Synthesis of PIPs at the early endosome membrane

D'Eustachio, P., Jupe, S., Orlic-Milacic, M., Rush, MG., Wakelam, M., Williams, MG.

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.

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.

18/11/2022
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 13 reactions (see Table of Contents)

https://reactome.org
Synthesis of PIPs at the early endosome membrane

Stable identifier: R-HSA-1660516

At the early endosome membrane, phosphatidylinositol 3,5-bisphosphate (PI(3,5)P2) is generated in two steps from phosphatidylinositol 3,4-bisphosphate PI(3,4)P2 by the action of various kinases and phosphatases (Sbrissa et al. 2007, Sbrissa et al. 2008, Cao et al. 2007, Cao et al. 2008, Arcaro et al. 2000, Kim et al. 2002).

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Username</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-08-12</td>
<td>Edited</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2011-10-18</td>
<td>Authored</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2012-05-14</td>
<td>Reviewed</td>
<td>Wakelam, M.</td>
</tr>
<tr>
<td>2017-02-24</td>
<td>Revised</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
PI(3,4)P2 is dephosphorylated to PI3P by INPP4A/B at the early endosome membrane

Location: Synthesis of PIPs at the early endosome membrane

Stable identifier: R-HSA-1676162

Type: transition

Compartments: cytosol, early endosome membrane

At the early endosome membrane, type I (INPP4A) (Norris et al. 1995, Ivetac et al. 2005) and type II inositol-3,4-bisphosphate 4-phosphatase (INPP4B) (Norris et al. 1997) colocalise with early and recycling endosomes through their C2 domains which bind to the phosphatidylinositol 3,4-bisphosphate (PI(3,4)P2) present in these membranes. It is here that phosphatidylinositol 3,4-bisphosphate (PI(3,4)P2) is dephosphorylated by INPP4A/B to phosphatidylinositol 3-phosphate (PI3P).

Preceded by: PI4P is phosphorylated to PI(3,4)P2 by PIK3C2A at the early endosome membrane

Followed by: PI3P is dephosphorylated to PI by MTM1:MTMR12, PI3P is phosphorylated to PI(3,5)P2 by PIKFYVE at the early endosome membrane, PI3P is dephosphorylated to PI by MTM proteins at the early endosome membrane

Literature references


Atkins, RC., Majerus, PW., Norris, FA. (1997). The cDNA cloning and characterization of inositol polyphosphate 4-phosphatase type II. Evidence for conserved alternative splicing in the 4-phosphatase family. J Biol Chem, 272, 23859-64.
<table>
<thead>
<tr>
<th>Editions</th>
<th>Date</th>
<th>Action</th>
<th>Person</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-08-12</td>
<td>Edited</td>
<td>Williams, MG.</td>
<td></td>
</tr>
<tr>
<td>2011-10-18</td>
<td>Authored</td>
<td>Williams, MG.</td>
<td></td>
</tr>
<tr>
<td>2012-05-14</td>
<td>Reviewed</td>
<td>Wakelam, M.</td>
<td></td>
</tr>
</tbody>
</table>
PI(4,5)P2, PI(3,4)P2 and PI(3,4,5)P3 are dephosphorylated to PI5P, PI3P and PI(3,4)P by INPP5F at the endosome membrane

**Location:** Synthesis of PIPs at the early endosome membrane

**Stable identifier:** R-HSA-8849969

**Type:** transition

**Compartments:** early endosome membrane, cytosol

Characterization of human INPP5F (SAC2) identified that it is a 4-phosphatase with highest activity against PI(4,5)P2, PI(3,4)P2, and PI(3,4,5)P3, generating PI(5)P, PI(3)P and PI(3,5)P2 respectively (Nakatsu et al. 2015, Hsu et al. 2015). Inpp5f-/- mice have elevated level of PIP3 and exhibit accentuated cardiac hypertrophy as measured by heart size, myocyte size and gene expression (Zhu et al. 2009).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-12-18</td>
<td>Authored</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2016-01-04</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2016-01-05</td>
<td>Reviewed</td>
<td>D'Eustachio, P.</td>
</tr>
</tbody>
</table>
PI3P is phosphorylated to PI(3,5)P2 by PIKFYVE at the early endosome membrane

**Location:** Synthesis of PIPs at the early endosome membrane

**Stable identifier:** R-HSA-1676168

**Type:** transition

**Compartments:** cytosol, early endosome membrane

**Inferred from:** PI3P is phosphorylated to PI(3,5)P2 by Pikfyve at the early endosome membrane (Mus musculus)

At the early endosome membrane, the PAS complex, consisting of FYVE finger-containing phosphoinositide kinase (PIKFYVE), yeast VAC14 homologue (VAC14), and polyphosphoinositide phosphatase aka SAC3 (FIG4), binds to the membrane via PIKFYVE's FYVE finger (Sbrissa et al. 2002, Cao et al. 2007). The PIKFYVE kinase component phosphorylates phosphatidylinositol 3-phosphate (PI3P) to phosphatidylinositol 3,5-bisphosphate PI(3,5)P2 (Sbrissa et al. 1999). The PAS complex is present in the cytosol and is recruited to the membrane (Sbrissa et al. 2007).

**Preceded by:** PI(3,4)P2 is dephosphorylated to PI3P by INPP4A/B at the early endosome membrane, PI is phosphorylated to PI3P by PIK3C2A/3 at the early endosome membrane, PI(3,5)P2 is dephosphorylated to PI3P by FIG4 at the early endosome membrane

**Followed by:** PI(3,5)P2 is dephosphorylated to PI5P by MTM proteins at the early endosome membrane, PI(3,5)P2 is dephosphorylated to PI3P by FIG4 at the early endosome membrane

**Literature references**


https://reactome.org

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-08-12</td>
<td>Edited</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2011-10-18</td>
<td>Authored</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2012-05-14</td>
<td>Reviewed</td>
<td>Wakelam, M.</td>
</tr>
</tbody>
</table>
PI(3,5)P2 is dephosphorylated to PI3P by FIG4 at the early endosome membrane

Location: Synthesis of PIPs at the early endosome membrane

Stable identifier: R-HSA-1676174

Type: transition

Compartments: cytosol, early endosome membrane

At the early endosome membrane, the PAS complex, consisting of FYVE finger-containing phosphoinositide kinase (PIKFYVE), yeast VAC14 homologue (VAC14), and polyphosphoinositide phosphatase aka SAC3 (FIG4), binds to the membrane via PIKFYVE's FYVE finger. The FIG4 phosphatase component dephosphorylates phosphatidylinositol 3,5-bisphosphate (PI(3,5)P2) to phosphatidylinositol 3-phosphate (PI3P) (Sbrissa et al. 2007, Sbrissa et al. 2008).

Preceded by: PI3P is phosphorylated to PI(3,5)P2 by PIKFYVE at the early endosome membrane

Followed by: PI3P is dephosphorylated to PI by MTM1:MTMR12, PI3P is dephosphorylated to PI by MTM proteins at the early endosome membrane, PI3P is phosphorylated to PI(3,5)P2 by PIKFYVE at the early endosome membrane

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-08-12</td>
<td>Edited</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2011-10-18</td>
<td>Authored</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2012-05-14</td>
<td>Reviewed</td>
<td>Wakelam, M.</td>
</tr>
</tbody>
</table>
PI(3,5)P2 is dephosphorylated to PI5P by MTM proteins at the early endosome membrane

**Location:** Synthesis of PIPs at the early endosome membrane

**Stable identifier:** R-HSA-1676105

**Type:** transition

**Compartments:** cytosol, early endosome membrane

At the early endosome membrane, myotubularin (MTM1), myotubularin-related protein 2 (MTMR2) and myotubularin-related protein 4 (MTMR4) dephosphorylate phosphatidylinositol 3,5-bisphosphate (PI(3,5)P2) to phosphatidylinositol 5-phosphate (PI5P).

The following lists the above proteins with their corresponding literature references: MTM1 (Cao et al. 2007, Cao et al. 2008), MTMR2 (Cao et al. 2008), and MTMR4 (Lorenzo et al. 2006).

**Preceded by:** PI3P is phosphorylated to PI(3,5)P2 by PIKFYVE at the early endosome membrane

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-08-12</td>
<td>Edited</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2011-10-18</td>
<td>Authored</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2012-05-14</td>
<td>Reviewed</td>
<td>Wakelam, M.</td>
</tr>
<tr>
<td>2017-01-10</td>
<td>Reviewed</td>
<td>Rush, MG.</td>
</tr>
<tr>
<td>2017-01-25</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
PI is phosphorylated to PI3P by PIK3C2A/3 at the early endosome membrane

**Location:** Synthesis of PIPs at the early endosome membrane

**Stable identifier:** R-HSA-1675939

**Type:** transition

**Compartments:** cytosol, early endosome membrane

At the early endosome membrane, phosphatidylinositol 3-kinase catalytic subunit type 3 (PIK3C3) aka VPS34 binds to phosphoinositide 3-kinase regulatory subunit 4 (PIK3R4). The PIK3C3:PIK3R4 complex and phosphatidylinositol-4-phosphate 3-kinase C2 domain-containing subunit alpha (PIK3C2A) phosphorylate phosphatidylinositol (PI) to phosphatidylinositol 3-phosphate (PI3P).


**Preceded by:** PI3P is dephosphorylated to PI by MTM proteins at the early endosome membrane

**Followed by:** PI3P is dephosphorylated to PI by MTM1:MTMR12, PI3P is phosphorylated to PI(3,5)P2 by PIKFYVE at the early endosome membrane, PI3P is dephosphorylated to PI by MTM proteins at the early endosome membrane

**Literature references**


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-08-12</td>
<td>Edited</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2011-10-18</td>
<td>Authored</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2012-05-14</td>
<td>Reviewed</td>
<td>Wakelam, M.</td>
</tr>
</tbody>
</table>
**PI3P is dephosphorylated to PI by MTM proteins at the early endosome membrane**

**Location:** Synthesis of PIPs at the early endosome membrane

**Stable identifier:** R-HSA-1676141

**Type:** transition

**Compartments:** cytosol, early endosome membrane

At the early endosome membrane, myotubularin (MTM1), myotubularin-related protein 2 (MTMR2), and myotubularin-related protein 4 (MTMR4) dephosphorylate phosphatidylinositol 3-phosphate (PI3P) to phosphatidylinositol (PI).


**Preceded by:** PI(3,4)P2 is dephosphorylated to PI3P by INPP4A/B at the early endosome membrane, PI is phosphorylated to PI3P by PIK3C2A/3 at the early endosome membrane, PI(3,5)P2 is dephosphorylated to PI3P by FIG4 at the early endosome membrane

**Followed by:** PI is phosphorylated to PI3P by PIK3C2A/3 at the early endosome membrane, PI is phosphorylated to PI4P by PI4K2A/B at the early endosome membrane

**Literature references**


<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-08-12</td>
<td>Edited</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2011-10-18</td>
<td>Authored</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2012-05-14</td>
<td>Reviewed</td>
<td>Wakelam, M.</td>
</tr>
<tr>
<td>2017-01-10</td>
<td>Reviewed</td>
<td>Rush, MG.</td>
</tr>
<tr>
<td>2017-01-25</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
MTMR12 binds MTM1

**Location:** Synthesis of PIPs at the early endosome membrane

**Stable identifier:** R-HSA-6809680

**Type:** binding

**Compartments:** cytosol

MTM1 forms a complex with MTMR12 (3 PAP), an enzymatically inactive myotubularin family member. MTMR12 promotes MTM1 recruitment to cytosolic vesicular structures, presumably early or late endosomes. Complex formation stabilizes both MTM1 and MTMR12 proteins (Caldwell et al. 1991, Nandurkar et al. 2003, Gupta et al. 2013).

**Followed by:** PI3P is dephosphorylated to PI by MTM1:MTMR12

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-11-13</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2017-01-10</td>
<td>Reviewed</td>
<td>Rush, MG.</td>
</tr>
<tr>
<td>2017-01-25</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
PI3P is dephosphorylated to PI by MTM1:MTMR12

**Location:** Synthesis of PIPs at the early endosome membrane

**Stable identifier:** R-HSA-6809720

**Type:** transition

**Compartments:** cytosol, early endosome membrane

Binding of MTMR12 to MTM1 enhances phosphatidylinositol-3-phosphatase activity of MTM1 at cytosolic vesicular structures, presumably early or late endosomes (Caldwell et al. 1991, Nandurkar et al. 2003, Gupta et al. 2013).

**Preceded by:** PI(3,4)P2 is dephosphorylated to PI3P by INPP4A/B at the early endosome membrane, PI is phosphorylated to PI3P by PIK3C2A/3 at the early endosome membrane, MTMR12 binds MTM1, PI(3,5)P2 is dephosphorylated to PI3P by FIG4 at the early endosome membrane

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Reviewer</th>
<th>User</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-11-13</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2017-01-10</td>
<td>Reviewed</td>
<td>Rush, MG.</td>
</tr>
<tr>
<td>2017-01-25</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>

https://reactome.org
MTMR12 binds MTMR2

Location: Synthesis of PIPs at the early endosome membrane

Stable identifier: R-HSA-6809707

Type: binding

Compartments: cytosol

MTMR2 forms a complex with MTMR12, an enzymatically inactive myotubularin family member. The consequences of this interaction on enzymatic activity and localization of MTMR2 have not been examined (Nandurkar et al. 2003).

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-11-13</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2017-01-10</td>
<td>Reviewed</td>
<td>Rush, MG.</td>
</tr>
<tr>
<td>2017-01-25</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
PI is phosphorylated to PI4P by PI4K2A/B at the early endosome membrane

Location: Synthesis of PIPs at the early endosome membrane

Stable identifier: R-HSA-1675974

Type: transition

Compartments: cytosol, early endosome membrane

At the early endosome membrane, phosphatidylinositol 4-kinase type 2-alpha/beta (PI4K2A/B) (Balla et al. 2002) phosphorylates phosphatidylinositol (PI) to produce phosphatidylinositol 4-phosphate (PI4P).

Preceded by: PI3P is dephosphorylated to PI by MTM proteins at the early endosome membrane

Followed by: PI4P is phosphorylated to PI(3,4)P2 by PIK3C2A at the early endosome membrane

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-08-12</td>
<td>Edited</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2011-10-18</td>
<td>Authored</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2012-05-14</td>
<td>Reviewed</td>
<td>Wakelam, M.</td>
</tr>
</tbody>
</table>
PI4P is phosphorylated to PI(3,4)P2 by PIK3C2A at the early endosome membrane

**Location:** Synthesis of PIPs at the early endosome membrane

**Stable identifier:** R-HSA-1676206

**Type:** transition

**Compartments:** cytosol, early endosome membrane

At the early endosome membrane, phosphatidylinositol-4-phosphate 3-kinase C2 domain-containing subunit alpha (PIK3C2A) (Krag et al. 2010, Arcaro et al. 2000) phosphorylates phosphatidylinositol 4-phosphate (PI4P) to phosphatidylinositol 3,4-bisphosphate (PI(3,4)P2).

**Preceded by:** PI is phosphorylated to PI4P by PI4K2A/B at the early endosome membrane

**Followed by:** PI(3,4)P2 is dephosphorylated to PI3P by INPP4A/B at the early endosome membrane

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-08-12</td>
<td>Edited</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2011-10-18</td>
<td>Authored</td>
<td>Williams, MG.</td>
</tr>
<tr>
<td>2012-05-14</td>
<td>Reviewed</td>
<td>Wakelam, M.</td>
</tr>
</tbody>
</table>
MTMR2 binds MTMR10

**Location:** Synthesis of PIPs at the early endosome membrane

**Stable identifier:** R-HSA-6810030

**Type:** binding

**Compartments:** cytosol

**Inferred from:** Mtmr2 binds MTMR10 (Homo sapiens)

Based on a high throughput study of human interactome in HeLa cells, MTMR2 forms a complex with MTMR10, an enzymatically inactive myotubularin family member. The function of this complex has not been examined (Hein et al. 2015).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-11-13</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2017-01-10</td>
<td>Reviewed</td>
<td>Rush, MG.</td>
</tr>
<tr>
<td>2017-01-25</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
Table of Contents

Introduction

- Synthesis of PIPs at the early endosome membrane
  - PI(3,4)P2 is dephosphorylated to PI3P by INPP4A/B at the early endosome membrane
  - PI(4,5)P2, PI(3,4)P2 and PI(3,4,5)P3 are dephosphorylated to PI5P, PI3P and PI(3,4)P by INPP5F at the endosome membrane
  - PI3P is phosphorylated to PI(3,5)P2 by PIKFYVE at the early endosome membrane
  - PI(3,5)P2 is dephosphorylated to PI3P by FIG4 at the early endosome membrane
  - PI(3,5)P2 is dephosphorylated to PI5P by MTM proteins at the early endosome membrane
  - PI is phosphorylated to PI3P by PIK3C2A/3 at the early endosome membrane
  - PI3P is dephosphorylated to PI by MTM proteins at the early endosome membrane
  - MTMR12 binds MTM1
  - MTMR12 binds MTMR2
  - PI is phosphorylated to PI4P by PI4K2A/B at the early endosome membrane
  - PI4P is phosphorylated to PI(3,4)P2 by PIK3C2A at the early endosome membrane
  - MTMR2 binds MTMR10

Table of Contents