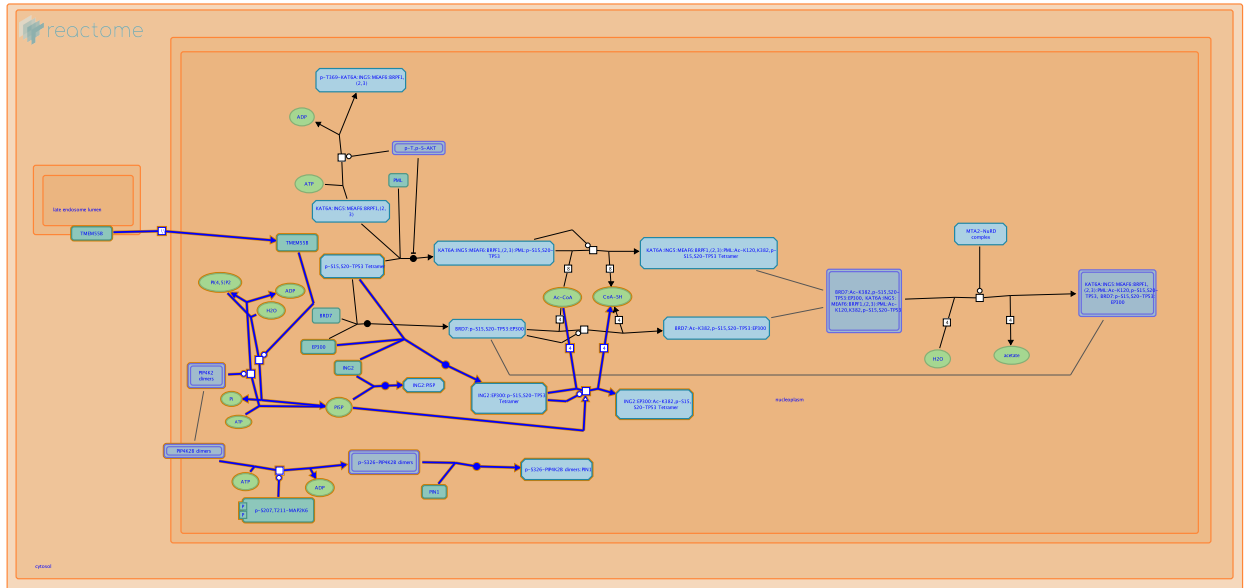


# PI5P Regulates TP53 Acetylation



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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

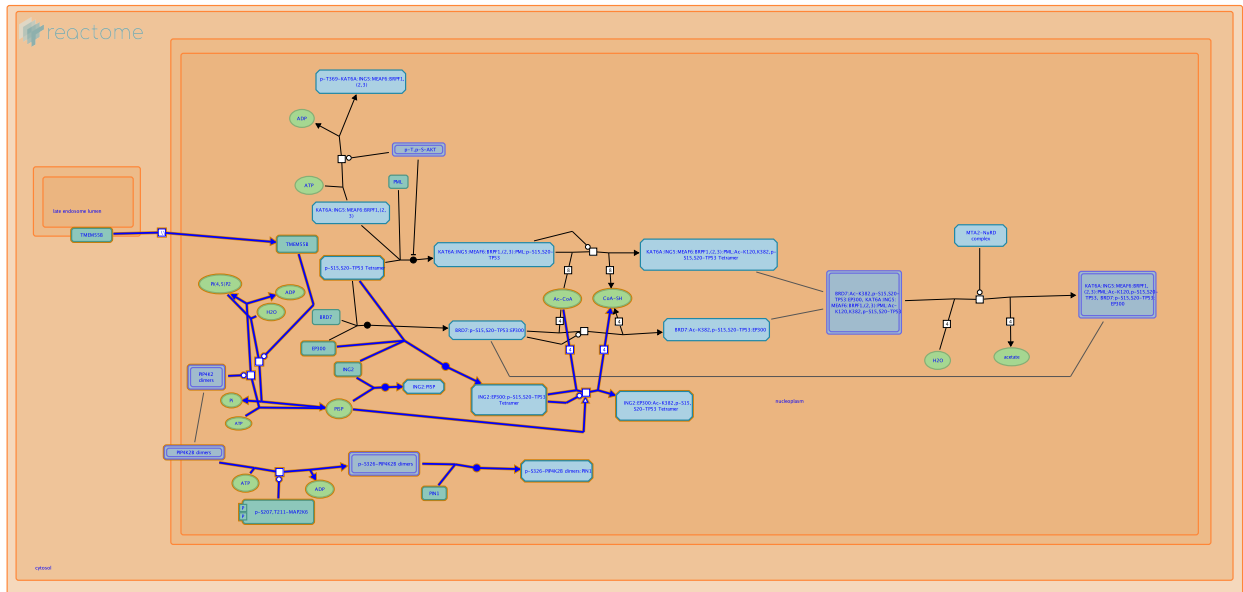
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- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. [↗](#)
- Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, 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. [↗](#)

Reactome database release: 77

This document contains 1 pathway and 8 reactions ([see Table of Contents](#))

# PI5P Regulates TP53 Acetylation [↗](#)

**Stable identifier:** R-HSA-6811555



Under conditions of cellular stress, nuclear levels of phosphatidylinositol-5-phosphate (PI5P) increase and, through interaction with ING2, result in nuclear retention/accumulation of ING2. ING2 binds TP53 (p53) and recruits histone acetyltransferase EP300 (p300) to TP53, leading to TP53 acetylation. Increased nuclear PI5P levels positively regulate TP53 acetylation (Ciruela et al. 2000, Gozani et al. 2003, Jones et al. 2006, Zou et al. 2007, Bultsma et al. 2010).

## Literature references

Ciruela, A., Hinchliffe, KA., Divecha, N., Irvine, RF. (2000). Nuclear targeting of the beta isoform of type II phosphatidylinositol phosphate kinase (phosphatidylinositol 5-phosphate 4-kinase) by its alpha-helix 7. *Biochem. J.*, 346, 587-91. [↗](#)

Bultsma, Y., Keune, WJ., Divecha, N. (2010). PIP4Kbeta interacts with and modulates nuclear localization of the high-activity PtdIns5P-4-kinase isoform PIP4Kalpha. *Biochem. J.*, 430, 223-35. [↗](#)

Gozani, O., Karuman, P., Jones, DR., Ivanov, D., Cha, J., Lugovskoy, AA. et al. (2003). The PHD finger of the chromatin-associated protein ING2 functions as a nuclear phosphoinositide receptor. *Cell*, 114, 99-111. [↗](#)

Zou, J., Marjanovic, J., Kisseleva, MV., Wilson, M., Majerus, PW. (2007). Type I phosphatidylinositol-4,5-bisphosphate 4-phosphatase regulates stress-induced apoptosis. *Proc. Natl. Acad. Sci. U.S.A.*, 104, 16834-9. [↗](#)

Jones, DR., Bultsma, Y., Keune, WJ., Halstead, JR., Elouarrat, D., Mohammed, S. et al. (2006). Nuclear PtdIns5P as a transducer of stress signaling: an in vivo role for PIP4Kbeta. *Mol. Cell*, 23, 685-95. [↗](#)

## Editions

2015-11-19	Authored	Orlic-Milacic, M.
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2016-06-28	Edited	Orlic-Milacic, M.

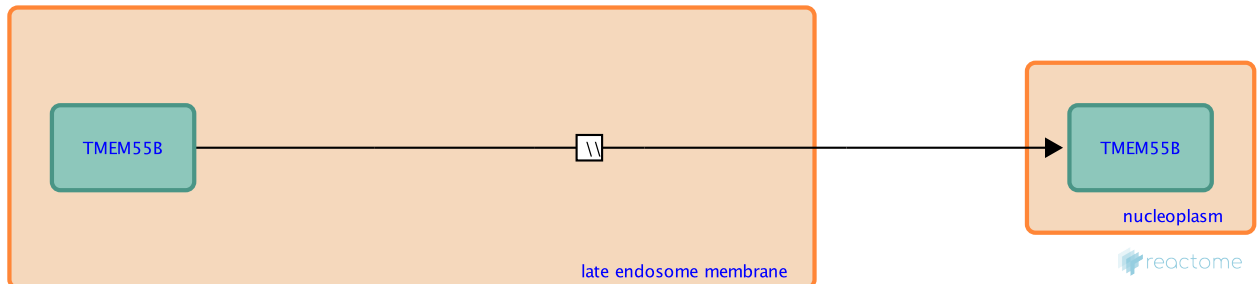
## TMEM55B translocates to the nucleus [↗](#)

**Location:** [PI5P Regulates TP53 Acetylation](#)

**Stable identifier:** R-HSA-6810392

**Type:** omitted

**Compartments:** late endosome membrane, nuclear envelope



Under conditions of cellular stress, TMEM55B (type I phosphatidylinositol 4,5-bisphosphate 4-phosphatase) translocates to the nucleus through an unknown mechanism (Zou et al. 2007).

**Followed by:** [PI\(4,5\)P2 is dephosphorylated to PI5P by TMEM55B in the nucleus](#)

### Literature references

Zou, J., Marjanovic, J., Kisseleva, MV., Wilson, M., Majerus, PW. (2007). Type I phosphatidylinositol-4,5-bisphosphate 4-phosphatase regulates stress-induced apoptosis. *Proc. Natl. Acad. Sci. U.S.A.*, 104, 16834-9. [↗](#)

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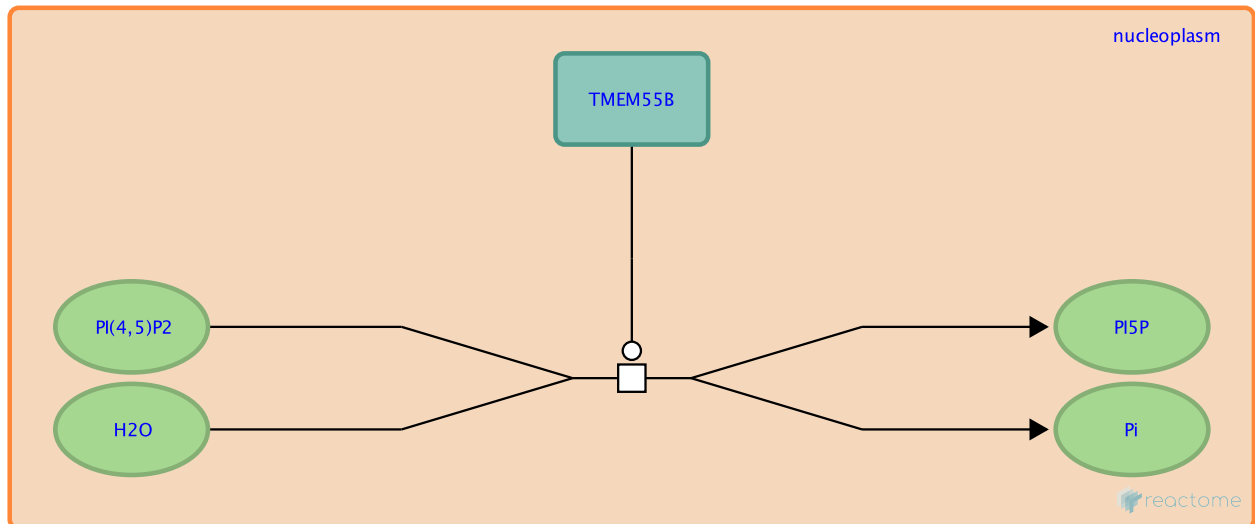
## PI(4,5)P2 is dephosphorylated to PI5P by TMEM55B in the nucleus ↗

**Location:** [PI5P Regulates TP53 Acetylation](#)

**Stable identifier:** R-HSA-6810410

**Type:** transition

**Compartments:** nucleoplasm



Translocation of TMEM55B (type I phosphatidylinositol 4,5-bisphosphate 4-phosphatase) to the nucleus under conditions of cellular stress leads to dephosphorylation of nuclear PI(4,5)P2 to PI5P, thus increasing the concentration of PI5P in the nucleus (Zou et al. 2007). PIP2 and its derivatives are not associated with nuclear envelope structures (Bornenkov et al. 1998) but localize to poorly defined subnuclear compartments called nuclear specks (reviewed by Barlow et al. 2010).

**Preceded by:** [TMEM55B translocates to the nucleus](#)

**Followed by:** [ING2 binds PI5P](#)

### Literature references

Zou, J., Marjanovic, J., Kisseleva, MV., Wilson, M., Majerus, PW. (2007). Type I phosphatidylinositol-4,5-bisphosphate 4-phosphatase regulates stress-induced apoptosis. *Proc. Natl. Acad. Sci. U.S.A.*, 104, 16834-9. ↗

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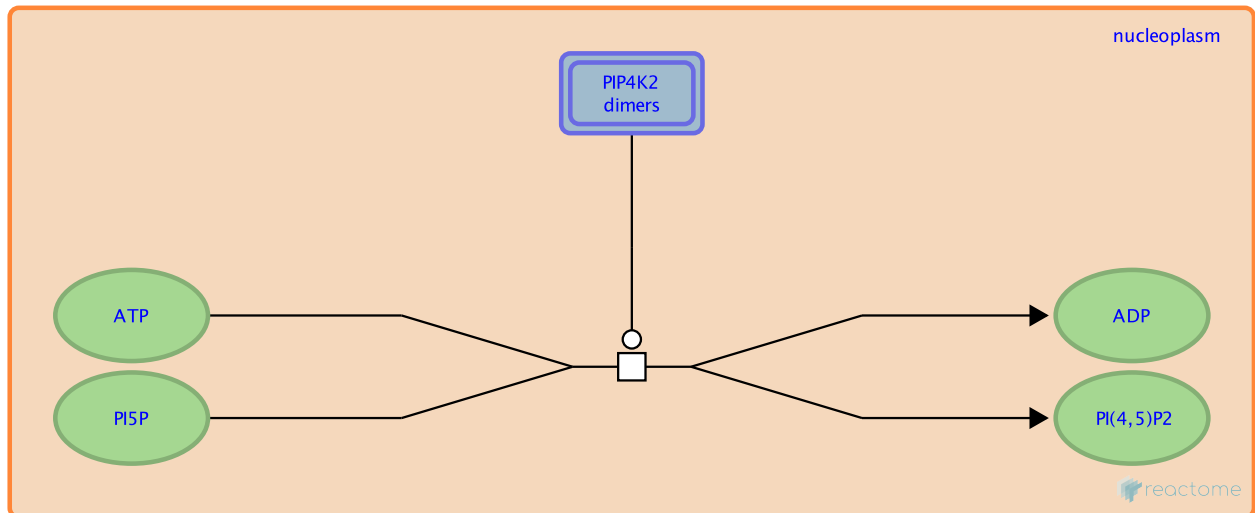
## PI5P is phosphorylated to PI(4,5)P2 by PIP4K2 dimers in the nucleus [↗](#)

**Location:** [PI5P Regulates TP53 Acetylation](#)

**Stable identifier:** R-HSA-6811522

**Type:** transition

**Compartments:** nucleoplasm



In the nucleus, phosphatidylinositol 5-phosphate (PI5P) is phosphorylated to phosphatidylinositol 4,5-bisphosphate (PI(4,5)P<sub>2</sub>) mainly by phosphatidylinositol-5-phosphate 4-kinase type-2 beta (PIP4K2B). In the nucleus, PIP4K2B predominantly functions as a homodimer or a heterodimer with PIP4K2A. A low level of PIP4K2A homodimers can also be found in the nucleus. Nuclear localization of PIP4K2C has not been examined but is assumed to be possible, at least through formation of heterodimers with PIP4K2B (Ciruela et al. 2000, Jones et al. 2006, Bultsma et al. 2010). Under conditions of cellular stress, nuclear PIP4K2B can be phosphorylated by p38 MAP kinases, resulting in PIP4K2B inactivation. The putative p38 target site, serine residue S326 of PIP4K2B, is conserved in PIP4K2A, but the role and mechanism of p38-mediated regulation of PIP4K2 isoforms has not been studied in detail (Jones et al. 2006).

### Literature references

Jones, DR., Bultsma, Y., Keune, WJ., Halstead, JR., Elouarrat, D., Mohammed, S. et al. (2006). Nuclear PtdIns5P as a transducer of stress signaling: an in vivo role for PIP4Kbeta. *Mol. Cell*, 23, 685-95. [↗](#)

Ciruela, A., Hinchliffe, KA., Divecha, N., Irvine, RF. (2000). Nuclear targeting of the beta isoform of type II phosphatidylinositol phosphate kinase (phosphatidylinositol 5-phosphate 4-kinase) by its alpha-helix 7. *Biochem. J.*, 346, 587-91. [↗](#)

Bultsma, Y., Keune, WJ., Divecha, N. (2010). PIP4Kbeta interacts with and modulates nuclear localization of the high-activity PtdIns5P-4-kinase isoform PIP4Kalpha. *Biochem. J.*, 430, 223-35. [↗](#)

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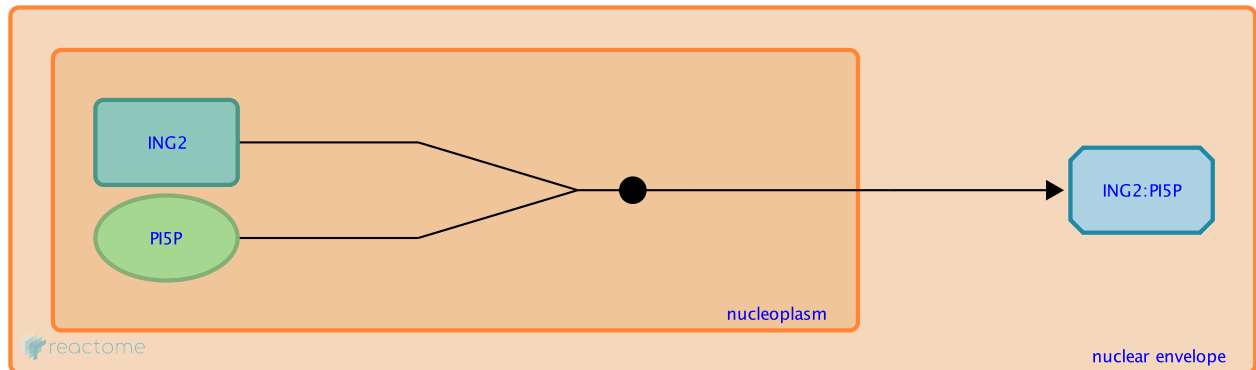
## ING2 binds PI5P ↗

**Location:** [PI5P Regulates TP53 Acetylation](#)

**Stable identifier:** R-HSA-6810376

**Type:** binding

**Compartments:** nucleoplasm, nuclear envelope



The PHD finger of ING2 binds phosphatidylinositol-5-phosphate (PI5P) (Gozani et al. 2003), which promotes nuclear retention of ING2 (Jones et al. 2006, Zou et al. 2007).

**Preceded by:** [PI\(4,5\)P2 is dephosphorylated to PI5P by TMEM55B in the nucleus](#)

### Literature references

- Gozani, O., Karuman, P., Jones, DR., Ivanov, D., Cha, J., Lugovskoy, AA. et al. (2003). The PHD finger of the chromatin-associated protein ING2 functions as a nuclear phosphoinositide receptor. *Cell*, 114, 99-111. ↗
- Jones, DR., Bultsma, Y., Keune, WJ., Halstead, JR., Elouarrat, D., Mohammed, S. et al. (2006). Nuclear PtdIns5P as a transducer of stress signaling: an in vivo role for PIP4Kbeta. *Mol. Cell*, 23, 685-95. ↗
- Zou, J., Marjanovic, J., Kisseleva, MV., Wilson, M., Majerus, PW. (2007). Type I phosphatidylinositol-4,5-bisphosphate 4-phosphatase regulates stress-induced apoptosis. *Proc. Natl. Acad. Sci. U.S.A.*, 104, 16834-9. ↗

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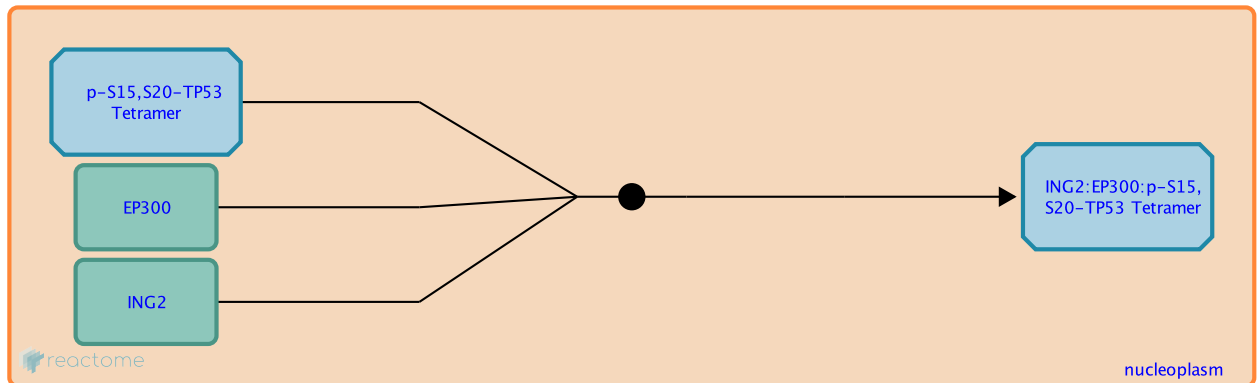
## ING2 recruits EP300 to TP53 ↗

**Location:** [PI3P Regulates TP53 Acetylation](#)

**Stable identifier:** R-HSA-6811479

**Type:** binding

**Compartments:** nucleoplasm



ING2 recruits histone acetyltransferase EP300 (p300) to TP53 (Padeux et al. 2005).

**Followed by:** [ING2-bound EP300 acetylates TP53](#)

### Literature references

Pedeux, R., Sengupta, S., Shen, JC., Demidov, ON., Saito, S., Onogi, H. et al. (2005). ING2 regulates the onset of replicative senescence by induction of p300-dependent p53 acetylation. *Mol. Cell. Biol.*, 25, 6639-48. ↗

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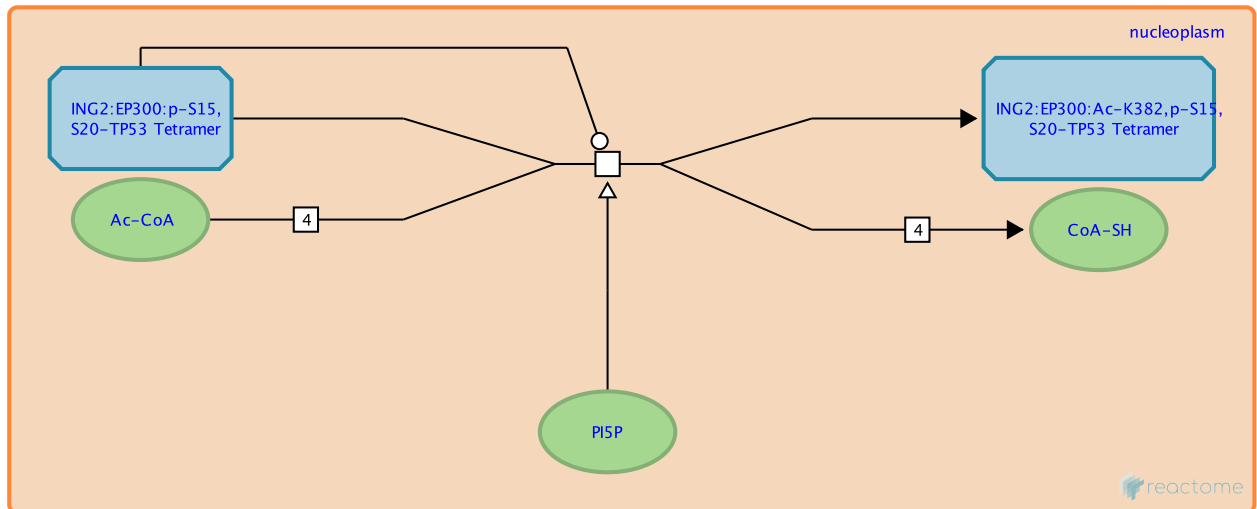
## ING2-bound EP300 acetylates TP53 ↗

**Location:** [PI5P Regulates TP53 Acetylation](#)

**Stable identifier:** R-HSA-6811508

**Type:** transition

**Compartments:** nucleoplasm



The histone acetyltransferase EP300 (p300), recruited to TP53 (p53) by ING2, acetylates TP53 on lysine residue K382, which may contribute to TP53-dependent apoptosis (Padeux et al. 2005). PI5P positively regulates TP53 acetylation (Zou et al. 2007), possibly by increasing the amount of ING2 in the nucleus (Gozani et al. 2003).

**Preceded by:** [ING2 recruits EP300 to TP53](#)

### Literature references

Pedeux, R., Sengupta, S., Shen, JC., Demidov, ON., Saito, S., Onogi, H. et al. (2005). ING2 regulates the onset of replicative senescence by induction of p300-dependent p53 acetylation. *Mol. Cell. Biol.*, 25, 6639-48. ↗

Gozani, O., Karuman, P., Jones, DR., Ivanov, D., Cha, J., Lugovskoy, AA. et al. (2003). The PHD finger of the chromatin-associated protein ING2 functions as a nuclear phosphoinositide receptor. *Cell*, 114, 99-111. ↗

Zou, J., Marjanovic, J., Kisseleva, MV., Wilson, M., Majerus, PW. (2007). Type I phosphatidylinositol-4,5-bisphosphate 4-phosphatase regulates stress-induced apoptosis. *Proc. Natl. Acad. Sci. U.S.A.*, 104, 16834-9. ↗

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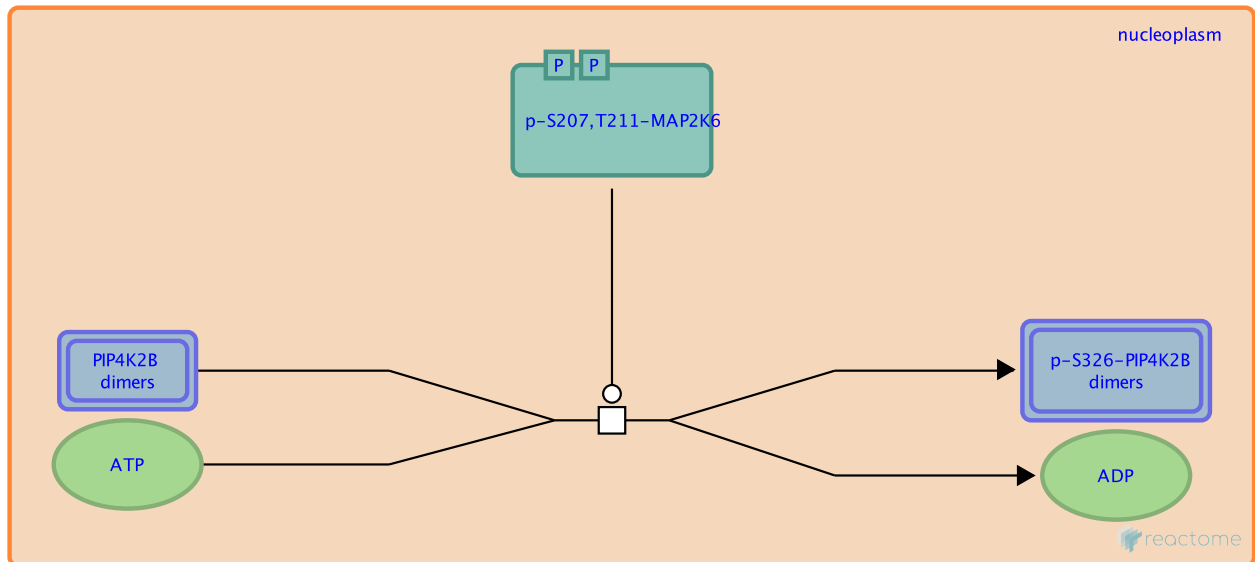
## MAP2K6 phosphorylates PIP4K2B ↗

**Location:** [PI5P Regulates TP53 Acetylation](#)

**Stable identifier:** R-HSA-8877691

**Type:** transition

**Compartments:** nucleoplasm



Under conditions of cellular stress, such as increased level of reactive oxygen species, MAP2K6 (MKK6), and possibly other kinases of the p38 MAPK family, phosphorylates PIP4K2B at serine residue S326. Threonine residue T322 of PIP4K2B is also phosphorylated under stress conditions, but the responsible kinase is not known. MAP2K6 may also phosphorylate PIP4K2A, but not PIP4K2C (Kuene et al. 2012).

**Followed by:** [PIN1 binds phosphorylated PIP4K2B](#)

### Literature references

Keune, WJ., Jones, DR., Bultsma, Y., Sommer, L., Zhou, XZ., Lu, KP. et al. (2012). Regulation of phosphatidylinositol-5-phosphate signaling by Pin1 determines sensitivity to oxidative stress. *Sci Signal*, 5, ra86. ↗

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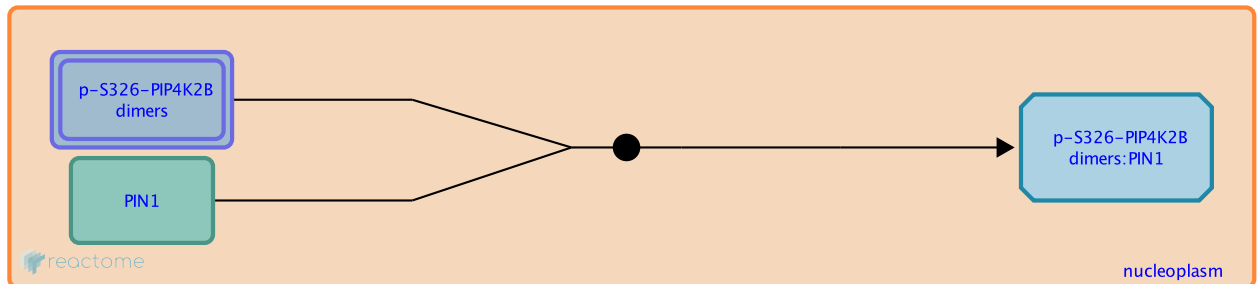
## PIN1 binds phosphorylated PIP4K2B ↗

**Location:** [PI5P Regulates TP53 Acetylation](#)

**Stable identifier:** R-HSA-8877692

**Type:** binding

**Compartments:** nucleoplasm



Peptidyl-prolyl cis-trans isomerase PIN1 binds to PIP4K2B phosphorylated at serine residue S326. PIP4K2B is phosphorylated at S326 under conditions of cellular stress, such as increased level of reactive oxygen species (ROS). Phosphorylation of PIP4K2B at threonine residue T322 may also contribute to PIN1 binding. PIN1 induces conformational change of PIP4K2B, resulting in inactivation of PIP4K2B dimers. This enables increase of the nuclear PI5P levels. PI5P positively regulates expression of genes involved in neutralization of ROS (Keune et al. 2012).

**Preceded by:** [MAP2K6 phosphorylates PIP4K2B](#)

### Literature references

Keune, WJ., Jones, DR., Bultsma, Y., Sommer, L., Zhou, XZ., Lu, KP. et al. (2012). Regulation of phosphatidylinositol-5-phosphate signaling by Pin1 determines sensitivity to oxidative stress. *Sci Signal*, 5, ra86. ↗

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