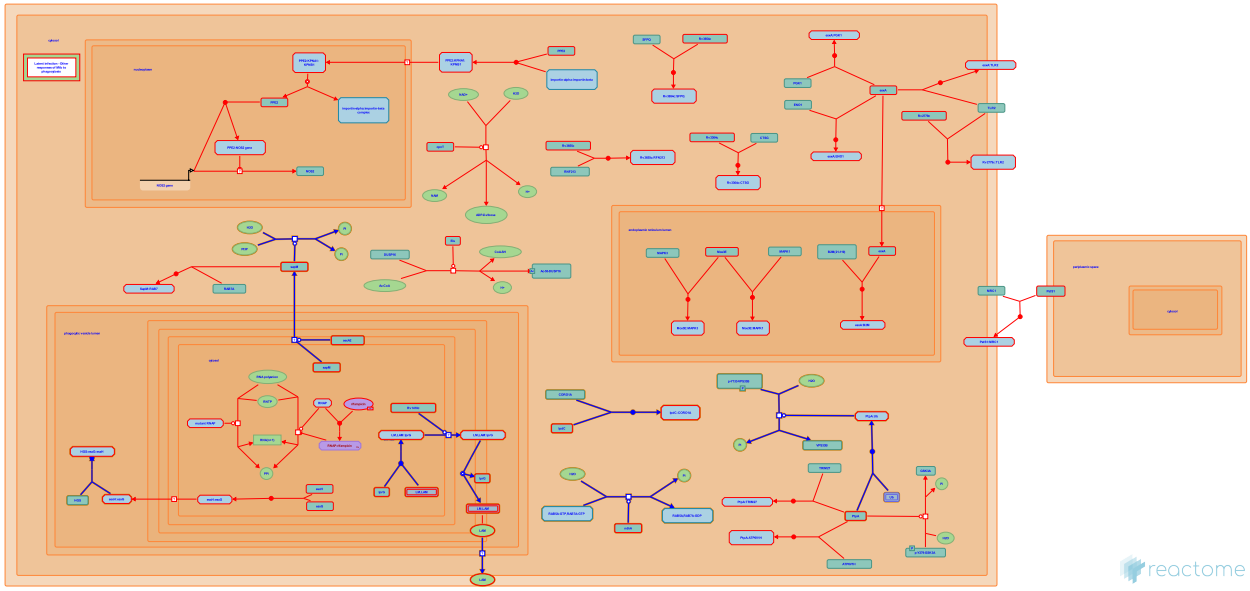
Prevention of phagosomal-lysosomal fusion



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07/05/2024

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. ↗

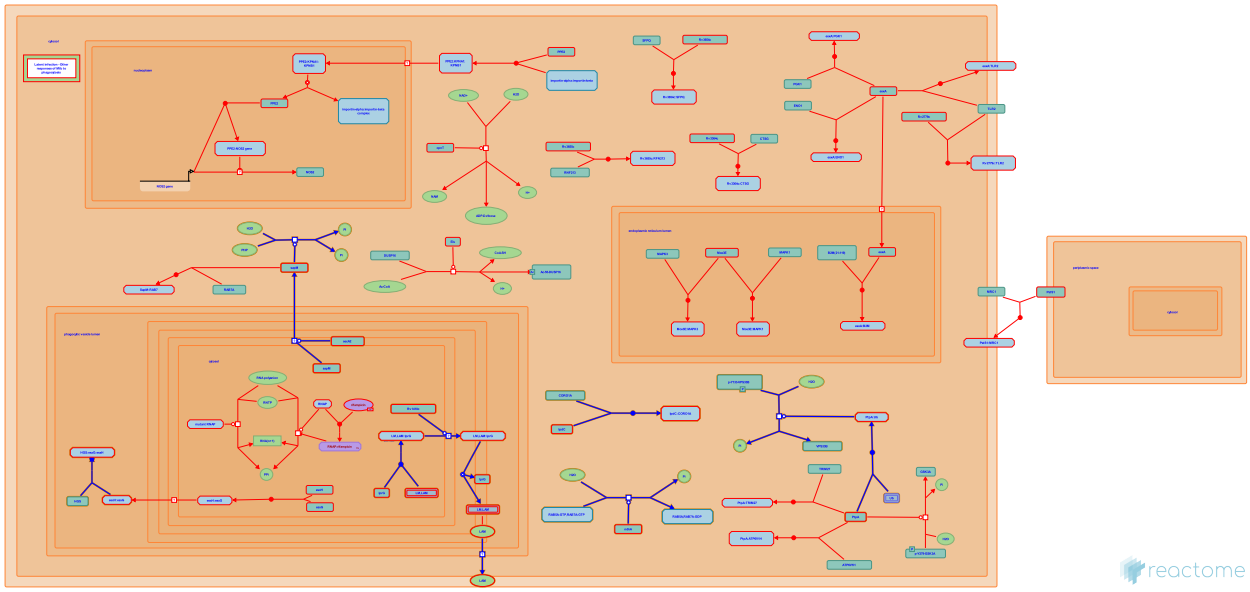
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Prevention of phagosomal-lysosomal fusion ↗

Stable identifier: R-HSA-9636383

Diseases: tuberculosis



Lipoarabinomannan (LAM) is transported to Mtb's outer cell wall. When Mtb is interned by the phagocyte, LAM is shedded into the phagocyte's membrane, gets incorporated into lipid rafts of the phagosomal membrane, where it acts to prevent phagosomal-lysosomal fusion (Welin et al. 2008, Gaur et al. 2014). Other processes that get inhibited include the cytoskeletal protein coronin-1A and the fusion mediator vacuolar protein sorting-associated protein 33B (VPS33B) (Deghmane et al. 2007, Bach et al. 2008). Also the Ras-related protein (Rab5) effector phosphatidylinositol 3-phosphate (PI3P) gets enzymatically depleted (Vergne et al. 2005).

Literature references

González-Nilo, FD., Banaei, N., Ehrt, S., Ren, K., Gaur, RL., Zare, RN. et al. (2014). LprG-mediated surface expression of lipoarabinomannan is essential for virulence of Mycobacterium tuberculosis. *PLoS Pathog., 10*, e1004376. ↗

Deretic, V., Belisle, J., Lucas, M., Vergne, I., Lee, HH., Chua, J. (2005). Mechanism of phagolysosome biogenesis block by viable Mycobacterium tuberculosis. *Proc. Natl. Acad. Sci. U.S.A., 102*, 4033-8. ↗

Hmama, Z., Av-Gay, Y., Bach, H., Wong, D., Papavinasasundaram, KG. (2008). Mycobacterium tuberculosis virulence is mediated by PtpA dephosphorylation of human vacuolar protein sorting 33B. *Cell Host Microbe, 3*, 316-22. ↗

Abdalla, H., Winberg, ME., Lerm, M., Rasmusson, B., Welin, A., Stendahl, O. et al. (2008). Incorporation of Mycobacterium tuberculosis lipoarabinomannan into macrophage membrane rafts is a prerequisite for the phagosomal maturation block. *Infect. Immun., 76*, 2882-7. ↗

Toyoshima, S., Hmama, Z., Av-Gay, Y., Deghmane, AE., Noubir, S., Itoh, S. et al. (2007). Lipoamide dehydrogenase mediates retention of coronin-1 on BCG vacuoles, leading to arrest in phagosome maturation. *J. Cell. Sci., 120*, 2796-806. ↗

Editions

2019-02-06	Authored	Stephan, R.
2019-02-13	Edited	Koile, I.
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lprG binds to LAM,LM ↗

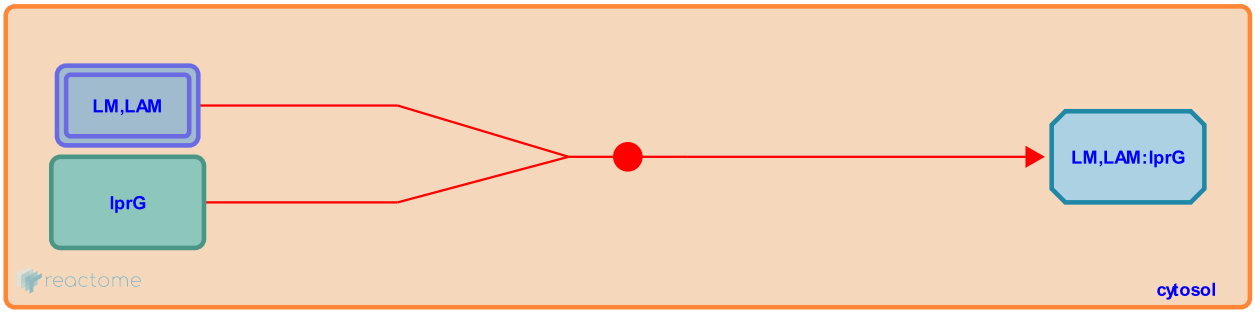
Location: Prevention of phagosomal-lysosomal fusion

Stable identifier: R-HSA-9697064

Type: binding

Compartments: cytosol

Diseases: tuberculosis



Lipoarabinomannan carrier protein (LprG) binds lipomannan (LM) and transports it to the outer cell wall (Shukla et al. 2014). LprG also binds and transports lipoarabinomannan (LAM), but in this case it specifically provides pockets for lipoglycan acyl chains and LAM polysaccharides (Shukla et al. 2014).

Followed by: Rv1410c transports lprG:LM,LAM from cytosol to the cell wall

Literature references

Harding, CV., Banaei, N., Boom, WH., Shi, L., McDonald, D., Athman, JJ. et al. (2014). Mycobacterium tuberculosis lipoprotein LprG binds lipoarabinomannan and determines its cell envelope localization to control phagolysosomal fusion. *PLoS Pathog., 10*, e1004471. ↗

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2019-02-06	Authored	Stephan, R.
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Rv1410c transports lprG:LM,LAM from cytosol to the cell wall ↗

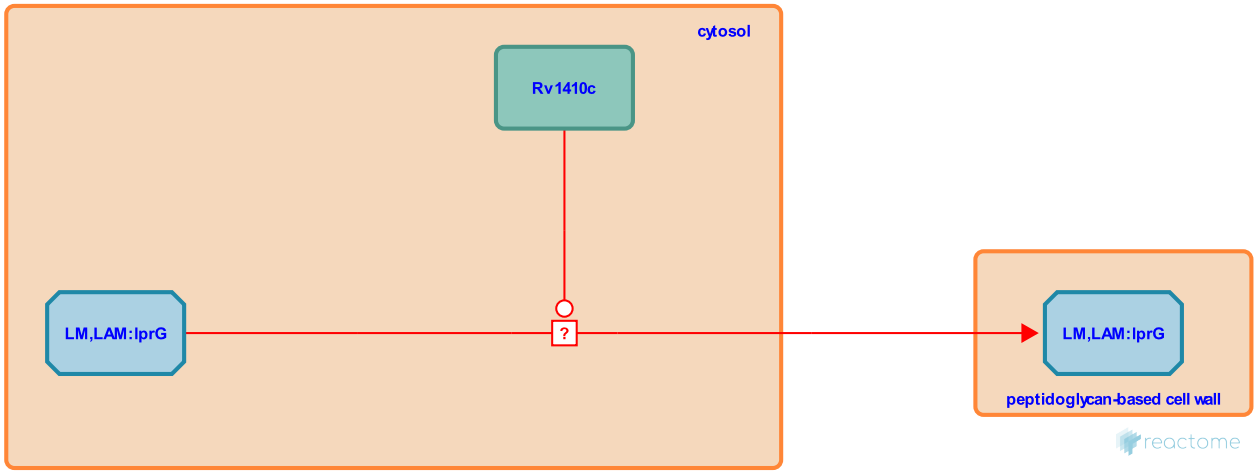
Location: Prevention of phagosomal-lysosomal fusion

Stable identifier: R-HSA-9697077

Type: uncertain

Compartments: cytosol, peptidoglycan-based cell wall

Diseases: tuberculosis



Lipoarabinomannan carrier protein (LprG) acts as a carrier of both lipoarabinomannan (LAM) and lipomannan (LM) through the Mtb plasma membrane, most likely transported by probable triacylglyceride transporter (Rv1410c) (Shukla et al. 2014, Martinot et al. 2016).

Preceded by: lprG binds to LAM,LM

Followed by: lprG dissociates from LAM,LM

Literature references

Iqbal, J., Layre, E., Seeliger, JC., Martinot, AJ., Moody, DB., Hussain, MM. et al. (2016). Mycobacterial Metabolic Syndrome: LprG and Rv1410 Regulate Triacylglyceride Levels, Growth Rate and Virulence in Mycobacterium tuberculosis. *PLoS Pathog., 12*, e1005351. ↗

Harding, CV., Banaei, N., Boom, WH., Shi, L., McDonald, D., Athman, JJ. et al. (2014). Mycobacterium tuberculosis lipoprotein LprG binds lipoarabinomannan and determines its cell envelope localization to control phagolysosomal fusion. *PLoS Pathog., 10*, e1004471. ↗

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lprG dissociates from LAM,LM ↗

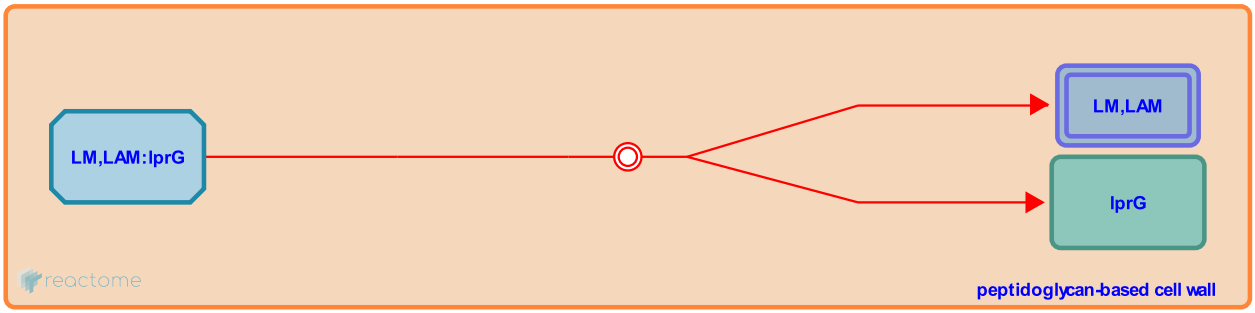
Location: Prevention of phagosomal-lysosomal fusion

Stable identifier: R-HSA-9697070

Type: dissociation

Compartments: peptidoglycan-based cell wall

Diseases: tuberculosis



Lipoarabinomannan carrier protein (LprG) dissociates from lipoarabinomannan (LAM) and lipomannan (LM) in the DIM/DIP cell wall layer after the transport from the Mtb cytosol (Shukla et al. 2014, Martinot et al. 2016).

Preceded by: Rv1410c transports lprG:LM,LAM from cytosol to the cell wall

Followed by: LAM translocates from the cell wall to the plasma membrane

Literature references

Iqbal, J., Layre, E., Seeliger, JC., Martinot, AJ., Moody, DB., Hussain, MM. et al. (2016). Mycobacterial Metabolic Syndrome: LprG and Rv1410 Regulate Triacylglyceride Levels, Growth Rate and Virulence in Mycobacterium tuberculosis. *PLoS Pathog., 12*, e1005351. ↗

Harding, CV., Banaei, N., Boom, WH., Shi, L., McDonald, D., Athman, JJ. et al. (2014). Mycobacterium tuberculosis lipoprotein LprG binds lipoarabinomannan and determines its cell envelope localization to control phagolysosomal fusion. *PLoS Pathog., 10*, e1004471. ↗

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LAM translocates from the cell wall to the plasma membrane ↗

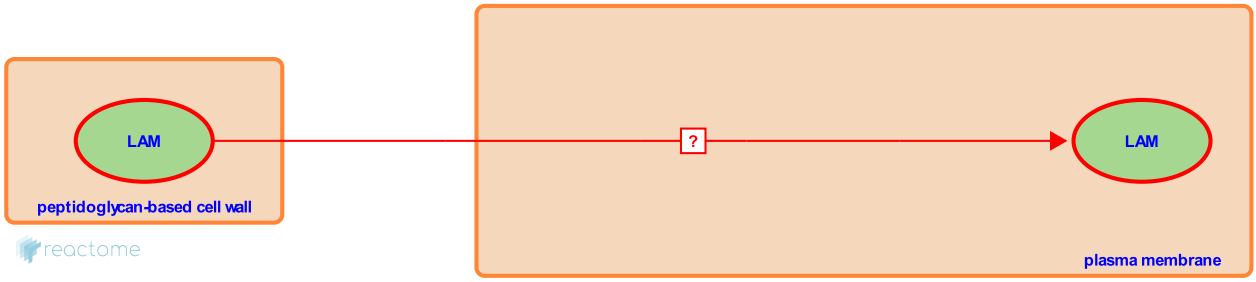
Location: Prevention of phagosomal-lysosomal fusion

Stable identifier: R-HSA-9636404

Type: uncertain

Compartments: plasma membrane, peptidoglycan-based cell wall

Diseases: tuberculosis



Lipoarabinomannan (LAM) is shedded from Mtb's outer cell wall into the phagocyte's plasma membrane (Welin et al. 2008).

Preceded by: lprG dissociates from LAM,LM

Literature references

Abdalla, H., Winberg, ME., Lerm, M., Rasmusson, B., Welin, A., Stendahl, O. et al. (2008). Incorporation of Mycobacterium tuberculosis lipoarabinomannan into macrophage membrane rafts is a prerequisite for the phagosomal maturation block. *Infect. Immun., 76*, 2882-7. ↗

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PtpA binds Ubiquitin ↗

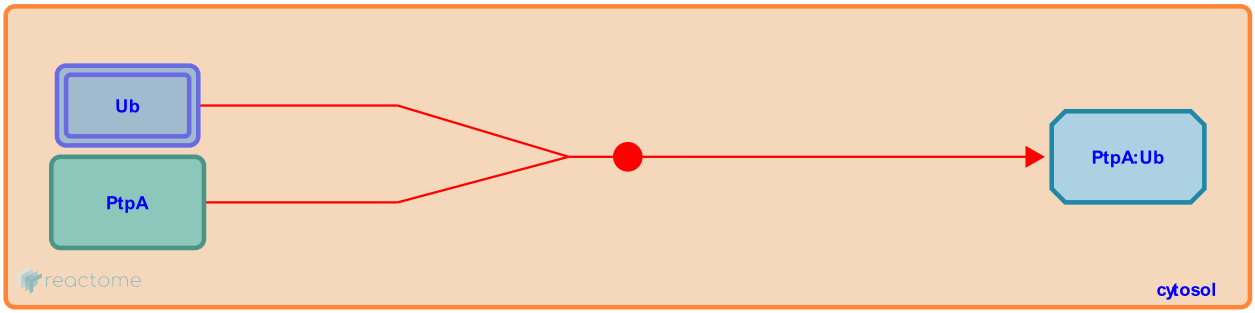
Location: Prevention of phagosomal-lysosomal fusion

Stable identifier: R-HSA-9636461

Type: binding

Compartments: cytosol

Diseases: tuberculosis



Protein-tyrosine phosphatase (ptpA) binds human ubiquitin (Ub), which is necessary for its phosphatase activity (Wang et al. 2015).

Followed by: PtpA:Ub dephosphorylates p-Y133-VPS33B

Literature references

Ge, PP., Gao, GF., Qiu, XB., Wang, J., Li, BX., Li, J. et al. (2015). Mycobacterium tuberculosis suppresses innate immunity by coopting the host ubiquitin system. *Nat. Immunol., 16*, 237-45. ↗

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PtpA:Ub dephosphorylates p-Y133-VPS33B ↗

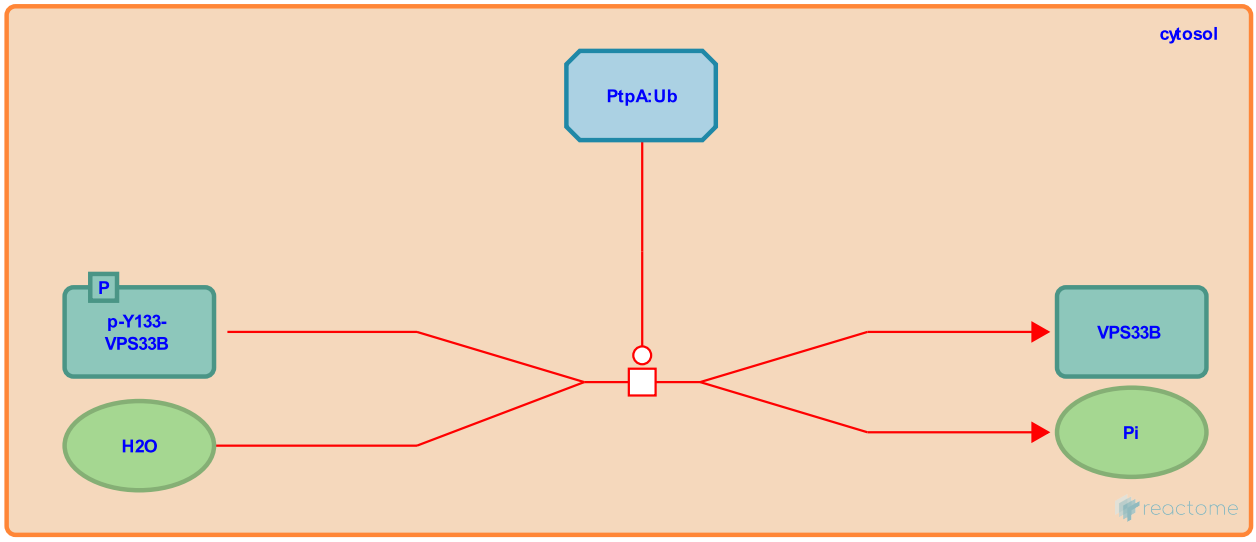
Location: Prevention of phagosomal-lysosomal fusion

Stable identifier: R-HSA-9636439

Type: transition

Compartments: cytosol

Diseases: tuberculosis



The Mtb enzyme protein-tyrosine phosphatase (ptpA) catalyzes the dephosphorylation of human vacuolar protein sorting-associated protein 33B (VPS33B) (Bach et al. 2008).

Preceded by: PtpA binds Ubiquitin

Literature references

Hmama, Z., Av-Gay, Y., Bach, H., Wong, D., Papavinasasundaram, KG. (2008). Mycobacterium tuberculosis virulence is mediated by PtpA dephosphorylation of human vacuolar protein sorting 33B. *Cell Host Microbe, 3*, 316-22. ↗

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lpdC binds to CORO1A ↗

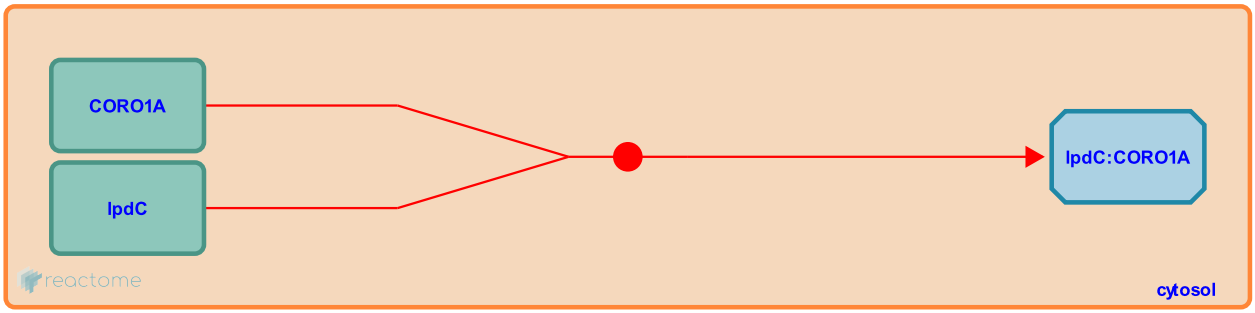
Location: Prevention of phagosomal-lysosomal fusion

Stable identifier: R-HSA-9636396

Type: binding

Compartments: cytosol

Diseases: tuberculosis



Mtb dihydrolipoyl dehydrogenase (lpdC) gets secreted and binds to human coronin-1A (CORO1A) (Deghmane et al. 2007).

Literature references

Toyoshima, S., Hmama, Z., Av-Gay, Y., Deghmane, AE., Noubir, S., Itoh, S. et al. (2007). Lipoamide dehydrogenase mediates retention of coronin-1 on BCG vacuoles, leading to arrest in phagosome maturation. *J. Cell. Sci., 120*, 2796-806. ↗

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SecA2 transports SapM from cytoplasm to cytosol ↗

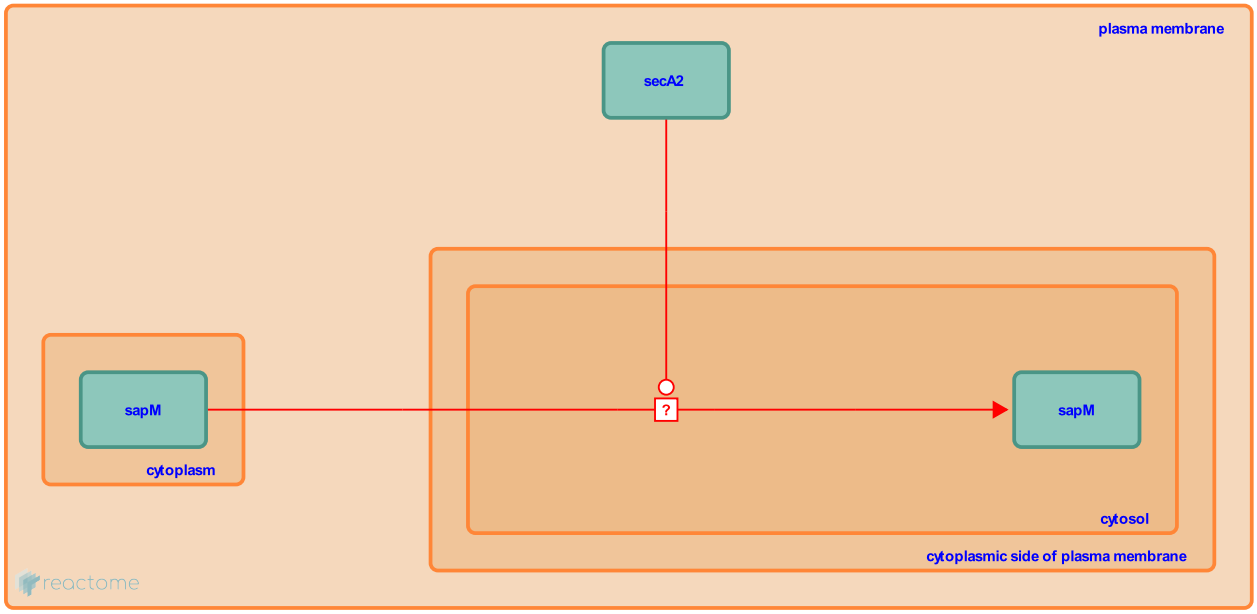
Location: Prevention of phagosomal-lysosomal fusion

Stable identifier: R-HSA-9636375

Type: uncertain

Compartments: cytosol

Diseases: tuberculosis



Mtb protein translocase subunit (SecA2) transports phosphatidylinositol-3-phosphatase (SapM) from Mtb's cytosol (called cytoplasm here) to the host's cytosol (Zulauf et al. 2018).

Followed by: SapM dephosphorylates PI3P

Literature references

Braunstein, M., Sullivan, JT., Zulauf, KE. (2018). The SecA2 pathway of Mycobacterium tuberculosis exports effectors that work in concert to arrest phagosome and autophagosome maturation. *PLoS Pathog., 14*, e1007011. ↗

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SapM dephosphorylates PI3P ↗

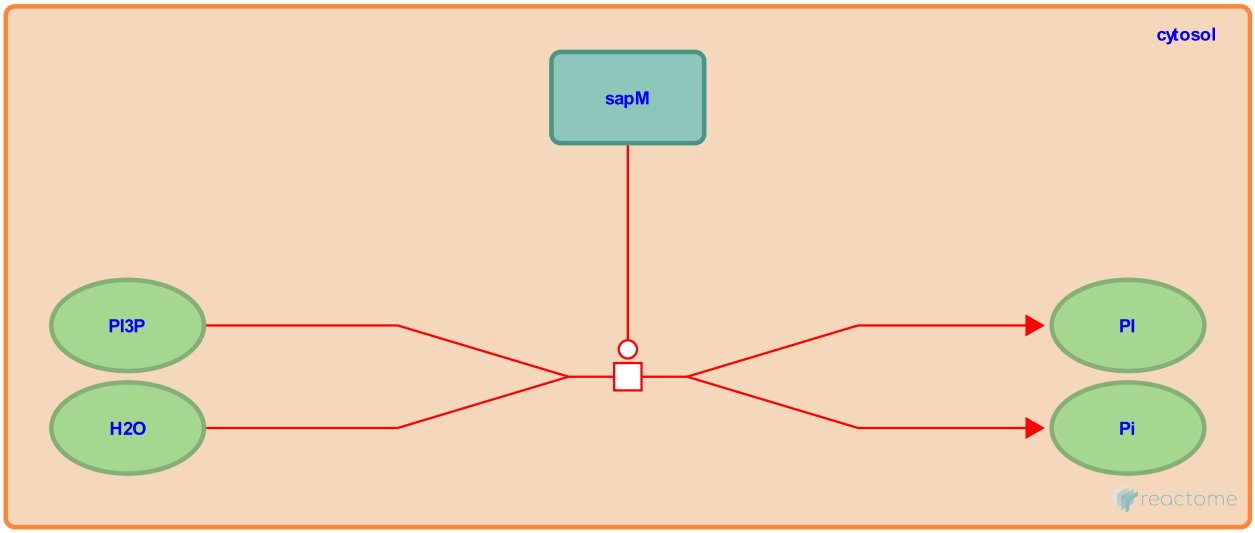
Location: Prevention of phagosomal-lysosomal fusion

Stable identifier: R-HSA-9636457

Type: transition

Compartments: cytosol

Diseases: tuberculosis



Phosphatidylinositol-3-phosphatase (SapM) catalyzes the dephoshorylation of phosphatidylinositol 3-phosphate (PI3P) to phosphatidylinositol (PI) (Vergne et al. 2005).

Preceded by: SecA2 transports SapM from cytoplasm to cytosol

Literature references

Deretic, V., Belisle, J., Lucas, M., Vergne, I., Lee, HH., Chua, J. (2005). Mechanism of phagolysosome biogenesis block by viable Mycobacterium tuberculosis. *Proc. Natl. Acad. Sci. U.S.A., 102*, 4033-8. ↗

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esxG:esxH binds HGS ↗

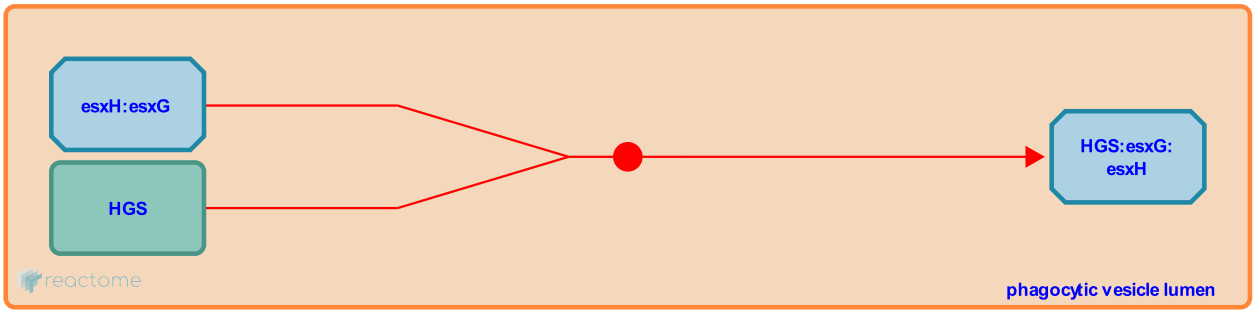
Location: Prevention of phagosomal-lysosomal fusion

Stable identifier: R-HSA-9635667

Type: binding

Compartments: phagocytic vesicle lumen

Diseases: tuberculosis



The complex of ESAT-6-like proteins esxG:esxH respond to sterile membrane damage, recognizing either the damaged membrane itself or recruited proteins (Mittal et al. 2016). The esxG:esxH complex disrupts membrane repair and host trafficking by binding to hepatocyte growth factor-regulated tyrosine kinase substrate (HGS/Hrs) a component of human ESCRT (Mehra et al. 2013).

Literature references

Thompson, V., Vidal, M., Hill, DE., Kubota, Y., Köster, S., Penberthy, K. et al. (2013). Mycobacterium tuberculosis type VII secreted effector EsxH targets host ESCRT to impair trafficking. *PLoS Pathog., 9*, e1003734. ↗

Uwase, G., Philips, JA., Köster, S., Hanson, PI., Tinaztepe, E., Mittal, E. et al. (2018). Mycobacterium tuberculosis Type VII Secretion System Effectors Differentially Impact the ESCRT Endomembrane Damage Response. *MBio, 9* . ↗

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ndkA dephosphorylates RAB5A:GTP,RAB7A:GTP ↗

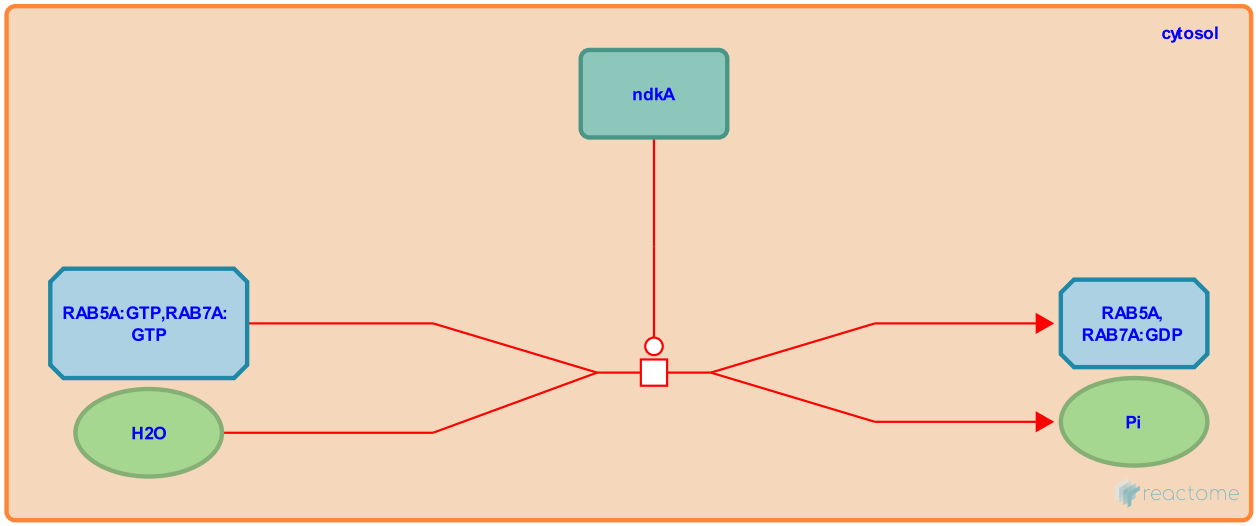
Location: Prevention of phagosomal-lysosomal fusion

Stable identifier: R-HSA-9636684

Type: transition

Compartments: cytosol

Diseases: tuberculosis



Ras-related protein with guanosine 5'-triphosphates bound to GTP (RAB5A:GTP,RAB7A:GTP) get deactivated through dephosphorylation of GTP via the GTPase-activating protein (GAP)-like activity of the Mtb nucleoside diphosphate kinase (ndkA) (Chopra et al. 2004, Sun et al. 2010).

Literature references

Hmama, Z., Liao, TY., Sun, J., Bucci, C., Lau, A., Wang, X. (2010). Mycobacterial nucleoside diphosphate kinase blocks phagosome maturation in murine RAW 264.7 macrophages. *PLoS ONE, 5*, e8769. ↗

Sharma, K., Ghildiyal, M., Chopra, P., Koduri, H., Singh, R., Tyagi, AK. et al. (2004). Nucleoside diphosphate kinase of Mycobacterium tuberculosis acts as GTPase-activating protein for Rho-GTPases. *FEBS Lett., 571*, 212-6. ↗

Editions

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