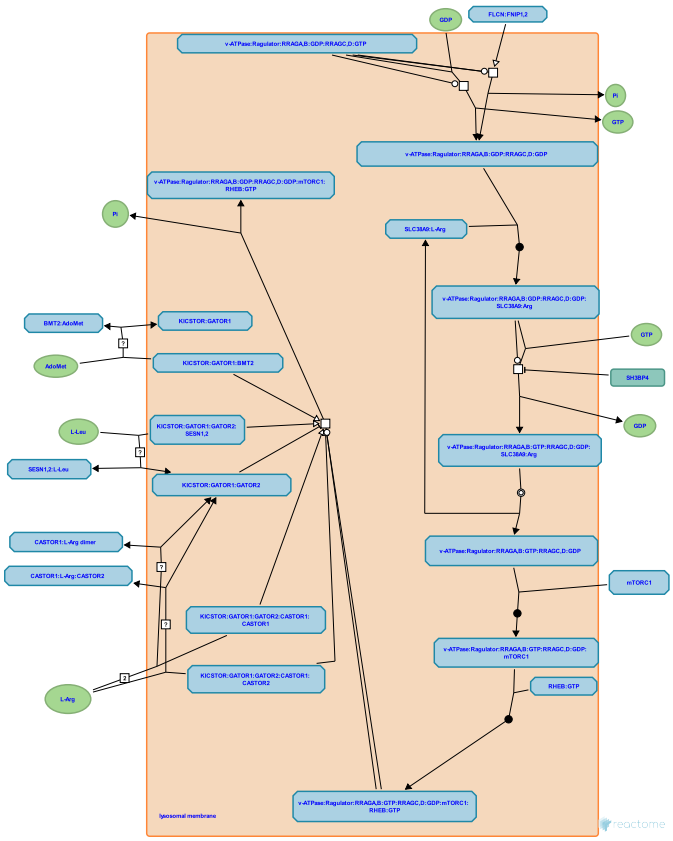
Amino acids regulate mTORC1



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

20/04/2024

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

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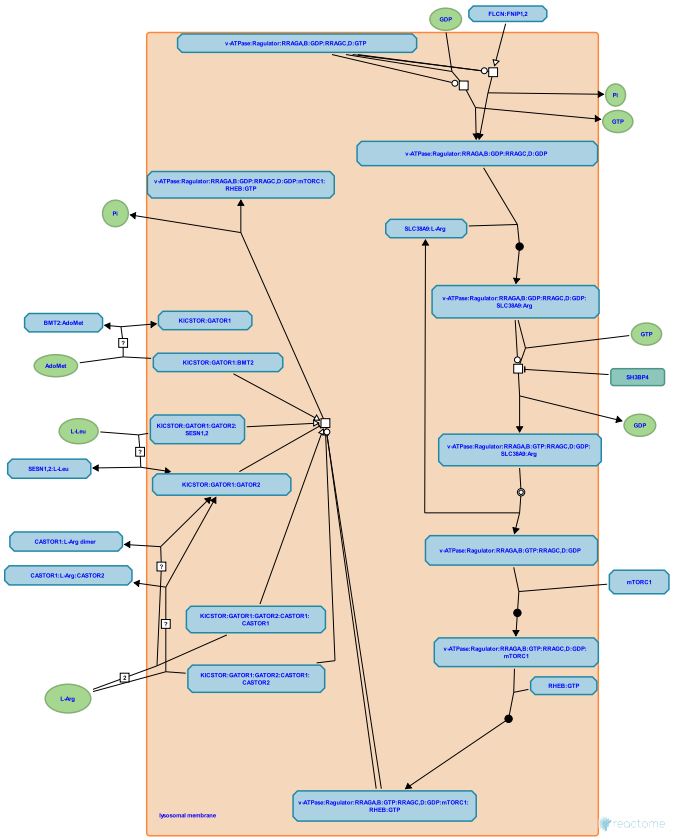
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Amino acids regulate mTORC1 ↗

Stable identifier: R-HSA-9639288



The mTORC1 complex acts as an integrator that regulates translation, lipid synthesis, autophagy, and cell growth in response to multiple inputs, notably glucose, oxygen, amino acids, and growth factors such as insulin (reviewed in Sabatini 2017, Meng et al. 2018, Kim and Guan 2019).

MTOR, the kinase subunit of mTORC1, is activated by interaction with RHEB:GTP at the cytosolic face of lysosomal membrane (Long et al. 2005, Tee et al. 2005, Long et al. 2007, Yang et al. 2017). Recruitment of mTORC1 to the lysosomal membrane is intricate and incompletely understood. At the center of the system is a complex of two small GTPases, the Rag heterodimer (RRAGA or RRAGB bound to RRAGC or RRAGD). The Rag heterodimer is tethered to the membrane by the Ragulator complex, which also binds the v-ATPase complex. The Rag heterodimer acts as a cross-regulating switch, with the binding of GTP by one subunit inhibiting the exchange of GDP for GTP by the other subunit (Shen et al. 2017). The active conformation of the Rag heterodimer that recruits mTORC1 to the lysosomal membrane is RRAGA,B:GTP:RRAGC,D:GDP while the inactive conformation, RRAGA,B:GDP:RRAGC,D:GTP, releases mTORC1 (Sancak et al. 2008, Kim et al. 2008, Sancak et al. 2010, Lawrence et al. 2018). GTPase activating proteins (GAPs) and guanyl nucleotide exchange factors (GEFs) acting upon the Rag heterodimer thereby regulate recruitment of mTORC1. RHEB:GTP at the lysosomal membrane also binds mTORC1 and directly activates mTORC1. During inactivation of mTORC1 in response to removal of amino acids, the TSC complex, a GAP for RHEB, is required in addition to the inactive Rag complex to release mTORC1 from RHEB and hence fully release mTORC1 from the lysosomal membrane (Demetriades et al. 2014).

Amino acids regulate recruitment of mTORC1 to the lysosomal membrane by at least 4 mechanisms (reviewed in Zhuang et al. 2019, Wolfson and Sabatini 2017, Yao et al. 2017). 1) Sestrin1 (SESN1) or Sestrin2 (SESN2) binds leucine and the Sestrin1,2:leucine complex is then released from the GATOR2 complex, allowing GATOR2 to positively regulate mTORC1 activation (Chantranupong et al. 2014, Parmigiani et al. 2014, Kim et al. 2015, Wolfson et al. 2016, Saxton et al. 2016). 2) CASTOR1 in a homodimer or a heterodimer with CASTOR2 binds arginine and the CASTOR1:arginine complex is likewise released from GATOR2, allowing GATOR2 to activate mTORC1 (Chantranupong et al. 2016, Saxton et al. 2016, Gai et al. 2016, Xia et al. 2016). 3) BMT2 (SAMTOR), a negative regulator of mTORC1 activation, binds S-adenosylmethionine (SAM), a derivative of methionine (Gu et al. 2017). The binding of SAM causes BMT2 to dissociate from GATOR1, allowing the activation of mTORC1. 4) The amino acid transporter SLC38A9 binds arginine and SLC38A9 then acts as a GEF to convert RRAGA,B:GDP to the active form, RRAGA,B:GTP (Rebsamen et al. 2015, Wang et al. 2015, Wyant et al. 2017, Shen and Sabatini 2018). Amino acid starvation also regulates the assembly of the V0 and V1 subunits of v-ATPase by an uncharacterized mechanism (Stransky and Forgac 2015) and v-ATPase is required for activation of mTORC1 by amino acids (Zoncu et al. 2011). Glutamine activates mTORC1 by a mechanism that is independent of the Rag GTPases, requires ARF1, but is not yet fully elucidated (Jewell et al. 2015).

Literature references

Proud, CG., Blenis, J., Tee, AR. (2005). Analysis of mTOR signaling by the small G-proteins, Rheb and RhebL1. *FEBS Lett., 579*, 4763-8.

Chen, WW., Sabatini, DM., Danai, LV., Abu-Remaileh, M., Wyant, GA., Vander Heiden, MG. et al. (2017). mTORC1 Activator SLC38A9 Is Required to Efflux Essential Amino Acids from Lysosomes and Use Protein as a Nutrient. *Cell, 171*, 642-654.e12.

Bigenzahn, JW., Huber, KV., Indiveri, C., Bennett, KL., Rebsamen, M., Superti-Furga, G. et al. (2015). SLC38A9 is a component of the lysosomal amino acid sensing machinery that controls mTORC1. *Nature, 519*, 477-81.

Wang, XX., Zhuang, Y., Yin, Y., He, J., He, S. (2019). Recent advances in understanding of amino acid signaling to mTORC1 activation. *Front Biosci (Landmark Ed), 24*, 971-982.

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Editions

2019-03-04	Authored, Edited	May, B.
2019-08-08	Reviewed	Sabatini, DM., Condon, KJ.

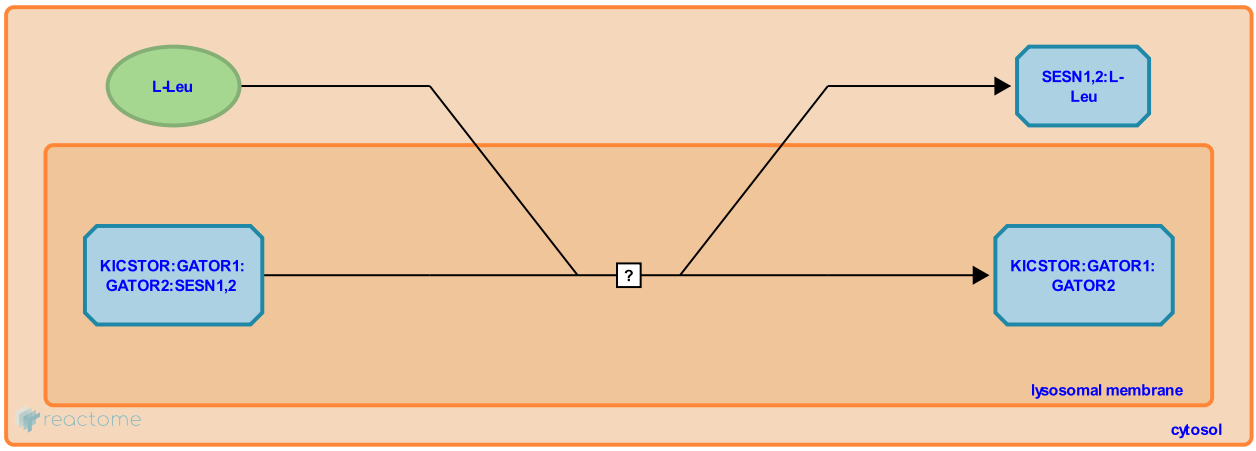
SESN1,2 binds L-leucine and dissociates from GATOR2

Location: Amino acids regulate mTORC1

Stable identifier: R-HSA-9639287

Type: uncertain

Compartments: lysosomal membrane



SESN2 (Sestrin2) and SESN1 (Sestrin1) each interact with the GATOR2 complex in the absence of leucine and, upon binding leucine, dissociate from the GATOR2 complex (Chantranupong et al. 2014, Parmigiani et al. 2014, Kim et al. 2015, Wolfson et al. 2016, Saxton et al. 2016). (SESN3 constitutively binds GATOR2 in the presence and absence of leucine.) When bound to GATOR2, the Sestrins appear to prevent GATOR2 from inhibiting GATOR1, a GTPase activator which negatively regulates mTORC1 activation by increasing the rate of hydrolysis of RRAGA,B:GTP to RRAGA,B:GDP. SESN1,2 complexed with GATOR2 therefore allows GATOR1 to maintain mTORC1 in the inactive state (Chantranupong et al. 2014, Parmigiani et al. 2014, Kim et al. 2015). L-leucine binds SESN1,2 and causes SESN1,2 to dissociate from GATOR2, allowing GATOR2 to inhibit GATOR1 and thereby maintain RRAGA,B in the active (GTP-bound) state (Wolfson et al. 2016, Saxton et al. 2016). GATOR1 is recruited to the lysosomal membrane by the KICSTOR complex (Wolfson et al. 2017, Peng et al. 2017).
Sestrins also appear to interact with the Rag heterodimer (Peng et al. 2014) though the interaction may be indirect (Budanov 2015).

Followed by: RRAGC,D hydrolyzes GTP, RRAGC,D exchanges GTP for GDP

Literature references

Budanov, AV. (2015). SESTRINs regulate mTORC1 via RRAGs: The riddle of GATOR. *Mol Cell Oncol, 2*, e997113.

Lee, JH., Semple, IA., Ro, SH., Cho, US., Guan, KL., Park, H. et al. (2015). Sestrin2 inhibits mTORC1 through modulation of GATOR complexes. *Sci Rep, 5*, 9502.

Sabatini, DM., Petri, S., Condon, KJ., Shen, K., Orozco, JM., Scaria, SM. et al. (2017). KICSTOR recruits GATOR1 to the lysosome and is necessary for nutrients to regulate mTORC1. *Nature, 543*, 438-442.

Sabatini, DM., Schwartz, TU., Wang, T., Pacold, ME., Saxton, RA., Chantranupong, L. et al. (2016). Structural basis for leucine sensing by the Sestrin2-mTORC1 pathway. *Science, 351*, 53-8.

Sabatini, DM., Scaria, SM., Spooner, E., Saxton, RA., Gygi, SP., Bar-Peled, L. et al. (2014). The Sestrins interact with GATOR2 to negatively regulate the amino-acid-sensing pathway upstream of mTORC1. *Cell Rep, 9*, 1-8.

Editions

2019-03-04	Authored, Edited	May, B.
2019-08-08	Reviewed	Sabatini, DM., Condon, KJ.

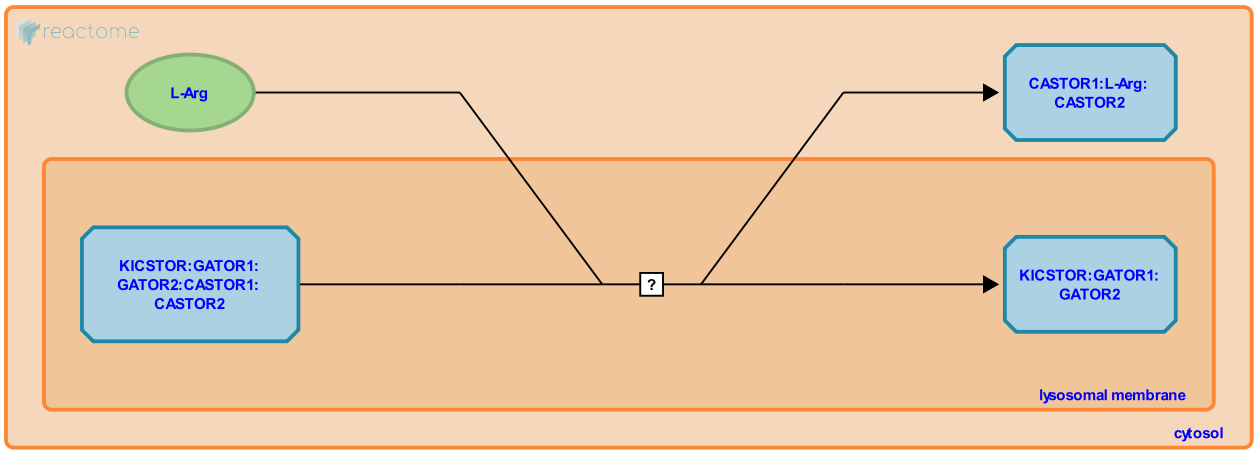
CASTOR1 in CASTOR1:CASTOR2 binds L-arginine and dissociates from GATOR2 ↗

Location: Amino acids regulate mTORC1

Stable identifier: R-HSA-9640237

Type: uncertain

Compartments: lysosomal membrane



CASTOR1 in a heterodimer with CASTOR2 interacts with the GATOR2 complex via the MIOS subunit of GATOR2 (Chantranupong et al. 2016, Gai et al. 2016). The ACT domains of the CASTOR1 subunit bind L-arginine (Chantranupong et al. 2016, Saxton et al. 2016, Xia et al. 2016, Gai et al. 2016) and CASTOR1:arginine dissociates from GATOR2, which then prevents GATOR1 from activating the GTPase of RRAGA,B (Chantranupong et al. 2016). GATOR1 is recruited to the lysosomal membrane by the KICSTOR complex (Wolfson et al. 2017).

Literature references

Sabatini, DM., Wang, T., Scaria, SM., Saxton, RA., Gygi, SP., Gygi, MP. et al. (2016). The CASTOR Proteins Are Arginine Sensors for the mTORC1 Pathway. *Cell, 165*, 153-164. ↗

Sabatini, DM., Petri, S., Condon, KJ., Shen, K., Orozco, JM., Scaria, SM. et al. (2017). KICSTOR recruits GATOR1 to the lysosome and is necessary for nutrients to regulate mTORC1. *Nature, 543*, 438-442. ↗

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Yang, C., Wang, Q., Gai, Z., Deng, W., Wang, L., Wu, G. (2016). Structural mechanism for the arginine sensing and regulation of CASTOR1 in the mTORC1 signaling pathway. *Cell Discov, 2*, 16051. ↗

Sabatini, DM., Schwartz, TU., Saxton, RA., Chantranupong, L., Knockenhauer, KE. (2016). Mechanism of arginine sensing by CASTOR1 upstream of mTORC1. *Nature, 536*, 229-33. ↗

Editions

2019-03-23	Authored, Edited	May, B.
2019-08-08	Reviewed	Sabatini, DM., Condon, KJ.

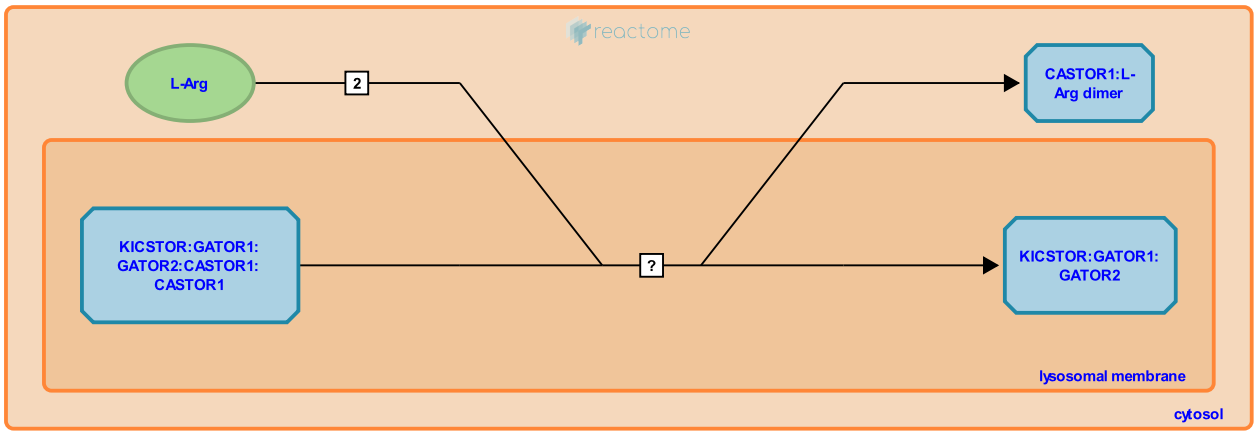
CASTOR1 homodimer binds L-arginine and dissociates from GATOR2 ↗

Location: Amino acids regulate mTORC1

Stable identifier: R-HSA-9657619

Type: uncertain

Compartments: lysosomal membrane



The CASTOR1 homodimer interacts with the GATOR2 complex via the MIOS subunit of GATOR2 (Chantranupong et al. 2016, Gai et al. 2016). The ACT domains of CASTOR1 bind L-arginine (Chantranupong et al. 2016, Saxton et al. 2016, Xia et al. 2016, Gai et al. 2016) and CASTOR1:arginine dissociates from GATOR2, which then prevents GATOR1 from activating the GTPase of RRAGA,B (Chantranupong et al. 2016). GATOR1 is recruited to the lysosomal membrane by the KICSTOR complex (Wolfson et al. 2017).

Literature references

Sabatini, DM., Wang, T., Scaria, SM., Saxton, RA., Gygi, SP., Gygi, MP. et al. (2016). The CASTOR Proteins Are Arginine Sensors for the mTORC1 Pathway. *Cell, 165*, 153-164. ↗

Sabatini, DM., Petri, S., Condon, KJ., Shen, K., Orozco, JM., Scaria, SM. et al. (2017). KICSTOR recruits GATOR1 to the lysosome and is necessary for nutrients to regulate mTORC1. *Nature, 543*, 438-442. ↗

Ding, J., Wang, R., Zhang, T., Xia, J. (2016). Structural insight into the arginine-binding specificity of CASTOR1 in amino acid-dependent mTORC1 signaling. *Cell Discov, 2*, 16035. ↗

Yang, C., Wang, Q., Gai, Z., Deng, W., Wang, L., Wu, G. (2016). Structural mechanism for the arginine sensing and regulation of CASTOR1 in the mTORC1 signaling pathway. *Cell Discov, 2*, 16051. ↗

Sabatini, DM., Schwartz, TU., Saxton, RA., Chantranupong, L., Knockenhauer, KE. (2016). Mechanism of arginine sensing by CASTOR1 upstream of mTORC1. *Nature, 536*, 229-33. ↗

Editions

2019-08-08	Reviewed	Sabatini, DM., Condon, KJ.

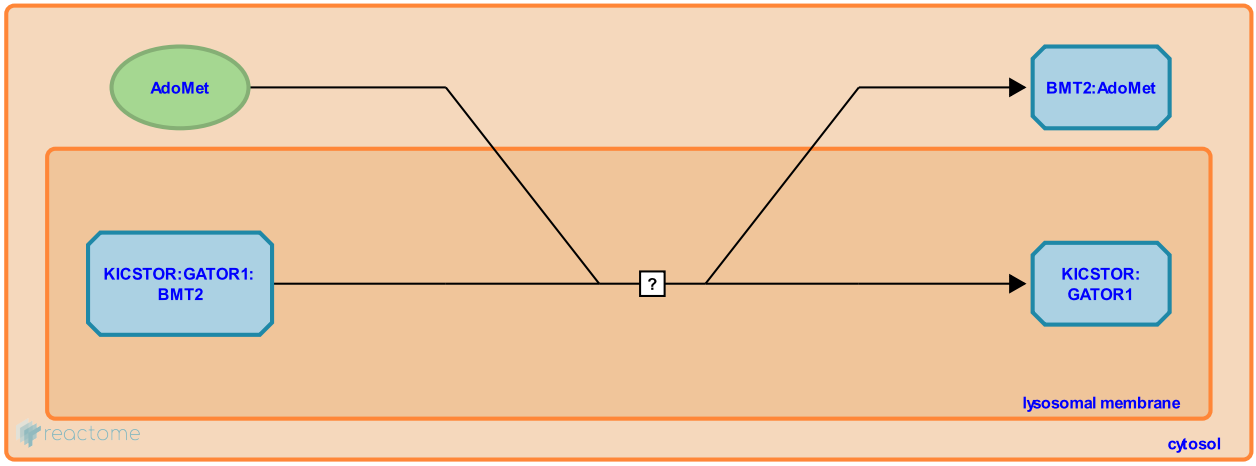
BMT2 (SAMTOR) binds S-adenosylmethionine and dissociates from KICSTOR:GATOR1

Location: Amino acids regulate mTORC1

Stable identifier: R-HSA-9640254

Type: uncertain

Compartments: lysosomal membrane



BMT2 (SAMTOR) binds GATOR1 and acts upstream of GATOR1 and KICSTOR to inhibit mTORC1 activation (Gu et al. 2017). Upon binding S-adenosymethionine, a metabolic derivative of the amino acid methionine, SAMTOR dissociates from GATOR1 and mTORC1 activity is increased through an uncharacterized mechanism (Gu et al. 2017). GATOR1 is recruited to the lysosomal membrane by the KICSTOR complex (Wolfson et al. 2017).

Literature references

Sabatini, DM., Scaria, SM., Gu, X., Saxton, RA., Gygi, SP., Liu, GY. et al. (2017). SAMTOR is an S-adenosylmethionine sensor for the mTORC1 pathway. *Science, 358*, 813-818.

Sabatini, DM., Petri, S., Condon, KJ., Shen, K., Orozco, JM., Scaria, SM. et al. (2017). KICSTOR recruits GATOR1 to the lysosome and is necessary for nutrients to regulate mTORC1. *Nature, 543*, 438-442.

Editions

2019-03-23	Authored, Edited	May, B.
2019-08-08	Reviewed	Sabatini, DM., Condon, KJ.

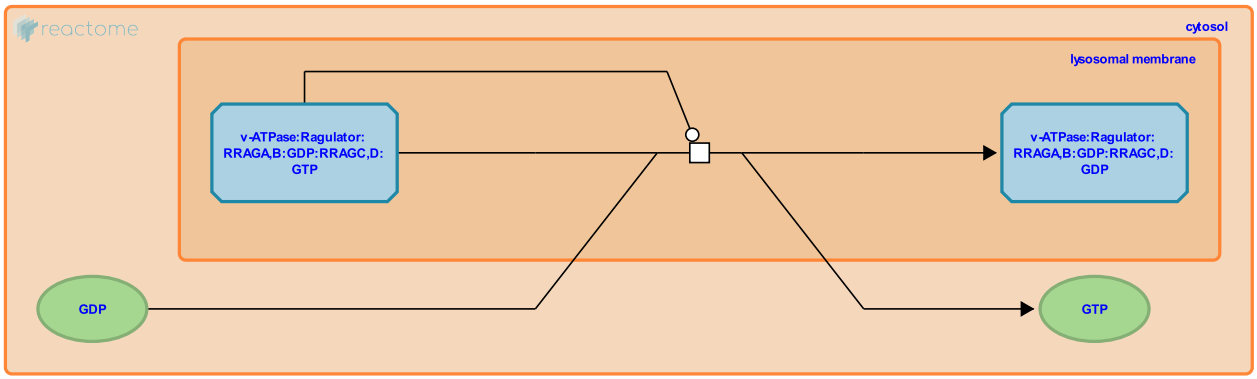
RRAGC,D exchanges GTP for GDP ↗

Location: Amino acids regulate mTORC1

Stable identifier: R-HSA-9639286

Type: transition

Compartments: lysosomal membrane



The Ragulator complex acts as an unconventional guanyl nucleotide exchange factor (GEF) that ejects GTP from RRAGC and, by inference, RRAGD (Shen and Sabatini 2018). (Other known GEFs cause ejection of GDP rather than GTP from their targets.) The GDP-bound form of RRAGC,D is the active form that recruits mTORC1 to the lysosomal membrane.

Preceded by: SESN1,2 binds L-leucine and dissociates from GATOR2

Followed by: v-ATPase:Ragulator:RagA,B:GDP:RagC,D:GDP binds SLC38A9:Arginine

Literature references

Sabatini, DM., Shen, K. (2018). Ragulator and SLC38A9 activate the Rag GTPases through noncanonical GEF mechanisms. *Proc. Natl. Acad. Sci. U.S.A., 115*, 9545-9550. ↗

Editions

2019-03-04	Authored, Edited	May, B.
2019-08-08	Reviewed	Sabatini, DM., Condon, KJ.

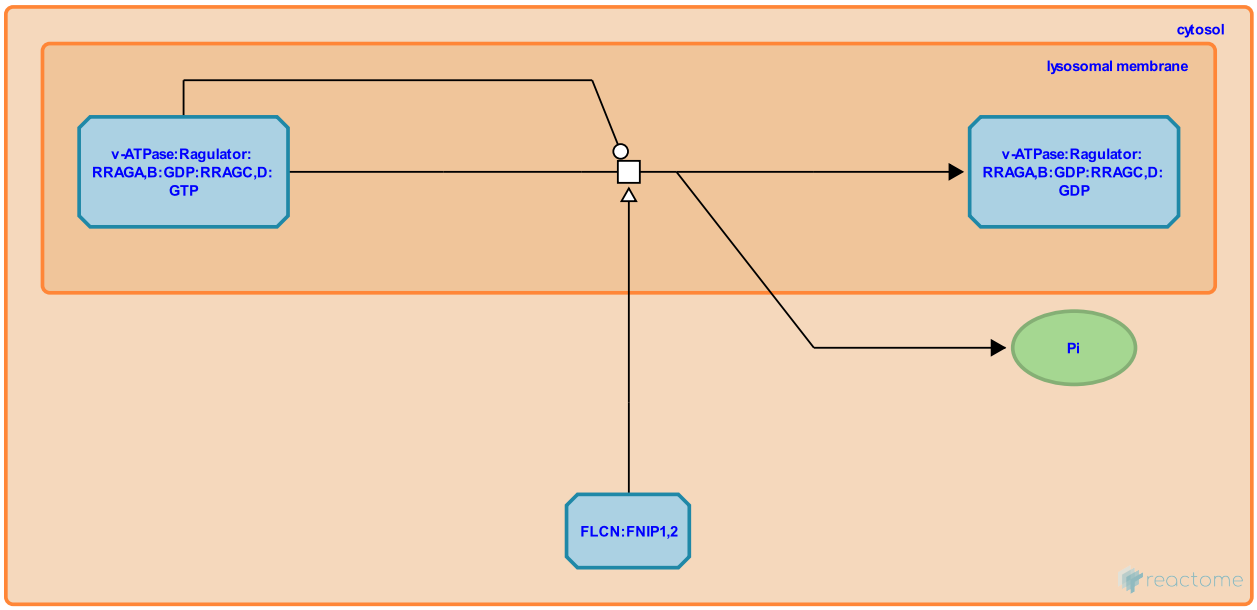
RRAGC,D hydrolyzes GTP ↗

Location: Amino acids regulate mTORC1

Stable identifier: R-HSA-9645598

Type: transition

Compartments: lysosomal membrane



RRAGC (RagC) and RRAGD (RagD) are guanyl nucleotide-binding proteins that hydrolyze GTP (Tsun et al. 2013, Shen et al. 2017). The GDP-bound form of RRAGC,D is the active form that recruits mTORC1 to the lysosomal membrane (Tsun et al. 2013). RRAGC,D forms a heterodimer with RRAGA,B that has two stable conformations: RRAGA,B:GTP:RRAGC,D:GDP (active) or RRAGA,B:GDP:RRAGC,D:GTP (inactive) (Shen et al. 2017). Folliculin (FLCN) complexed with FNIP1 or FNIP2 interacts with RRAGA (Petit et al. 2013) and acts as a GTPase activator (GAP) for RRAGC:GTP and RRAGD:GTP (Tsun et al. 2013). FLCN is located at the lysosomal membrane during amino acid starvation and in the cytosol during amino acid stimulation (Tsun et al. 2013).

Preceded by: SESN1,2 binds L-leucine and dissociates from GATOR2

Literature references

Sabatini, DM., Wang, T., Zoncu, R., Spooner, E., Tsun, ZY., Bar-Peled, L. et al. (2013). The folliculin tumor suppressor is a GAP for the RagC/D GTPases that signal amino acid levels to mTORC1. *Mol. Cell, 52*, 495-505. ↗

Sabatini, DM., Choe, A., Shen, K. (2017). Intersubunit Crosstalk in the Rag GTPase Heterodimer Enables mTORC1 to Respond Rapidly to Amino Acid Availability. *Mol. Cell, 68*, 552-565.e8. ↗

Ferguson, SM., Petit, CS., Roczniak-Ferguson, A. (2013). Recruitment of folliculin to lysosomes supports the amino acid-dependent activation of Rag GTPases. *J. Cell Biol., 202*, 1107-22. ↗

Editions

2019-05-06	Authored, Edited	May, B.
2019-08-08	Reviewed	Sabatini, DM., Condon, KJ.

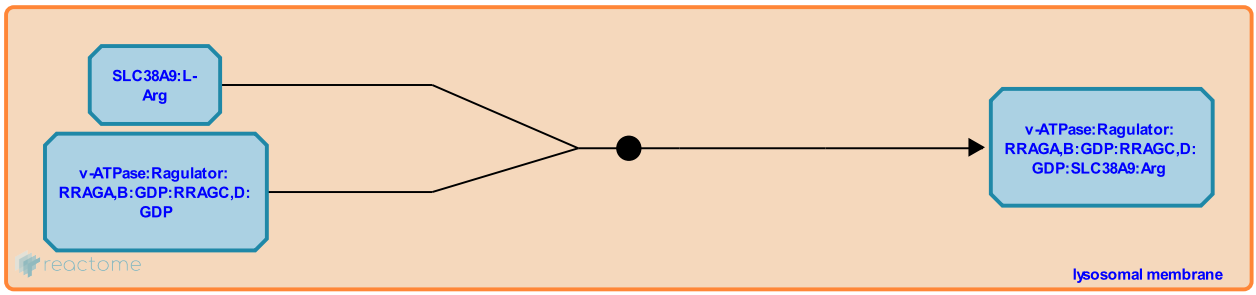
v-ATPase:Ragulator:RagA,B:GDP:RagC,D:GDP binds SLC38A9:Arginine ↗

Location: Amino acids regulate mTORC1

Stable identifier: R-HSA-9640175

Type: binding

Compartments: lysosomal membrane



The N-terminal domain of SLC38A9 bound to L-arginine interacts indirectly with the Ragulator complex via the Rag GTPases RRAGA and RRAGC (Wang et al. 2015, Rebsamen et al. 2015, Wyant et al. 2017, Shen and Sabatini 2018).

Preceded by: RRAGC,D exchanges GTP for GDP

Followed by: RRAGA,B exchanges GDP for GTP

Literature references

Sabatini, DM., Shen, K. (2018). Ragulator and SLC38A9 activate the Rag GTPases through noncanonical GEF mechanisms. *Proc. Natl. Acad. Sci. U.S.A., 115*, 9545-9550. ↗

Sabatini, DM., Wang, T., Zoncu, R., Jones, TD., Comb, W., Park, J. et al. (2015). Metabolism. Lysosomal amino acid transporter SLC38A9 signals arginine sufficiency to mTORC1. *Science, 347*, 188-94. ↗

Bigenzahn, JW., Huber, KV., Indiveri, C., Bennett, KL., Rebsamen, M., Superti-Furga, G. et al. (2015). SLC38A9 is a component of the lysosomal amino acid sensing machinery that controls mTORC1. *Nature, 519*, 477-81. ↗

Chen, WW., Sabatini, DM., Danai, LV., Abu-Remaileh, M., Wyant, GA., Vander Heiden, MG. et al. (2017). mTORC1 Activator SLC38A9 Is Required to Efflux Essential Amino Acids from Lysosomes and Use Protein as a Nutrient. *Cell, 171*, 642-654.e12. ↗

Editions

2019-03-23	Authored, Edited	May, B.
2019-08-08	Reviewed	Sabatini, DM., Condon, KJ.

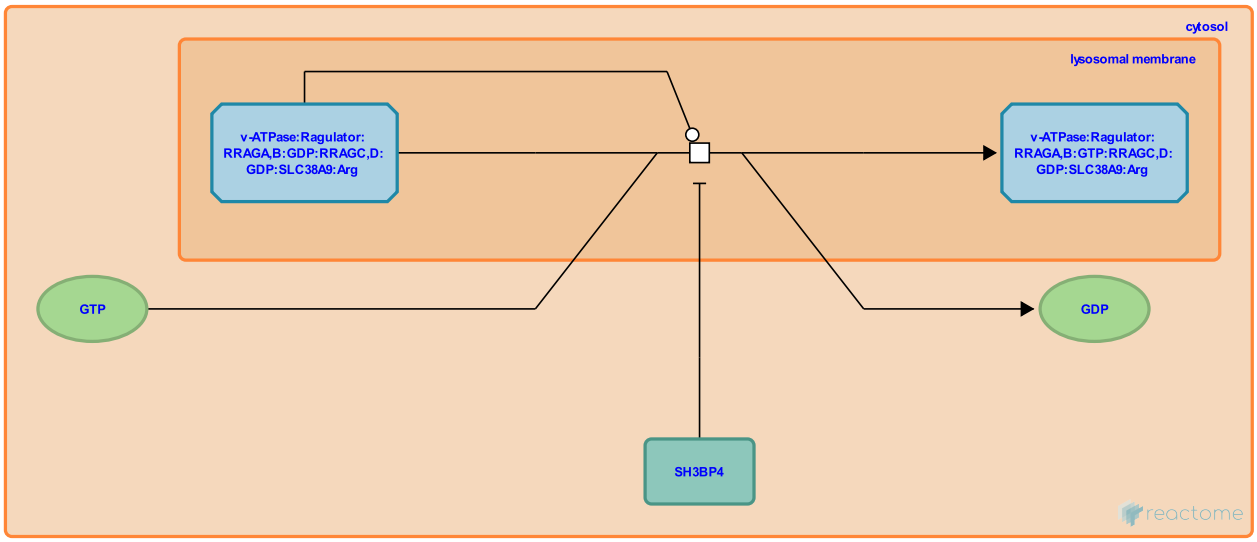
RRAGA,B exchanges GDP for GTP ↗

Location: Amino acids regulate mTORC1

Stable identifier: R-HSA-9640167

Type: transition

Compartments: lysosomal membrane



Upon binding L-arginine, SLC38A9 acts as a guanyl nucleotide exchange factor (GEF) that enhances the conversion of RRAGA:GDP (RagA:GDP, and by inference RRAGB:GDP, RagB:GDP) to RRAGA:GTP, the active form (Shen and Sabatini 2018). The Ragulator complex also shows GEF activity for RRAGA,B (Bar-Peled et al. 2012). SH3BP4 inhibits loading of GTP onto RRAGB during amino acid starvation (Kim et al. 2012). The binding of GTP by RRAGA,B appears to inhibit binding of GTP by RRAGC,D (Shen et al. 2017).

Preceded by: v-ATPase:Ragulator:RagA,B:GDP:RagC,D:GDP binds SLC38A9:Arginine

Followed by: v-ATPase:Ragulator:RRAGA,B:GTP:RRAGC,D:GDP:SLC38A9:Arginine dissociates yielding v-ATPase:Ragulator:RRAGA,B:GTP:RRAGC,D:GDP and SLC38A9:Arginine

Literature references

Sabatini, DM., Shen, K. (2018). Ragulator and SLC38A9 activate the Rag GTPases through noncanonical GEF mechanisms. *Proc. Natl. Acad. Sci. U.S.A., 115*, 9545-9550. ↗

Stone, M., Dunlevy, JR., Kim, YM., Kim, DH., Griffin, TJ., Kim, YG. et al. (2012). SH3BP4 is a negative regulator of amino acid-Rag GTPase-mTORC1 signaling. *Mol. Cell, 46*, 833-46. ↗

Sabatini, DM., Zoncu, R., Bar-Peled, L., Schweitzer, LD. (2012). Ragulator is a GEF for the rag GTPases that signal amino acid levels to mTORC1. *Cell, 150*, 1196-208. ↗

Sabatini, DM., Choe, A., Shen, K. (2017). Intersubunit Crosstalk in the Rag GTPase Heterodimer Enables mTORC1 to Respond Rapidly to Amino Acid Availability. *Mol. Cell, 68*, 552-565.e8. ↗

Editions

2019-03-23	Authored, Edited	May, B.
2019-08-08	Reviewed	Sabatini, DM., Condon, KJ.

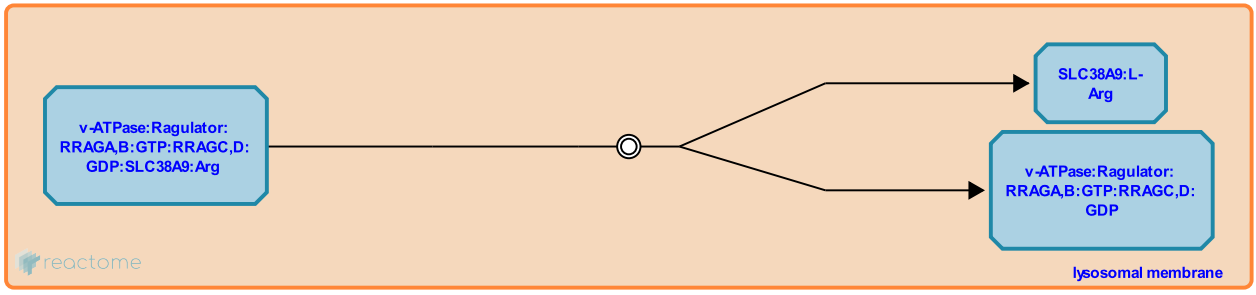
v-ATPase:Ragulator:RRAGA,B:GTP:RRAGC,D:GDP:SLC38A9:Arginine dissociates yielding v-ATPase:Ragulator:RRAGA,B:GTP:RRAGC,D:GDP and SLC38A9:Arginine ↗

Location: Amino acids regulate mTORC1

Stable identifier: R-HSA-9640168

Type: dissociation

Compartments: lysosomal membrane



RRAGA:GTP (RagA:GTP) binds poorly to SLC38A9, therefore SLC39A9 is believed to dissociate from RRAGA:GTP after RRAGA exchanges GDP for GTP (Shen and Sabatini 2018). In this way one molecule of SLC38A9 can enhance the exchange of GDP for GTP for many molecules of RRAGA (Shen and Sabatini 2018).

Preceded by: RRAGA,B exchanges GDP for GTP

Followed by: v-ATPase:Ragulator:RRAGA,B:GTP:RRAGC,D:GDP binds mTORC1

Literature references

Sabatini, DM., Shen, K. (2018). Ragulator and SLC38A9 activate the Rag GTPases through noncanonical GEF mechanisms. *Proc. Natl. Acad. Sci. U.S.A., 115*, 9545-9550. ↗

Editions

2019-03-23	Authored, Edited	May, B.
2019-08-08	Reviewed	Sabatini, DM., Condon, KJ.

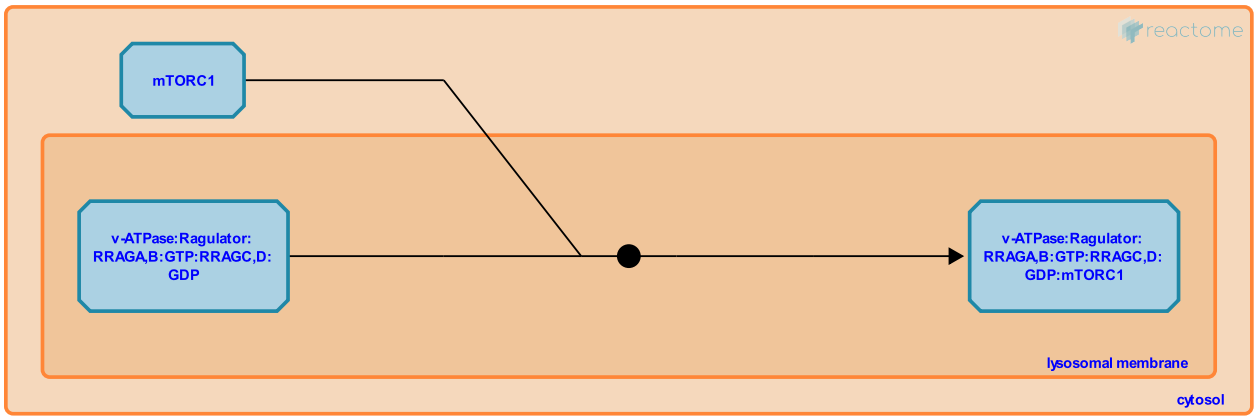
v-ATPase:Ragulator:RRAGA,B:GTP:RRAGC,D:GDP binds mTORC1 ↗

Location: Amino acids regulate mTORC1

Stable identifier: R-HSA-9645608

Type: binding

Compartments: lysosomal membrane



The heterodimer comprising RRAGA,B:GTP and RRAGC,D:GDP (RagA:GTP or RagB:GTP complexed with RagC:GDP or RagD:GDP) forms the active conformation of the Rag complex that recruits the mTORC1 complex from the cytosol to the lysosomal membrane (Kim et al. 2008, Sancak et al. 2008, Sancak et al. 2010) where RHEB activates the protein kinase activity of mTORC1. Hydrolysis of ATP by the v-ATPase complex is also required for recruitment of mTORC1 (Zoncu et al. 2011). The active state of the RRAGA,B:RRAGC,D heterodimer is less stably associated with the Ragulator complex and appears to cycle with mTORC1 between the lysosomal membrane and the cytosol (Lawrence et al. 2018). The cycling may provide a mechanism for attenuating mTORC1 signaling.

Preceded by: v-ATPase:Ragulator:RRAGA,B:GTP:RRAGC,D:GDP:SLC38A9:Arginine dissociates yielding v-ATPase:Ragulator:RRAGA,B:GTP:RRAGC,D:GDP and SLC38A9:Arginine

Followed by: mTORC1 binds RHEB:GTP

Literature references

Sabatini, DM., Zoncu, R., Sancak, Y., Bar-Peled, L., Nada, S., Markhard, AL. (2010). Ragulator-Rag complex targets mTORC1 to the lysosomal surface and is necessary for its activation by amino acids. *Cell, 141*, 290-303. ↗

Sabatini, DM., Sancak, Y., Zoncu, R., Bar-Peled, L., Efeyan, A., Wang, S. (2011). mTORC1 senses lysosomal amino acids through an inside-out mechanism that requires the vacuolar H(+)-ATPase. *Science, 334*, 678-83. ↗

Thoreen, CC., Shaul, YD., Sabatini, DM., Sancak, Y., Bar-Peled, L., Lindquist, RA. et al. (2008). The Rag GTPases bind raptor and mediate amino acid signaling to mTORC1. *Science, 320*, 1496-501. ↗

Guan, KL., Neufeld, TP., Kim, E., Goraksha-Hicks, P., Li, L. (2008). Regulation of TORC1 by Rag GTPases in nutrient response. *Nat. Cell Biol., 10*, 935-45. ↗

Rappold, R., Zoncu, R., Cho, KF., Kim, DJ., Hurley, JH., Moldavski, O. et al. (2018). A nutrient-induced affinity switch controls mTORC1 activation by its Rag GTPase-Ragulator lysosomal scaffold. *Nat. Cell Biol., 20*, 1052-1063. ↗

Editions

2019-05-13	Authored, Edited	May, B.
2019-08-08	Reviewed	Sabatini, DM., Condon, KJ.

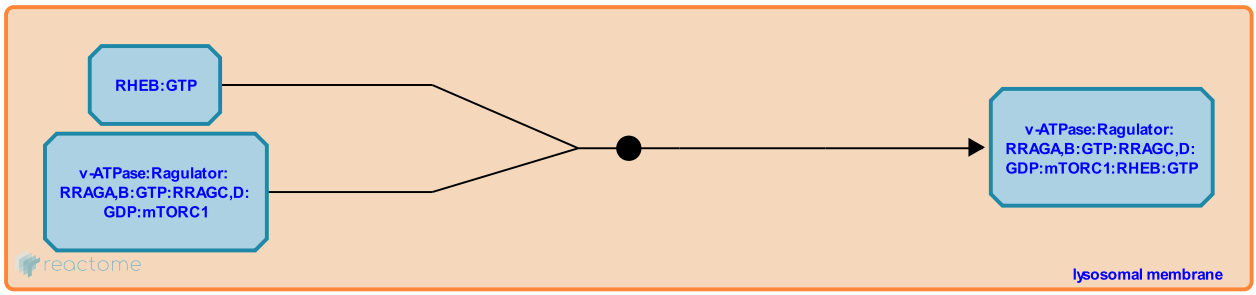
mTORC1 binds RHEB:GTP ↗

Location: Amino acids regulate mTORC1

Stable identifier: R-HSA-9646468

Type: binding

Compartments: lysosomal membrane



RHEB:GTP interacts with mTORC1 and activates the kinase activity of mTORC1 (Long et al. 2005, Tee et al. 2005, Long et al. 2007, Yang et al. 2017). RHEB binds the catalytic domain of the MTOR subunit of the mTORC1 complex (Long et al. 2005, Yang et al. 2017). The interaction of RHEB with mTORC1 is independent of the guanyl nucleotide bound by RHEB while the activation of MTOR is dependent on GTP bound to RHEB (Long et al. 2005). The binding of MTOR to RHEB is dependent on amino acid sufficiency (Long et al. 2005) due to association of mTORC1 with the Rag heterodimer at the lysosomal membrane.

Preceded by: v-ATPase:Ragulator:RRAGA,B:GTP:RRAGC,D:GDP binds mTORC1

Literature references

Busch, S., Lin, Y., Long, X., Avruch, J., Ortiz-Vega, S. (2007). The Rheb switch 2 segment is critical for signaling to target of rapamycin complex 1. *J. Biol. Chem., 282*, 18542-51. ↗

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Yonezawa, K., Ortiz-Vega, S., Avruch, J., Lin, Y., Long, X. (2005). Rheb binds and regulates the mTOR kinase. *Curr Biol, 15*, 702-13. ↗

Proud, CG., Blenis, J., Tee, AR. (2005). Analysis of mTOR signaling by the small G-proteins, Rheb and RhebL1. *FEBS Lett., 579*, 4763-8. ↗

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Editions

2019-05-24	Authored, Edited	May, B.
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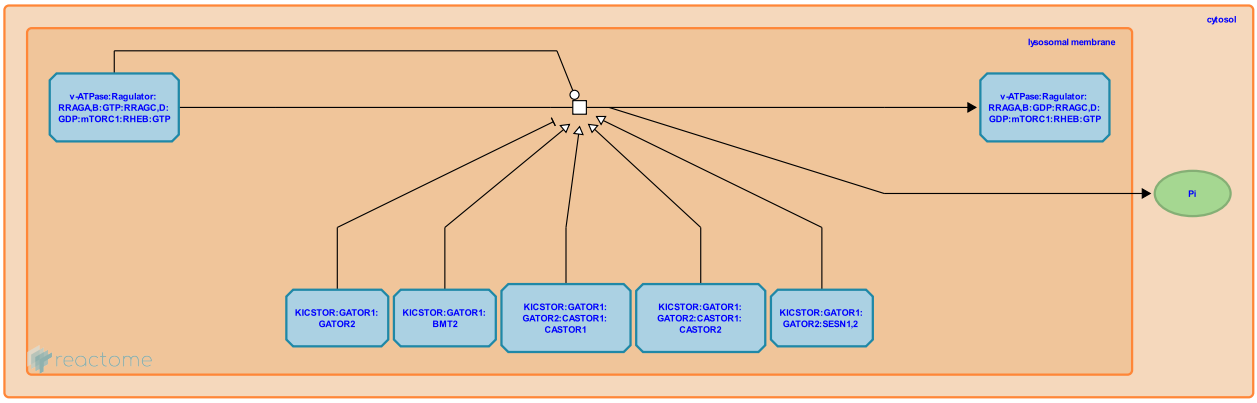
RRAGA,B hydrolyzes GTP ↗

Location: Amino acids regulate mTORC1

Stable identifier: R-HSA-9640195

Type: transition

Compartments: lysosomal membrane



The GTPase activity of RRAGA,B hydrolyzes GTP to GDP (Bar-Peled et al. 2013). RRAGA and RRAGB lack detectable GTPase activity in the absence of a GTPase activating protein (Schurmann et al. 1995). The NPRL2 subunit of the GATOR1 complex acts as a GTPase activator of RRAGA,B and thereby controls the guanyl nucleotide bound to RRAGA,B (Bar-Peled et al. 2013, Shen et al. 2019). GATOR2 antagonizes GATOR1 (Bar-Peled et al. 2013). During amino acid deficiency, Sestrins (SESN1 and SESN2) (Chantranupong et al. 2014, Parmigiani et al. 2014, Peng et al. 2014, Kim et al. 2015, Wolfson et al. 2016, Saxton et al. 2016) and CASTOR1 (Chantranupong et al. 2016, Saxton et al. 2016, Gai et al. 2016, Xia et al. 2016) bound to GATOR2 prevent GATOR2 from antagonizing GATOR1 (Bar-Peled et al. 2013). BMT2 (SAMTOR) bound to GATOR1 enhances inhibition of mTORC1 activation by GATOR1 (Gu et al. 2017).

Literature references

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Sabatini, DM., Scaria, SM., Saxton, RA., Chantranupong, L., Cantor, JR., Shen, K. et al. (2016). Sestrin2 is a leucine sensor for the mTORC1 pathway. *Science, 351*, 43-8. ↗

Peng, M., Li, MO., Yin, N. (2014). Sestrins function as guanine nucleotide dissociation inhibitors for Rag GTPases to control mTORC1 signaling. *Cell, 159*, 122-133. ↗

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Editions

2019-03-11	Authored, Edited	May, B.
2019-08-08	Reviewed	Sabatini, DM., Condon, KJ.

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