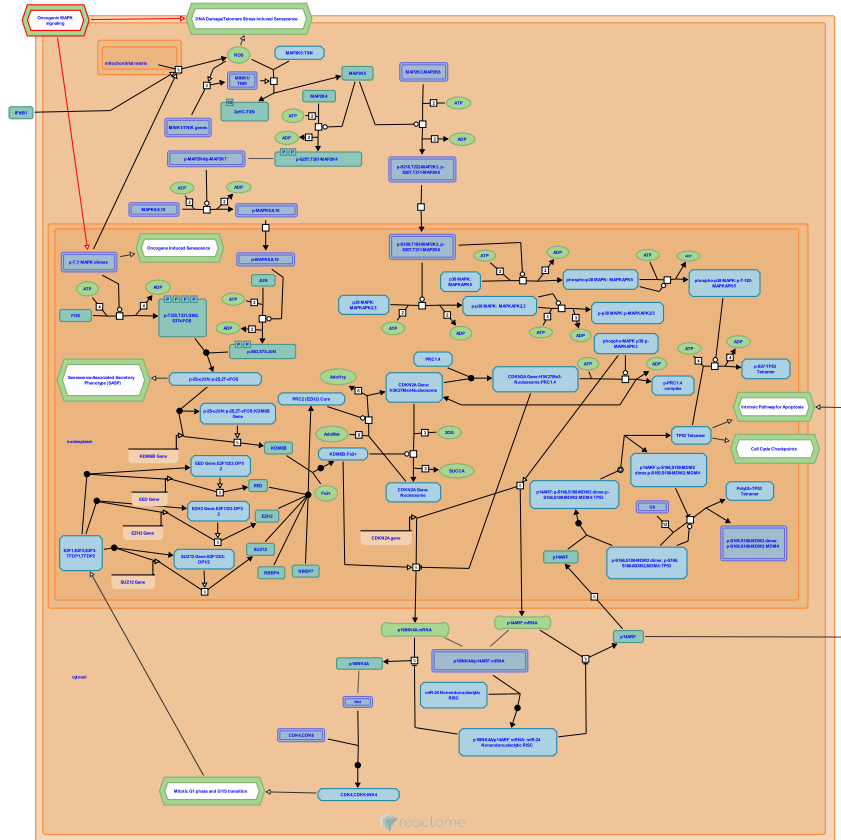


Oxidative Stress Induced Senescence



Bennett, DC., D'Eustachio, P., Gay, NJ., Gillespie, ME., Inga, A., Luo, F., Matthews, L., Orlic-Milacic, M., Rizos, H., Roger, PP., Samarajiwa, S., Shamovsky, V., Vegi, NM., Zaccara, S.

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

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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](https://reactome.org/textbook/).

29/04/2024

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).

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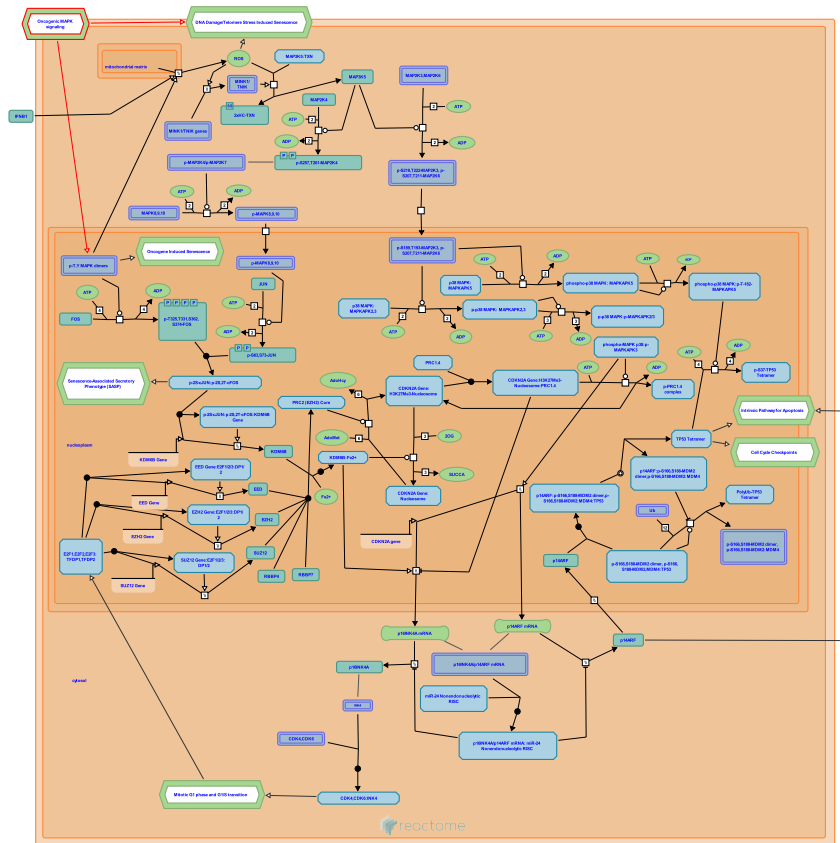
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Reactome database release: 88

This document contains 1 pathway and 40 reactions ([see Table of Contents](#))

Oxidative Stress Induced Senescence ↗

Stable identifier: R-HSA-2559580



Oxidative stress, caused by increased concentration of reactive oxygen species (ROS) in the cell, can happen as a consequence of mitochondrial dysfunction induced by the oncogenic RAS (Moiseeva et al. 2009) or independent of oncogenic signaling. Prolonged exposure to interferon-beta (IFNB, IFN-beta) also results in ROS increase (Moiseeva et al. 2006). ROS oxidize thioredoxin (TXN), which causes TXN to dissociate from the N-terminus of MAP3K5 (ASK1), enabling MAP3K5 to become catalytically active (Saitoh et al. 1998). ROS also stimulate expression of Ste20 family kinases MINK1 (MINK) and TNIK through an unknown mechanism, and MINK1 and TNIK positively regulate MAP3K5 activation (Nicke et al. 2005).

MAP3K5 phosphorylates and activates MAP2K3 (MKK3) and MAP2K6 (MKK6) (Ichijo et al. 1997, Takekawa et al. 2005), which act as p38 MAPK kinases, as well as MAP2K4 (SEK1) (Ichijo et al. 1997, Matsuura et al. 2002), which, together with MAP2K7 (MKK7), acts as a JNK kinase.

MKK3 and MKK6 phosphorylate and activate p38 MAPK alpha (MAPK14) and beta (MAPK11) (Raingeaud et al. 1996), enabling p38 MAPKs to phosphorylate and activate MAPKAPK2 (MK2) and MAPKAPK3 (MK3) (Ben-Levy et al. 1995, Clifton et al. 1996, McLaughlin et al. 1996, Sithanandam et al. 1996, Meng et al. 2002, Lukas et al. 2004, White et al. 2007), as well as MAPKAPK5 (PRAK) (New et al. 1998 and 2003, Sun et al. 2007).

Phosphorylation of JNKs (MAPK8, MAPK9 and MAPK10) by MAP3K5-activated MAP2K4 (Deacon and Blank 1997, Fleming et al. 2000) allows JNKs to migrate to the nucleus (Mizukami et al. 1997) where they phosphorylate JUN. Phosphorylated JUN binds FOS phosphorylated by ERK1 or ERK2, downstream of activated RAS (Okazaki and Sagata 1995, Murphy et al. 2002), forming the activated protein 1 (AP-1) complex (FOS:JUN heterodimer) (Glover and Harrison 1995, Ainbinder et al. 1997).

Activation of p38 MAPKs and JNKs downstream of MAP3K5 (ASK1) ultimately converges on transcriptional regulation of CDKN2A locus. In dividing cells, nucleosomes bound to the CDKN2A locus are trimethylated on lysine residue 28 of histone H3 (HIST1H3A) by the Polycomb repressor complex 2 (PRC2), creating the H3K27Me3 (Me3K-28-HIST1H3A) mark (Bracken et al. 2007, Kotake et al. 2007). The expression of Polycomb constituents of PRC2 (Kuzmichev et al. 2002) - EZH2, EED and SUZ12 - and thereby formation of the PRC2, is positively

regulated in growing cells by E2F1, E2F2 and E2F3 (Weinmann et al. 2001, Bracken et al. 2003). H3K27Me3 mark serves as a docking site for the Polycomb repressor complex 1 (PRC1) that contains BMI1 (PCGF4) and is therefore named PRC1.4, leading to the repression of transcription of p16INK4A and p14ARF from the CDKN2A locus, where PRC1.4 mediated repression of p14ARF transcription in humans may be context dependent (Voncken et al. 2005, Dietrich et al. 2007, Agherbi et al. 2009, Gao et al. 2012). MAPKAPK2 and MAPKAPK3, activated downstream of the MAP3K5-p38 MAPK cascade, phosphorylate BMI1 of the PRC1.4 complex, leading to dissociation of PRC1.4 complex from the CDKN2A locus and upregulation of p14ARF transcription (Voncken et al. 2005). AP-1 transcription factor, formed as a result of MAP3K5-JNK signaling, as well as RAS signaling, binds the promoter of KDM6B (JMJD3) gene and stimulates KDM6B expression. KDM6B is a histone demethylase that removes H3K27Me3 mark i.e. demethylates lysine K28 of HIST1H3A, thereby preventing PRC1.4 binding to the CDKN2A locus and allowing transcription of p16INK4A (Agger et al. 2009, Barradas et al. 2009, Lin et al. 2012).

p16INK4A inhibits phosphorylation-mediated inactivation of RB family members by CDK4 and CDK6, leading to cell cycle arrest (Serrano et al. 1993). p14ARF inhibits MDM2-mediated degradation of TP53 (p53) (Zhang et al. 1998), which also contributes to cell cycle arrest in cells undergoing oxidative stress. In addition, phosphorylation of TP53 by MAPKAPK5 (PRAK) activated downstream of MAP3K5-p38 MAPK signaling, activates TP53 and contributes to cellular senescence (Sun et al. 2007).

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Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

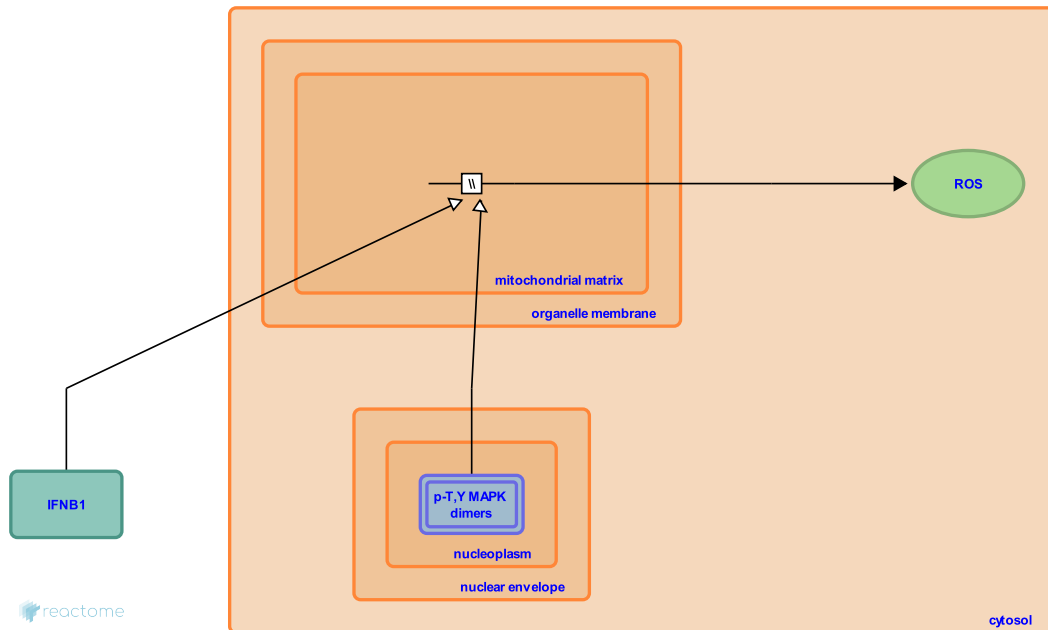
RAS signaling and prolonged interferon-beta stimulation promote generation of reactive oxygen species (ROS) ↗

Location: Oxidative Stress Induced Senescence

Stable identifier: R-HSA-3223236

Type: omitted

Compartments: mitochondrial matrix, cytosol



Oncogenic RAS signaling leads to mitochondrial dysfunction, resulting in increased mitochondrial production of reactive oxygen species (ROS), which contributes to cellular senescence (Moiseeva et al. 2009). The exact biochemical mechanism of RAS-induced mitochondrial dysfunction has not been established. Prolonged exposure to interferon-beta (INFB, INF-beta) also results in increased ROS concentration in the cell and triggers cellular senescence (Moiseeva et al. 2006). Although the positive regulation of ROS production by interferon signaling is well documented (Huang et al. 2007, Yang et al. 2007, Yim et al. 2012), the precise mechanism is not known.

Followed by: [Expression of MINK1/TNIK is positively regulated by ROS](#), [ROS oxidize thioredoxin and activate MAP3K5](#)

Literature references

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Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

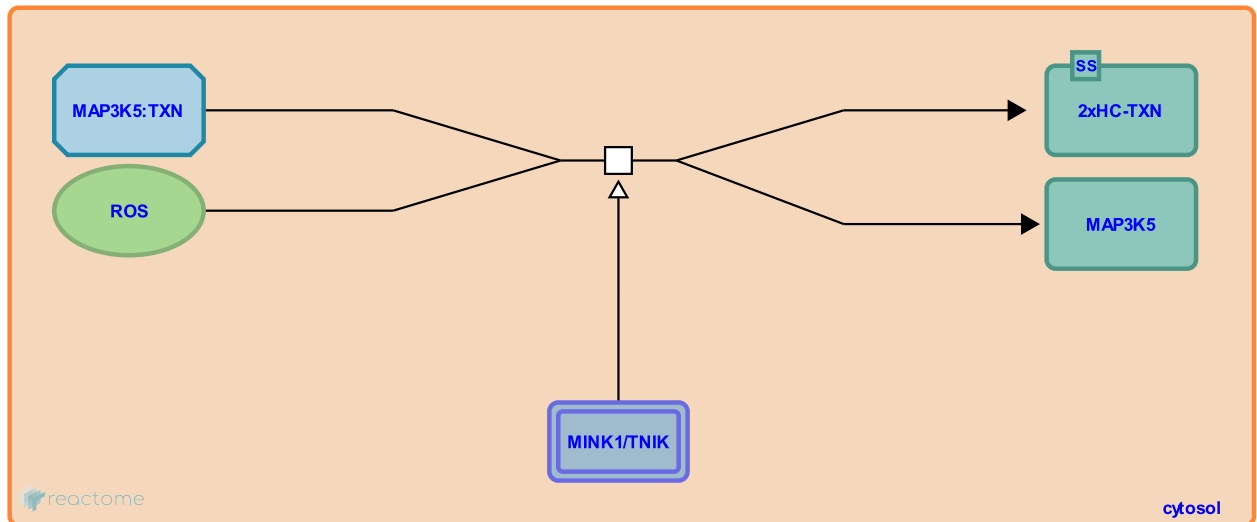
ROS oxidize thioredoxin and activate MAP3K5 ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3225851

Type: transition

Compartments: cytosol



When in reduced form, TXN (thioredoxin) binds the amino terminus of MAP3K5 (ASK1) and inhibits its kinase activity. Once reactive oxygen species (ROS) oxidize TXN, TXN dissociates from MAP3K5, enabling MAP3K5 to phosphorylate downstream targets (Saitoh et al. 1998). Increased expression and activity of MINK1 (MINK) (and possibly other Ste20 family kinases TNIK and MAP4K), which is induced by ROS generated as a consequence of oncogenic RAS signaling, may contribute to MAP3K5 activation (Nicke et al. 2005).

Preceded by: [RAS signaling and prolonged interferon-beta stimulation promote generation of reactive oxygen species \(ROS\)](#)

Followed by: [MAP3K5 \(ASK1\) phosphorylates MAP2K4 \(SEK1\)](#), [MAP3K5 phosphorylates MKK3 and MKK6](#)

Literature references

Kawabata, M., Fujii, M., Sawada, Y., Nishitoh, H., Ichijo, H., Saitoh, M. et al. (1998). Mammalian thioredoxin is a direct inhibitor of apoptosis signal-regulating kinase (ASK) 1. *EMBO J.*, 17, 2596-606. ↗

Peters, G., Cowling, V., Nicke, B., Downward, J., Berns, K., Bernards, R. et al. (2005). Involvement of MINK, a Ste20 family kinase, in Ras oncogene-induced growth arrest in human ovarian surface epithelial cells. *Mol. Cell*, 20, 673-85. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

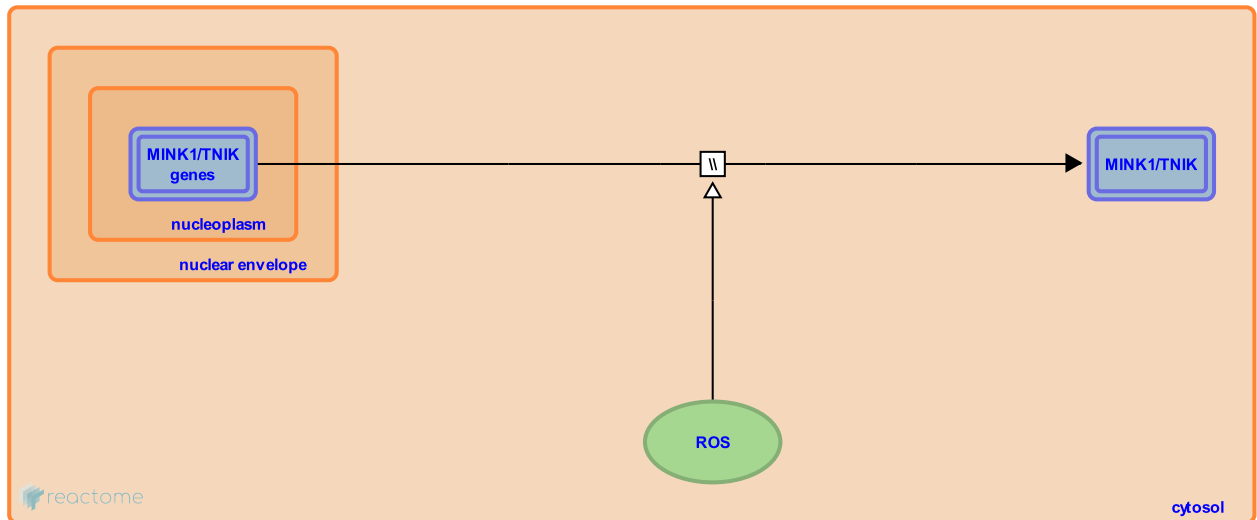
Expression of MINK1/TNIK is positively regulated by ROS ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3225867

Type: omitted

Compartments: cytosol



Reactive oxygen species (ROS) generated as a consequence of oncogenic RAS signaling induce expression and activation of Ste20 family kinases MINK1 (MINK), TNIK and, possibly, MAP4K4, which contributes to growth arrest and cellular senescence (Nicke et al. 2005).

Preceded by: [RAS signaling and prolonged interferon-beta stimulation promote generation of reactive oxygen species \(ROS\)](#)

Literature references

Peters, G., Cowling, V., Nicke, B., Downward, J., Berns, K., Bernards, R. et al. (2005). Involvement of MINK, a Ste20 family kinase, in Ras oncogene-induced growth arrest in human ovarian surface epithelial cells. *Mol. Cell*, 20, 673-85. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

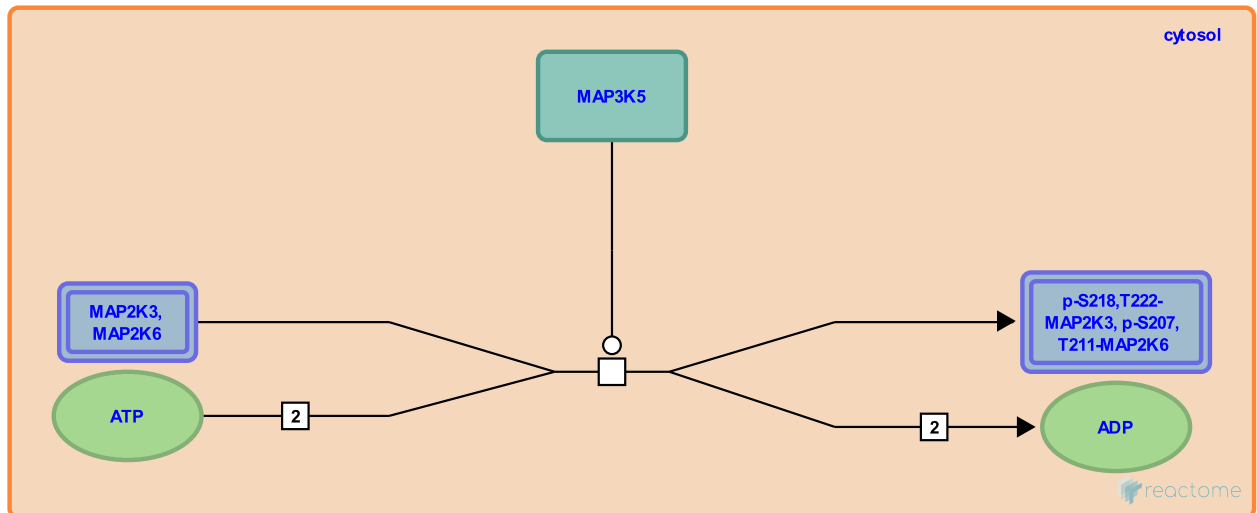
MAP3K5 phosphorylates MKK3 and MKK6 ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3228469

Type: transition

Compartments: cytosol



MAP3K5 (ASK1) phosphorylates and activates MAP2K3 (MKK3) and MAP2K6 (MKK6) (Ichijo et al. 1997). A conserved docking site, DVD, at the C-terminus of MAP2K3 and MAP2K6 is needed for the interaction with MAP3K5 and MAP3K5-mediated activation (Takekawa et al. 2005).

Preceded by: [ROS oxidize thioredoxin and activate MAP3K5](#)

Followed by: [Phosphorylated MKK3/MKK6 migrates to nucleus](#)

Literature references

Tatebayashi, K., Saito, H., Takekawa, M. (2005). Conserved docking site is essential for activation of mammalian MAP kinase kinases by specific MAP kinase kinase kinases. *Mol. Cell*, 18, 295-306. ↗

Nishida, E., Irie, K., Ichijo, H., Matsumoto, K., Saitoh, M., ten Dijke, P. et al. (1997). Induction of apoptosis by ASK1, a mammalian MAPKKK that activates SAPK/JNK and p38 signaling pathways. *Science*, 275, 90-4. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

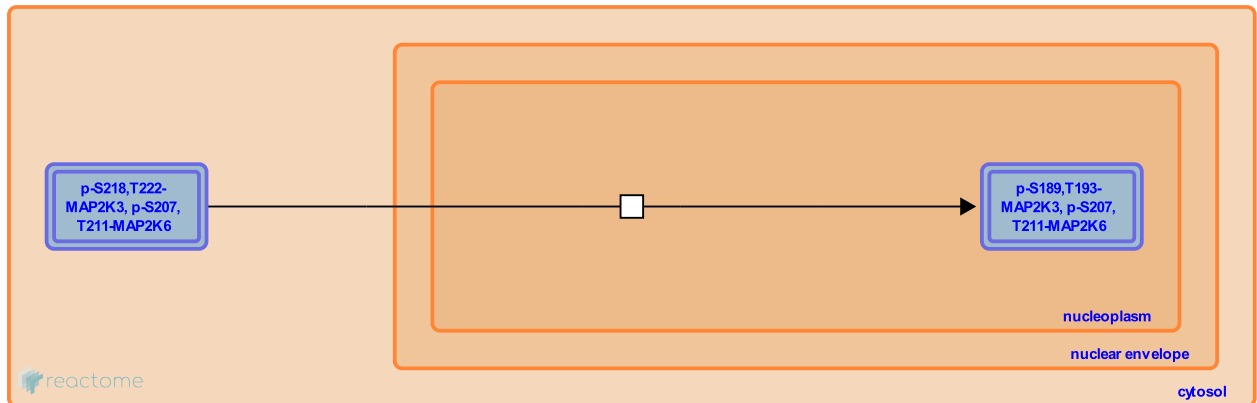
Phosphorylated MKK3/MKK6 migrates to nucleus ↗

Location: Oxidative Stress Induced Senescence

Stable identifier: R-HSA-450296

Type: transition

Compartments: nucleoplasm, cytosol



The p38 activators MKK3 (MAP2K3) and MKK6 (MAP2K6) were present in both the nucleus and the cytoplasm, consistent with a role in activating p38 in the nucleus.

Preceded by: MAP3K5 phosphorylates MKK3 and MKK6

Followed by: Activated human MKK3/MKK6 phosphorylates p38 MAPK complexed with MAPKAPK5, Activated human MKK3/MKK6 phosphorylates p38 MAPK complexed with MAPKAPK2 or MAPKAPK3

Literature references

Marshall, CJ., Hooper, S., Paterson, HF., Ben-Levy, R., Wilson, R. (1998). Nuclear export of the stress-activated protein kinase p38 mediated by its substrate MAPKAP kinase-2. *Curr Biol*, 8, 1049-57. ↗

Gupta, S., Davis, RJ., Ulevitch, RJ., Han, J., Raingeaud, J., Dickens, M. et al. (1995). Pro-inflammatory cytokines and environmental stress cause p38 mitogen-activated protein kinase activation by dual phosphorylation on tyrosine and threonine. *J Biol Chem*, 270, 7420-6. ↗

Editions

2009-12-16	Authored	Shamovsky, V.
2010-02-28	Reviewed	Gillespie, ME.
2010-02-28	Edited	Shamovsky, V.

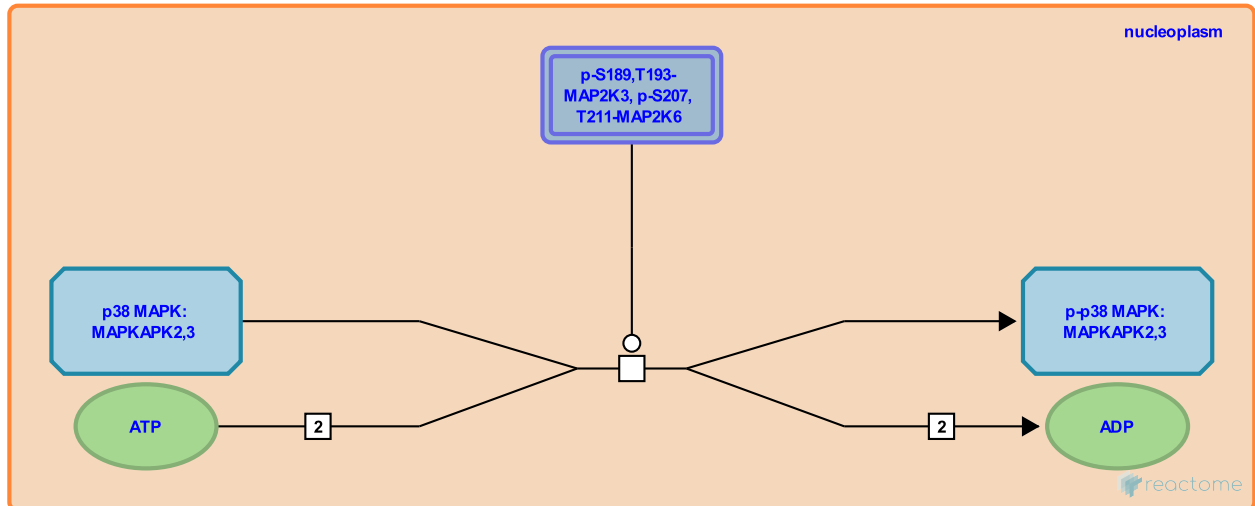
Activated human MKK3/MKK6 phosphorylates p38 MAPK complexed with MAPKAPK2 or MAPKAPK3 ↗

Location: Oxidative Stress Induced Senescence

Stable identifier: R-HSA-450333

Type: transition

Compartments: nucleoplasm



The MAPK level components of this cascade are p38MAPK-alpha, -beta, -gamma and -sigma. All of those isoforms are activated by phosphorylation of the Thr and Tyr in the Thr-Gly-Tyr motif in their activation loops.

Preceded by: Phosphorylated MKK3/MKK6 migrates to nucleus

Followed by: Active p38 MAPK phosphorylates MAPKAPK2 or 3

Literature references

Davis, RJ., Whitmarsh, AJ., Derijard, B., Raingeaud, J., Barrett, T. (1996). MKK3- and MKK6-regulated gene expression is mediated by the p38 mitogen-activated protein kinase signal transduction pathway. *Mol Cell Biol*, 16, 1247-55. ↗

Gupta, S., Davis, RJ., Ulevitch, RJ., Han, J., Raingeaud, J., Dickens, M. et al. (1995). Pro-inflammatory cytokines and environmental stress cause p38 mitogen-activated protein kinase activation by dual phosphorylation on tyrosine and threonine. *J Biol Chem*, 270, 7420-6. ↗

Editions

2009-12-16	Authored	Shamovsky, V.
2010-02-28	Reviewed	Gillespie, ME.
2010-02-28	Edited	Shamovsky, V.

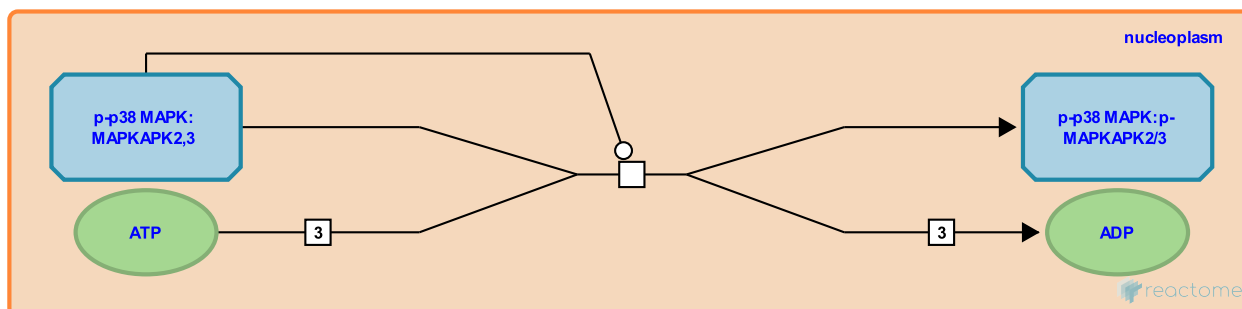
Active p38 MAPK phosphorylates MAPKAPK2 or 3 ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-450222

Type: transition

Compartments: nucleoplasm



Human p38 MAPK alpha forms a complex with MK2 even when the signaling pathway is not activated. This heterodimer is found mainly in the nucleus. The crystal structure of the unphosphorylated p38alpha-MK2 heterodimer was determined. The C-terminal regulatory domain of MK2 binds in the docking groove of p38 MAPK alpha, and the ATP-binding sites of both kinases are at the heterodimer interface (ter Haar et al. 2007).

Upon activation, p38 MAPK alpha activates MK2 by phosphorylating Thr-222, Ser-272, and Thr-334 (Ben-Levy et al. 1995).

The phosphorylation of MK2 at Thr-334 attenuates the affinity of the binary complex MK2:p38 alpha by an order of magnitude and leads to a large conformational change of an autoinhibitory domain in MK2. This conformational change unmasks not only the MK2 substrate-binding site but also the MK2 nuclear export signal (NES) thus leading to the MK2:p38 alpha translocation from the nucleus to the cytoplasm. Cytoplasmic active MK2 then phosphorylates downstream targets such as the heat-shock protein HSP27 and tristetraprolin (TTP) (Meng et al. 2002, Lukas et al. 2004, White et al. 2007).

MAPKAPK (MAPK-activated protein) kinase 3 (MK3, also known as 3pK) has been identified as the second p38 MAPK-activated kinase that is stimulated by different stresses (McLaughlin et al. 1996; Sithanandam et al. 1996; reviewed in Gaestel 2006). MK3 shows 75% sequence identity to MK2 and, like MK2, is activated by p38 MAPK alpha and p38 MAPK beta. MK3 phosphorylates peptide substrates with kinetic constants similar to MK2 and phosphorylates the same serine residues in HSP27 at the same relative rates as MK2 (Clifton et al. 1996) indicating an identical phosphorylation-site consensus sequence. Hence, it is assumed that its substrate spectrum is either identical to or at least overlapping with MK2.

Preceded by: [Activated human MKK3/MKK6 phosphorylates p38 MAPK complexed with MAPKAPK2 or MAPKAPK3](#)

Followed by: [p-MAPKAPK3 phosphorylates BMI1](#)

Literature references

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- Marshall, CJ., Ben-Levy, R., Attwood, P., Morrice, N., Leighton, IA., Cohen, P. et al. (1995). Identification of novel phosphorylation sites required for activation of MAPKAP kinase-2. *EMBO J*, 14, 5920-30. ↗
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Liu, X., Lepre, C., Prabhakar, P., Ter Haar, E. (2007). Crystal structure of the p38 alpha-MAPKAP kinase 2 heterodimer. *J Biol Chem*, 282, 9733-9. [↗](#)

Editions

2009-12-16	Authored	Shamovsky, V.
2010-02-28	Reviewed	Gillespie, ME.
2010-02-28	Edited	Shamovsky, V.

MAP3K5 (ASK1) phosphorylates MAP2K4 (SEK1) ↗

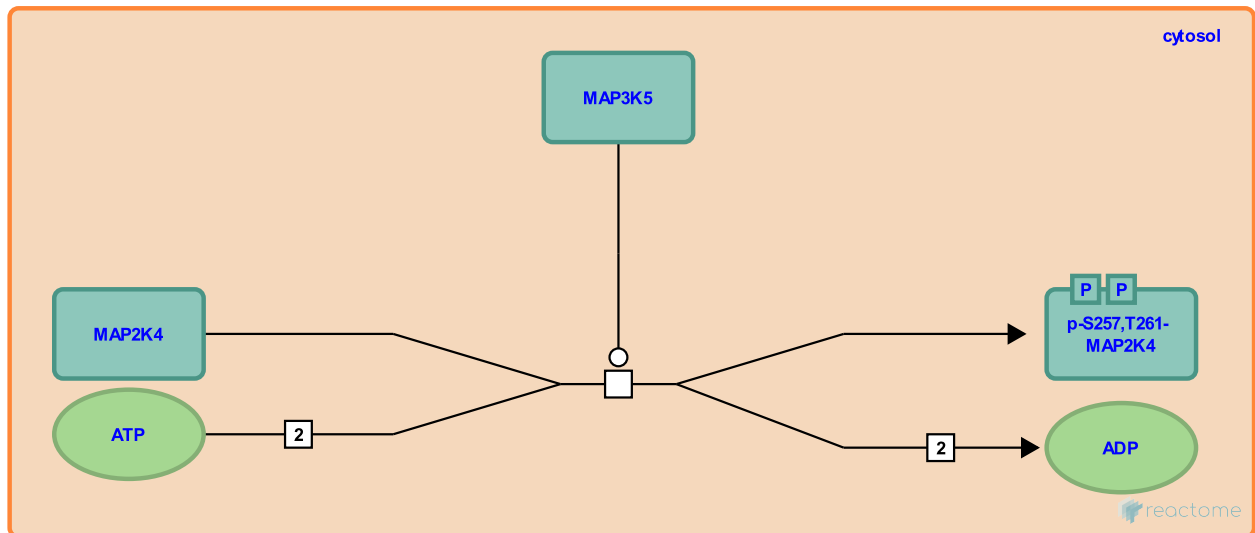
Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3229152

Type: transition

Compartments: cytosol

Inferred from: [MAP3K5 \(ASK1\) phosphorylates Map2k4\(Sek1\) \(Homo sapiens\)](#)



MAP3K5 (ASK1) phosphorylates and activates MAP2K4 (SEK1) (Ichijo et al. 1997). MAP3K5-mediated phosphorylation of MAP2K4 may be facilitated by MAPK8IP3 (JSAP1) (Matsuura et al. 2002).

Preceded by: [ROS oxidize thioredoxin and activate MAP3K5](#)

Literature references

Amagasa, T., Ito, M., Ichijo, H., Nishitoh, H., Matsuzawa, A., Yoshioka, K. et al. (2002). Phosphorylation-dependent scaffolding role of JSAP1/JIP3 in the ASK1-JNK signaling pathway. A new mode of regulation of the MAP kinase cascade. *J. Biol. Chem.*, 277, 40703-9. ↗

Nishida, E., Irie, K., Ichijo, H., Matsumoto, K., Saitoh, M., ten Dijke, P. et al. (1997). Induction of apoptosis by ASK1, a mammalian MAPKKK that activates SAPK/JNK and p38 signaling pathways. *Science*, 275, 90-4. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

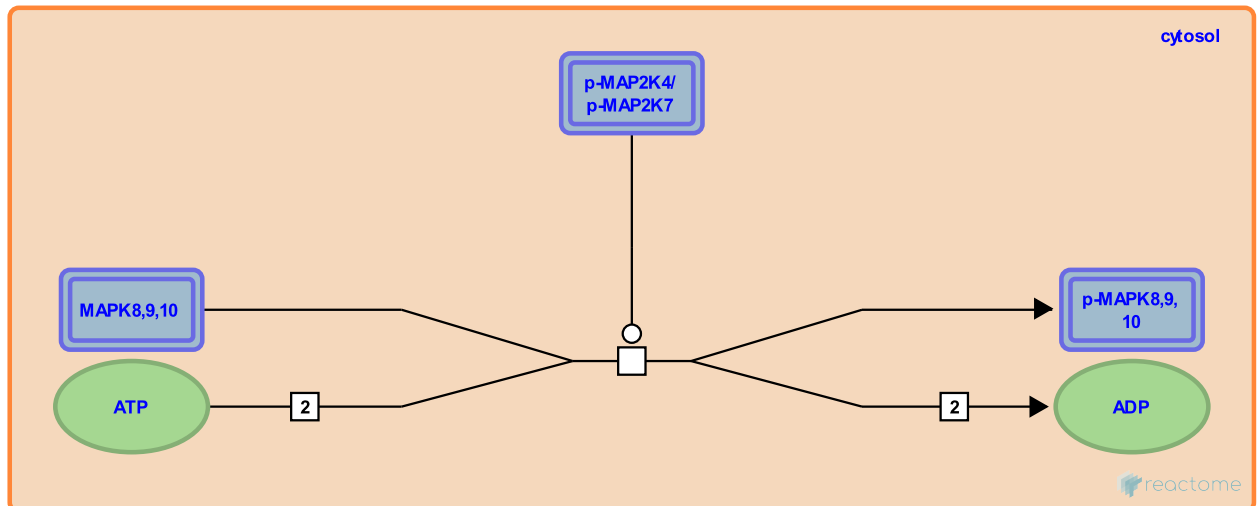
Phosphorylation of human JNKs by activated MKK4/MKK7 ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-168162

Type: transition

Compartments: cytosol



Activated human JNK kinases (MKK4 and MKK7) phosphorylate Thr183 and Tyr185 residues in the characteristic Thr-Pro-Tyr phosphoacceptor loop of each JNK.

JNK is differentially regulated by MKK4 and MKK7 depending on the stimulus. MKK7 is the primary activator of JNK in TNF, LPS, and PGN responses. However, TLR3 cascade requires both MKK4 and MKK7. Some studies reported that in three JNK isoforms tested MKK4 shows a striking preference for the tyrosine residue (Tyr-185), and MKK7 a striking preference for the threonine residue (Thr-183).

Followed by: [Activated human JNKs migrate to nucleoplasm](#)

Literature references

- Wang, X., Jin, JW., Boot-Handford, RP., Tournier, C., Robinson, AC., Dajas-Bailador, F. et al. (2007). Targeted deletion of the mitogen-activated protein kinase kinase 4 gene in the nervous system causes severe brain developmental defects and premature death. *Mol Cell Biol*, 27, 7935-46. ↗
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- Blank, JL., Deacon, K. (1997). Characterization of the mitogen-activated protein kinase kinase 4 (MKK4)/c-Jun NH2-terminal kinase 1 and MKK3/p38 pathways regulated by MEK kinases 2 and 3. MEK kinase 3 activates MKK3 but does not cause activation of p38 kinase in vivo. *J Biol Chem*, 272, 14489-96. ↗

Editions

2005-11-10	Authored	Luo, F.
2006-04-24	Reviewed	Gay, NJ.
2009-12-16	Edited, Revised	Shamovsky, V.

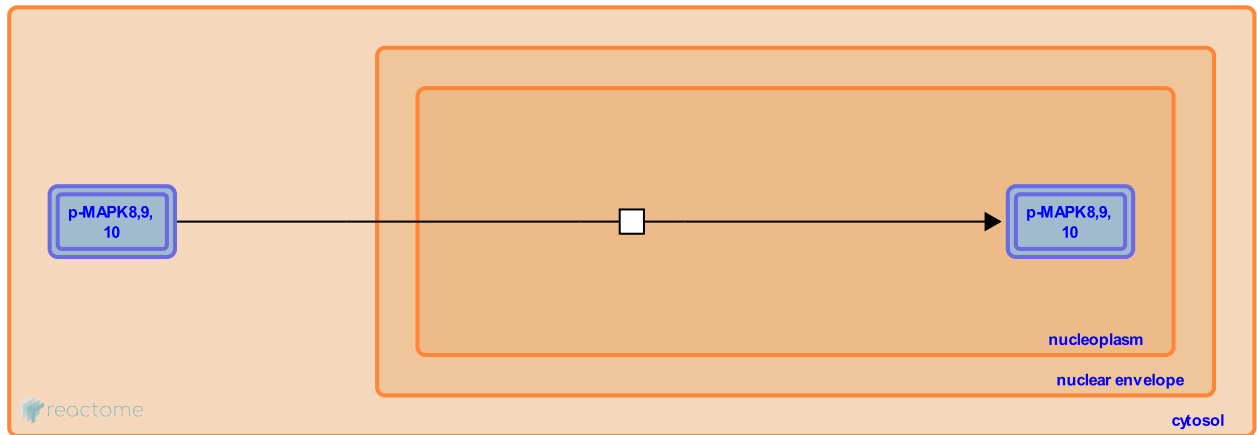
Activated human JNKs migrate to nucleoplasm ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-450348

Type: transition

Compartments: nucleoplasm, cytosol



c-Jun NH2 terminal kinase (JNK) plays a role in conveying signals from the cytosol to the nucleus, where they associate and activate their target transcription factors.

Preceded by: [Phosphorylation of human JNKs by activated MKK4/MKK7](#)

Followed by: [Activated JNKs phosphorylate c-JUN](#)

Literature references

Nimpf, J., Lutz, C., Enzinger, C., Baier-Bitterlich, G., Jenny, M., Boecklinger, K. et al. (2002). Evidence of functional modulation of the MEKK/JNK/cJun signaling cascade by the low density lipoprotein receptor-related protein (LRP). *J Biol Chem*, 277, 43143-51. ↗

Yoshida, K., Morimoto, S., Mizukami, Y., Yoshioka, K. (1997). A novel mechanism of JNK1 activation. Nuclear translocation and activation of JNK1 during ischemia and reperfusion. *J Biol Chem*, 272, 16657-62. ↗

Boyle, DL., Sundarraj, M., Chabaud-Riou, M., Firestein, GS., Hammaker, D. (2003). Expression of the MAPK kinases MKK-4 and MKK-7 in rheumatoid arthritis and their role as key regulators of JNK. *Arthritis Rheum*, 48, 2450-60. ↗

Editions

2009-12-16	Authored	Shamovsky, V.
2010-02-28	Reviewed	Gillespie, ME.
2010-02-28	Edited	Shamovsky, V.

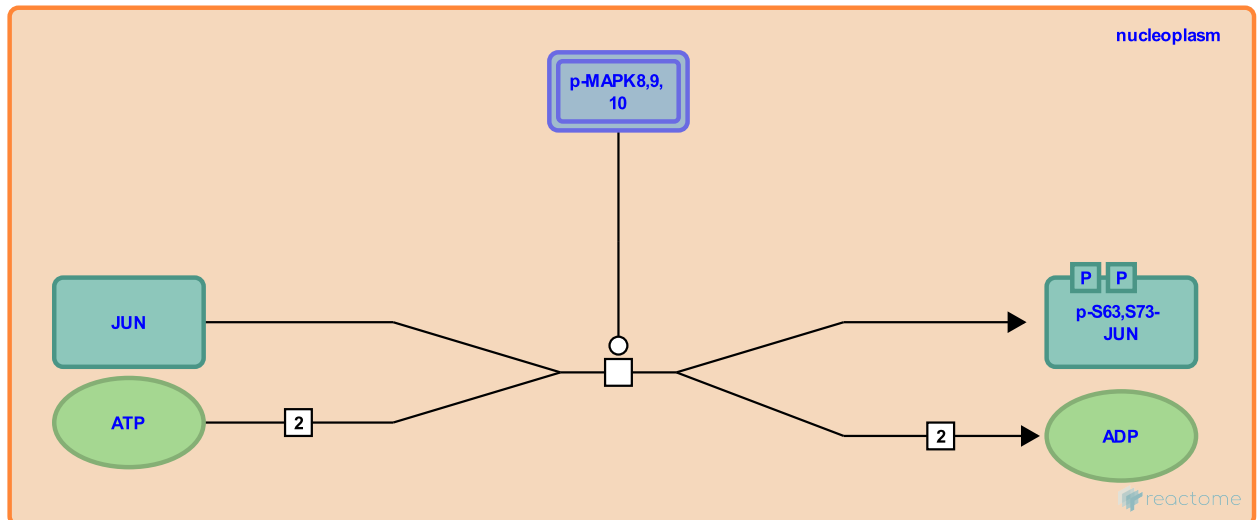
Activated JNKs phosphorylate c-JUN ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-168136

Type: transition

Compartments: nucleoplasm



JNK (c-Jun N-terminal Kinase) phosphorylates several transcription factors including c-Jun after translocation to the nucleus.

Preceded by: [Activated human JNKs migrate to nucleoplasm](#)

Followed by: [Formation of Activated Protein 1 \(AP-1\) complex. cFOS/c-JUN heterodimer.](#)

Literature references

Raivich, G. (2008). c-Jun expression, activation and function in neural cell death, inflammation and repair. *J Neurochem*, 107, 898-906. ↗

Ferrand, N., Prunier, C., Atfi, A., Gauthier, JM., Dennler, S. (2000). c-Jun inhibits transforming growth factor beta-mediated transcription by repressing Smad3 transcriptional activity. *J Biol Chem*, 275, 28858-65. ↗

Editions

2005-11-10	Authored	Luo, F.
2006-04-24	Reviewed	Gay, NJ.
2009-12-16	Edited, Revised	Shamovsky, V.

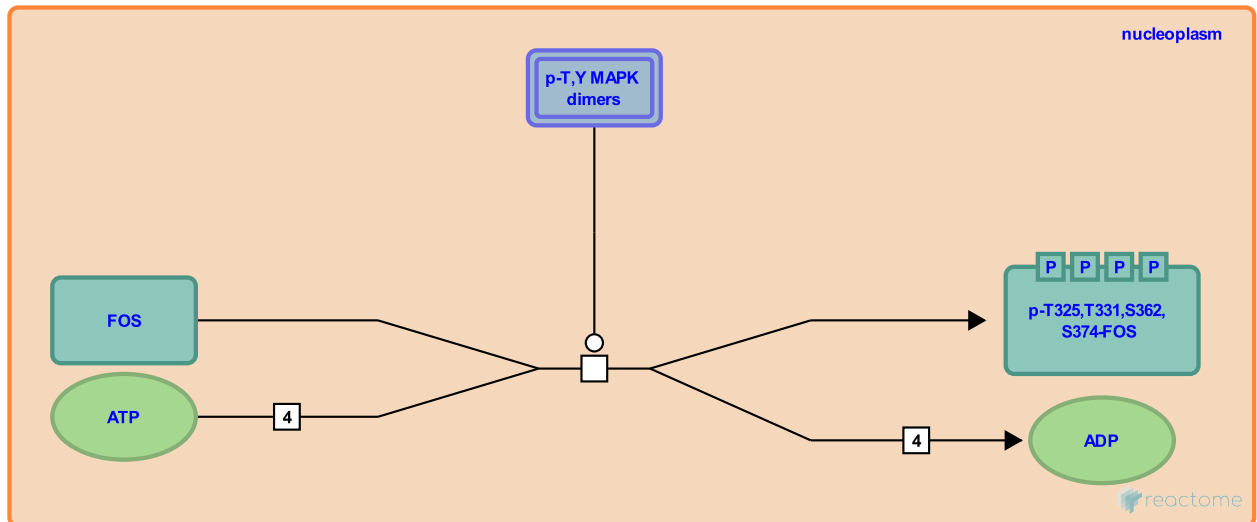
c-FOS activation by phospho ERK1/2 ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-450325

Type: transition

Compartments: nucleoplasm



The Fos proteins(c-Fos, FosB, Fra1 and Fra2), which cannot homodimerize, form stable heterodimers with Jun proteins and thereby enhance their DNA binding activity.

On activation of the MAPK pathway, Ser-374 of Fos is phosphorylated by ERK1/2 and Ser-362 is phosphorylated by RSK1/2, the latter kinases being activated by ERK1/2. If stimulation of the MAPK pathway is sufficiently sustained, ERK1/2 can dock on an upstream FTYP amino acid motif, called the DEF domain (docking site for ERKs, FXFP), and phosphorylate Thr-331 and Thr-325.

Phosphorylation at specific sites enhances the transactivating potential of several AP-1 proteins, including Jun and Fos, without having any effect on their DNA binding activities. Thus, phosphorylation of Ser-362 and Ser-374 stabilizes c-Fos but has no demonstrated role in the control of transcriptional activity. On the contrary, phosphorylation of Thr-325 and Thr-331 enhances c-Fos transcriptional activity but has no demonstrated effect on protein turnover.

Followed by: [Formation of Activated Protein 1 \(AP-1\) complex. cFOS/c-JUN heterodimer.](#)

Literature references

Sagata, N., Okazaki, K. (1995). The Mos/MAP kinase pathway stabilizes c-Fos by phosphorylation and augments its transforming activity in NIH 3T3 cells. *EMBO J*, 14, 5048-59. ↗

Murphy, LO., Blenis, J., Chen, RH., Fingar, DC., Smith, S. (2002). Molecular interpretation of ERK signal duration by immediate early gene products. *Nat Cell Biol*, 4, 556-64. ↗

Editions

2009-12-16	Authored	Shamovsky, V.
2010-02-28	Reviewed	Gillespie, ME.
2010-02-28	Edited	Shamovsky, V.

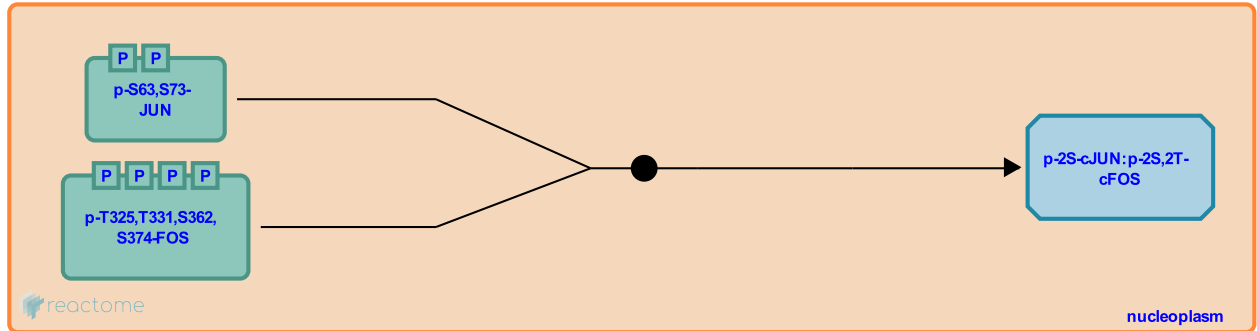
Formation of Activated Protein 1 (AP-1) complex. cFOS/c-JUN heterodimer. ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-450292

Type: binding

Compartments: nucleoplasm



The bZIP domains of Jun and Fos form an X-shaped α -helical structure, which binds to the palindromic AP-1 site (TGAGTCA) (Glover and Harrison, 1995).

Preceded by: [Activated JNKs phosphorylate c-JUN](#), [c-FOS activation by phospho ERK1/2](#)

Followed by: [ERK1/2-activated AP1 complex binds KDM6B promoter](#)

Literature references

Glover, JN., Harrison, SC. (1995). Crystal structure of the heterodimeric bZIP transcription factor c-Fos-c-Jun bound to DNA. *Nature*, 373, 257-61. ↗

Daniel, V., Pinkus, R., Bergelson, S., Ainbinder, E. (1997). Regulatory mechanisms involved in activator-protein-1 (AP-1)-mediated activation of glutathione-S-transferase gene expression by chemical agents. *Eur J Biochem*, 243, 49-57. ↗

Editions

2005-11-16	Authored	Luo, F.
2006-04-24	Reviewed	Gay, NJ.
2009-12-16	Edited, Revised	Shamovsky, V.

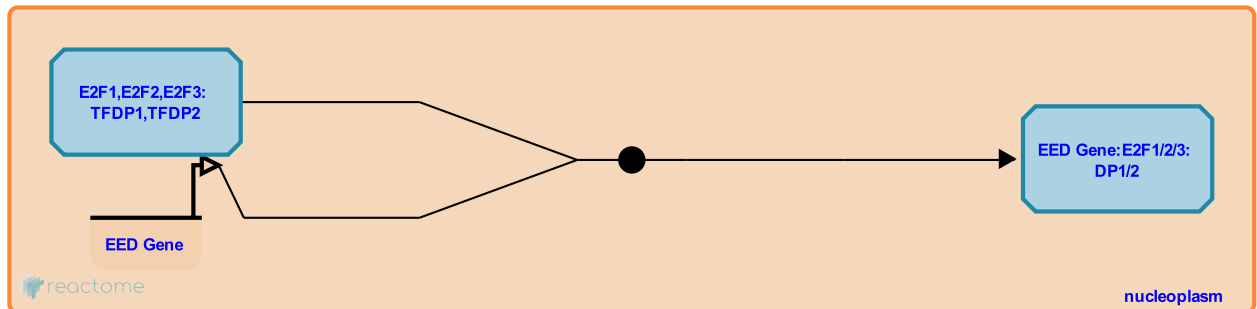
E2F1/2/3:DP1/2 binds EED gene promoter ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3240765

Type: binding

Compartments: nucleoplasm



EED gene contains several E2F binding sites in its promoter, and these E2F-binding sites are needed for the responsiveness of EED promoter to E2F1, E2F2 and E2F3. Only E2F1 with intact DNA-binding domain stimulates EED transcription. Binding of E2F3 to EED promoter was directly demonstrated by ChIP (Bracken et al. 2003).

Followed by: [E2F1/2/3 stimulates EED transcription](#)

Literature references

Helin, K., Bracken, AP., Prosperini, E., Capra, M., Colli, E., Pasini, D. (2003). EZH2 is downstream of the pRB-E2F pathway, essential for proliferation and amplified in cancer. *EMBO J.*, 22, 5323-35. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

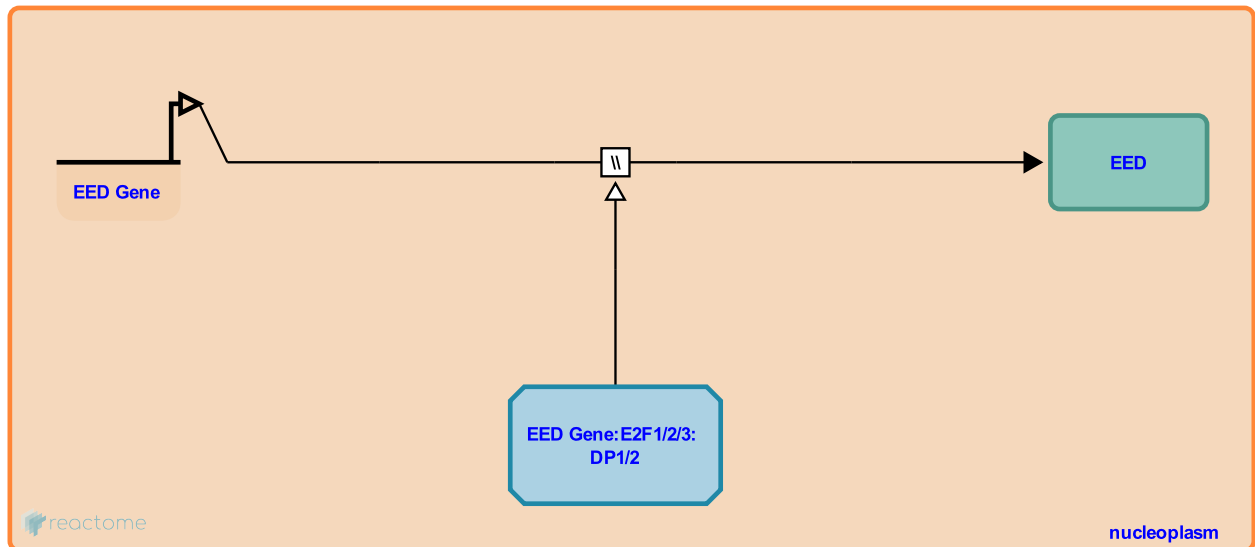
E2F1/2/3 stimulates EED transcription ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3240782

Type: omitted

Compartments: nucleoplasm



In growing cells, the transcription of EED gene, which codes for a subunit of the Polycomb repressor complex 2 (PRC2), is stimulated by E2F1, E2F2 and E2F3 that bind E2F sites in the EED promoter. Direct binding to EED promoter was directly experimentally examined and confirmed only for E2F3, while it was also demonstrated that E2F1-mediated stimulation of EED gene transcription depends on the intact DNA-binding domain of E2F1. E2F4 also binds EED promoter directly, with the strongest enrichment in G0 (Bracken et al. 2003).

Preceded by: [E2F1/2/3:DP1/2 binds EED gene promoter](#)

Followed by: [Formation of PRC2-EZH2 complex](#)

Literature references

Helin, K., Bracken, AP., Prosperini, E., Capra, M., Colli, E., Pasini, D. (2003). EZH2 is downstream of the pRB-E2F pathway, essential for proliferation and amplified in cancer. *EMBO J.*, 22, 5323-35. ↗

Editions

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2013-09-03	Reviewed	Samarajiwa, S.

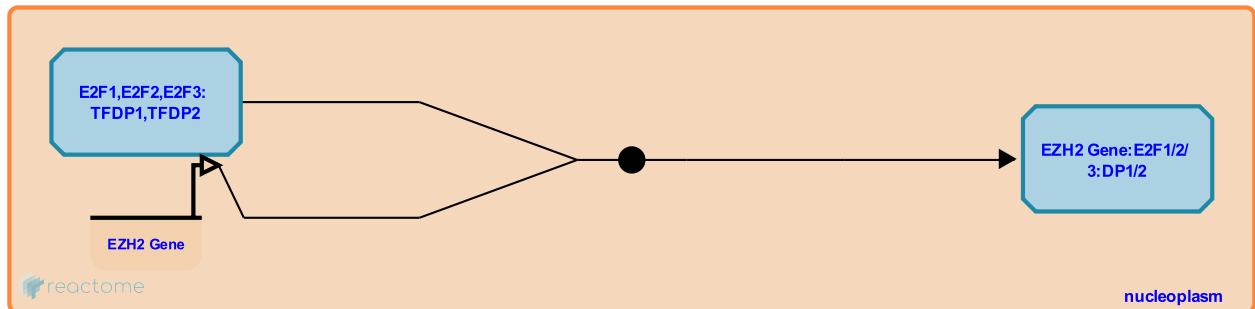
E2F1/2/3:DP1/2 binds EZH2 gene promoter ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3240777

Type: binding

Compartments: nucleoplasm



EZH2 gene contains several E2F binding sites in its promoter, and these E2F-binding sites are needed for the responsiveness of EZH2 promoter to E2F1, E2F2 and E2F3. Only E2F1 with intact DNA-binding domain stimulates EZH2 transcription. Binding of E2F3 to EZH2 promoter was directly demonstrated by CHIP (Bracken et al. 2003).

Followed by: [E2F1/2/3 stimulates EZH2 transcription](#)

Literature references

Helin, K., Bracken, AP., Prosperini, E., Capra, M., Colli, E., Pasini, D. (2003). EZH2 is downstream of the pRB-E2F pathway, essential for proliferation and amplified in cancer. *EMBO J.*, 22, 5323-35. ↗

Editions

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2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

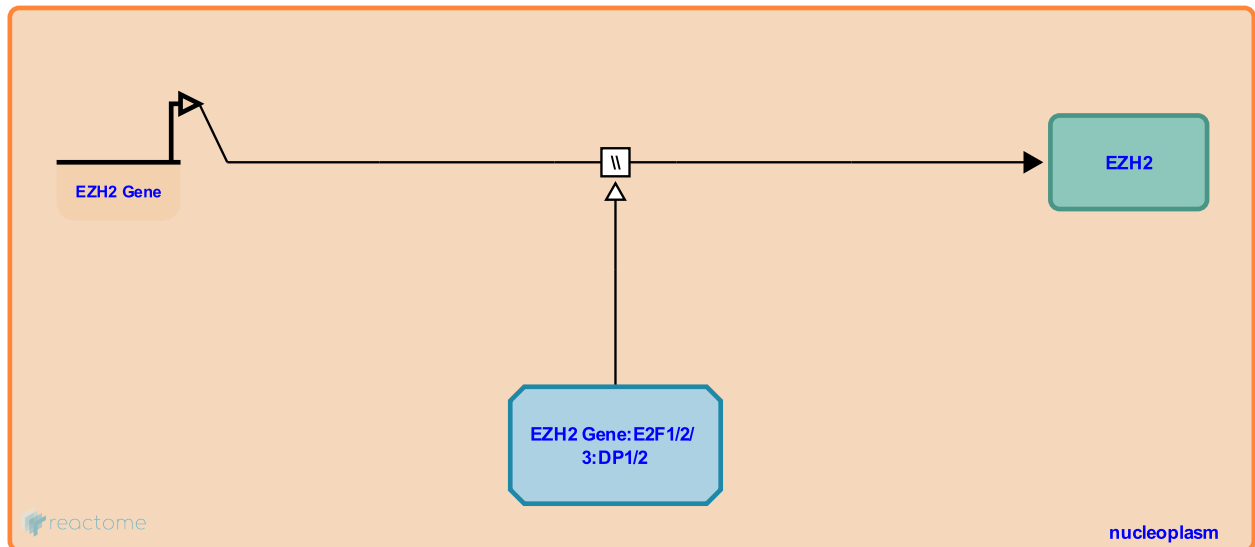
E2F1/2/3 stimulates EZH2 transcription ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3240783

Type: omitted

Compartments: nucleoplasm



In growing cells, the transcription of EZH2 methyltransferase gene, which codes for a subunit of the Polycomb repressor complex 2 (PRC2), is stimulated by E2F1, E2F2 and E2F3 that bind E2F sites in the EZH2 promoter. Direct binding to EZH2 promoter was directly experimentally examined and confirmed only for E2F3, while it was also demonstrated that E2F1-mediated stimulation of EZH2 gene transcription depends on the intact DNA-binding domain of E2F1. E2F4 also binds EZH2 promoter directly, with the strongest enrichment in G0, which is likely needed for repression of EZH2 transcription in non-growing cells (Bracken et al. 2003).

Preceded by: [E2F1/2/3:DP1/2 binds EZH2 gene promoter](#)

Followed by: [Formation of PRC2-EZH2 complex](#)

Literature references

Helin, K., Bracken, AP., Prosperini, E., Capra, M., Colli, E., Pasini, D. (2003). EZH2 is downstream of the pRB-E2F pathway, essential for proliferation and amplified in cancer. *EMBO J.*, 22, 5323-35. ↗

Editions

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2013-09-03	Reviewed	Samarajiwa, S.

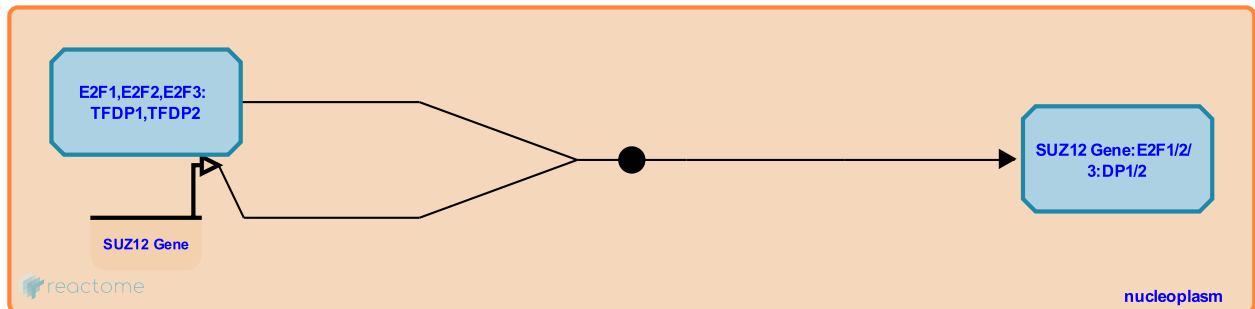
E2F1/2/3:DP1/2 binds SUZ12 gene promoter ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3240766

Type: binding

Compartments: nucleoplasm



E2F1, E2F2, E2F3 and E2F4 are all able to bind the promoter of SUZ12 (ChET 9) (Weinmann et al 2001), a subunit of the Polycomb repressor complex 2 (PRC2).

Followed by: [E2F1/2/3 stimulates SUZ12 transcription](#)

Literature references

Bartley, SM., Weinmann, AS., Farnham, PJ., Zhang, T., Zhang, MQ. (2001). Use of chromatin immunoprecipitation to clone novel E2F target promoters. *Mol. Cell. Biol.*, 21, 6820-32. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

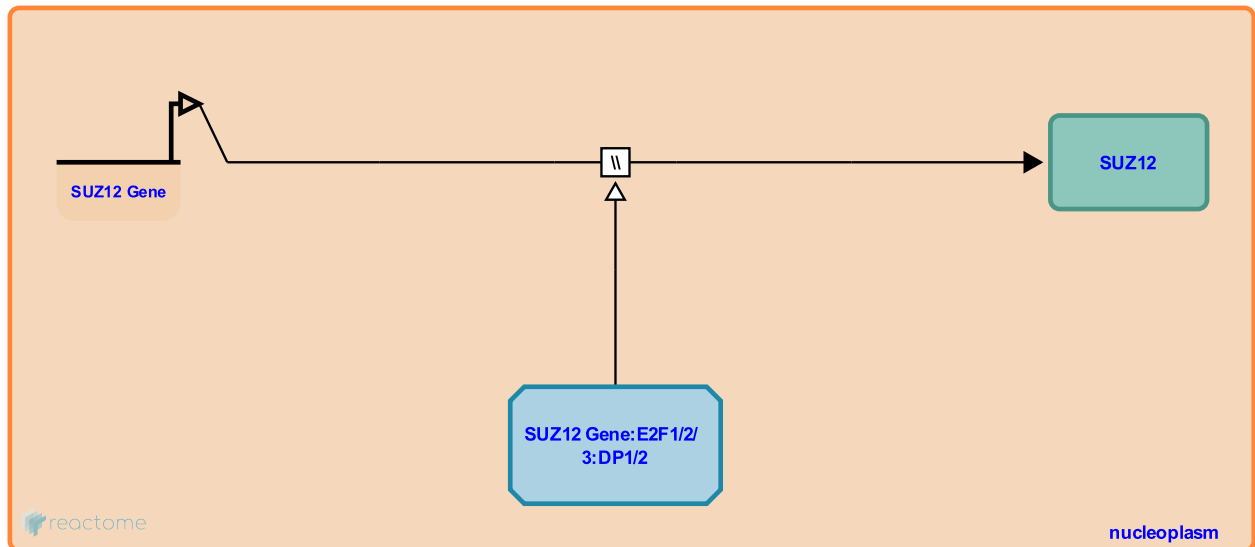
E2F1/2/3 stimulates SUZ12 transcription [↗](#)

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3240787

Type: omitted

Compartments: nucleoplasm



E2F1 was directly shown to activate the transcription from the SUZ12 promoter, and it is assumed that E2F2 and E2F3, which also bind SUZ12 promoter, are able to activate SUZ12 transcription (Weinmann et al. 2001).

Preceded by: [E2F1/2/3:DP1/2 binds SUZ12 gene promoter](#)

Followed by: [Formation of PRC2-EZH2 complex](#)

Literature references

Bartley, SM., Weinmann, AS., Farnham, PJ., Zhang, T., Zhang, MQ. (2001). Use of chromatin immunoprecipitation to clone novel E2F target promoters. *Mol. Cell. Biol.*, 21, 6820-32. [↗](#)

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

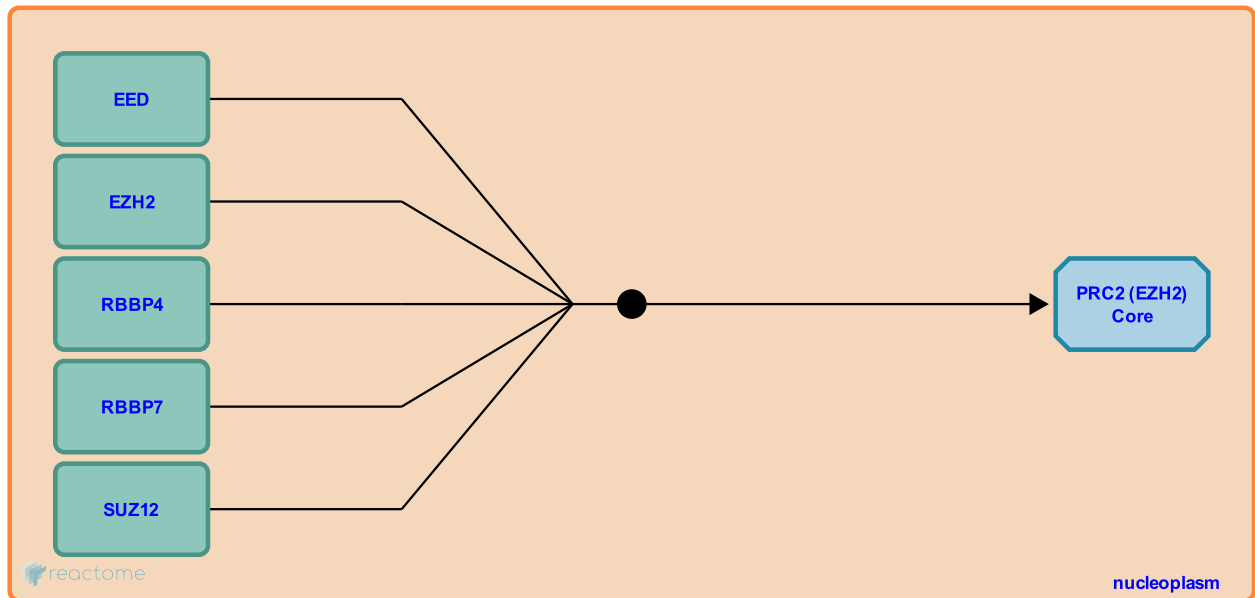
Formation of PRC2-EZH2 complex ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3240957

Type: binding

Compartments: nucleoplasm



The Polycomb repressor complex 2, PRC2-EZH2, consists of 5 proteins: EZH2, EED, RBBP4 (RBAP48), RBBP7 (RBAP46) and SUZ12, and is evolutionarily conserved. While RBBP4 and RBBP7 are proteins involved in various chromatin remodeling complexes, EZH2, EED and SUZ12 belong to the Polycomb group. EZH2 is also a member of the SET family of histone methyltransferases, and PRC2 trimethylates lysine residues K10 and K28 of HIST1H3A (histone H3), with K28 being the preferred site (Kuzmichev et al. 2002).

Preceded by: [E2F1/2/3 stimulates EED transcription](#), [E2F1/2/3 stimulates EZH2 transcription](#), [E2F1/2/3 stimulates SUZ12 transcription](#)

Followed by: [PRC2-EZH2 trimethylates nucleosomes associated with CDKN2A promoter](#)

Literature references

Nishioka, K., Reinberg, D., Kuzmichev, A., Tempst, P., Erdjument-Bromage, H. (2002). Histone methyltransferase activity associated with a human multiprotein complex containing the Enhancer of Zeste protein. *Genes Dev*, 16, 2893-905. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

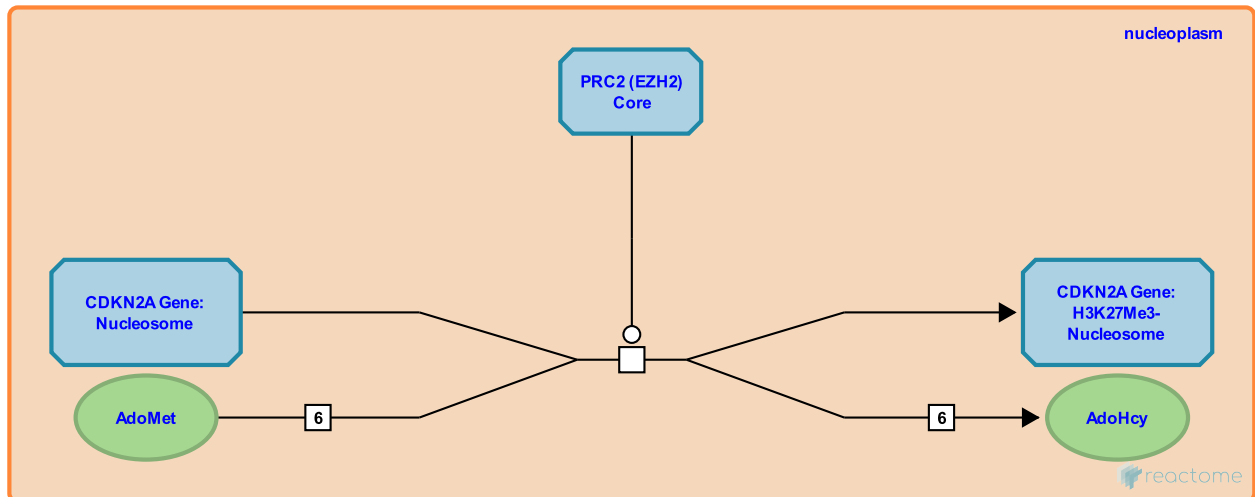
PRC2-EZH2 trimethylates nucleosomes associated with CDKN2A promoter ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3240295

Type: transition

Compartments: nucleoplasm



The Polycomb repressor complex 2 (PRC2) trimethylates histone HIST1H3A (H3) on lysine residue 28, producing an H3K27Me3 mark along the CDKN2A locus. The H3K27Me3 subsequently serves as a docking site for the PRC1.4 complex that includes BMI1 and CBX8 or CBX7 and acts to repress p16INK4A and, probably p14ARF transcription (Bracken et al. 2007). Proteins of the RB family may be involved in the regulation of enzymatic activity or the recruitment of PRC2 to the CDKN2A locus (Kotake et al. 2007). Conflicting results exist on the regulation of p14ARF expression by Polycomb group (PcG) proteins involved in the formation of PRC2 and PRC1. While p14ARF does not seem to be regulated by PcGs in human fibroblasts, in contrast to mouse embryonic fibroblasts - MEFs (Bracken et al. 2007), experiments on human CD34+ bone marrow cells (Bracken et al. 2007) and U2OS osteosarcoma cell line (Voncken et al. 2005) implicate PcGs in the regulation of p14ARF transcription.

Preceded by: [Formation of PRC2-EZH2 complex](#)

Followed by: [KDM6B demethylates H3K27me3 on p16INK4A promoter](#)

Literature references

Xiong, Y., Sage, J., Viatour, P., Zhang, Y., Kotake, Y., Cao, R. (2007). pRB family proteins are required for H3K27 trimethylation and Polycomb repression complexes binding to and silencing p16INK4alpha tumor suppressor gene. *Genes Dev.*, 21, 49-54. ↗

Helin, K., Gargiulo, G., Minucci, S., Dietrich, N., Bracken, AP., Marine, JC. et al. (2007). The Polycomb group proteins bind throughout the INK4A-ARF locus and are disassociated in senescent cells. *Genes Dev.*, 21, 525-30. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

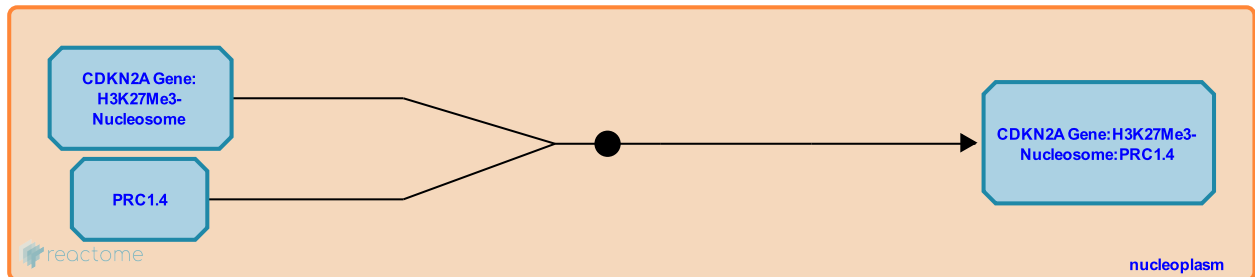
PRC1.4 complex binds H3K27Me3 nucleosomes on CDKN2A promoter ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3229089

Type: binding

Compartments: nucleoplasm



PRC1.4 complex, which includes PCGF4 (BMI1), RING1 (RING1A) and RNF2 (RING1B) ubiquitin ligases and CBX proteins (Gao et al. 2012), binds nucleosomes trimethylated on the lysine residue 28 of histone H3 (Me3K-28-HIST1H3A, also known as H3K27Me3), located on CDKN2A promoter (Dietrich et al. 2007, Agherbi et al. 2009, Voncken et al. 2005), through interaction of BMI1 and CBX proteins with Me3K-28-HIST1H3A mark (Gao et al. 2012, Dietrich et al. 2007).

Followed by: [p-MAPKAPK3 phosphorylates BMI1](#)

Literature references

- Helin, K., Schjerling, CK., Dietrich, N., Koseki, H., Bracken, AP., Hansen, KH. et al. (2007). Bypass of senescence by the polycomb group protein CBX8 through direct binding to the INK4A-ARF locus. *EMBO J.*, 26, 1637-48. ↗
- Parisi, F., Sawai, A., Gao, Z., Kluger, Y., Reinberg, D., Zhang, J. et al. (2012). PCGF homologs, CBX proteins, and RYBP define functionally distinct PRC1 family complexes. *Mol. Cell*, 45, 344-56. ↗
- Agherbi, H., Serrano, M., Chasson, L., Verthuy, C., Djabali, M., Gaussmann-Wenger, A. (2009). Polycomb mediated epigenetic silencing and replication timing at the INK4a/ARF locus during senescence. *PLoS ONE*, 4, e5622. ↗
- Ludwig, S., Voncken, JW., Neufeld, B., Kubben, N., Niessen, H., Dahlmans, V. et al. (2005). MAPKAP kinase 3pK phosphorylates and regulates chromatin association of the polycomb group protein Bmi1. *J. Biol. Chem.*, 280, 5178-87. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

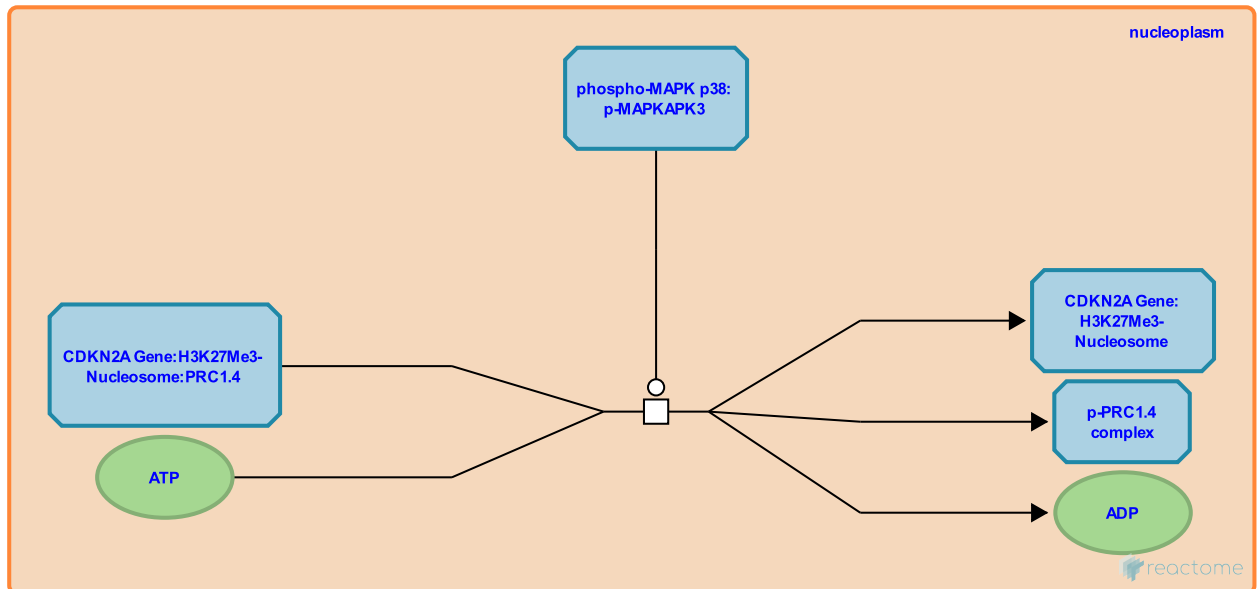
p-MAPKAPK3 phosphorylates BMI1 [↗](#)

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3229102

Type: transition

Compartments: nucleoplasm



In response to stress-activated p38 signaling, MAPKAPK3 phosphorylates BMI1, leading to the dissociation of the PRC1.4 complex from chromatin and transcription of p14-ARF (Voncken et al. 2005).

Preceded by: [Active p38 MAPK phosphorylates MAPKAPK2 or 3](#), [PRC1.4 complex binds H3K27Me3 nucleosomes on CDKN2A promoter](#)

Followed by: [MAPKAPK2/3-mediated removal of PRC1.4 complex stimulates p14ARF transcription](#)

Literature references

Ludwig, S., Voncken, JW., Neufeld, B., Kubben, N., Niessen, H., Dahlmans, V. et al. (2005). MAPKAP kinase 3pK phosphorylates and regulates chromatin association of the polycomb group protein Bmi1. *J. Biol. Chem.*, 280, 5178-87. [↗](#)

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

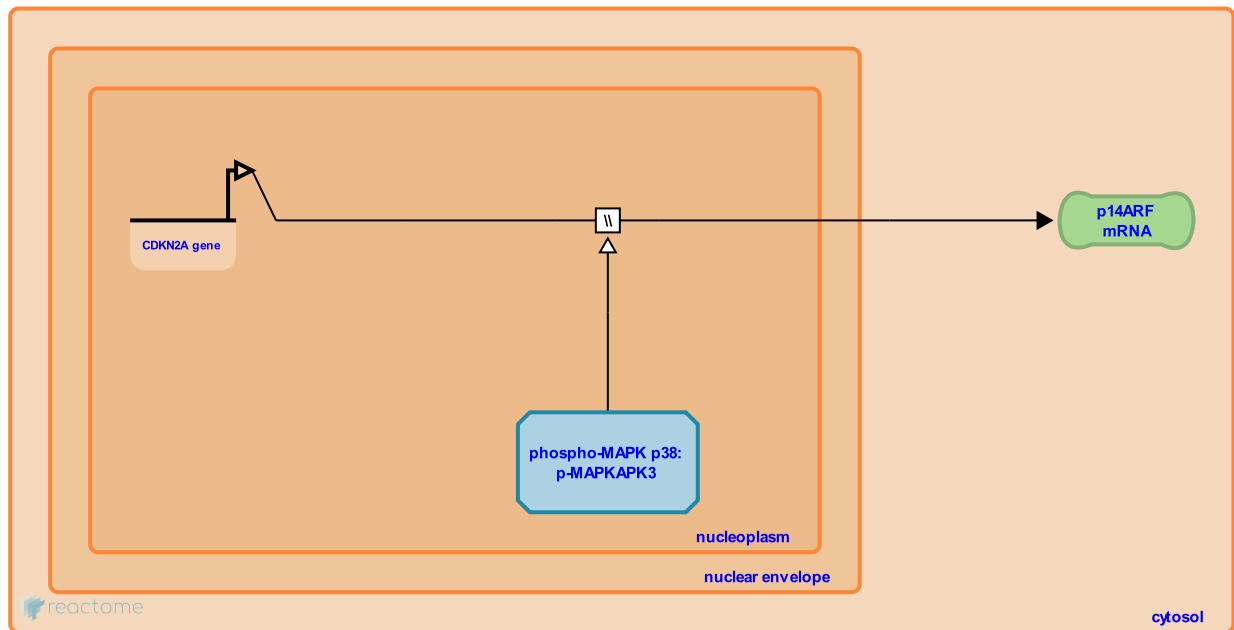
MAPKAPK2/3-mediated removal of PRC1.4 complex stimulates p14ARF transcription ↗

Location: Oxidative Stress Induced Senescence

Stable identifier: R-HSA-3229138

Type: omitted

Compartments: nucleoplasm, cytosol



Transcription of p14ARF in response to oxidative stress induced p38 signaling is positively regulated by MAPKAPK3-mediated phosphorylation of BMI1 and the subsequent dissociation of the PRC1.4 complex from the CDKN2A locus (Voncken et al. 2005).

Preceded by: p-MAPKAPK3 phosphorylates BMI1

Followed by: miR-24 binds p16INK4A and p14ARF mRNAs

Literature references

Ludwig, S., Voncken, JW., Neufeld, B., Kubben, N., Niessen, H., Dahlmans, V. et al. (2005). MAPKAP kinase 3pK phosphorylates and regulates chromatin association of the polycomb group protein Bmi1. *J. Biol. Chem.*, 280, 5178-87. ↗

Editions

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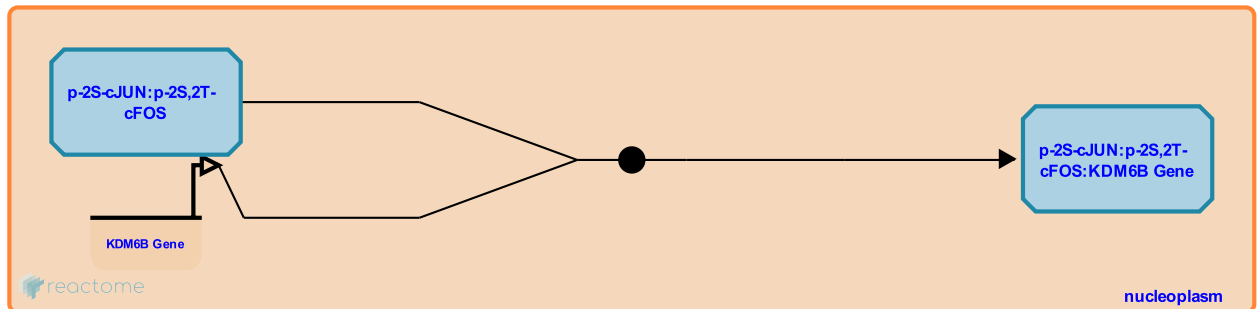
ERK1/2-activated AP1 complex binds KDM6B promoter ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3222533

Type: binding

Compartments: nucleoplasm



Binding of the AP-1 (JUN:FOS) subunit JUN to the KDM6B (JMJD3) promoter, as well as the transcription of KDM6B gene increases after ERK activation (Lin et al. 2012).

Preceded by: [Formation of Activated Protein 1 \(AP-1\) complex. cFOS/c-JUN heterodimer.](#)

Followed by: [AP-1 complex stimulates KDM6B transcription](#)

Literature references

Wang, CC., Lin, TY., Lin, WC., Yang, HC., Shieh, SY., Lai, PL. et al. (2012). Loss of the candidate tumor suppressor BTG3 triggers acute cellular senescence via the ERK-JMJD3-p16(INK4a) signaling axis. *Oncogene*, 31, 3287-97. ↗

Helin, K., Rudkjaer, L., Christensen, J., Andersen, G., Agger, K., Williams, K. et al. (2009). The H3K27me3 demethylase JMJD3 contributes to the activation of the INK4A-ARF locus in response to oncogene- and stress-induced senescence. *Genes Dev.*, 23, 1171-6. ↗

Testa, G., Notarbartolo, S., Prosperini, E., De Santa, F., Natoli, G., Totaro, MG. (2007). The histone H3 lysine-27 demethylase Jmjd3 links inflammation to inhibition of polycomb-mediated gene silencing. *Cell*, 130, 1083-94. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

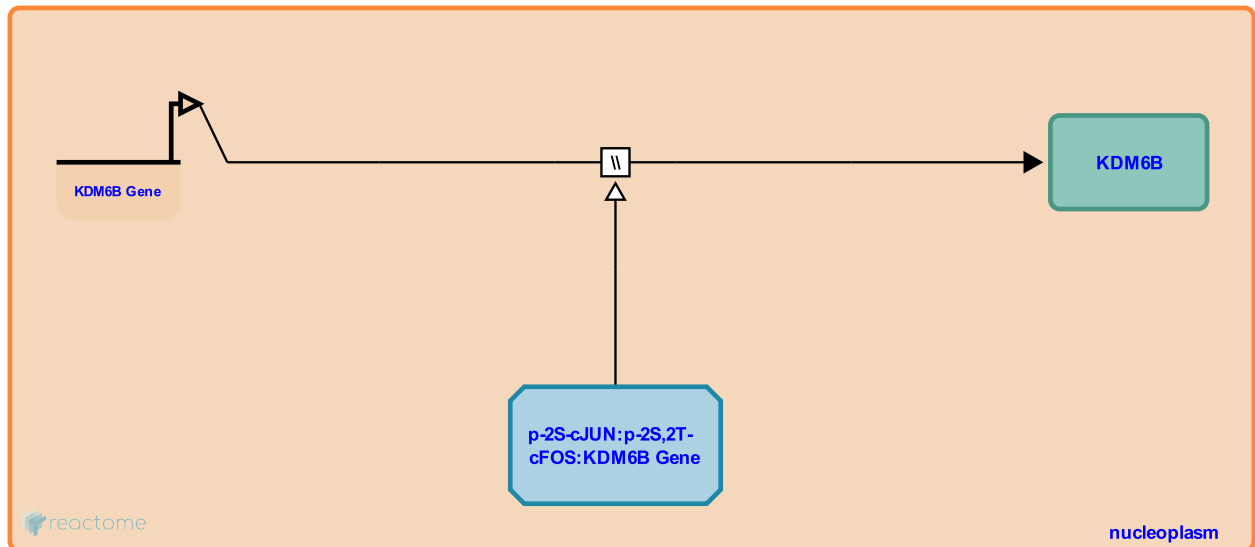
AP-1 complex stimulates KDM6B transcription ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3222546

Type: omitted

Compartments: nucleoplasm



Binding of the AP-1 (JUN:FOS) subunit JUN to the KDM6B (JMJD3) promoter, as well as the transcription of KDM6B gene increases after ERK activation (Lin et al. 2012).

Preceded by: [ERK1/2-activated AP1 complex binds KDM6B promoter](#)

Followed by: [KDM6B binds iron](#)

Literature references

Wang, CC., Lin, TY., Lin, WC., Yang, HC., Shieh, SY., Lai, PL. et al. (2012). Loss of the candidate tumor suppressor BTG3 triggers acute cellular senescence via the ERK-JMJD3-p16(INK4a) signaling axis. *Oncogene*, 31, 3287-97. ↗

Editions

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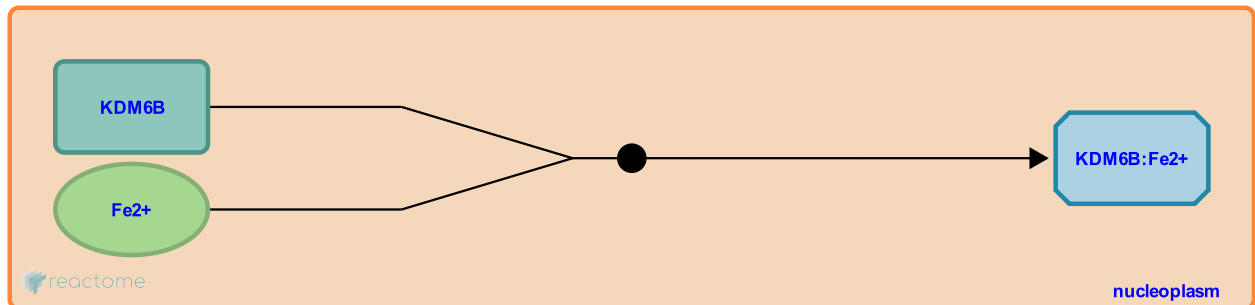
KDM6B binds iron [↗](#)

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-8979071

Type: binding

Compartments: nucleoplasm



KDM6B (JMJD3) binds iron. Formation of complex with Fe(II) is needed for the catalytic activity of KDM6B (De Santa et al. 2007).

Preceded by: [AP-1 complex stimulates KDM6B transcription](#)

Followed by: [KDM6B demethylates H3K27me3 on p16INK4A promoter](#)

Literature references

Testa, G., Notarbartolo, S., Prosperini, E., De Santa, F., Natoli, G., Totaro, MG. (2007). The histone H3 lysine-27 demethylase Jmjd3 links inflammation to inhibition of polycomb-mediated gene silencing. *Cell*, 130, 1083-94. [↗](#)

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

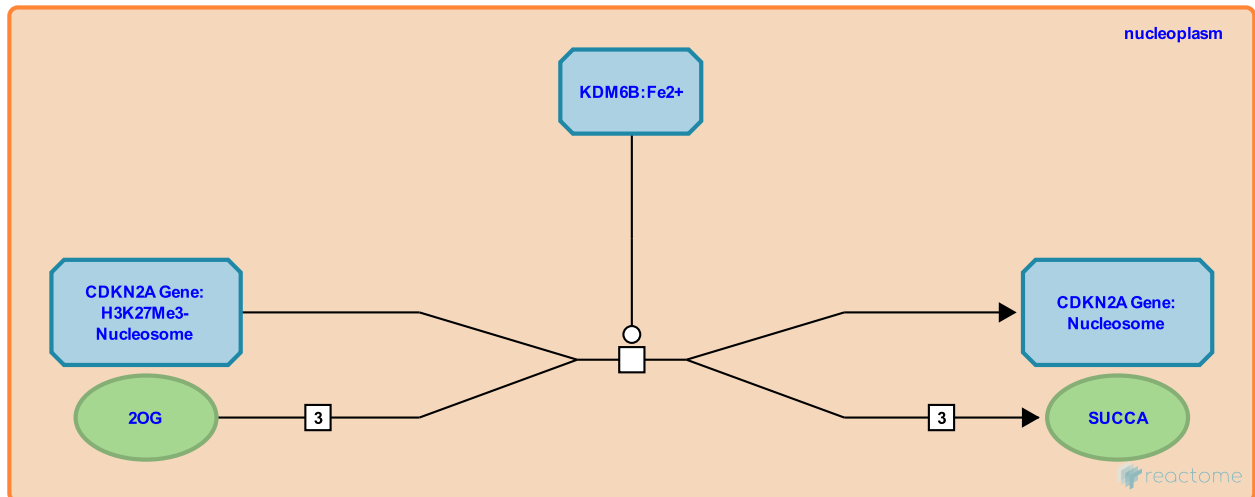
KDM6B demethylates H3K27me3 on p16INK4A promoter ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3222593

Type: transition

Compartments: nucleoplasm



Histone demethylase KDM6B (JMJD3) demethylates H3K27Me3 marks i.e. removes methyl groups from lysine 28 of histone HIST1H3A on CDKN2A locus, thereby activating CDKN2A transcription. In human cells, H3K27Me3 marks are predominantly found around the first exon of p16INK4A, and KDM6B therefore activates p16INK4A transcription but not p14ARF transcription. In mouse cells, H3K27Me3 marks are found throughout the Cdkn2a locus and Kdm6b demethylase activity induces transcription of both p16Ink4a and p19Arf. KDM6B action promotes both the oncogene-induced and oxidative stress-induced senescence (Agger et al. 2009, Barradas et al. 2009).

Preceded by: [PRC2-EZH2 trimethylates nucleosomes associated with CDKN2A promoter](#), [KDM6B binds iron](#)

Followed by: [Demethylation of H3K27Me3 by KDM6B stimulates p16INK4A transcription, while binding of PRC1.4 complex to H3K27Me3 represses p16INK4A transcription](#)

Literature references

Helin, K., Rudkjaer, L., Christensen, J., Andersen, G., Agger, K., Williams, K. et al. (2009). The H3K27me3 demethylase JMJD3 contributes to the activation of the INK4A-ARF locus in response to oncogene- and stress-induced senescence. *Genes Dev.*, 23, 1171-6. ↗

Peters, G., Banck, M., Zhou, MM., Gil, J., Walsh, MJ., Li, S. et al. (2009). Histone demethylase JMJD3 contributes to epigenetic control of INK4a/ARF by oncogenic RAS. *Genes Dev.*, 23, 1177-82. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

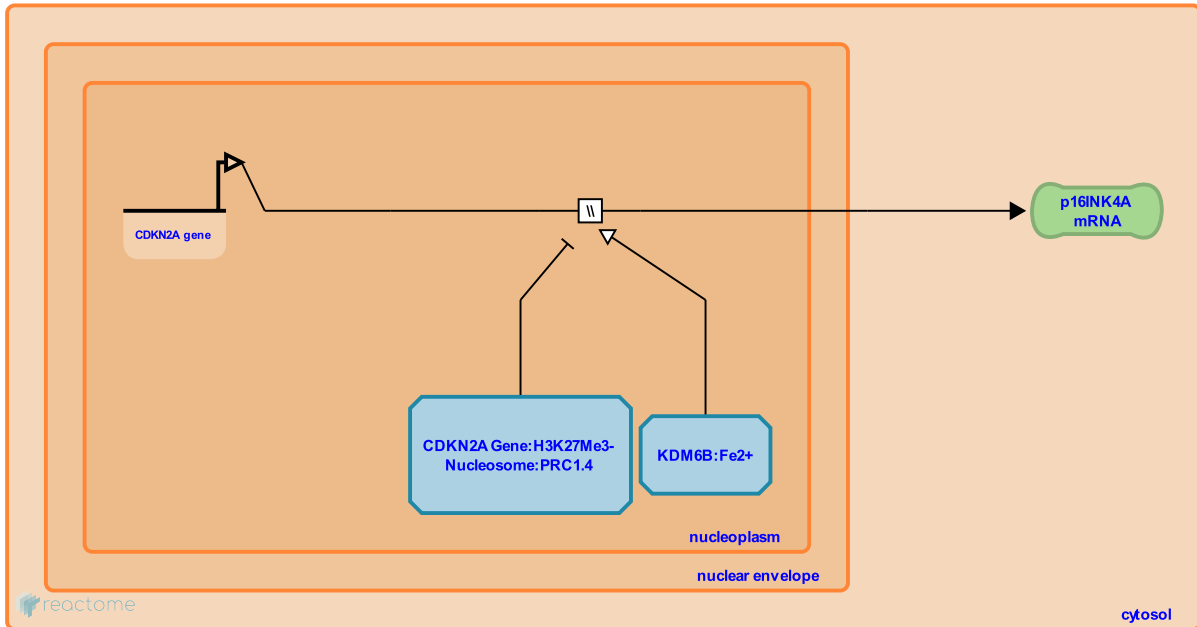
Demethylation of H3K27Me3 by KDM6B stimulates p16INK4A transcription, while binding of PRC1.4 complex to H3K27Me3 represses p16INK4A transcription [↗](#)

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3223200

Type: omitted

Compartments: nucleoplasm, cytosol



While binding of the PRC1.4 complex to the H3K27Me3 mark on the promoter of p16INK4A inhibits p16INK4A transcription (Dietrich et al. 2007, Agherbi et al. 2009), KDM6B-mediated demethylation of lysine 28 of histone HIST1H3A (the removal of H3K27Me3 mark) stimulates p16INK4A transcription (Agger et al. 2009, Barradas et al. 2009).

Preceded by: [KDM6B demethylates H3K27me3 on p16INK4A promoter](#)

Followed by: [miR-24 binds p16INK4A and p14ARF mRNAs, Translation of p16INK4A mRNA is inhibited by miR-24](#)

Literature references

- Helin, K., Rudkjaer, L., Christensen, J., Andersen, G., Agger, K., Williams, K. et al. (2009). The H3K27me3 demethylase JMJD3 contributes to the activation of the INK4A-ARF locus in response to oncogene- and stress-induced senescence. *Genes Dev.*, 23, 1171-6. [↗](#)
- Helin, K., Schjerling, CK., Dietrich, N., Koseki, H., Bracken, AP., Hansen, KH. et al. (2007). Bypass of senescence by the polycomb group protein CBX8 through direct binding to the INK4A-ARF locus. *EMBO J.*, 26, 1637-48. [↗](#)
- Agherbi, H., Serrano, M., Chasson, L., Verthuy, C., Djabali, M., Gaussmann-Wenger, A. (2009). Polycomb mediated epigenetic silencing and replication timing at the INK4a/ARF locus during senescence. *PLoS ONE*, 4, e5622. [↗](#)
- Peters, G., Banck, M., Zhou, MM., Gil, J., Walsh, MJ., Li, S. et al. (2009). Histone demethylase JMJD3 contributes to epigenetic control of INK4a/ARF by oncogenic RAS. *Genes Dev.*, 23, 1177-82. [↗](#)

Editions

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2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

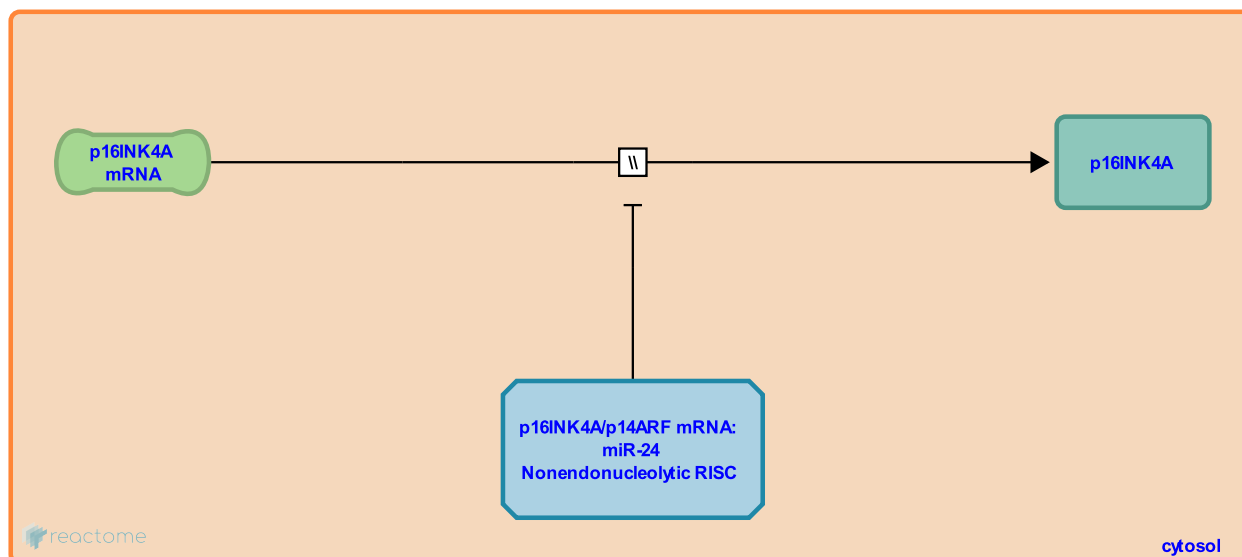
Translation of p16INK4A mRNA is inhibited by miR-24 ↗

Location: Oxidative Stress Induced Senescence

Stable identifier: R-HSA-3209114

Type: omitted

Compartments: cytosol



MicroRNA miR-24 inhibits translation of p16INK4A mRNA without causing mRNA degradation. This results in high p16INK4A transcript level accompanied by low p16INK4A protein level (Lal et al. 2008). p16INK4A acts as the inhibitor of cyclin-dependent kinases CDK4 and CDK6 which phosphorylate and inhibit RB1 protein thereby promoting G1 to S transition and cell cycle progression (Serrano et al. 1993).

Preceded by: miR-24 binds p16INK4A and p14ARF mRNAs, Demethylation of H3K27Me3 by KDM6B stimulates p16INK4A transcription, while binding of PRC1.4 complex to H3K27Me3 represses p16INK4A transcription

Followed by: Association of INK4 family proteins with CDK4/6

Literature references

Yang, X., Pullmann, R., Gorospe, M., Dykxhoorn, D., Lal, A., Martindale, J.L. et al. (2008). p16(INK4a) translation suppressed by miR-24. *PLoS ONE*, 3, e1864. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.
2019-10-18	Reviewed	Vegi, NM.
2019-11-01	Edited	Orlic-Milacic, M.

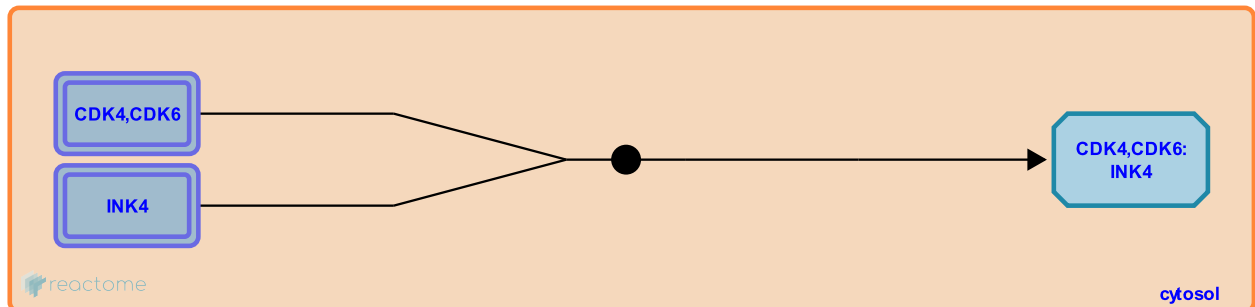
Association of INK4 family proteins with CDK4/6 [↗](#)

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-182594

Type: binding

Compartments: cytosol



Prior to mitogen activation, the inhibitory proteins of the INK4 family (p15, p16, p18, and p19) associate with the catalytic domains of free CDK4 and CDK6, preventing their association with D type cyclins (CCND1, CCND2 and CCND3), and thus their activation and their inhibitory phosphorylation of the RB family (Serrano et al. 1993, Hannon and Beach 1994, Guan et al. 1994, Guan et al. 1996, Parry et al. 1995). Inactivation and defects of RB1 strongly upregulate p16INK4A (Parry et al. 1995).

Preceded by: [Translation of p16INK4A mRNA is inhibited by miR-24](#)

Literature references

- Hannon, GJ., Serrano, M., Beach, D. (1993). A new regulatory motif in cell-cycle control causing specific inhibition of cyclin D/CDK4. *Nature*, 366, 704-7. [↗](#)
- Matera, AG., Xiong, Y., Guan, KL., Zariwala, M., Li, Y., O'Keefe, CL. et al. (1996). Isolation and characterization of p19INK4d, a p16-related inhibitor specific to CDK6 and CDK4. *Mol Biol Cell*, 7, 57-70. [↗](#)
- Peters, G., Bates, S., Mann, DJ., Parry, D. (1995). Lack of cyclin D-Cdk complexes in Rb-negative cells correlates with high levels of p16INK4/MTS1 tumour suppressor gene product. *EMBO J.*, 14, 503-11. [↗](#)
- Hannon, GJ., Beach, D. (1994). p15INK4B is a potential effector of TGF-beta-induced cell cycle arrest. *Nature*, 371, 257-61. [↗](#)
- Matera, AG., Xiong, Y., Guan, KL., Nichols, MA., Li, Y., O'Keefe, CL. et al. (1994). Growth suppression by p18, a p16INK4/MTS1- and p14INK4B/MTS2-related CDK6 inhibitor, correlates with wild-type pRb function. *Genes Dev*, 8, 2939-52. [↗](#)

Editions

2005-10-07	Edited	Matthews, L.
2006-07-10	Authored	Matthews, L.
2013-09-03	Reviewed	Samarajiwa, S.
2016-10-07	Edited	Orlic-Milacic, M.
2016-11-04	Reviewed	Roger, PP.
2019-04-23	Reviewed	Bennett, DC.

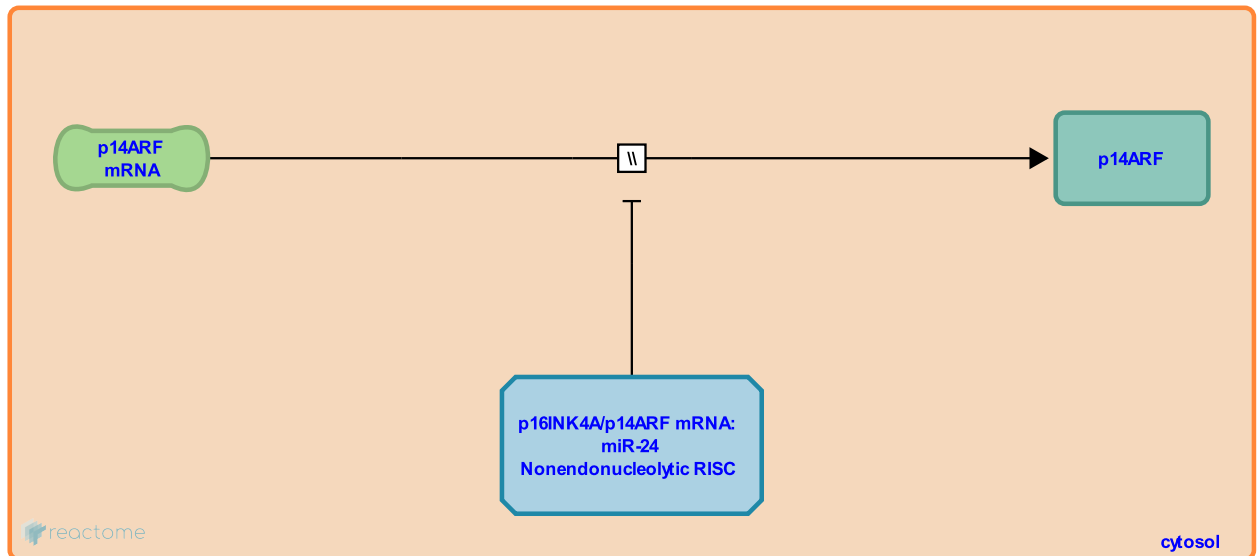
Translation of p14ARF mRNA is inhibited by miR-24 ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3209111

Type: omitted

Compartments: cytosol



MicroRNA miR-24 inhibits translation of p14ARF mRNA without causing mRNA degradation. This results in high p14ARF transcript level accompanied by low p14ARF protein level (To et al. 2012).

Preceded by: [miR-24 binds p16INK4A and p14ARF mRNAs](#)

Followed by: [p14ARF translocates to the nucleus](#)

Literature references

Thériault, BL., Gallie, BL., To, KH., Pajovic, S. (2012). Regulation of p14ARF expression by miR-24: a potential mechanism compromising the p53 response during retinoblastoma development. *BMC Cancer*, 12, 69. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

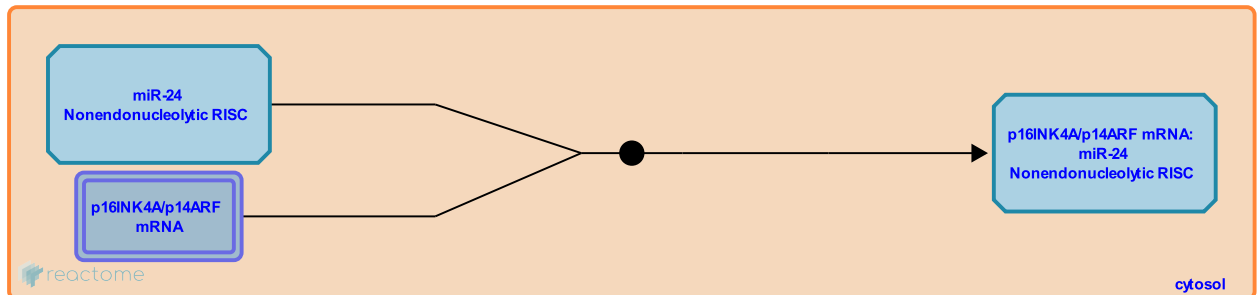
miR-24 binds p16INK4A and p14ARF mRNAs ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3209151

Type: binding

Compartments: cytosol



MicroRNA miR-24 is able to bind both p16INK4A mRNA (Lal et al. 2008) and p14ARF mRNA (To et al. 2012) through their shared 3'UTR. miR-24 inhibits translation of p16INK4A and p14ARF mRNAs, but does not induce mRNA degradation, resulting in expression of high levels of p16INK4A and p14ARF transcripts, while protein levels of p16INK4A and p14ARF are low (Lal et al. 2008, To et al. 2012).

Preceded by: [MAPKAPK2/3-mediated removal of PRC1.4 complex stimulates p14ARF transcription](#), [Demethylation of H3K27Me3 by KDM6B stimulates p16INK4A transcription](#), while binding of PRC1.4 complex to H3K27Me3 represses p16INK4A transcription

Followed by: [Translation of p14ARF mRNA is inhibited by miR-24](#), [Translation of p16INK4A mRNA is inhibited by miR-24](#)

Literature references

Yang, X., Pullmann, R., Gorospe, M., Dykxhoorn, D., Lal, A., Martindale, JL. et al. (2008). p16(INK4a) translation suppressed by miR-24. *PLoS ONE*, 3, e1864. ↗

Thériault, BL., Gallie, BL., To, KH., Pajovic, S. (2012). Regulation of p14ARF expression by miR-24: a potential mechanism compromising the p53 response during retinoblastoma development. *BMC Cancer*, 12, 69. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.
2019-10-18	Reviewed	Vegi, NM.
2019-11-01	Edited	Orlic-Milacic, M.

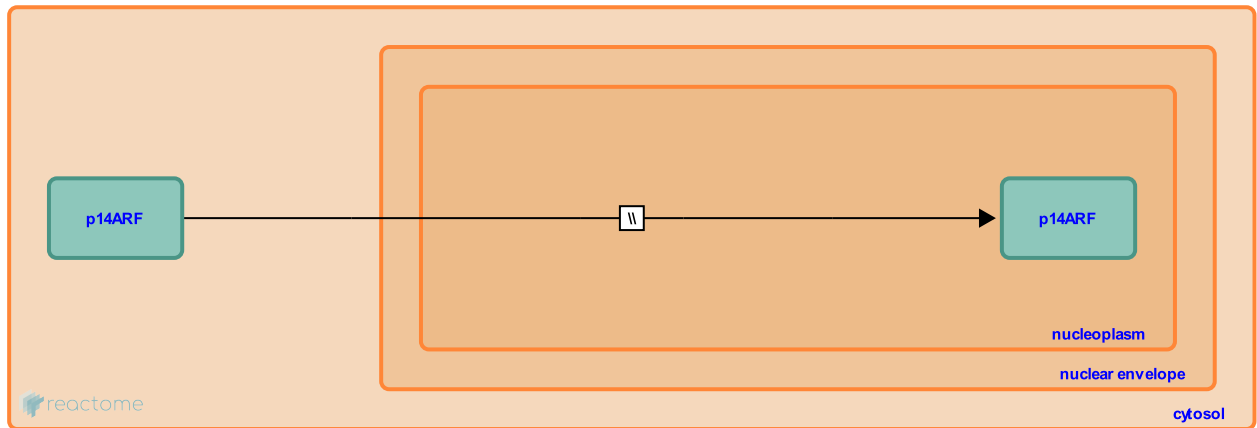
p14ARF translocates to the nucleus ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-9645672

Type: omitted

Compartments: nucleoplasm, cytosol



p14ARF is mainly localized inside the nucleus, specifically the nucleolus (Zhang and Xiong 1999, Lindstrom et al. 2000), similar to its mouse orthologue p19ARF (Tao and Levine 1999).

Preceded by: [Translation of p14ARF mRNA is inhibited by miR-24](#)

Followed by: [p14ARF forms a ternary complex with MDM2 and TP53](#)

Literature references

Klangby, U., Lindström, MS., Inoue, R., Wiman, KG., Pisa, P., Asker, CE. (2000). Immunolocalization of human p14(ARF) to the granular component of the interphase nucleolus. *Exp. Cell Res.*, 256, 400-10. ↗

Editions

2019-06-28	Authored	Orlic-Milacic, M.
2019-07-08	Reviewed	Rizos, H.
2019-07-16	Edited	Orlic-Milacic, M.
2019-08-12	Reviewed	Bennett, DC.

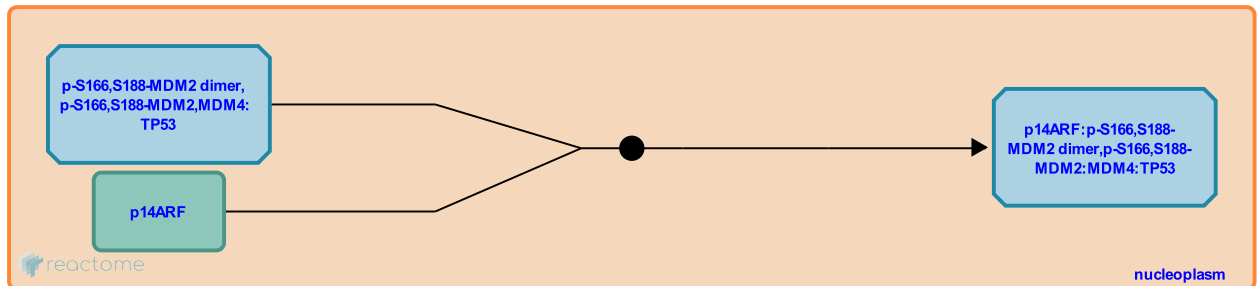
p14ARF forms a ternary complex with MDM2 and TP53 ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-6804998

Type: binding

Compartments: nucleoplasm



p14ARF forms a complex with TP53-bound MDM2 by interacting with the C-terminus of MDM2, while the N-terminus of MDM2 is involved in TP53 (p53) binding. p14ARF cannot associate with TP53 in the absence of MDM2 (Zhang et al. 1998).

Preceded by: [p14ARF translocates to the nucleus](#)

Followed by: [p14ARF sequesters MDM2](#)

Literature references

Zhang, Y., Xiong, Y., Yarbrough, WG. (1998). ARF promotes MDM2 degradation and stabilizes p53: ARF-INK4a locus deletion impairs both the Rb and p53 tumor suppression pathways. *Cell*, 92, 725-34. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

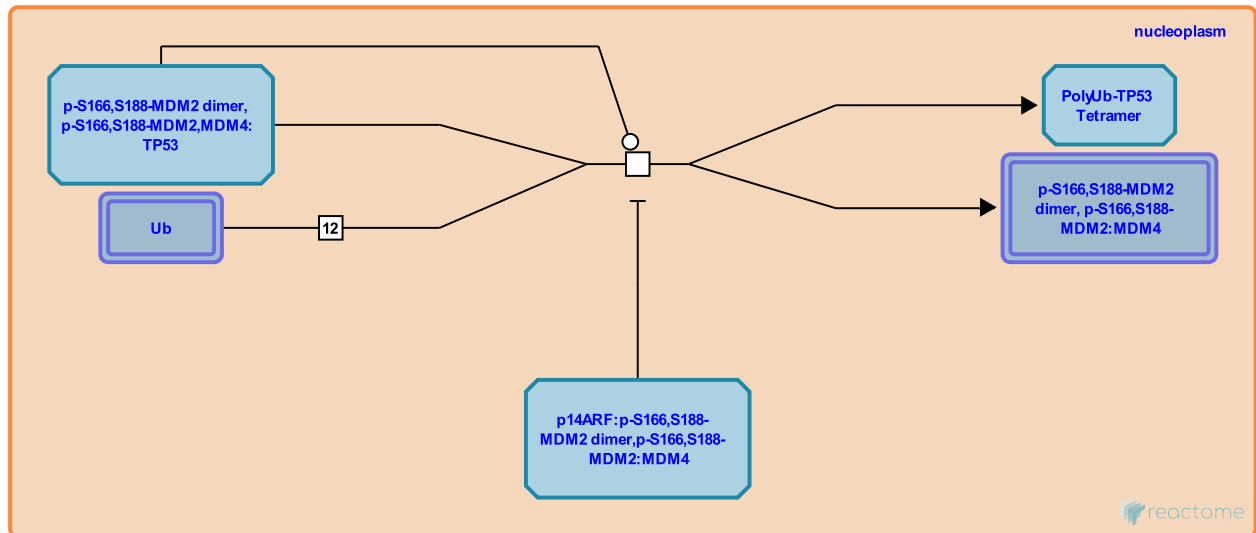
MDM2 ubiquitinates TP53 ↗

Location: Oxidative Stress Induced Senescence

Stable identifier: R-HSA-6804879

Type: transition

Compartments: nucleoplasm



MDM2 is an ubiquitin ligase whose expression is positively regulated by TP53 (p53) (Wu et al. 1993). MDM2 binds TP53 tetramer (Maki 1999) and promotes its ubiquitination and subsequent degradation (Fuchs et al. 1998). Formation of MDM2 homodimers (Cheng et al. 2011) or heterodimers with MDM4 (MDMX) is needed for efficient ubiquitination of TP53 (Linares et al. 2003). While MDM2-TP53 binding occurs at the amino-terminus of TP53, MDM2 ubiquitinates TP53 lysine residues at the carboxy-terminus. Acetylation of those lysines can inhibit MDM2-dependent ubiquitination (Li et al. 2002).

Literature references

- Gu, W., Luo, J., Brooks, CL., Li, M. (2002). Acetylation of p53 inhibits its ubiquitination by Mdm2. *J. Biol. Chem.*, 277, 50607-11. ↗
- Levine, AJ., Olson, D., Bayle, JH., Wu, X. (1993). The p53-mdm-2 autoregulatory feedback loop. *Genes Dev.*, 7, 1126-32. ↗
- Chen, L., Chen, J., Cheng, Q., Li, B., Cross, B., Li, Z. (2011). Regulation of MDM2 E3 ligase activity by phosphorylation after DNA damage. *Mol. Cell. Biol.*, 31, 4951-63. ↗
- Fuchs, SY., Adler, V., Ronai, Z., Wu, X., Buschmann, T. (1998). Mdm2 association with p53 targets its ubiquitination. *Oncogene*, 17, 2543-7. ↗
- Vousden, KH., Weissman, AM., Jensen, JP., Ludwig, RL., Fang, S. (2000). Mdm2 is a RING finger-dependent ubiquitin protein ligase for itself and p53. *J. Biol. Chem.*, 275, 8945-51. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

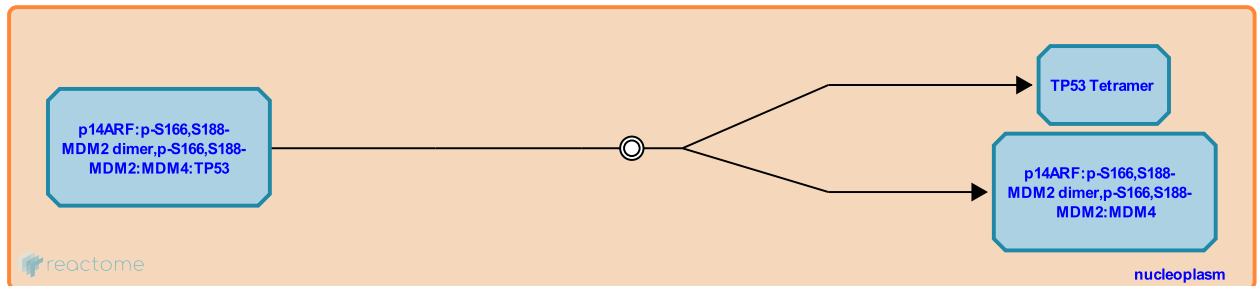
p14ARF sequesters MDM2 ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-6804996

Type: dissociation

Compartments: nucleoplasm



Binding of p14ARF to MDM2 decreases the half-life of MDM2, likely through promoting MDM2 degradation. Thus, p14ARF inhibits MDM2-mediated ubiquitination and degradation of TP53 (Zhang et al. 1998).

Preceded by: [p14ARF forms a ternary complex with MDM2 and TP53](#)

Literature references

Zhang, Y., Xiong, Y., Yarbrough, WG. (1998). ARF promotes MDM2 degradation and stabilizes p53: ARF-INK4a locus deletion impairs both the Rb and p53 tumor suppression pathways. *Cell*, 92, 725-34. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

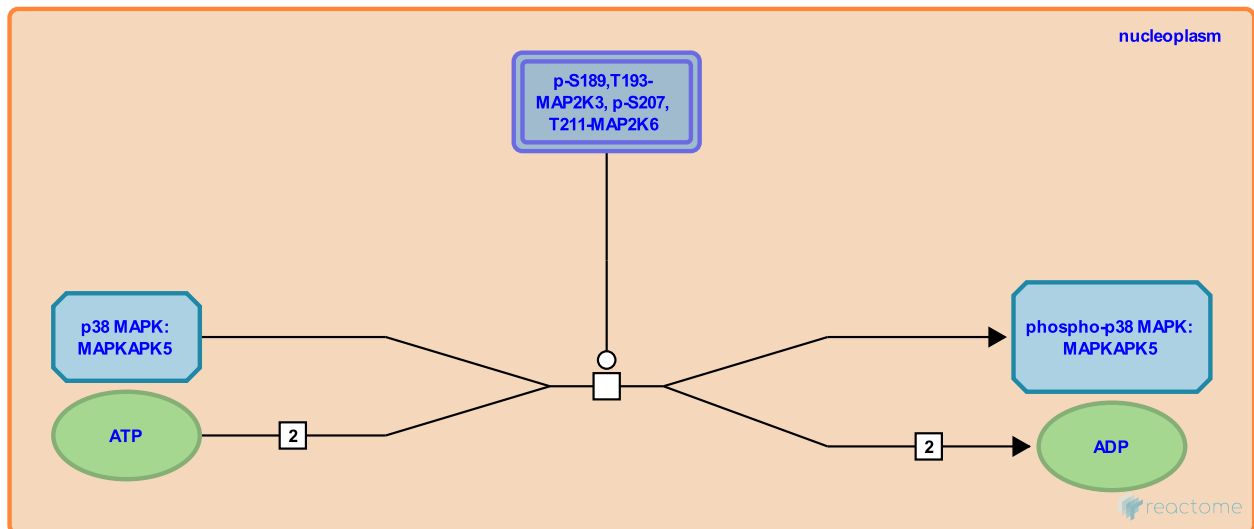
Activated human MKK3/MKK6 phosphorylates p38 MAPK complexed with MAPKAPK5 ↗

Location: Oxidative Stress Induced Senescence

Stable identifier: R-HSA-3238999

Type: transition

Compartments: nucleoplasm



MAPKAPK5 (PRAK) forms a complex with MAPK14 (p38 alpha) or MAPK11 (p38 beta) irrespective of the phosphorylation status and kinase activity of MAPKAPK5, MAPK14 and MAPK11 (New et al. 2003). Phosphorylation of p38 alpha and p38 beta by MKK3 or MKK6 (Raingeaud et al. 1996), however, is required for the subsequent activation of MAPKAPK5 by p38 MAPK (New et al. 1998, Sun et al. 2007).

Preceded by: Phosphorylated MKK3/MKK6 migrates to nucleus

Followed by: Active p38 MAPK phosphorylates MAPKAPK5

Literature references

- Jiang, Y., Han, J., New, L. (2003). Regulation of PRAK subcellular location by p38 MAP kinases. *Mol. Biol. Cell*, 14, 2603-16. ↗
- Li, Y., Yamout, M., Sun, P., Frangou, CG., Yates, JR., Liao, R. et al. (2007). PRAK is essential for ras-induced senescence and tumor suppression. *Cell*, 128, 295-308. ↗
- Davis, RJ., Whitmarsh, AJ., Derijard, B., Raingeaud, J., Barrett, T. (1996). MKK3- and MKK6-regulated gene expression is mediated by the p38 mitogen-activated protein kinase signal transduction pathway. *Mol Cell Biol*, 16, 1247-55. ↗
- Kato, Y., Zhu, W., Han, J., Liu, K., Flood, LJ., Zhao, M. et al. (1998). PRAK, a novel protein kinase regulated by the p38 MAP kinase. *EMBO J.*, 17, 3372-84. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

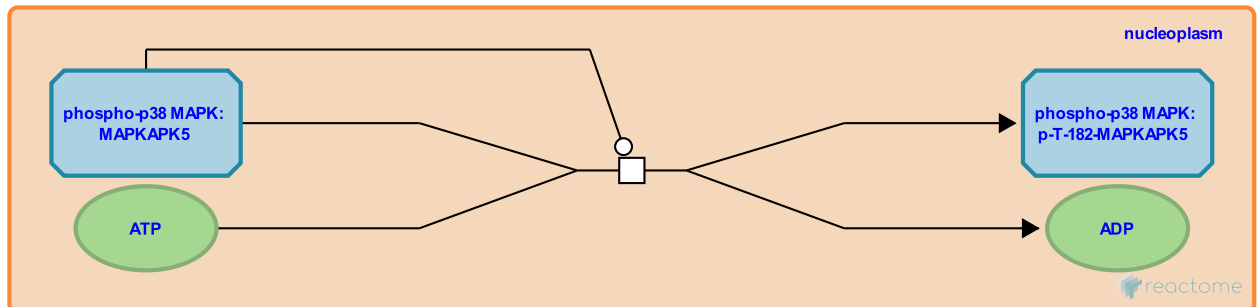
Active p38 MAPK phosphorylates MAPKAPK5 ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3239019

Type: transition

Compartments: nucleoplasm



MAPK14 (p38 alpha) and MAPK11 (p38 beta) phosphorylate MAPKAPK5 (PRAK) on threonine residue 182, located in the conserved LMTP site in the T-loop of the kinase domain. Phosphorylation of T182 is necessary for the MAPKAPK5 catalytic activity (New et al. 1998).

Preceded by: [Activated human MKK3/MKK6 phosphorylates p38 MAPK complexed with MAPKAPK5](#)

Followed by: [MAPKAPK5 phosphorylates TP53](#)

Literature references

Kato, Y., Zhu, W., Han, J., Liu, K., Flood, LJ., Zhao, M. et al. (1998). PRAK, a novel protein kinase regulated by the p38 MAP kinase. *EMBO J.*, 17, 3372-84. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.

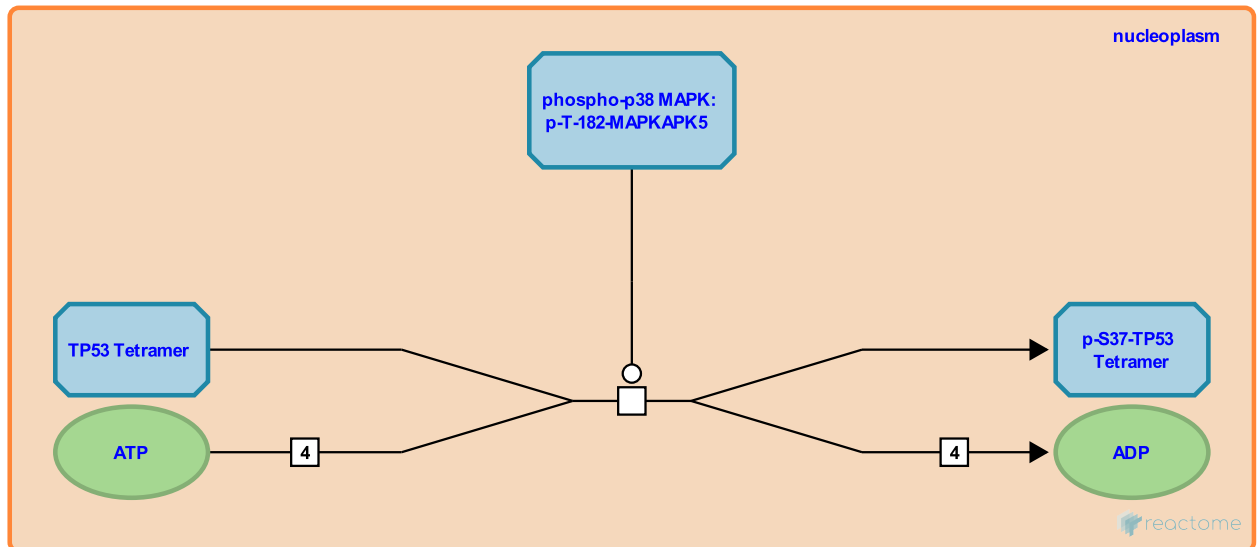
MAPKAPK5 phosphorylates TP53 ↗

Location: [Oxidative Stress Induced Senescence](#)

Stable identifier: R-HSA-3239014

Type: transition

Compartments: nucleoplasm



Activated MAPKAPK5 (PRAK) phosphorylates TP53 (p53) on serine residue S37, thereby activating it. MAPKAPK5-mediated phosphorylation of TP53 promotes growth arrest and senescence induced by oncogenic RAS, but is not needed for TP53-dependent growth arrest in response to DNA damage (Sun et al. 2007).

Preceded by: [Active p38 MAPK phosphorylates MAPKAPK5](#)

Literature references

Li, Y., Yamout, M., Sun, P., Frangou, CG., Yates, JR., Liao, R. et al. (2007). PRAK is essential for ras-induced senescence and tumor suppression. *Cell*, 128, 295-308. ↗

Editions

2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

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