RAB geranylgeranylation

Palsuledesai, CC., Rothfels, K.

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

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

25/02/2020
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: 71

This document contains 1 pathway and 5 reactions (see Table of Contents)
Human cells have more than 60 RAB proteins that are involved in trafficking of proteins in the endolysosomal system. These small GTPases contribute to trafficking specificity by localizing to the membranes of different endocytic compartments and interacting with effectors such as sorting adaptors, tethering factors, kinases, phosphatases and tubular-vesicular cargo (reviewed in Stenmark et al, 2009; Wandinger-Ness and Zerial, 2014). RAB localization depends on a number of factors including C-terminal prenylation, the sequence of an upstream hypervariable region and what nucleotide is bound (Chavrier et al, 1991; Ullrich et al, 1993; Soldati et al, 1994; Farnsworth et al, 1994; Seabra, 1996; Wu et al, 2010; reviewed in Stenmark, 2009; Wandinger-Ness and Zerial, 2014). In the active, GTP-bound form, prenylated RAB proteins are membrane associated, while in the inactive GDP-bound form, RABs are extracted from the target membrane and exist in a soluble form in complex with GDP dissociation inhibitors (GDIs) (Ullrich et al, 1993; Soldati et al, 1994; Gavriljuk et al, 2013). Conversion between the inactive and active form relies on the activities of RAB guanine nucleotide exchange factors (GEFs) and GTPase activating proteins (GAPs) (Yoshimura et al, 2010; Wu et al, 2011; Pan et al, 2006; Frasa et al, 2012; reviewed in Stenmark, 2009; Wandinger-Ness and Zerial, 2014).

Newly synthesized RABs are bound by a RAB escort protein, CHM (also known as REP1) or CHML (REP2) (Alexandrov et al, 1994; Shen and Seabra, 1996). CHM/REP proteins are the substrate-binding component of the trimeric RAB geranylgeranyltransferase enzyme (GGTaseII) along with the two catalytic subunits RABGGTA and RABGGTB (reviewed in Gutkowska and Swiezewska, 2012; Palsulesdesai and Distefano, 2015). REP proteins recruit the unmodified RAB in its GDP-bound state to the GGTase for sequential geranylgeranylation at one or two C-terminal cysteine residues (Alexandrov et al, 1994; Seabra et al 1996; Shen and Seabra, 1996; Baron and Seabra, 2008). After geranylgeranylation, CHM/REP proteins remain in complex with the geranylgeranylated RAB and escort it to its target membrane, where its activity is regulated by GAPs, GEFs, GDIs and membrane-bound GDI displacement factors (GDFs) (Sivars et al, 2003; reviewed in Stenmark, 2009; Wandinger-Ness and Zerial, 2014).

Literature references


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016-06-03</td>
<td>Authored, Edited</td>
<td>Rothfels, K.</td>
</tr>
<tr>
<td>2016-08-04</td>
<td>Reviewed</td>
<td>Palsuledesai, CC.</td>
</tr>
</tbody>
</table>
**FarC-PTP4A2 binds RABGGTB**

**Location:** RAB geranylgeranylation

**Stable identifier:** R-HSA-8870457

**Type:** binding

**Compartments:** cytosol

PTP4A2, also known as PRL2, is a member of the protein tyrosine phosphatase family. Farnesylated PTP4A2 interacts with RABGGTB, one of the two catalytic subunits of the RAB geranylgeranyl transferase complex and prevents its association with the other catalytic subunit RABGBTA (Si et al, 2001). In this way, binding of PTP4A2 acts as a negative regulator of RAB geranylgeranylation (reviewed in Gutkowska and Swiezewska, 2012).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016-06-08</td>
<td>Authored, Edited</td>
</tr>
<tr>
<td>2016-08-04</td>
<td>Reviewed</td>
</tr>
</tbody>
</table>

Rothfels, K.  
Palsuledesai, CC.
RABGGTA and RABGGTB bind

**Location:** RAB geranylgeranylation

**Stable identifier:** R-HSA-8870461

**Type:** binding

**Compartments:** cytosol

RABGGTA and RABGGTB are the two catalytic subunits of a trimeric RAB geranylgeranyl transferase complex (GGTase); the third subunit is the RAB binding subunit CHM or CHML (reviewed in Leung et al, 2006; Gutkowska and Swiezewska, 2012). RABGGTB also interacts in a mutually exclusive way with PT-P4A2, preventing formation of a functional germagnerylgeranyl transferase complex (Si et al, 2001; Baron and Seabra, 2008). Newly synthesized RAB proteins are singly or more commonly doubly geranylgeranylated near their C-termini by the GGTase. Geranylgeranylation promotes association of active RAB proteins with membranes. Membrane association is additionally modulated by the nucleotide state of the GTPase through regulatory proteins such as guanine nucleotide exchange factors (GEFs), GTPase activating proteins (GAPs) and GDP Dissociation Inhibitors (GDIs), among others (reviewed in Stenmark et al, 2009; Wandinger-Ness and Zerial, 2014). An exception to this is RAB13, which has recently been shown to be membrane-associated even in the inactive state and to traffic on vesicles independently of geranylgeranylation (Ioannou et al, 2016).

**Followed by:** RGGT binds the RAB-binding subunit

**Literature references**


RGGT binds the RAB-binding subunit

**Location:** RAB geranylgeranylation

**Stable identifier:** R-HSA-8870465

**Type:** binding

**Compartments:** cytosol

The catalytic dimer of RGGTA and B interacts with RAB-escorting proteins 1 or 2 (CHM and CHML, also known as REP-1 and REP-2) to form a functional trimeric RAB geranylgeranyl transferase complex that is capable of binding and geranylgeranylation newly synthesized RAB proteins (Baron and Seabra, 2008; reviewed in Leung et al, 2006; Gutkowska and Swiezewska, 2012). There are two models for the formation of a functional enzyme:substrate complex. In the classical model, unprenylated RAB first binds to REP and is subsequently presented to the catalytic subunits of the GGTase. Incorporation of geranylgeranyl pyrophosphate (GGPP) strengthens the interaction between enzyme and substrate (Andres et al, 1993; Thomä et al, 2001a). In the alternate route, which is depicted in this pathway, RGGTA and RGGTB first bind to REP in a GGPP-dependent manner in the absence of the RAB substrate. Unprenylated RABs then bind to the fully formed GGTase for geranylgeranylation (Thoma et al, 2001b; Baron and Seabra, 2008).

**Preceded by:** RABGGTA and RABGGTB bind

**Followed by:** RGGT:CHM binds RABs

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Edition</th>
<th>Date</th>
<th>Revision</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2016-06-08</td>
<td>Authored, Edited</td>
<td>Rothfels, K.</td>
</tr>
<tr>
<td></td>
<td>2016-08-04</td>
<td>Reviewed</td>
<td>Palsuledesai, CC.</td>
</tr>
</tbody>
</table>
RGGT:CHM binds RABs

**Location:** RAB geranylgeranylation

**Stable identifier:** R-HSA-8870466

**Type:** binding

**Compartments:** cytosol

CHM and CHML are the substrate-binding subunits of the RAB geranylgeranyltransferase (GGTase) complex. CHMs, also known as RAB escort proteins (REPs) bind to unprenylated RAB proteins in the GDP bound state (Seabra, 1996). In the classical model of RAB recruitment, CHM proteins first bind the unprenylated RAB alone and then present it to the catalytic dimer of the RAB GGTase, while in the alternative model, depicted here, RAB recruitment occurs after the GGPP-dependent formation of a highly stable trimeric GGTase complex (Andres et al, 1993; Thoma et al, 2001a; Thoma et al 2001b; Baron and Seabra, 2008). After geranylgeranylation, binding of additional GGPP to the GGTase promotes release of the CHM:RAB complex, possibly through an allosteric mechanism (Baron and Seabra, 2008). CHM proteins remain in complex with the RABs after geranylgeranylation, dissociating after the RAB has been transferred to the target membrane (Alexandrov et al, 1994; Shen and Seabra, 1996; Baron and Seabra, 2008).

**Preceded by:** RGGT binds the RAB-binding subunit

**Followed by:** RGGT geranylgeranylates RAB proteins

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016-06-08</td>
<td>Authored, Edited</td>
<td>Rothfels, K.</td>
</tr>
<tr>
<td>2016-08-04</td>
<td>Reviewed</td>
<td>Palsuledesai, CC.</td>
</tr>
</tbody>
</table>
RGGT geranylgeranylates RAB proteins

Location: RAB geranylgeranylation

Stable identifier: R-HSA-8870469

Type: transition

Compartments: cytosol

RAB geranylgeranyltransferase (GGTase) recognizes and geranylgeranylates cysteine residues in -CXCX, -CCXX or -XXCC motifs in the C-termini of RAB proteins. Most RAB proteins are doubly geranylgeranylated, most likely in a sequential fashion, but some are only singly modified (Baron and Seabra, 2008; Farnsworth et al 1994; Wilson et al, 1996; Overmeyer et al, 2001; Khosravi-Far et al, 1991; Joberty et al, 1993; Catherman et al, 2013; Leung et al, 2007; Maurer-Stroh et al, 2007). In most cases, geranylgeranylation is required for proper localization and function of the RAB proteins. After geranylgeranylation, RABs remain associated with the RAB escort protein CHM or CHML, which dissociates when the GTPase reaches its target membrane (Alexandrov et al, 1994; Seabra et al, 1996; Shen and Seabra, 1996). Release of the geranylgeranyl RAB:CHM complex from the catalytic subunits is promoted by the binding of additional GGPP to the enzyme (Baron and Seabra, 2008). Once prenylated, RABs cycle between active GTP bound forms that are membrane associated, and inactive GDP bound forms that are cytosolic and associated with RAB GDP dissociation inhibitor (GDI) proteins. Conversion between these states is governed by the activities of guanine nucleotide exchange factors (GEFs), which promote the exchange of GDP for GTP, and GTPase activating proteins (GAPs), which stimulate the intrinsic GTPase activity of RABs (Ulrich et al, 1993; Soldati et al, 1994; reviewed in Wandinger-Ness and Zerial, 2014; Stenmark, 2009).

Preceded by: RGGT:CHM binds RABs

Literature references


https://reactome.org
<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016-06-08</td>
<td>Authored, Edited</td>
<td>Rothfels, K.</td>
</tr>
<tr>
<td>2016-08-04</td>
<td>Reviewed</td>
<td>Palsuledesai, CC.</td>
</tr>
</tbody>
</table>
Table of Contents

Introduction 1

RAB geranylgeranylation 2
  ➢ FarC-PTP4A2 binds RABGGTB 4
  ➢ RABGGTA and RABGGTB bind 5
  ➢ RGGT binds the RAB-binding subunit 7
  ➢ RGGT:CHM binds RABs 8
  ➢ RGGT geranylgeranylates RAB proteins 9

Table of Contents 11