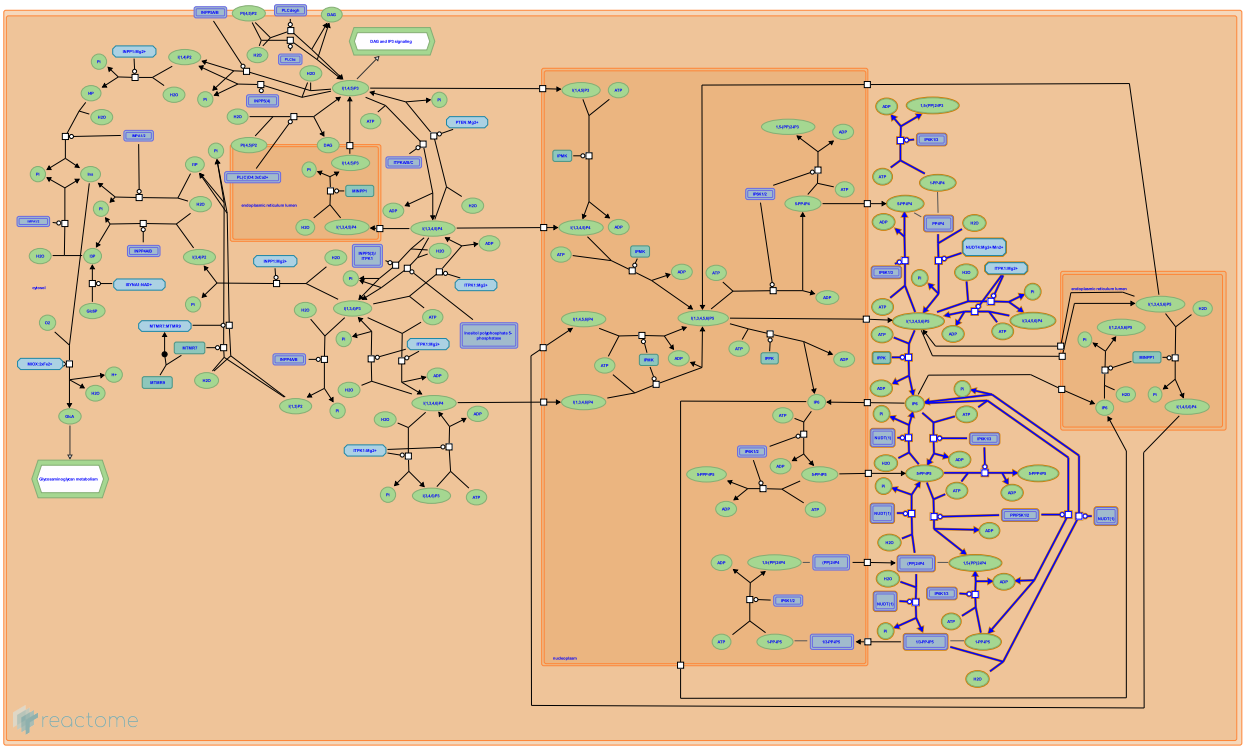
# Synthesis of pyrophosphates in the cytosol



Williams, MG., Wundenberg, T.

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



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.

01/05/2024

# 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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

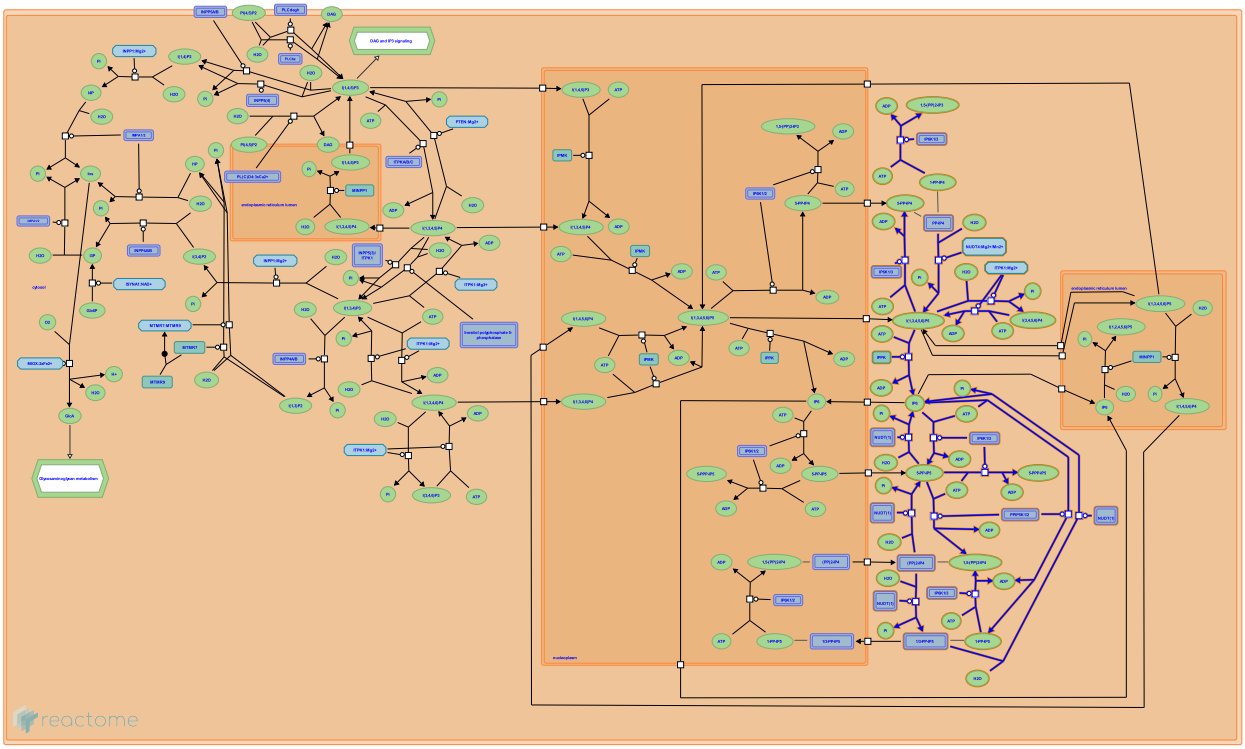
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

## Synthesis of pyrophosphates in the cytosol ↗

**Stable identifier:** R-HSA-1855167



Inositol phosphates such as IP4, IP5 and IP6 are converted to an even wider variety of IPs including the di- and triphospho inositol phosphates, also known as pyrophosphates (Irvine & Schell 2001, Alcazar-Romain & Wente 2008, York 2006, Monserrate and York 2010, Ho et al. 2002, Saiardi et al. 2001, Draskovic et al. 2008, Choi et al. 2007, Caffrey et al. 2000, Leslie et al. 2002).

## Literature references


Monserrate, JP., York, JD. (2010). Inositol phosphate synthesis and the nuclear processes they affect. *Curr Opin Cell Biol, 22*, 365-73. ↗

Wente, SR., Alcázar-Román, AR. (2008). Inositol polyphosphates: a new frontier for regulating gene expression. *Chromosoma, 117*, 1-13. ↗

Schell, MJ., Irvine, RF. (2001). Back in the water: the return of the inositol phosphates. *Nat Rev Mol Cell Biol, 2*, 327-38 . ↗

Ilc, G., Bhandari, R., Burton, A., Kovacevic, M., Saiardi, A., Podobnik, M. et al. (2008). Inositol hexakisphosphate kinase products contain diphosphate and triphosphate groups. *Chem Biol, 15*, 274-86. ↗

Safrany, ST., Leslie, NR., McLennan, AG. (2002). Cloning and characterisation of hAps1 and hAps2, human diadenosine polyphosphate-metabolising Nudix hydrolases. *BMC Biochem, 3*, 20. ↗


## Editions

| | | |
|---|---|---|
| 2011-10-28 | Authored, Edited | Williams, MG. |
| 2012-11-07 | Reviewed | Wundenberg, T. |

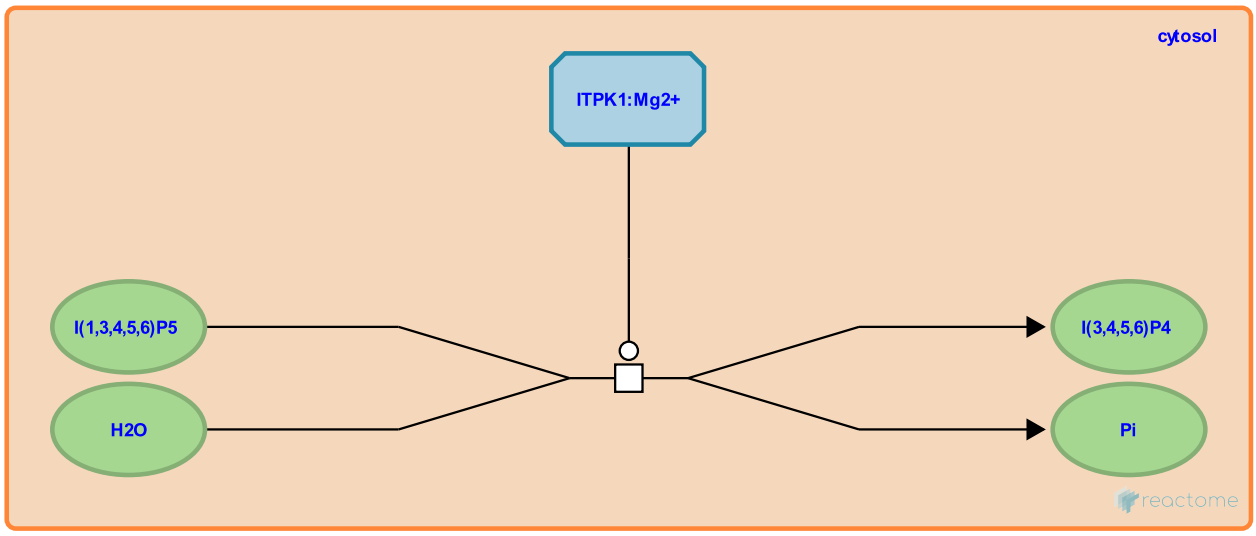
## I(1,3,4,5,6)P5 is dephosphorylated to I(3,4,5,6)P4 by ITPK1 in the cytosol

**Location:** Synthesis of pyrophosphates in the cytosol

**Stable identifier:** R-HSA-1855219

**Type:** transition

**Compartments:** cytosol




Inositol-tetrakisphosphate 1-kinase (ITPK1) dephosphorylates inositol 1,3,4,5,6-pentakisphosphate (I(1,3,4,5,6)P5) to inositol 3,4,5,6-tetrakisphosphate (I(3,4,5,6)P4) (Ho et al. 2002).

**Preceded by:** I(3,4,5,6)P4 is phosphorylated to I(1,3,4,5,6)P5 by ITPK1 in the cytosol, PP-IP4 is dephosphorylated to I(1,3,4,5,6)P5 by NUDT4 in the cytosol

**Followed by:** I(3,4,5,6)P4 is phosphorylated to I(1,3,4,5,6)P5 by ITPK1 in the cytosol

### Literature references

Zhang, T., Kwon, YU., Potter, BV., Carew, MA., Chung, SK., Riley, AM. et al. (2002). Regulation of Ins(3,4,5,6)P(4) signaling by a reversible kinase/phosphatase. *Curr Biol, 12,* 477-82.

### Editions

| | | |
|---|---|---|
| 2011-10-28 | Authored, Edited | Williams, MG. |
| 2012-11-07 | Reviewed | Wundenberg, T. |

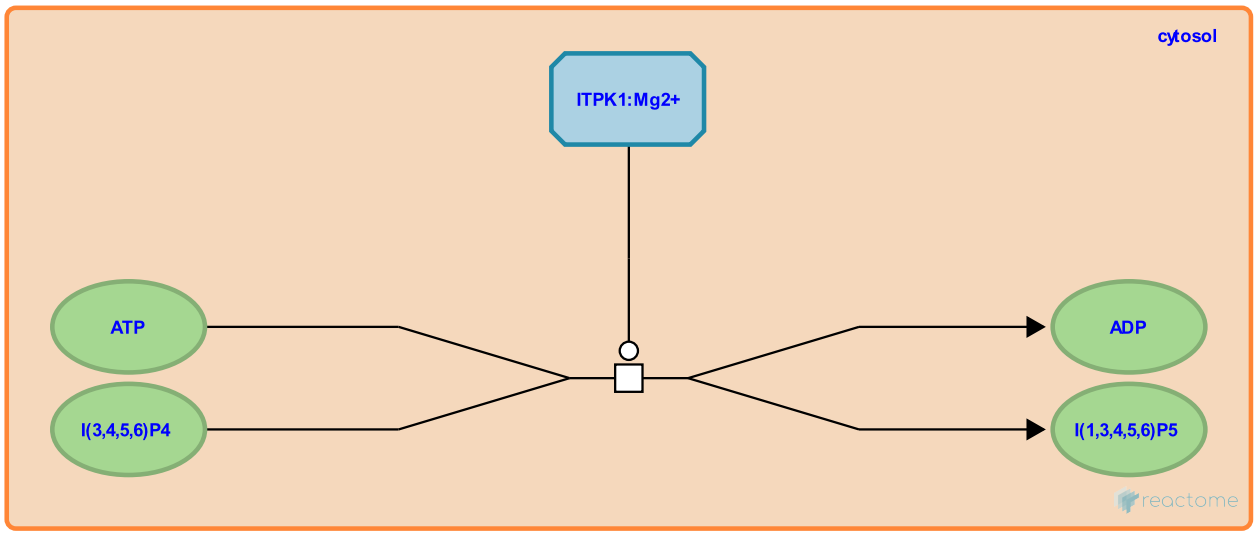
## I(3,4,5,6)P4 is phosphorylated to I(1,3,4,5,6)P5 by ITPK1 in the cytosol ↗

**Location:** Synthesis of pyrophosphates in the cytosol

**Stable identifier:** R-HSA-1855162

**Type:** transition

**Compartments:** cytosol




Inositoltetrakisphosphate 1-kinase (ITPK1) phosphorylates inositol 3,4,5,6-tetrakisphosphate (I(3,4,5,6)P4) to inositol 1,3,4,5,6-pentakisphosphate (I(1,3,4,5,6)P5) (Yang & Shears 2000).

**Preceded by:** I(1,3,4,5,6)P5 is dephosphorylated to I(3,4,5,6)P4 by ITPK1 in the cytosol

**Followed by:** I(1,3,4,5,6)P5 is dephosphorylated to I(3,4,5,6)P4 by ITPK1 in the cytosol, I(1,3,4,5,6)P5 is phosphorylated to 5-PP-IP4 by IP6K1/3 in the cytosol, I(1,3,4,5,6)P5 is phosphorylated to IP6 by IPPK in the cytosol

### Literature references

Yang, X., Shears, SB. (2000). Multitasking in signal transduction by a promiscuous human Ins(3,4,5,6)P(4) 1-kinase/Ins(1,3,4)P(3) 5/6-kinase. *Biochem J, 351*, 551-5. ↗

### Editions

| | | |
|---|---|---|
| 2011-10-28 | Authored, Edited | Williams, MG. |
| 2012-11-07 | Reviewed | Wundenberg, T. |

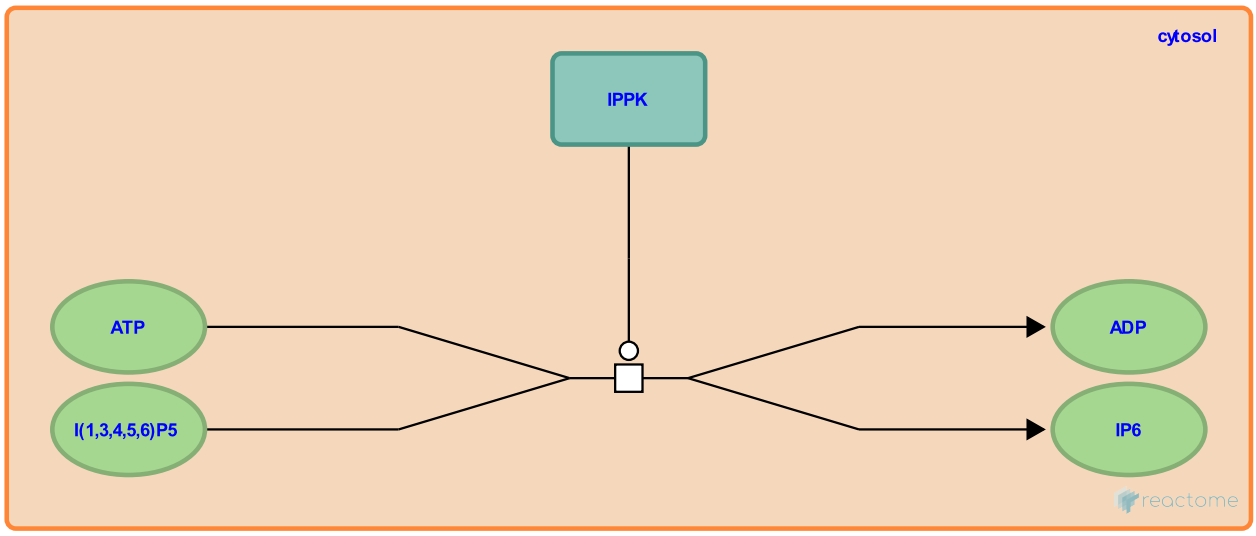
## I(1,3,4,5,6)P5 is phosphorylated to IP6 by IPPK in the cytosol ↗

**Location:** Synthesis of pyrophosphates in the cytosol

**Stable identifier:** R-HSA-1855179

**Type:** transition

**Compartments:** cytosol




Inositolpentakisphosphate 2-kinase (IPPK), also known as IP52K, phosphorylates inositol 1,3,4,5,6-pentakisphosphate (I(1,3,4,5,6)P5) to inositol 1,2,3,4,5,6-hexakisphosphate (IP6) (Verbski et al. 2002, Brehm et al. 2007, Choi et al. 2007).

**Preceded by:** I(3,4,5,6)P4 is phosphorylated to I(1,3,4,5,6)P5 by ITPK1 in the cytosol, PP-IP4 is dephosphorylated to I(1,3,4,5,6)P5 by NUDT4 in the cytosol

**Followed by:** IP6 is phosphorylated to 1-PP-IP5 by PPIP5K1/2 in the cytosol, IP6 is phosphorylated to 5-PP-IP5 by IP6K1/3 in the cytosol

## Literature references

Nalaskowski, MM., Windhorst, S., Schenk, TM., Kobras, M., Brehm, MA., Mayr, GW. et al. (2007). Intracellular localization of human Ins(1,3,4,5,6)P5 2-kinase. *Biochem J, 408*, 335-45. ↗

Cho, J., Williams, J., Falck, JR., Choi, JH., Shears, SB. (2007). Purification, sequencing, and molecular identification of a mammalian PP-InsP5 kinase that is activated when cells are exposed to hyperosmotic stress. *J Biol Chem, 282* , 30763-75. ↗

Wente, SR., Majerus, PW., Kisseleva, MV., Wilson, MP., Verbsky, JW. (2002). The synthesis of inositol hexakisphosphate. Characterization of human inositol 1,3,4,5,6-pentakisphosphate 2-kinase. *J Biol Chem, 277*, 31857-62. ↗

## Editions

| | | |
|---|---|---|
| 2011-10-28 | Authored, Edited | Williams, MG. |
| 2012-11-07 | Reviewed | Wundenberg, T. |

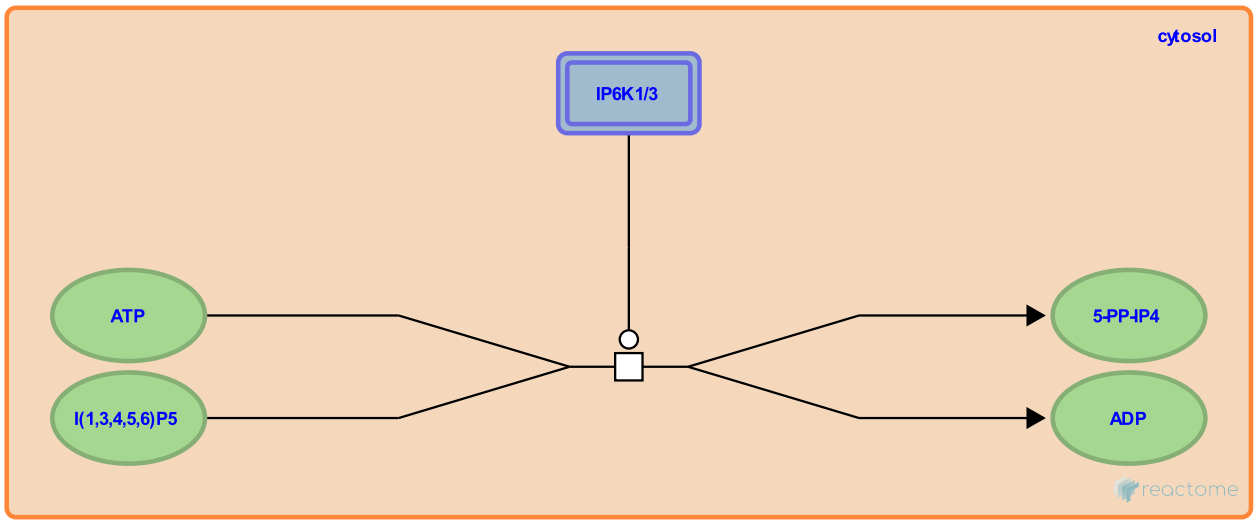
## I(1,3,4,5,6)P5 is phosphorylated to 5-PP-IP4 by IP6K1/3 in the cytosol ↗

**Location:** Synthesis of pyrophosphates in the cytosol

**Stable identifier:** R-HSA-1855223

**Type:** transition

**Compartments:** cytosol




Inositol hexakisphosphate kinase 1 (IP6K1) and 3 (IP6K3) phosphorylate inositol 1,3,4,5,6-pentakisphosphate (I(1,3,4,5,6)P5) to inositol 5-diphospho-(1,3,4,6)-tetrakisphosphate (5-PP-IP4) (Saiardi et al. 2001, Saiardi et al. 2000, Draskovic et al. 2008).

**Preceded by:** I(3,4,5,6)P4 is phosphorylated to I(1,3,4,5,6)P5 by ITPK1 in the cytosol, PP-IP4 is dephosphorylated to I(1,3,4,5,6)P5 by NUDT4 in the cytosol

**Followed by:** 1-PP-IP4 is phosphorylated to 1,5-(PP)2-IP3 by IP6K1/3 in the cytosol, PP-IP4 is dephosphorylated to I(1,3,4,5,6)P5 by NUDT4 in the cytosol

### Literature references


Saiardi, A., Snyder, SH., Caffrey, JJ., Shears, SB. (2000). The inositol hexakisphosphate kinase family. Catalytic flexibility and function in yeast vacuole biogenesis. *J Biol Chem, 275*, 24686-92. ↗

Ilc, G., Bhandari, R., Burton, A., Kovacevic, M., Saiardi, A., Podobnik, M. et al. (2008). Inositol hexakisphosphate kinase products contain diphosphate and triphosphate groups. *Chem Biol, 15*, 274-86. ↗

Nagata, E., Saiardi, A., Snyder, SH., Snowman, AM., Luo, HR. (2001). Identification and characterization of a novel inositol hexakisphosphate kinase. *J Biol Chem, 276*, 39179-85. ↗


### Editions

| | | |
|---|---|---|
| 2011-10-28 | Authored, Edited | Williams, MG. |
| 2012-11-07 | Reviewed | Wundenberg, T. |

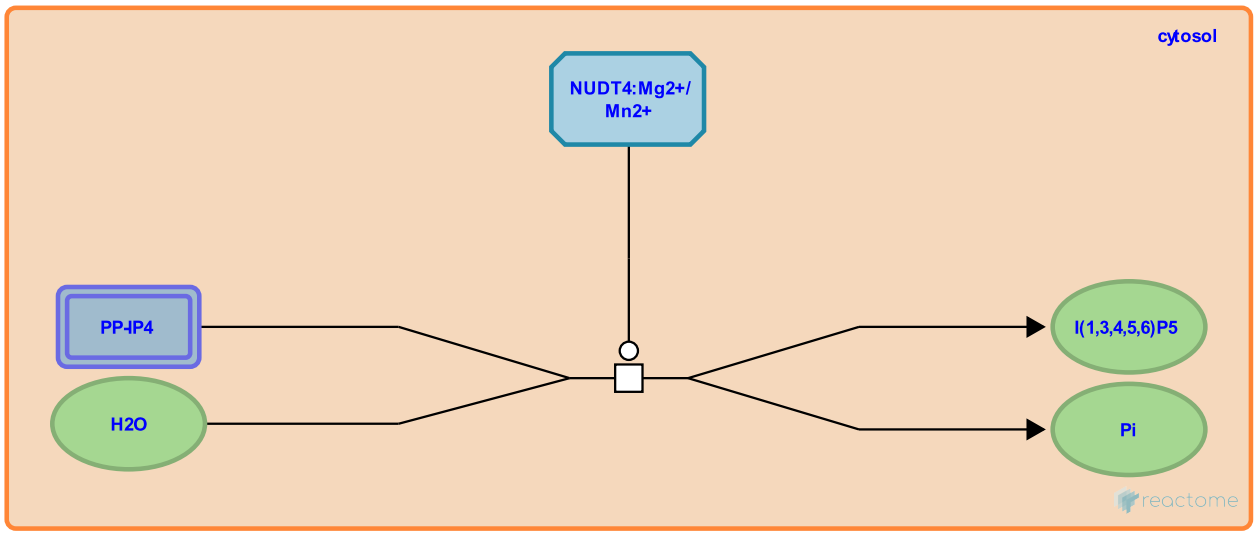
## PP-IP4 is dephosphorylated to I(1,3,4,5,6)P5 by NUDT4 in the cytosol ↗

**Location:** Synthesis of pyrophosphates in the cytosol

**Stable identifier:** R-HSA-1855166

**Type:** transition

**Compartments:** cytosol




Diphosphoinositol polyphosphate phosphohydrolase 2, also known as nucleoside diphosphate-linked moiety X motif 4 (NUDT4), dephosphorylates diphospho- tetrakisphosphate (PP-IP4) to inositol 1,3,4,5,6-pentakisphosphate (I(1,3,4,5,6)P5). The products made are: inositol 5-diphospho-1,3,4,6-tetrakisphosphate (5-PP-IP4); inositol 1-diphospho-3,4,5,6-tetrakisphosphate (1-PP-IP4); and inositol 3-diphospho-1,4,5,6-tetrakisphosphate (3-PP-IP4).

The following lists the above protein with its corresponding literature references: NUDT4 (Saiardi et al. 2001, Saiardi et al. 2000).

**Preceded by:** I(1,3,4,5,6)P5 is phosphorylated to 5-PP-IP4 by IP6K1/3 in the cytosol

**Followed by:** I(1,3,4,5,6)P5 is dephosphorylated to I(3,4,5,6)P4 by ITPK1 in the cytosol, I(1,3,4,5,6)P5 is phosphorylated to 5-PP-IP4 by IP6K1/3 in the cytosol, I(1,3,4,5,6)P5 is phosphorylated to IP6 by IPPK in the cytosol

## Literature references

Saiardi, A., Snyder, SH., Caffrey, JJ., Shears, SB. (2000). The inositol hexakisphosphate kinase family. Catalytic flexibility and function in yeast vacuole biogenesis. *J Biol Chem, 275*, 24686-92. ↗

Nagata, E., Saiardi, A., Snyder, SH., Snowman, AM., Luo, HR. (2001). Identification and characterization of a novel inositol hexakisphosphate kinase. *J Biol Chem, 276*, 39179-85. ↗

## Editions

| | | |
|---|---|---|
| 2011-10-28 | Authored, Edited | Williams, MG. |
| 2012-11-07 | Reviewed | Wundenberg, T. |

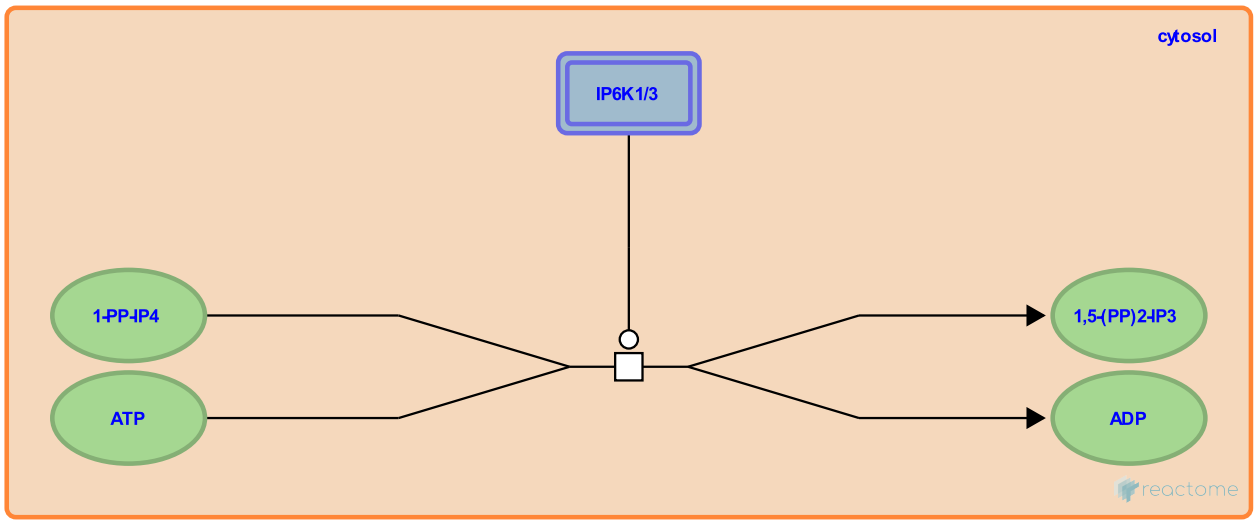
## 1-PP-IP4 is phosphorylated to 1,5-(PP)2-IP3 by IP6K1/3 in the cytosol ↗

**Location:** Synthesis of pyrophosphates in the cytosol

**Stable identifier:** R-HSA-1855193

**Type:** transition

**Compartments:** cytosol




Inositol hexakisphosphate kinase 1 (IP6K1) and 3 (IP6K3) phosphorylate inositol 1-diphospho-3,4,5,6-tetrakisphosphate (1-PP-IP4) to form inositol 1,5-bisdiphospho-3,4,6-trisphosphate (1,5-(PP)2-IP3) (Saiardi et al. 2001, Saiardi et al. 2000, Draskovic et al. 2008).

**Preceded by:** I(1,3,4,5,6)P5 is phosphorylated to 5-PP-IP4 by IP6K1/3 in the cytosol

### Literature references


Saiardi, A., Snyder, SH., Caffrey, JJ., Shears, SB. (2000). The inositol hexakisphosphate kinase family. Catalytic flexibility and function in yeast vacuole biogenesis. *J Biol Chem, 275*, 24686-92. ↗

Ilc, G., Bhandari, R., Burton, A., Kovacevic, M., Saiardi, A., Podobnik, M. et al. (2008). Inositol hexakisphosphate kinase products contain diphosphate and triphosphate groups. *Chem Biol, 15*, 274-86. ↗

Nagata, E., Saiardi, A., Snyder, SH., Snowman, AM., Luo, HR. (2001). Identification and characterization of a novel inositol hexakisphosphate kinase. *J Biol Chem, 276*, 39179-85. ↗


### Editions

| | | |
|---|---|---|
| 2011-10-28 | Authored, Edited | Williams, MG. |
| 2012-11-07 | Reviewed | Wundenberg, T. |

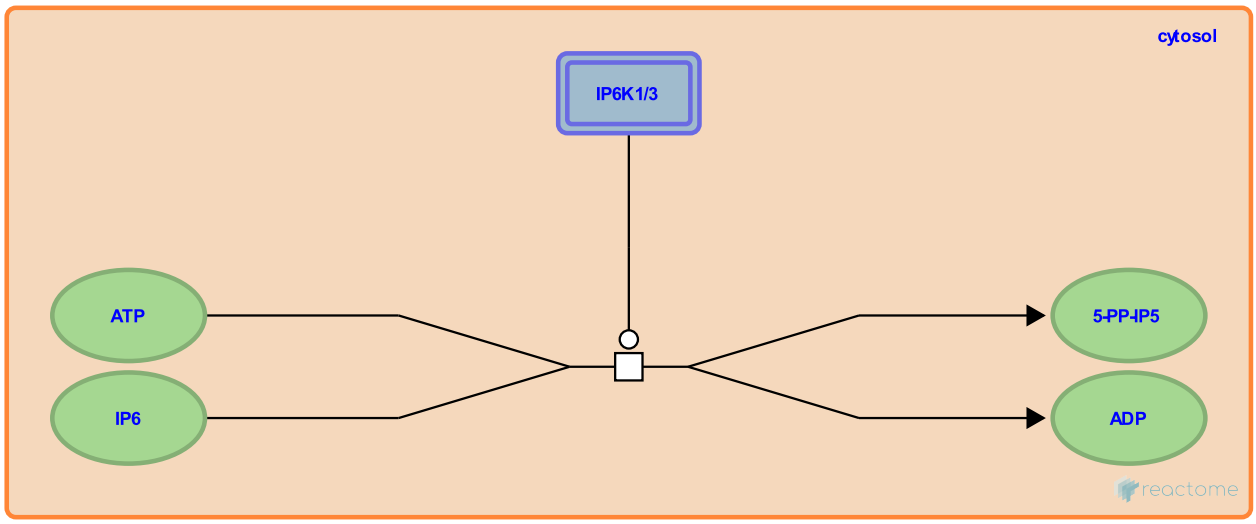
## IP6 is phosphorylated to 5-PP-IP5 by IP6K1/3 in the cytosol ↗

**Location:** Synthesis of pyrophosphates in the cytosol

**Stable identifier:** R-HSA-1855227

**Type:** transition

**Compartments:** cytosol




Inositol hexakisphosphate kinase 1 (IP6K1) and 3 (IP6K3) phosphorylate inositol 1,2,3,4,5,6-hexakisphosphate (IP6) to inositol 5-diphospho-1,2,3,4,6-pentakisphosphate (5-PP-IP5).

The following lists the above proteins with their corresponding literature references: IP6K1 (Saiardi et al. 2001, Mulugu et al. 2007, Draskovic et al. 2008; Lin et al. 2009) and IP6K3 (Saiardi et al. 2001, Draskovic et al. 2008).

**Preceded by:** 1/3 PP-IP5 is dephosphorylated to IP6 by NUDT(1) in the cytosol, I(1,3,4,5,6)P5 is phosphorylated to IP6 by IPPK in the cytosol, 5-PP-IP5 is dephosphorylated to IP6 by NUDT(1) in the cytosol

**Followed by:** 5-PP-IP5 is phosphorylated to 5-PPP-IP5 by IP6K1/3 in the cytosol, 5-PP-IP5 is dephosphorylated to IP6 by NUDT(1) in the cytosol, 5-PP-IP5 is phosphorylated to 1,5-(PP)2-IP4 by PPIP5K1/2 in the cytosol

## Literature references


Falck, JR., Ribeiro, AA., Mayr, GW., Choi, JH., York, JD., Vogel, G. et al. (2009). Structural analysis and detection of biological inositol pyrophosphates reveal that the family of VIP/diphosphoinositol pentakisphosphate kinases are 1/3-kinases. *J Biol Chem, 284*, 1863-72. ↗

Ilc, G., Bhandari, R., Burton, A., Kovacevic, M., Saiardi, A., Podobnik, M. et al. (2008). Inositol hexakisphosphate kinase products contain diphosphate and triphosphate groups. *Chem Biol, 15*, 274-86. ↗

Nagata, E., Saiardi, A., Snyder, SH., Snowman, AM., Luo, HR. (2001). Identification and characterization of a novel inositol hexakisphosphate kinase. *J Biol Chem, 276*, 39179-85. ↗

Haystead, TA., Dollins, DE., Ribeiro, AA., Otto, JC., Bai, W., York, JD. et al. (2007). A conserved family of enzymes that phosphorylate inositol hexakisphosphate. *Science, 316*, 106-9. ↗


## Editions

| | | |
|---|---|---|
| 2011-10-28 | Authored, Edited | Williams, MG. |
| 2012-11-07 | Reviewed | Wundenberg, T. |

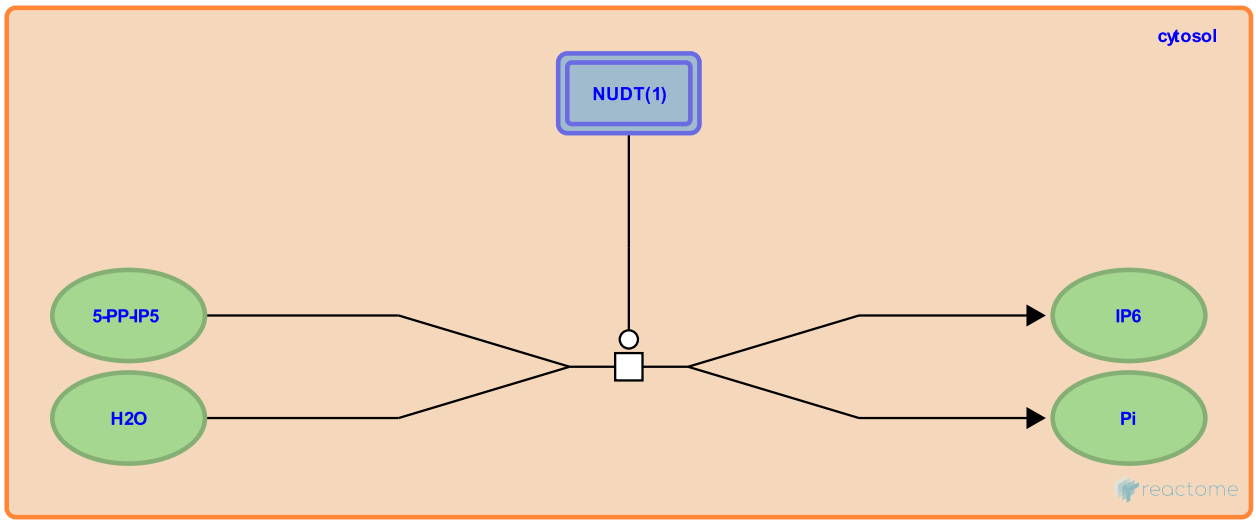
## 5-PP-IP5 is dephosphorylated to IP6 by NUDT(1) in the cytosol ↗

**Location:** Synthesis of pyrophosphates in the cytosol

**Stable identifier:** R-HSA-1855198

**Type:** transition

**Compartments:** cytosol




Diphosphoinositol polyphosphate phosphohydrolases (DIPP), also known as nucleoside diphosphate-linked moiety X motif (NUDT) proteins, dephosphorylate inositol 5-diphospho-1,2,3,4,6-pentakisphosphate (5-PP-IP5) to inositol 1,2,3,4,5,6-hexakisphosphate (IP6). The NUDT proteins involved are: nucleoside diphosphate-linked moiety X motif 3 (NUDT3), 4 (NUDT4), 10 (NUDT10), and 11 (NUDT11).

The following lists the above proteins with their corresponding literature references: NUDT3 (Safrany et al. 1999, Safrany et al. 1998, Yang et al. 1999, Caffrey et al. 2000), NUDT4 (Caffrey et al. 2000), NUDT10 (Leslie et al. 2002, Hidaka et al. 2002) and NUDT11 (Leslie et al. 2002, Hidaka et al. 2002).

**Preceded by:** IP6 is phosphorylated to 5-PP-IP5 by IP6K1/3 in the cytosol, (PP)2-IP4 is dephosphorylated to 5-PP-IP5 by NUDT(1) in the cytosol

**Followed by:** IP6 is phosphorylated to 1-PP-IP5 by PPIP5K1/2 in the cytosol, IP6 is phosphorylated to 5-PP-IP5 by IP6K1/3 in the cytosol

### Literature references


Safrany, ST., Yang, X., Shears, SB. (1999). Site-directed mutagenesis of diphosphoinositol polyphosphate phosphohydrolase, a dual specificity NUDT enzyme that attacks diadenosine polyphosphates and diphosphoinositol polyphosphates. *J Biol Chem, 274*, 35434-40. ↗

Barnes, LD., Safrany, ST., Falck, JR., Ingram, SW., Cartwright, JL., Shears, SB. et al. (1999). The diadenosine hexaphosphate hydrolases from Schizosaccharomyces pombe and Saccharomyces cerevisiae are homologues of the human diphosphoinositol polyphosphate phosphohydrolase. Overlapping substrate specificities in a MutT-type protein. *J Biol Chem, 274*, 21735-40. ↗

Barnes, LD., Nickel, GC., Zhang, T., Hidaka, K., Falck, JR., Caffrey, JJ. et al. (2002). An adjacent pair of human NUDT genes on chromosome X are preferentially expressed in testis and encode two new isoforms of diphosphoinositol polyphosphate phosphohydrolase. *J Biol Chem, 277*, 32730-8. ↗

Safrany, ST., Leslie, NR., McLennan, AG. (2002). Cloning and characterisation of hAps1 and hAps2, human diadenosine polyphosphate-metabolising Nudix hydrolases. *BMC Biochem, 3*, 20. ↗

Safrany, ST., Caffrey, JJ., Yang, X., Shears, SB. (2000). Discovery of molecular and catalytic diversity among human diphosphoinositol-polyphosphate phosphohydrolases. An expanding Nudt family. *J Biol Chem, 275*, 12730-6. ↗

## Editions

| | | |
|---|---|---|
| 2011-10-28 | Authored, Edited | Williams, MG. |
| 2012-11-07 | Reviewed | Wundenberg, T. |

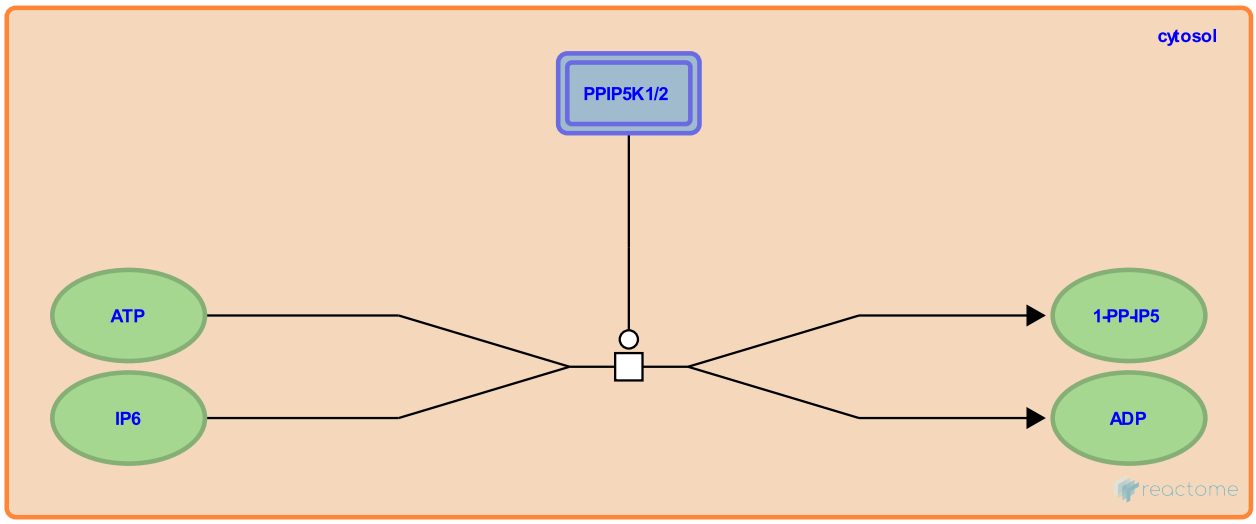
## IP6 is phosphorylated to 1-PP-IP5 by PPIP5K1/2 in the cytosol ↗

**Location:** Synthesis of pyrophosphates in the cytosol

**Stable identifier:** R-HSA-1855216

**Type:** transition

**Compartments:** cytosol




Inositol hexakisphosphate and diphosphoinositol-pentakisphosphate kinase 1/2 (PPIP5K1) and 2 (PPIP5K2) phosphorylate inositol 1,2,3,4,5,6-hexakisphosphate (IP6) to inositol 1-diphospho-2,3,4,5,6-pentakisphosphate (1-PP-IP5)) (Fridy et al. 2007, Mulugu et al. 2007, Choi et al. 2007, Lin et al. 2009; Wang et al. 2011).

**Preceded by:** 1/3 PP-IP5 is dephosphorylated to IP6 by NUDT(1) in the cytosol, I(1,3,4,5,6)P5 is phosphorylated to IP6 by IPPK in the cytosol, 5-PP-IP5 is dephosphorylated to IP6 by NUDT(1) in the cytosol

**Followed by:** 1/3 PP-IP5 is dephosphorylated to IP6 by NUDT(1) in the cytosol, 1-PP-IP5 is phosphorylated to 1,5-(PP)2-IP4 by IP6K1/3 in the cytosol

### Literature references


Falck, JR., Ribeiro, AA., Mayr, GW., Choi, JH., York, JD., Vogel, G. et al. (2009). Structural analysis and detection of biological inositol pyrophosphates reveal that the family of VIP/diphosphoinositol pentakisphosphate kinases are 1/3-kinases. *J Biol Chem, 284*, 1863-72. ↗

Cho, J., Williams, J., Falck, JR., Choi, JH., Shears, SB. (2007). Purification, sequencing, and molecular identification of a mammalian PP-InsP5 kinase that is activated when cells are exposed to hyperosmotic stress. *J Biol Chem, 282* , 30763-75. ↗

Dollins, DE., Otto, JC., York, JD., Fridy, PC. (2007). Cloning and characterization of two human VIP1-like inositol hexakisphosphate and diphosphoinositol pentakisphosphate kinases. *J Biol Chem, 282*, 30754-62. ↗

Falck, JR., Wang, H., Shears, SB., Hall, TM. (2012). Structural basis for an inositol pyrophosphate kinase surmounting phosphate crowding. *Nat. Chem. Biol., 8*, 111-6. ↗

Haystead, TA., Dollins, DE., Ribeiro, AA., Otto, JC., Bai, W., York, JD. et al. (2007). A conserved family of enzymes that phosphorylate inositol hexakisphosphate. *Science, 316*, 106-9. ↗


### Editions

| | | |
|---|---|---|
| 2011-10-28 | Authored, Edited | Williams, MG. |
| 2012-11-07 | Reviewed | Wundenberg, T. |

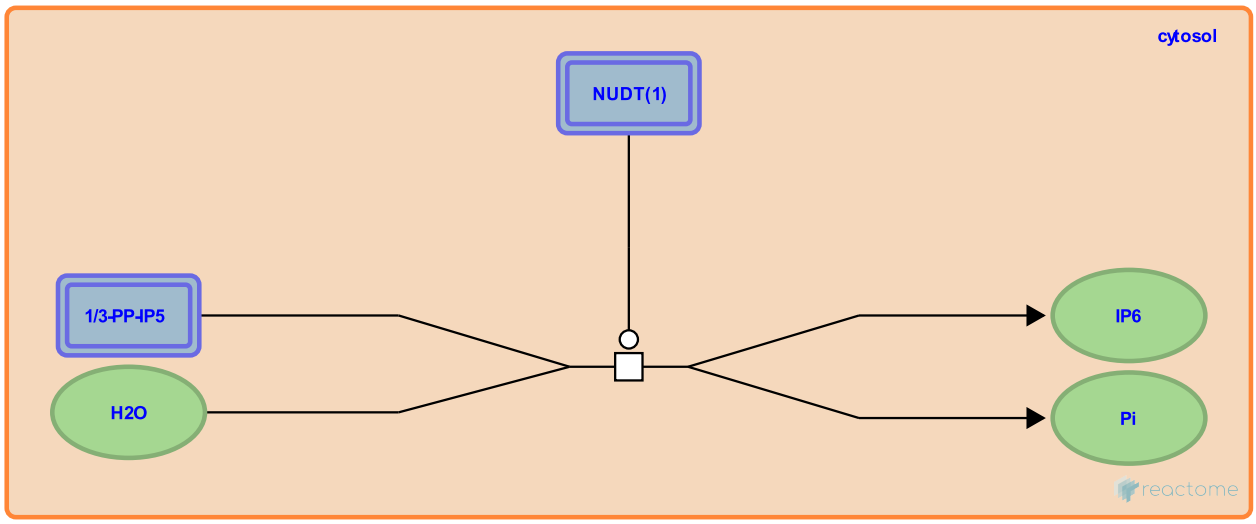
## 1/3 PP-IP5 is dephosphorylated to IP6 by NUDT(1) in the cytosol ↗

**Location:** Synthesis of pyrophosphates in the cytosol

**Stable identifier:** R-HSA-2023971

**Type:** transition

**Compartments:** cytosol




Diphosphoinositol polyphosphate phosphohydrolases, also known as nucleoside diphosphate-linked moiety X motif (NUDT) proteins, dephosphorylate inositol diphospho-pentakisphosphate (PP-IP5) to inositol 1,2,3,4,5,6-hexakisphosphate (IP6). The NUDT proteins involved are: nucleoside diphosphate-linked moiety X motif 3 (NUDT3), 4 (NUDT4), 10 (NUDT10), and 11 (NUDT11). The reactants consumed are: inositol 1-diphospho-2,3,4,5,6-pentakisphosphate (1-PP-IP5) and 3-diphospho-1,2,4,5,6-pentakisphosphate (3-PP-IP5).

The following lists the above proteins with their corresponding literature references: NUDT3 (Safrany et al. 1999, Safrany et al. 1998, Yang et al. 1999, Caffrey et al. 2000), NUDT4 (Caffrey et al. 2000), NUDT10 (Leslie et al. 2002, Hidaka et al. 2002) and NUDT11 (Leslie et al. 2002, Hidaka et al. 2002).

**Preceded by:** IP6 is phosphorylated to 1-PP-IP5 by PPIP5K1/2 in the cytosol, (PP)2-IP4 is dephosphorylated to 1/3-PP-IP5 by NUDT(1) in the cytosol

**Followed by:** IP6 is phosphorylated to 5-PP-IP5 by IP6K1/3 in the cytosol, IP6 is phosphorylated to 1-PP-IP5 by PPIP5K1/2 in the cytosol

## Literature references


Safrany, ST., Yang, X., Shears, SB. (1999). Site-directed mutagenesis of diphosphoinositol polyphosphate phosphohydrolase, a dual specificity NUDT enzyme that attacks diadenosine polyphosphates and diphosphoinositol polyphosphates. *J Biol Chem, 274*, 35434-40. ↗

Barnes, LD., Safrany, ST., Falck, JR., Ingram, SW., Cartwright, JL., Shears, SB. et al. (1999). The diadenosine hexaphosphate hydrolases from Schizosaccharomyces pombe and Saccharomyces cerevisiae are homologues of the human diphosphoinositol polyphosphate phosphohydrolase. Overlapping substrate specificities in a MutT-type protein. *J Biol Chem, 274*, 21735-40. ↗

Barnes, LD., Nickel, GC., Zhang, T., Hidaka, K., Falck, JR., Caffrey, JJ. et al. (2002). An adjacent pair of human NUDT genes on chromosome X are preferentially expressed in testis and encode two new isoforms of diphosphoinositol polyphosphate phosphohydrolase. *J Biol Chem, 277*, 32730-8. ↗

Safrany, ST., Leslie, NR., McLennan, AG. (2002). Cloning and characterisation of hAps1 and hAps2, human diadenosine polyphosphate-metabolising Nudix hydrolases. *BMC Biochem, 3*, 20. ↗

Safrany, ST., Caffrey, JJ., Yang, X., Shears, SB. (2000). Discovery of molecular and catalytic diversity among human diphosphoinositol-polyphosphate phosphohydrolases. An expanding Nudt family. *J Biol Chem, 275*, 12730-6. ↗

## Editions

| | | |
|---|---|---|
| 2011-10-28 | Authored, Edited | Williams, MG. |
| 2012-11-07 | Reviewed | Wundenberg, T. |

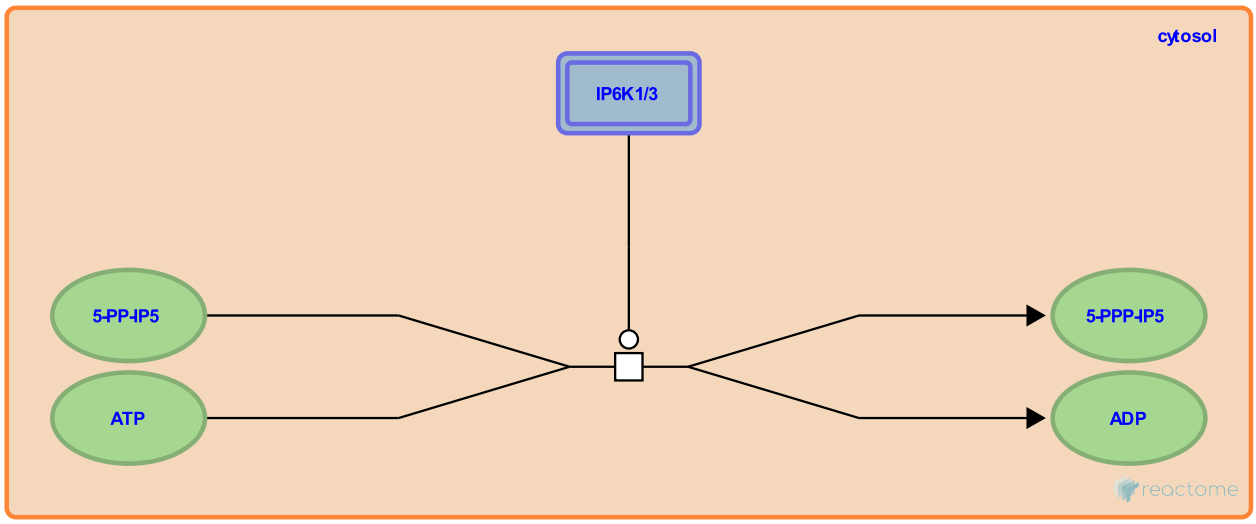
## 5-PP-IP5 is phosphorylated to 5-PPP-IP5 by IP6K1/3 in the cytosol ↗

**Location:** Synthesis of pyrophosphates in the cytosol

**Stable identifier:** R-HSA-1855158

**Type:** transition

**Compartments:** cytosol




Inositol hexakisphosphate kinase 1 (IP6K1) and 3 (IP6K3) phosphorylate inositol 5-diphospho-1,2,3,4,6-pentakisphosphate (5-PP-IP5) to inositol 5-triphospho- 1,2,3,4,6-pentakisphosphate (5-PPP-IP5).

The following lists the above proteins with their corresponding literature references: IP6K1 (Saiardi et al. 2001, Draskovic et al. 2008) and IP6K3 (Saiardi et al. 2001, Draskovic et al. 2008).

**Preceded by:** IP6 is phosphorylated to 5-PP-IP5 by IP6K1/3 in the cytosol, (PP)2-IP4 is dephosphorylated to 5-PP-IP5 by NUDT(1) in the cytosol

### Literature references

Ilc, G., Bhandari, R., Burton, A., Kovacevic, M., Saiardi, A., Podobnik, M. et al. (2008). Inositol hexakisphosphate kinase products contain diphosphate and triphosphate groups. *Chem Biol, 15*, 274-86. ↗

Nagata, E., Saiardi, A., Snyder, SH., Snowman, AM., Luo, HR. (2001). Identification and characterization of a novel inositol hexakisphosphate kinase. *J Biol Chem, 276*, 39179-85. ↗

### Editions

| | | |
|---|---|---|
| 2011-10-28 | Authored, Edited | Williams, MG. |
| 2012-11-07 | Reviewed | Wundenberg, T. |

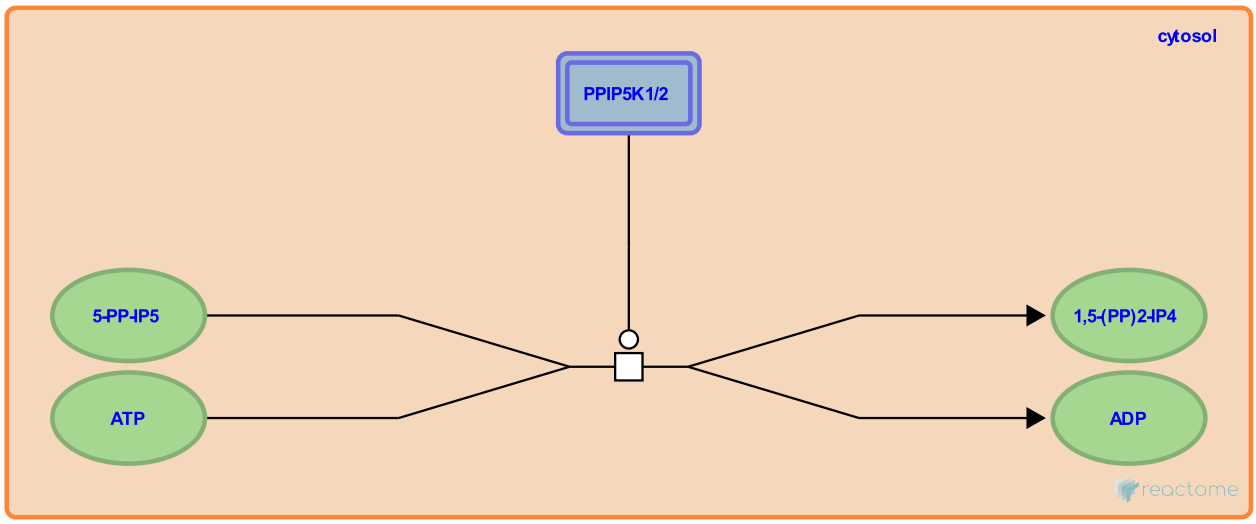
## 5-PP-IP5 is phosphorylated to 1,5-(PP)2-IP4 by PPIP5K1/2 in the cytosol ↗

**Location:** Synthesis of pyrophosphates in the cytosol

**Stable identifier:** R-HSA-1855182

**Type:** transition

**Compartments:** cytosol




Inositol hexakisphosphate and diphosphoinositol-pentakisphosphate kinase 1/2 (PPIP5K1) and 2 (PPIP5K2) phosphorylate inositol 5-diphospho-1,2,3,4,6-pentakisphosphate (5-PP-IP5) to inositol 1,5-bisdiphospho-2,3,4,6-tetrakisphosphate (1,5-(PP)2-IP4) (Fridy et al. 2007, Mulugu et al. 2007, Choi et al. 2007, Lin et al. 2009).

**Preceded by:** IP6 is phosphorylated to 5-PP-IP5 by IP6K1/3 in the cytosol, (PP)2-IP4 is dephosphorylated to 5-PP-IP5 by NUDT(1) in the cytosol

**Followed by:** (PP)2-IP4 is dephosphorylated to 5-PP-IP5 by NUDT(1) in the cytosol, (PP)2-IP4 is dephosphorylated to 1/3-PP-IP5 by NUDT(1) in the cytosol

### Literature references


Falck, JR., Ribeiro, AA., Mayr, GW., Choi, JH., York, JD., Vogel, G. et al. (2009). Structural analysis and detection of biological inositol pyrophosphates reveal that the family of VIP/diphosphoinositol pentakisphosphate kinases are 1/3-kinases. *J Biol Chem, 284*, 1863-72. ↗

Cho, J., Williams, J., Falck, JR., Choi, JH., Shears, SB. (2007). Purification, sequencing, and molecular identification of a mammalian PP-InsP5 kinase that is activated when cells are exposed to hyperosmotic stress. *J Biol Chem, 282* , 30763-75. ↗

Dollins, DE., Otto, JC., York, JD., Fridy, PC. (2007). Cloning and characterization of two human VIP1-like inositol hexakisphosphate and diphosphoinositol pentakisphosphate kinases. *J Biol Chem, 282*, 30754-62. ↗

Haystead, TA., Dollins, DE., Ribeiro, AA., Otto, JC., Bai, W., York, JD. et al. (2007). A conserved family of enzymes that phosphorylate inositol hexakisphosphate. *Science, 316*, 106-9. ↗


### Editions

| | | |
|---|---|---|
| 2011-10-28 | Authored, Edited | Williams, MG. |
| 2012-11-07 | Reviewed | Wundenberg, T. |

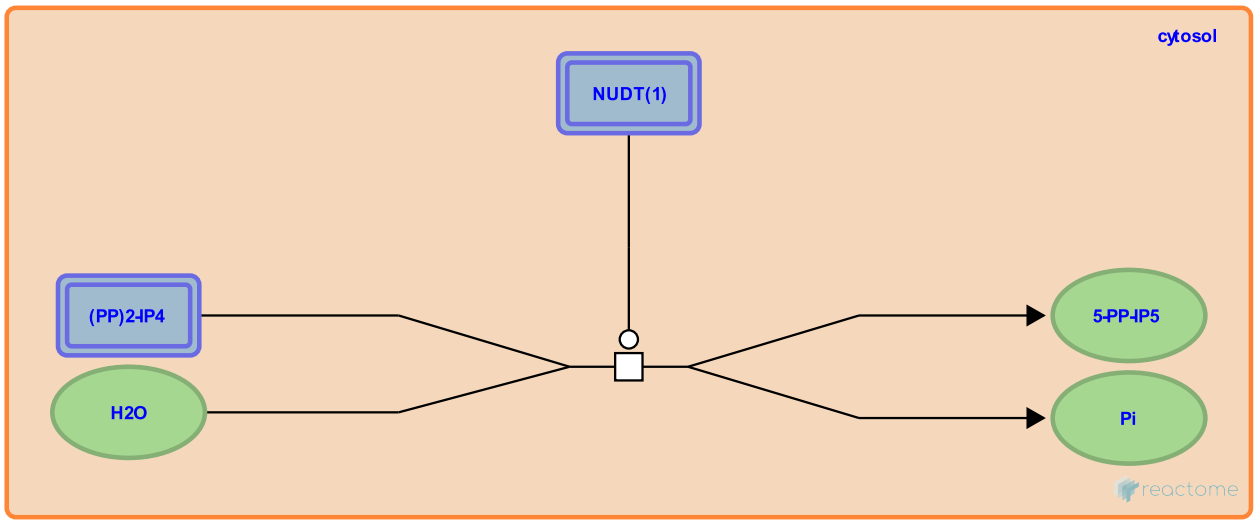
## (PP)2-IP4 is dephosphorylated to 5-PP-IP5 by NUDT(1) in the cytosol ↗

**Location:** Synthesis of pyrophosphates in the cytosol

**Stable identifier:** R-HSA-1855165

**Type:** transition

**Compartments:** cytosol




Diphosphoinositol polyphosphate phosphohydrolases (DIPP), also known as nucleoside diphosphate-linked moiety X motif (NUDT) proteins, dephosphorylate inositol bisdiphospho-tetrakisphosphate ((PP)2-IP4) to inositol 5-diphospho-1,2,3,4,6-pentakisphosphate (5-PP-IP5). The NUDT proteins involved are: nucleoside diphosphate-linked moiety X motif 3 (NUDT3), 4 (NUDT4), 10 (NUDT10), and 11 (NUDT11). The reactants consumed are: inositol 1,5-bisdiphospho-2,3,4,6-tetrakisphosphate (1,5-(PP)2-IP4) and inositol 3,5-bisdiphospho-1,2,4,6-tetrakisphosphate (3,5-(PP)2-IP4).

The following lists the above proteins with their corresponding literature references: NUDT3 (Safrany et al. 1999, Safrany et al. 1998, Yang et al. 1999, Caffrey et al. 2000), NUDT4 (Caffrey et al. 2000), NUDT10 (Leslie et al. 2002, Hidaka et al. 2002) and NUDT11 (Leslie et al. 2002, Hidaka et al. 2002).

**Preceded by:** 1-PP-IP5 is phosphorylated to 1,5-(PP)2-IP4 by IP6K1/3 in the cytosol, 5-PP-IP5 is phosphorylated to 1,5-(PP)2-IP4 by PPIP5K1/2 in the cytosol

**Followed by:** 5-PP-IP5 is phosphorylated to 5-PPP-IP5 by IP6K1/3 in the cytosol, 5-PP-IP5 is dephosphorylated to IP6 by NUDT(1) in the cytosol, 5-PP-IP5 is phosphorylated to 1,5-(PP)2-IP4 by PPIP5K1/2 in the cytosol

### Literature references


Safrany, ST., Yang, X., Shears, SB. (1999). Site-directed mutagenesis of diphosphoinositol polyphosphate phosphohydrolase, a dual specificity NUDT enzyme that attacks diadenosine polyphosphates and diphosphoinositol polyphosphates. *J Biol Chem, 274*, 35434-40. ↗

Barnes, LD., Safrany, ST., Falck, JR., Ingram, SW., Cartwright, JL., Shears, SB. et al. (1999). The diadenosine hexaphosphate hydrolases from Schizosaccharomyces pombe and Saccharomyces cerevisiae are homologues of the human diphosphoinositol polyphosphate phosphohydrolase. Overlapping substrate specificities in a MutT-type protein. *J Biol Chem, 274*, 21735-40. ↗

Safrany, ST., Leslie, NR., McLennan, AG. (2002). Cloning and characterisation of hAps1 and hAps2, human diadenosine polyphosphate-metabolising Nudix hydrolases. *BMC Biochem, 3*, 20. ↗

Barnes, LD., Nickel, GC., Zhang, T., Hidaka, K., Falck, JR., Caffrey, JJ. et al. (2002). An adjacent pair of human NUDT genes on chromosome X are preferentially expressed in testis and encode two new isoforms of diphosphoinositol polyphosphate phosphohydrolase. *J Biol Chem, 277*, 32730-8. ↗

Safrany, ST., Caffrey, JJ., Yang, X., Shears, SB. (2000). Discovery of molecular and catalytic diversity among human diphosphoinositol-polyphosphate phosphohydrolases. An expanding Nudt family. *J Biol Chem, 275*, 12730-6. ↗

## Editions

| | | |
|---|---|---|
| 2011-10-28 | Authored, Edited | Williams, MG. |
| 2012-11-07 | Reviewed | Wundenberg, T. |

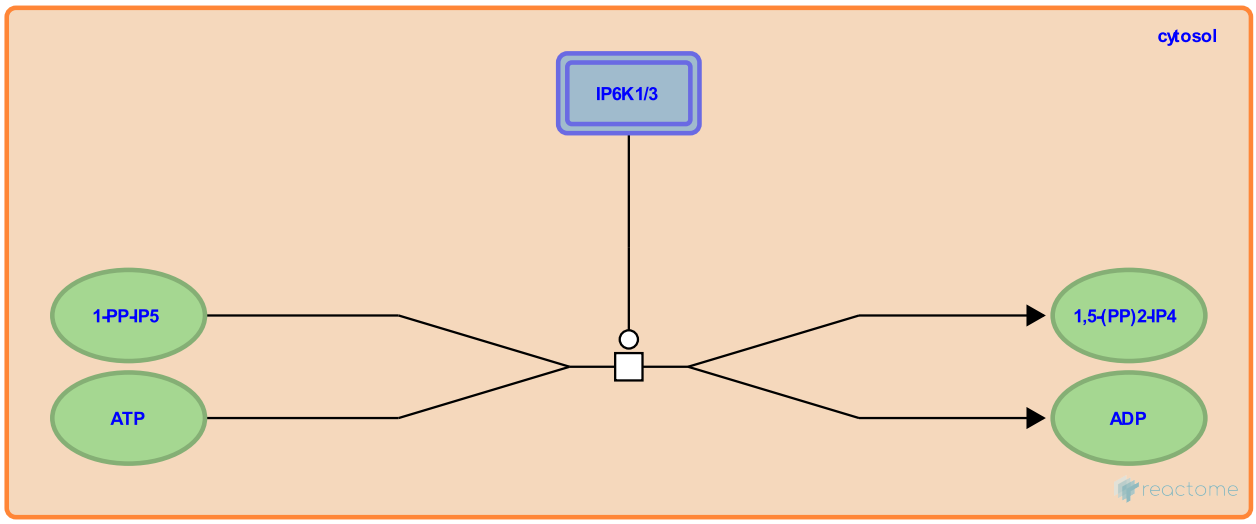
## 1-PP-IP5 is phosphorylated to 1,5-(PP)2-IP4 by IP6K1/3 in the cytosol ↗

**Location:** Synthesis of pyrophosphates in the cytosol

**Stable identifier:** R-HSA-1855194

**Type:** transition

**Compartments:** cytosol




Inositol hexakisphosphate kinase 1 (IP6K1) and 3 (IP6K3) phosphorylate 1-diphospho-2,3,4,5,6-pentakisphosphate (1-PP-IP5) to form inositol 1,5-bisdiphospho-2,3,4,6-tetrakisphosphate (1,5-(PP)2-IP4) (Saiardi et al. 2001, Mulugu et al. 2007).

**Preceded by:** IP6 is phosphorylated to 1-PP-IP5 by PPIP5K1/2 in the cytosol, (PP)2-IP4 is dephosphorylated to 1/3-PP-IP5 by NUDT(1) in the cytosol

**Followed by:** (PP)2-IP4 is dephosphorylated to 5-PP-IP5 by NUDT(1) in the cytosol, (PP)2-IP4 is dephosphorylated to 1/3-PP-IP5 by NUDT(1) in the cytosol

### Literature references

Nagata, E., Saiardi, A., Snyder, SH., Snowman, AM., Luo, HR. (2001). Identification and characterization of a novel inositol hexakisphosphate kinase. *J Biol Chem, 276*, 39179-85. ↗

Haystead, TA., Dollins, DE., Ribeiro, AA., Otto, JC., Bai, W., York, JD. et al. (2007). A conserved family of enzymes that phosphorylate inositol hexakisphosphate. *Science, 316*, 106-9. ↗

### Editions

| | | |
|---|---|---|
| 2011-10-28 | Authored, Edited | Williams, MG. |
| 2012-11-07 | Reviewed | Wundenberg, T. |

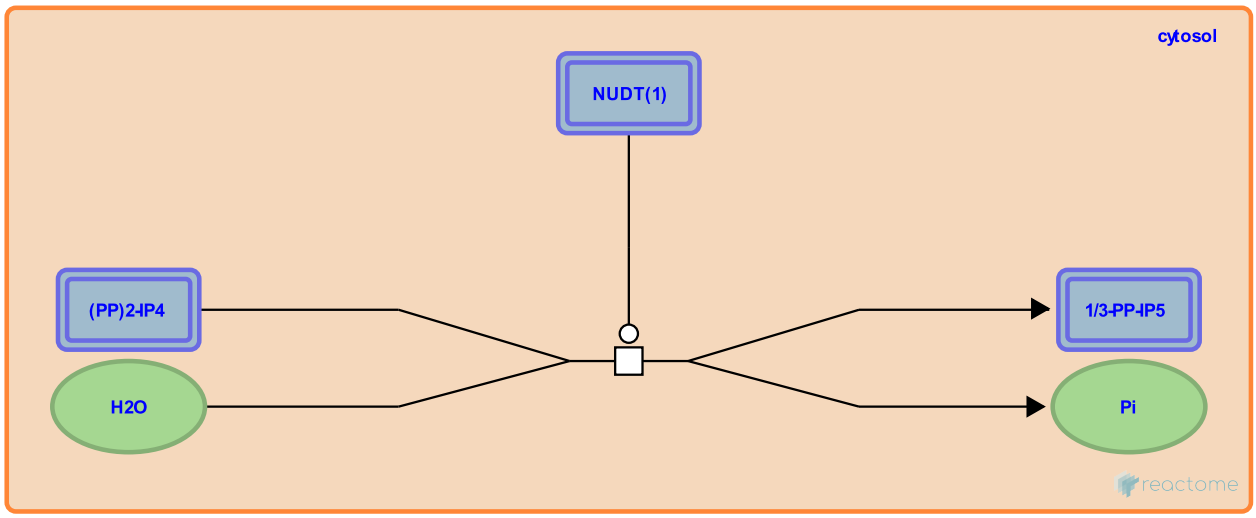
## (PP)2-IP4 is dephosphorylated to 1/3-PP-IP5 by NUDT(1) in the cytosol ↗

**Location:** Synthesis of pyrophosphates in the cytosol

**Stable identifier:** R-HSA-2023973

**Type:** transition

**Compartments:** cytosol




Diphosphoinositol polyphosphate phosphohydrolases (DIPP), also known as nucleoside diphosphate-linked moiety X motif (NUDT) proteins, dephosphorylate inositol bisdiphospho-tetrakisphosphate ((PP)2-IP4) to inositol diphospho-pentakisphosphate (PP-IP5). The NUDT proteins involved are: nucleoside diphosphate-linked moiety X motif 3 (NUDT3), 4 (NUDT4), 10 (NUDT10), and 11 (NUDT11). The reactants consumed are: inositol 1,5-bisdiphospho-2,3,4,6-tetrakisphosphate (1,5-(PP)2-IP4) and inositol 3,5-bisdiphospho-1,2,4,6-tetrakisphosphate (3,5-(PP)2-IP4). The products made are: inositol 1-diphospho-2,3,4,5,6-pentakisphosphate (1-PP-IP5) and 3-diphospho-1,2,4,5,6-pentakisphosphate (3-PP-IP5).

The following lists the above proteins with their corresponding literature references: NUDT3 (Safrany et al. 1999, Safrany et al. 1998, Yang et al. 1999, Caffrey et al. 2000), NUDT4 (Caffrey et al. 2000), NUDT10 (Leslie et al. 2002, Hidaka et al. 2002) and NUDT11 (Leslie et al. 2002, Hidaka et al. 2002).

**Preceded by:** 1-PP-IP5 is phosphorylated to 1,5-(PP)2-IP4 by IP6K1/3 in the cytosol, 5-PP-IP5 is phosphorylated to 1,5-(PP)2-IP4 by PPIP5K1/2 in the cytosol

**Followed by:** 1/3 PP-IP5 is dephosphorylated to IP6 by NUDT(1) in the cytosol, 1-PP-IP5 is phosphorylated to 1,5-(PP)2-IP4 by IP6K1/3 in the cytosol

### Literature references


Safrany, ST., Yang, X., Shears, SB. (1999). Site-directed mutagenesis of diphosphoinositol polyphosphate phosphohydrolase, a dual specificity NUDT enzyme that attacks diadenosine polyphosphates and diphosphoinositol polyphosphates. *J Biol Chem, 274*, 35434-40. ↗

Barnes, LD., Safrany, ST., Falck, JR., Ingram, SW., Cartwright, JL., Shears, SB. et al. (1999). The diadenosine hexaphosphate hydrolases from Schizosaccharomyces pombe and Saccharomyces cerevisiae are homologues of the human diphosphoinositol polyphosphate phosphohydrolase. Overlapping substrate specificities in a MutT-type protein. *J Biol Chem, 274*, 21735-40. ↗

Safrany, ST., Leslie, NR., McLennan, AG. (2002). Cloning and characterisation of hAps1 and hAps2, human diadenosine polyphosphate-metabolising Nudix hydrolases. *BMC Biochem, 3*, 20. ↗

Barnes, LD., Nickel, GC., Zhang, T., Hidaka, K., Falck, JR., Caffrey, JJ. et al. (2002). An adjacent pair of human NUDT genes on chromosome X are preferentially expressed in testis and encode two new isoforms of diphosphoinositol polyphosphate phosphohydrolase. *J Biol Chem, 277*, 32730-8. ↗

Safrany, ST., Caffrey, JJ., Yang, X., Shears, SB. (2000). Discovery of molecular and catalytic diversity among human diphosphoinositol-polyphosphate phosphohydrolases. An expanding Nudt family. *J Biol Chem, 275*, 12730-6. ↗

## Editions

| | | |
|---|---|---|
| 2011-10-28 | Authored, Edited | Williams, MG. |
| 2012-11-07 | Reviewed | Wundenberg, T. |

# Table of Contents