C6:C7 hydrophobic complex. Although little is known about chicken C7, in this module we assume that chicken C7 behaves as its human counterpart. Expression of C7 mRNA was observed in various chicken tissues - liver, brain, kidney, lung and heart [Mikrou A and Zarkadis IK 2010].

Preceded by: Formation of C5b:C6

Followed by: C5b:C6:C7 inserts into the target cell membrane

Literature references

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. ↗

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C5b:C6:C7 inserts into the target cell membrane ↗

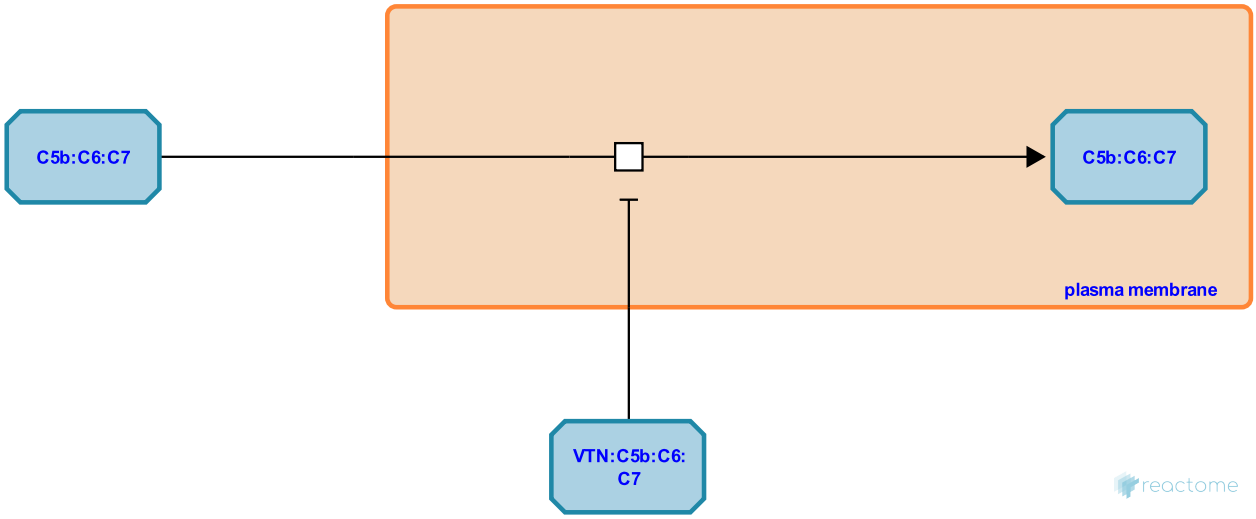
Location: Formation of membrane attack complex (MAC)

Stable identifier: R-GGA-2132133

Type: transition

Compartments: plasma membrane, extracellular region

Inferred from: C7 binds C5b:C6 (Homo sapiens)



Upon binding of C7 to C5b:C6, the trimolecular C5b:C6:C7 complex undergoes a conformational transition that allows insertion of this complex into the lipid bilayer of the target cell membrane.

Preceded by: Formation of C5b:C6:C7

Followed by: C8 binds to C5b:C6:C7 complement complex

Literature references

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. ↗

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C8 binds to C5b:C6:C7 complement complex ↗

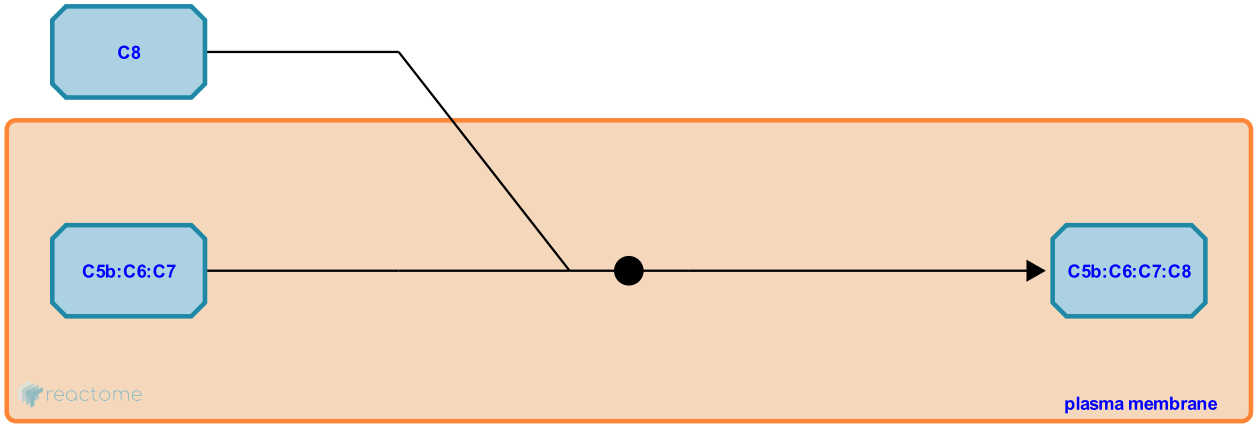
Location: Formation of membrane attack complex (MAC)

Stable identifier: R-GGA-2132094

Type: binding

Compartments: plasma membrane, extracellular region

Inferred from: C8 binds C5b:C6:C7 (Homo sapiens)



In mammals, C8 binds to the membrane-bound C5b:C6:C7 complex. Some lytic activity is expressed by C5b-C8 alone, although efficient hemolytic activity of complement is achieved upon interaction of C5b-C8 complex with complement C9. Mammalian C8 consist of 3 chains - alpha and gamma chains are covalently linked by a disulfide bond, while beta chain is bound by noncovalent forces. This module annotates predicted chicken amino acid sequences of C8 alpha, C8 beta and C8 gamma.

Preceded by: C5b:C6:C7 inserts into the target cell membrane

Followed by: C5b:C6:C7:C8 and C9 bind to form membrane attack complex (MAC)

Literature references

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. ↗

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C5b:C6:C7:C8 and C9 bind to form membrane attack complex (MAC) ↗

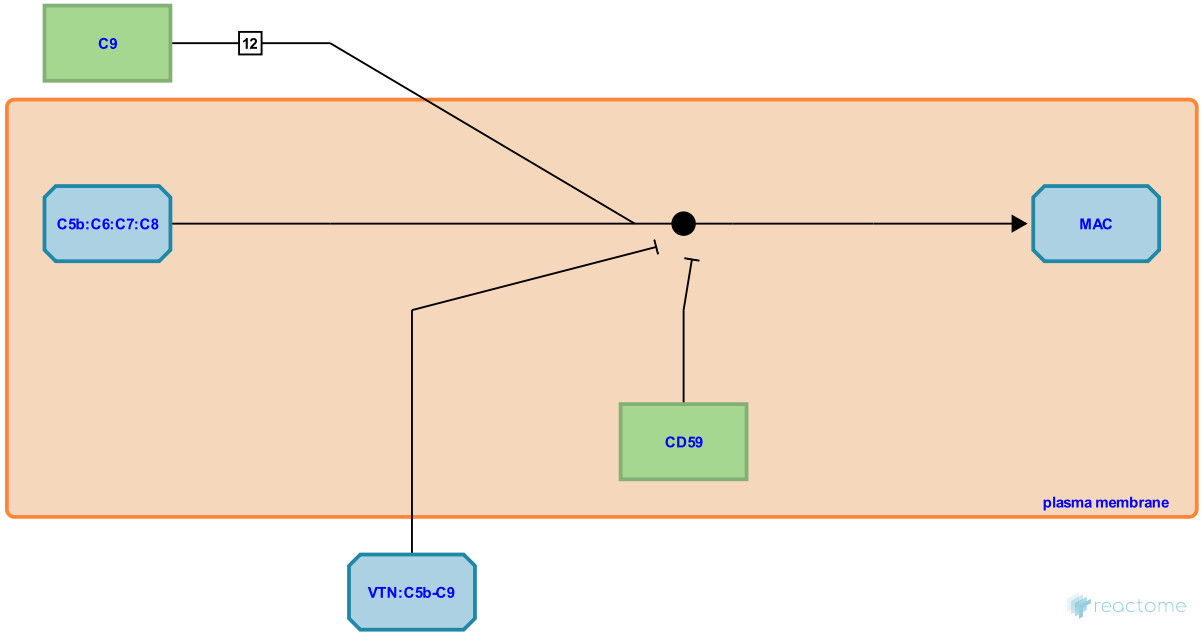
Location: Formation of membrane attack complex (MAC)

Stable identifier: R-GGA-2132221

Type: binding

Compartments: plasma membrane, extracellular region

Inferred from: C9 binds C5b:C6:C7:C8 (Homo sapiens)



Complement C9 is the final component incorporated into the membrane attack complex (MAC). Human C9 interacts with and polymerizes around C5b-C8 complex forming a C9 cylinder that is inserted into a target membrane leading to a lysis of the target cell [Podack ER et al 1982]. Deficiency of complement C9 is fairly common in the Japanese and Korean population [Hayama K et al 1989; Kang HJ et al 2005]. Without C9 component, human MAC consisting of C5b through C8 is able to lyse sheep red blood cells (CH50 test), although its efficiency is lower than that of the normal C5b-C9 MAC [Lint TF et al 1980; Harriman GR et al 1981].

An orthologue of mammalian C9 has not been identified in chicken genome. While it's possible that chicken genome lacks C9 gene (taking into account that the loss of C9 in human is not considered to be a major problem), in this Reactome project we annotated hypothetical chicken C9 protein, since not only mammals, but fish and amphibians seem to have the full set of MAC structural genes including C9 [Li L et al 2007; McLin et al 2008]. In addition, various chicken tissues were reported to express an orthologue of mammalian CD59 which inhibits C9 binding to the C5-C8 complex [Mikrou A and Zarkadis IK 2010].
MACs create pores in the membrane leading to cell death.

Preceded by: C8 binds to C5b:C6:C7 complement complex

Literature references

Wunderlich, AC., Braude, AI., Lint, TF., Esser, AF., Harriman, GR., Podack, ER. et al. (1981). The role of C9 in complement-mediated killing of Neisseria. *J Immunol, 127*, 2386-90. ↗

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McLin, VA., Hu, CH., Shah, R., Jamrich, M. (2008). Expression of complement components coincides with early patterning and organogenesis in Xenopus laevis. *Int J Dev Biol, 52*, 1123-33. ↗

Li, L., Chang, MX., Nie, P. (2007). Molecular cloning, promoter analysis and induced expression of the complement component C9 gene in the grass carp Ctenopharyngodon idella. *Vet Immunol Immunopathol, 118*, 270-82. ↗

Zeitz, HJ., Lint, TF., Gewurz, H. (1980). Inherited deficiency of the ninth component of complement in man. *J Immunol, 125*, 2252-7. ↗

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