Synthesis of PIPs at the plasma membrane


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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 33 reactions (see Table of Contents)
At the plasma membrane, subsequent phosphorylation of phosphatidylinositol 4-phosphate (PI4P) produces phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) and phosphatidylinositol 3,4,5-trisphosphate (PI(3,4,5)P3) while the actions of various other kinases and phosphatases produces phosphatidylinositol 3-phosphate (PI3P), phosphatidylinositol 5-phosphate (PI5P), phosphatidylinositol 3,4-bisphosphate (PI(3,4)P2), and phosphatidylinositol 3,5-bisphosphate (PI(3,5)P2) (Zhang et al. 1997, Gurung et al. 2003, Guo et al. 1999, Vanhaesebroeck et al. 1997, Tolias et al. 1998, Schaletzky et al. 2003, Kim et al. 2002, Clarke et al. 2010). Many of the phosphatidylinositol phosphatases that act at the plasma membrane belong to the myotubularin family. Enzymatically inactive myotubularin family members can heterodimerize with catalytically active myotubularins to regulate their stability, activity and/or substrate specificity (Berger et al. 2006, Zou et al. 2012).

**Literature references**


## Editions

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PI4P is phosphorylated to PI(4,5)P2 by PIP5K1A-C at the plasma membrane

Location: Synthesis of PIPs at the plasma membrane

Stable identifier: R-HSA-1676082

Type: transition

Compartments: plasma membrane, cytosol

At the plasma membrane, phosphatidylinositol-4-phosphate 5-kinase type-1 alpha (PIP5K1A), beta (PIP5K1B), and gamma (PIP5K1C) phosphorylate phosphatidylinositol 4-phosphate (PI4P) to produce phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2).

The following lists the above proteins with their corresponding literature references: PIP5K1A (Halstead et al. 2006, Zhang et al. 1997), PIP5K1B (Zhang et al. 1997), and PIP5K1C (Di Paolo et al. 2002).

This reaction is of particular interest because its regulation by small GTPases of the RHO and ARF families, not yet annotated here, ties the process of phosphatidylinositol phosphate biosynthesis to regulation of the actin cytoskeleton and vesicular trafficking, and hence to diverse aspects of cell motility and signalling (Oude Weernink et al. 2004, 2007).

Preceded by: PI(4,5)P2 is dephosphorylated to PI4P by SYNJ/INPP5[1] at the plasma membrane, PI(3,4)P2 is dephosphorylated to PI4P by PTEN at the plasma membrane, PI is phosphorylated to PI4P by PI4K2A/B at the plasma membrane

Followed by: PI(4,5)P2 is dephosphorylated to PI4P by SYNJ/INPP5[1] at the plasma membrane, PI(4,5)P2 is phosphorylated to PI(3,4,5)P3 by PIK3C[1] at the plasma membrane

Literature references


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PI(4,5)P2 is dephosphorylated to PI4P by SYNJ/INPP5[1] at the plasma membrane

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-1676177

**Type:** transition

**Compartments:** plasma membrane, cytosol

At the plasma membrane, Synaptojanin-1 (SYNJ1) and -2 (SYNJ2), inositol polyphosphate 5-phosphatase K (INPP5K) aka SKIP, phosphatidylinositol 4,5-bisphosphate 5-phosphatase A (INPP5J) aka PIPP dephosphorylate phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) to form phosphatidylinositol 4-phosphate (PI4P). SYNJ1/2 both have an N-terminal Sac1-like domain, a central 5-phosphatase domain and a C-terminal proline-rich segment, with this latter part being the most divergent part of the protein sequence.


**Preceded by:** PI4P is phosphorylated to PI(4,5)P2 by PIP5K1A-C at the plasma membrane, PTEN dephosphorylates PIP3, PI5P is phosphorylated to PI(4,5)P2 by PIP4K2 dimers at the plasma membrane

**Followed by:** PI4P is phosphorylated to PI(3,4)P2 by PI3K3C[2] at the plasma membrane, PI4P is phosphorylated to PI(4,5)P2 by PI4K1A-C at the plasma membrane, PI4P is dephosphorylated to PI by SYNJ at the plasma membrane

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**PI(4,5)P2 is phosphorylated to PI(3,4,5)P3 by PIK3C[1] at the plasma membrane**

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-1676048

**Type:** transition

**Compartments:** plasma membrane, cytosol

At the plasma membrane, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunits form complexes with regulatory subunits. These complexes phosphorylate phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) to phosphatidylinositol 3,4,5-trisphosphate (PI(3,4,5)P3) (Stephens et al. 1997). The PI(4,5)P2 3-kinase complexes involved are: PI(4,5)P2 3-kinase catalytic subunit alpha isoform (PIK3CA) bound to PI 3-kinase regulatory subunit alpha/beta/gamma (PIK3R1/2/3); beta (PIK3CB) bound to PIK3R1/2/3; delta (PIK3CD) bound to PIK3R1/2/3; and gamma (PIK3CG) bound to PI 3-kinase regulatory subunit 5 (PIK3R5) or 6 (PIK3R6).


**Preceded by:** PI4P is phosphorylated to PI(4,5)P2 by PIP5K1A-C at the plasma membrane, PTEN dephosphorylates PIP3, PI5P is phosphorylated to PI(4,5)P2 by PIP4K2 dimers at the plasma membrane

**Followed by:** PI(3,4,5)P3 is dephosphorylated to PI(3,4)P2 by INPP5[2] at the plasma membrane, PTEN dephosphorylates PIP3

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At the plasma membrane, phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase aka phosphatase and tensin homolog (PTEN) dephosphorylates phosphatidylinositol 3,4,5-trisphosphate (PI(3,4,5)P3) to phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) (Maehama & Dixon 1998, Myers et al. 1998, Das et al. 2003). The PI3K network is negatively regulated by phospholipid phosphatases that dephosphorylate PIP3, thus hampering AKT activation (Myers et al. 1998). The tumour suppressor PTEN is the primary phospholipid phosphatase.

Early studies indicated that magnesium ion, Mg2+, was needed for the catalytic activity of PTEN isolated from bovine thymus (Kabuyama et al. 1996). Subsequent studies have shown that PTEN was catalytically active in buffers free of magnesium and magnesium was not detected as part of the PTEN crystal (Lee et al. 1999).

**Preceded by:** PI(4,5)P2 is phosphorylated to PI(3,4,5)P3 by PIK3C[1] at the plasma membrane, PI(3,4)P2 is phosphorylated to PI(3,4,5)P3 by PIP5K1A-C at the plasma membrane

**Followed by:** PI(4,5)P2 is phosphorylated to PI(3,4,5)P3 by PIK3C[1] at the plasma membrane, PI(4,5)P2 is dephosphorylated to PI4P by SYNJ/INPP5[1] at the plasma membrane

**Literature references**


**PI(3,4)P2 is phosphorylated to PI(3,4,5)P3 by PIP5K1A-C at the plasma membrane**

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-1675773

**Type:** transition

**Compartments:** plasma membrane, cytosol

At the plasma membrane, phosphatidylinositol-4-phosphate 5-kinase type-1 alpha (PIP5K1A), beta (PIP5K1B), and gamma (PIP5K1C) phosphorylate phosphatidylinositol 3,4-bisphosphate (PI(3,4)P2) to produce phosphatidylinositol 3,4,5-trisphosphate (PI(3,4,5)P3). This is a minor reaction, however, and its physiological role is uncertain.

The following lists the above proteins with their corresponding literature references: PIP5K1A (Zhang et al. 1997, Tolias et al. 1998), PIP5K1B (Zhang et al. 1997, Tolias et al. 1998), and PIP5K1C (Wenk et al. 2001, Di Paolo et al. 2002, Krauss et al. 2003).

**Preceded by:** PI(3,4,5)P3 is dephosphorylated to PI(3,4)P2 by INPP5[2] at the plasma membrane, PI4P is phosphorylated to PI(3,4)P2 by PI3K3C[2] at the plasma membrane, PI3P is phosphorylated to PI(3,4)P2 by PIP4K2/5K1 at the plasma membrane

**Followed by:** PI(3,4,5)P3 is dephosphorylated to PI(3,4)P2 by INPP5[2] at the plasma membrane, PTEN dephosphorylates PIP3

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PI(3,4,5)P3 is dephosphorylated to PI(3,4)P2 by INPP5[2] at the plasma membrane

Location: Synthesis of PIPs at the plasma membrane

Stable identifier: R-HSA-1675949

Type: transition

Compartments: plasma membrane, cytosol

At the plasma membrane, phosphatidylinositol 5-phosphatases dephosphorylate phosphatidylinositol 3,4,5-trisphosphate (PI(3,4,5)P3) to phosphatidylinositol 3,4-bisphosphate (PI(3,4)P2). The phosphatidylinositol 5-phosphatases involved are: inositol polyphosphate 5-phosphatase K (INPP5K) aka SKIP (Ijuin et al. 2000, Gurung et al. 2003), phosphatidylinositol 4,5-bisphosphate 5-phosphatase A (INPP5J) aka PIPP (Gurung et al. 2003, Mochizuki & Takenawa 1999), phosphatidylinositol-3,4,5-trisphosphate 5-phosphatase 1 (INPP5D) aka SHIP1 (Drayer et al. 1995, Kavanaugh et al. 1996, Dunant et al. 2000), and phosphatidylinositol-3,4,5-trisphosphate 5-phosphatase 2 (INPPL1) aka SHIP2 (Habib et al. 1998, Wisniewski et al. 1999, Pesesse et al. 2001).

Preceded by: PI(4,5)P2 is phosphorylated to PI(3,4,5)P3 by PIK3C[1] at the plasma membrane, PI(3,4)P2 is phosphorylated to PI(3,4,5)P3 by PIP5K1A-C at the plasma membrane

Followed by: PTPN13:PLEKHA1,2 bind PI(3,4)P2, PI(3,4)P2 is phosphorylated to PI(3,4,5)P3 by PIP5K1A-C at the plasma membrane, PI(3,4)P2 is dephosphorylated to PI3P by INPP4A/B at the plasma membrane, PI(3,4)P2 is dephosphorylated to PI4P by PTEN at the plasma membrane

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PI4P is phosphorylated to PI(3,4)P2 by PI3K3C[2] at the plasma membrane

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-1676109

**Type:** transition

**Compartments:** plasma membrane, cytosol

At the plasma membrane, phosphatidylinositol-4,5-bisphosphate (PI(4,5)P2) 3-kinase catalytic subunits form complexes with regulatory subunits. These complexes along with phosphatidylinositol-4-phosphate 3-kinase C2 domain-containing subunits alpha (PIK3C2A), beta (PIK3C2B), and gamma (PIK3C2G) phosphorylate phosphatidylinositol 4-phosphate (PI4P) to phosphatidylinositol 3,4-bisphosphate (PI(3,4)P2). The PI(4,5)P2 3-kinase complexes involved are: PI(4,5)P2 3-kinase catalytic subunit alpha isoform (PIK3CA) bound to PI 3-kinase regulatory subunit alpha/beta/gamma (PIK3R1/2/3); beta (PIK3CB) bound to PIK3R1/2/3; delta (PIK3CD) bound to PIK3R1/2/3; delta (PIK3CD) bound to PIK3R1/2/3; and gamma (PIK3CG) bound to PI 3-kinase regulatory subunit 5 (PIK3R5) or 6 (PIK3R6).


**Preceded by:** PI(4,5)P2 is dephosphorylated to PI4P by SYNJ/INPP5[1] at the plasma membrane, PI(3,4)P2 is dephosphorylated to PI4P by PTEN at the plasma membrane, PI is phosphorylated to PI4P by PI4K2A/B at the plasma membrane

**Followed by:** PTPN13:PLEKHA1,2 bind PI(3,4)P2, PI(3,4)P2 is phosphorylated to PI(3,4,5)P3 by PIP5K1A-C at the plasma membrane, PI(3,4)P2 is dephosphorylated to PI3P by INPP4A/B at the plasma membrane, PI(3,4)P2 is dephosphorylated to PI4P by PTEN at the plasma membrane

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Literature references


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At the plasma membrane, phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase aka phosphatase and tensin homolog (PTEN) dephosphorylates phosphatidylinositol 3,4,5-bisphosphate (PI(3,4,5)P3) to phosphatidylinositol 4-phosphate (PI4P) (Myers et al. 1998, Das et al. 2003).

Early studies indicated that magnesium ion, Mg2+, was needed for the catalytic activity of PTEN isolated from bovine thymus (Kabuyama et al. 1996). Subsequent studies have shown that PTEN was catalytically active in buffers free of magnesium and magnesium was not detected as part of the PTEN crystal (Lee et al. 1999).

Preceded by: PI(3,4,5)P3 is dephosphorylated to PI(3,4)P2 by INPP5[2] at the plasma membrane, PI4P is phosphorylated to PI(3,4)P2 by PI3K3C[2] at the plasma membrane, PI3P is phosphorylated to PI(3,4)P2 by PIP4K2/5K1 at the plasma membrane

Followed by: PI4P is phosphorylated to PI(3,4)P2 by PI3K3C[2] at the plasma membrane, PI4P is phosphorylated to PI(4,5)P2 by PIP5K1A-C at the plasma membrane, PI4P is dephosphorylated to PI by SYNJ at the plasma membrane

**Literature references**


**PI3P is phosphorylated to PI(3,4)P2 by PIP4K2/5K1 at the plasma membrane**

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-1676145

**Type:** transition

**Compartments:** plasma membrane, cytosol

At the plasma membrane, phosphatidylinositol-5-phosphate 4-kinase type-2 alpha (PIP4K2A) and beta (PIP4K2B) homodimers and heterodimers (Clarke et al. 2010), along with phosphatidylinositol-4-phosphate 5-kinase type-1 alpha (PIP5K1A), beta (PIP5K1B), and gamma (PIP5K1C) phosphorylate phosphatidylinositol 3-phosphate (PI3P) to phosphatidylinositol 3,4-bisphosphate (PI(3,4)P2).


**Preceded by:** PI(3,4)P2 is dephosphorylated to PI3P by INPP4A/B at the plasma membrane, PI(3,5)P2 is dephosphorylated to PI3P by SYNJ at the plasma membrane

**Followed by:** PI(3,4)P2 is phosphorylated to PI(3,4,5)P3 by PIP5K1A-C at the plasma membrane, PI(3,4)P2 is dephosphorylated to PI3P by INPP4A/B at the plasma membrane, PI(3,4)P2 is dephosphorylated to PI4P by PTEN at the plasma membrane

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PI(3,4)P2 is dephosphorylated to PI3P by INPP4A/B at the plasma membrane

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-1676164

**Type:** transition

**Compartments:** plasma membrane, cytosol

At the plasma membrane, type I and type II inositol-3,4-bisphosphate 4-phosphatase (INPP4A) (Norris et al. 1995, Ivetac et al. 2005) and (INPP4B) (Norris et al. 1997) dephosphorylate phosphatidylinositol 3,4-bisphosphate (PI(3,4)P2) to phosphatidylinositol 3-phosphate (PI3P).

**Preceded by:** PI(3,4,5)P3 is dephosphorylated to PI(3,4)P2 by INPP5 at the plasma membrane, PI4P is phosphorylated to PI(3,4)P2 by PI3K3C2 at the plasma membrane, PI3P is phosphorylated to PI(3,4)P2 by PIP4K2/5K1 at the plasma membrane

**Followed by:** PI3P is dephosphorylated to PI by the MTMR2:SBF2 tetramer at the plasma membrane, PI3P is dephosphorylated to PI by MTMR9-bound MTMR8 or MTMR6 at the plasma membrane, PI3P is phosphorylated to PI(3,4)P2 by PIP4K2/5K1 at the plasma membrane, PI3P is phosphorylated to PI(3,5)P2 by PIP5K1A/B at the plasma membrane

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**PI3P is dephosphorylated to PI by SYNJ/MTMs at the plasma membrane**

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-1675994

**Type:** transition

**Compartments:** plasma membrane, cytosol


**Preceded by:** PI(3,4)P2 is dephosphorylated to PI3P by INPP4A/B at the plasma membrane, PI(3,5)P2 is dephosphorylated to PI3P by SYNJ at the plasma membrane

**Followed by:** PI is phosphorylated to PI5P by PIP5K1A/B at the plasma membrane, PI is phosphorylated to PI4P by PI4K2A/B at the plasma membrane

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PTPN13:PLEKHA1,2 bind PI(3,4)P2

Location: Synthesis of PIPs at the plasma membrane

Stable identifier: R-HSA-8870332

Type: binding

Compartments: plasma membrane

Insulin sensitivity is critically dependent on the activity of PI3K (phosphoinositide 3-kinase) and generation of the phosphatidylinositol 3,4, 5-triphosphate (PIP3,PtdIns(3,4,5)P(3)) second messenger. Increasing evidence suggests that one of the immediate breakdown products of PIP3, phosphatidylinositol 3,4-diphosphate (PIP2, PtdIns(3,4)P(2)), might also function as a signalling molecule by controlling a negative-feedback loop that down-regulates the insulin and PI3K network. The pleckstrin homology domain-containing family A members 1 and 2 (PLEKHA1 and PLEKHA2, aka TAPP1 and TAPP2 respectively) can both specifically bind PIP2. PLEKHA1 and 2 are constitutively bound to tyrosine-protein phosphatase non-receptor type 13 (PTPN13, aka PTPL1) via its first PDZ domain and this interaction keeps PLEKHA1 and 2 localised to the cytosol (Kimber et al. 2003). With increasing PIP2 levels, produced by PI3K activity on PIP3, PTPN13-bound PLEKHA1 and 2 translocate to the plasma membrane where they bind PIP2 (Marshall et al. 2002, Wullschleger et al. 2011).

Preceded by: PI(3,4,5)P3 is dephosphorylated to PI(3,4)P2 by INPP5[2] at the plasma membrane, PI4P is phosphorylated to PI(3,4)P2 by PI3K3C[2] at the plasma membrane

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Proteins with the plekstrin homology (PH) domain are able to bind specific phosphoinositides. Pleckstrin homology domain-containing family A members 3 and 8 (PLEKHA3 and PLEKHA8 aka FAPP1 and FAPP2) specifically bind phosphoinositide 4-phosphate (PI4P, PtdIns(4)P), a key intermediate in the synthesis of phosphoinositide 4,5-diphosphate (PIP2). PLEKHA3 and 8 are localised to the trans-Golgi network (TGN) where they interact with PI4P and the small GTPase ADP-ribosylation factor (ARF1) through their PH domains and mediate the transport of lipid cargo from the Golgi to the plasma membrane (Godi et al. 1999, Godi et al. 2004).

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The second messenger phosphatidylinositol 3,4,5-trisphosphate (PIP3, PtdIns(3,4,5)P) is generated by the action of phosphoinositide 3-kinase (PI3K) in response to growth factors and insulin and regulates a range of cellular processes. Proteins containing the plekstrin homology (PH) domain can interact specifically with PIP3 or its immediate breakdown product, phosphatidylinositol 3,4-diphosphate (PIP2, PtdIns(3,4)P). Proteins with a PH domain have also been found to bind to PIs other than PIP3 or PIP2. Pleckstrin homology domain-containing family A member 4 (PLEKHA4 aka PEPP1) is able to specifically bind phosphatidylinositol 3-phosphate (PI3P) but not other phosphoinositides (Dowler et al. 2000). Two related isoforms of PLEKHA4, PLEKHA5 and 6 (PEPP2 and PEPP3), possess a very similar PH domain sequence, indicating that they may also interact with PI3P (Dowler et al. 2000, Yamada et al. 2012). These proteins may function as adaptor molecules since they possess no obvious catalytic moieties.

**Literature references**


MTMR6 binds MTMR9

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-6809309

**Type:** binding

**Compartments:** cytosol

MTMR6 binds to MTMR9, an enzymatically inactive myotubularin family member, which leads to increased catalytic activity of MTMR6 (Zou et al. 2009).

**Literature references**


**Editions**

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MTMR8 binds MTMR9

Location: Synthesis of PIPs at the plasma membrane

Stable identifier: R-HSA-6809254

Type: binding

Compartments: nucleoplasm

MTMR8 binds to MTMR9, an enzymatically inactive myotubularin family member, which results in increased stability and increased catalytic activity of MTMR8 (Zou et al. 2012).

Literature references


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PI3P is dephosphorylated to PI by MTMR9-bound MTMR8 or MTMR6 at the plasma membrane

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-6809325

**Type:** transition

**Compartments:** plasma membrane, cytosol

Formation of a complex with MTMR9 results in a 4-fold increase of the phosphatidylinositol-3-phosphatase catalytic activity of MTMR8 and a modest increase of the catalytic activity of MTMR6 (Zou et al. 2012).

**Preceded by:** PI(3,4)P2 is dephosphorylated to PI3P by INPP4A/B at the plasma membrane, PI(3,5)P2 is dephosphorylated to PI3P by SYNJ at the plasma membrane

**Literature references**


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PI is phosphorylated to PI5P by PIP5K1A/B at the plasma membrane

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-1675810

**Type:** transition

**Compartments:** plasma membrane, cytosol

At the plasma membrane, phosphatidylinositol-4-phosphate 5-kinase type-1 alpha (PIP5K1A) and beta (PIP5K1B) phosphorylate phosphatidylinositol (PI) to produce phosphatidylinositol 5-phosphate (PI5P) (Tolias et al. 1998).

**Preceded by:** PI3P is dephosphorylated to PI by SYNJ/MTMs at the plasma membrane, PI4P is dephosphorylated to PI by SYNJ at the plasma membrane

**Followed by:** PI5P is phosphorylated to PI(4,5)P2 by PIP4K2 dimers at the plasma membrane

**Literature references**


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PI3P is phosphorylated to PI(3,5)P2 by PIP5K1A/B at the plasma membrane

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-1676134

**Type:** transition

**Compartments:** plasma membrane, cytosol

At the plasma membrane, phosphatidylinositol-4-phosphate 5-kinase type-1 alpha (PIP5K1A) and beta (PIP5K1B) phosphorylate phosphatidylinositol 3-phosphate (PI3P) to phosphatidylinositol 3,5-bisphosphate (PI(3,5)P2) (Tolias et al. 1998).

**Preceded by:** PI(3,4)P2 is dephosphorylated to PI3P by INPP4A/B at the plasma membrane, PI(3,5)P2 is dephosphorylated to PI3P by SYNJ at the plasma membrane

**Followed by:** PI(3,5)P2 is dephosphorylated to PI5P by the MTMR2:SBF2 tetramer at the plasma membrane, PI(3,5)P2 is dephosphorylated to PI5P by MTMR9-bound MTMR6 or MTMR8 at the plasma membrane, PI(3,5)P2 is dephosphorylated to PI3P by SYNJ at the plasma membrane, PI(3,5)P2 is dephosphorylated to PI5P by SYNJ/MTMs at the plasma membrane

**Literature references**


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PI(3,5)P2 is dephosphorylated to PI3P by SYNJ at the plasma membrane

Location: Synthesis of PIPs at the plasma membrane

Stable identifier: R-HSA-1675836

Type: transition

Compartments: plasma membrane, cytosol

At the plasma membrane, synaptic inositol-1,4,5-trisphosphate 5-phosphatase 1 aka synaptojanin-1 (SYNJ1) (Guo et al. 1999, Mani et al. 2007) and -2 (SYNJ2) (Malecz et al. 2000) dephosphorylate phosphatidylinositol 3,5-bisphosphate (PI(3,5)P2) to phosphatidylinositol 3-phosphate (PI3P).

Preceded by: PI3P is phosphorylated to PI(3,5)P2 by PIP5K1A/B at the plasma membrane

Followed by: PI3P is dephosphorylated to PI by the MTMR2:SBF2 tetramer at the plasma membrane, PI3P is dephosphorylated to PI by MTMR9-bound MTMR8 or MTMR6 at the plasma membrane, PI3P is dephosphorylated to PI by SYNJ/MTMs at the plasma membrane, PI3P is phosphorylated to PI(3,4)P2 by PIP4K2/5K1 at the plasma membrane, PI3P is phosphorylated to PI(3,5)P2 by PIP5K1A/B at the plasma membrane

Literature references


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https://www.reactome.org
PI(3,5)P2 is dephosphorylated to PI5P by SYNJ/MTMs at the plasma membrane

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-1676203

**Type:** transition

**Compartments:** plasma membrane, cytosol

At the plasma membrane, synaptojanin-1 aka Synaptic inositol-1,4,5-trisphosphate 5-phosphatase 1 (SYNJ1) (Guo et al. 1999), -2 (SYNJ2) and some myotubularins (MTMs) dephosphorylate phosphatidylinositol 3,5-bisphosphate (PI(3,5)P2) to phosphatidylinositol 5-phosphate (PI5P). The MTMs involved are: myotubulin (MTM1) (Cao et al. 2007, Tronchere et al. 2004, Schaletzky et al. 2003, Laporte et al. 2002) and myotubulin-related proteins 1 (MTMR1) (Tronchere et al. 2004), 3 (MTMR3) (Walker et al. 2001, Lorenzo et al. 2005), 6 (MTMR6) (Schaletzky et al. 2003, Choudhury et al. 2006), and 14 (MTMR14) (Tosch et al. 2006).

**Preceded by:** PI3P is phosphorylated to PI(3,5)P2 by PIP5K1A/B at the plasma membrane

**Followed by:** PI5P is phosphorylated to PI(4,5)P2 by PIP4K2 dimers at the plasma membrane

**Literature references**


https://www.reactome.org
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PI(3,5)P2 is dephosphorylated to PI5P by MTMR9-bound MTMR6 or MTMR8 at the plasma membrane

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-6809320

**Type:** transition

**Compartments:** plasma membrane, cytosol

Formation of a complex with MTMR9 results in a 30-fold increase of phosphatidylinositol-(3,5)-bisphosphate 3-phosphatase catalytic activity of MTMR6 and a modest increase in the catalytic activity of MTMR8 (Zou et al. 2009, Zou et al. 2012).

**Preceded by:** PI3P is phosphorylated to PI(3,5)P2 by PIP5K1A/B at the plasma membrane

**Literature references**


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**PI5P is phosphorylated to PI(4,5)P2 by PIP4K2 dimers at the plasma membrane**

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-1675776

**Type:** transition

**Compartments:** plasma membrane, cytosol

At the plasma membrane, phosphatidylinositol-5-phosphate 4-kinase type-2 alpha (PIP4K2A), beta (PIP4K2B) and gamma (PIP4K2C) homodimers and heterodimers (Clarke et al. 2010, Clarke and Irvine 2013, Clarke et al. 2015) phosphorylate phosphatidylinositol 5-phosphate (PI5P) to phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2).

The following lists the above proteins with their corresponding literature references: PIP4K2A (Rameh et al. 1997, Clarke et al. 2008, Clarke and Irvine 2013), PIP4K2B (Rameh et al. 1997, Clarke and Irvine 2013) and PIP4K2C (Clarke and Irvine 2013, Clarke et al. 2015).

**Preceded by:** PI is phosphorylated to PI5P by PIP5K1A/B at the plasma membrane, PI(3,5)P2 is dephosphorylated to PI5P by SYNJ/MTMs at the plasma membrane

**Followed by:** PI(4,5)P2 is dephosphorylated to PI4P by SYNJ/INPP5[1] at the plasma membrane, PI(4,5)P2 is phosphorylated to PI(3,4,5)P3 by PIK3C[1] at the plasma membrane

**Literature references**


https://www.reactome.org

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PI is phosphorylated to PI4P by PI4K2A/B at the plasma membrane

Location: Synthesis of PIPs at the plasma membrane

Stable identifier: R-HSA-1675780

Type: transition

Compartments: plasma membrane, cytosol

At the plasma membrane, phosphatidylinositol 4-kinase type 2-alpha (PI4K2A) (Balla et al. 2002, Minogue et al. 2001) and beta (PI4K2B) (Balla et al. 2002, Wei et al. 2002) phosphorylate phosphatidylinositol (PI) to phosphatidylinositol 4-phosphate (PI4P).

Preceded by: PI3P is dephosphorylated to PI by SYNJ/MTMs at the plasma membrane, PI4P is dephosphorylated to PI by SYNJ at the plasma membrane

Followed by: PI4P is phosphorylated to PI(3,4)P2 by PI3K3C[2] at the plasma membrane, PI4P is phosphorylated to PI(4,5)P2 by PIP5K1A-C at the plasma membrane, PI4P is dephosphorylated to PI by SYNJ at the plasma membrane

Literature references


Wei, YJ., Sun, HQ., Yamamoto, M., Wlodarski, P., Kunii, K., Martínez, M. et al. (2002). Type II phosphatidylinositol 4-kinase beta is a cytosolic and peripheral membrane protein that is recruited to the plasma membrane and activated by Rac-GTP. J Biol Chem, 277, 46586-93.

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https://www.reactome.org
PI4P is dephosphorylated to PI by SYNJ at the plasma membrane

Location: Synthesis of PIPs at the plasma membrane

Stable identifier: R-HSA-1675988

Type: transition

Compartments: plasma membrane, cytosol

At the plasma membrane, synaptic inositol-1,4,5-trisphosphate 5-phosphatase 1 aka Synaptojanin-1 (SYNJ1) (Guo et al. 1999, Mani et al. 2007, Johenning et al. 2004) and -2 (SYNJ2) (Malecz et al. 2000) dephosphorylate phosphatidylinositol 4-phosphate (PI4P) phosphatidylinositol (PI). The SAC1 domains of SYNJ1 and SYNJ2 demonstrate 4-phosphatase activity.

Preceded by: PI(4,5)P2 is dephosphorylated to PI4P by SYNJ/INPP5[1] at the plasma membrane, PI(3,4)P2 is dephosphorylated to PI4P by PTEN at the plasma membrane, PI is phosphorylated to PI4P by PI4K2A/B at the plasma membrane

Followed by: PI is phosphorylated to PI5P by PIP5K1A/B at the plasma membrane, PI is phosphorylated to PI4P by PI4K2A/B at the plasma membrane

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MTMR2 dimerizes

Location: Synthesis of PIPs at the plasma membrane

Stable identifier: R-HSA-6809785

Type: binding

Compartments: cytosol

Inferred from: Mtmr2 homodimerizes (Mus musculus)

MTMR2 forms a homodimer (Berger et al. 2006).

Followed by: MTMR2 binds SBF2

Literature references


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MTMR2 binds SBF2

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-6809793

**Type:** binding

**Compartments:** cytosol

**Inferred from:** Mtmr2 binds Sbf2 (Mus musculus)

MTMR2 dimer forms a complex with myotubularin protein SBF2 (MTMR13, an enzymatically inactive myotubularin family member) dimer. Binding to SBF2 sequesters MTMR2 from endosomal membranes to the cytosol (Berger et al. 2006).

**Preceded by:** MTMR2 dimerizes

**Followed by:** PI(3,5)P2 is dephosphorylated to PI5P by the MTMR2:SBF2 tetramer at the plasma membrane, PI3P is dephosphorylated to P1 by the MTMR2:SBF2 tetramer at the plasma membrane

**Literature references**


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PI(3,5)P2 is dephosphorylated to PI5P by the MTMR2:SBF2 tetramer at the plasma membrane

Location: Synthesis of PIPs at the plasma membrane

Stable identifier: R-HSA-6809944

Type: transition

Compartments: plasma membrane, cytosol

Inferred from: PI(3,5)P2 is dephosphorylated to PI5P by the Mtmr2:Sbf2 tetramer at the plasma membrane (Mus musculus)

Formation of a complex with SBF2 (MTMR13) dramatically increases phosphatidylinositol-(3,5)-bisphosphate 3-phosphatase catalytic activity of MTMR2. Since SBF2 sequesters MTRM2 from endosome membranes, the MTMR2 presumably acts on the plasma membrane-associated substrate (Berger et al. 2006).

Preceded by: PI3P is phosphorylated to PI(3,5)P2 by PIP5K1A/B at the plasma membrane, MTMR2 binds SBF2

Literature references


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PI3P is dephosphorylated to PI by the MTMR2:SBF2 tetramer at the plasma membrane

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-6809975

**Type:** transition

**Compartments:** plasma membrane, cytosol

**Inferred from:** PI3P is dephosphorylated to PI by the Mtmr2:Sbf2 tetramer at the plasma membrane (Mus musculus)

Formation of the complex with SBF2 (MTMR13) dramatically increases phosphatidylinositol-3-phosphatase catalytic activity of MTMR2. Since SBF2 sequesters MTRM2 from endosome membranes, the MTMR2 presumably acts on the plasma membrane-associated substrate (Berger et al. 2006).

**Preceded by:** PI(3,4)P2 is dephosphorylated to PI3P by INPP4A/B at the plasma membrane, PI(3,5)P2 is dephosphorylated to PI3P by SYNJ at the plasma membrane, MTMR2 binds SBF2

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**BMX phosphorylates RUFY1**

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-8871373

**Type:** transition

**Compartments:** cytosol

RUN and FYVE domain-containing protein 1 (RUFY1, aka RABIP4, ZFYVE12) associates with phosphatidylinositol 3-phosphate in membranes of early endosomes and may participate in early endosomal membrane trafficking of the glucose transporter GLUT4. RUFY1 is broadly expressed, with highest levels in lung, testis, kidney and brain. RUFY1 is localised to the cytoplasm and early endosomal membrane, the latter being the predominant localisation after RUFY1 is phosphorylated. Cytoplasmic tyrosine-protein kinase BMX (BMX, aka ETK) is a downstream tyrosine kinase of PI3-kinase which, through its SH2 and SH3 domains, binds to and phosphorylates RUFY1 at Tyr-281 and Tyr 292. These phosphorylations are essential for endosomal localisation (Yang et al. 2002).

**Literature references**


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p-Y281,292-RUFY1 translocates from cytosol to early endosome membrane

Location: Synthesis of PIPs at the plasma membrane

Stable identifier: R-HSA-8871370

Type: omitted

Compartments: cytosol, early endosome membrane

RUN and FYVE domain-containing protein 1 (RUFY1, aka RABIP4, ZFYVE12) associates with phosphatidylinositol 3-phosphate in membranes of early endosomes and may participate in early endosomal membrane trafficking of the glucose transporter GLUT4. RUFY1 is localised to the cytoplasm and early endosomal membrane, the latter being the predominant localisation after RUFY1 is phosphorylated. Cytoplasmic tyrosine-protein kinase BMX (BMX, aka ETK) is a downstream tyrosine kinase of PI3-kinase which, through its SH2 and SH3 domains, binds to and phosphorylates RUFY1 at Tyr-281 and Tyr 292. These phosphorylations are essential for endosomal localisation (Yang et al. 2002).

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<td>2016-05-16</td>
<td>Authored, Edited</td>
<td>Jassal, B.</td>
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<tr>
<td>2016-07-15</td>
<td>Reviewed</td>
<td>D'Eustachio, P.</td>
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</table>
p-Y281,292-RUFY1 binds PI3P

**Location:** Synthesis of PIPs at the plasma membrane

**Stable identifier:** R-HSA-8871376

**Type:** binding

**Compartments:** early endosome membrane

RUN and FYVE domain-containing protein 1 (RUFY1, aka RABIP4, ZFYVE12) associates with phosphatidylinositol 3-phosphate in membranes of early endosomes and may participate in early endosomal membrane trafficking. RUFY1 is localised to the cytoplasm and early endosomal membrane, the latter being the predominant localisation after RUFY1 is phosphorylated. Cytoplasmic tyrosine-protein kinase BMX (BMX, aka ETK) is a downstream tyrosine kinase of PI3-kinase which, through its SH2 and SH3 domains, binds to and phosphorylates RUFY1 at Tyr-281 and Tyr 292. These phosphorylations are essential for endosomal localisation (Yang et al. 2002).

**Literature references**


**Editions**

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<tr>
<th>Edition Date</th>
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p-Y281,292-RUFY1 binds RAB4A:GTP, RAB5:GTP, RAB14:GTP

Location: Synthesis of PIPs at the plasma membrane

Stable identifier: R-HSA-8871366

Type: binding

Compartments: early endosome membrane

RUN and FYVE domain-containing protein 1 (RUFY1, aka RABIP4, ZFYVE12), together with Ras-related proteins RAB4A, 5 and 14, could play an important role in GLUT4 trafficking in adipocytes and skeletal muscle (Kitagishi & Matsuda 2013, Larance et al. 2005, Mari et al. 2006, Fouraux et al. 2004).

Literature references


Editions

2016-05-16  Authored, Edited  Jassal, B.
2016-07-15  Reviewed  D'Eustachio, P.
## Table of Contents

**Introduction**

1. Synthesis of PIPs at the plasma membrane
   - PI4P is phosphorylated to PI(4,5)P2 by PIP5K1A-C at the plasma membrane
   - PI(4,5)P2 is dephosphorylated to PI4P by SYNJ/INPP5[1] at the plasma membrane
   - PI(4,5)P2 is phosphorylated to PI(3,4,5)P3 by PIK3C[1] at the plasma membrane
   - PTEN dephosphorylates PI3P
   - PI(3,4,5)P3 is dephosphorylated to PI(3,4)P2 by INPP5[2] at the plasma membrane
   - PI3P is phosphorylated to PI(3,4)P2 by PI3K3C[2] at the plasma membrane
   - PI(3,4)P2 is dephosphorylated to PI4P by PTEN at the plasma membrane
   - PI3P is phosphorylated to PI(3,4)P2 by PIP4K2/5K1 at the plasma membrane
   - PI(3,4)P2 is dephosphorylated to PI3P by INPP4A/B at the plasma membrane
   - PI3P is dephosphorylated to PI by SYNJ/MTMs at the plasma membrane
   - PTPN13:PLEKHA1,2 bind PI(3,4)P2
   - PLEKHA3,8 bind PI4P, ARF1
   - PLEKHA4,(5,6) bind PI3P
   - MTMR6 binds MTMR9
   - MTMR8 binds MTMR9
   - PI3P is dephosphorylated to PI by MTMR9-bound MTMR8 or MTMR6 at the plasma membrane
   - PI is phosphorylated to PI5P by PIP5K1A/B at the plasma membrane
   - PI3P is phosphorylated to PI(3,5)P2 by PIP5K1A/B at the plasma membrane
   - PI(3,5)P2 is dephosphorylated to PI3P by SYNJ at the plasma membrane
   - PI(3,5)P2 is dephosphorylated to PI5P by SYNJ/MTMs at the plasma membrane
   - PI(3,5)P2 is dephosphorylated to PI5P by the MTMR2:SBF2 tetramer at the plasma membrane
   - PI3P is dephosphorylated to PI by the MTMR2:SBF2 tetramer at the plasma membrane
   - BMX phosphorylates RUFY1
   - p-Y281,292-RUFY1 translocates from cytosol to early endosome membrane
   - p-Y281,292-RUFY1 binds PI3P

https://www.reactome.org
p-Y281,292-RUFY1 binds RAB4A:GTP, RAB5:GTP, RAB14:GTP