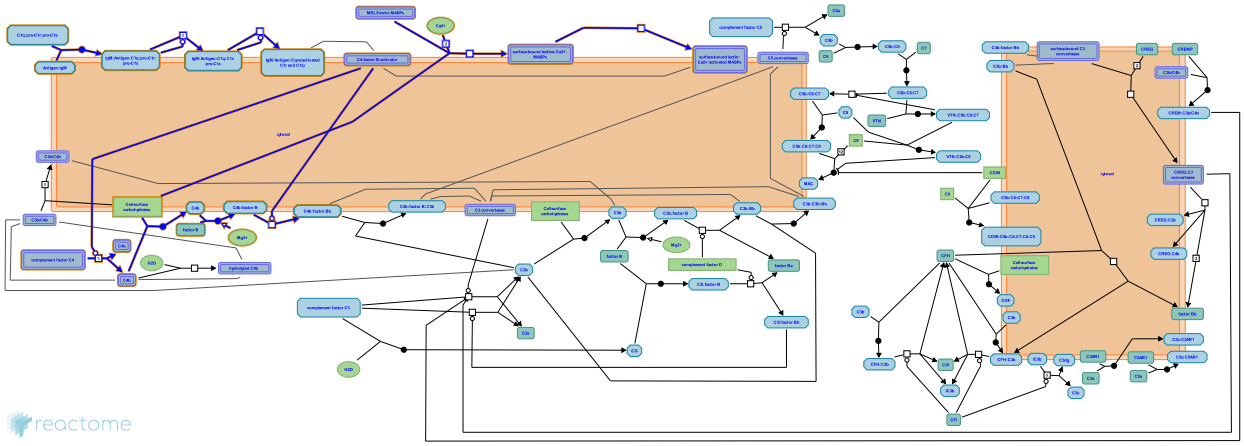
Creation of classical C3 convertase



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28/04/2024

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

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. ↗

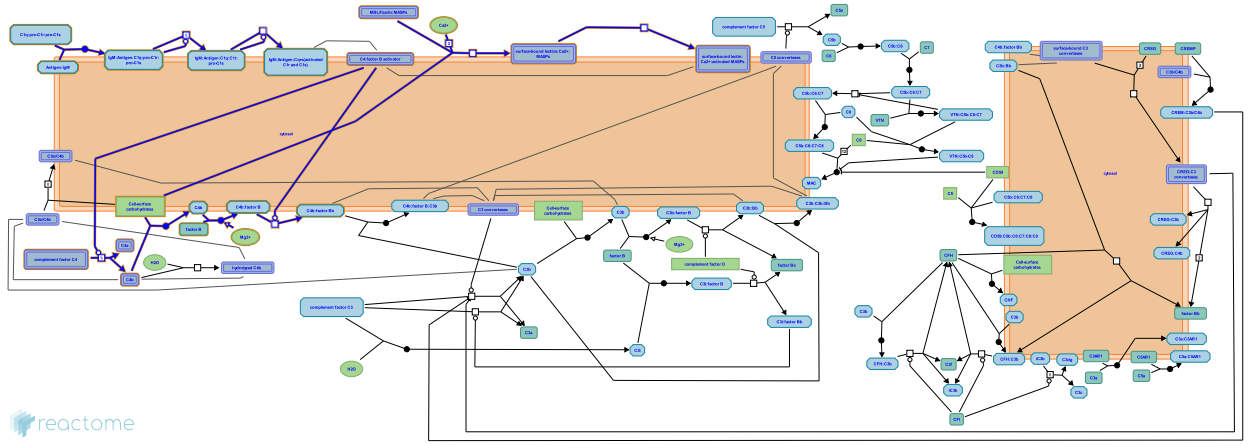
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 3 pathways and 4 reactions (see Table of Contents)

Creation of classical C3 convertase ↗

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).

Literature references

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. ↗

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

Welinder, KG., Koch, C., Kjalke, M. (1993). Structural analysis of chicken factor B-like protease and comparison with mammalian complement proteins factor B and C2. *J Immunol, 151*, 4147-52. ↗

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

Nonaka, M., Goetz, W., Flajnik, MF., Ohta, Y., Hossain, MZ. (2006). Ancestral organization of the MHC revealed in the amphibian Xenopus. *J. Immunol., 176*, 3674-85. ↗

Editions

2012-11-07	Reviewed	D'Eustachio, P.
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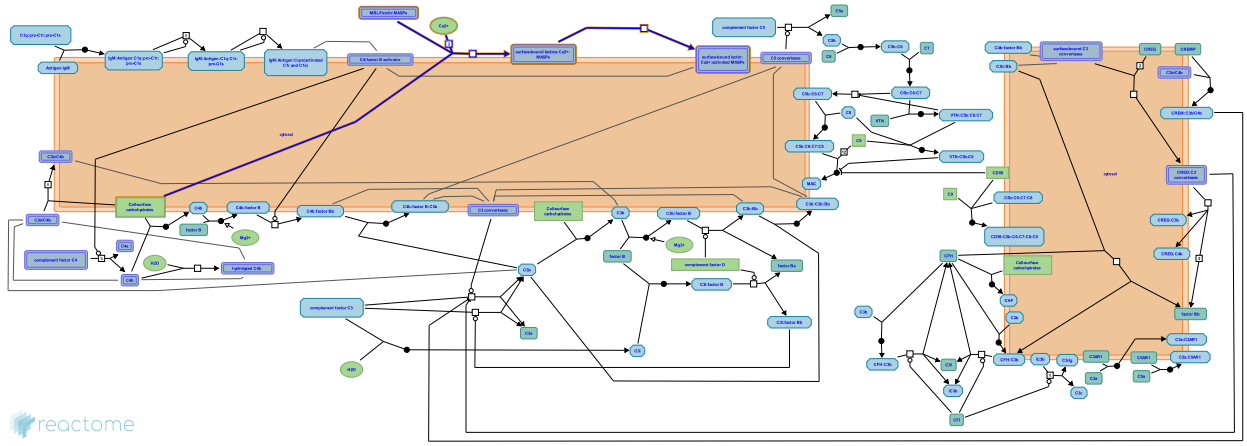
Lectin-mediated initiation of complement cascade ↗

Location: Creation of classical C3 convertase

Stable identifier: R-GGA-2132270



Activation of lectin pathway begins when mannan-binding lectin (MBL, also called mannose-binding protein, MBP) or ficolins bind to cell-surface carbohydrates on the target cell in the presence of Ca2+. Surface bound lectins are assembled with MBL-associated serine proteases (MASPs) [Turner MW et al 1996, Fujita T et al 2004]. The lectin-MASP complex cleaves C4 and C2 complements to generate their active fragments. The active fragments - C4b and C2b, form C3 convertase [Wallis R et al 2007].

Most of the components of chicken lectin pathway (MBL, ficolin, MASP2, MASP3, MAp19) have been mapped, cloned and characterized (Laursen SB and Nielsen OL 2000; Lynch NJ et al 2005).

Literature references

Laursen, SB., Nielsen, OL. (2000). Mannan-binding lectin (MBL) in chickens: molecular and functional aspects. *Dev Comp Immunol, 24*, 85-101. ↗

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. ↗

Turner, MW. (1996). The lectin pathway of complement activation. *Res Immunol, 147*, 110-5. ↗

Fujita, T. (2002). Evolution of the lectin-complement pathway and its role in innate immunity. *Nat Rev Immunol, 2*, 346-53. ↗

Endo, Y., Fujita, T., Matsushita, M. (2004). The lectin-complement pathway--its role in innate immunity and evolution. *Immunol Rev, 198*, 185-202. ↗

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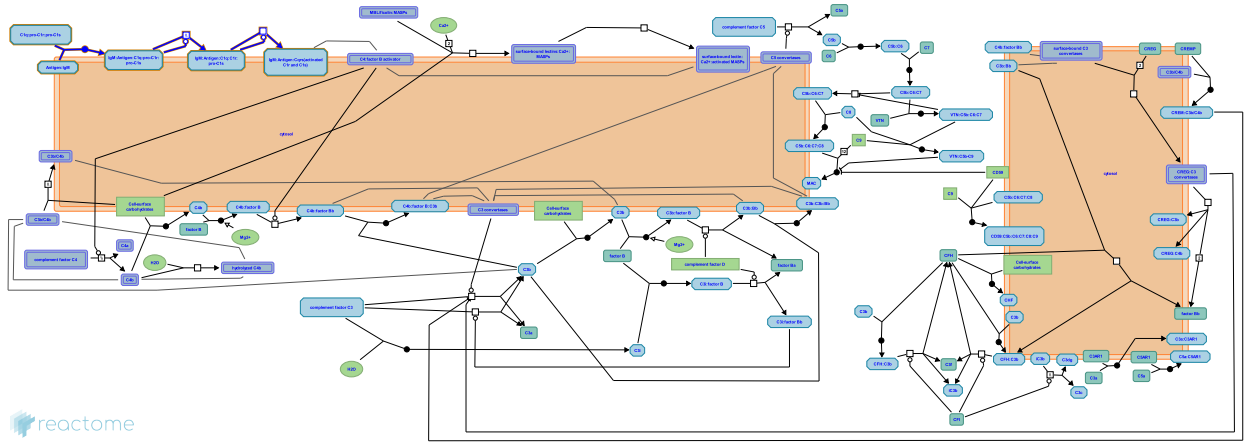
Classical antibody-mediated complement activation ↗

Location: Creation of classical C3 convertase

Stable identifier: R-GGA-2132286

Inferred from: Classical antibody-mediated complement activation (Homo sapiens)



In mammals, the classical pathway is initiated by binding of antibody molecules (IgM or IgG) to an antigen, followed by binding of complement protein C1q. Two molecules each of C1r and C1s bind to C1q to form an active C1 complex. The activated C1 complex cleaves C4 to generate C4a and C4b. C4b fragment binds the nearby target cell surface. The activated C1 complex then cleaves and activates C2 which has bound to C4b, yielding a C4b:C2a complex (C3 convertase). C3 convertase, in turn, cleaves the third component of complement C3 to form C3a and C3b. A single C3 convertase can generate hundreds molecules of C3b, which can directly bind to the target surface. Opsonization with C3b fragments mark the target cell for phagocytosis. C3b can also bind to the C3 convertase yielding C5 convertase (C4b:C2a:C3b), which cleaves C5 into C5a and C5b. C5b is an active fragment which initiates a membrane attack complex (MAC) formation (Janeway CA et al. 2001).

Literature references

Davison, F., Kaspers, B., Schat, KA. (2008). Avian Innate Immune Responses, Avian Immunology.

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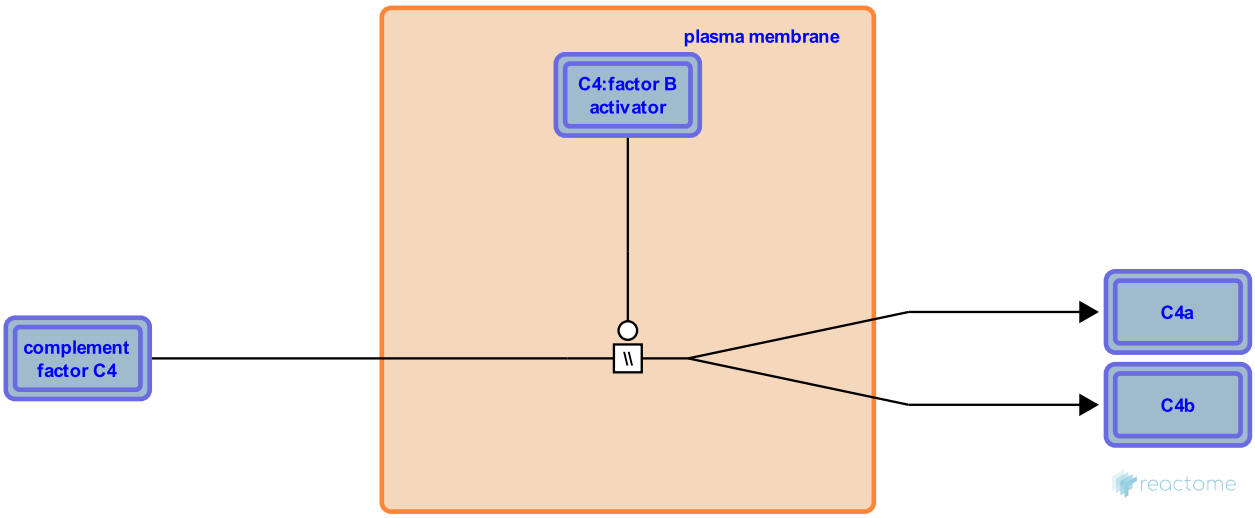
Proteolytic cleavage of complement factor C4 ↗

Location: Creation of classical C3 convertase

Stable identifier: R-GGA-2132233

Type: omitted

Compartments: plasma membrane, extracellular region



C4 is cleaved by activated protease C1s in the classical pathway or MASPs in the lectin-mediated pathway producing two fragments C4a and C4b. The larger fragment C4b binds covalently to the target surface due to a highly reactive thioester bond which becomes exposed upon cleavage. Chicken C4 shares 37% amino acid sequence identity with its human counterpart. Correlation between chicken MBL concentration and C4 deposition was observed in chicken sera [Norup LR and Juul-Madsen HR 2007].

The exact cleavage site in chicken C4 is unknown.

Followed by: C4b binds to target cell surface

Literature references

Juul-Madsen, HR., Norup, LR. (2007). An assay for measuring the mannan-binding lectin pathway of complement activation in chickens. *Poult Sci, 86*, 2322-6. ↗

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C4b binds to target cell surface ↗

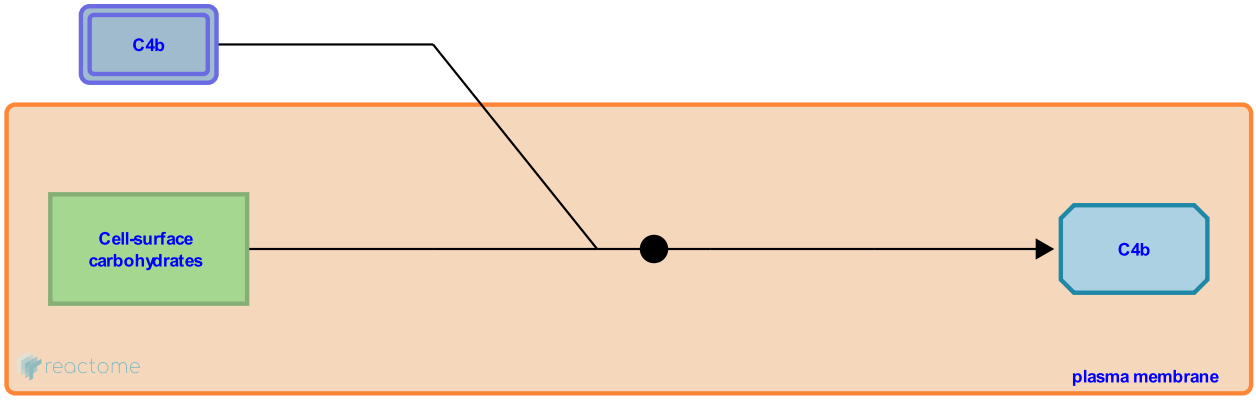
Location: Creation of classical C3 convertase

Stable identifier: R-GGA-2132248

Type: binding

Compartments: plasma membrane, extracellular region

Inferred from: C4b binds to cell surface (Homo sapiens)



Cleavage of C4 exposes an active thioester bond on the large fragment C4b that allows it to bind covalently to hydroxyl or amino groups on target surfaces. This binding is regulated by the hydrolysis reaction that irreversibly inactivates C4b [Law SK and Dodds AW 1997; Dodds AW et al 1996]. Surface-bound C4b forms the basis for the formation of C3/C5 convertases.

This event was inferred from the curated human reaction.

Preceded by: Proteolytic cleavage of complement factor C4

Followed by: Formation of C4b:factor B complex

Literature references

Juul-Madsen, HR., Norup, LR. (2007). An assay for measuring the mannan-binding lectin pathway of complement activation in chickens. *Poult Sci, 86*, 2322-6. ↗

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Formation of C4b:factor B complex ↗

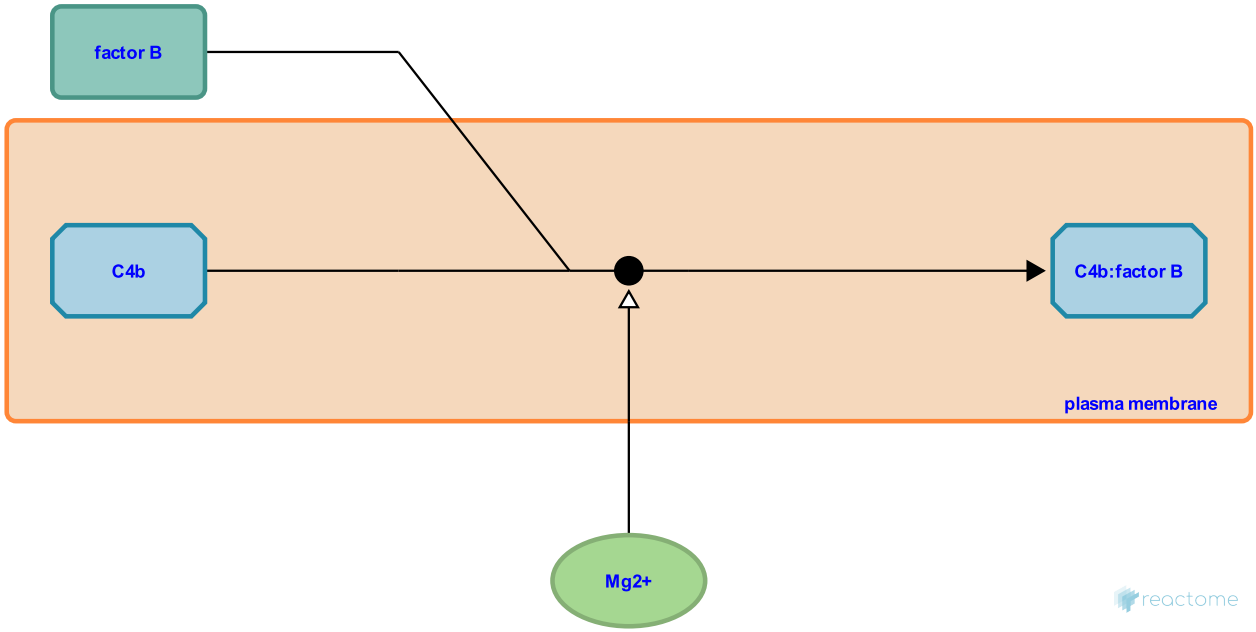
Location: Creation of classical C3 convertase

Stable identifier: R-GGA-2132096

Type: binding

Compartments: plasma membrane, extracellular region

Inferred from: Formation of Classical C3 convertase (C4b:C2a complex) (Homo sapiens)



Mammalian C2 binds to surface-bound C4b to form the C4b:C2 complex, which is subsequently cleaved by C1s or MASPs to form the classical C3 convertase - C4b:C2b (Laich A & Sim RB 2001; Wallis R et al 2007).

The chicken event was inferred from the curated human reaction. A homologue for C2 was not found in chickens (Barta O & Hubbert NL 1978). It was assumed that the role of C2 may be fulfilled by the chicken complement factor B-like protease (factor B), an evolutionary remnant of a common C2/factor B ancestor (Kjalke M et al. 1993; Salter-Cid L & Flajnik MF 1995). Chicken factor B-like protease (factor B) is a glycoprotein of 95 kDa. Activation of chicken serum complement with inulin cleaved factor B into an N-terminal Ba fragment of 37 kDa and a C-terminal Bb fragment of 60 kDa (Kjalke M et al. 1993). The whole protein and the two fragments were purified by affinity chromatography using mAb to chicken Ba or Bb followed by ion exchange chromatography (Kjalke M et al. 1993). Amino acid sequencing showed that the chicken factor B was cleaved at a site homologous to that cleaved in mammalian complement components B and C2 on activation. Limited tryptic digestion of the B-like protease generated fragments similar to Ba and Bb (Kjalke M et al. 1993). Comparison of chicken Ba to human and mouse C2b and Ba showed 42 to 45% sequence identity with respect to C2b fragments, and 46 to 49% sequence identity with respect to Ba fragments (Kjalke M et al. 1993). Thus, chicken factor B-like protease seemed to be equally related to mammalian complement components B and C2, and the B-like protease is thought to represent the present-day descendant of a common ancestral protein for mammalian B and C2 (Kjalke M et al. 1993).

Preceded by: C4b binds to target cell surface

Followed by: Cleavage of factor B to form classical C3 convertase

Literature references

Sim, RB., Dodds, AW., Mitchell, DA., Schwaeble, WJ., Reid, KB., Wallis, R. (2007). Molecular interactions between MASP-2, C4, and C2 and their activation fragments leading to complement activation via the lectin pathway. *J Biol Chem, 282*, 7844-51. ↗

Welinder, KG., Koch, C., Kjalke, M. (1993). Structural analysis of chicken factor B-like protease and comparison with mammalian complement proteins factor B and C2. *J Immunol, 151*, 4147-52. ↗

Sim, RB., Laich, A. (2001). Complement C4bC2 complex formation: an investigation by surface plasmon resonance. *Biochim Biophys Acta, 1544*, 96-112. ↗

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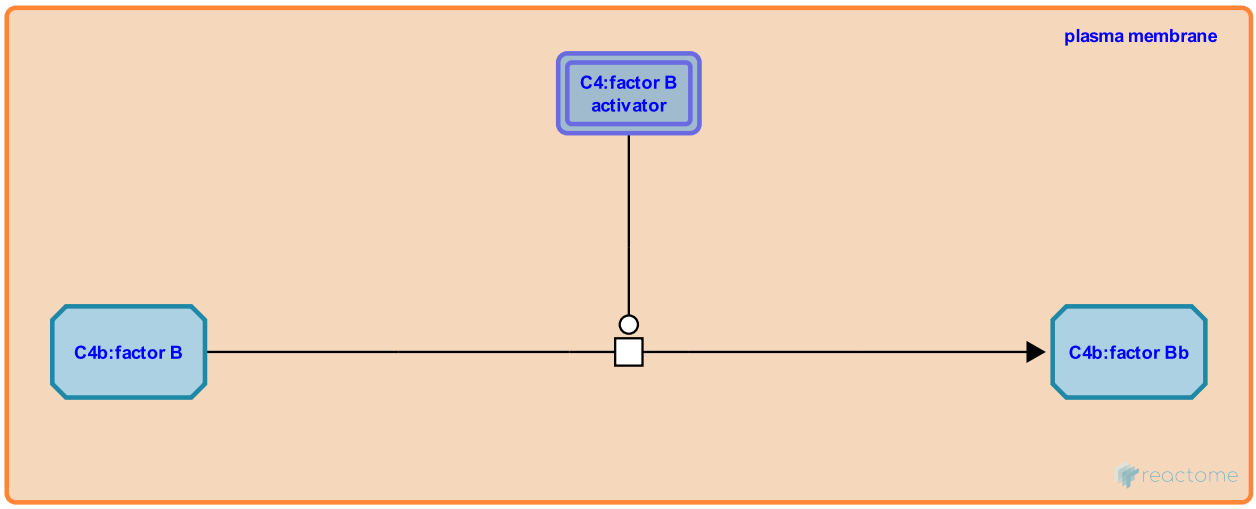
Cleavage of factor B to form classical C3 convertase ↗

Location: Creation of classical C3 convertase

Stable identifier: R-GGA-2132222

Type: transition

Compartments: plasma membrane



In mammals, C2 binds to surface-bound C4b to form the C4b:C2 complex, which makes C2 susceptible to cleavage by C1s or MASPs. C1s or MASPs cleaves C2 producing the C4b:C2b complex with the active serine protease component C2b. C4b:C2b remains on the target surface as a C3 convertase of the classical and lectin-mediated pathways (Laich A and Sim RB 2001; Wallis R et al 2007).

A homologue for C2 was not found in chickens (Barta O & Hubbert NL 1978). It was assumed that the role of C2 may be fulfilled by the chicken complement factor B-like protease (factor B), an evolutionary remnant of a common C2/factor B ancestor (Kjalke M et al. 1993; Salter-Cid L & Flajnik MF 1995). Chicken factor B-like protease (factor B) is a glycoprotein of 95 kDa. Activation of chicken serum complement with inulin cleaved factor B into an N-terminal Ba fragment of 37 kDa and a C-terminal Bb fragment of 60 kDa (Kjalke M et al. 1993). The whole protein and the two fragments were purified by affinity chromatography using mAb to chicken Ba or Bb followed by ion exchange chromatography (Kjalke M et al. 1993). Amino acid sequencing showed that the chicken factor B was cleaved at a site homologous to that cleaved in mammalian complement components B and C2 on activation. Limited tryptic digestion of the B-like protease generated fragments similar to Ba and Bb (Kjalke M et al. 1993). Comparison of chicken Ba to human and mouse C2b and Ba showed 42 to 45% sequence identity with respect to C2b fragments, and 46 to 49% sequence identity with respect to Ba fragments (Kjalke M et al. 1993). Thus, chicken factor B-like protease seemed to be equally related to mammalian complement components B and C2, and the B-like protease is thought to represent the present-day descendant of a common ancestral protein for mammalian B and C2 (Kjalke M et al. 1993).

Preceded by: Formation of C4b:factor B complex

Literature references

Welinder, KG., Koch, C., Kjalke, M. (1993). Structural analysis of chicken factor B-like protease and comparison with mammalian complement proteins factor B and C2. *J Immunol, 151*, 4147-52. ↗

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