Synthesis of IP3 and IP4 in the cytosol

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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.

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Literature references


Reactome database release: 72

This document contains 1 pathway and 12 reactions (see Table of Contents)
An array of inositol trisphosphate (IP3) and tetrakisphosphate (IP4) molecules are synthesised by the action of various kinases and phosphatases in the cytosol (Irvine & Schell 2001, Bunney & Katan 2010).

**Literature references**


**Editions**

2011-10-28 Authored, Edited Williams, MG.
**PI(4,5)P2 is hydrolysed to I(1,4,5)P3 and DAG by cytosolic PLC[2] at the plasma membrane**

**Location:** Synthesis of IP3 and IP4 in the cytosol

**Stable identifier:** R-HSA-1855177

**Type:** transition

**Compartments:** cytosol, plasma membrane

At the plasma membrane, a group of phospholipase C (“PLC(bz)”) proteins hydrolyse phosphatidylinositol 4,5 bisphosphate (PI(4,5)P2) to inositol 1,4,5 trisphosphate (I(1,4,5)P3) and diacylglycerol (DAG). This group of phospholipase C proteins lack a PH domain and so are cytosolic. Their C2 domains bind to PI(4,5)P2 at the membrane. The PLC-beta proteins are thought to be responsible for the majority of PI(4,5)P2 hydrolysis.


**Followed by:** I(1,4,5)P3 is phosphorylated to I(1,3,4,5)P4 by ITPKA/B/C in the cytosol

**Literature references**


**Editions**

2011-10-28 Authored, Edited Williams, MG.

https://www.reactome.org
PI(4,5)P2 is hydrolysed to I(1,4,5)P3 and DAG by tethered PLC[1] at the plasma membrane

**Location:** Synthesis of IP3 and IP4 in the cytosol

**Stable identifier:** R-HSA-1855221

**Type:** transition

**Compartments:** plasma membrane, cytosol

A group of phospholipase C proteins (“PLC(degh)”’) bind to the plasma membrane via their PH domains. These phospholipases hydrolyse phosphatidylinositol 4,5 bisphosphate (PI(4,5)P2) to inositol 1,4,5 tri-sphosphate (I(1,4,5)P3) and diacylglycerol (DAG). The C2 domains of the enzymes bind to PI(4,5)P2 at the membrane.

The phospholipase C isoforms involved and their corresponding literature references are: phosphoinositide phospholipase C delta-1(PLCD1) (Cheng et al. 1995); epsilon-1 (PLCE1) (Song et al. 2001, Lopez et al. 2001); delta-3 (PLCD3) (Pawelczyk & Matecki 1997); gamma-1 (PLCG1) (Harita et al. 2009, Baldassare et al. 1989); gamma-2 (PLCG2) (Banno et al. 1988); eta-1 (PLCH1) (Hwang et al. 2005); and eta-2 (PLCH2) (Zhou et al 2005).

**Followed by:** I(1,4,5)P3 is phosphorylated to I(1,3,4,5)P4 by ITPKA/B/C in the cytosol

**Literature references**


PL(C)D4:3xCa2+ hydrolse PI(4,5)P2 to I(1,4,5)P3 and DAG at the ER membrane

**Location:** Synthesis of IP3 and IP4 in the cytosol

**Stable identifier:** R-HSA-1855214

**Type:** transition

**Compartments:** endoplasmic reticulum membrane, cytosol

At the endoplasmic reticulum (ER) membrane, 1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase delta-4 (PLCD4) and phospholipase D4 (PLD4) hydrolyse phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) to inositol 1,4,5-trisphosphate (I(1,4,5)P3) and diacylglycerol (DAG). Both lipases are thought to require three Ca2+ ions per subunit for activity. PLD4 is attached to the ER membrane via its PH domain while its C2 domain binds to the PI(4,5)P2 in the membrane (Lee et al. 2004). Overexpression or dysregulated expression of PLCD4 may initiate oncogenesis in certain tissues through upregulation of ErbB expression and activation of ERK pathway. PLCD4 can therefore be a useful tumor marker for breast or testicular cancer tissues (Leung et al. 2004).

**Followed by:** I(1,4,5)P3 is phosphorylated to I(1,3,4,5)P4 by ITPKA/B/C in the cytosol

**Literature references**


**Editions**

2011-10-28 Authored, Edited Williams, MG.
Inositol-trisphosphate 3-kinase A (ITPKA), B (ITPKB), and C (ITPKC) phosphorylate inositol 1,4,5-trisphosphate (I(1,4,5)P3) to inositol 1,3,4,5-tetrakisphosphate (I(1,3,4,5)P4) (Dewaste et al. 2003).

**Preceded by:** PI(4,5)P2 is hydrolysed to I(1,4,5)P3 and DAG by tethered PLC[1] at the plasma membrane, PI(4,5)P2 is hydrolysed to I(1,4,5)P3 and DAG by cytosolic PLC[2] at the plasma membrane, PL(C)D4:3xCa2+ hydrolyse PI(4,5)P2 to I(1,4,5)P3 and DAG at the ER membrane, I(1,3,4,5)P4 is dephosphorylated to I(1,4,5)P3 by PTEN in the cytosol

**Followed by:** I(1,3,4,5)P4 is dephosphorylated to I(1,4,5)P3 by PTEN in the cytosol, I(1,3,4,5)P4 is dephosphorylated to I(1,3,4)P3 by INPP5[3]/ITPK1 in the cytosol, I(1,3,4,5)P4 is dephosphorylated to I(1,3,4)P3 by INPP5B at the plasma membrane

**Literature references**

I(1,3,4,5)P4 is dephosphorylated to I(1,4,5)P3 by PTEN in the cytosol

**Location:** Synthesis of IP3 and IP4 in the cytosol

**Stable identifier:** R-HSA-1855205

**Type:** transition

**Compartments:** cytosol

Phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase aka phosphatase and tensin homolog (PTEN) dephosphorylates inositol 1,3,4,5-tetrakisphosphate (I(1,3,4,5)P4) to inositol 1,4,5-trisphosphate (I(1,4,5)P3) (Maehama & Dixon 1998, Han et al. 2000).

**Preceded by:** I(1,4,5)P3 is phosphorylated to I(1,3,4,5)P4 by ITPKA/B/C in the cytosol, I(1,3,4)P3 is phosphorylated to I(1,3,4,5)P4 by ITPK1 in the cytosol

**Followed by:** I(1,4,5)P3 is phosphorylated to I(1,3,4,5)P4 by ITPKA/B/C in the cytosol

**Literature references**


**Editions**

2011-10-28 Authored, Edited Williams, MG.
**I(1,3,4,5)P4 is dephosphorylated to I(1,3,4)P3 by INPP5[3]/ITPK1 in the cytosol**

**Location:** Synthesis of IP3 and IP4 in the cytosol

**Stable identifier:** R-HSA-1855218

**Type:** transition

**Compartments:** cytosol

A group of inositol phosphatases and the broad specificity enzyme inositol-tetrakisphosphate 1-kinase (ITPK1) dephosphorylate inositol 1,3,4,5-tetrakisphosphate (I(1,3,4,5)P4) to inositol 1,3,4-trisphosphate (I(1,3,4)P3). The group of inositol phosphatases involved are: inositol polyphosphate 5-phosphatase OCRL-1 (OCRL), phosphatidylinositol-3,4,5-trisphosphate 5-phosphatase 1 (INPP5D) aka SHIP1, phosphatidylinositol-3,4,5-trisphosphate 5-phosphatase 2 (INPPL1) aka SHIP2, phosphatidylinositol 4,5-bisphosphate 5-phosphatase A (INPP5J) aka PIPP, and synaptic inositol-1,4,5-trisphosphate 5-phosphatase 1 (SYNJ1).

The following lists the above proteins with their corresponding literature references: OCRL (Chang et al. 2002, Zhang et al. 1995, Zhang et al. 1998, Schmid et al. 2004); INPP5D (Drayer et al. 1996, Kavanaugh et al. 1996); INPPL1 (Chi et al. 2004); INPP5J (Mochizuki & Thompson 1999); SYNJ1 (Schmid et al. 2004); ITPK1 (Ho et al. 2002).

**Preceded by:** I(1,4,5)P3 is phosphorylated to I(1,3,4,5)P4 by ITPKA/B/C in the cytosol, I(1,3,4)P3 is phosphorylated to I(1,3,4,5)P4 by ITPK1 in the cytosol

**Followed by:** I(1,3,4)P3 is phosphorylated to I(1,3,4,5)P4 by ITPK1 in the cytosol, I(1,3,4)P3 is phosphorylated to I(1,3,4,6)P4 by ITPK1 in the cytosol

**Literature references**


https://www.reactome.org


Editions

2011-10-28 Authored, Edited

Williams, MG.
I(1,3,4,5)P4 is dephosphorylated to I(1,3,4)P3 by INPP5B at the plasma membrane

**Location:** Synthesis of IP3 and IP4 in the cytosol

**Stable identifier:** R-HSA-1855213

**Type:** transition

**Compartments:** plasma membrane, cytosol

Type II inositol-1,4,5-trisphosphate 5-phosphatase (INPP5B) is attached to the plasma membrane where it dephosphorylates inositol 1,3,4,5-tetrakisphosphate (I(1,3,4,5)P4) to inositol 1,3,4-trisphosphate (I(1,3,4)P3 (Jefferson & Majerus 1995, Ross et al. 1991, Schmid et al. 2004). INPP5B is isoprenylated at its C-terminus for membrane attachment.

**Preceded by:** I(1,4,5)P3 is phosphorylated to I(1,3,4,5)P4 by ITPKA/B/C in the cytosol, I(1,3,4)P3 is phosphorylated to I(1,3,4,5)P4 by ITPK1 in the cytosol

**Followed by:** I(1,3,4)P3 is phosphorylated to I(1,3,4,5)P4 by ITPK1 in the cytosol, I(1,3,4)P3 is phosphorylated to I(1,3,4,6)P4 by ITPK1 in the cytosol

**Literature references**


**Editions**

2011-10-28 Authored, Edited Williams, MG.
I(1,3,4)P3 is phosphorylated to I(1,3,4,5)P4 by ITPK1 in the cytosol

**Location:** Synthesis of IP3 and IP4 in the cytosol

**Stable identifier:** R-HSA-1855172

**Type:** transition

**Compartments:** cytosol

The broad-specificity enzyme inositol-tetrakisphosphate 1-kinase (ITPK1) phosphorylates inositol 1,3,4-trisphosphate (I(1,3,4)P3) to inositol 1,3,4,5-tetrakisphosphate (I(1,3,4,5)P4) (Wilson & Majerus 1996).

**Preceded by:** I(1,3,4,5)P4 is dephosphorylated to I(1,3,4)P3 by INPP5B at the plasma membrane, I(1,3,4,6)P4 is dephosphorylated to I(1,3,4)P3 by ITPK1 in the cytosol

**Followed by:** I(1,3,4,5)P4 is dephosphorylated to I(1,4,5)P3 by PTEN in the cytosol, I(1,3,4,5)P4 is dephosphorylated to I(1,3,4)P3 by INPP5B at the plasma membrane

**Literature references**


**Editions**

2011-10-28 Authored, Edited Williams, MG.
I(1,3,4)P3 is phosphorylated to I(1,3,4,6)P4 by ITPK1 in the cytosol

Location: Synthesis of IP3 and IP4 in the cytosol

Stable identifier: R-HSA-1855197

Type: transition

Compartments: cytosol

Inositol-tetrakisphosphate 1-kinase (ITPK1) phosphorylates inositol 1,3,4-trisphosphate (I(1,3,4)P3) to inositol 1,3,4,6-tetrakisphosphate (I(1,3,4,6)P4) (Wilson & Majerus 1996, Yang & Shears 2000).

Preceded by: I(1,3,4,5)P4 is dephosphorylated to I(1,3,4)P3 by INPP5B at the plasma membrane, I(1,3,4,6)P4 is dephosphorylated to I(1,3,4)P3 by ITPK1 in the cytosol

Followed by: I(1,3,4,6)P4 is dephosphorylated to I(3,4,6)P3 by ITPK1 in the cytosol

Literature references


Editions

2011-10-28 Author, Edited Williams, MG.
**I(1,3,4,6)P4 is dephosphorylated to I(1,3,4)P3 by ITPK1 in the cytosol**

**Location:** Synthesis of IP3 and IP4 in the cytosol

**Stable identifier:** R-HSA-1855171

**Type:** transition

**Compartments:** cytosol

Inositol-tetrakisphosphate 1-kinase (ITPK1) dephosphorylates inositol 1,3,4,6-tetrakisphosphate (I(1,3,4,6)P4) to inositol 1,3,4-trisphosphate (I(1,3,4)P3) (Ho et al. 2002).

**Preceded by:** I(1,3,4)P3 is phosphorylated to I(1,3,4,6)P4 by ITPK1 in the cytosol, I(3,4,6)P3 is phosphorylated to I(1,3,4,6)P4 by ITPK1 in the cytosol

**Followed by:** I(1,3,4)P3 is phosphorylated to I(1,3,4,5)P4 by ITPK1 in the cytosol, I(1,3,4)P3 is phosphorylated to I(1,3,4,6)P4 by ITPK1 in the cytosol

**Literature references**


**Editions**

2011-10-28 Authoring, Editing Williams, MG.
I(1,3,4,6)P4 is dephosphorylated to I(3,4,6)P3 by ITPK1 in the cytosol

**Location:** Synthesis of IP3 and IP4 in the cytosol

**Stable identifier:** R-HSA-1855159

**Type:** transition

**Compartments:** cytosol

Inositol-tetrakisphosphate 1-kinase (ITPK1) dephosphorylates inositol 1,3,4,6-tetrakisphosphate (I(1,3,4,6)P4) to inositol 3,4,6-trisphosphate (I(3,4,6)P3) (Ho et al. 2002).

**Preceded by:** I(1,3,4)P3 is phosphorylated to I(1,3,4,6)P4 by ITPK1 in the cytosol, I(3,4,6)P3 is phosphorylated to I(1,3,4,6)P4 by ITPK1 in the cytosol

**Followed by:** I(3,4,6)P3 is phosphorylated to I(1,3,4,6)P4 by ITPK1 in the cytosol

**Literature references**


**Editions**

2011-10-28 Authored, Edited Williams, MG.
Inositol-tetrakisphosphate 1-kinase (ITPK1) phosphorylates inositol 3,4,6-trisphosphate (I(3,4,6)P3) to inositol 1,3,4,6-tetrakisphosphate (I(1,3,4,6)P4) (Ho et al. 2002).

Preceded by: I(1,3,4,6)P4 is dephosphorylated to I(3,4,6)P3 by ITPK1 in the cytosol

Followed by: I(1,3,4,6)P4 is dephosphorylated to I(1,3,4)P3 by ITPK1 in the cytosol, I(1,3,4,6)P4 is dephosphorylated to I(3,4,6)P3 by ITPK1 in the cytosol

Literature references


Editions

2011-10-28 Authored, Edited Williams, MG.
Introduction

- Synthesis of IP3 and IP4 in the cytosol
  - PI(4,5)P2 is hydrolysed to I(1,4,5)P3 and DAG by cytosolic PLC[2] at the plasma membrane
  - PI(4,5)P2 is hydrolysed to I(1,4,5)P3 and DAG by tethered PLC[1] at the plasma membrane
  - PL(C)D4:3xCa2+ hydrolse PI(4,5)P2 to I(1,4,5)P3 and DAG at the ER membrane
  - I(1,4,5)P3 is phosphorylated to I(1,3,4,5)P4 by ITPKA/B/C in the cytosol
  - I(1,3,4,5)P4 is dephosphorylated to I(1,4,5)P3 by PTEN in the cytosol
  - I(1,3,4,5)P4 is dephosphorylated to I(1,3,4)P3 by INPP5[3]/ITPK1 in the cytosol
  - I(1,3,4)P3 is phosphorylated to I(1,3,4,5)P4 by ITPK1 in the cytosol
  - I(1,3,4)P3 is phosphorylated to I(1,3,4,6)P4 by ITPK1 in the cytosol
  - I(1,3,4,6)P4 is dephosphorylated to I(1,3,4)P3 by ITPK1 in the cytosol
  - I(1,3,4,6)P4 is dephosphorylated to I(3,4,6)P3 by ITPK1 in the cytosol
  - I(3,4,6)P3 is phosphorylated to I(1,3,4,6)P4 by ITPK1 in the cytosol

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