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.

13/11/2022

https://reactome.org
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


Reactome database release: 82

This document contains 1 pathway and 21 reactions (see Table of Contents)
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


Editions

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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**


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**


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https://reactome.org
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

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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).

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

Literature references


**Cysmethynil binds ICMT:Zn2+**

**Location:** RAS processing

**Stable identifier:** R-HSA-9656775

**Type:** binding

**Compartments:** endoplasmic reticulum membrane, cytosol

**Diseases:** cancer

Cysmethynil 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).

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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


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


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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

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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 trans locate to plasma membrane

Literature references


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


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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).

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

**Literature references**


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**RAS proteins bind 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

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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 suppression 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


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

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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

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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-Alcalá 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

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**Preceded by:** S-Farn-Me KRAS4B binds calmodulin

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

**Literature references**


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/de-palmitoylation 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

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https://reactome.org
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).

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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 recycling 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**


**Editions**

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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 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**


**Editions**

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