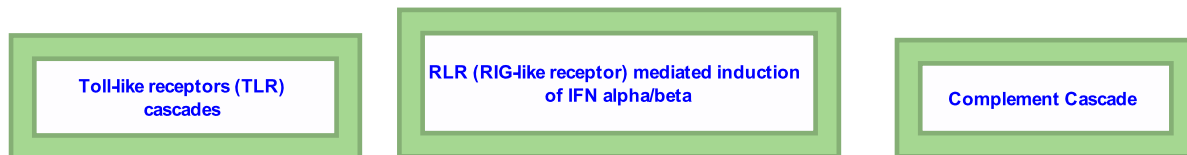


# Innate Immune System



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

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

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of [Creative Commons Attribution 4.0 International \(CC BY 4.0\) License](#). For more information see our [license](#).

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](#).

27/04/2024

## 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 4 pathways ([see Table of Contents](#))

## Innate Immune System [↗](#)

**Stable identifier:** R-GGA-2422406



 reactome

Innate immunity also known as nonspecific immunity provides the first line of host defense against invading organisms. The availability of the full *Gallus gallus* genome sequence enabled identification of genes involved in chicken innate immune responses.

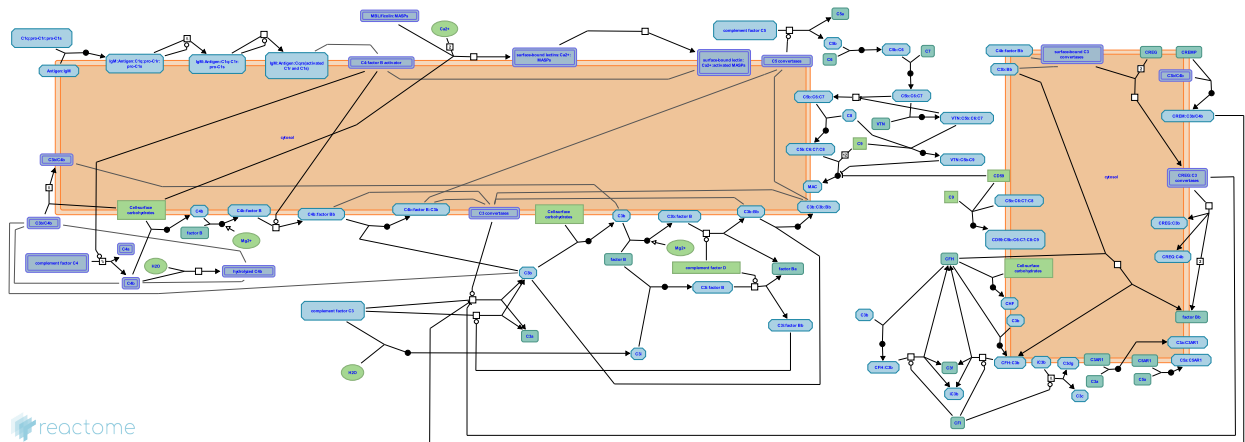
### **Editions**

2012-06-07	Authored	Shamovsky, V.
2012-11-05	Reviewed	D'Eustachio, P.
2012-11-13	Edited	Shamovsky, V.

## Complement Cascade ↗

**Location:** Innate Immune System

**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 Ca<sup>2+</sup> 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

Lukert, PD., De Buyscher, EV., Brown, J., Fletcher, OJ., Skeeles, JK. (0). Infectious bursal disease viral infections. II. The relationship of age, complement levels, virus-neutralizing antibody, clotting, and lesions. *Avian Dis.*, 23, 107-117. ↗

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. ↗

Lukert, PD., De Buyscher, EV., Brown, J., Fletcher, OJ., Skeeles, JK. (0). Infectious bursal disease viral infections. I. Complement and virus-neutralizing antibody response following infection of susceptible chickens. *Avian Dis.*, 23, 95-106. [↗](#)

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. [↗](#)

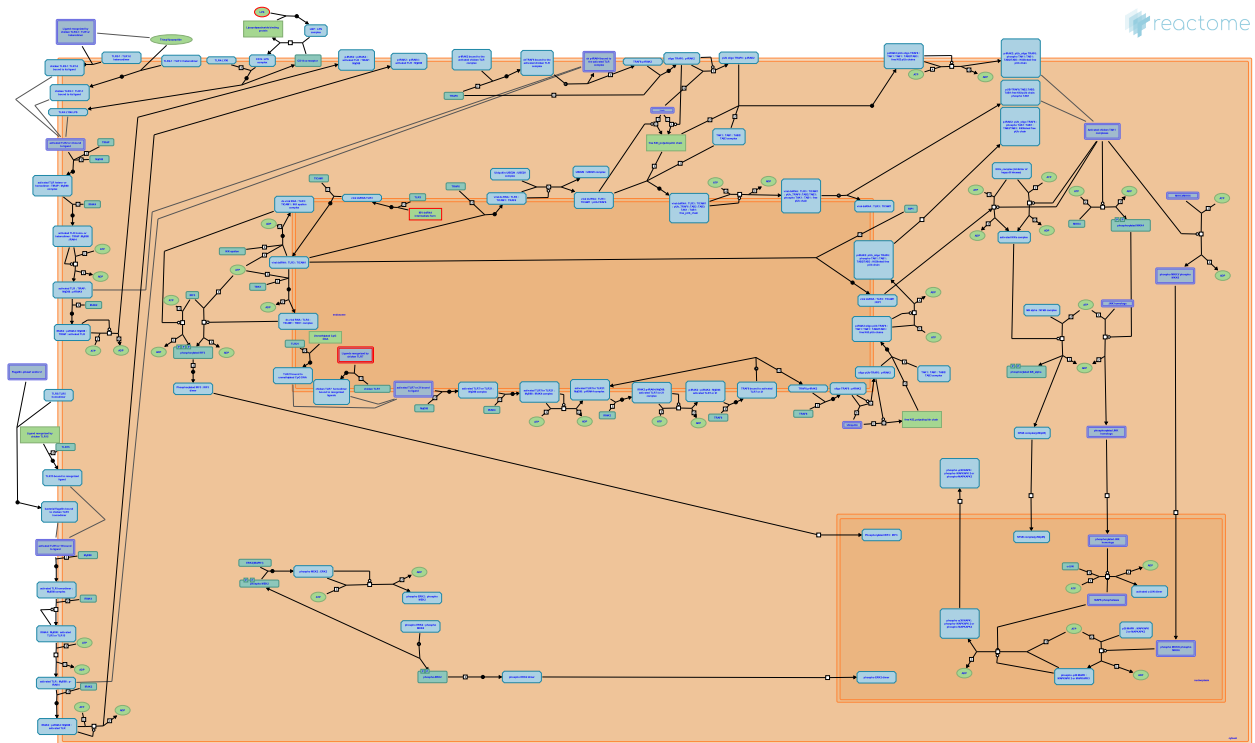
## Editions

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.

## Toll-like receptors (TLR) cascades ↗

**Location:** Innate Immune System

**Stable identifier:** R-GGA-437987



Toll-like receptors (TLRs) are a group of highly conserved pathogen recognition receptors which initiate and regulate the immune response by controlling cytokine and chemokines expression.

Mammalian and avian lineages diverged from the common ancestor approximately 300 millions years ago. Although most of the genes encoding proteins of the chicken TLR cascade molecules have not been cloned and characterized directly, analyses of the chicken genome sequence has defined ten TLRs [Lynn et al. 2003, Temperley ND et al. 2008]. The avian TLR repertoire consists of single orthologs of mammalian TLRs 3, 4, 5 and 7 and distinct new chicken genes TLR15 and TLR21. The TLR2 subfamily is represented by tandemly duplicated avian TLR2 and TLR1 genes and consists of two isoforms of each gene - TLR2 type1 and 2, TLR1 type1 and 2. No functional orthologs of mammalian TLR8, TLR9 and TLR10 have been detected in the chicken genome. However, chicken heterophils and spleen cells are responsive to the broad range of mammalian TLR antagonists including ligands that stimulate mammalian TLR7/8 and TLR9 [Schwarz et al. 2007, He et al. 2006, Kogut et al. 2007].

TLR signaling pathways are highly conserved among vertebrates and the chicken proteins involved in the TLR signaling cascade show moderate to high identity with their human counterparts [Yilmaz et al. 2005, Temperley et al. 2008, Cormican et al. 2009]. Thus, a homology-based strategy was used to reconstruct most parts of the chicken TLR pathways in this Reactome module.

All TLRs share a similar structure consisting of N-terminus ectodomain with several leucine-rich regions (LRR), one or two trans-membrane domains and an intracellular C-terminus Toll/Interleukin-1 receptor domain (TIR).

Activation of TLR pathways occurs upon recognition and interaction with conserved motifs expressed by invading microbes, also known as pathogen-associated molecular patterns (PAMPs). Each TLR recognizes specific PAMPs.

Upon PAMP binding TLRs form heterodimers (TLR2 subfamily) or homodimers (all other TLRs). Activated TLRs recruit one or several TIR adaptor proteins myeloid differentiation primary response gene 88 (MyD88), TIR domain containing adaptor protein (TIRAP or MAL), TIR domain-containing adapter protein inducing IFN-beta (TRIF or TIKAM-1), and TRIF related adaptor molecule (TRAM). The fifth known adaptor SARM binds TIR as a negative competitor to TRIF.

All TLRs except TLR3 can initiate downstream signaling through MyD88 adaptor protein. In the MyD88-dependent pathway, once the adaptor is bound to TLR, it leads to recruitment of IL1 receptor associated kinase family IRAK, followed by activation of tumour necrosis factor receptor-associated factor 6 (TRAF6). TRAF6 is an ubiquitin E3

ligase, which in turn induces TGF-beta activating kinase 1 (TAK1) autophosphorylation. Once activated, TAK1 can ultimately mediate the induction of the transcription factor NF-kB or the mitogen-activated protein kinases (MAPK), such as JNK, p38 and ERK. This results in the translocation of the activated NF-kB and MAPKs to the nucleus and the initiation of appropriate gene transcription leading to the production of many proinflammatory cytokines and antimicrobial peptides.

In contrast to other TLRs, TLR3 functions only through the MyD88-independent signaling cascade, recruiting TRIF, which in turn leads to the interferon regulatory factor 3 or 7 (IRF3/7) activation. Activated IRF3 or 7 mediates innate anti-viral responses through interferon-beta expression.

Mammalian TLR4 can ultimately utilize both MyD88-dependent (controlled by the MyD88-TIRAP pair of adaptors) and MyD88-independent (controlled by TRAM-TRIF adaptor proteins) signaling pathways, in contrast, chicken TLR4 signaling is mediated by MyD88-TIRAP exclusively.

## Literature references

- O'Neill, LA., Carpenter, S. (2009). Recent insights into the structure of Toll-like receptors and post-translational modifications of their associated signalling proteins. *Biochem J*, 422, 1-10. [↗](#)
- de Zoete, MR., Vaezirad, MM., Kestra, AM., Bouwman, LI., van Putten, JP. (2013). Unique features of chicken Toll-like receptors. *Dev. Comp. Immunol.*, 41, 316-23. [↗](#)
- Lloyd, AT., Lynn, DJ., O'Farrelly, C. (2003). In silico identification of components of the Toll-like receptor (TLR) signaling pathway in clustered chicken expressed sequence tags (ESTs). *Vet Immunol Immunopathol*, 93, 177-84. [↗](#)
- Burt, DW., Berlin, S., Temperley, ND., Griffin, DK., Paton, IR. (2008). Evolution of the chicken Toll-like receptor gene family: a story of gene gain and gene loss. *BMC Genomics*, 9, 62. [↗](#)
- Smith, AL., Boyd, A., Philbin, VJ. (2007). Conserved and distinct aspects of the avian Toll-like receptor (TLR) system: implications for transmission and control of bird-borne zoonoses. *Biochem Soc Trans*, 35, 1504-7. [↗](#)

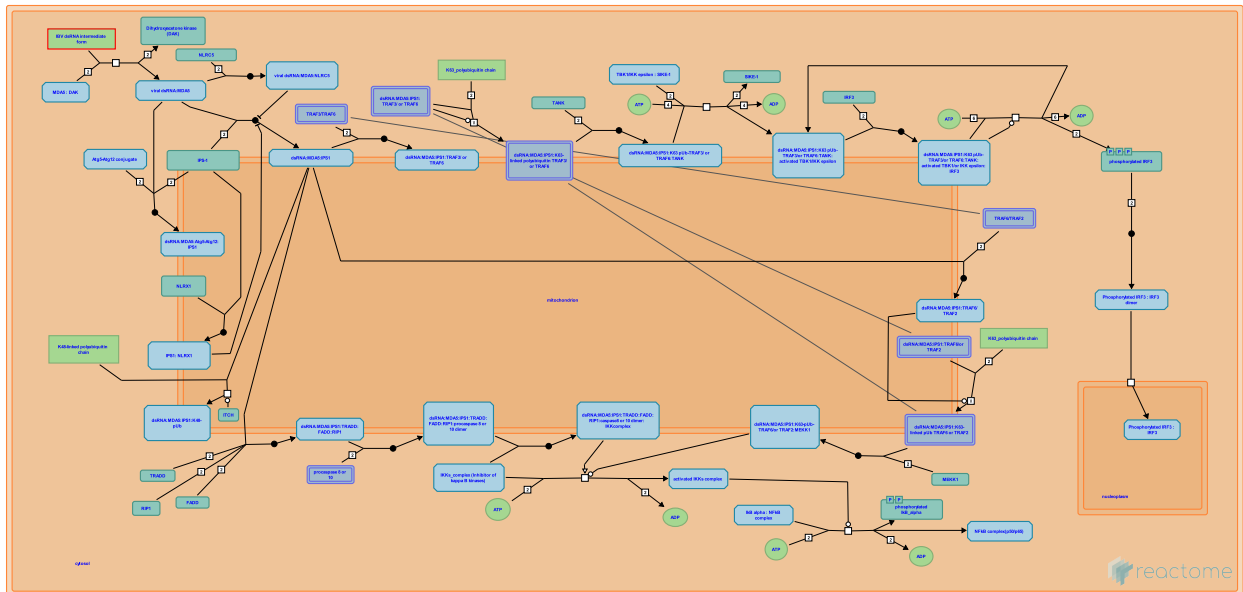
## Editions

2009-11-11	Authored	Shamovsky, V.
2010-05-23	Reviewed	D'Eustachio, P.
2010-05-24	Edited	Shamovsky, V.

# RLR (RIG-like receptor) mediated induction of IFN alpha/beta ↗

Location: Innate Immune System

Stable identifier: R-GGA-1227887



In human, RIG-I-like receptor (RLR) family is crucial for triggering response to cytosolic viral RNA. RLR family is composed of retinoic acid-inducible gene 1 protein (RIG-I), melanoma differentiation-associated protein 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2) [Yoneyama et al 2005].

RIG1, MDA5 and LGP2 are cytosolic multidomain proteins. They all contain a central DexD/H-box RNA helicase/adenosine triphosphatase (ATPase) domain that can bind viral RNA, and a C-terminal regulatory domain (RD) that prevents signaling in the absence of viral RNA. RIG-I and MDA5, but not LGP2, also encode two N-terminal caspase activation and recruitment domains (CARDs) that transmit the signal by binding to CARD domain of mitochondrial IFN-beta promoter stimulator protein (IPS-1; also known as MAVS, VISA or Cardif). This CARD-CARD interaction leads to production of IFN alpha/beta and pro inflammatory cytokines. LGP2 that lacks CARD motifs but binds viral RNA is believed to regulate RLR signaling, however the mechanism of the regulation remains unclear; LGP2 was reported to act as negative regulator [Yoneyama et al 2005; Komuro and Horvath 2006; Saito et al 2007], while other studies suggested that LGP2 may cooperate with RIG-1 and MDA5 in sensing certain viral RNA [Venkataraman et al 2007; Satoh et al 2010].

Primary chick embryo cells produced IFN-alpha in response to Newcastle disease virus (NDV) and produced both IFN-alpha and IFN-beta in response to vaccinia virus or influenza A [Shwartz H et al 2004]. Those viruses have been reported to induce TLR3, RIG-1 and MDA5 signaling in mammals [Delaloye J et al 2009, Kato H et al 2006, Childs et al 2007]. Although RLR signaling is conserved among vertebrates[Sarkar D et al 2008; Zou J et al 2009 and Feng H et al 2011], analysis of chicken genome revealed only orthologs for mammalian MDA5 and LGP2, while RIG-1 gene was not identified [Sarkar D et al 2008; Zou J et al 2009; and Barber MR et al 2010].

## Literature references

Webster, RG., Barber, MR., Magor, KE., Aldridge JR, Jr. (2010). Association of RIG-I with innate immunity of ducks to influenza. *Proc Natl Acad Sci U S A*, 107, 5913-8. ↗

Fisher, PB., Desalle, R., Sarkar, D. (2008). Evolution of MDA-5/RIG-I-dependent innate immunity: independent evolution by domain grafting. *Proc Natl Acad Sci U S A*, 105, 17040-5. ↗

Kikuchi, M., Loo, YM., Fujita, T., Matsumoto, K., Imaizumi, T., Taira, K. et al. (2005). Shared and unique functions of the DEXD/H-box helicases RIG-I, MDA5, and LGP2 in antiviral innate immunity. *J Immunol*, 175, 2851-8. ↗



## Editions

2011-01-05	Authored	Shamovsky, V.
2011-05-11	Edited	Shamovsky, V.
2011-05-16	Reviewed	Garapati, P V.

# Table of Contents

- Introduction 1
- ❖ Innate Immune System 2
  - ❖ Complement Cascade 3
  - ❖ Toll-like receptors (TLR) cascades 5
  - ❖ RLR (RIG-like receptor) mediated induction of IFN alpha/beta 7
- Table of Contents 9