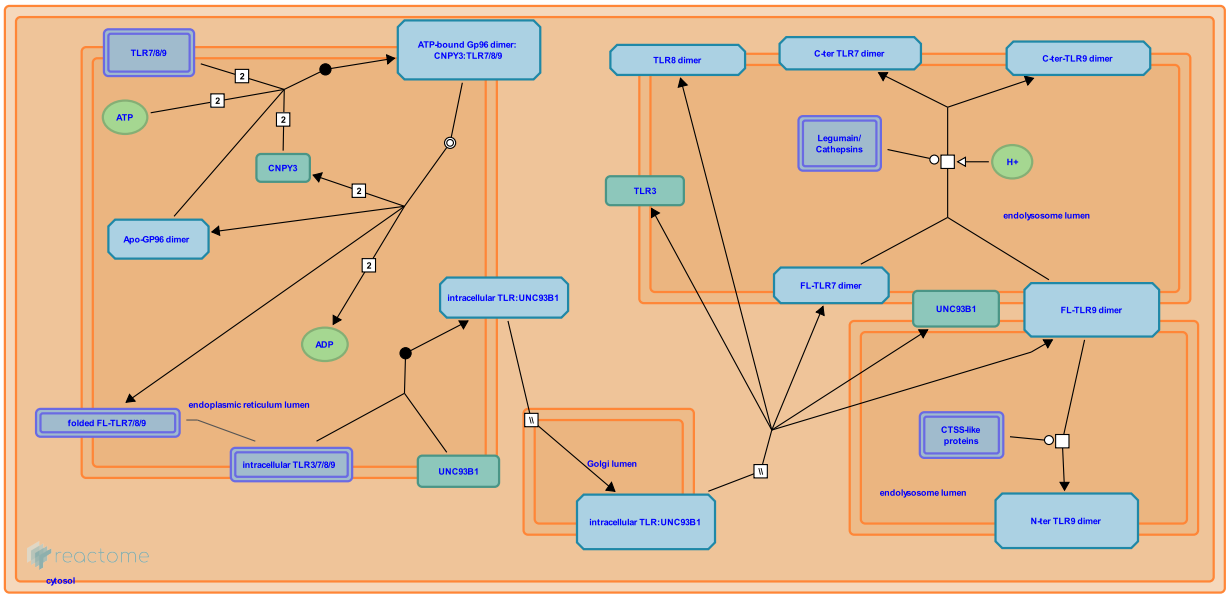
Trafficking and processing of endosomal TLR



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04/05/2024

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. ↗

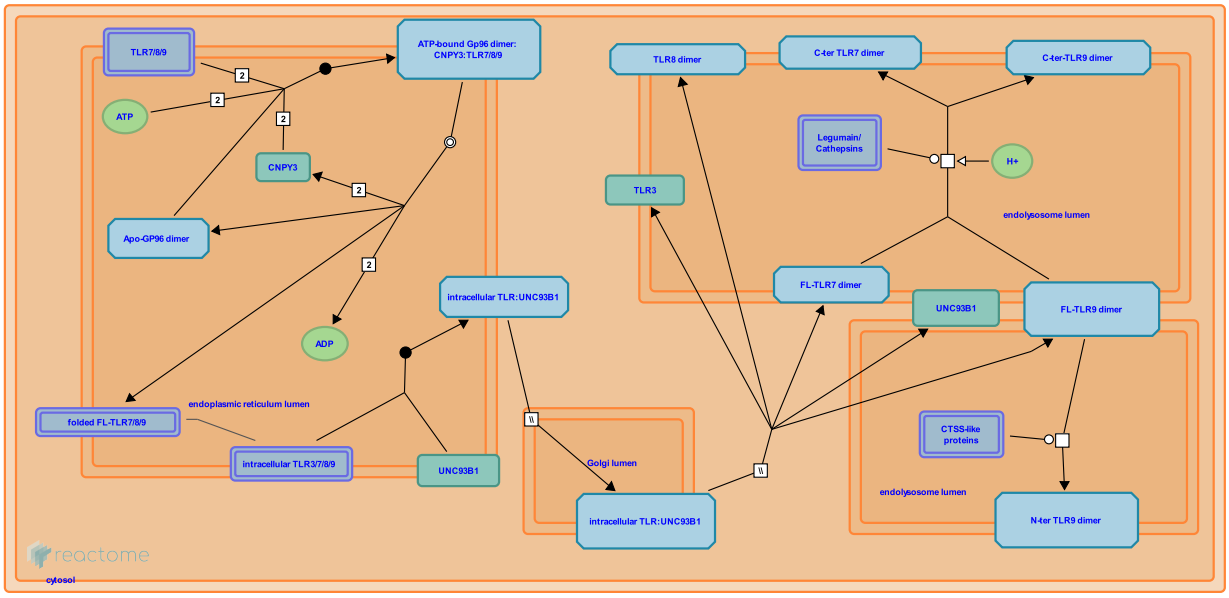
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Trafficking and processing of endosomal TLR ↗

Stable identifier: R-HSA-1679131



Mammalian TLR3, TLR7, TLR8, TLR9 are endosomal receptors that sense nucleic acids that have been released from endocytosed/phagocytosed bacteria, viruses or parasites. These TLRs have a ligand-recognition domain that faces the lumen of the endosome (which is topologically equivalent to the outside of the cell), a transmembrane domain, and a signaling domain that faces the cytosol.

Under normal conditions, self nucleic acids are not recognized by TLRs due to multiple levels of regulation including receptor compartmentalization, trafficking and proteolytic processing (Barton GM et al 2006, Ewald SE et al 2008). At steady state TLR3, TLR7, TLR8, TLR9 reside primarily in the endoplasmic reticulum (ER), however, their activation by specific ligands only occurs within acidified endolysosomal compartments (Hacker H et al 1998, Funami K et al 2004, Gibbard RJ et al 2006). Several chaperon proteins associate with TLRs in the ER to provide efficient translocation to endolysosome. Upon reaching endolysosomal compartments the ectodomains of TLR7 and TLR9 are proteolytically cleaved by cysteine endoproteases. Both full-length and cleaved C-terminus of TLR9 bind CpG-oligodeoxynucleotides, however it has been proposed that only the processed receptor is functional.

Although similar cleavage of TLR3 has been reported by Ewald et al 2011, other studies demonstrated that the N-terminal region of TLR3 ectodomain was implicated in ligand binding, thus TLR3 may function as a full-length receptor (Liu L et al 2008, Tokisue T et al 2008).

There are no data on TLR8 processing, although the cell biology of TLR8 is probably similar to TLR9 and TLR7 (Gibbard RJ et al 2006, Wei T et al 2009).

Literature references

Barton, GM., Kagan, JC., Medzhitov, R. (2006). Intracellular localization of Toll-like receptor 9 prevents recognition of self DNA but facilitates access to viral DNA. *Nat Immunol, 7*, 49-56. ↗

Morley, PJ., Gibbard, RJ., Gay, NJ. (2006). Conserved features in the extracellular domain of human toll-like receptor 8 are essential for pH-dependent signaling. *J Biol Chem, 281*, 27503-11. ↗

Stark, RW., Jamitzky, F., Gong, J., Heckl, WM., Rössle, SC., Wei, T. (2009). Homology modeling of human Toll-like receptors TLR7, 8, and 9 ligand-binding domains. *Protein Sci, 18*, 1684-91. ↗

Miethke, T., Sparwasser, T., Hacker, H., Heeg, K., Schmid, R., Lipford, GB. et al. (1998). CpG-DNA-specific activation of antigen-presenting cells requires stress kinase activity and is preceded by non-specific endocytosis and endosomal maturation. *EMBO J, 17*, 6230-40. ↗

de Bouteiller, O., Caux, C., Hubac, S., Merck, E., Trinchieri, G., Benguigui, B. et al. (2005). Recognition of double-stranded RNA by human toll-like receptor 3 and downstream receptor signaling requires multimerization and an acidic pH. *J Biol Chem, 280*, 38133-45. ↗

Editions

2011-10-19	Authored	Shamovsky, V.
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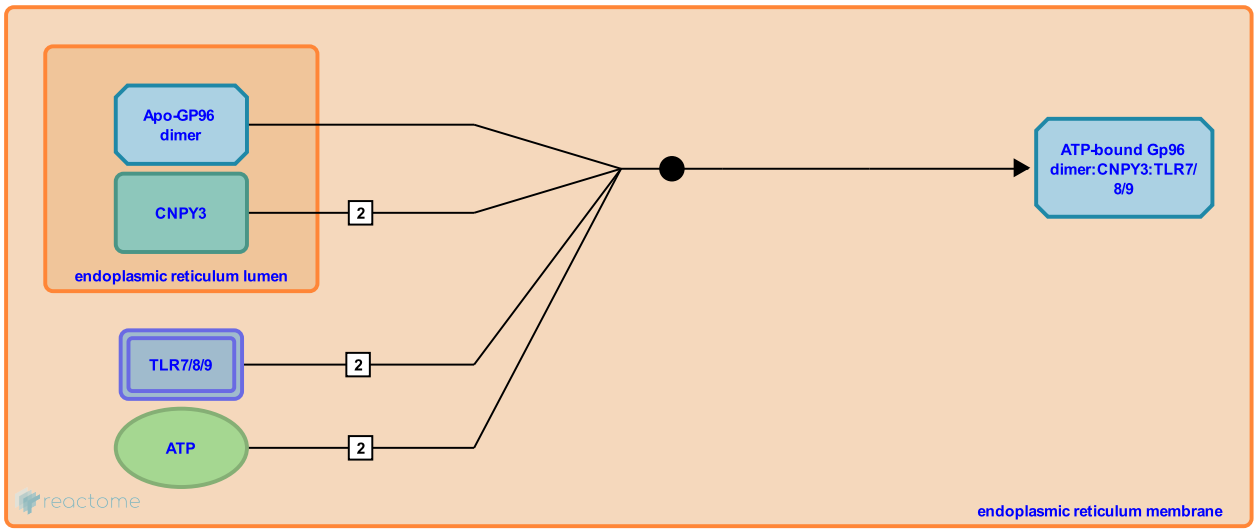
TLR folding by chaperones GP96 and CNPY3 ↗

Location: Trafficking and processing of endosomal TLR

Stable identifier: R-HSA-1678923

Type: binding

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



GP96 (also known as GRP94, HSP90b1), a paralogue of HSP90 in the endoplasmic reticulum, acts as a chaperone for some integrines and Toll-like receptors. Macrophages or B-cells from gp96 knockout mice have abrogated function of TLR2, 4, 5, 7 and 9, but not TLR3 (Yang Y et al 2007, Liu B and Li Z 2008, Staron M et al 2010). GP96 interacts with TLRs and integrines via its C-terminal hydrophobic domain, formed by residues 652-678 (Wu S et al 2012). GP96 functions as a V-shaped dimer in ATP-dependent manner, however it remains unclear how ATP hydrolysis-dependent conformational changes of GP96 are regulated (Li Z and Srivastava PK 1993).

GP96 forms a complex with co-chaperone CNPY3, also known as PRAT4A. GP96-CNPY3 promotes the proper post-translational ectodomain folding of TLRs, but not TLR3 (Liu B et al 2010).

Followed by: Folded full-length TLR7/8/9 dissociates from the GP96:CNPY3 complex

Literature references

Liu, B., Li, Z. (2008). Endoplasmic reticulum HSP90b1 (gp96, grp94) optimizes B-cell function via chaperoning integrin and TLR but not immunoglobulin. *Blood, 112*, 1223-30. ↗

Dai, J., Liu, B., Lefrançois, L., Srivastava, PK., Yang, Y., Zammit, DJ. et al. (2007). Heat shock protein gp96 is a master chaperone for toll-like receptors and is important in the innate function of macrophages. *Immunity, 26*, 215-26. ↗

Guo, B., Liu, B., Gewirth, D., Wu, S., Hong, F., Li, Z. (2012). The Molecular Chaperone gp96/GRP94 Interacts With Toll-Like Receptors And Integrins Via Its C-Terminal Hydrophobic Domain. *J Biol Chem*. ↗

Bona, R., Staron, M., Liu, B., Han, D., Li, Y., Qiu, Z. et al. (2010). Folding of Toll-like receptors by the HSP90 paralogue gp96 requires a substrate-specific cochaperone. *Nat Commun, 1*, 79. ↗

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Editions

2011-10-19	Authored	Shamovsky, V.
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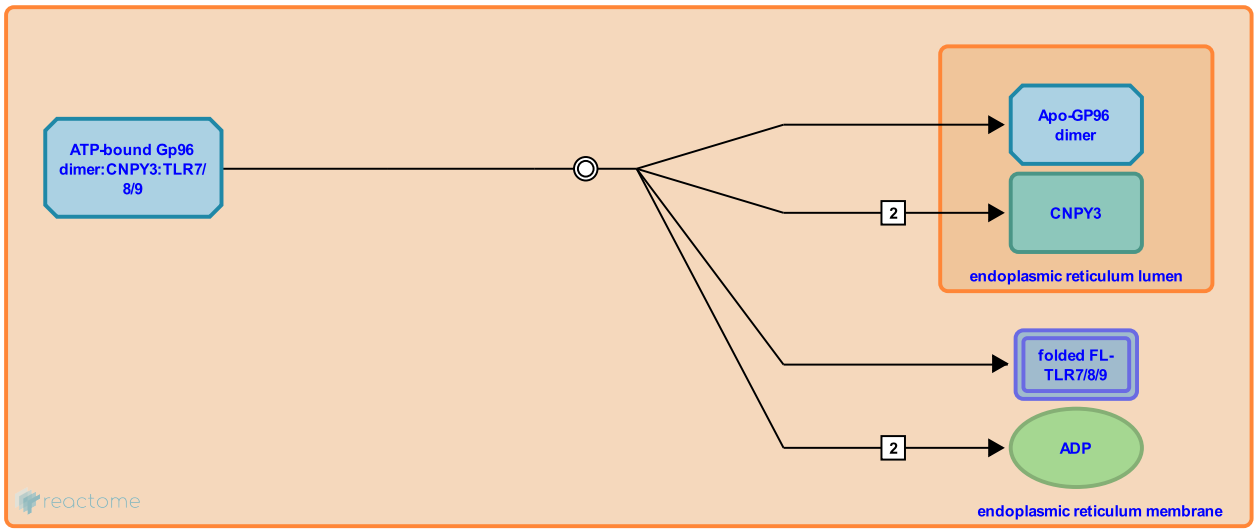
Folded full-length TLR7/8/9 dissociates from the GP96:CNPY3 complex ↗

Location: Trafficking and processing of endosomal TLR

Stable identifier: R-HSA-1678944

Type: dissociation

Compartments: endoplasmic reticulum membrane, endoplasmic reticulum lumen



Folded TLR9 dissociates from GP96:CNPY3 complex (Liu B et al 2010) and translocates to the endolysosome with the aid of the membrane protein UNC93b. Here we assume that TLR7 and TLR8 behave in a similar manner.

Preceded by: TLR folding by chaperones GP96 and CNPY3

Followed by: Full-length TLR3/7/8/9 binds to UNC93B1

Literature references

Bona, R., Staron, M., Liu, B., Han, D., Li, Y., Qiu, Z. et al. (2010). Folding of Toll-like receptors by the HSP90 paralogue gp96 requires a substrate-specific cochaperone. *Nat Commun, 1*, 79. ↗

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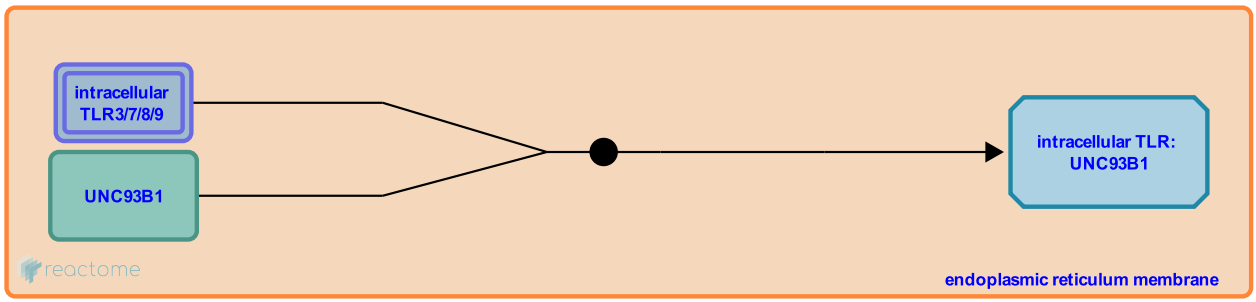
Full-length TLR3/7/8/9 binds to UNC93B1 ↗

Location: Trafficking and processing of endosomal TLR

Stable identifier: R-HSA-1678921

Type: binding

Compartments: endoplasmic reticulum membrane



Mammalian UNC93B1, a multi-transmembrane protein, directly associates with transmembrane domains of TLR3, TLR7, TLR8 and TLR9 (and mouse TLR13) in the ER and facilitates their translocation to endolysosome compartments (Brinkmann et al 2007; Kim et al 2008; Itoh H et al 2011). Mutant mouse and human cells that lack functional UNC93B1 showed disrupted signaling via the endosomal TLRs (Taneda K et al 2006; Fukui et al 2009; Kim YM et al 2008; Qi R et al 2010; Koehn J et al 2007). Furthermore, defects in the human gene encoding UNC93B1 are associated with the increased susceptibility to herpes simplex encephalitis (HSE) in children (Casrouge A et al 2006).

TLR7 and TLR9 compete for UNC931-dependent trafficking and under normal circumstances TLR9 predominates over TLR7. This preference for TLR9 is mediated by an N-terminal domain in UNC93B1 and is reversed to TLR7 if UNC93B1 loses the preferential N-terminal binding site via mutation of aspartate at position 34. Loss of binding to TLR9 and preferential association with TLR7 resulted in hyperresponsiveness to RNA ligands (Fukui et al 2009).

TLR3 appears to translocate to the endosomal compartment with equal efficiency regardless of the presence or absence of the N-terminal domain that mediates preference for TLR9. Thus, endosomal TLR trafficking is orchestrated by UNC93B1 which determines how efficiently each TLR is able to move from the ER to the endolysosomes to initiate host responses.

Preceded by: Folded full-length TLR7/8/9 dissociates from the GP96:CNPY3 complex

Followed by: Endosomal TLRs pass through the Golgi

Literature references

San Mateo, L., Mills, J., Schreiter, J., Jordan, JL., Lamb, R., Ranjith-Kumar, CT. et al. (2010). Secretion of the human Toll-like receptor 3 ectodomain is affected by single nucleotide polymorphisms and regulated by Unc93b1. *J Biol Chem, 285*, 36635-44. ↗

Beutler, B., Abel, L., Alcais, A., Dulac, O., Lebon, P., Lorenzo, L. et al. (2006). Herpes simplex virus encephalitis in human UNC-93B deficiency. *Science, 314*, 308-12. ↗

Beutler, B., Matsumoto, F., Miyake, K., Tabeta, K., Saitoh, S., Fukui, R. et al. (2009). Unc93B1 biases Toll-like receptor responses to nucleic acid in dendritic cells toward DNA- but against RNA-sensing. *J Exp Med, 206*, 1339-50. ↗

Beutler, B., Sovath, S., Cooke, M., Herskovits, AA., Tabeta, K., Goode, J. et al. (2006). The Unc93b1 mutation 3d disrupts exogenous antigen presentation and signaling via Toll-like receptors 3, 7 and 9. *Nat Immunol, 7*, 156-64. ↗

Beutler, B., Ploegh, HL., Spooner, E., Kim, YM., Hoebe, K., Brinkmann, MM. (2007). The interaction between the ER membrane protein UNC93B and TLR3, 7, and 9 is crucial for TLR signaling. *J Cell Biol, 177*, 265-75. ↗

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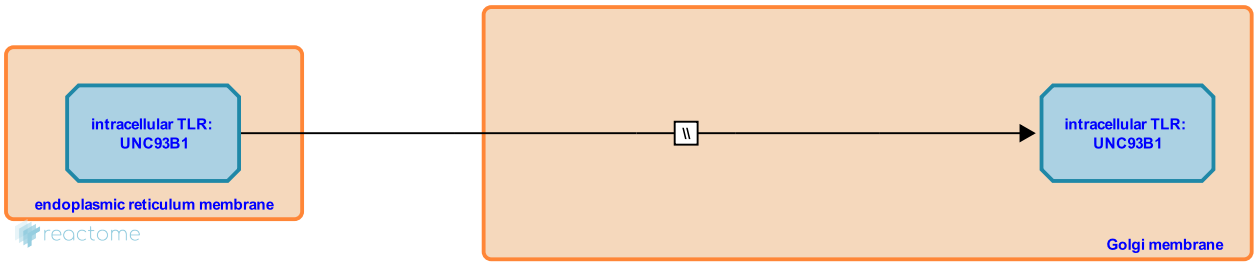
Endosomal TLRs pass through the Golgi ↗

Location: Trafficking and processing of endosomal TLR

Stable identifier: R-HSA-1678998

Type: omitted

Compartments: Golgi membrane, endoplasmic reticulum lumen



TLRs traffic through the Golgi complex by the conventional secretory pathway and are routed to endolysosomes where they bind their ligands (Chockalingam A et al 2008, Ewald SE et al 2011). .

Preceded by: Full-length TLR3/7/8/9 binds to UNC93B1

Followed by: UNC93B1 delivers endosomal full-length TLRs to endolysosome

Literature references

Blum, LK., Cameron, JL., Brooks, JC., Chockalingam, A., Leifer, CA. (2009). TLR9 traffics through the Golgi complex to localize to endolysosomes and respond to CpG DNA. *Immunol Cell Biol, 87*, 209-17. ↗

Barton, GM., Lee, J., Ewald, SE., Wang, M., Bogyo, M., Engel, A. (2011). Nucleic acid recognition by Toll-like receptors is coupled to stepwise processing by cathepsins and asparagine endopeptidase. *J Exp Med, 208*, 643-51. ↗

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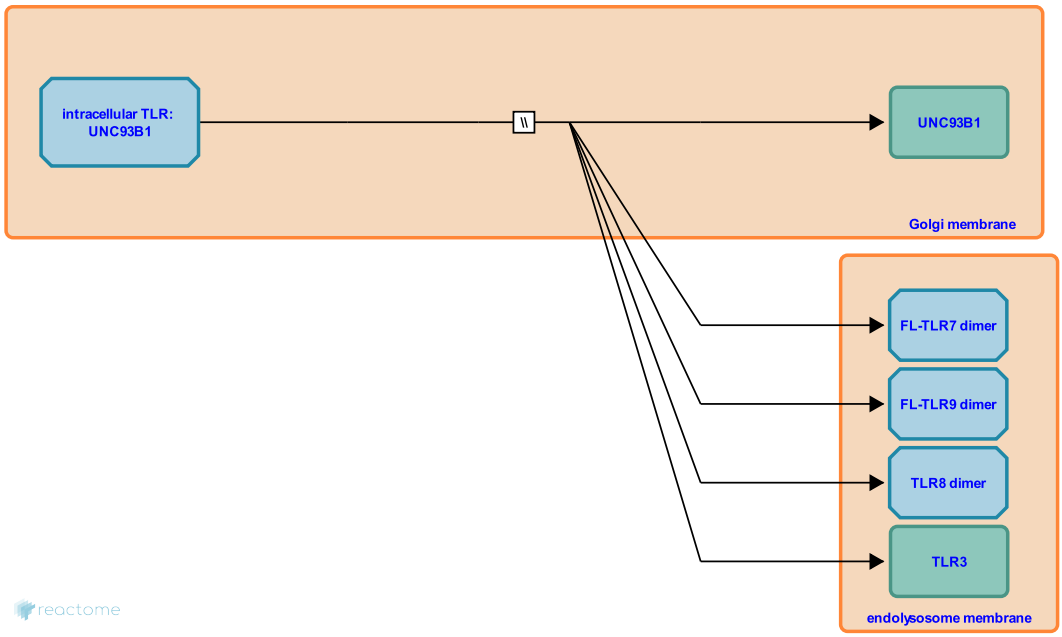
UNC93B1 delivers endosomal full-length TLRs to endolysosome ↗

Location: Trafficking and processing of endosomal TLR

Stable identifier: R-HSA-1678927

Type: omitted

Compartments: Golgi membrane, endolysosome membrane



TLR3, 7, 8 and 9 activation occurs within acidified endolysosomal compartments. Inhibition of endosome acidification with bafilomicin A or chloroquine abrogated TLR's-mediated responses to pathogen-derived nucleic acids (Hacker H et al 1998, Funami K et al 2004, Gibbard RJ et al 2006, Kuznik A et al 2011). Upon stimulation, TLR3, 7, and 9 (and possibly TLR8) are transported to the signaling endosomes by UNC93B1, whereby they become functional receptors and bind to their specific ligands (Kim et al 2008, Ewald et al 2011). Although UNC93B1 is critically involved in TLRs trafficking it was dispensable for ligand binding by these TLRs (Kim YM et al 2008).

Preceded by: Endosomal TLRs pass through the Golgi

Followed by: TLR9 processing at neutral pH, TLR processing at low pH

Literature references

Morley, PJ., Gibbard, RJ., Gay, NJ. (2006). Conserved features in the extracellular domain of human toll-like receptor 8 are essential for pH-dependent signaling. *J Biol Chem, 281*, 27503-11. ↗

Lien, E., Fitzgerald, KA., Nilsen, NJ., Latz, E., Monks, BG., Schoenemeyer, A. et al. (2004). TLR9 signals after translocating from the ER to CpG DNA in the lysosome. *Nat Immunol, 5*, 190-8. ↗

Miethke, T., Sparwasser, T., Hacker, H., Heeg, K., Schmid, R., Lipford, GB. et al. (1998). CpG-DNA-specific activation of antigen-presenting cells requires stress kinase activity and is preceded by non-specific endocytosis and endosomal maturation. *EMBO J, 17*, 6230-40. ↗

Matsumoto, M., Oshiumi, H., Funami, K., Akazawa, T., Seya, T., Yamamoto, A. (2004). The cytoplasmic 'linker region' in Toll-like receptor 3 controls receptor localization and signaling. *Int Immunol, 16*, 1143-54. ↗

Ploegh, HL., Kim, YM., Paquet, ME., Brinkmann, MM. (2008). UNC93B1 delivers nucleotide-sensing toll-like receptors to endolysosomes. *Nature, 452*, 234-8. ↗

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2012-02-28	Reviewed	Leifer, CA., Rose II, WA.

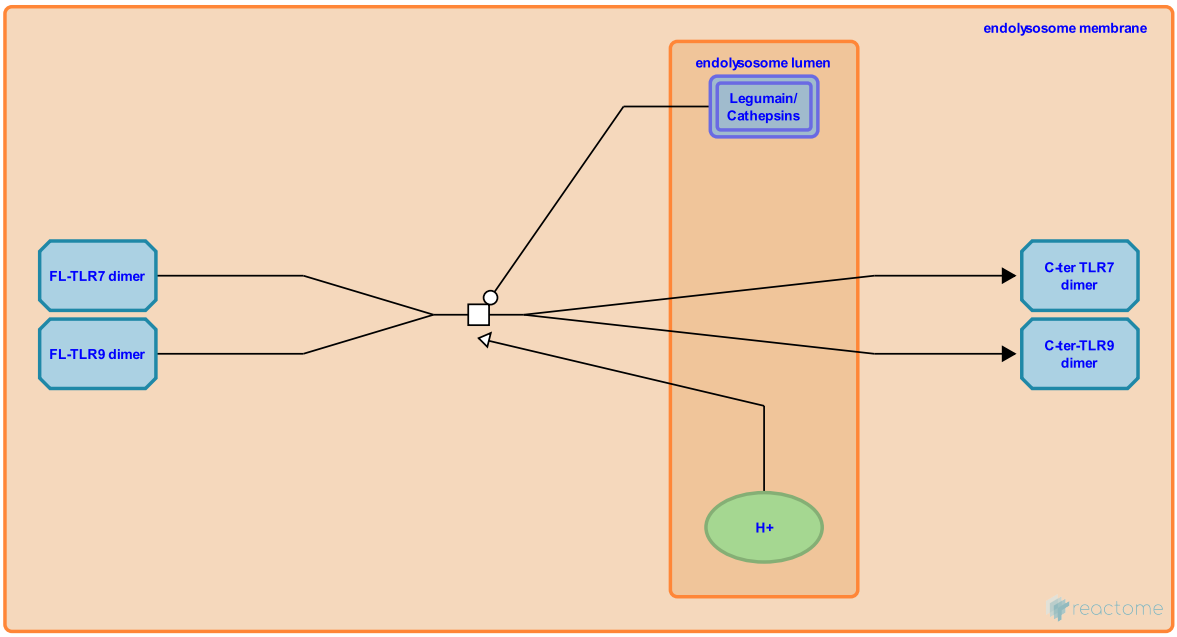
TLR processing at low pH ↗

Location: Trafficking and processing of endosomal TLR

Stable identifier: R-HSA-1678920

Type: transition

Compartments: endolysosome membrane



Endosome maturation (acidification) is required for both the activation of TLR9 and TLR7 through proteolytic cleavage and the disassembly of pathogens, thereby releasing the TLR ligands within them. TLR7 and TLR9 are cleaved within their ectodomains by pH-sensitive cysteine endopeptidases. Cathepsins (CTS) B, K, L, and S, and asparagine endopeptidase (AEP, also known as legumain) have been implicated in endolysosomal TLR processing, however, several groups have reported somewhat controversial results on the role of specific proteases (Matsumoto F et al 2008, Park B et al 2008, Ewald SE et al 2008, Ewald SE et al 2011, Sepulveda FE et al 2009).

One study showed that TLR9 proteolysis is a multistep process with the initial cleavage that can be mediated by AEP or multiple members of the cathepsin family. The second event is mediated exclusively by cathepsins. TLR7 and TLR3 were reported to be cleaved in a similar manner (Ewald SE et al 2011). Cleavage of TLR3 is not shown in this reaction, since other studies demonstrated that the N-terminal region of TLR3 ectodomain was implicated in ligand binding, suggesting that TLR3 may function as a full-length receptor (Liu L et al 2008, Tokisue T et al 2008).

Both full-length receptor and cleaved fragment corresponding to the C-terminal part of TLR9 were capable to bind ligand, however only the 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).

Preceded by: UNC93B1 delivers endosomal full-length TLRs to endolysosome

Literature references

Ploegh, HL., Lee, CC., Spooner, E., Kim, YM., Park, B., Brinkmann, MM. (2008). Proteolytic cleavage in an endolysosomal compartment is required for activation of Toll-like receptor 9. *Nat Immunol, 9*, 1407-14. ↗

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

Matsumoto, F., Miyake, K., Akashi-Takamura, S., Kusumoto, Y., Tanimura, N., Kobayashi, T. et al. (2008). Cathepsins are required for Toll-like receptor 9 responses. *Biochem Biophys Res Commun, 367*, 693-9. ↗

Barton, GM., Lee, J., Ewald, SE., Wang, M., Bogyo, M., Engel, A. (2011). Nucleic acid recognition by Toll-like receptors is coupled to stepwise processing by cathepsins and asparagine endopeptidase. *J Exp Med, 208*, 643-51. ↗

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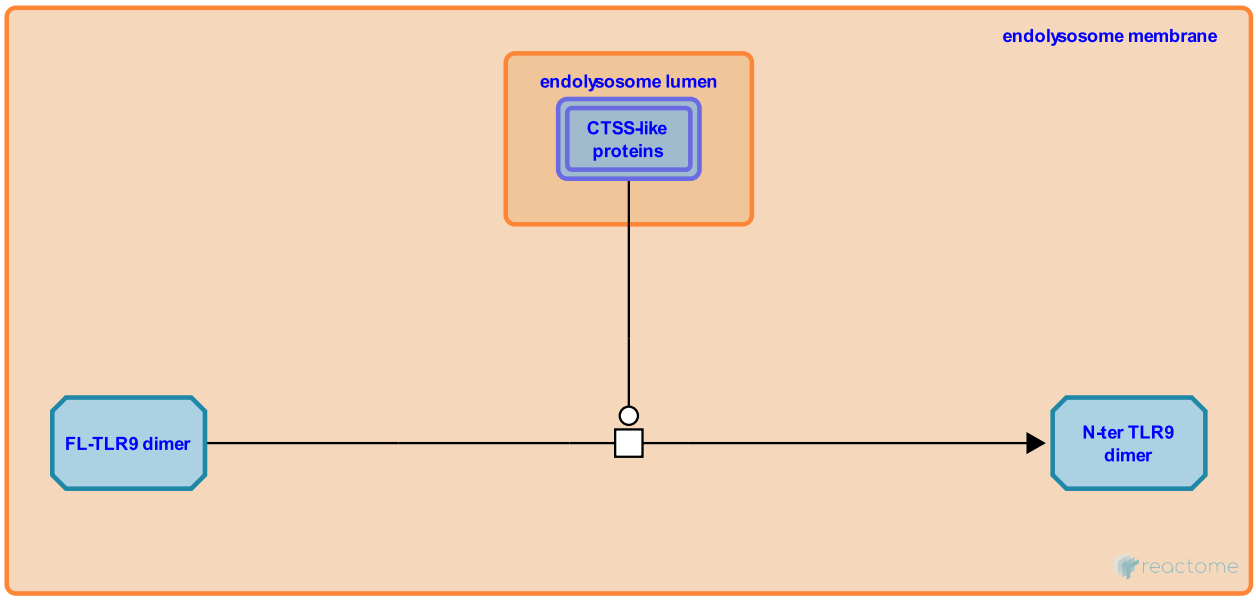
TLR9 processing at neutral pH ↗

Location: Trafficking and processing of endosomal TLR

Stable identifier: R-HSA-1678981

Type: transition

Compartments: endolysosome 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).

Preceded by: UNC93B1 delivers endosomal full-length TLRs to endolysosome

Literature references

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

Editions

2011-10-19	Authored	Shamovsky, V.
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