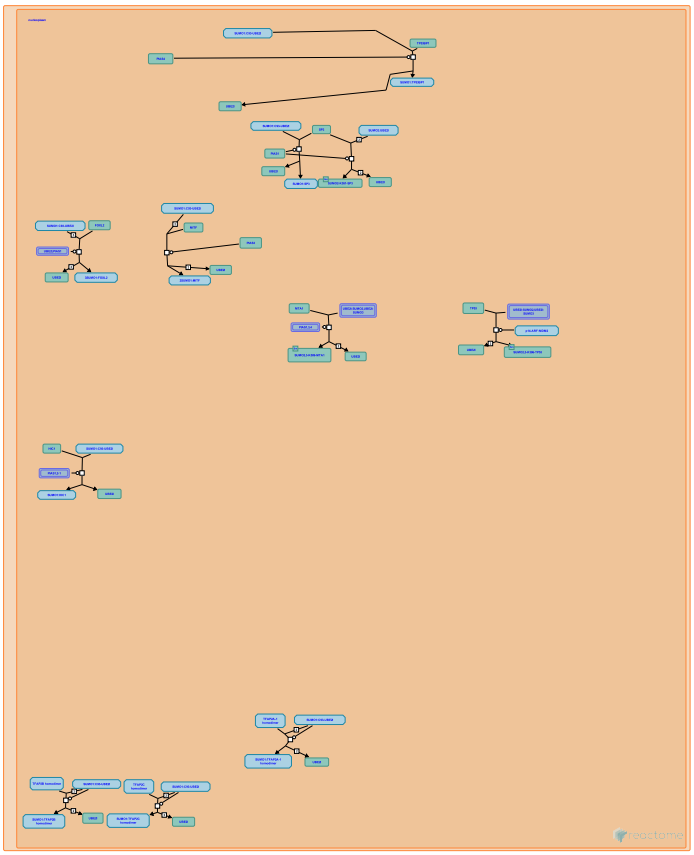
SUMOylation of transcription factors



Bae, J., Bogachek, MV., Crisponi, L., Dawid, IB., Fisher, DE., Galanty, Y., Kumar, R., Leprince, D., May, B., Orlic-Milacic, M., Suske, G., Vousden, KH., Weigel, RJ., Zarelli, VE.

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

22/10/2020

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. ↗

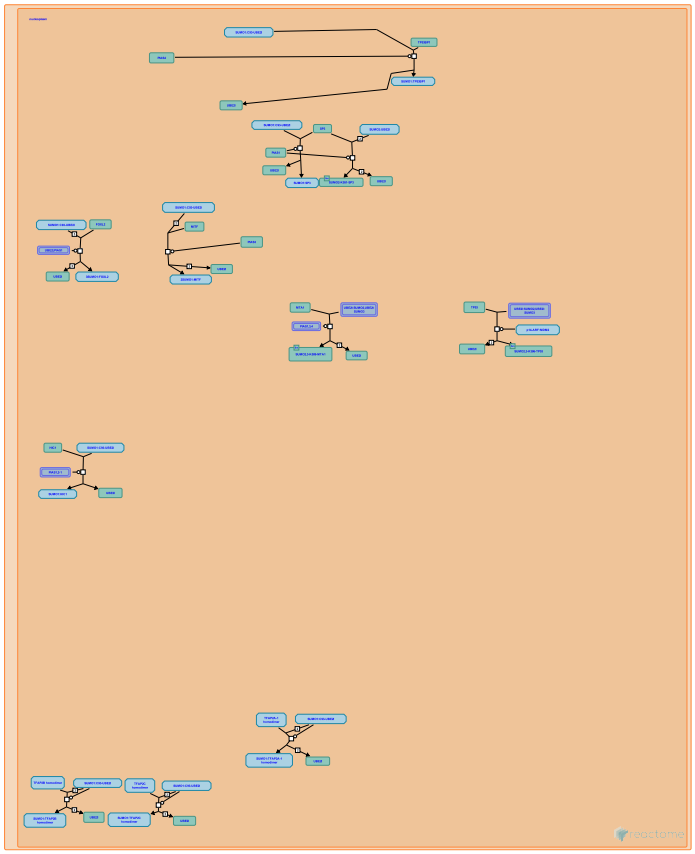
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

SUMOylation of transcription factors ↗

Stable identifier: R-HSA-3232118

Compartments: nucleoplasm



Proteins classified as transcription factors constitute a disproportionate number of SUMOylation targets. In most cases SUMOylation inhibits transcriptional activation, however in some cases such as TP53 (p53) SUMOylation can enhance activation. Inhibition of transcription by SUMOylation may be due to interference with DNA binding, re-localization to inactive nuclear bodies, or recruitment of repressive cofactors such as histone deacetylases (reviewed in Girdwood et al. 2004, Gill 2005).

Literature references

Lomelí, H., Vázquez, M. (2011). Emerging roles of the SUMO pathway in development. *Cell. Mol. Life Sci., 68*, 4045-64. ↗

Girdwood, DW., Tatham, MH., Hay, RT. (2004). SUMO and transcriptional regulation. *Semin. Cell Dev. Biol., 15*, 201-10. ↗

Ouyang, J., Valin, A., Gill, G. (2009). Regulation of transcription factor activity by SUMO modification. *Methods Mol. Biol., 497*, 141-52. ↗

Garcia-Dominguez, M., Reyes, JC. (2009). SUMO association with repressor complexes, emerging routes for transcriptional control. *Biochim. Biophys. Acta, 1789*, 451-9. ↗

Gill, G. (2005). Something about SUMO inhibits transcription. *Curr. Opin. Genet. Dev., 15*, 536-41. ↗

Editions

2013-03-23	Authored, Edited	May, B.
2015-10-04	Reviewed	May, B.

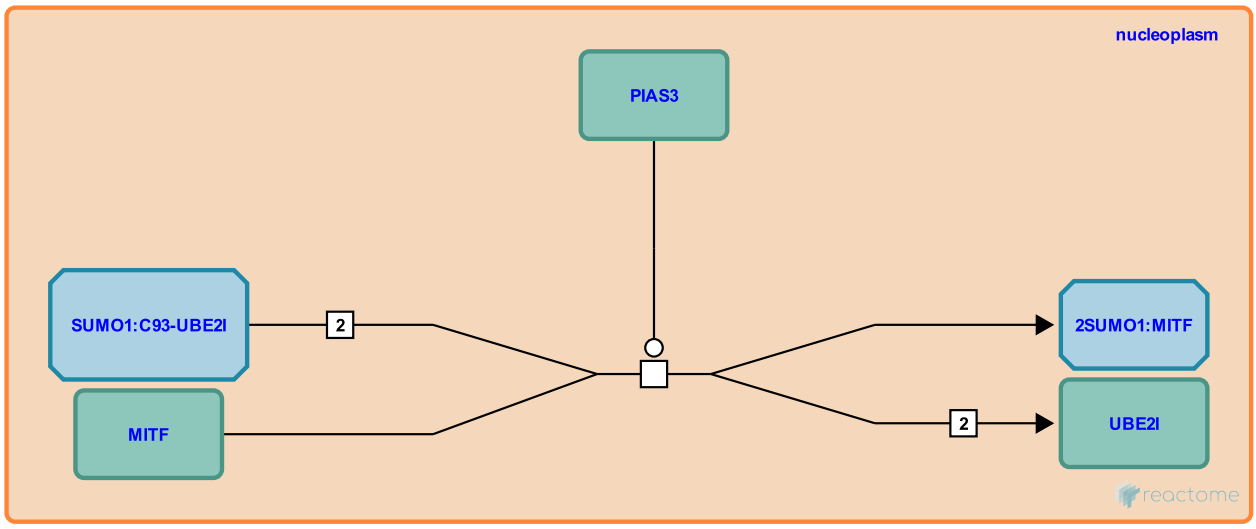
PIAS3 SUMOylates MITF with SUMO1 ↗

Location: SUMOylation of transcription factors

Stable identifier: R-HSA-3232162

Type: transition

Compartments: nucleoplasm



PIAS3 SUMOylates MITF with SUMO1 at lysine-289 and lysine-423 (lysine-182 and lysine-316 of the M2 isoform, Miller et al. 2005). SUMOylation reduces transcriptional activation by MITF at promoters containing multiple binding sites for MITF.

Literature references

Miller, AJ., Levy, C., Davis, IJ., Razin, E., Fisher, DE. (2005). Sumoylation of MITF and its related family members TFE3 and TFEB. *J. Biol. Chem., 280*, 146-55. ↗

Editions

2013-03-23	Authored, Edited	May, B.
2015-10-10	Reviewed	Fisher, DE.

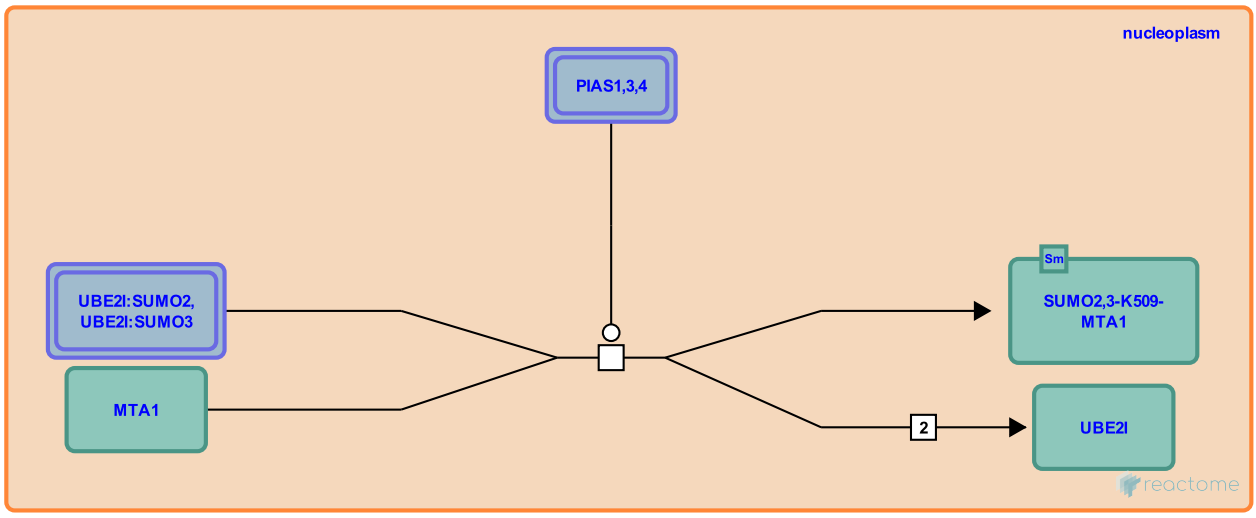
PIAS1,3,4 SUMOylate MTA1 with SUMO2,3 ↗

Location: SUMOylation of transcription factors

Stable identifier: R-HSA-3465545

Type: transition

Compartments: nucleoplasm



PIAS1,3,4 SUMOylate MTA1 with SUMO2,3 at lysine-509 (Cong et al. 2011). SUMOylation increases the repressor activity of MTA1 at the PS2 promoter (Cong et al. 2011).

Literature references

Cong, L., Pakala, SB., Ohshiro, K., Li, DQ., Kumar, R. (2011). SUMOylation and SUMO-interacting motif (SIM) of metastasis tumor antigen 1 (MTA1) synergistically regulate its transcriptional repressor function. *J. Biol. Chem., 286*, 43793-808. ↗

Editions

2013-05-16	Authored, Edited	May, B.
2015-10-10	Reviewed	Kumar, R.

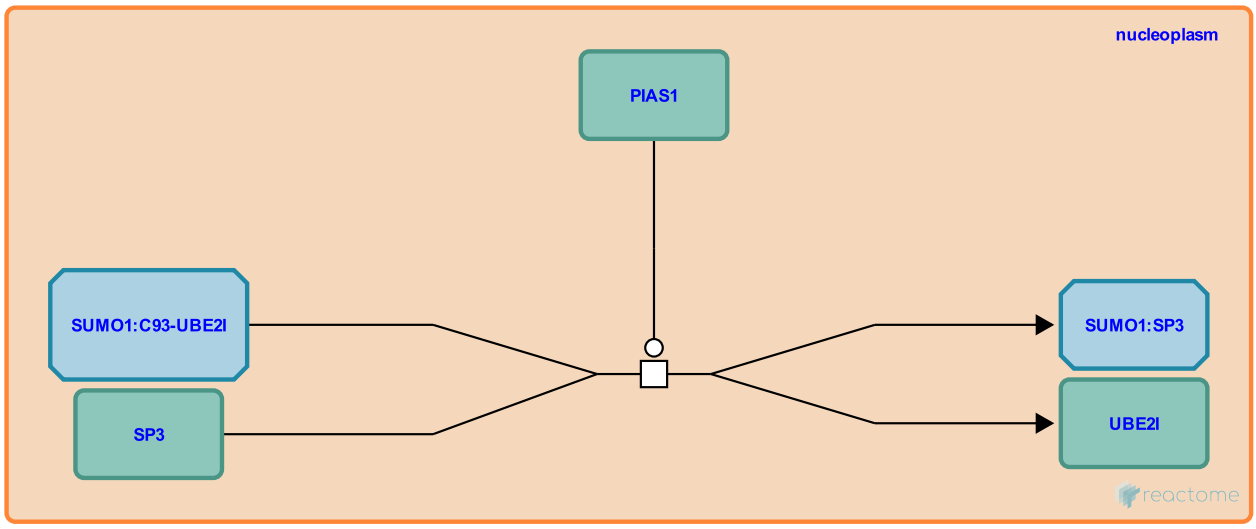
PIAS1 SUMOylates SP3 with SUMO1 ↗

Location: SUMOylation of transcription factors

Stable identifier: R-HSA-3247493

Type: transition

Compartments: nucleoplasm



PIAS1 SUMOylates SP3 with SUMO1 at lysine-551 (Ross et al. 2002, Sapetschnig et al. 2002, Sapetschnig et al. 2004, Spengler et al. 2005, Ellis et al. 2006, Impens et al. 2014). A minor amount of SUMOylation is also observed at lysine-120 (Ross et al. 2002). The effects of SUMOylation on the activities of isoforms of SP3 are promoter-dependent (Sapetschnig et al. 2004). Generally SUMOylation reduces the transcription activation capacity of the long and the short isoforms of Sp3 (Ross et al. 2002, Sapetschnig et al 2004, Ellis et al 2006). Mechanistically, SUMO attachment to Sp3 serves as a molecular beacon for the recruitment of chromatin-modifying machineries that impose epigenetic silencing (inferred from Drosophila homologs in Stielow et al. 2008a, inferred from mouse homologs in Stielow et al. 2008b).

Literature references

Sapetschnig, A., Rischitor, G., Braun, H., Doll, A., Schergaut, M., Melchior, F. et al. (2002). Transcription factor Sp3 is silenced through SUMO modification by PIAS1. *EMBO J., 21*, 5206-15. ↗

Ross, S., Best, JL., Zon, LI., Gill, G. (2002). SUMO-1 modification represses Sp3 transcriptional activation and modulates its subnuclear localization. *Mol. Cell, 10*, 831-42. ↗

Sapetschnig, A., Koch, F., Rischitor, G., Mennenga, T., Suske, G. (2004). Complexity of translationally controlled transcription factor Sp3 isoform expression. *J. Biol. Chem., 279*, 42095-105. ↗

Spengler, ML., Kennett, SB., Moorefield, KS., Simmons, SO., Brattain, MG., Horowitz, JM. (2005). Sumoylation of internally initiated Sp3 isoforms regulates transcriptional repression via a Trichostatin A-insensitive mechanism. *Cell. Signal., 17*, 153-66. ↗

Ellis, DJ., Dehm, SM., Bonham, K. (2006). The modification of Sp3 isoforms by SUMOylation has differential effects on the SRC1A promoter. *Gene, 379*, 68-78. ↗

Editions

2013-03-30	Authored, Edited	May, B.
2015-10-10	Reviewed	Suske, G.

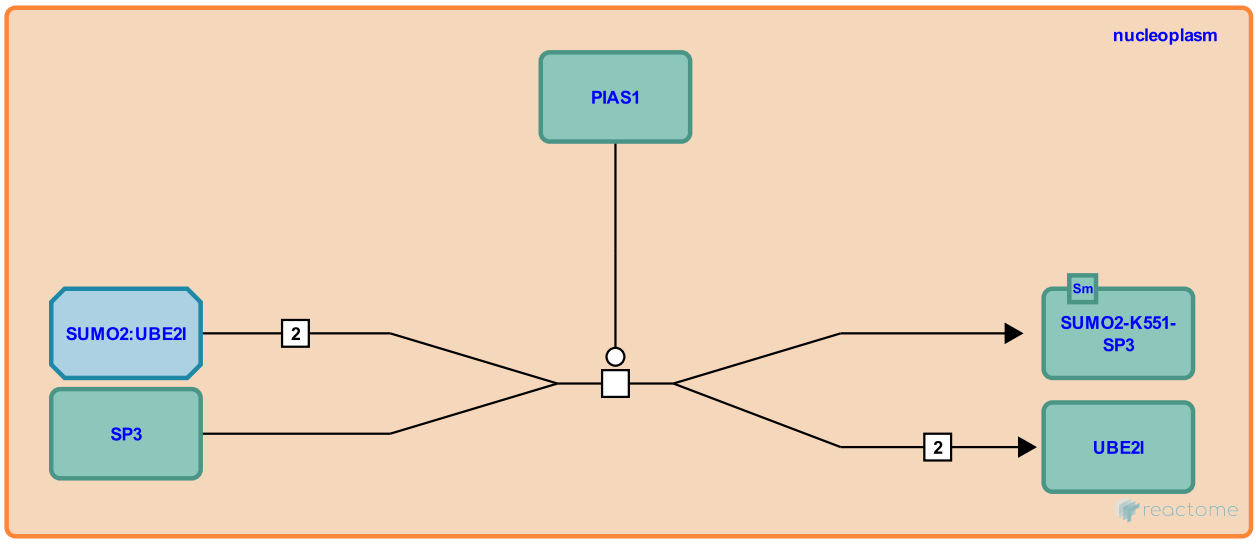
PIAS1 SUMOylates SP3 with SUMO2 ↗

Location: SUMOylation of transcription factors

Stable identifier: R-HSA-6804468

Type: transition

Compartments: nucleoplasm



PIAS1 SUMOylates SP3 with SUMO2 at lysine-551 (Sapetschnig et al. 2002, Galisson et al. 2011, Tammsalu et al. 2014, Hendriks et al. 2015). SUMOylation reduces the transcription activation capacity of the long and the short isoforms of Sp3 (Sapetschnig et al 2004). Mechanistically, SUMO attachment to Sp3 serves as a molecular beacon for the recruitment of chromatin-modifying machineries that impose epigenetic silencing (inferred from Drosophila homologs in Stielow et al. 2008a, inferred from mouse homologs in Stielow et al. 2008b).

Literature references

Tammsalu, T., Matic, I., Jaffray, EG., Ibrahim, AF., Tatham, MH., Hay, RT. (2014). Proteome-wide identification of SUMO2 modification sites. *Sci Signal, 7*, rs2. ↗

Impens, F., Radoshevich, L., Cossart, P., Ribet, D. (2014). Mapping of SUMO sites and analysis of SUMOylation changes induced by external stimuli. *Proc. Natl. Acad. Sci. U.S.A., 111*, 12432-7. ↗

Stielow, B., Sapetschnig, A., Wink, C., Krüger, I., Suske, G. (2008). SUMO-modified Sp3 represses transcription by provoking local heterochromatic gene silencing. *EMBO Rep., 9*, 899-906. ↗

Stielow, B., Sapetschnig, A., Krüger, I., Kunert, N., Brehm, A., Boutros, M. et al. (2008). Identification of SUMO-dependent chromatin-associated transcriptional repression components by a genome-wide RNAi screen. *Mol. Cell, 29*, 742-54. ↗

Sapetschnig, A., Rischitor, G., Braun, H., Doll, A., Schergaut, M., Melchior, F. et al. (2002). Transcription factor Sp3 is silenced through SUMO modification by PIAS1. *EMBO J., 21*, 5206-15. ↗

Editions

2015-10-10	Authored, Edited	May, B.
2015-10-10	Reviewed	Suske, G.

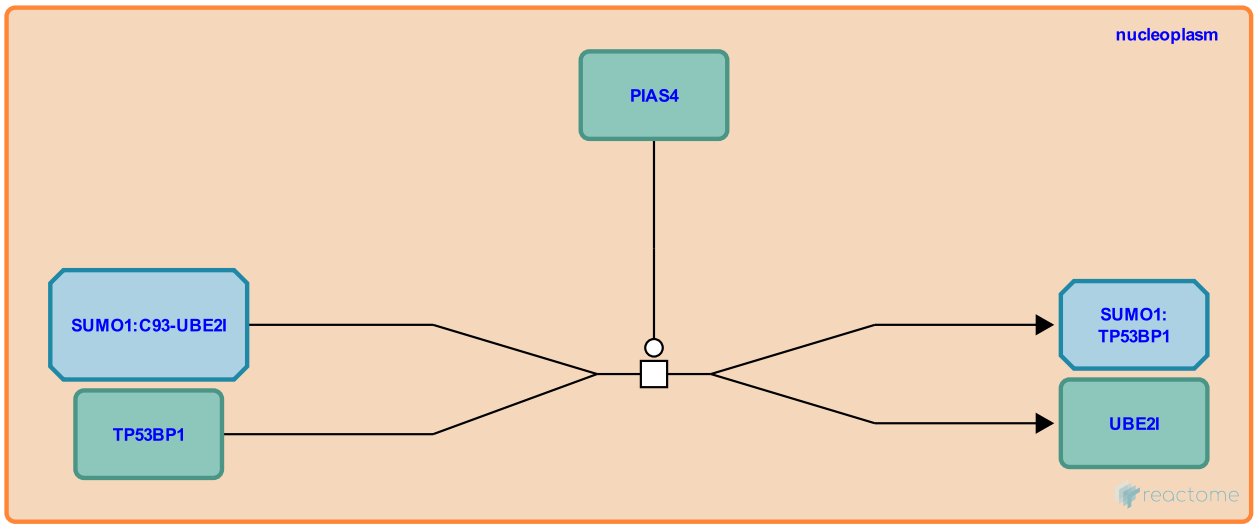
PIAS4 SUMOylates TP53BP1 with SUMO1 ↗

Location: SUMOylation of transcription factors

Stable identifier: R-HSA-2997723

Type: transition

Compartments: nucleoplasm



PIAS4 SUMOylates TP53BP1 with SUMO1 in response to double-strand breaks in DNA (Galanty et al. 2009, Impens et al. 2014). Overall, like TP53BP1, SUMO1,2,3, UBE2I, PIAS1 and PIAS4 are all observed to accumulate at double-strand breaks.

Literature references

Galanty, Y., Belotserkovskaya, R., Coates, J., Polo, S., Miller, KM., Jackson, SP. (2009). Mammalian SUMO E3-ligases PIAS1 and PIAS4 promote responses to DNA double-strand breaks. *Nature, 462*, 935-9. ↗

Impens, F., Radoshevich, L., Cossart, P., Ribet, D. (2014). Mapping of SUMO sites and analysis of SUMOylation changes induced by external stimuli. *Proc. Natl. Acad. Sci. U.S.A., 111*, 12432-7. ↗

Editions

2013-01-19	Authored, Edited	May, B.
2015-10-10	Reviewed	Galanty, Y.

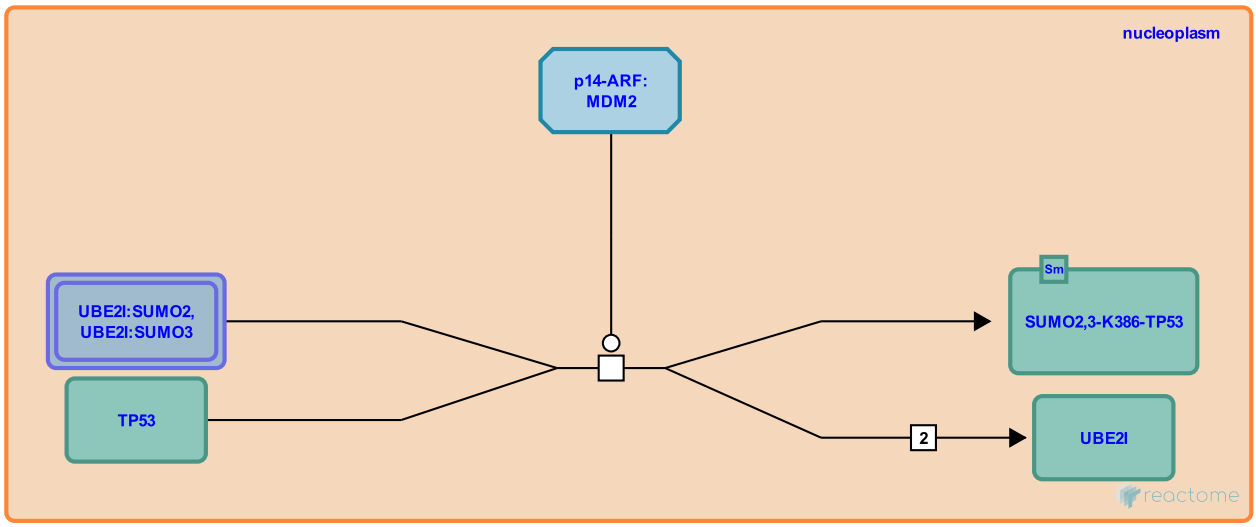
MDM2 SUMOylates TP53 with SUMO2,3 ↗

Location: SUMOylation of transcription factors

Stable identifier: R-HSA-2997706

Type: transition

Compartments: nucleoplasm



MDM2 in a complex with CDKN2A (p14-ARF) SUMOylates TP53 (p53) with SUMO2,3 at lysine-386 (Stindt et al. 2011, Hendriks et al. 2014, Tammsalu et al. 2014). SUMOylation decreases transcriptional activation by TP53 at some genes and decreases repression by TP53 at other genes (Stindt et al. 2011).

Literature references

Stindt, MH., Carter, S., Vigneron, AM., Ryan, KM., Vousden, KH. (2011). MDM2 promotes SUMO-2/3 modification of p53 to modulate transcriptional activity. *Cell Cycle, 10*, 3176-88. ↗

Hendriks, IA., D'Souza, RC., Yang, B., Verlaan-de Vries, M., Mann, M., Vertegaal, AC. (2014). Uncovering global SUMOylation signaling networks in a site-specific manner. *Nat. Struct. Mol. Biol., 21*, 927-36. ↗

Tammsalu, T., Matic, I., Jaffray, EG., Ibrahim, AF., Tatham, MH., Hay, RT. (2014). Proteome-wide identification of SUMO2 modification sites. *Sci Signal, 7*, rs2. ↗

Editions

2013-01-19	Authored, Edited	May, B.
2016-01-07	Reviewed	Vousden, KH.

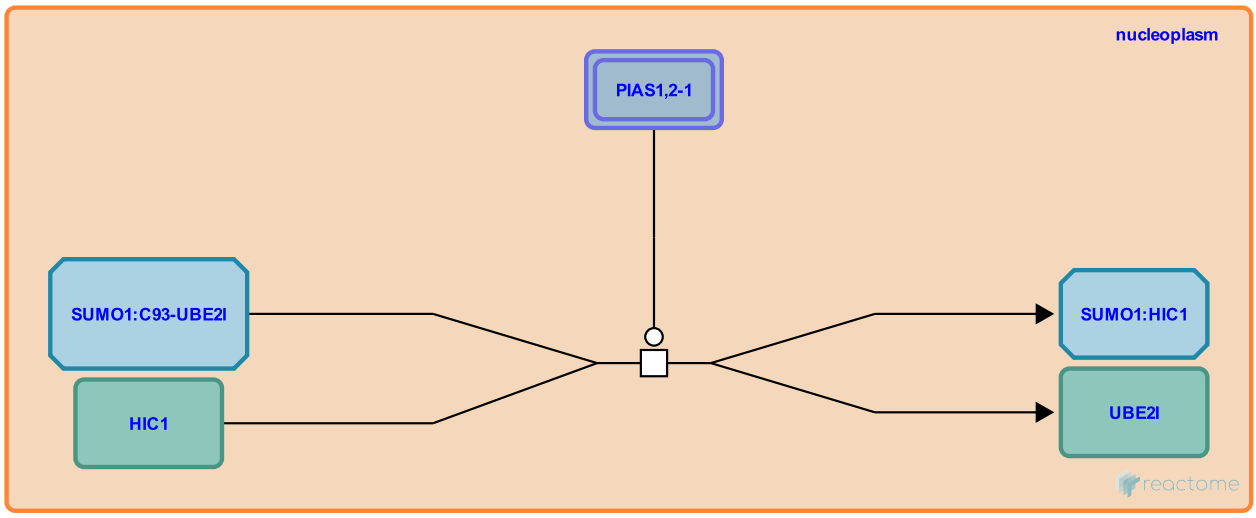
PIAS1,2-1 SUMOylate HIC1 with SUMO1 ↗

Location: SUMOylation of transcription factors

Stable identifier: R-HSA-4090281

Type: transition

Compartments: nucleoplasm



PIAS1,2-1 SUMOylate deacetylated HIC1 at lysine-333 (lysine 314 of HIC1 isoform 2) with SUMO1 (Stankovic-Valentin et al. 2007). Acetylation of HIC1 at lysine-333 inhibits SUMOylation. SUMOylation increases transcription repression by HIC1 (Stankovic-Valentin et al. 2007) and favors the interaction of HIC1 with MTA1 (Van Rechem et al., Mol Cell Biol, 2010) and MTA3 (Paget et al. 2016) notably during the DNA damage response (DDR) to non-repairable double strand breaks (DSBs).(Dehennaut et al. 2013). This increase of HIC1 SUMOylation during the DDR to DSBs is strictly dependent on the ATM kinase (Paget et al. 2016). SUMOylation of HIC1 is dispensable for DNA repair since the non-SUMOylatable point mutant E316A is as efficient as wt HIC1 in Comet assays which measure the repair of DSBs (Paget et al. 2016).

Literature references

Stankovic-Valentin, N., Deltour, S., Seeler, J., Pinte, S., Vergoten, G., Guérardel, C. et al. (2007). An acetylation/deacetylation-SUMOylation switch through a phylogenetically conserved psiKXEP motif in the tumor suppressor HIC1 regulates transcriptional repression activity. *Mol. Cell. Biol., 27*, 2661-75. ↗

Dehennaut, V., Loison, I., Dubuissez, M., Nassour, J., Abbadie, C., Leprince, D. (2013). DNA double-strand breaks lead to activation of hypermethylated in cancer 1 (HIC1) by SUMOylation to regulate DNA repair. *J. Biol. Chem., 288*, 10254-64. ↗

Van Rechem, C., Boulay, G., Pinte, S., Stankovic-Valentin, N., Guérardel, C., Leprince, D. (2010). Differential regulation of HIC1 target genes by CtBP and NuRD, via an acetylation/SUMOylation switch, in quiescent versus proliferating cells. *Mol. Cell. Biol., 30*, 4045-59. ↗

Paget, S., Dubuissez, M., Dehennaut, V., Nassour, J., Harmon, BT., Spruyt, N. et al. (2016). HIC1 (hypermethylated in cancer 1) SUMOylation is dispensable for DNA repair but is essential for the apoptotic DNA damage response (DDR) to irreparable DNA double-strand breaks (DSBs). *Oncotarget*. ↗

Editions

2013-08-07	Authored, Edited	May, B.
2017-01-12	Edited, Reviewed	Leprince, D.

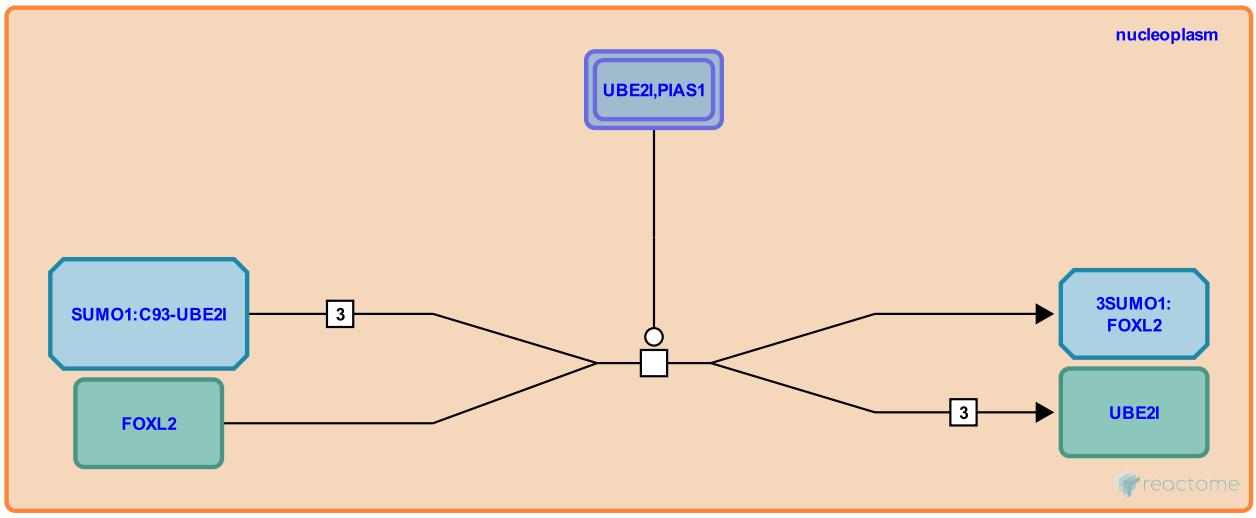
UBE2I (UBC9), PIAS1 SUMOylate FOXL2 with SUMO1 ↗

Location: SUMOylation of transcription factors

Stable identifier: R-HSA-3968414

Type: transition

Compartments: nucleoplasm



UBC9 and PIAS1 SUMOylate FOXL2 with SUMO1 (Kuo et al. 2009, Marongiu et al 2010, Georges et al. 2011). This modification changes its cellular localization, stability and transcriptional activity (Marongiu et al, 2010). SUMOylation localizes FOXL2 to PML bodies in the nucleus. SUMOylation is required for repression of transcription by FOXL2 at the StAR promoter and reduces transactivation by FOXL2 at the PER2 promoter. Hypophosphorylation of serine-33 correlates with SUMOylation and stablization of FOXL2, leading to enhanced transcriptional activation of TNF-R1, FAS, caspase 8, p21, and aromatase (Kim et al. 2014).

Literature references

Kuo, FT., Bentsi-Barnes, IK., Barlow, GM., Bae, J., Pisarska, MD. (2009). Sumoylation of forkhead L2 by Ubc9 is required for its activity as a transcriptional repressor of the Steroidogenic Acute Regulatory gene. *Cell. Signal., 21*, 1935-44. ↗

Marongiu, M., Deiana, M., Meloni, A., Marcia, L., Puddu, A., Cao, A. et al. (2010). The forkhead transcription factor Foxl2 is sumoylated in both human and mouse: sumoylation affects its stability, localization, and activity. *PLoS ONE, 5*, e9477. ↗

Georges, A., Benayoun, BA., Marongiu, M., Dipietromaria, A., L'Hôte, D., Todeschini, AL. et al. (2011). SUMOylation of the Forkhead transcription factor FOXL2 promotes its stabilization/activation through transient recruitment to PML bodies. *PLoS ONE, 6*, e25463. ↗

Kim, JH., Kim, YH., Kim, HM., Park, HO., Ha, NC., Kim, TH. et al. (2014). FOXL2 posttranslational modifications mediated by GSK3β determine the growth of granulosa cell tumours. *Nat Commun, 5*, 2936. ↗

Editions

2013-07-21	Authored, Edited	May, B.
2017-01-12	Edited, Reviewed	Bae, J.
2017-01-12	Edited, Reviewed	Crisponi, L.

SUMOylation of TFAP2A with SUMO1 ↗

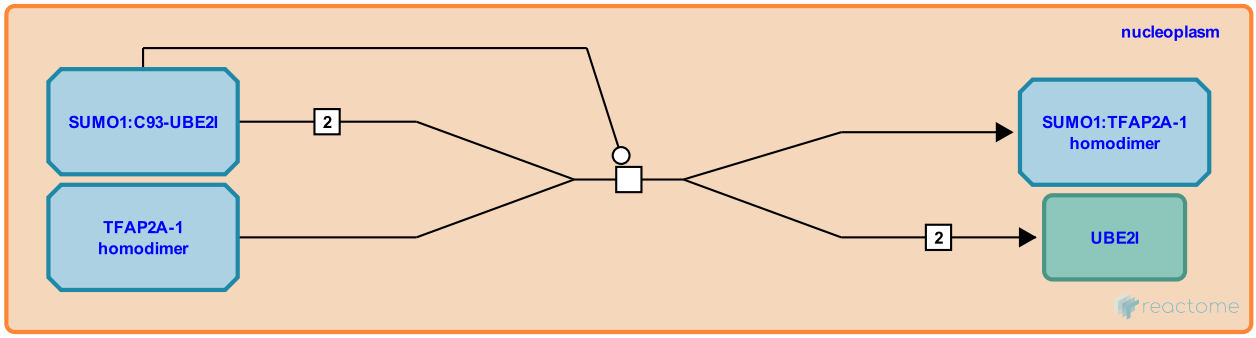
Location: SUMOylation of transcription factors

Stable identifier: R-HSA-3234081

Type: transition

Compartments: nucleoplasm

Inferred from: SUMOylation of TFAP2C with SUMO1 (Homo sapiens)



UBE2I (UBC9) interacts with TFAP2A, TFAP2B and TFAP2C, and the interaction site has been mapped to the C terminal region of TFAP2C; SUMOylation occurs on lysine-10 (Eloranta and Hurst 2002). As lysine-10 is conserved in TFAP2A and TFAP2B, SUMOylation of these factors is assumed to be on lysine-10 (Eloranta and Hurst 2002; Impens et al. 2014). SUMOylation causes a reduction in AP-2 transcriptional activation function but is required for its repressive function. A dominant negative mutant of UBC9 led to increased activation and reduced repressor function of TFAP2A and C, supporting the role of UBC9 in SUMOylation (Eloranta and Hurst 2002; Berlato et al. 2011). Isoform 1a of TFAP2A is SUMOylated, isoforms 1b and 1c lack lysine 10 and are not SUMOylated (Berlato et al. 2011). TFAP2D and TFAP2E lack lysine-10 and are thus assumed not to be SUMOylated. SUMOylation of TFAP2A blocked its ability to induce the expression of luminal genes and repression of basal genes (Bogachek et al. 2014). Disruption of the sumoylation pathway by knockdown of sumoylation enzymes, mutation of the SUMO-target lysine of TFAP2A, or treatment with sumoylation inhibitors induced MET in basal breast cancers, which was dependent on TFAP2A(Bogachek et al. 2014).

Literature references

Eloranta, JJ., Hurst, HC. (2002). Transcription factor AP-2 interacts with the SUMO-conjugating enzyme UBC9 and is sumolated in vivo. *J. Biol. Chem., 277*, 30798-804. ↗

Berlato, C., Chan, KV., Price, AM., Canosa, M., Scibetta, AG., Hurst, HC. (2011). Alternative TFAP2A isoforms have distinct activities in breast cancer. *Breast Cancer Res., 13*, R23. ↗

Impens, F., Radoshevich, L., Cossart, P., Ribet, D. (2014). Mapping of SUMO sites and analysis of SUMOylation changes induced by external stimuli. *Proc. Natl. Acad. Sci. U.S.A., 111*, 12432-7. ↗

Bogachek, MV., Chen, Y., Kulak, MV., Woodfield, GW., Cyr, AR., Park, JM. et al. (2014). Sumoylation pathway is required to maintain the basal breast cancer subtype. *Cancer Cell, 25*, 748-61. ↗

Editions

2013-03-27	Authored, Edited	May, B.
2016-03-14	Edited	Orlic-Milacic, M.
2016-05-04	Reviewed	Dawid, IB., Zarelli, VE.
2016-05-17	Reviewed	Weigel, RJ., Bogachek, MV.

SUMOylation of TFAP2B with SUMO1 ↗

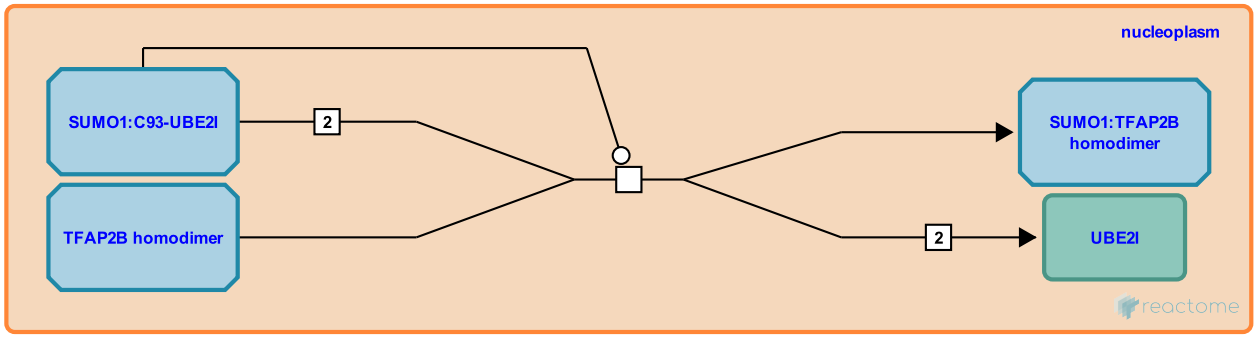
Location: SUMOylation of transcription factors

Stable identifier: R-HSA-3234084

Type: transition

Compartments: nucleoplasm

Inferred from: SUMOylation of TFAP2C with SUMO1 (Homo sapiens)



UBE2I (UBC9) interacts with the C terminal region of TFAP2B (Eloranta and Hurst 2002). As inferred from TFAP2C, SUMOylation of TFAP2B occurs at lysine in the VKYE motif and. therefore UBC9 is assumed to catalyze the ligation of SUMO1 to TFAP2B.

Literature references

Eloranta, JJ., Hurst, HC. (2002). Transcription factor AP-2 interacts with the SUMO-conjugating enzyme UBC9 and is sumolated in vivo. *J. Biol. Chem., 277*, 30798-804. ↗

Editions

2013-03-27	Authored, Edited	May, B.
2016-03-14	Edited	Orlic-Milacic, M.
2016-05-04	Reviewed	Dawid, IB., Zarelli, VE.
2016-05-17	Reviewed	Weigel, RJ., Bogachek, MV.

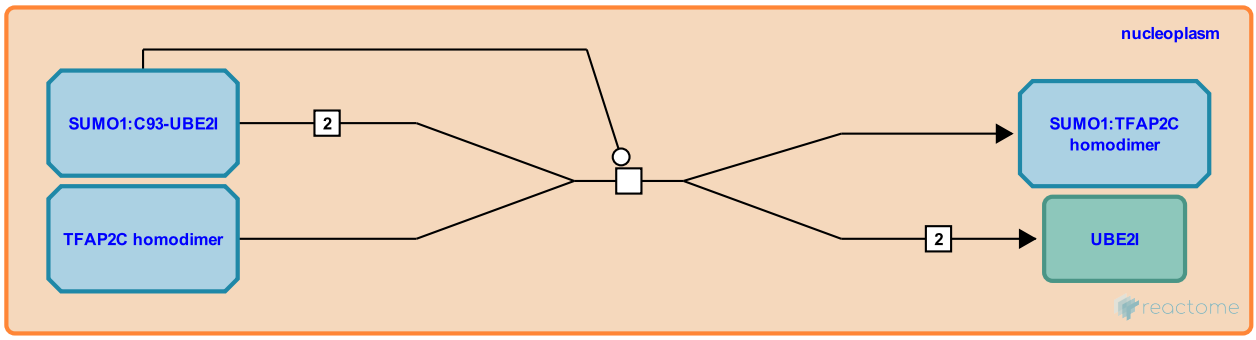
SUMOylation of TFAP2C with SUMO1 ↗

Location: SUMOylation of transcription factors

Stable identifier: R-HSA-3234094

Type: transition

Compartments: nucleoplasm



UBE2I (UBC9) interacts with the C-terminal region of TFAP2C (Eloranta and Hurst 2002). SUMOylation of TFAP2C occurs at lysine-10 and causes a reduction in its transcriptional activation activity. A dominant negative mutant of UBC9 led to increased activity of TFAP2C therefore UBC9 is assumed to catalyze the ligation of SUMO1 to TFAP2C.

Literature references

Eloranta, JJ., Hurst, HC. (2002). Transcription factor AP-2 interacts with the SUMO-conjugating enzyme UBC9 and is sumolated in vivo. *J. Biol. Chem., 277*, 30798-804. ↗

Editions

2013-03-27	Authored, Edited	May, B.
2016-03-14	Edited	Orlic-Milacic, M.
2016-05-04	Reviewed	Dawid, IB., Zarelli, VE.
2016-05-17	Reviewed	Weigel, RJ., Bogachek, MV.

Table of Contents