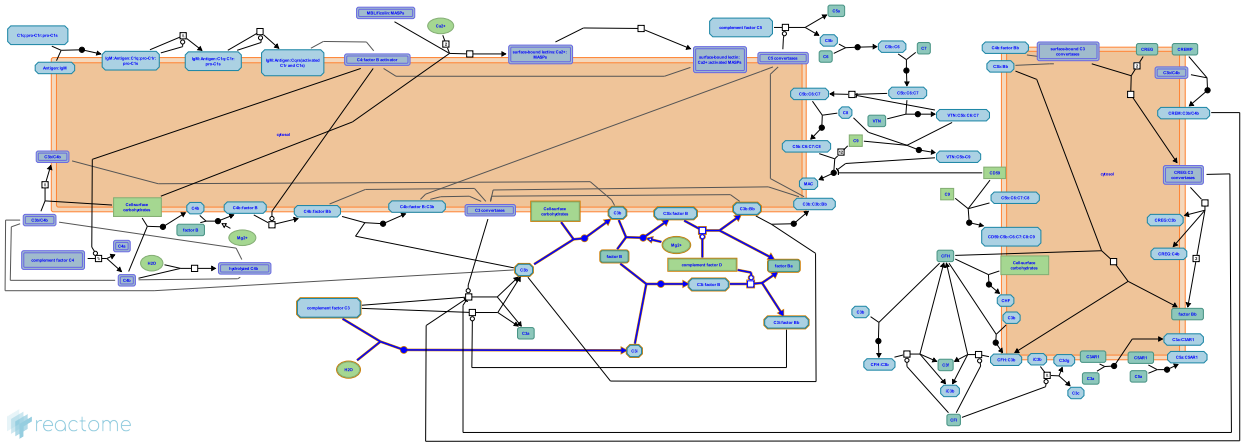
Creation of alternative pathway C3 convertase



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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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. ↗

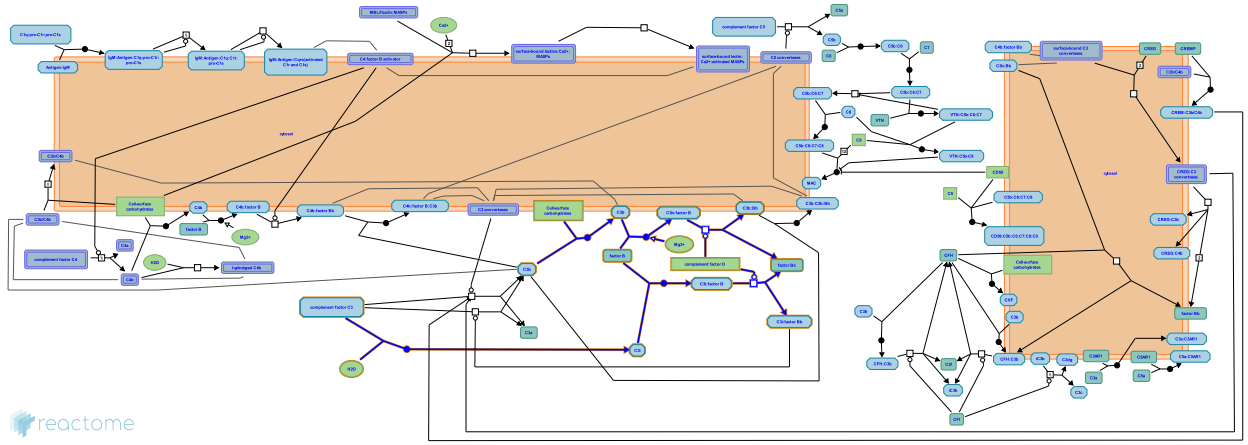
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Creation of alternative pathway C3 convertase ↗

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 Mg2+, but not Ca2+ 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 occured independently of Ca2+ 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.

Literature references

Kai, C., Ohta, H., Yamanouchi, K., Yoshikawa, Y. (1983). Activation of chicken alternative complement pathway by fowlpox virus-infected cells. *Infect. Immun., 42*, 721-7. ↗

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. ↗

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

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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. ↗

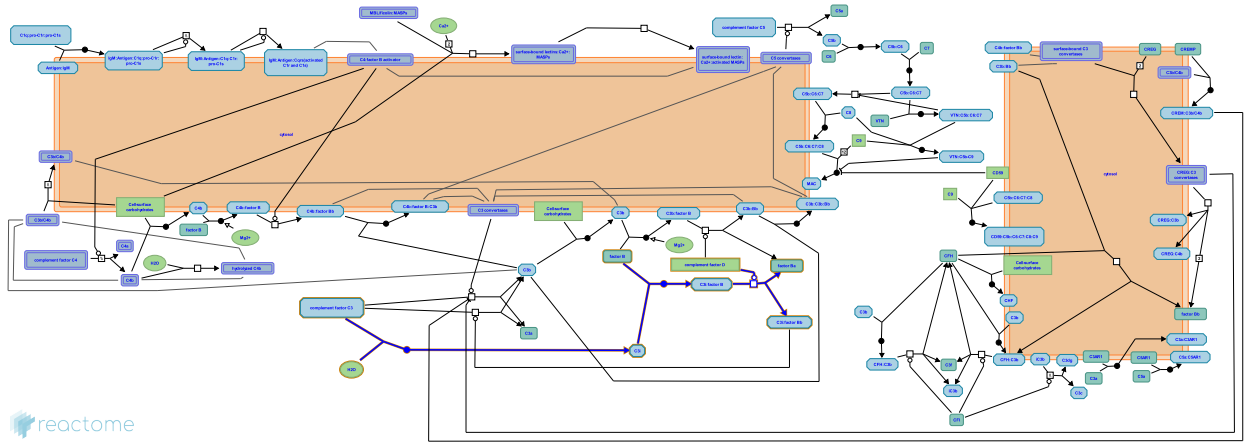
Editions

2012-11-07	Reviewed	D'Eustachio, P.
2012-12-20	Authored	Shamovsky, V.
2013-01-31	Reviewed	Jupe, S.
2013-11-20	Edited	Shamovsky, V.

Formation of fluid-phase convertase C3 ↗

Location: Creation of alternative pathway C3 convertase

Stable identifier: R-GGA-2132293



In human, small amounts of hydrolyzed C3 (C3(H20) or C3i) are continuously formed in the fluid phase following spontaneous hydrolysis of the internal thioester bond of C3. C3i can bind to factor B which, in turn, is cleaved by factor D yielding an alternative fluid-phase C3 convertase, C3i:Bb.

Chicken factor B-like protease was shown to create a functional C3 convertase [Jensen LB & Koch C 1991]. Although an orthologue of human factor D has not been identified in the chicken genome, this chicken module describes a cleavage of factor B-like protease as an essential step of the chicken alternative complement pathway.

Literature references

Jensen, LB., Koch, C. (1991). An assay for complement factor B in species at different levels of evolution. *Dev. Comp. Immunol., 15*, 173-9. ↗

Pangburn, MK., Muller-Eberhard, HJ. (1983). Initiation of the alternative complement pathway due to spontaneous hydrolysis of the thioester of C3. *Ann N Y Acad Sci, 421*, 291-8. ↗

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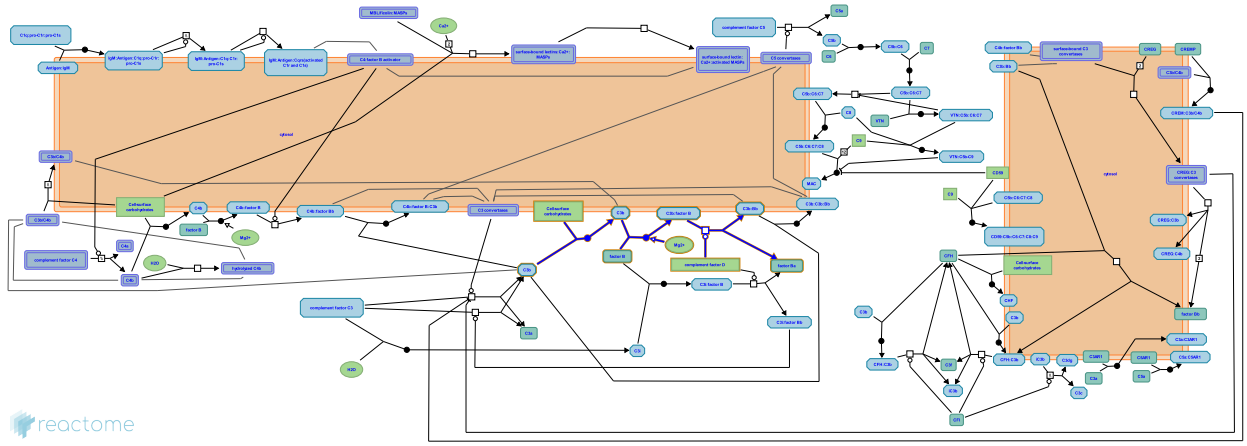
Formation of membrane-bound convertase C3 ↗

Location: Creation of alternative pathway C3 convertase

Stable identifier: R-GGA-2132273



C3b, a product of the enzymatic action of C3 convertases on C3, is itself a constituent of the alternative pathway C3 convertase. It covalently binds to target cell membranes to initiate the formation of C3 convertase, which leads to a continuously cycling feedback loop.

Literature references

Levine, RP., Law, SK. (1977). Interaction between the third complement protein and cell surface macromolecules. *Proc Natl Acad Sci U S A, 74*, 2701-5. ↗

Schreiber, RD., Pangburn, MK., Muller-Eberhard, HJ., Lesavre, PH. (1978). Initiation of the alternative pathway of complement: recognition of activators by bound C3b and assembly of the entire pathway from six isolated proteins. *Proc Natl Acad Sci U S A, 75*, 3948-52. ↗

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