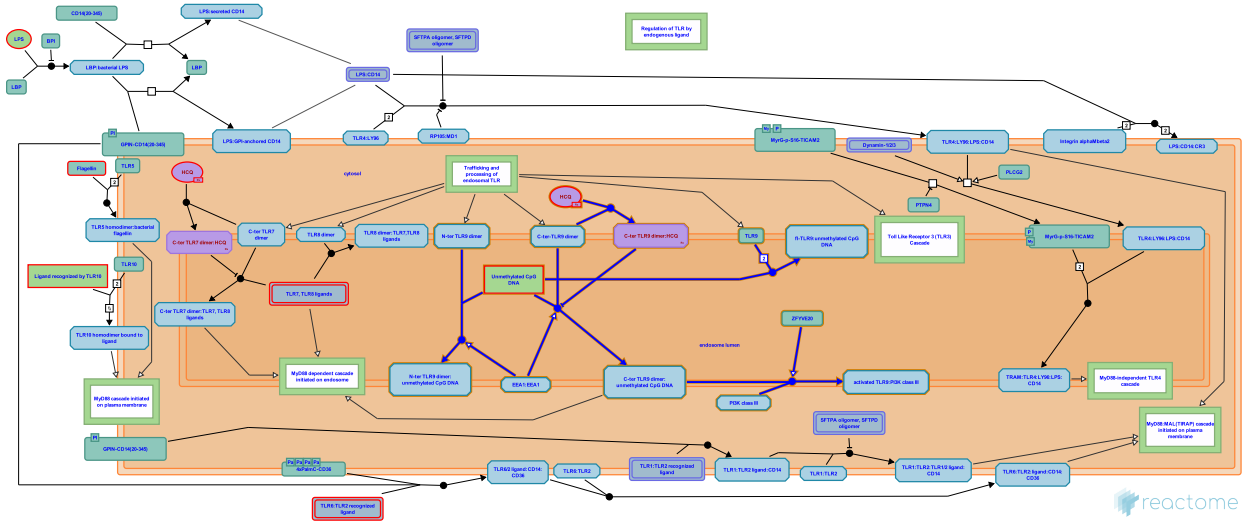
Toll Like Receptor 9 (TLR9) Cascade



Gale M, Jr., Gillespie, ME., Jassal, B., Luo, F., Shamovsky, V., Shoichet, BK., de Bono, B.

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26/01/2021

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. ↗

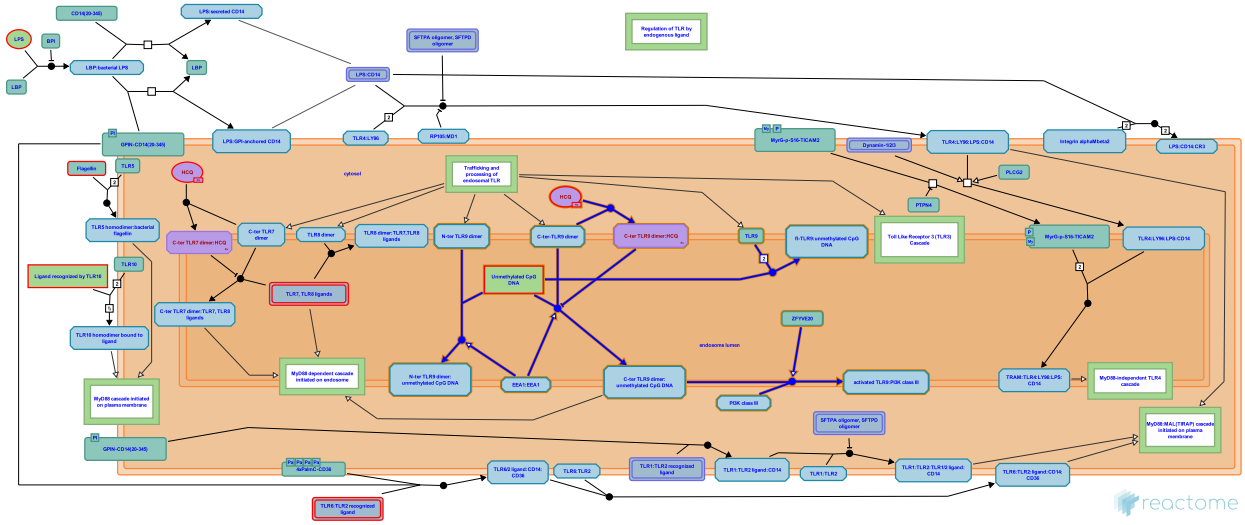
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Toll Like Receptor 9 (TLR9) Cascade ↗

Stable identifier: R-HSA-168138

Compartments: cytosol, endosome membrane, nucleoplasm



CpG DNA is an unusual Pathogen-Associated Molecular Pattern (PAMP). Cytosine methylation exists in mammalian but not bacterial cells, and most (but not all) CpG in the mammalian genome is methylated. Therefore, unmethylated CpG DNA may signal the presence of microbial infection. Evidence of CpG recognition by TLR9 was demonstrated both in human and mouse, and this type of signaling requires its internalization into late endosomal/lysosomal compartments. TLR9 has been reported to be able to discern different types of CpG motifs, and therefore that it presumably recognizes CpG DNA directly. It appears that over evolutionary periods, TLR9 molecules expressed by different species have diverged. This has led to differences in the precise sequence motif (CpG dinucleotide plus flanking regions) that optimally stimulate the innate immune system of different animals.

Literature references

Takeshita, F., Gursel, I., Ishii, KJ., Suzuki, K., Gursel, M., Klinman, DM. (2004). Signal transduction pathways mediated by the interaction of CpG DNA with Toll-like receptor 9. *Semin Immunol, 16*, 17-22. ↗

Editions

2005-11-10	Authored	Luo, F.
2006-10-31	Reviewed	Gale M, Jr.
2010-09-22	Revised	Shamovsky, V.
2010-10-29	Reviewed	Gillespie, ME.
2010-11-15	Edited	Shamovsky, V.

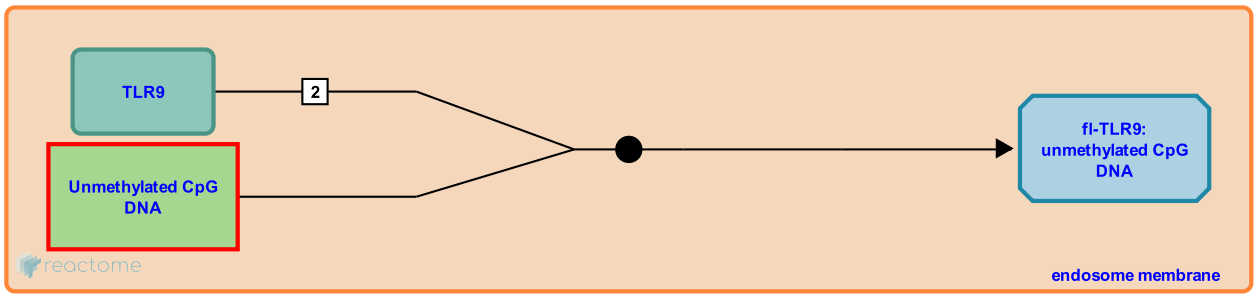
Engulfed CpG DNA binds to endosomal full-length TLR9 ↗

Location: Toll Like Receptor 9 (TLR9) Cascade

Stable identifier: R-HSA-1679589

Type: binding

Compartments: endosome membrane



Both the full-length receptor and cleaved fragment corresponding to the C-terminal part of TLR9 were capable to bind ligand, however only processed form (TLR9 C-ter, aa 471-1032) was shown to bind MyD88 and induce signaling in different mouse cells (Ewald SE et al 2008,).

Literature references

Wagner, H. (2004). The immunobiology of the TLR9 subfamily. *Trends Immunol, 25*, 381-6. ↗

Chockalingam, A., Cameron, JL., Brooks, JC., Leifer, CA. (2011). Negative regulation of signaling by a soluble form of toll-like receptor 9. *Eur J Immunol, 41*, 2176-84. ↗

Ewald, SE., Lee, BL., Lau, L., Wickliffe, KE., Shi, GP., Chapman, HA. et al. (2008). The ectodomain of Toll-like receptor 9 is cleaved to generate a functional receptor. *Nature, 456*, 658-62. ↗

Editions

2011-09-21	Authored	Shamovsky, V.
2012-02-09	Reviewed	Gillespie, ME.
2012-02-19	Edited	Shamovsky, V.

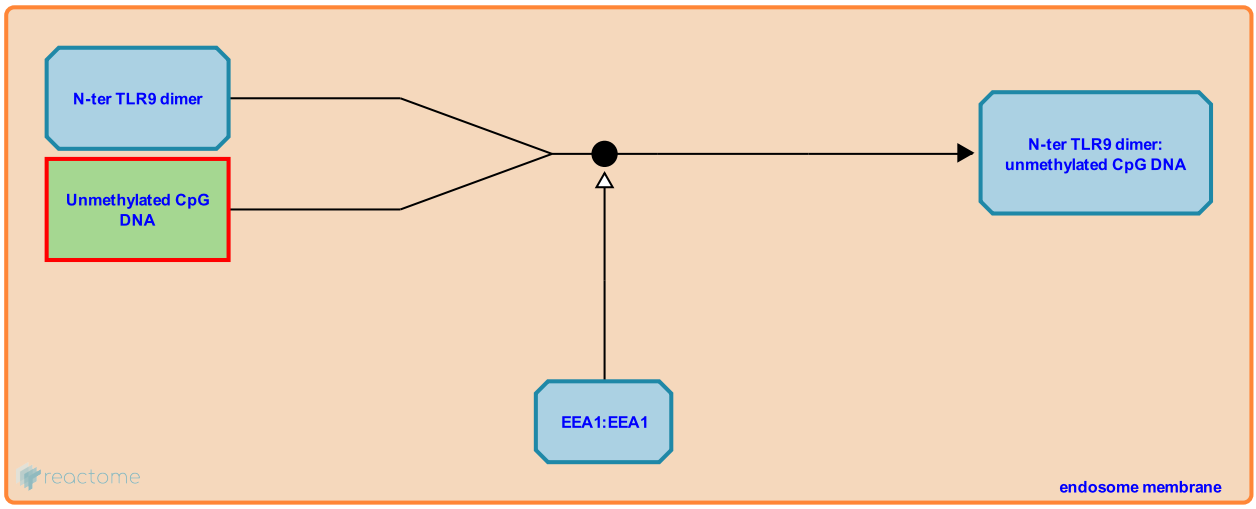
Engulfed CpG DNA binds to endosomal N-ter TLR9 dimer ↗

Location: Toll Like Receptor 9 (TLR9) Cascade

Stable identifier: R-HSA-1679098

Type: binding

Compartments: endosome membrane



TLR9 traffics to an endosomal vesicle where it is processed by cathepsin S at neural pH to generate an N-terminal product (TLR9 N-ter, aa 1-723). The N-terminal fragment of TLR9 also binds ligand, but in contrast to the C-terminal fragment it inhibits TLR9 signaling. Thus, a proper balance between the two proteolytic events probably regulates TLR9-mediated host responses. (Chockalingam A et al 2011).

Literature references

Wagner, H. (2004). The immunobiology of the TLR9 subfamily. *Trends Immunol, 25*, 381-6. ↗

Chockalingam, A., Cameron, JL., Brooks, JC., Leifer, CA. (2011). Negative regulation of signaling by a soluble form of toll-like receptor 9. *Eur J Immunol, 41*, 2176-84. ↗

Editions

2011-09-21	Authored	Shamovsky, V.
2012-02-09	Reviewed	Gillespie, ME.
2012-02-19	Edited	Shamovsky, V.

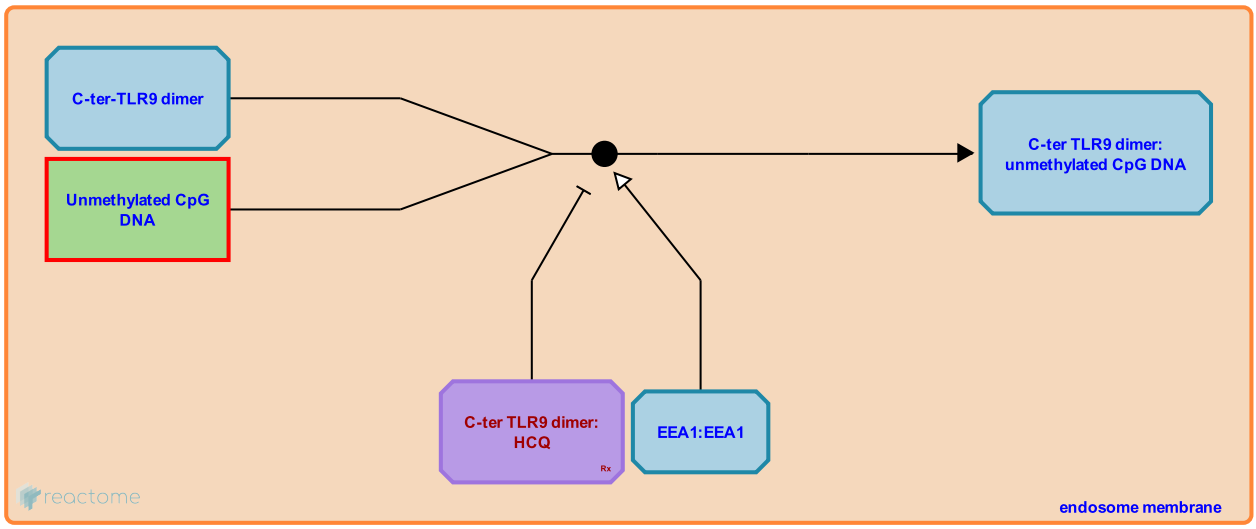
Engulfed CpG DNA binds to endosomal C-ter TLR9 ↗

Location: Toll Like Receptor 9 (TLR9) Cascade

Stable identifier: R-HSA-187895

Type: binding

Compartments: endosome membrane



Synthetic oligodeoxynucleotides (ODN) expressing non-methylated CpG motifs patterned after those present in bacterial DNA have characteristic immunomodulatory effects. CpG DNA is recognized as a pathogen-associated molecular pattern by TLR9, and triggers a rapid innate immune response.

Followed by: Rab5-mediated recruitment of class III PI3K to TLR9

Literature references

Wagner, H. (2004). The immunobiology of the TLR9 subfamily. *Trends Immunol, 25*, 381-6. ↗

Chockalingam, A., Cameron, JL., Brooks, JC., Leifer, CA. (2011). Negative regulation of signaling by a soluble form of toll-like receptor 9. *Eur J Immunol, 41*, 2176-84. ↗

Editions

2011-08-12	Edited	Shamovsky, V.

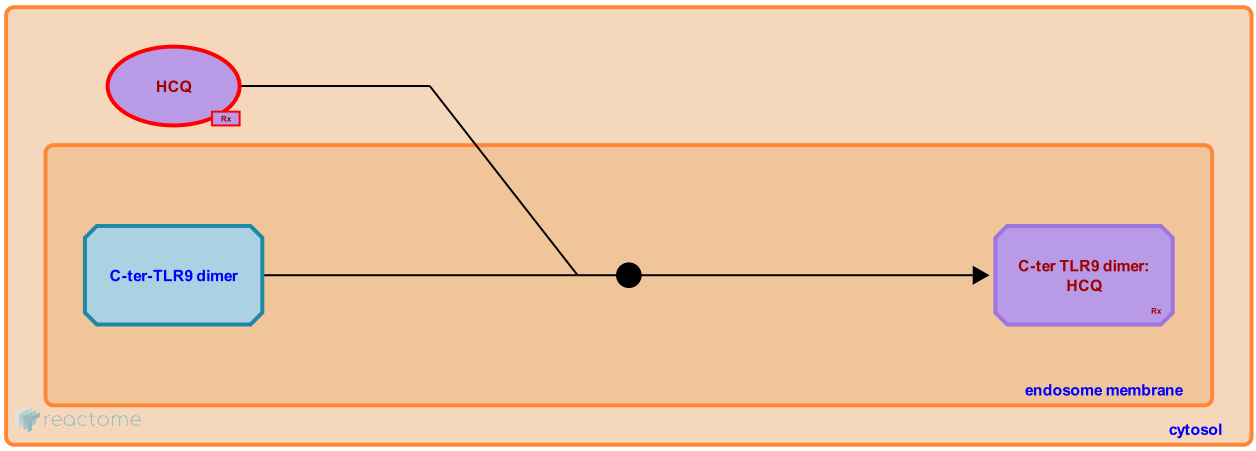
C-ter TLR9 dimer binds HCQ ↗

Location: Toll Like Receptor 9 (TLR9) Cascade

Stable identifier: R-HSA-9679045

Type: binding

Compartments: endosome membrane, cytosol



Toll-like receptor 9 (TLR9) is a key component of innate and adaptive immunity. It controls the host immune response against pathogens by stimulating dendritic cells and macrophages to secrete interferon alpha and other proinflammatory and regulatory cytokines (Lenert 2010). Hydroxychloroquine (HCQ) binds and antagonises TLR9 (Lamphier et al. 2014), and thus inhibits interferon alpha production. HCQ is used clinically to treat systemic lupus erythromatosis and other autoimmune disorders (Costedoat Chalumeau et al. 2014).

HCQ's immunomodulatory properties may be useful for treatment of patients with COVID-19 (Sinha & Balayla 2020, Colson et al. 2020, Gautret et al. 2020).

Literature references

Lamphier, M., Zheng, W., Latz, E., Spyvee, M., Hansen, H., Rose, J. et al. (2014). Novel small molecule inhibitors of TLR7 and TLR9: mechanism of action and efficacy in vivo. *Mol. Pharmacol., 85*, 429-40. ↗

Costedoat-Chalumeau, N., Dunogué, B., Morel, N., Le Guern, V., Guettrot-Imbert, G. (2014). Hydroxychloroquine: a multifaceted treatment in lupus. *Presse Med, 43*, e167-80. ↗

Editions

2020-03-23	Authored, Edited	Jassal, B.
2020-05-14	Reviewed	Shoichet, BK.

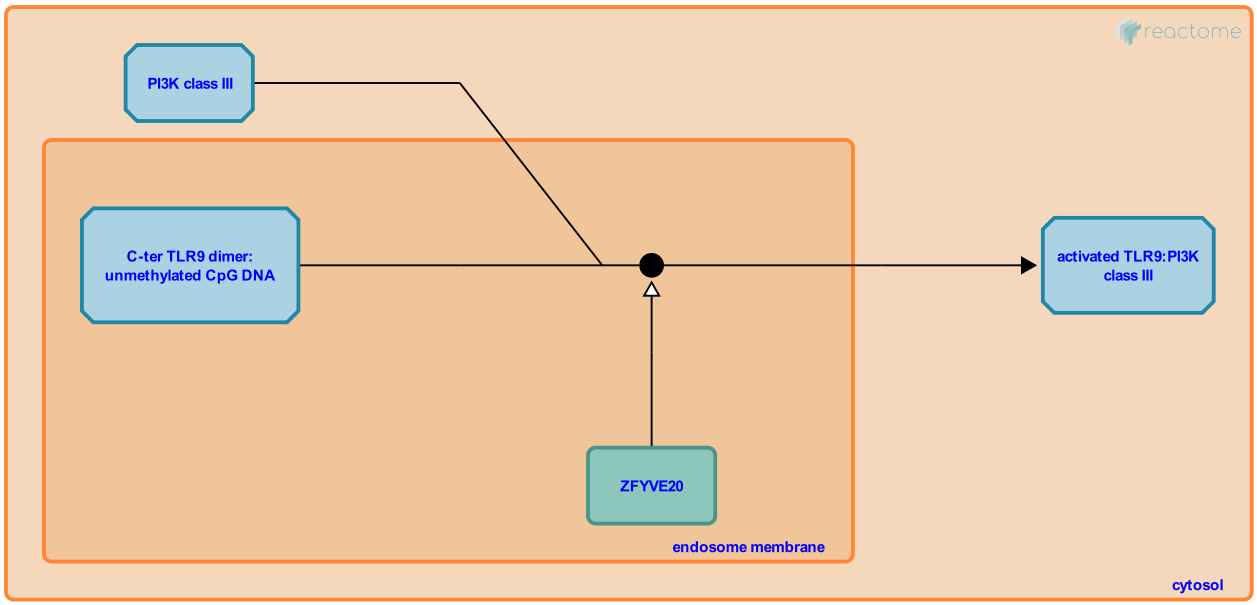
Rab5-mediated recruitment of class III PI3K to TLR9 ↗

Location: Toll Like Receptor 9 (TLR9) Cascade

Stable identifier: R-HSA-188002

Type: binding

Compartments: endosome membrane, cytosol



TLR9 signaling has the uncommon property of triggering PI3K-mediated cascades via Rab5.

Preceded by: Engulfed CpG DNA binds to endosomal C-ter TLR9

Literature references

Takeshita, F., Gursel, I., Ishii, KJ., Suzuki, K., Gursel, M., Klinman, DM. (2004). Signal transduction pathways mediated by the interaction of CpG DNA with Toll-like receptor 9. *Semin Immunol, 16*, 17-22. ↗

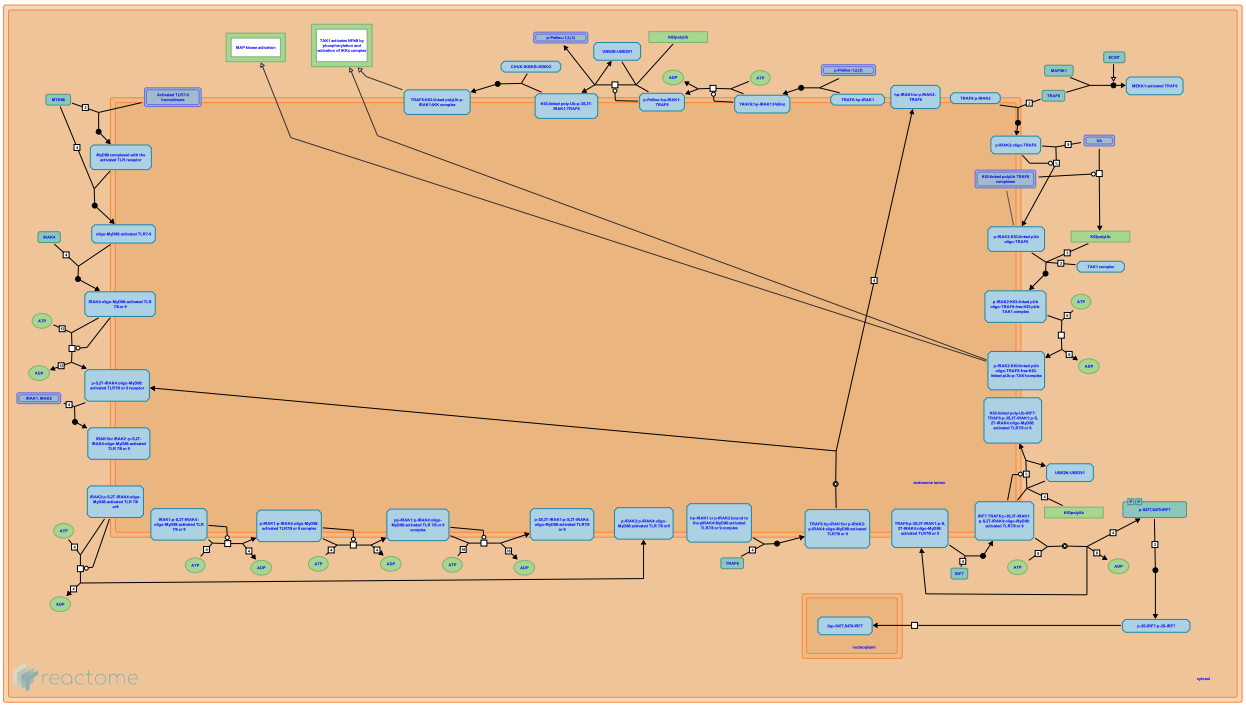
Hoarau, C., Gérard, B., Lescanne, E., Henry, D., François, S., Lacapère, JJ. et al. (2007). TLR9 activation induces normal neutrophil responses in a child with IRAK-4 deficiency: involvement of the direct PI3K pathway. *J. Immunol., 179*, 4754-65. ↗

MyD88 dependent cascade initiated on endosome ↗

Location: Toll Like Receptor 9 (TLR9) Cascade

Stable identifier: R-HSA-975155

Compartments: cytosol, endosome membrane, nucleoplasm



Upon binding of their ligands, TLR7/8 and TLR9 recruit a cytoplasmic adaptor MyD88 and IRAKs, downstream of which the signaling pathways are divided to induce either inflammatory cytokines or type I IFNs.

Literature references

Cherfils-Vicini, J., Platonova, S., Gillard, M., Laurans, L., Validire, P., Caliandro, R. et al. (2010). Triggering of TLR7 and TLR8 expressed by human lung cancer cells induces cell survival and chemoresistance. *J. Clin. Invest., 120*, 1285-97. ↗

Gangloff, M., Gay, NJ. (2004). MD-2: the Toll 'gatekeeper' in endotoxin signalling. *Trends Biochem Sci, 29*, 294-300. ↗

Hanten, JA., Vasilakos, JP., Riter, CL., Neys, L., Lipson, KE., Alkan, SS. et al. (2008). Comparison of human B cell activation by TLR7 and TLR9 agonists. *BMC Immunol., 9*, 39. ↗

Editions

2005-08-16	Authored	de Bono, B.
2010-10-29	Reviewed	Gillespie, ME.
2010-11-15	Edited	Shamovsky, V.

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