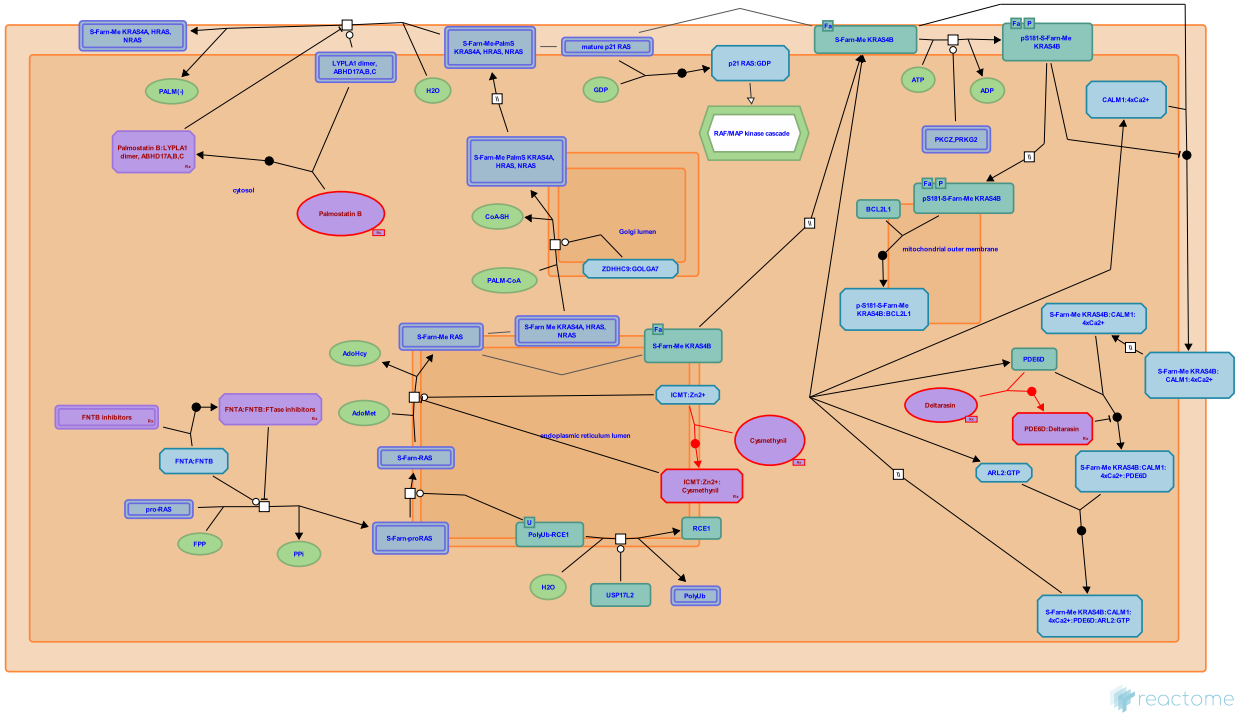
RAS processing



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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. ↗

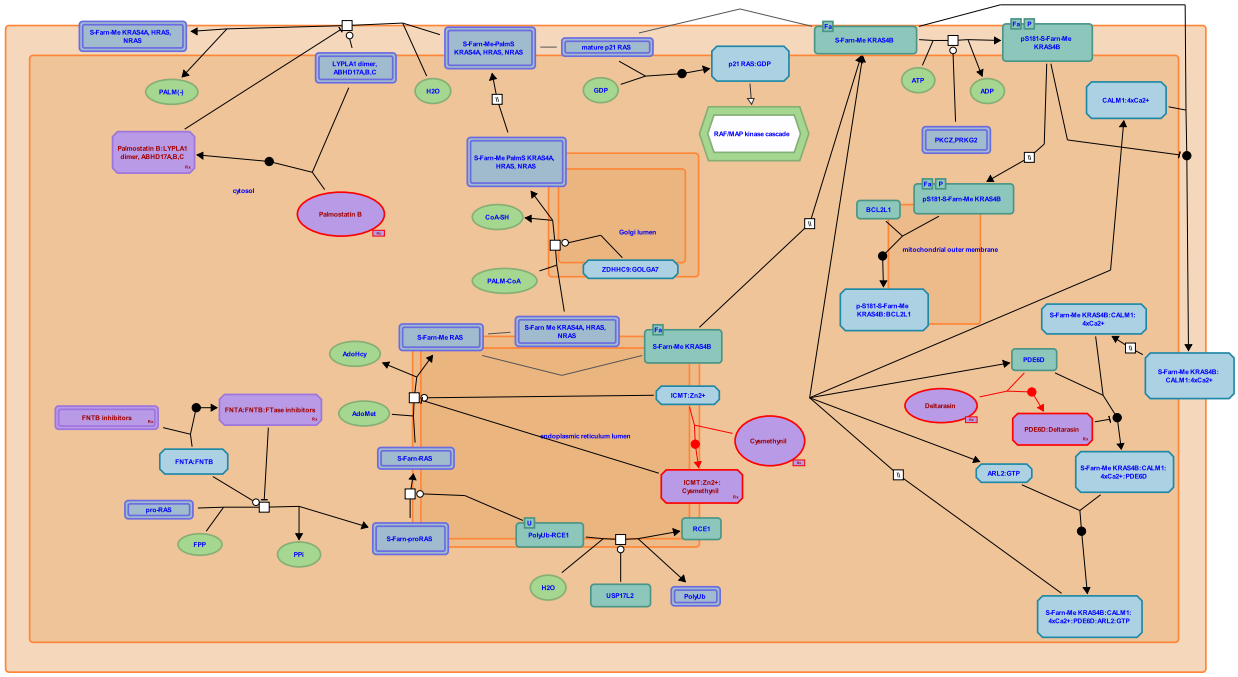
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

RAS processing ↗

Stable identifier: R-HSA-9648002



RAS proteins undergo several processing steps during maturation including farnesylation, carboxy-terminal cleavage and carboxymethylation, among others. These steps are required for their membrane localization and function and ultimately for their ability to activate RAF (reviewed in Gysin et al, 2011; Ahearn et al, 2018).

Literature references

McCormick, F., Salt, M., Young, A., Gysin, S. (2011). Therapeutic strategies for targeting ras proteins. *Genes Cancer, 2*, 359-72. ↗

Philips, MR., Zhou, M., Ahearn, I. (2018). Posttranslational Modifications of RAS Proteins. *Cold Spring Harb Perspect Med, 8*. ↗

Editions

2019-10-25	Authored	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.
2020-05-26	Edited	Rothfels, K.

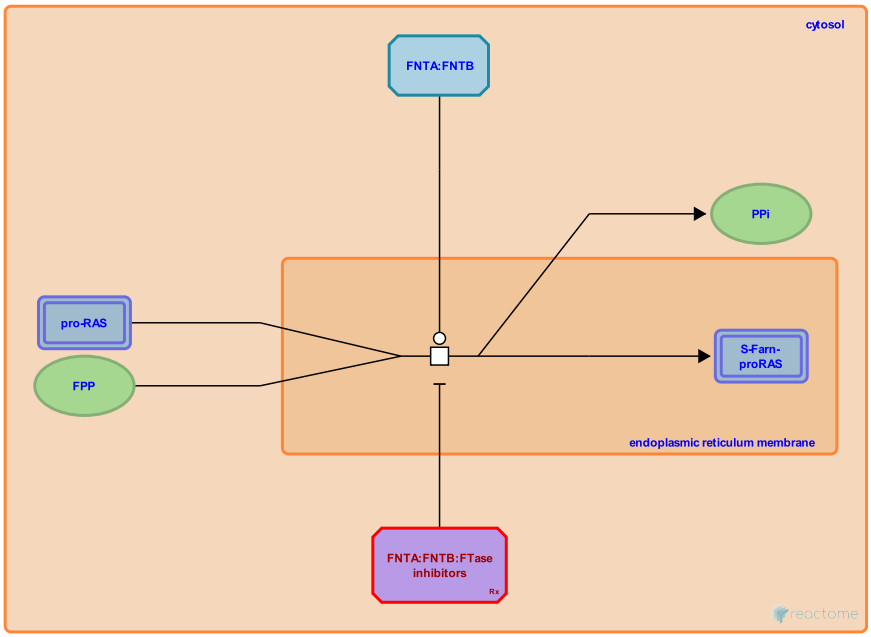
pro-RAS proteins are farnesylated ↗

Location: RAS processing

Stable identifier: R-HSA-9647978

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



RAS proteins are isoprenylated at a CaaX motif in the hypervariable region, where a is an aliphatic amino acid and X is any amino acid (Casey et al, 1989; Dharmaiah et al, 2016; reviewed in Ahean et al, 2018). Geranylgeranylation is favoured when X is leucine, while all other amino acids at this position favour farnesylation by farnesyltransferase (Casey et al, 1989; Reid et al, 2004).

Followed by: RCE1 cleaves S-Farn proRAS proteins

Literature references

Casey, PJ., Reid, TS., Beese, LS., Terry, KL. (2004). Crystallographic analysis of CaaX prenyltransferases complexed with substrates defines rules of protein substrate selectivity. *J. Mol. Biol., 343*, 417-33. ↗

Der, CJ., Solski, PA., Casey, PJ., Buss, JE. (1989). p21ras is modified by a farnesyl isoprenoid. *Proc. Natl. Acad. Sci. U.S.A., 86*, 8323-7. ↗

Dharmaiah, S., Bindu, L., Ghirlando, R., Frank, PH., McCormick, F., Gillette, WK. et al. (2016). Structural basis of recognition of farnesylated and methylated KRAS4b by PDEδ. *Proc. Natl. Acad. Sci. U.S.A., 113*, E6766-E6775. ↗

Philips, MR., Zhou, M., Ahearn, I. (2018). Posttranslational Modifications of RAS Proteins. *Cold Spring Harb Perspect Med, 8*. ↗

Editions

2019-10-25	Authored	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.
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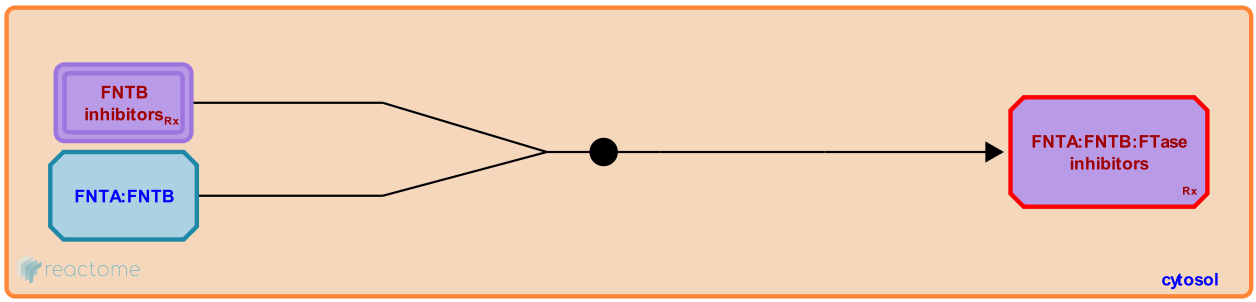
FNTB inhibitors bind FNTA:FNTB ↗

Location: RAS processing

Stable identifier: R-HSA-9647987

Type: binding

Compartments: cytosol



Because prenylation is important for RAS membrane localization and function, inhibition of this step of RAS processing was viewed as a promising early therapeutic target for RAS-driven cancers (reviewed in Gysin et al, 2011). Farnesyltransferase inhibitors such as lonafarnib and tipifarnib are small molecule CaaX competitive inhibitors that inhibit cell growth of a range of cancer cell lines and tumor xenografts (Njoroge et al, 1998; End et al, 2001; Liu et al, 1998; Ashar et al, 2001). Unfortunately, the clinical use of these drugs is hampered by the fact that both KRAS and NRAS can be geranylgeranylated when FTase is inhibited, restoring membrane localization and function (Fiordalisi et al, 2003). FTase inhibitors may have clinical use in the treatment of HRAS driven cancers, such as bladder and thyroid cancers (reviewed in Gysin et al, 2011; Lu et al, 2016).

Lonafarnib is a farnesyltransferase inhibitor of growth factor signalling that prevented SARS-CoV-2 replication in Caco-2 and UKF-RC-2 cells at clinically achievable concentrations (Klann et al, 2020).

Literature references

Devine, A., Sanz, G., Skrzat, S., Angibaud, P., Fuery, CJ., Wouters, W. et al. (2001). Characterization of the antitumor effects of the selective farnesyl protein transferase inhibitor R115777 in vivo and in vitro. *Cancer Res., 61*, 131-7. ↗

Desai, J., Njoroge, FG., Remiszewski, S., Deskus, J., Alvarez, CS., Ganguly, AK. et al. (1998). (+)-4-[2-[4-(8-Chloro-3,10-dibromo-6,11-dihydro-5H-benzo[5, 6]cyclohepta[1,2-b]- pyridin-11(R)-yl)-1-piperidinyl]-2-oxo-ethyl]-1-piperidine-carboxamid e (SCH-66336): a very potent farnesyl protein transferase inhibitor as a novel antitumor agent. *J. Med. Chem., 41*, 4890-902. ↗

McCormick, F., Salt, M., Young, A., Gysin, S. (2011). Therapeutic strategies for targeting ras proteins. *Genes Cancer, 2*, 359-72. ↗

Ciesek, S., Cinatl, J., Tascher, G., Münch, C., Bojkova, D., Klann, K. (2020). Growth Factor Receptor Signaling Inhibition Prevents SARS-CoV-2 Replication. *Mol Cell, 80*, 164-174.e4. ↗

Njoroge, FG., Remiszewski, S., Lee, S., Doll, RJ., Syed, J., Ferrari, E. et al. (1998). Antitumor activity of SCH 66336, an orally bioavailable tricyclic inhibitor of farnesyl protein transferase, in human tumor xenograft models and wap-ras transgenic mice. *Cancer Res., 58*, 4947-56. ↗

Editions

2019-10-25	Authored	Rothfels, K.
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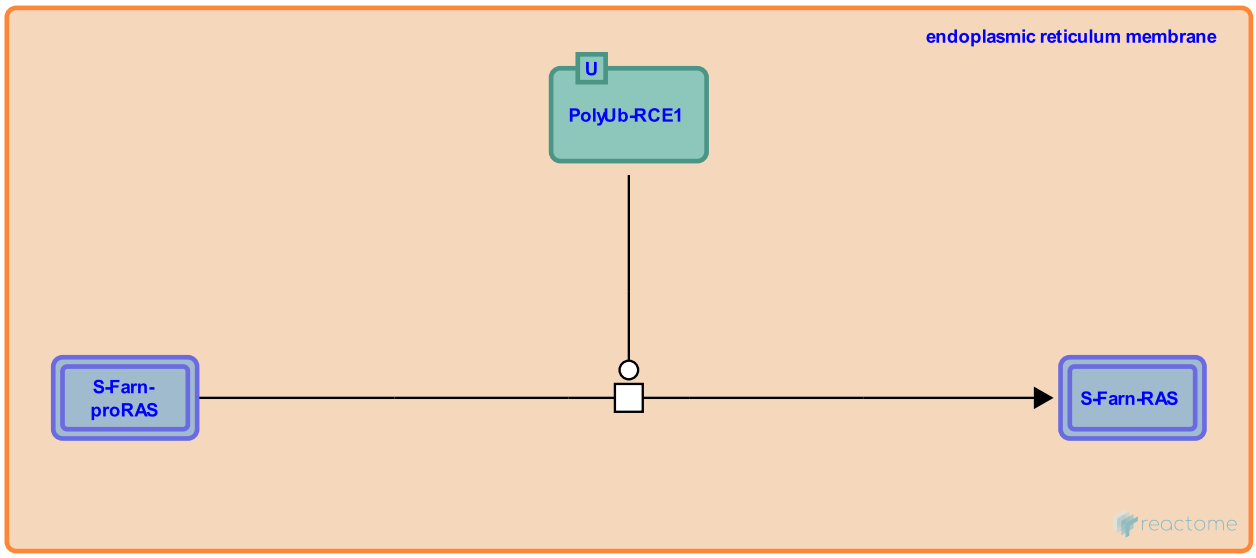
RCE1 cleaves S-Farn proRAS proteins ↗

Location: RAS processing

Stable identifier: R-HSA-9647999

Type: transition

Compartments: endoplasmic reticulum membrane



After prenylation, RAS proteins undergo C-terminal endoproteolysis by RAS-converting enzyme I (RCE1), which removes the aaX residues of the CaaX motif (Otto et al, 1999; Hollander et al, 2000; reviewed in Hampton et al, 2018; Ahearn et al, 2018). RCE1-mediated cleavage is required for RAS plasma membrane localization and function (Michaelson et al, 2005). RCE1 is ubiquitinated in its active form, and deubiquitination by USP17L2 abrogates its catalytic activity and inhibits signaling through the RAS-RAF MAP kinase pathway (Burrows et al, 2009). RCE1 has thus been investigated as a potential therapeutic target in RAS driven disease. Despite some promising studies, the effects of RCE1 inactivation appear unpredictable and can lead to unexpected activation of RAS signaling through mechanisms that are not fully understood (Bergo et al, 2002; Aiyagari et al, 2003; Kim et al, 1999; Chen et al, 1998; Chen et al, 1999; Wahlstrom et al, 2007).

Preceded by: pro-RAS proteins are farnesylated

Followed by: ICMT methylates S-Farn RAS proteins

Literature references

Taylor, BR., Aurora, V., Aiyagari, AL., Shannon, KM., Young, SG. (2003). Hematologic effects of inactivating the Ras processing enzyme Rce1. *Blood, 101*, 2250-2. ↗

Ali, W., Philips, M., Silletti, J., Chiu, VK., Michaelson, D., Bergo, M. et al. (2005). Postprenylation CAAX processing is required for proper localization of Ras but not Rho GTPases. *Mol. Biol. Cell, 16*, 1606-16. ↗

Kim, E., Casey, PJ., Otto, JC., Young, SG. (1999). Cloning and characterization of a mammalian prenyl protein-specific protease. *J. Biol. Chem., 274*, 8379-82. ↗

Frommer, E., Hollander, I., Mallon, R. (2000). Human ras-converting enzyme (hRCE1) endoproteolytic activity on K-ras-derived peptides. *Anal. Biochem., 286*, 129-37. ↗

Kim, E., Casey, PJ., Ashby, M., Shannon, K., Taylor, B., Otto, JC. et al. (1999). Disruption of the mouse Rce1 gene results in defective Ras processing and mislocalization of Ras within cells. *J. Biol. Chem., 274*, 8383-90. ↗

Editions

2019-10-25	Authored	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.
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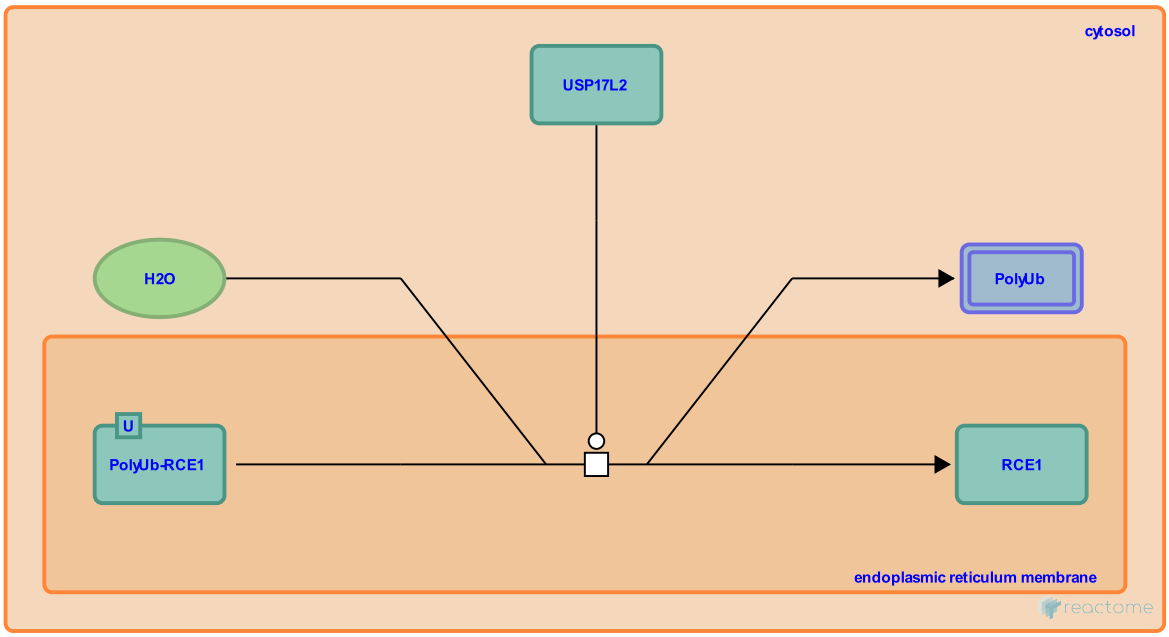
USP17L2 deubiquitinates RCE1 ↗

Location: RAS processing

Stable identifier: R-HSA-9653514

Type: transition

Compartments: endoplasmic reticulum membrane, cytosol



USP17L2, also known as USP17, deubiquitinates RCE1 (RAS-converting enzyme 1), inactivating it. Loss of RCE1 activity after USP17L2-mediated deubiquitination interferes with RAS localization and function and prevents downstream signaling through the RAF MAP kinase cascade (Burrows et al, 2009).

Literature references

McFarlane, C., Scott, CJ., De la Vega, M., Johnston, JA., McGrattan, MJ., Kelvin, AA. et al. (2009). USP17 regulates Ras activation and cell proliferation by blocking RCE1 activity. *J. Biol. Chem., 284*, 9587-95. ↗

Editions

2019-10-25	Authored	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.
2020-05-26	Edited	Rothfels, K.

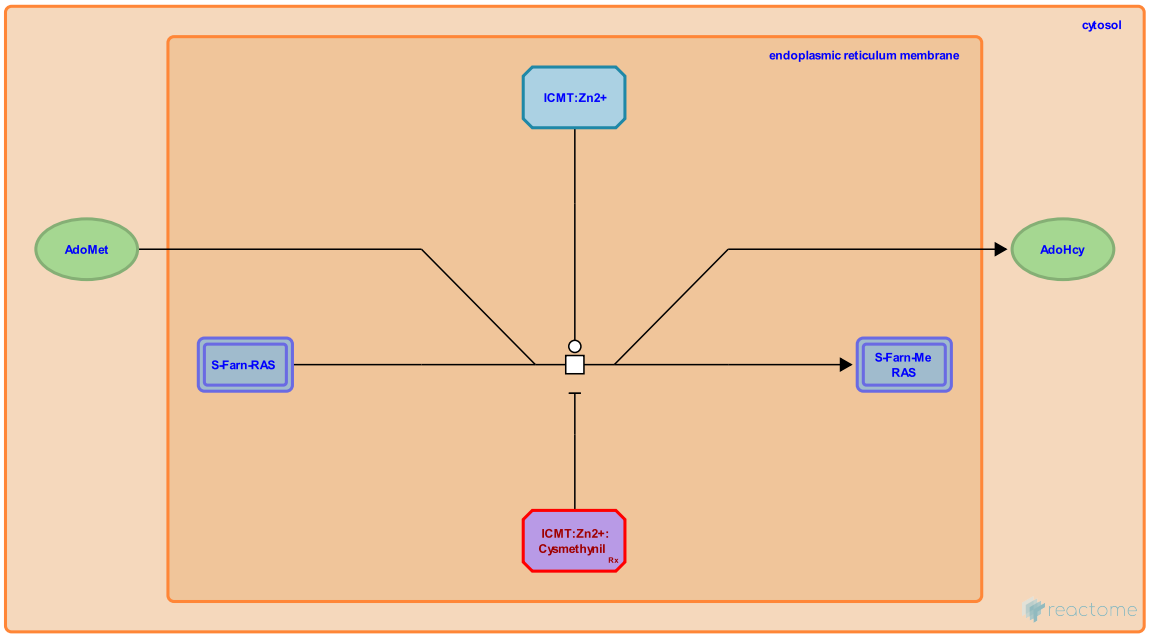
ICMT methylates S-Farn RAS proteins ↗

Location: RAS processing

Stable identifier: R-HSA-9647977

Type: transition

Compartments: endoplasmic reticulum membrane



RAS proteins undergo C-terminal carboxymethylation by isoprenylcysteine methyltransferase (ICMT) (Yang et al, 2011; Dharmaiah et al, 2016; reviewed in Gysin et al, 2011; Ahearn et al, 2018). LIke prenylation, methylation is required for plasma membrane localization and function of RAS proteins, and disruption of ICMT or interference with the methylation reaction inhibits cell growth and KRAS-dependent transformation (Chiu et al, 2004; Michaelson et al, 2005; Bergo et al, 2004; Wahlstrom et al, 2008; Winter-Vann et al, 2003). Consistent with this, a number of small molecule inhibitors of ICMT have been shown to decrease tumor proliferation (Wang et al, 2009; Manu et al, 2017; Sun et al, 2016).

Preceded by: RCE1 cleaves S-Farn proRAS proteins

Followed by: S-farn Me-HRAS, -NRAS and -KRAS4A are palmitoylated, Mature S-Farn-Me KRAS4B translocates to plasma membrane

Literature references

Chuah, C., Bunte, RM., Asari, K., Casey, PJ., Sun, WT., Xiang, W. et al. (2016). Inhibition of isoprenylcysteine carboxylmethyltransferase augments BCR-ABL1 tyrosine kinase inhibition-induced apoptosis in chronic myeloid leukemia. *Exp. Hematol., 44*, 189-93.e2. ↗

Kamen, BA., Casey, PJ., Bergo, MO., Melnyk, S., Young, SG., Winter-Vann, AM. et al. (2003). Targeting Ras signaling through inhibition of carboxyl methylation: an unexpected property of methotrexate. *Proc. Natl. Acad. Sci. U.S.A. , 100*, 6529-34. ↗

Ali, W., Philips, M., Silletti, J., Chiu, VK., Michaelson, D., Bergo, M. et al. (2005). Postprenylation CAAX processing is required for proper localization of Ras but not Rho GTPases. *Mol. Biol. Cell, 16*, 1606-16. ↗

Zhang, Z., Yang, J., Kulkarni, K., Mas-Droux, C., Manolaridis, I., Barford, D. et al. (2011). Mechanism of isoprenylcysteine carboxyl methylation from the crystal structure of the integral membrane methyltransferase ICMT. *Mol. Cell, 44*, 997-1004. ↗

Dharmaiah, S., Bindu, L., Ghirlando, R., Frank, PH., McCormick, F., Gillette, WK. et al. (2016). Structural basis of recognition of farnesylated and methylated KRAS4b by PDEδ. *Proc. Natl. Acad. Sci. U.S.A., 113*, E6766-E6775. ↗

Editions

2019-10-25	Authored	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.
2020-05-26	Edited	Rothfels, K.

Cysmethynil binds ICMT:Zn2+ ↗

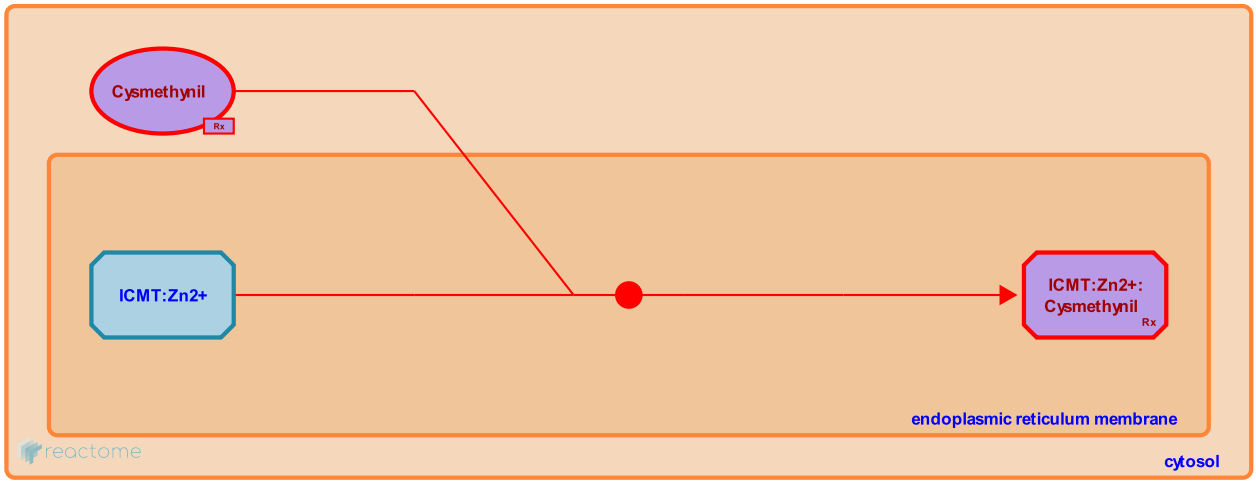
Location: RAS processing

Stable identifier: R-HSA-9656775

Type: binding

Compartments: endoplasmic reticulum membrane, cytosol

Diseases: cancer



Cysmethnil is a small molecule inhibitor of ICMT that has been shown to reduce proliferation of cancer cell lines by promoting apoptosis (Winter-Vann et al, 2005; Wang et al, 2010; Judd et al, 2011; Sun et al, 2016; Manu et al, 2017). Cysmethynil is a poor candidate for clinical trials due to low solubility and other physical characteristics. A number of related small molecule inhibitors with improved physical properties are under investigation (Lau et al, 2014; Ramanujulu et al, 2013).

Literature references

Chuah, C., Bunte, RM., Asari, K., Casey, PJ., Sun, WT., Xiang, W. et al. (2016). Inhibition of isoprenylcysteine carboxylmethyltransferase augments BCR-ABL1 tyrosine kinase inhibition-induced apoptosis in chronic myeloid leukemia. *Exp. Hematol., 44*, 189-93.e2. ↗

Kamen, BA., Casey, PJ., Bergo, MO., Melnyk, S., Young, SG., Winter-Vann, AM. et al. (2003). Targeting Ras signaling through inhibition of carboxyl methylation: an unexpected property of methotrexate. *Proc. Natl. Acad. Sci. U.S.A. , 100*, 6529-34. ↗

Guo, D., Yang, T., Wirawan, M., Casey, PJ., Lau, HY., Wang, M. et al. (2014). An improved isoprenylcysteine carboxylmethyltransferase inhibitor induces cancer cell death and attenuates tumor growth in vivo. *Cancer Biol. Ther., 15*, 1280-91. ↗

Hoang, KC., Roth, B., Valppu, L., Brown, B., Judd, WR., Wettstein, D. et al. (2011). Discovery and SAR of methylated tetrahydropyranyl derivatives as inhibitors of isoprenylcysteine carboxyl methyltransferase (ICMT). *J. Med. Chem., 54*, 5031-47. ↗

Casey, PJ., Wang, M., Liu, S., Coolman, B., Zhou, J., Hossain, MS. et al. (2010). Inhibition of isoprenylcysteine carboxylmethyltransferase induces autophagic-dependent apoptosis and impairs tumor growth. *Oncogene, 29*, 4959-70. ↗

Editions

2019-10-25	Authored	Rothfels, K.
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2020-05-26	Edited	Rothfels, K.

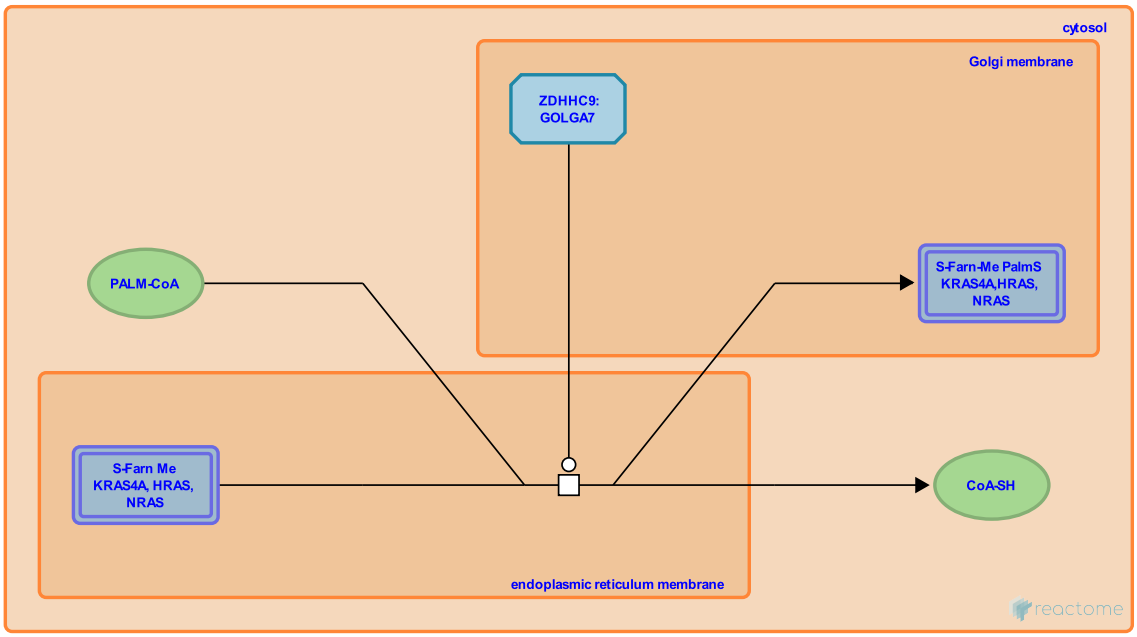
S-farn Me-HRAS, -NRAS and -KRAS4A are palmitoylated ↗

Location: RAS processing

Stable identifier: R-HSA-9647982

Type: transition

Compartments: endoplasmic reticulum membrane, Golgi membrane



After carboxymethylation, HRAS, NRAS and KRAS4A are palmitoylated on cysteine residues upstream of the CaaX motif (residue C179 in KRAS4A, C181 in NRAS and C181 and C184 in HRAS). KRAS4B lacks upstream cysteine residues and does not undergo palmitoylation (Hancock et al, 1989; Swarthout et al, 2005; reviewed in Gysin et al, 2011; Ahearn et al, 2018). Palmitoylation is catalyzed by the DHHC9:GOLGA7 complex at the Golgi membrane (Swarthout et al, 2008).

Preceded by: ICMT methylates S-Farn RAS proteins

Followed by: mature RAS proteins translocate to plasma membrane

Literature references

McCormick, F., Salt, M., Young, A., Gysin, S. (2011). Therapeutic strategies for targeting ras proteins. *Genes Cancer, 2*, 359-72. ↗

Hancock, JF., Childs, JE., Magee, AI., Marshall, CJ. (1989). All ras proteins are polyisoprenylated but only some are palmitoylated. *Cell, 57*, 1167-77. ↗

Philips, MR., Zhou, M., Ahearn, I. (2018). Posttranslational Modifications of RAS Proteins. *Cold Spring Harb Perspect Med, 8*. ↗

Linder, ME., Deschenes, RJ., Croke, MR., Swarthout, JT., Lobo, S., Farh, L. et al. (2005). DHHC9 and GCP16 constitute a human protein fatty acyltransferase with specificity for H- and N-Ras. *J. Biol. Chem., 280*, 31141-8. ↗

Editions

2019-10-25	Authored	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.
2020-05-26	Edited	Rothfels, K.

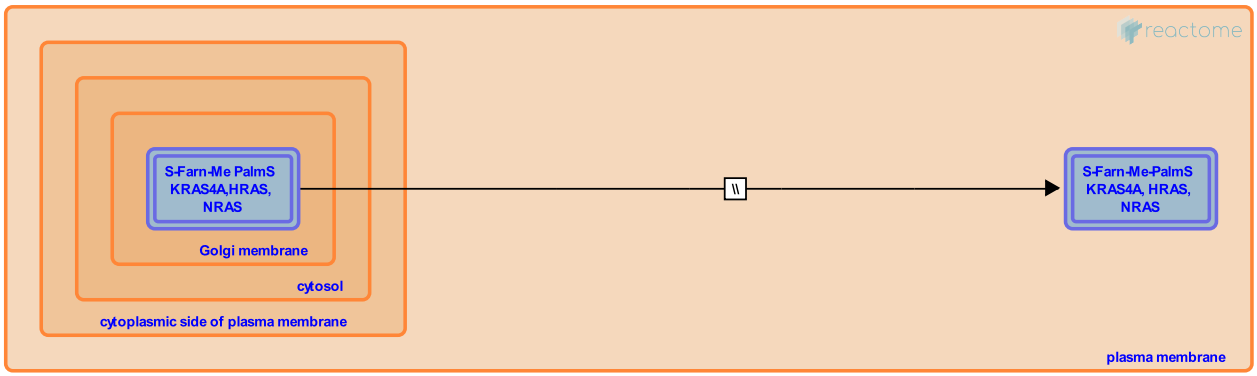
mature RAS proteins translocate to plasma membrane ↗

Location: RAS processing

Stable identifier: R-HSA-9647980

Type: omitted

Compartments: plasma membrane, Golgi membrane



After farnesylation, C-terminal proteolysis, carboxymethylation and palmitoylation, RAS proteins translocate to the plasma membrane (reviewed in Gysin et al, 2011).

Preceded by: S-farn Me-HRAS, -NRAS and -KRAS4A are palmitoylated

Followed by: RAS proteins are depalmitoylated, mature p21 RAS binds GDP

Literature references

McCormick, F., Salt, M., Young, A., Gysin, S. (2011). Therapeutic strategies for targeting ras proteins. *Genes Cancer, 2,* 359-72. ↗

Editions

2019-10-25	Authored	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.
2020-05-26	Edited	Rothfels, K.

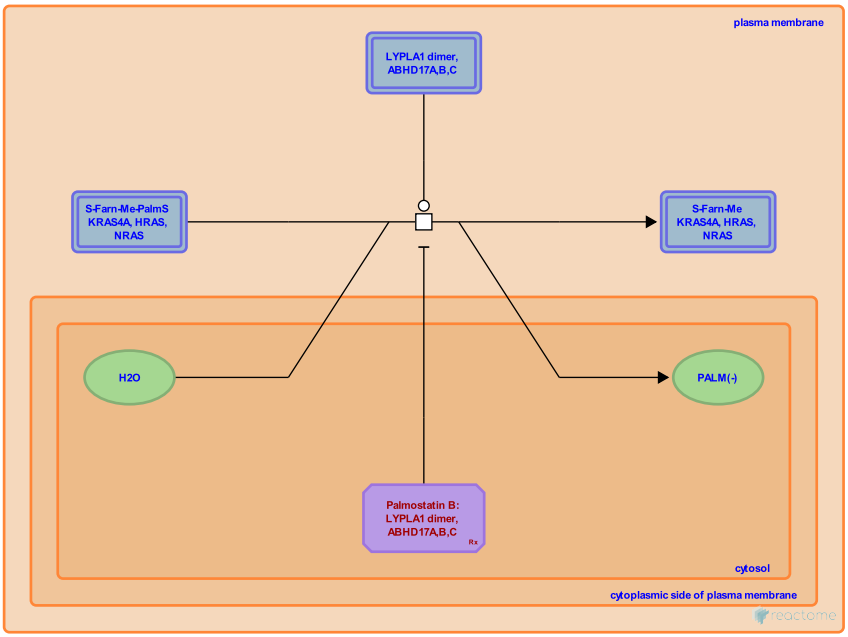
RAS proteins are depalmitoylated ↗

Location: RAS processing

Stable identifier: R-HSA-9647994

Type: transition

Compartments: plasma membrane



RAS proteins undergo a dynamic palmitoylation and depalmitoylation cycle that regulates their association with membranes and thus their localization and function (Hancock et al, 1989; Swarthout et al, 2005; reviewed in Gysin et al, 2011; Lin et al, 2017; Ahearn et al, 2018). Depalmitoylation is catalyzed by the acyl-protein thioesterase LYPLA1, also known as APT1, or by members of the ABHD17 family (Dekker et al, 2010; Lin and Conibear, 2015; reviewed in Lin et al, 2017).

Preceded by: mature RAS proteins translocate to plasma membrane

Literature references

Waldmann, H., Bastiaens, PI., Rusch, M., Vartak, N., Brunsveld, L., Rocks, O. et al. (2010). Small-molecule inhibition of APT1 affects Ras localization and signaling. *Nat. Chem. Biol., 6*, 449-56. ↗

McCormick, F., Salt, M., Young, A., Gysin, S. (2011). Therapeutic strategies for targeting ras proteins. *Genes Cancer, 2*, 359-72. ↗

Hancock, JF., Childs, JE., Magee, AI., Marshall, CJ. (1989). All ras proteins are polyisoprenylated but only some are palmitoylated. *Cell, 57*, 1167-77. ↗

Philips, MR., Zhou, M., Ahearn, I. (2018). Posttranslational Modifications of RAS Proteins. *Cold Spring Harb Perspect Med, 8*. ↗

Conibear, E., Davis, NG., Lin, DTS. (2017). Targeting the Ras palmitoylation/depalmitoylation cycle in cancer. *Biochem. Soc. Trans., 45*, 913-921. ↗

Editions

2019-10-25	Authored	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.
2020-05-26	Edited	Rothfels, K.

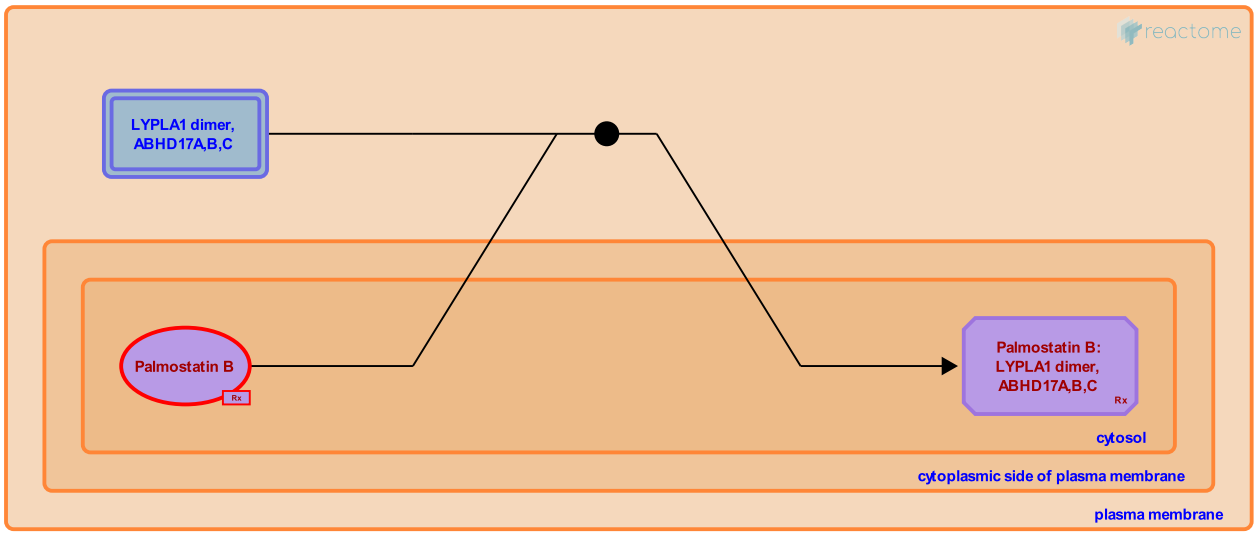
Palmostatin B binds RAS depalmitoylases ↗

Location: RAS processing

Stable identifier: R-HSA-9647991

Type: binding

Compartments: plasma membrane



Palmostatin B binds to acylthioesterases and inhibits their activity, resulting in RAS proteins that are stably palmitoylated (Dekker et al, 2010; Lin and Conibear, 2015; reviewed in Lin et al, 2017). Although this inhibition might be predicted to promote sustained RAS-dependent signaling, in fact interruption of the palmitoylation-depalmitoylation cycle results in generalized redistribution of RAS proteins to all cellular membranes, impairing function (Dekker et al, 2010). Consistent with this, Inhibition of RAS acyl protein thioesterases has been shown to have some use in restricting the proliferation of NRAS-driven melanomas (Rusch et al, 2011; Hedberg et al, 2011; Xu et al, 2012; Vujic et al, 2016).

Literature references

Murphy, R., Posch, C., Rappersberger, K., Vujic, M., Moy, A., Esteve-Puig, R. et al. (2016). Acyl protein thioesterase 1 and 2 (APT-1, APT-2) inhibitors palmostatin B, ML348 and ML349 have different effects on NRAS mutant melanoma cells. *Oncotarget, 7*, 7297-306. ↗

Waldmann, H., Bastiaens, PI., Rusch, M., Vartak, N., Brunsveld, L., Rocks, O. et al. (2010). Small-molecule inhibition of APT1 affects Ras localization and signaling. *Nat. Chem. Biol., 6*, 449-56. ↗

Conibear, E., Davis, NG., Lin, DTS. (2017). Targeting the Ras palmitoylation/depalmitoylation cycle in cancer. *Biochem. Soc. Trans., 45*, 913-921. ↗

Renner, S., Waldmann, H., Bon, RS., Dekker, FJ., Bastiaens, PI., Gerding-Reimers, C. et al. (2011). Development of highly potent inhibitors of the Ras-targeting human acyl protein thioesterases based on substrate similarity design. *Angew. Chem. Int. Ed. Engl., 50*, 9832-7. ↗

Triola, G., Waldmann, H., Rusch, M., Dekker, FJ., Bürger, M., Brockmeyer, A. et al. (2011). Identification of acyl protein thioesterases 1 and 2 as the cellular targets of the Ras-signaling modulators palmostatin B and M. *Angew. Chem. Int. Ed. Engl., 50*, 9838-42. ↗

Editions

2019-10-25	Authored	Rothfels, K.
2020-05-04	Reviewed	Gavathiotis, E.
2020-05-26	Edited	Rothfels, K.

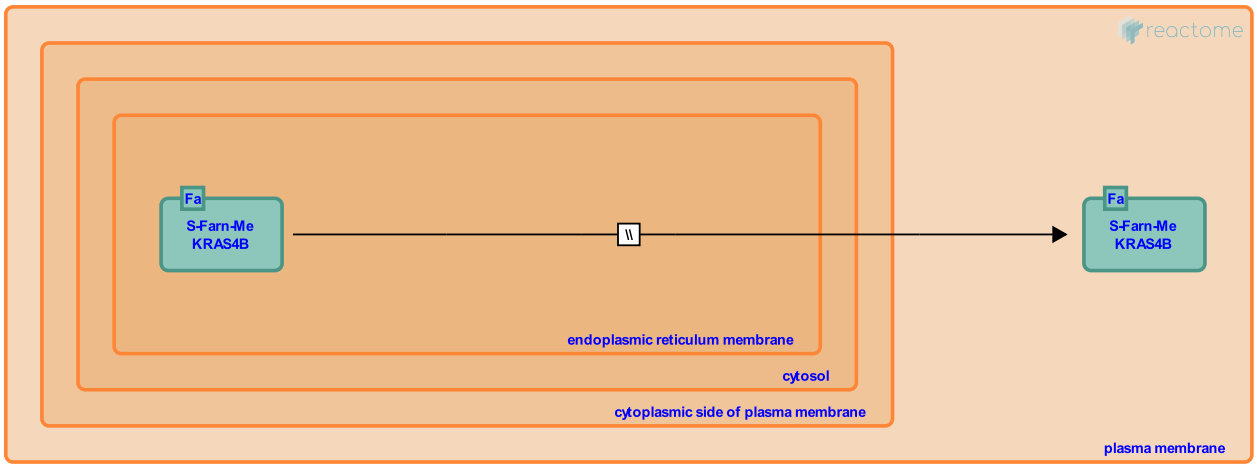
Mature S-Farn-Me KRAS4B translocates to plasma membrane ↗

Location: RAS processing

Stable identifier: R-HSA-9649732

Type: omitted

Compartments: endoplasmic reticulum membrane, plasma membrane



After farnesylation, C-terminal proteolysis and carboxymethylation, KRAS4B translocates to the plasma membrane (reviewed in Gysin et al, 2011). Localization at the plasma membrane is facilitated by an electrostatic interaction between the polybasic residues in the hypervariable region of KRAS4B and the negatively charged phospholipids of the plasma membrane (Hancock et al, 1990; Yeung et al, 2008).

Preceded by: ICMT methylates S-Farn RAS proteins

Followed by: S-Farn-Me KRAS4B binds calmodulin, KRAS4B is phosphorylated on serine 181, mature p21 RAS binds GDP

Literature references

Silvius, J., Gilbert, GE., Yeung, T., Shi, J., Kapus, A., Grinstein, S. (2008). Membrane phosphatidylserine regulates surface charge and protein localization. *Science, 319*, 210-3. ↗

Hancock, JF., Marshall, CJ., Paterson, H. (1990). A polybasic domain or palmitoylation is required in addition to the CAAX motif to localize p21ras to the plasma membrane. *Cell, 63*, 133-9. ↗

McCormick, F., Salt, M., Young, A., Gysin, S. (2011). Therapeutic strategies for targeting ras proteins. *Genes Cancer, 2*, 359-72. ↗

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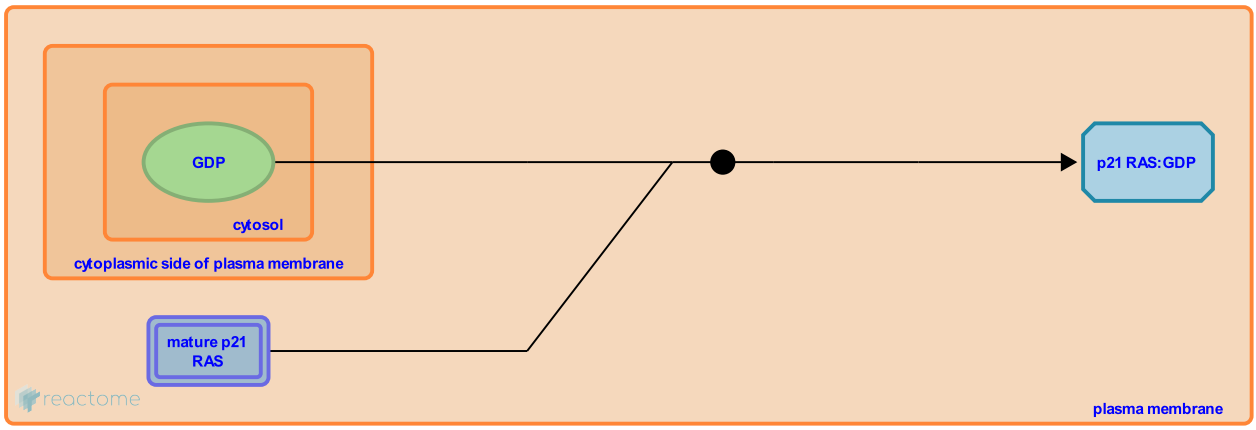
mature p21 RAS binds GDP ↗

Location: RAS processing

Stable identifier: R-HSA-9649733

Type: binding

Compartments: plasma membrane



RAS proteins bind GDP with picomolar affinity as part of the RAS:GTP cycle (reviewed in Hennig et al, 2015; Pei et al, 2019; Prior et al, 2012). RAS proteins in the GDP-bound form are inactive. Interaction with guanine nucleotide exchange factors (GEFs) enhances the slow rate of intrinsic GDP dissociation, allowing GTP to bind and activate the protein (reviewed in Henning et al, 2015).

Preceded by: mature RAS proteins translocate to plasma membrane, Mature S-Farn-Me KRAS4B translocates to plasma membrane

Literature references

Markwart, R., Esparza-Franco, MA., Ladds, G., Rubio, I., Hennig, A. (2015). Ras activation revisited: role of GEF and GAP systems. *Biol. Chem., 396*, 831-48. ↗

Chen, K., Liao, H., Pei, D. (2018). Targeting Ras with Macromolecules. *Cold Spring Harb Perspect Med, 8*. ↗

Lewis, PD., Mattos, C., Prior, IA. (2012). A comprehensive survey of Ras mutations in cancer. *Cancer Res., 72*, 2457-67. ↗

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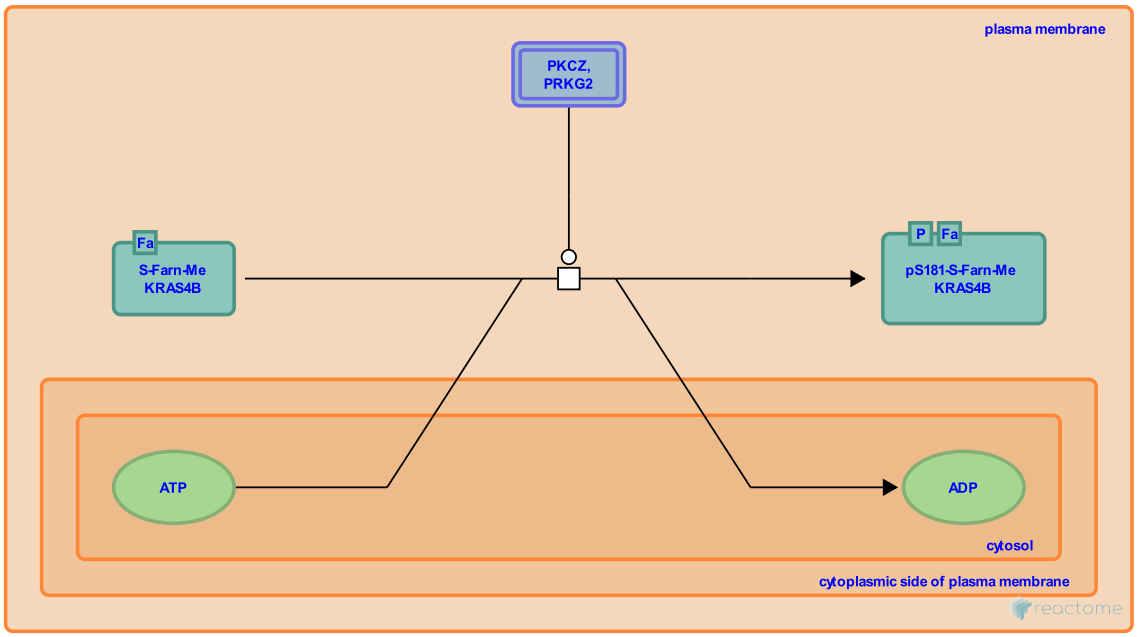
KRAS4B is phosphorylated on serine 181 ↗

Location: RAS processing

Stable identifier: R-HSA-9653503

Type: transition

Compartments: plasma membrane, cytosol



KRAS4B is phosphorylated on serine 181 by PKC theta or cGMP dependent protein kinase 2 (PRKG2) (Bivona et al, 2006; Alvarez-Moya et al, 2010; Cho et al, 2016; reviewed in Ahearn et al, 2018). Serine 181 lies in a polybasic region unique to KRAS upstream of the CaaX motif. Phosphorylation at this position decreases the affinity of KRAS4B for the membrane and promotes internalization (Bivona et al, 2006; Barcelo et al, 2013; Jang et al, 2015). S181 phosphorylation has been shown to restrict cellular proliferation and oncogenesis in part by promoting BCL2L (also known as BCL-XL)-dependent apoptosis (Bivona et al, 2006; Mohammad et al, 1998; Kollar et al, 2014). Phosphorylation at S181 may also interfere with the binding of calmodulin to KRAS4B, thus disrupting calmodulin-dependent supression of signaling downstream of RAS (Wang et al, 2001; Villalonga et al, 2001).

Preceded by: Mature S-Farn-Me KRAS4B translocates to plasma membrane

Followed by: pS181-S-Farn-Me KRAS4B translocates to the outer mitochondrial membrane

Literature references

Balmain, A., Galeas, J., Wang, MT., To, MD., McCormick, F., Delrosario, R. et al. (2015). K-Ras Promotes Tumorigenicity through Suppression of Non-canonical Wnt Signaling. *Cell, 163*, 1237-1251. ↗

Pazourek, J., Kollár, P., Rajchard, J., Balounová, Z. (2014). Marine natural products: bryostatins in preclinical and clinical studies. *Pharm Biol, 52*, 237-42. ↗

Tebar, F., Beckett, AJ., Agell, N., Barceló, C., Prior, I., Paco, N. et al. (2013). Oncogenic K-ras segregates at spatially distinct plasma membrane signaling platforms according to its phosphorylation status. *J. Cell. Sci., 126*, 4553-9. ↗

Vaitkevicius, VK., Sarkar, FH., Dergham, ST., Almatchy, VP., Flake, TM., Al-Katib, AA. et al. (1998). Establishment of a human pancreatic tumor xenograft model: potential application for preclinical evaluation of novel therapeutic agents. *Pancreas, 16*, 19-25. ↗

Cho, KJ., Capon, RJ., Casteel, DE., Hancock, JF., Lacey, E., Cunha, SR. et al. (2016). AMPK and Endothelial Nitric Oxide Synthase Signaling Regulates K-Ras Plasma Membrane Interactions via Cyclic GMP-Dependent Protein Kinase 2. *Mol. Cell. Biol., 36*, 3086-3099. ↗

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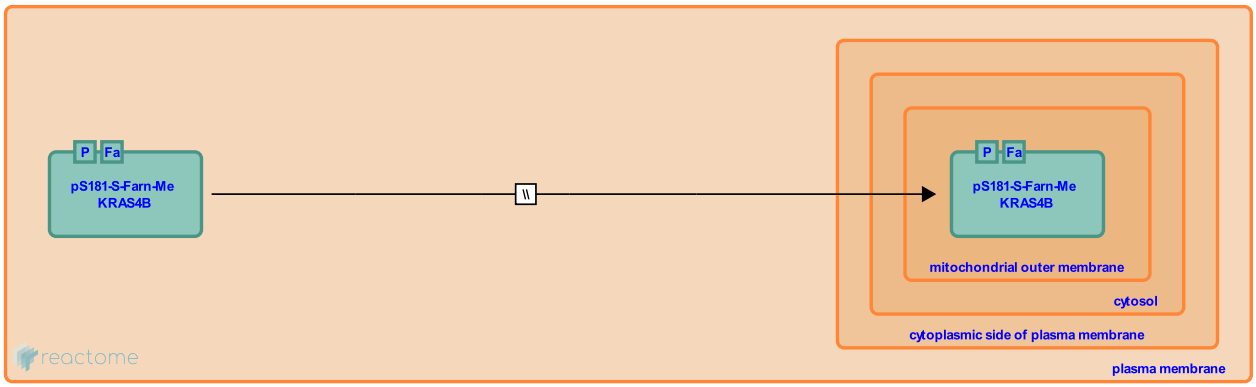
pS181-S-Farn-Me KRAS4B translocates to the outer mitochondrial membrane ↗

Location: RAS processing

Stable identifier: R-HSA-9653592

Type: omitted

Compartments: plasma membrane, mitochondrial outer membrane



PKC- or -PRKG2-dependent phosphorylation of KRAS4B at serine 181 promotes its trafficking to intracellular membranes, including the mitochondrial outer membrane where it interacts with BCL2L1 (also known as BCL-XL) to promote apoptosis (Bivona et al, 2006; Barcelo et al, 2013; Jang et al, 2015; reviewed in Ahearn et al, 2018).

Preceded by: KRAS4B is phosphorylated on serine 181

Followed by: pS181-S-Farn-Me KRAS4B binds BCL2L1

Literature references

Tebar, F., Beckett, AJ., Agell, N., Barceló, C., Prior, I., Paco, N. et al. (2013). Oncogenic K-ras segregates at spatially distinct plasma membrane signaling platforms according to its phosphorylation status. *J. Cell. Sci., 126*, 4553-9. ↗

Philips, MR., Zhou, M., Ahearn, I. (2018). Posttranslational Modifications of RAS Proteins. *Cold Spring Harb Perspect Med, 8*. ↗

Philips, MR., Bivona, TG., Thompson, CB., Ahearn, IM., Mor, A., Pérez De Castro, I. et al. (2006). PKC regulates a farnesyl-electrostatic switch on K-Ras that promotes its association with Bcl-XL on mitochondria and induces apoptosis. *Mol. Cell, 21*, 481-93. ↗

Nussinov, R., Tarasova, NI., Khavrutskii, L., Jang, H., Abraham, SJ., Gaponenko, V. et al. (2015). Mechanisms of membrane binding of small GTPase K-Ras4B farnesylated hypervariable region. *J. Biol. Chem., 290*, 9465-77. ↗

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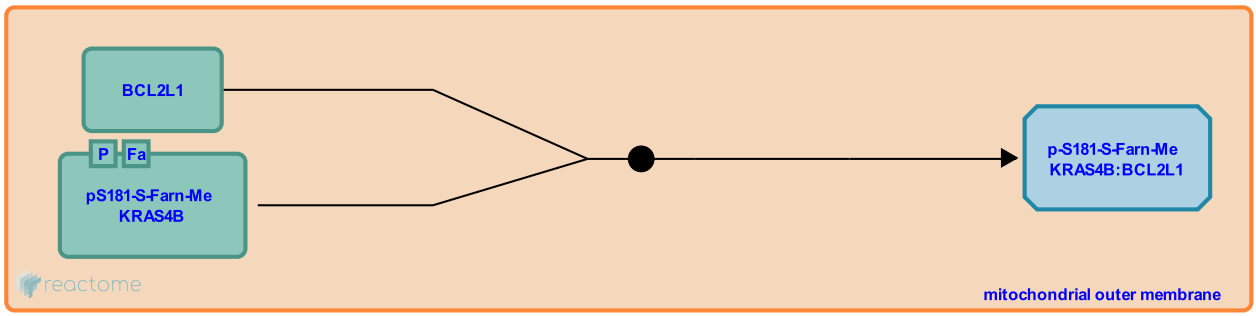
pS181-S-Farn-Me KRAS4B binds BCL2L1 ↗

Location: RAS processing

Stable identifier: R-HSA-9653595

Type: binding

Compartments: mitochondrial outer membrane



At the mitochondrial outer membrane, phosphorylated KRAS4B binds BCL2L1 (also known as BCL-XL) to promote apoptosis (Bivona et al, 2006; reviewed in Ahearn et al, 2018).

Preceded by: pS181-S-Farn-Me KRAS4B translocates to the outer mitochondrial membrane

Literature references

Philips, MR., Zhou, M., Ahearn, I. (2018). Posttranslational Modifications of RAS Proteins. *Cold Spring Harb Perspect Med, 8*. ↗

Philips, MR., Bivona, TG., Thompson, CB., Ahearn, IM., Mor, A., Pérez De Castro, I. et al. (2006). PKC regulates a farnesyl-electrostatic switch on K-Ras that promotes its association with Bcl-XL on mitochondria and induces apoptosis. *Mol. Cell, 21*, 481-93. ↗

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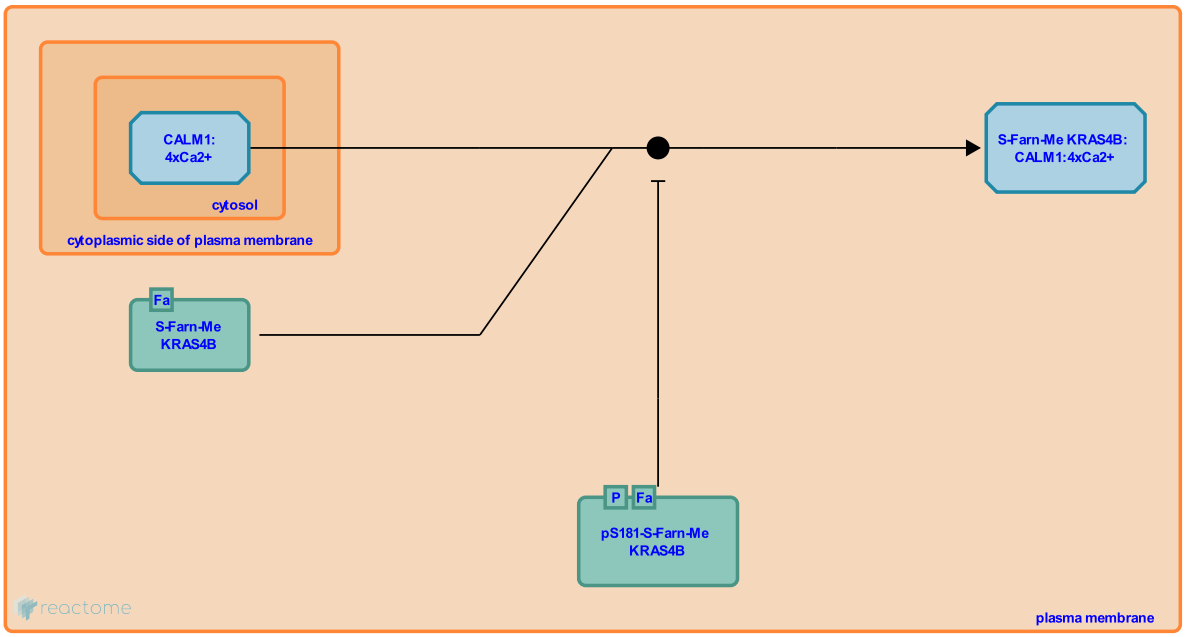
S-Farn-Me KRAS4B binds calmodulin ↗

Location: RAS processing

Stable identifier: R-HSA-9653585

Type: binding

Compartments: plasma membrane, cytosol



KRAS4B, unique among RAS isoforms, has been shown to bind to calmodulin (Villalonga et al, 2001; Lopez-Alcala et al, 2008). This interaction is thought to decrease the affinity of KRAS4B for the plasma membrane (Fivaz and Meyer, 2005; Sidhu et al, 2003; reviewed in Ahearn et al, 2018; Nussinov et al, 2015). Interaction between oncogenic KRAS4B and calmodulin has been shown to promote tumorigenesis by interfering with the activation of CAMK2. This in turn relieves the suppression of beta-catenin dependent signaling mediated by the non-canonical WNT signaling pathway (Wang et al, 2015).
The interaction between KRAS4B and calmodulin is inhibited by PKC- or PRKG2-dependent KRAS4B phosphorylation at serine 181 (Wang et al, 2015; Alvarez-Moya et al, 2010; reviewed in Ahearn et al, 2018).

Preceded by: Mature S-Farn-Me KRAS4B translocates to plasma membrane

Followed by: Calmodulin dissociates KRAS4B from the plasma membrane

Literature references

Balmain, A., Galeas, J., Wang, MT., To, MD., McCormick, F., Delrosario, R. et al. (2015). K-Ras Promotes Tumorigenicity through Suppression of Non-canonical Wnt Signaling. *Cell, 163*, 1237-1251. ↗

Lopez-Alcalá, C., Villalonga, P., Alvarez-Moya, B., Agell, N., Calvo, M., Bachs, O. (2008). Identification of essential interacting elements in K-Ras/calmodulin binding and its role in K-Ras localization. *J. Biol. Chem., 283*, 10621-31. ↗

Meyer, T., Fivaz, M. (2005). Reversible intracellular translocation of KRas but not HRas in hippocampal neurons regulated by Ca2+/calmodulin. *J. Cell Biol., 170*, 429-41. ↗

Villalonga, P., Rocamora, N., Bosch, M., Agell, N., Gil, J., López-Alcalá, C. et al. (2001). Calmodulin binds to K-Ras, but not to H- or N-Ras, and modulates its downstream signaling. *Mol. Cell. Biol., 21*, 7345-54. ↗

Philips, MR., Zhou, M., Ahearn, I. (2018). Posttranslational Modifications of RAS Proteins. *Cold Spring Harb Perspect Med, 8*. ↗

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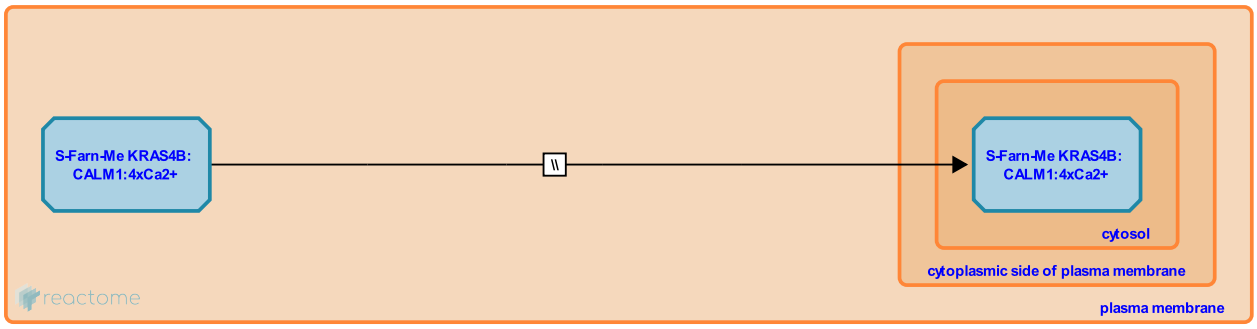
Calmodulin dissociates KRAS4B from the plasma membrane ↗

Location: RAS processing

Stable identifier: R-HSA-9654521

Type: omitted

Compartments: plasma membrane, cytosol



Ca2+/calmodulin-binding to KRAS4B dissociates it from the plasma membrane independent of nucleotide state (Firaz et al, 2005; Sidhu et al, 2003; Sperlich et al, 2016; reviewed in Shimashu et al, 2017).

Preceded by: S-Farn-Me KRAS4B binds calmodulin

Followed by: PDE6D binds S-Farn-Me KRAS4B:CALM:4 Ca2+

Literature references

Meyer, T., Fivaz, M. (2005). Reversible intracellular translocation of KRas but not HRas in hippocampal neurons regulated by Ca2+/calmodulin. *J. Cell Biol., 170*, 429-41. ↗

Weise, K., Waldmann, H., Winter, R., Sperlich, B., Kapoor, S. (2016). Regulation of K-Ras4B Membrane Binding by Calmodulin. *Biophys. J., 111*, 113-22. ↗

McCormick, F., Nissley, DV., Simanshu, DK. (2017). RAS Proteins and Their Regulators in Human Disease. *Cell, 170*, 17-33. ↗

Bhullar, RP., Clough, RR., Sidhu, RS. (2003). Ca2+/calmodulin binds and dissociates K-RasB from membrane. *Biochem. Biophys. Res. Commun., 304*, 655-60. ↗

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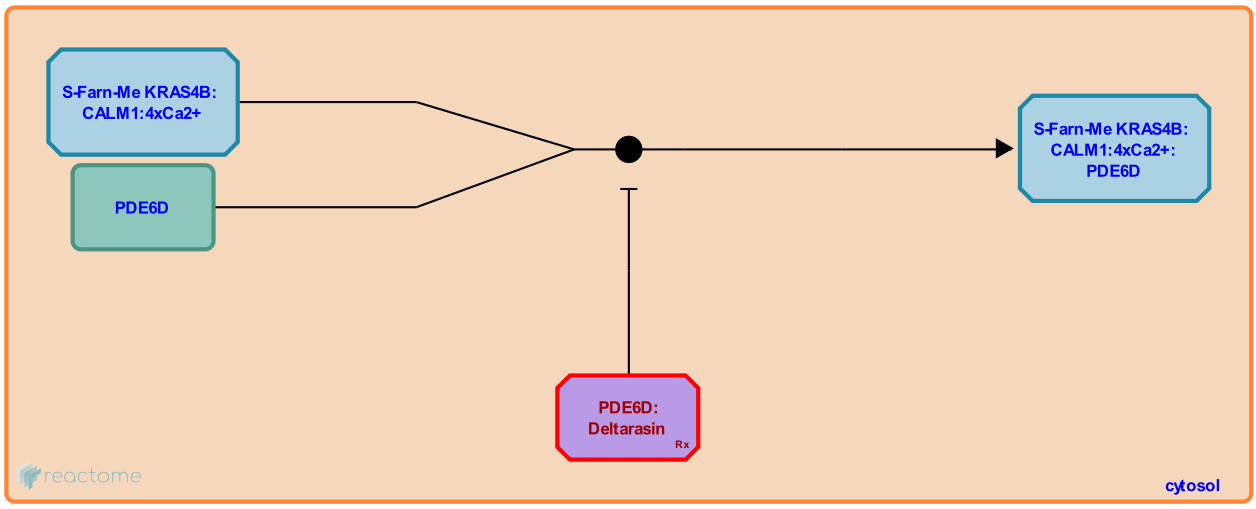
PDE6D binds S-Farn-Me KRAS4B:CALM:4 Ca2+

Location: RAS processing

Stable identifier: R-HSA-9654525

Type: binding

Compartments: cytosol



PDE6D binds to prenylated KRAS4B after calmodulin-stimulated dissociation from the plasma membrane (Chandra et al, 2011; Zhang et al, 2004; Weise et al, 2012; Dharmaiah et al, 2016; reviewed in Schmick et al, 2015; Baehr et al, 2014). Interaction with PDE6D may facilitate the return of KRAS4B to the plasma membrane by promoting subsequent interaction with ARL2 or ARL3 (Ismail et al, 2011; Schmick et al, 2014; Sperlich et al, 2016). This pathway counters the tendency of KRAS4B to diffuse throughout the extensive endomembrane system of the cell, in a manner analogous to the dynamic palmitoylation/depalmitoylation cycle for NRAS and HRAS (Dekker et al, 2010; Rocks et al, 2010; Schmick et al, 2014; reviewed in Schmick et al, 2015).

Preceded by: Calmodulin dissociates KRAS4B from the plasma membrane

Followed by: ARL2:GTP bind PDE6D on KRAS4B

Literature references

Chandra, A., Huang, ZP., Pechlivanis, M., Gerauer, M., Ellinger, B., Waldmann, H. et al. (2010). The palmitoylation machinery is a spatially organizing system for peripheral membrane proteins. *Cell, 141*, 458-71.

Waldmann, H., Bastiaens, PI., Rusch, M., Vartak, N., Brunsveld, L., Rocks, O. et al. (2010). Small-molecule inhibition of APT1 affects Ras localization and signaling. *Nat. Chem. Biol., 6*, 449-56.

Dharmaiah, S., Bindu, L., Ghirlando, R., Frank, PH., McCormick, F., Gillette, WK. et al. (2016). Structural basis of recognition of farnesylated and methylated KRAS4b by PDEδ. *Proc. Natl. Acad. Sci. U.S.A., 113*, E6766-E6775.

Rusinova, A., Chandra, A., Triola, G., Bierbaum, M., Waldmann, H., Bastiaens, PI. et al. (2011). Arl2-GTP and Arl3-GTP regulate a GDI-like transport system for farnesylated cargo. *Nat. Chem. Biol., 7*, 942-9.

Weise, K., Waldmann, H., Winter, R., Sperlich, B., Kapoor, S. (2016). Regulation of K-Ras4B Membrane Binding by Calmodulin. *Biophys. J., 111*, 113-22.

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Deltarasin binds PDE6D ↗

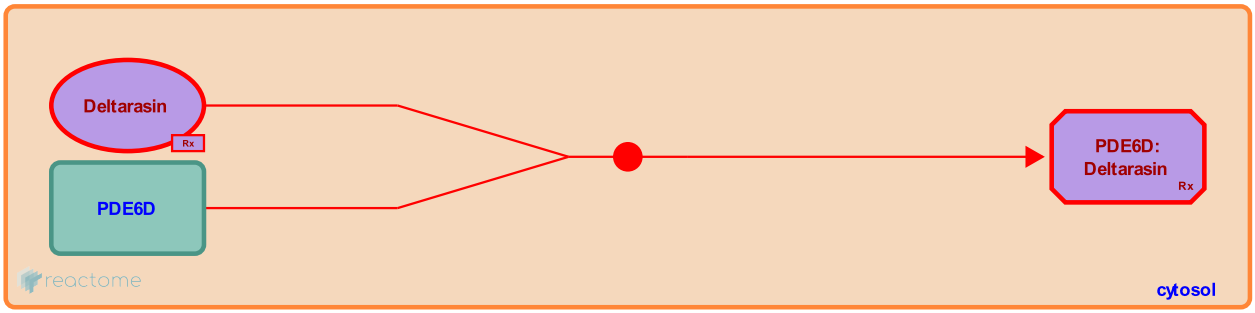
Location: RAS processing

Stable identifier: R-HSA-9656781

Type: binding

Compartments: cytosol

Diseases: cancer



Deltarasin is a small molecule inhibitor of PDE6D that binds in the farnesyl-binding pocket of the enzyme and prevents interaction with KRAS4B and other farnesylated proteins (Zimmerman et al, 2013). PDE6D inhibition results in RAS protein mislocalization and reduces cellular proliferation and increase cell death in KRAS-dependent pancreatic cell lines (Zimmerman et al, 2013; reviewed in Shimansu et al, 2017). Other farnesyl-pocket binding small molecule inhibitors are also under development (Papke et al, 2016).

Literature references

Chandra, A., Triola, G., Ismail, S., Waldmann, H., Hoffmann, M., Zimmermann, G. et al. (2013). Small molecule inhibition of the KRAS-PDEδ interaction impairs oncogenic KRAS signalling. *Nature, 497*, 638-42. ↗

Nussbaumer, P., Al Saabi, A., Vogel, HA., Heinelt, K., Schultz-Fademrecht, C., Ismail, S. et al. (2016). Identification of pyrazolopyridazinones as PDEδ inhibitors. *Nat Commun, 7*, 11360. ↗

McCormick, F., Nissley, DV., Simanshu, DK. (2017). RAS Proteins and Their Regulators in Human Disease. *Cell, 170*, 17-33. ↗

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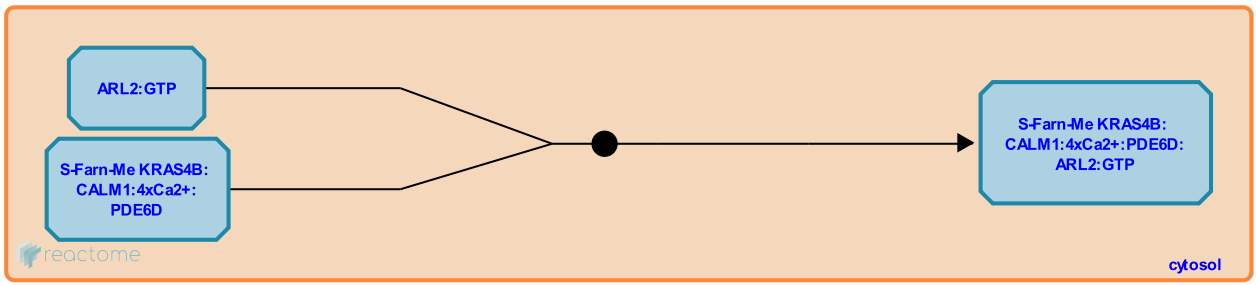
ARL2:GTP bind PDE6D on KRAS4B ↗

Location: RAS processing

Stable identifier: R-HSA-9654523

Type: binding

Compartments: cytosol



ARL2:GTP binds to an allosteric site on PDE6D, promoting a conformational change in PDE6D that releases the prenyl group on KRAS4B (Ismail et al, 2011; Schmick et al, 2014; reviewed in Schmick et al, 2015). Although the details remain to be fully established, it is possible that after release from PDE6D, KRAS4B is recycled to the plasma membrane by virtue of interaction with the negatively charged membrane of recyling endosomes (Chen et al, 2010; Schmick et al, 2014; reviewed in Schmick et al, 2015).

Preceded by: PDE6D binds S-Farn-Me KRAS4B:CALM:4 Ca2+

Followed by: KRAS4B recycles to the plasma membrane

Literature references

Rusinova, A., Chandra, A., Triola, G., Bierbaum, M., Waldmann, H., Bastiaens, PI. et al. (2011). Arl2-GTP and Arl3-GTP regulate a GDI-like transport system for farnesylated cargo. *Nat. Chem. Biol., 7*, 942-9. ↗

Schmick, M., Rossmannek, L., Kovacevic, M., Truxius, DC., Bastiaens, PIH., Papke, B. et al. (2014). KRas localizes to the plasma membrane by spatial cycles of solubilization, trapping and vesicular transport. *Cell, 157*, 459-471. ↗

Schmick, M., Bastiaens, PI., Kraemer, A. (2015). Ras moves to stay in place. *Trends Cell Biol., 25*, 190-7. ↗

Yan, J., Li, X., Zhang, Y., Zeng, S., Chen, B., Zou, W. et al. (2010). Endocytic sorting and recycling require membrane phosphatidylserine asymmetry maintained by TAT-1/CHAT-1. *PLoS Genet., 6*, e1001235. ↗

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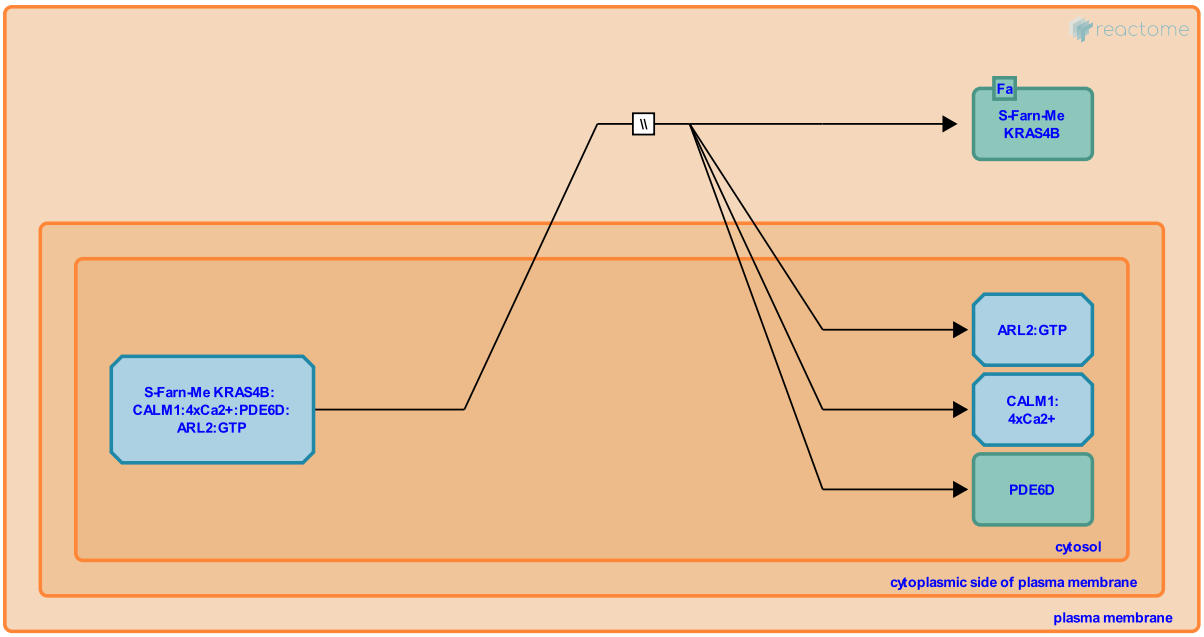
KRAS4B recycles to the plasma membrane ↗

Location: RAS processing

Stable identifier: R-HSA-9654533

Type: omitted

Compartments: plasma membrane, cytosol



ARL2:GTP facilitates the release of the farnesyl group on KRAS4B by promoting a conformational change in PDE6D (Ismail et al, 2011; Schmick et al, 2014). This step is required for the proper localization of KRAS4B at the plasma membrane, but the complete details of this are not fully established. Newly liberated KRAS4B by interact with the negatively charged membrane of recycling endosome and in this way be targeted back to the plasma membrane (Chen et al, 2010; Schmick et al, 2014; reviewed in Schmick et al, 2015

Preceded by: ARL2:GTP bind PDE6D on KRAS4B

Literature references

Rusinova, A., Chandra, A., Triola, G., Bierbaum, M., Waldmann, H., Bastiaens, PI. et al. (2011). Arl2-GTP and Arl3-GTP regulate a GDI-like transport system for farnesylated cargo. *Nat. Chem. Biol., 7*, 942-9. ↗

Schmick, M., Rossmannek, L., Kovacevic, M., Truxius, DC., Bastiaens, PIH., Papke, B. et al. (2014). KRas localizes to the plasma membrane by spatial cycles of solubilization, trapping and vesicular transport. *Cell, 157*, 459-471. ↗

Schmick, M., Bastiaens, PI., Kraemer, A. (2015). Ras moves to stay in place. *Trends Cell Biol., 25*, 190-7. ↗

Yan, J., Li, X., Zhang, Y., Zeng, S., Chen, B., Zou, W. et al. (2010). Endocytic sorting and recycling require membrane phosphatidylserine asymmetry maintained by TAT-1/CHAT-1. *PLoS Genet., 6*, e1001235. ↗

Editions

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