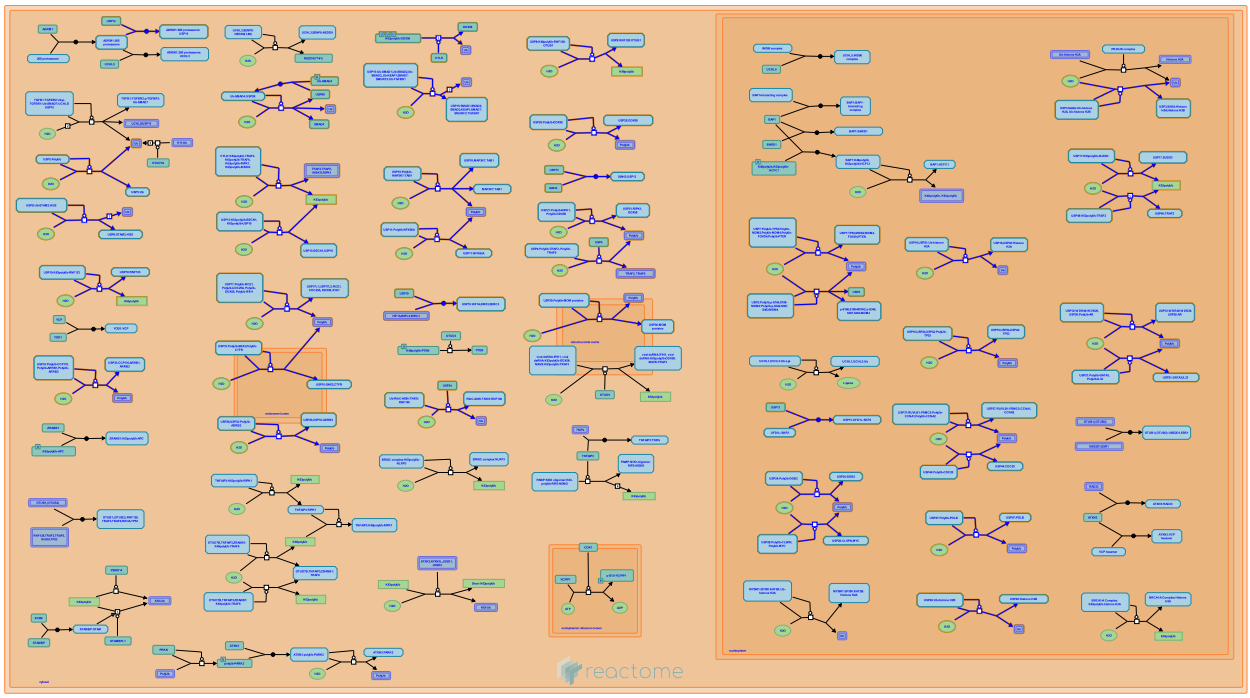
Ub-specific processing proteases



Akira, S., Contreras, O., Garapati, P V., Gillespie, ME., Huang, T., Inga, A., Jassal, B., Jupe, S., Kawai, T., Kikuchi, A., Meldal, BH., Orlic-Milacic, M., Rajakulendran, N., Rothfels, K., Williams, MG., Zaccara, S., van Amerongen, R.

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

01/04/2024

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).

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. ↗

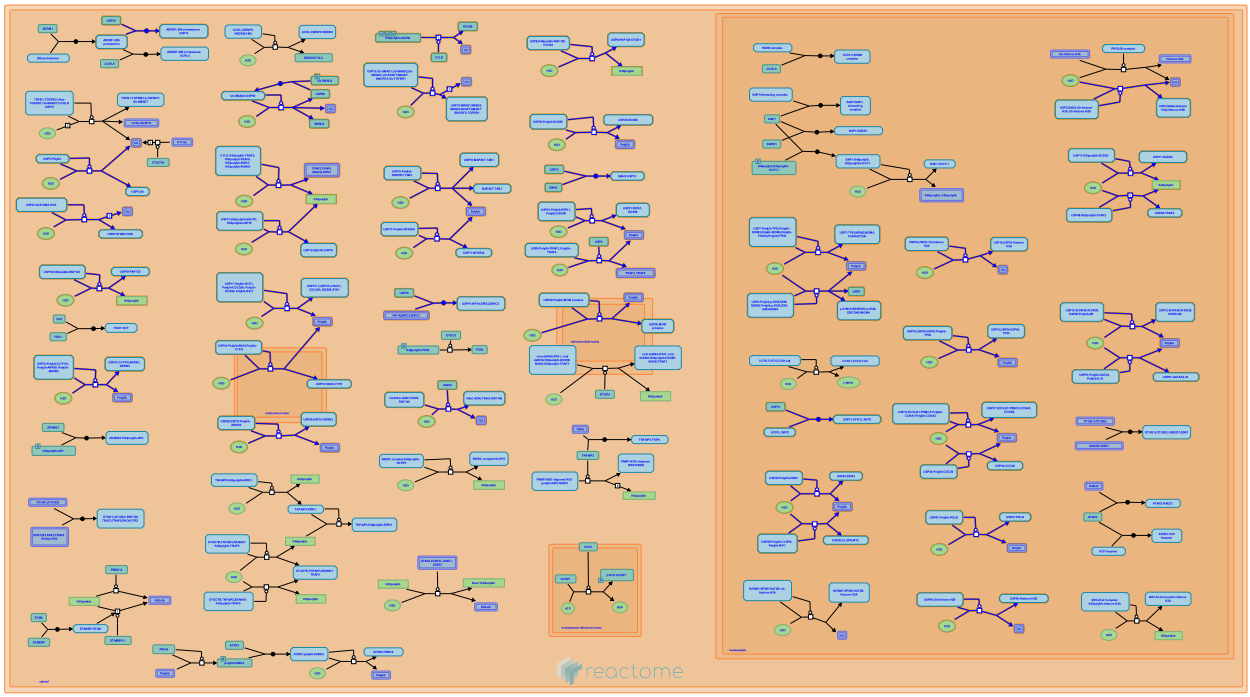
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Ub-specific processing proteases ↗

Stable identifier: R-HSA-5689880



Ub-specific processing proteases (USPs) are the largest of the DUB families with more than 50 members in humans. The USP catalytic domain varies considerably in size and consists of six conserved motifs with N- or C-terminal extensions and insertions occurring between the conserved motifs (Ye et al. 2009). Two highly conserved regions comprise the catalytic triad, the Cys-box (Cys) and His-box (His and Asp/Asn) (Nijman et al. 2005, Ye et al. 2009, Reyes-Turcu & Wilkinson 2009). They recognize their substrates by interactions of the variable regions with the substrate protein directly, or via scaffolds or adapters in multiprotein complexes.

Literature references

Sixma, TK., Luna-Vargas, MP., Nijman, SM., Velds, A., Brummelkamp, TR., Bernards, R. et al. (2005). A genomic and functional inventory of deubiquitinating enzymes. *Cell, 123*, 773-86. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

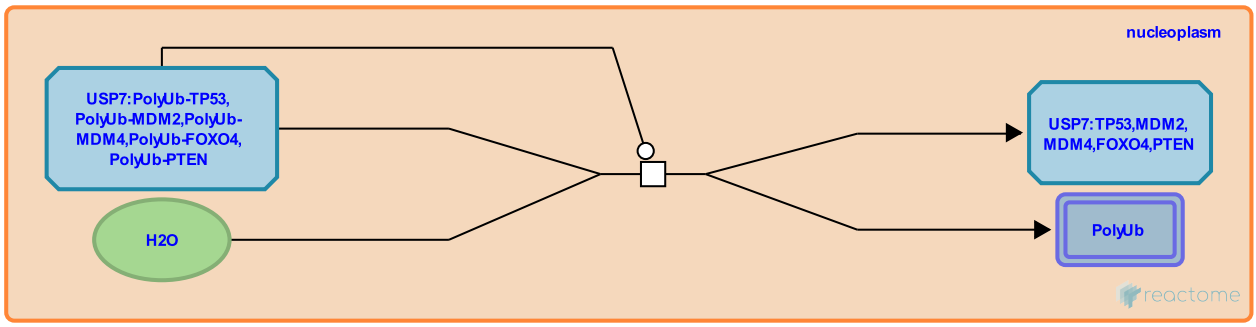
USP7 deubiquitinates TP53,MDM2,MDM4,FOXO4, PTEN ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5689950

Type: transition

Compartments: nucleoplasm



USP7 (HAUSP) is able to deubiquitinate many substrates. It is a key regulator of the tumor suppressor TP53 (p53) (Vousden & Lu 2002). It can act on TP53 directly, or indirectly by acting on the E3 ligase MDM2, which can ubiquitinate TP53 (Chene 2003, Li et al. 2002, 2004, Kon et al. 2010). USP7 also regulates MDM4 (Mdmx), a structural homolog of MDM2 (Meulmeester et al. 2005, Chen 2012). USP7 interacts with and deubiquitinates FOXO4 in response to oxidative stress (van der Horst et al. 2006) and reduces monoubiquitinylation of PTEN, presumably on the previously identified lysine residues 13 and 289 (Trotman et al. 2007), reducing nuclear PTEN levels (Song et al. 2008).

Literature references

Maurice, MM., de Vries-Smits, AM., van der Horst, A., van den Broek, N., Burgering, BM., van Triest, MH. et al. (2006). FOXO4 transcriptional activity is regulated by monoubiquitination and USP7/HAUSP. *Nat. Cell Biol., 8*, 1064-73. ↗

Gu, W., Luo, J., Nikolaev, AY., Shiloh, A., Chen, D., Qin, J. et al. (2002). Deubiquitination of p53 by HAUSP is an important pathway for p53 stabilization. *Nature, 416*, 648-53. ↗

Gu, W., Brooks, CL., Kon, N., Li, M. (2004). A dynamic role of HAUSP in the p53-Mdm2 pathway. *Mol. Cell, 13*, 879-86. ↗

Maurice, MM., Dirks, RW., Jochemsen, AG., Abraham, TE., Ovaa, H., Meulmeester, E. et al. (2005). Loss of HAUSP-mediated deubiquitination contributes to DNA damage-induced destabilization of Hdmx and Hdm2. *Mol. Cell, 18*, 565-76. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

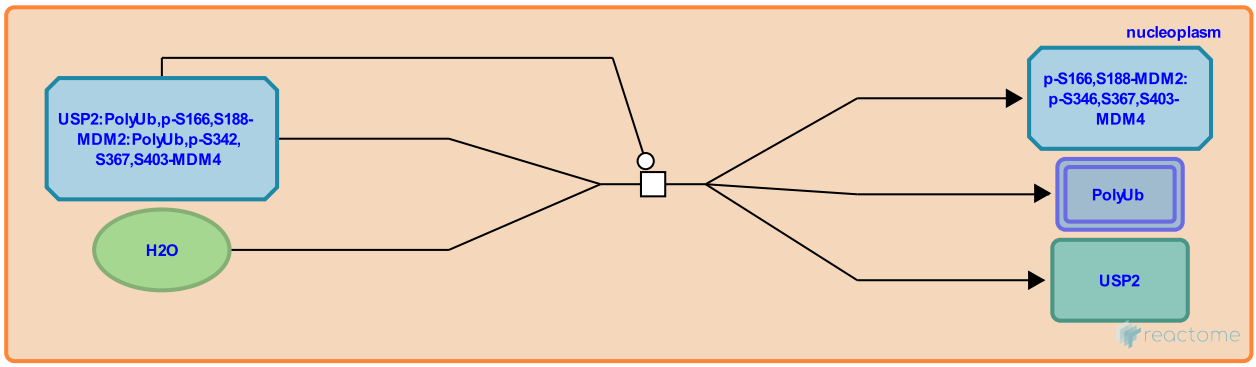
USP2 deubiquitinates MDM2,MDM4 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5689972

Type: transition

Compartments: nucleoplasm



The ubiquitin protease USP2 deubiquitinates MDM2 and MDM4 but not TP53 (Stevenson et al. 2007, Allende-Vega et al. 2010).

Literature references

Allende-Vega, N., Sparks, A., Saville, MK., Lane, DP. (2010). MdmX is a substrate for the deubiquitinating enzyme USP2a. *Oncogene, 29*, 432-41. ↗

Saville, MK., Lane, DP., Sparks, A., Xirodimas, DP., Stevenson, LF., Allende-Vega, N. (2007). The deubiquitinating enzyme USP2a regulates the p53 pathway by targeting Mdm2. *EMBO J., 26*, 976-86. ↗

Editions

2015-10-14	Authored, Edited	Orlic-Milacic, M.
2016-02-04	Reviewed	Inga, A., Zaccara, S.

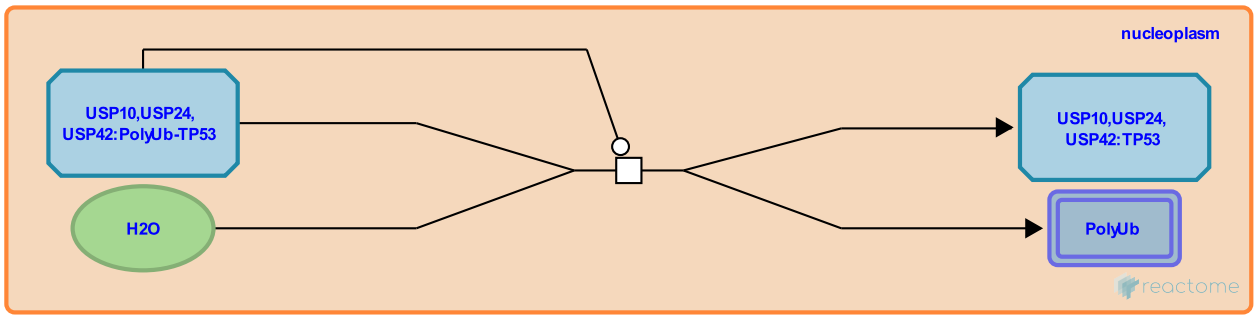
USP10,USP24,USP42 deubiquitinate TP53 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5689973

Type: transition

Compartments: nucleoplasm



USP10 specifically deubiquitinate p53 and not MDM2 (Yuan et al. 2010). USP24 and USP42 also can deubiquitinate p53, regulating the DNA damage response following UV-damage (Hock et al. 2011, Zhang et al. 2015).

Literature references

Lou, Z., Cheville, JC., Yuan, J., Luo, K., Zhang, L. (2010). USP10 regulates p53 localization and stability by deubiquitinating p53. *Cell, 140*, 384-96. ↗

Carter, S., Vigneron, AM., Ludwig, RL., Hock, AK., Vousden, KH. (2011). Regulation of p53 stability and function by the deubiquitinating enzyme USP42. *EMBO J., 30*, 4921-30. ↗

Harris, TK., Lubin, A., Zhang, L., Gong, F., Nemzow, L., Sun, Z. et al. (2015). The deubiquitinating enzyme USP24 is a regulator of the UV damage response. *Cell Rep, 10*, 140-7. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

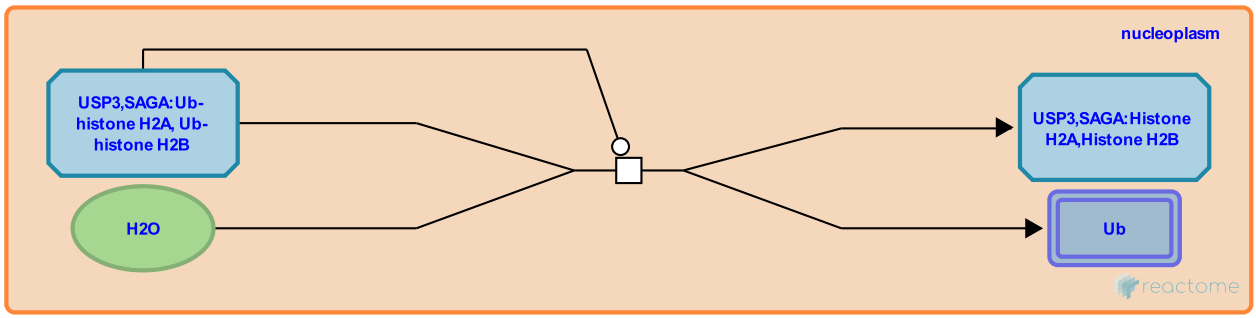
USP3,SAGA deubiquitinate Histone H2A,H2B ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5690080

Type: transition

Compartments: nucleoplasm



USP3 dynamically associates with chromatin and deubiquitinates H2A and H2B in vivo. The ZnF-UBP domain of USP3 mediates the H2A-USP3 interaction (Nicassio et al. 2007). USP22, a component of the hSAGA transcriptional coactivator complex, is able to deubiquitinate Histone H2A and H2B (Zhang et al. 2008, Zhao et al. 2008).

Literature references

Houtsmuller, AB., Corrado, N., Di Fiore, PP., Marteijn, JA., Vissers, JH., Nicassio, F. et al. (2007). Human USP3 is a chromatin modifier required for S phase progression and genome stability. *Curr. Biol., 17*, 1972-7. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

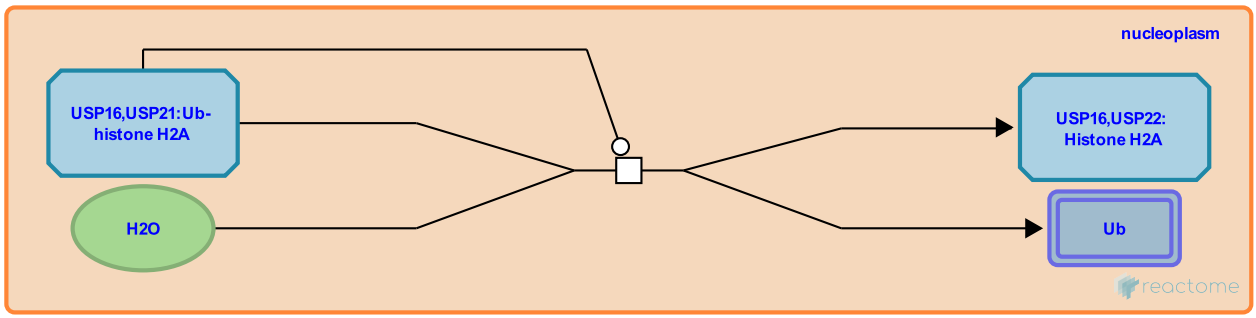
USP16,USP21 deubiquitinate Histone H2A ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5690157

Type: transition

Compartments: nucleoplasm



USP16 and USP21 can associate with and deubiquitinate H2A (Joo et al. 2007, Zhang et al. 2014, Nakagawa et al. 2008).

Literature references

Yang, H., Zhang, Z., Wang, H. (2014). The histone H2A deubiquitinase USP16 interacts with HERC2 and fine-tunes cellular response to DNA damage. *J. Biol. Chem., 289*, 32883-94. ↗

Kajitani, T., Koji, T., Ohdan, H., Nakagawa, T., Ito, T., Ikura, T. et al. (2008). Deubiquitylation of histone H2A activates transcriptional initiation via trans-histone cross-talk with H3K4 di- and trimethylation. *Genes Dev., 22*, 37-49. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

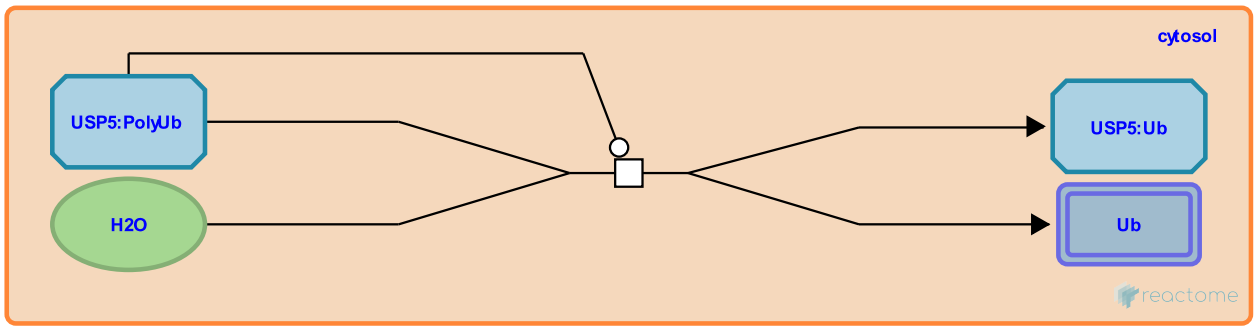
USP5 cleaves polyubiquitin ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5690152

Type: transition

Compartments: cytosol



USP5 (Isopeptidase T) cleaves linear and branched polyubiquitin (polyUb) with a preference for branched polymers (Wilkonson et al. 1995). It is Involved in the disassembly of unattached lysine-48-linked (K48) polyUb. It also binds linear and K63-linked polyUb with a lower affinity (Dayal et al. 2009).

Literature references

Tashayev, VL., Pickart, CM., Wilkinson, KD., O'Connor, LB., Larsen, CN., Kasperek, E. (1995). Metabolism of the polyubiquitin degradation signal: structure, mechanism, and role of isopeptidase T. *Biochemistry, 34*, 14535-46. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

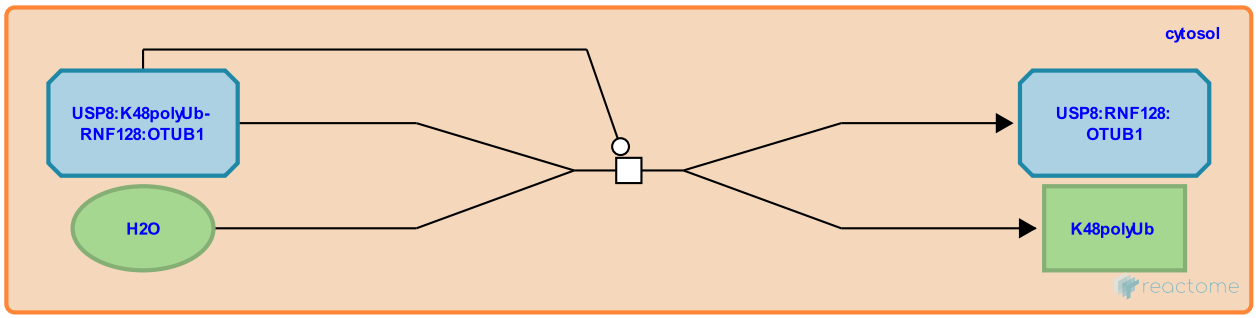
USP8 deubiquitinates RNF128 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5690196

Type: transition

Compartments: cytosol



The ubiquitin E3 ligase RNF128 (GRAIL) is regulated by auto-K48-linked ubiquitination, which leads to its proteasomal degradation. RNF128 is bound but not deubiquitinated by OTUB1. USP8 binds the RNF128:OTUB1 complex to remove the ubiquitin attached to GRAIL (Soares et al. 2004, Whiting et al. 2011).

Literature references

Skrenta, H., Lovelace, P., Seroogy, C., Engleman, E., Soares, L., Chung, CD. et al. (2004). Two isoforms of otubain 1 regulate T cell anergy via GRAIL. *Nat. Immunol., 5*, 45-54. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

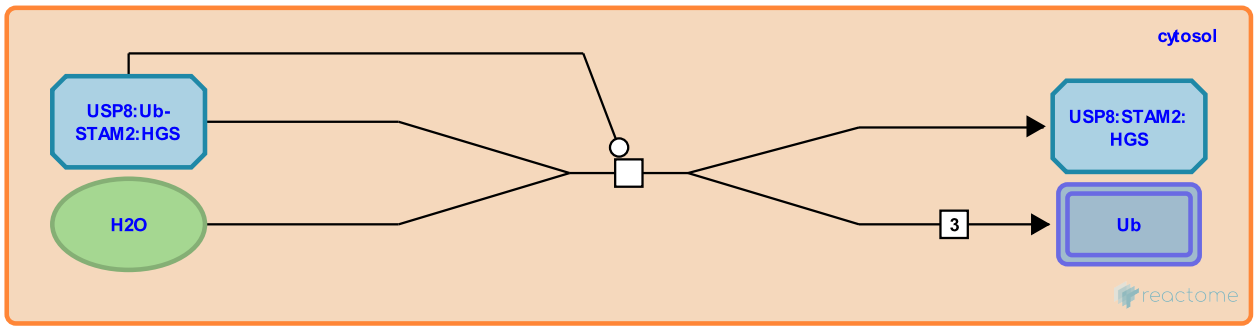
USP8 deubiquitinates STAM2:HGS ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-6782628

Type: transition

Compartments: cytosol



Monoubiquitination of cell surface receptors is a sorting signal that leads to receptor trafficking from endosomes to lysosomes. Ubiquitinated protein sorting is carried out by class E vacuolar protein sorting (Vps) proteins. Some of these proteins are regulated by monoubiquitination. The Hrs-STAM complex, which is essential for the initial step of the sorting pathway, binds the deubiquitinating enzymes USP8 (UBPY) and STAMBP (AMSH). These bind STAM2 at the same site and may compete for binding (Kato et al. 2000). STAM2 stability is dramatically reduced in USP8 knockdown cells suggesting that its degradation is reduced by the DUB action of USP8 (Row et al. 2006).

Literature references

Miyazawa, K., Kitamura, N., Kato, M. (2000). A deubiquitinating enzyme UBPY interacts with the Src homology 3 domain of Hrs-binding protein via a novel binding motif PX(V/I)(D/N)RXXKP. *J. Biol. Chem., 275*, 37481-7. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

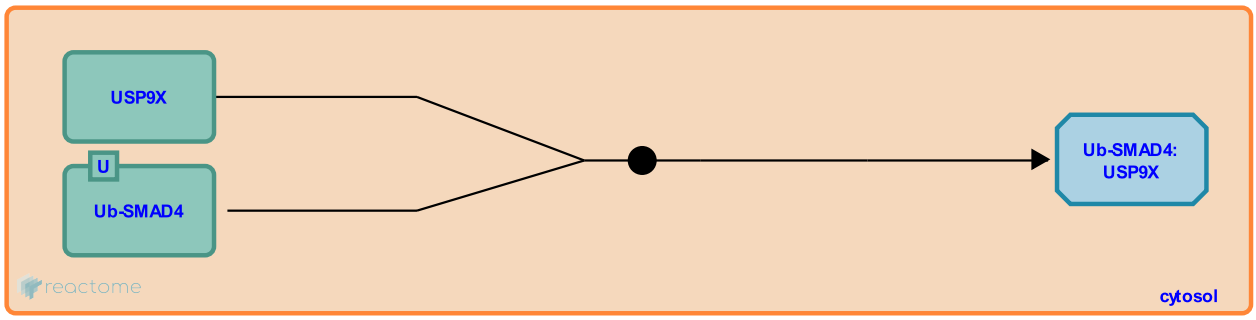
USP9X (FAM) binds to ubiquitinated SMAD4 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-870479

Type: binding

Compartments: cytosol



In the cytosol, a ubiquitin hydrolase USP9X (FAM) binds to ubiquitinated SMAD4 (Dupont et al. 2009).

Followed by: USP9X (FAM) deubiquitinates SMAD4

Literature references

Stinchfield, MJ., Montagner, M., Morsut, L., Piccolo, S., Inui, M., Moro, S. et al. (2009). FAM/USP9x, a deubiquitinating enzyme essential for TGFbeta signaling, controls Smad4 monoubiquitination. *Cell, 136*, 123-35. ↗

Editions

2010-06-08	Authored	Williams, MG.
2012-04-05	Revised	Orlic-Milacic, M.
2012-04-10	Edited	Jassal, B.
2012-05-14	Reviewed	Huang, T.
2022-05-02	Reviewed	Contreras, O.
2022-05-09	Edited	Orlic-Milacic, M.

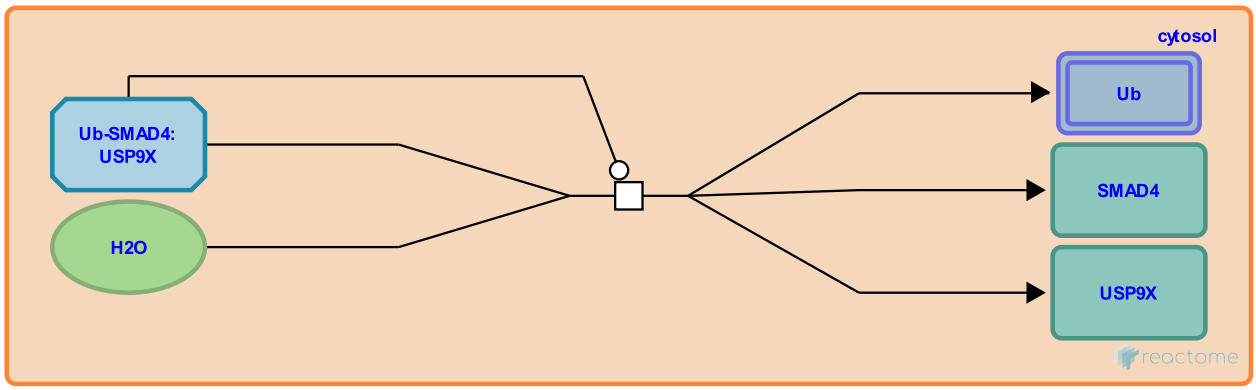
USP9X (FAM) deubiquitinates SMAD4 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-870437

Type: transition

Compartments: cytosol



USP9X (FAM) deubiquitinates SMAD4, thereby opposing the negative regulatory activity of TRIM33 (Ectodermin) (Dupont et al. 2009).

Preceded by: USP9X (FAM) binds to ubiquitinated SMAD4

Literature references

Stinchfield, MJ., Montagner, M., Morsut, L., Piccolo, S., Inui, M., Moro, S. et al. (2009). FAM/USP9x, a deubiquitinating enzyme essential for TGFbeta signaling, controls Smad4 monoubiquitination. *Cell, 136*, 123-35. ↗

Editions

2010-06-08	Authored	Williams, MG.
2012-04-10	Edited	Jassal, B.
2012-05-14	Reviewed	Huang, T.
2022-05-02	Reviewed	Contreras, O.
2022-05-09	Edited	Orlic-Milacic, M.

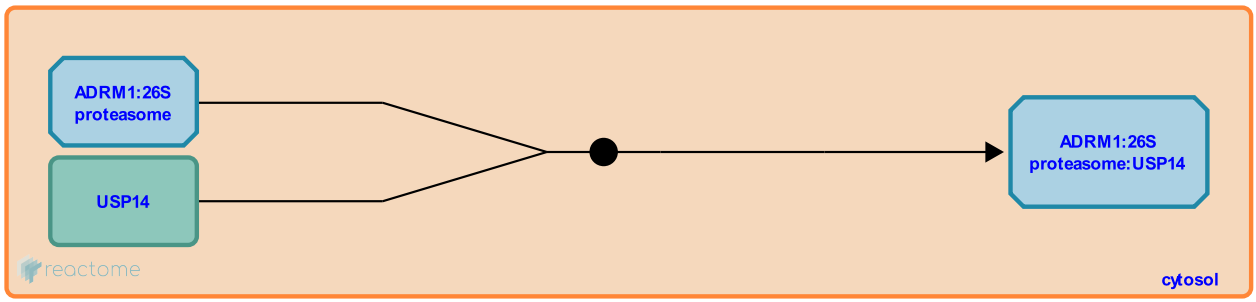
ADRM1:26S proteaseome binds USP14 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5689539

Type: binding

Compartments: cytosol



ADRM1 (Rpn13) interacts with the 26S proteasome base unit PRDM1 (Rpn2) via its amino-terminus and is found in the majority of 26S proteasomes. ADRM1 can bind K48-linked di-Ubiquitin (Schreiner et al. 2008, Husnjak et al. 2008) and several de-ubiquitinating enzymes (DUBs) including PSDM14 (Rpn11, POH1), part of the 26S proteasome, and USP14 (Borodovsky et al. 2001, Reyes-Turcu et al. 2009). These proteasome-associated DUBs disassemble poly-Ub chains and recycle ubiquitin during proteasomal degradation. They may also act to prevent the degradation of mis-tagged proteins.

Literature references

Overkleeft, HS., Ploegh, HL., Kessler, BM., Borodovsky, A., Wilkinson, KD., Casagrande, R. (2001). A novel active site-directed probe specific for deubiquitylating enzymes reveals proteasome association of USP14. *EMBO J., 20,* 5187-96. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

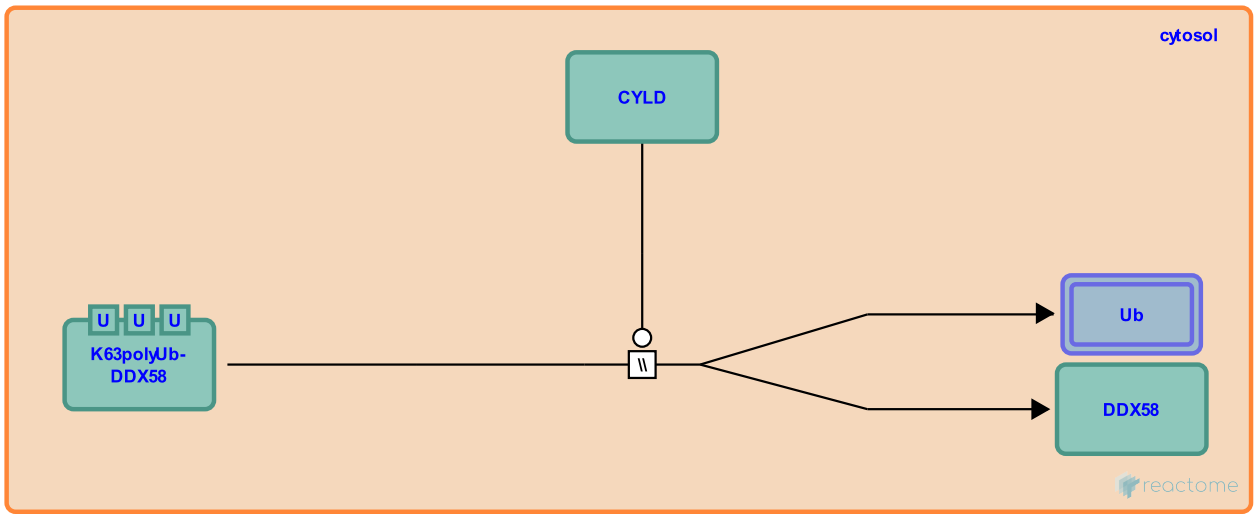
CYLD mediated deubiquitination of DDX58 (RIG-I) ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-936390

Type: omitted

Compartments: cytosol



CYLD is an ovarian tumor (OTU) domain-containing deubiquitinating enzyme (DUB) and has been identified as a negative regulator of DDX58 (RIG-I) mediated antiviral signaling. CYLD associates with the CARD domain of DDX58 and removes K63-linked ubiquitin from the DDX58 CARDs that are conjugated by the E3 ubiquitin ligase, TRIM25 and RNF135.

Literature references

Horvath, CM., Moran, TM., Yount, JS., Ng, A., Legarda-Addison, D., Xavier, R. et al. (2008). The tumour suppressor CYLD is a negative regulator of RIG-I-mediated antiviral response. *EMBO Rep, 9*, 930-6. ↗

Wright, A., Lee, AJ., Zhang, M., Sun, SC., Jin, W., Imaizumi, T. et al. (2008). Regulation of IkappaB kinase-related kinases and antiviral responses by tumor suppressor CYLD. *J Biol Chem, 283*, 18621-6. ↗

Editions

2010-08-02	Authored	Garapati, P V.
2010-08-23	Edited	Garapati, P V.
2010-10-30	Reviewed	Akira, S., Kawai, T.

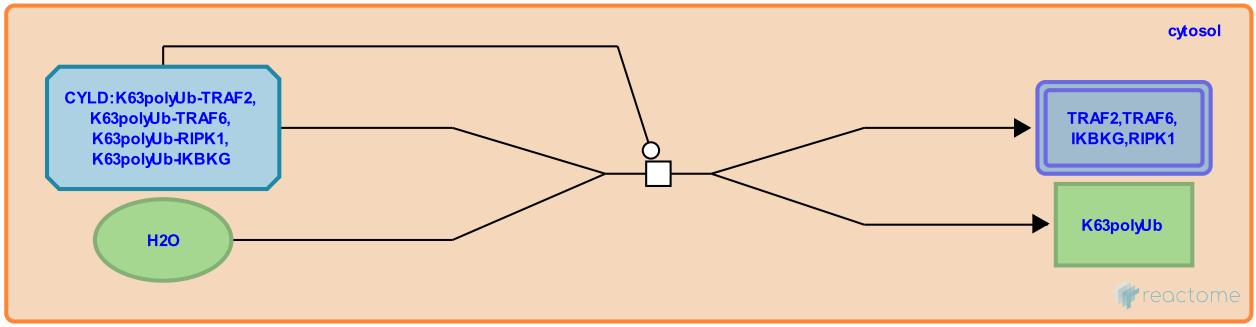
CYLD deubiquitinates K63polyUb-TRAF2,K63polyUb-TRAF6,K63polyUb-RIPK1,K63polyUb-IKBKG ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5696627

Type: transition

Compartments: cytosol



CYLD removes Lys63-linked ubiquitin chains, acting as a negative regulator of NF-kappa-B signaling (Trompouki et al. 2003). It deubiquitinates several NF-kappa-B regulators including TRAF2, TRAF6 (Kovalenko et al. 2003, Trompouki et al. 2003), IKBKG (NEMO) (Brummelkamp et al. 2003), and RIPK1 (Wright et al. 2007).

Literature references

Cantarella, G., Wallach, D., Courtois, G., Chable-Bessia, C., Israel, A., Kovalenko, A. (2003). The tumour suppressor CYLD negatively regulates NF-kappaB signalling by deubiquitination. *Nature, 424*, 801-5. ↗

Ashworth, A., Farmer, H., Trompouki, E., Tsichritzis, T., Hatzivassiliou, E., Mosialos, G. (2003). CYLD is a deubiquitinating enzyme that negatively regulates NF-kappaB activation by TNFR family members. *Nature, 424*, 793-6. ↗

Chang, M., Sun, SC., Wright, A., Zhang, M., Lee, AJ., Reiley, WW. et al. (2007). Regulation of early wave of germ cell apoptosis and spermatogenesis by deubiquitinating enzyme CYLD. *Dev. Cell, 13*, 705-16. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

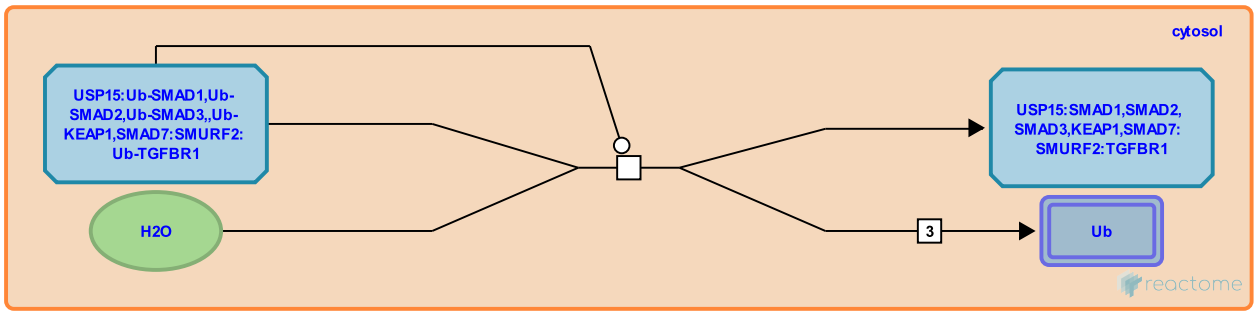
USP15 deubiquitinates SMAD1,SMAD2,SMAD3, SMAD7:SMURF,KEAP1 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-6781764

Type: transition

Compartments: cytosol



USP15 is a ubiquitin-specific protease (Baker et al. 1999) reported to act on several substrates. It promotes deubiquitination of monoubiquitinated R-SMADs, indirectly promoting the activation of TGF-beta target genes (Inui et al. 2011). USP15 binds the SMAD7:SMURF2 complex, deubiquitinating and stabilizing the type I TGFBeta receptor (TGFBR1), leading to enhanced TGF-Beta signalling (Eichorn et al. 2012). USP15 deubiquitinates KEAP1, which suppresses the Nrf2 pathway (Villeneuve et al. 2013).

Literature references

White, JA., Baker, RT., Sutherland, GR., Wang, XW., Woollatt, E. (1999). Identification, functional characterization, and chromosomal localization of USP15, a novel human ubiquitin-specific protease related to the UNP oncoprotein, and a systematic nomenclature for human ubiquitin-specific proteases. *Genomics, 59*, 264-74. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

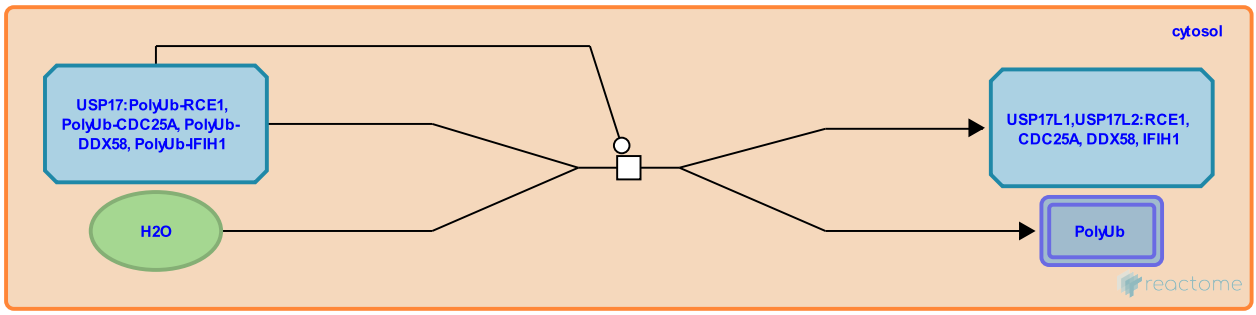
USP17 deubiquitinates RCE1, CDC25A, DDX58, IFIH1 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5696600

Type: transition

Compartments: cytosol



USP17 regulates cell proliferation by deubiquitinating and inhibiting RCE1, which influences the localization and activation of the small GTPases NRAS and HRAS (Burrows et al. 2009). In addition, USP17 mediates deubiquitination of CDC25A, which prevents CDC25A degradation by the proteasome during the G1/S and G2/M phases, promoting cell-cycle progression (Pereq et al. 2010). USP17 cleaves Lys-48 and Lys-63-linked polyubiquitin chains from the cytoplasmic innate immune receptors DDX58 (RIG-I) and IFIH1 (MDA5), which increases activation of the IFN-beta promoter, part of the cellular response to viral infection (Chen et al. 2010). USP17 expression is upregulated by interleukin-4 and interleukin-6 (Burrows et al. 2004).

Literature references

Shu, HB., Liu, Y., Tan, B., Chen, R., Zhang, L., Zhong, B. (2010). The ubiquitin-specific protease 17 is involved in virus-triggered type I IFN signaling. *Cell Res., 20*, 802-11. ↗

McFarlane, C., Scott, CJ., De la Vega, M., Johnston, JA., McGrattan, MJ., Kelvin, AA. et al. (2009). USP17 regulates Ras activation and cell proliferation by blocking RCE1 activity. *J. Biol. Chem., 284*, 9587-95. ↗

O'Rourke, KM., Pereg, Y., Komuves, L., French, DM., Dey, A., Liu, BY. et al. (2010). Ubiquitin hydrolase Dub3 promotes oncogenic transformation by stabilizing Cdc25A. *Nat. Cell Biol., 12*, 400-6. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

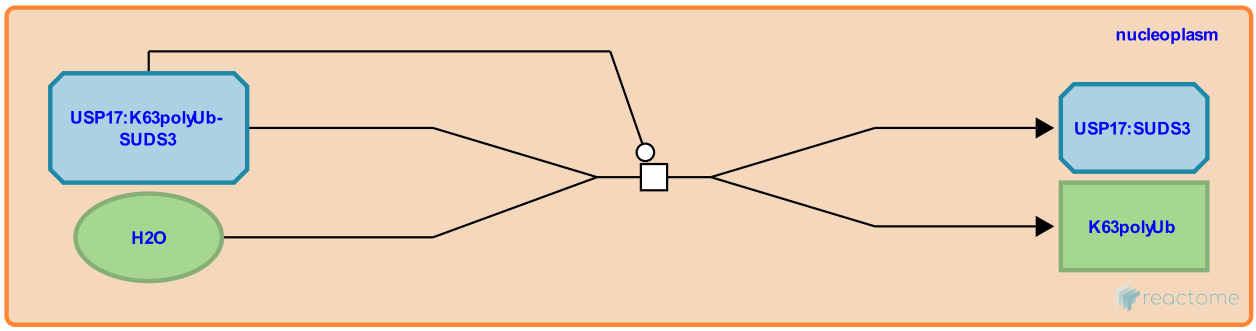
USP17 deubiquitinates SUDS3 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-6782820

Type: transition

Compartments: nucleoplasm



USP17 removes Lys-63-linked ubiquitin chains from SDS3, a key component of the histone deacetylase (HDAC)-dependent Sin3A co-repressor complex, serving to maintain its HDAC activity (Ramakrishna et al. 2011).

Literature references

Ahn, WS., Suresh, B., Lee, EJ., Ramakrishna, S., Baek, KH., Lee, HJ. (2011). Lys-63-specific deubiquitination of SDS3 by USP17 regulates HDAC activity. *J. Biol. Chem., 286*, 10505-14. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

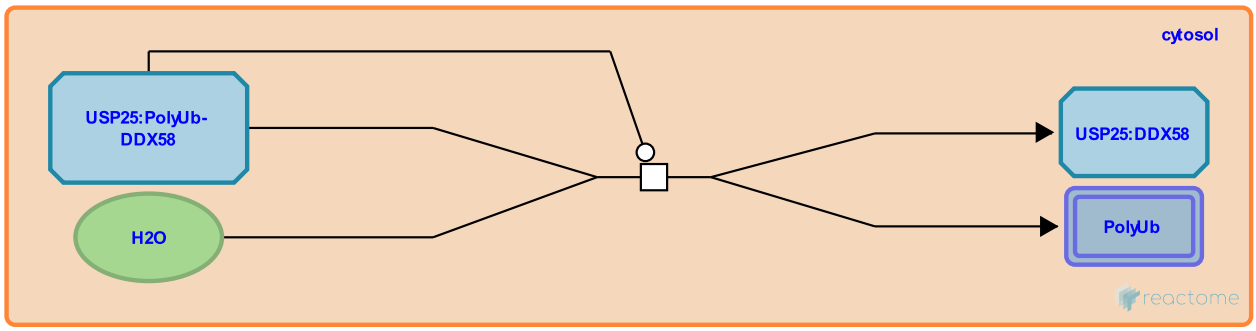
USP25 deubiquitinates DDX58 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5696564

Type: transition

Compartments: cytosol



USP25, a negative regulator of the virus-triggered type I IFN signaling pathway, cleaves lysine 48- and lysine 63-linked polyubiquitin chains in vitro and in vivo from DDX58 (Retinoic acid-inducible gene I (RIG-I)), Tumor necrosis factor (TNF) receptor-associated factor 2 (TRAF2) and TRAF6 to inhibit RIG-I-like receptor-mediated IFN signaling (Zhong et al. 2013).

Literature references

Zhong, H., Chen, H., Shang, M., Ouyang, H., Ouyang, C., Fang, L. et al. (2013). Ubiquitin-specific proteases 25 negatively regulates virus-induced type I interferon signaling. *PLoS ONE, 8*, e80976. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

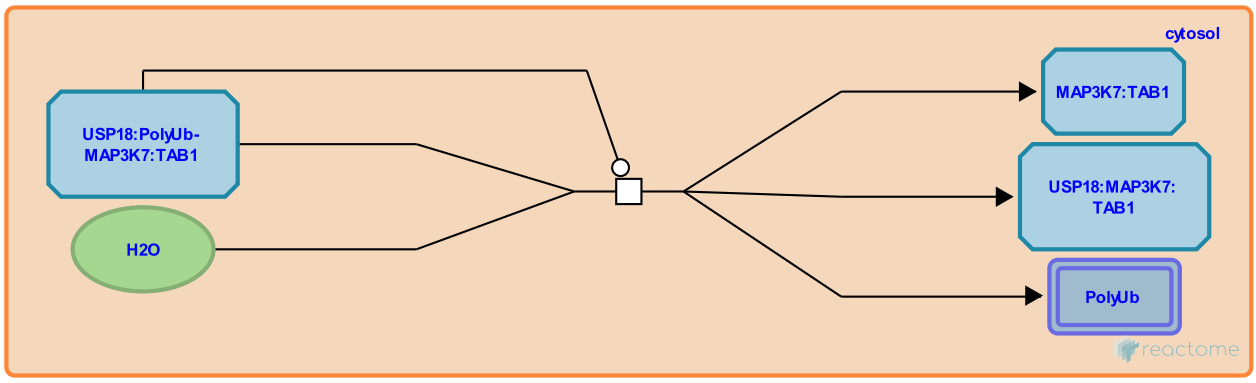
USP18 deubiquitinates TAK1:TAB1 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5696534

Type: transition

Compartments: cytosol



Ubiquitination plays a key role in the regulation of signaling via TAK1 (Chen 2012). USP18 catalyzes the deubiquitination of the TAK1:TAB1 complex, reversing TAK1 activating ubiquitination, which restricts activation of NF-kappaB, NFAT and JNK and in decreases the expression of IL2 in T cells after TCR activation (Liu et al. 2013).

Literature references

Tian, Q., Dong, C., Yan, M., Gorjestani, S., Liu, X., Zhang, DE. et al. (2013). USP18 inhibits NF-κB and NFAT activation during Th17 differentiation by deubiquitinating the TAK1-TAB1 complex. *J. Exp. Med., 210*, 1575-90. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

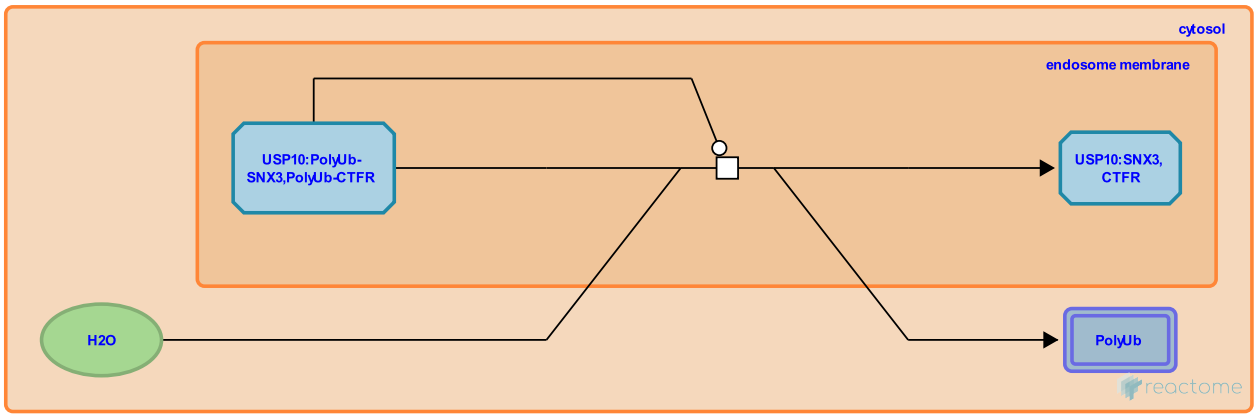
USP10 deubiquitinates SNX3, CFTR ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-6782106

Type: transition

Compartments: endosome membrane, cytosol



USP10 deubiquitinates and stabilizes endogenous SNX3 and consequently promotes cell surface expression of ENaC (Boulkroun et al. 2008). USP10 deubiquitinates CFTR in early endosomes thereby enhancing its endocytic recycling (Bomberger et al. 2009).

Literature references

Bomberger, JM., Barnaby, RL., Stanton, BA. (2009). The deubiquitinating enzyme USP10 regulates the post-endocytic sorting of cystic fibrosis transmembrane conductance regulator in airway epithelial cells. *J. Biol. Chem., 284*, 18778-89. ↗

Boulkroun, S., Lagnaz, D., Staub, O., Ruffieux-Daidié, D., Charles, RP., Vitagliano, JJ. et al. (2008). Vasopressin-inducible ubiquitin-specific protease 10 increases ENaC cell surface expression by deubiquitylating and stabilizing sorting nexin 3. *Am. J. Physiol. Renal Physiol., 295*, F889-900. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

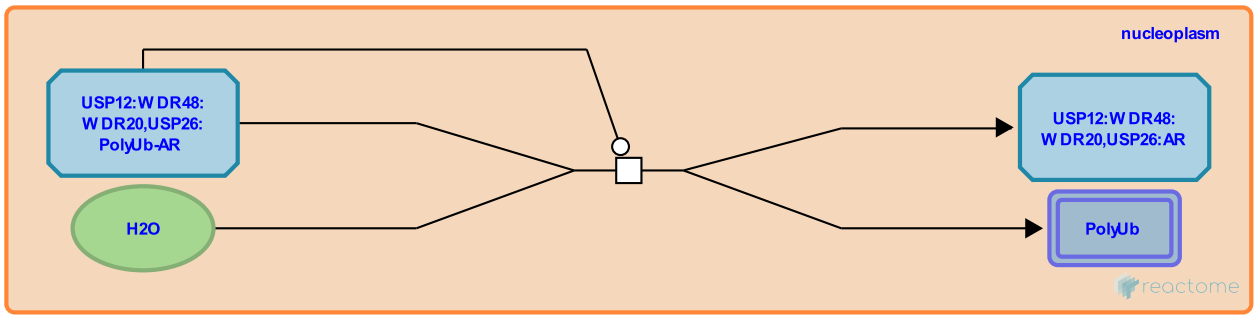
USP12, USP26 deubiquitinate AR ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5696605

Type: transition

Compartments: nucleoplasm



USP12 (as part of a complex with WDR48 and WDR20) and USP26 can bind the androgen receptor and promote its deubiquitination (Faus et al. 2005, Burska et al. 2013, Dirac & Bernards 2010). USP26 is specifically expressed in testis tissue and is a potential infertility gene (Stouffs et al. 2005).

Literature references

Bernards, R., Dirac, AM. (2010). The deubiquitinating enzyme USP26 is a regulator of androgen receptor signaling. *Mol. Cancer Res., 8*, 844-54. ↗

Gaughan, L., O'Neill, D., Logan, IR., Harle, VJ., Burska, UL., Robson, CN. et al. (2013). Deubiquitinating enzyme Usp12 is a novel co-activator of the androgen receptor. *J. Biol. Chem., 288*, 32641-50. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

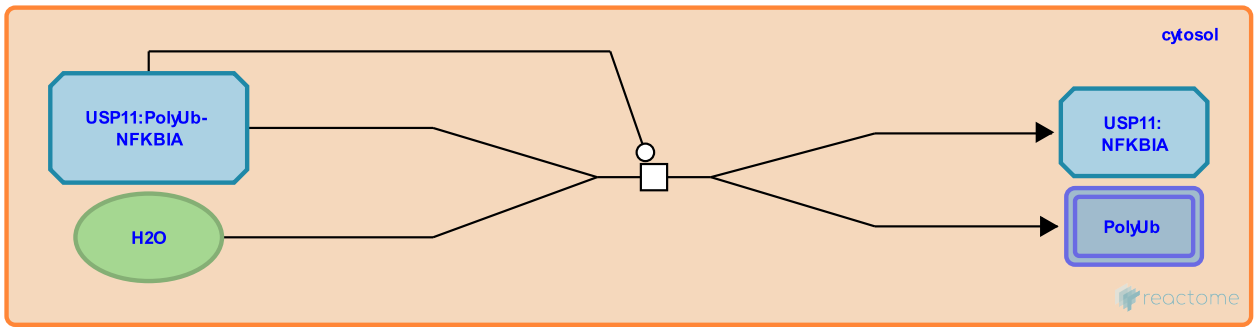
USP11 deubiquitinates NFKBIA ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-6781897

Type: transition

Compartments: cytosol



USP11 associates with and deubiquitinates NFKBIA (IkappaBalpha), downregulating TNFalpha-mediated NF-kappaB activation (Sun et al. 2010).

Literature references

Fan, Y., Fu, S., Shi, Y., Mao, R., Sun, W., Zhang, T. et al. (2010). USP11 negatively regulates TNFalpha-induced NF-kappaB activation by targeting on IkappaBalpha. *Cell. Signal., 22*, 386-94. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

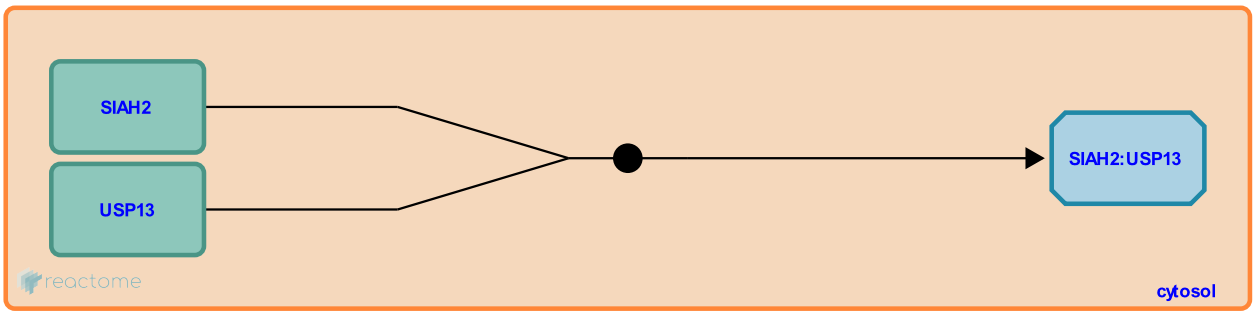
USP13 binds SIAH2 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-6781899

Type: binding

Compartments: cytosol



USP13 mediates stabilization of the E3-ligase SIAH2 independently of deubiquitinase activity by binding and impairing SIAH2 autoubiquitination (Scortegagna et al. 2011).

Literature references

Scortegagna, M., Gu, W., Kim, H., Kluger, H., Subtil, T., Qi, J. et al. (2011). USP13 enzyme regulates Siah2 ligase stability and activity via noncatalytic ubiquitin-binding domains. *J. Biol. Chem.*, *286*, 27333-41. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

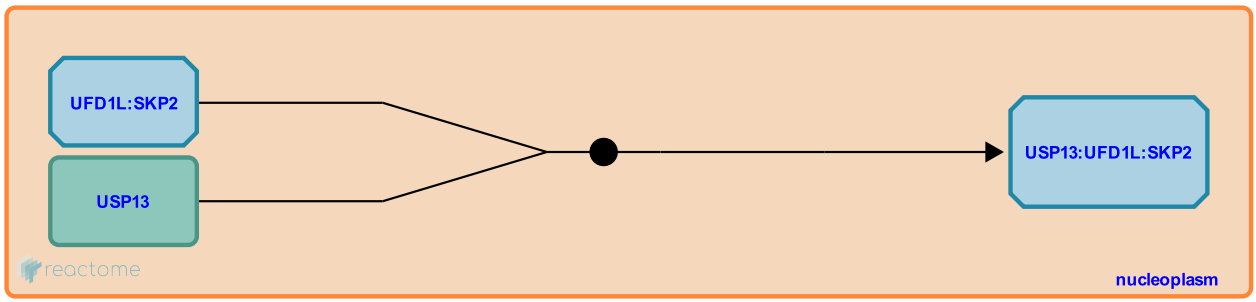
USP13 binds UFD1L:SKP2 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-6781922

Type: binding

Compartments: nucleoplasm



In the nucleus USP13 binds UFD1 which acts as a scaffold connecting USP13 to SKP2. USP13 mediates the deubiquitination of SKP2, thereby regulating endoplasmic reticulum-associated degradation (ERAD) by counteracting APC/C(Cdh1)-mediated SKP2 ubiquitination (Chen et al. 2011).

Literature references

Gutierrez, GJ., Ronai, ZA., Chen, M. (2011). Ubiquitin-recognition protein Ufd1 couples the endoplasmic reticulum (ER) stress response to cell cycle control. *Proc. Natl. Acad. Sci. U.S.A., 108*, 9119-24. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

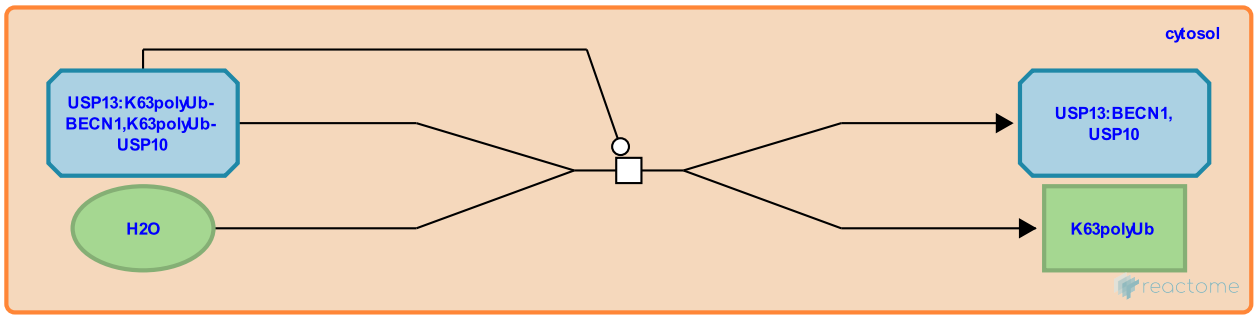
USP13 deubiquitinates BECN1,USP10

Location: Ub-specific processing proteases

Stable identifier: R-HSA-6781779

Type: transition

Compartments: cytosol



USP13 preferentially cleaves Lys-63-linked polyubiquitin chains (Zhang et al. 2011). It mediates deubiquitination of BECN1, a key regulator of autophagy, which stabilizes PIK3C3/VPS34-containing complexes. USP13 can deubiquitinate USP10, an essential regulator of TP53 stability (Liu et al. 2011).

Literature references

Xia, H., Choi, A., Ma, D., Zhang, L., Norberg, HV., Zhu, Z. et al. (2011). Beclin1 controls the levels of p53 by regulating the deubiquitination activity of USP10 and USP13. *Cell, 147*, 223-34.

Zhou, CJ., Song, AX., Zhang, YH., Zhou, ZR., Hu, HY. (2011). Domain analysis reveals that a deubiquitinating enzyme USP13 performs non-activating catalysis for Lys63-linked polyubiquitin. *PLoS ONE, 6*, e29362.

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

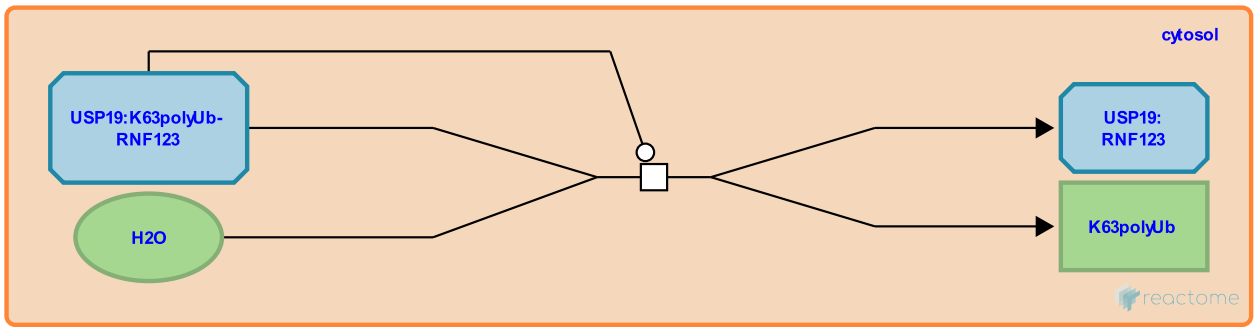
USP19 deubiquitinates RNF123 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-6781814

Type: transition

Compartments: cytosol



USP19 is a deubiquitinating enzyme with a preference towards Lys-63-linked ubiquitin chains (Iphofer et al. 2012). It deubiquitinates RNF123, preventing its proteasomal degradation which in turn stimulates CDKN1B ubiquitin-dependent degradation and thereby cell proliferation (Lu et al. 2009).

Literature references

Adegoke, OA., Peng, J., Bedard, N., Nepveu, A., Lu, Y., Nakayama, KI. et al. (2009). USP19 deubiquitinating enzyme supports cell proliferation by stabilizing KPC1, a ubiquitin ligase for p27Kip1. *Mol. Cell. Biol., 29*, 547-58. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

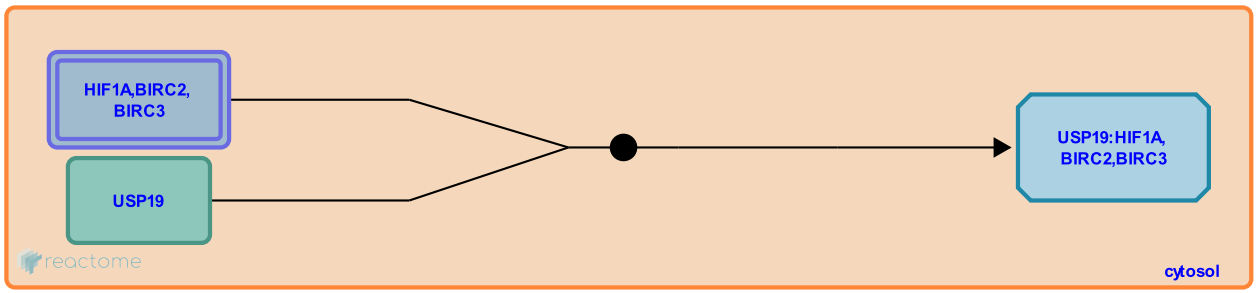
USP19 binds HIF1A,BIRC2,BIRC3

Location: Ub-specific processing proteases

Stable identifier: R-HSA-6781797

Type: binding

Compartments: cytosol



USP19 promotes the stability of BIRC2 (c-IAP1) and BIRC3 (c-IAP2) by preventing them from self-ubiquitinating (Mei et al. 2011). Similarly, USP19 promotes the stability of the hypoxia-inducible factor 1-alpha (HIF-1a), with a mechanism that is independent of its catalytic activity (Altun et al. 2012).

Literature references

Hahn, AA., Mei, Y., Yang, X., Hu, S. (2011). The USP19 deubiquitinase regulates the stability of c-IAP1 and c-IAP2. *J. Biol. Chem., 286*, 35380-7.

Paschke, J., Altun, M., Hassink, G., Liu, H., Pereira, T., Velasco, K. et al. (2012). Ubiquitin-specific protease 19 (USP19) regulates hypoxia-inducible factor 1α (HIF-1α) during hypoxia. *J. Biol. Chem., 287*, 1962-9.

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

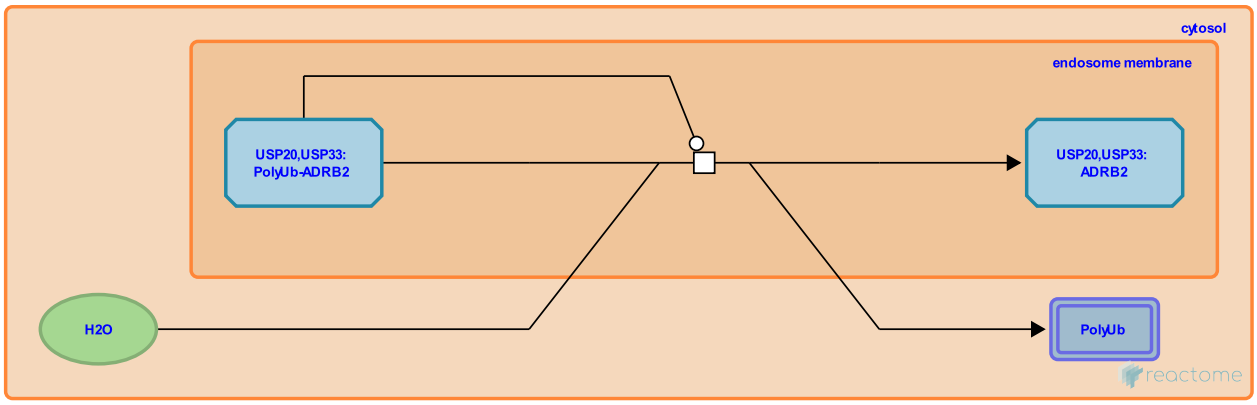
USP20, USP33 deubiquitinate ADRB2 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5696968

Type: transition

Compartments: endosome membrane, cytosol



USP20 and USP33 act as a regulators of G-protein coupled receptor (GPCR) signaling by mediating the deubiquitination of the beta-2 adrenergic receptor (ADRB2), prolonging agonist stimulation and inhibiting lysosomal trafficking (Berthouze et al. 2009).

Literature references

Shenoy, SK., Berthouze, M., Venkataramanan, V., Li, Y. (2009). The deubiquitinases USP33 and USP20 coordinate beta2 adrenergic receptor recycling and resensitization. *EMBO J., 28,* 1684-96. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

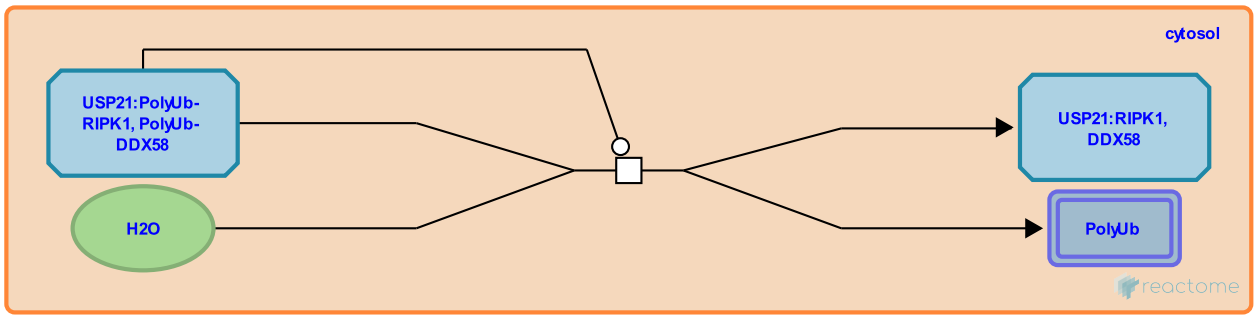
USP21 deubiquitinates RIPK1,DDX58 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5690159

Type: transition

Compartments: cytosol



USP21 is not required for normal development (Pannu et al. 2015) but is essential in innate and adaptive immune responses (Tao et al. 2014). It negatively regulates NFkB signaling by deubiquitinating Receptor-interacting protein 1 (RIPK1) (Xu et al. 2010) and DDX58 (RIG-I), thereby down-regulating antiviral responses independently of the A20 ubiquitin-editing complex (Fan et al. 2014).

Literature references

Fan, Y., Zhang, D., Jung, JU., Chen, Z., An, L., Mao, R. et al. (2014). USP21 negatively regulates antiviral response by acting as a RIG-I deubiquitinase. *J. Exp. Med., 211*, 313-28. ↗

Cao, G., Xu, G., Gu, X., Wang, H., Shi, Y., Tan, X. et al. (2010). Ubiquitin-specific peptidase 21 inhibits tumor necrosis factor alpha-induced nuclear factor kappaB activation via binding to and deubiquitinating receptor-interacting protein 1. *J. Biol. Chem., 285*, 969-78. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

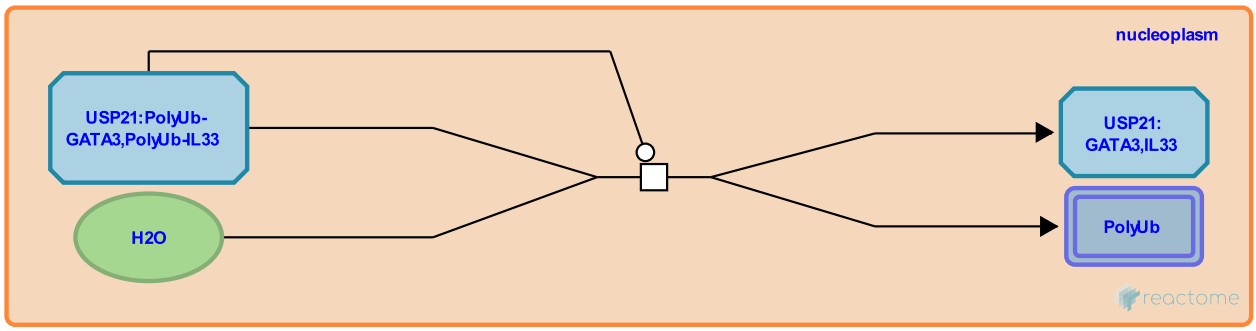
USP21 deubiquitinates GATA3,IL33 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-6783177

Type: transition

Compartments: nucleoplasm



Though not required for normal development (Pannu et al. 2015), USP21 is essential in innate and adaptive immune responses (Tao et al. 2014). It deubiquitinates the Th2 specific transcription factor GATA3. This positive regulation is important for the function of regulatory T cells (Zhang et al. 2013). USP21 also deubiquitinates IL-33, which is both a cytokine and a chromatin-associated nuclear protein known as Nuclear factor from high endothelial venule (NF-HEV), which is associated with many inflammatory diseases (Garlanda et al. 2013). IL-33 can bind to the RELA (NFkB p65) promoter region, inducing endothelial cell activation (Choi et al. 2012). Depletion of USP21 reduces IL-33 protein levels and IL-33-mediated RELA promoter activity (Tao et al. 2014).

Literature references

Yang, J., Gao, Z., Chen, C., Pan, L., Li, B., Shi, G. et al. (2013). Identification of the E3 deubiquitinase ubiquitin-specific peptidase 21 (USP21) as a positive regulator of the transcription factor GATA3. *J. Biol. Chem., 288*, 9373-82. ↗

Piccioni, M., Tao, L., Song, H., Chen, C., Li, B., Shi, G. (2014). Deubiquitination and stabilization of IL-33 by USP21. *Int J Clin Exp Pathol, 7*, 4930-7. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

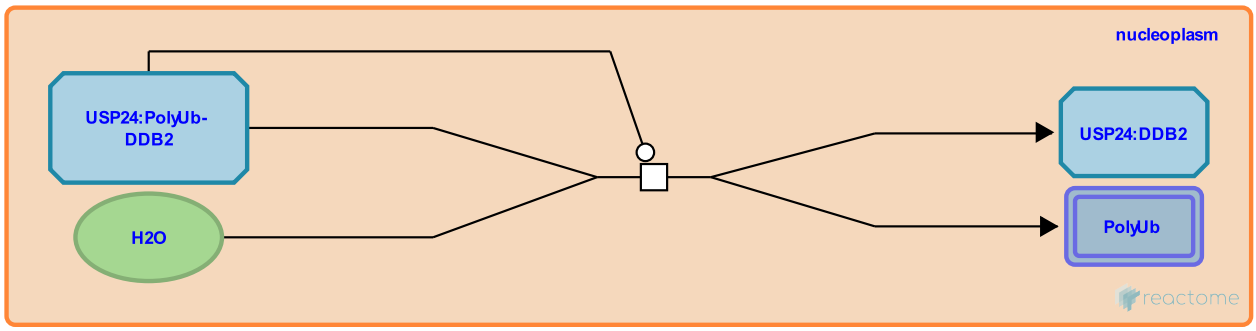
USP24 deubiquitinates DDB2 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5696997

Type: transition

Compartments: nucleoplasm



USP24 deubiquitinates DDB2, which is involved in the nucleotide excision repair pathway, preventing its proteasomal degradation (Zhang et al. 2012).

Literature references

Lubin, A., Zhang, L., Gong, F., Sun, Z., Chen, H. (2012). The deubiquitinating protein USP24 interacts with DDB2 and regulates DDB2 stability. *Cell Cycle, 11*, 4378-84. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

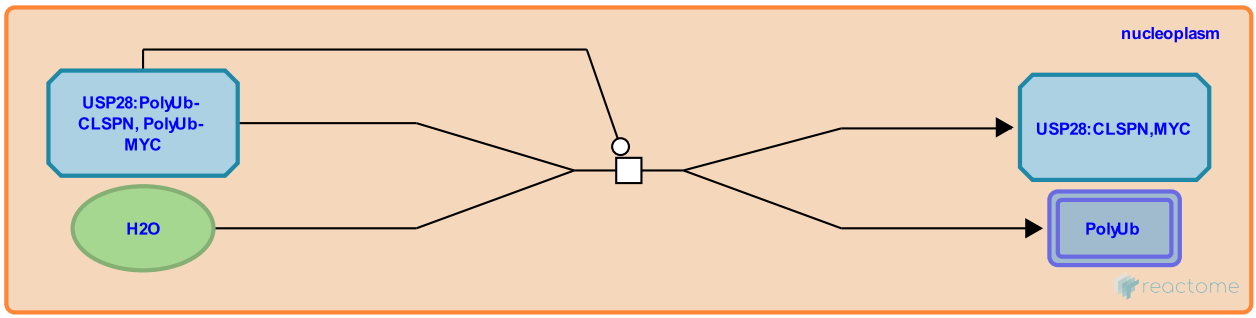
USP28 deubiquitinates CLSPN and MYC ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5696914

Type: transition

Compartments: nucleoplasm



USP28 is Involved in DNA damage induced apoptosis by specifically stabilizing and deubiquitinating proteins of the DNA damage pathway including CLSPN (Zhang et al. 2006). It also binds to the nucleoplasmic alpha isoform of Fbw7, counteracting FBW7 ubiquitin ligase activity by deubiquitinating MYC in the nucleoplasm, which reduces MYC proteasomal degradation (Popov et al. 2007).

Literature references

Elledge, SJ., Mak, TW., Zaugg, K., Zhang, D. (2006). A role for the deubiquitinating enzyme USP28 in control of the DNA-damage response. *Cell, 126*, 529-42. ↗

Popov, N., Schülein, C., Eilers, M., Llamazares, M., Herold, S. (2007). Fbw7 and Usp28 regulate myc protein stability in response to DNA damage. *Cell Cycle, 6*, 2327-31. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

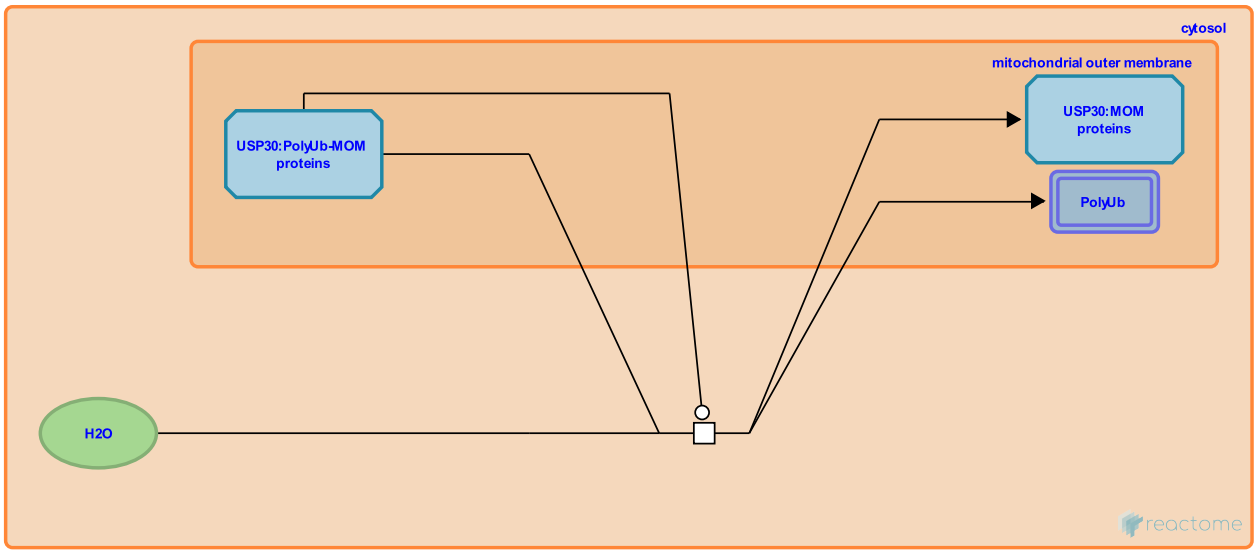
USP30 deubiquitinates Ub-MOM proteins ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5696872

Type: transition

Compartments: cytosol, mitochondrial outer membrane



USP30 is a deubiquitinating enzyme that associates with the mitochondrial outer membrane. RNAi depletion of USP30 induces elongated, interconnected mitochondria, suggesting that USP30 contributes to mitochondrial morphology (Nakamura & Hirose 2008). Overexpression of USP30 removes ubiquitin attached to damaged mitochondria by PARK2 (Parkin), preventing PARK2-induced mitophagy, whereas reducing USP30 enhances mitochondrial degradation in neurons. Multiple mitochondrial substrates were found to be oppositely regulated by PARK2 and USP30. Knockdown of USP30 rescues defective mitophagy caused by pathogenic mutations in parkin and improves mitochondrial integrity in parkin- or Pink1-deficient flies. Knockdown of Usp30 in dopaminergic neurons protects flies against paraquat toxicity in vivo, ameliorating defects in dopamine levels, motor function, and organismal survival (Bingol et al. 2014).

Literature references

Kirkpatrick, DS., Reichelt, M., Bingol, B., Song, Q., Sheng, M., Tea, JS. et al. (2014). The mitochondrial deubiquitinase USP30 opposes parkin-mediated mitophagy. *Nature, 510*, 370-5. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

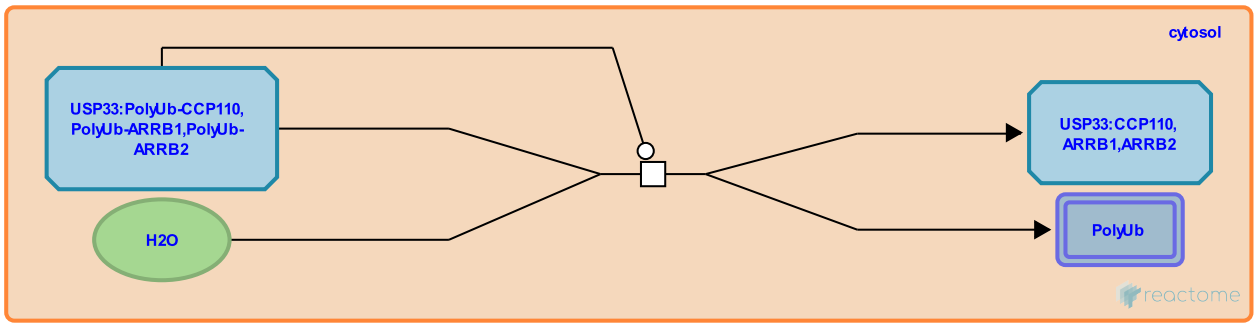
USP33 deubiquitinates CCP110,ARRB ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5696945

Type: transition

Compartments: cytosol



USP33 regulates centrosome duplication by mediating deubiquitination and stabilization of CCP110 in S and G2/M phase (Li et al. 2013) and regulates G-protein coupled receptor (GPCR) signaling by deubiquitinating beta-arrestins (ARRB1 and ARRB2) (Shenoy et al. 2009).

Literature references

Seeley, ES., Dynlacht, BD., Fu, W., Li, J., D'Angiolella, V., Kobayashi, T. et al. (2013). USP33 regulates centrosome biogenesis via deubiquitination of the centriolar protein CP110. *Nature, 495*, 255-9. ↗

Shenoy, SK., Ahn, S., Berthouze, M., Shukla, AK., Wilkinson, KD., Lefkowitz, RJ. et al. (2009). Beta-arrestin-dependent signaling and trafficking of 7-transmembrane receptors is reciprocally regulated by the deubiquitinase USP33 and the E3 ligase Mdm2. *Proc. Natl. Acad. Sci. U.S.A., 106*, 6650-5. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

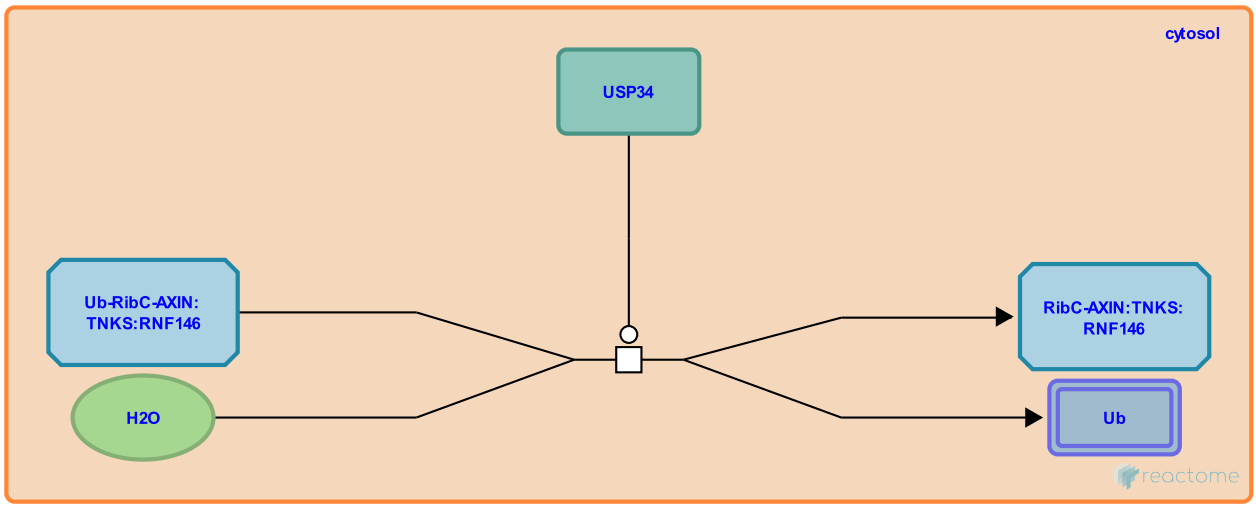
USP34 deubiquitinates AXIN1,AXIN2

Location: Ub-specific processing proteases

Stable identifier: R-HSA-3640872

Type: transition

Compartments: cytosol



UBP34 (also known as USP34) is a ubiquitin protease that co-precipitates in AXIN-containing complexes. In vitro studies show that the core domain of UBP34 is able to deubiquitinate AXIN purified from HEK293 transfected cells, and knockdown of UBP34 reduces AXIN1 protein levels in vivo. Treatment of UBP34-knockdown cells with the tankyrase inhibitor XAV939 reverses the degradation of AXIN, suggesting that the activity of UBP34 counteracts the tankyrase-dependent ubiquitination and degradation of AXIN. UBP34 plays a not-fully characterized role in the nuclear accumulation of AXIN, where AXIN is thought to positively regulate beta-catenin mediated transcription (Lui et al, 2011).

Literature references

Lacroix, C., Lui, TT., Leach, CA., Daulat, AM., Ahmed, SM., Angers, S. et al. (2011). The ubiquitin-specific protease USP34 regulates axin stability and Wnt/?-catenin signaling. *Mol. Cell. Biol., 31*, 2053-65.

Editions

2013-05-27	Authored	Rothfels, K.
2013-10-03	Edited	Gillespie, ME.
2014-01-22	Reviewed	Rajakulendran, N.
2014-02-15	Reviewed	van Amerongen, R.
2014-04-22	Reviewed	Kikuchi, A.

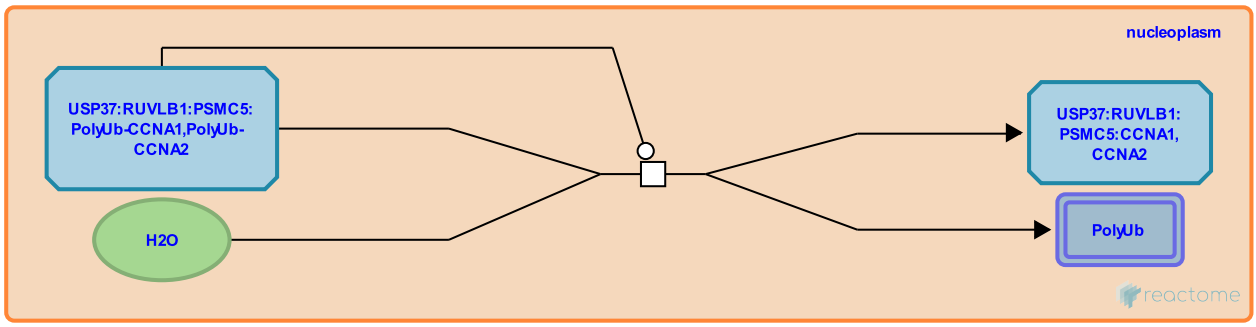
USP37:RUVLB1:PSMC5 deubiquitinates CCNA1,CCNA2 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5697009

Type: transition

Compartments: nucleoplasm



USP37 deubiquitinates Lys-11-linked polyubiquitin chains from cyclin-A (CCNA1 and CCNA2), which opposes the Lys-11-linked polyubiquitination mediated by the anaphase-promoting complex (APC/C) during G1/S transition, thereby promoting S phase entry. Phosphorylation by CDK2 at Ser-628 during G1/S phase maximizes USP37 deubiquitinase activity (Huang et al. 2011).

Literature references

Kirkpatrick, DS., Huang, X., Lill, JR., Lee, G., Summers, MK., Fang, G. et al. (2011). Deubiquitinase USP37 is activated by CDK2 to antagonize APC(CDH1) and promote S phase entry. *Mol. Cell, 42*, 511-23. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

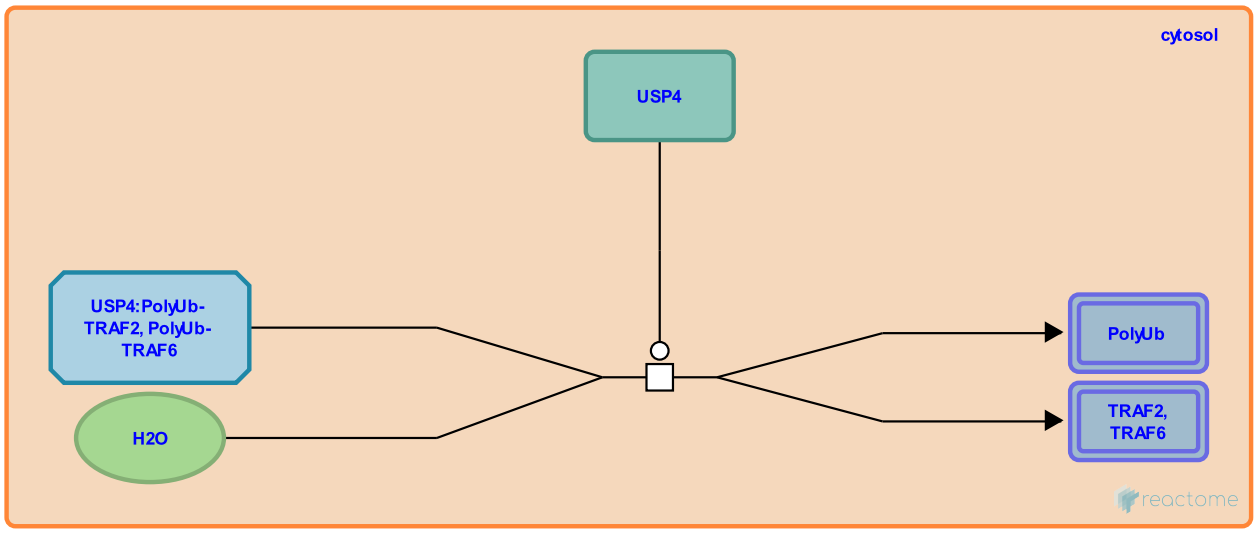
USP4 deubiquitinate TRAF2,TRAF6 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-8869456

Type: transition

Compartments: cytosol



USP4 specifically interacts with tumor necrosis factor (TNF) receptor-associated factor 2 (TRAF2) and TRAF6 but not TRAF3. It deubiquitinates both TRAF2 and TRAF6 in vivo and in vitro, negatively regulating TNFalpha and IL-1beta-induced NF-kappaB activation and cancer cell migration (Xiao et al. 2012). USP25, a negative regulator of the virus-triggered type I IFN signaling pathway, cleaves lysine 48- and lysine 63-linked polyubiquitin chains in vitro and in vivo from DDX58 (Retinoic acid-inducible gene I (RIG-I)), TRAF2, and TRAF6 to inhibit RIG-I-like receptor-mediated IFN signaling (Zhong et al. 2013).

Literature references

Wang, P., Li, H., Luo, J., Chen, H., Wang, R., Chen, J. et al. (2012). Ubiquitin-specific protease 4 (USP4) targets TRAF2 and TRAF6 for deubiquitination and inhibits TNFα-induced cancer cell migration. *Biochem. J., 441*, 979-86. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

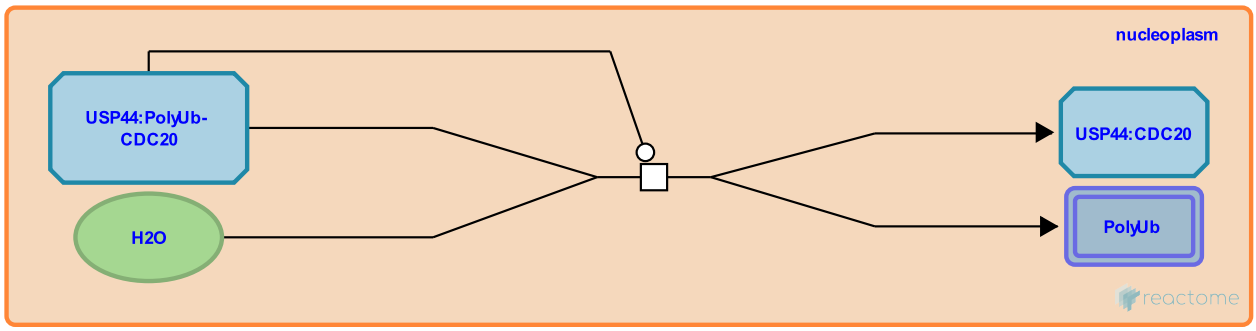
USP44 deubiquitinates CDC20 ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5696958

Type: transition

Compartments: nucleoplasm



USP44 specifically mediates the deubiquitination of CDC20, which promotes the association of MAD2L1 and CDC20, which in turn increases the stabilty of the MAD2L1-CDC20-APC/C ternary complex (Mitotic Checkpoint Complex), thereby preventing premature activation of the Anaphase Promoting Complex/Cyclosome (APC/C) (Stegmeier et al. 2007).

Literature references

Sowa, ME., Kirschner, MW., Rape, M., McDonald ER, 3rd., Sorger, PK., Li, MZ. et al. (2007). Anaphase initiation is regulated by antagonistic ubiquitination and deubiquitination activities. *Nature, 446*, 876-81. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

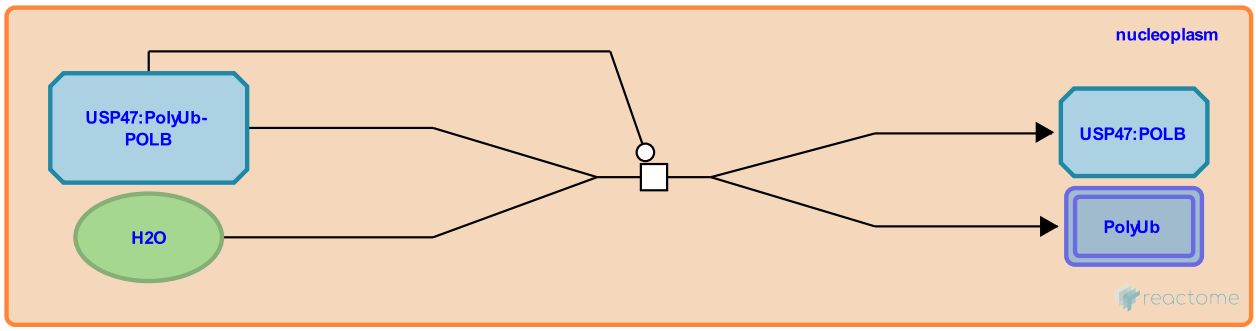
USP47 deubiquitinates POLB ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5696947

Type: transition

Compartments: nucleoplasm



USP47 specifically deubiquitinates monoubiquitinated DNA polymerase beta (POLB), increasing its stability and thereby playing a role in base-excision repair (Parsons et al. 2011).

Literature references

Kessler, BM., Edelmann, MJ., Dianov, GL., Parsons, JL., Khoronenkova, SV., Dianova, II. (2011). USP47 is a deubiquitylating enzyme that regulates base excision repair by controlling steady-state levels of DNA polymerase β. *Mol. Cell, 41*, 609-15. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

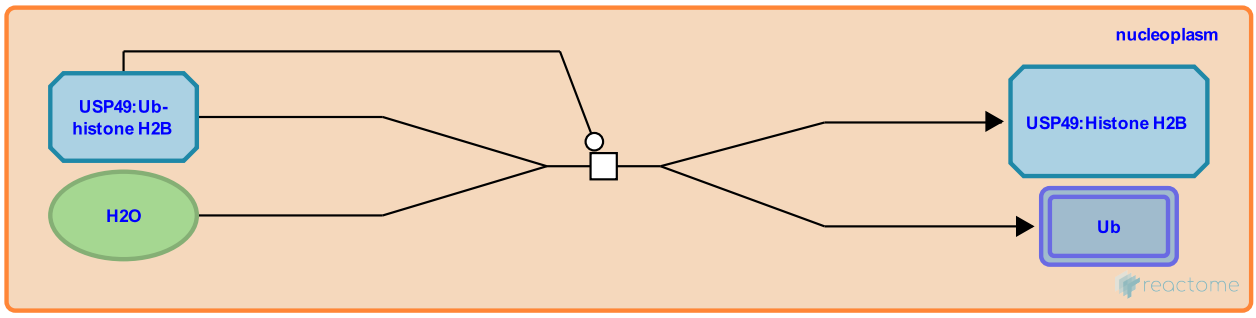
USP49 deubiquitinates H2B ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-5696960

Type: transition

Compartments: nucleoplasm



USP49 is a histone H2B-specific deubiquitinase that forms a complex with RuvB-like1 (RVB1) and PSMC5 (SUG1) (Zhang et al. 2013).

Literature references

Ma, L., Chen, S., Jones, A., Renfrow, M., Tempst, P., Joo, HY. et al. (2013). USP49 deubiquitinates histone H2B and regulates cotranscriptional pre-mRNA splicing. *Genes Dev., 27*, 1581-95. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

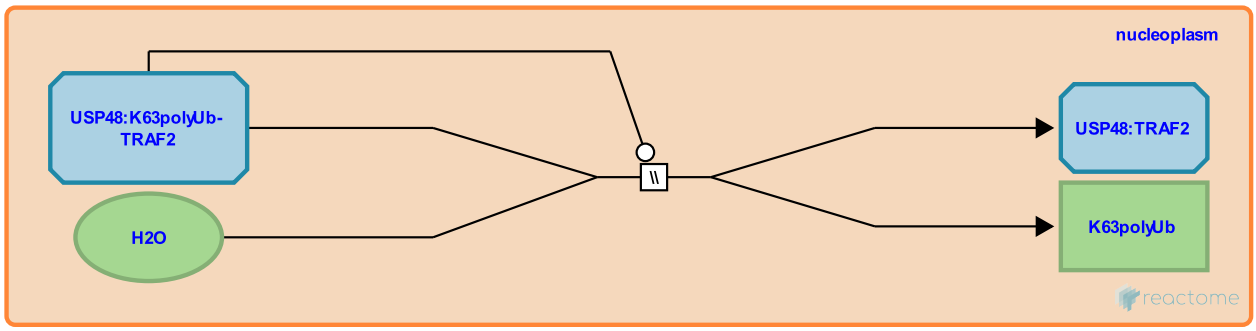
USP48 cleaves polyubiquitin ↗

Location: Ub-specific processing proteases

Stable identifier: R-HSA-8862184

Type: omitted

Compartments: nucleoplasm



USP48 (confusingly referred to as USP31 in some literature) is a deubiquitinating enzyme that cleaves preferentially lysine-63-linked polyubiquitin chains. USP48 can also cleave lysine-48-linked polyubiquitin chains albeit to a lesser extent. USP48 can interact with TRAF2, and overexpression of USP48 inhibits NF-?B activation suggesting that it may remove ubiquitin from TRAF2, TRAF6 or another essential intermediate that lies downstream of TRAFs.

Literature references

Kieff, E., Arsenakis, M., Hatzivassiliou, EG., Michailidou, G., Mosialos, G., Tzimas, C. (2006). Human ubiquitin specific protease 31 is a deubiquitinating enzyme implicated in activation of nuclear factor-kappaB. *Cell. Signal., 18,* 83-92. ↗

Editions

2015-04-16	Authored	Jupe, S.
2016-05-05	Edited	Jupe, S.
2016-05-16	Reviewed	Meldal, BH.

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