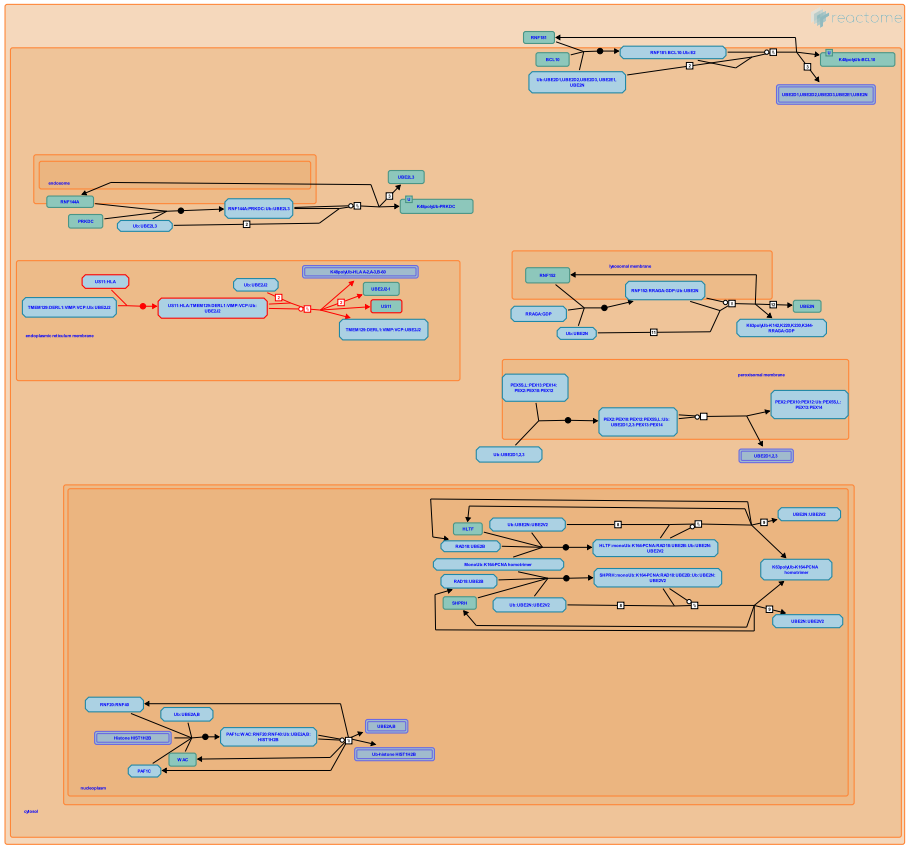
E3 ubiquitin ligases ubiquitinate target proteins



Azevedo, JE., Cimprich, KA., Deng, L., Fransen, M., Lehner, PJ., Lin, WC., May, B., Myung, K., Pomerantz, JL., Van Veldhoven, PP., Yu, X., Zhu, B., van den Boomen, DJ.

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

This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

02/05/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

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

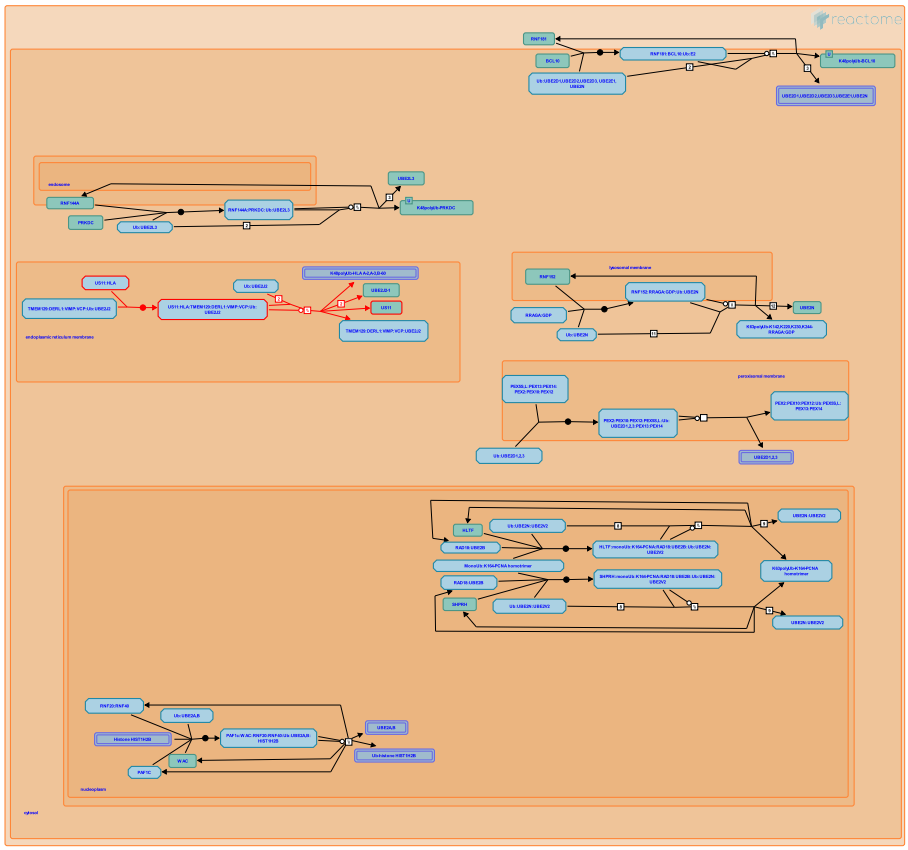
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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

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

E3 ubiquitin ligases ubiquitinate target proteins ↗

Stable identifier: R-HSA-8866654



E3 ubiquitin ligases catalyze the transfer of an ubiquitin from an E2-ubiquitin conjugate to a target protein. Generally, ubiquitin is transferred via formation of an amide bond to a particular lysine residue of the target protein, but ubiquitylation of cysteine, serine and threonine residues in a few targeted proteins has also been demonstrated (reviewed in McDowell and Philpott 2013, Berndsen and Wolberger 2014). Based on protein homologies, families of E3 ubiquitin ligases have been identified that include RING-type ligases (reviewed in Deshaies et al. 2009, Metzger et al. 2012, Metzger et al. 2014), HECT-type ligases (reviewed in Rotin et al. 2009, Metzger et al. 2012), and RBR-type ligases (reviewed in Dove et al. 2016). A subset of the RING-type ligases participate in CULLIN-RING ligase complexes (CRLs which include SCF complexes, reviewed in Lee and Zhou 2007, Genschik et al. 2013, Skaar et al. 2013, Lee et al. 2014).
Some E3-E2 combinations catalyze mono-ubiquitination of the target protein (reviewed in Nakagawa and Nakayama 2015). Other E3-E2 combinations catalyze conjugation of further ubiquitin monomers to the initial ubiquitin, forming polyubiquitin chains. (It may also be possible for some E3-E2 combinations to preassemble polyubiquitin and transfer it as a unit to the target protein.) Ubiquitin contains several lysine (K) residues and a free alpha amino group to which further ubiquitin can be conjugated. Thus different types of polyubiquitin are possible: K11 linked polyubiquitin is observed in endoplasmic reticulum-associated degradation (ERAD), K29 linked polyubiquitin is observed in lysosomal degradation, K48 linked polyubiquitin directs target proteins to the proteasome for degradation, whereas K63 linked polyubiquitin generally acts as a scaffold to recruit other proteins in several cellular processes, notably DNA repair (reviewed in Komander et al. 2009).

Literature references

Lee, J., Zhou, P. (2007). DCAFs, the missing link of the CUL4-DDB1 ubiquitin ligase. *Mol Cell, 26*, 775-80. ↗

Lechner, E., Sumara, I., Genschik, P. (2013). The emerging family of CULLIN3-RING ubiquitin ligases (CRL3s): cellular functions and disease implications. *EMBO J., 32*, 2307-20. ↗

Klevit, RE., Rittinger, K., Dove, KK., Stieglitz, B., Duncan, ED. (2016). Molecular insights into RBR E3 ligase ubiquitin transfer mechanisms. *EMBO Rep., 17*, 1221-35. ↗

Wolberger, C., Berndsen, CE. (2014). New insights into ubiquitin E3 ligase mechanism. *Nat. Struct. Mol. Biol., 21*, 301-7. ↗

Komander, D. (2009). The emerging complexity of protein ubiquitination. *Biochem. Soc. Trans., 37*, 937-53. ↗

Editions

2016-04-02	Authored, Edited	May, B.
2016-11-03	Reviewed	Azevedo, JE.

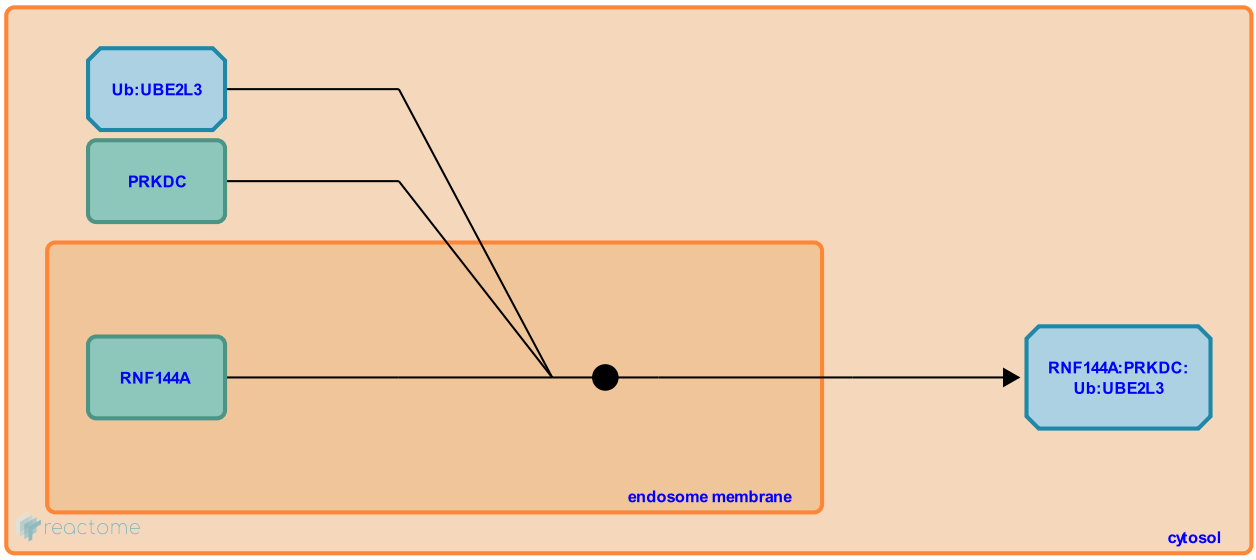
RNF144A binds PRKDC and Ubiquitin:UBE2L3 ↗

Location: E3 ubiquitin ligases ubiquitinate target proteins

Stable identifier: R-HSA-8938770

Type: binding

Compartments: endosome membrane, cytosol



The ubiquitin E3 ligase RNF144A located on endosomal membranes (Ho et al. 2015) binds the catalytic subunit of DNA-dependent protein kinase (PRKDC, DNA-PKcs) and the E2-ubiquitin conjugate UBE2L3:Ubiquitin (UBCH7:Ubiquitin) located in the cytoplasm (Ho et al. 2014).

Followed by: RNF144A polyubiquitinates PRKDC

Literature references

Lin, WC., Mahanic, CS., Ho, SR., Lee, YJ. (2014). RNF144A, an E3 ubiquitin ligase for DNA-PKcs, promotes apoptosis during DNA damage. *Proc. Natl. Acad. Sci. U.S.A., 111*, E2646-55. ↗

Lin, WC., Ho, SR., Lee, YJ. (2015). Regulation of RNF144A E3 Ubiquitin Ligase Activity by Self-association through Its Transmembrane Domain. *J. Biol. Chem., 290*, 23026-38. ↗

Editions

2016-09-11	Authored, Edited	May, B.
2016-10-18	Reviewed	Lin, WC.

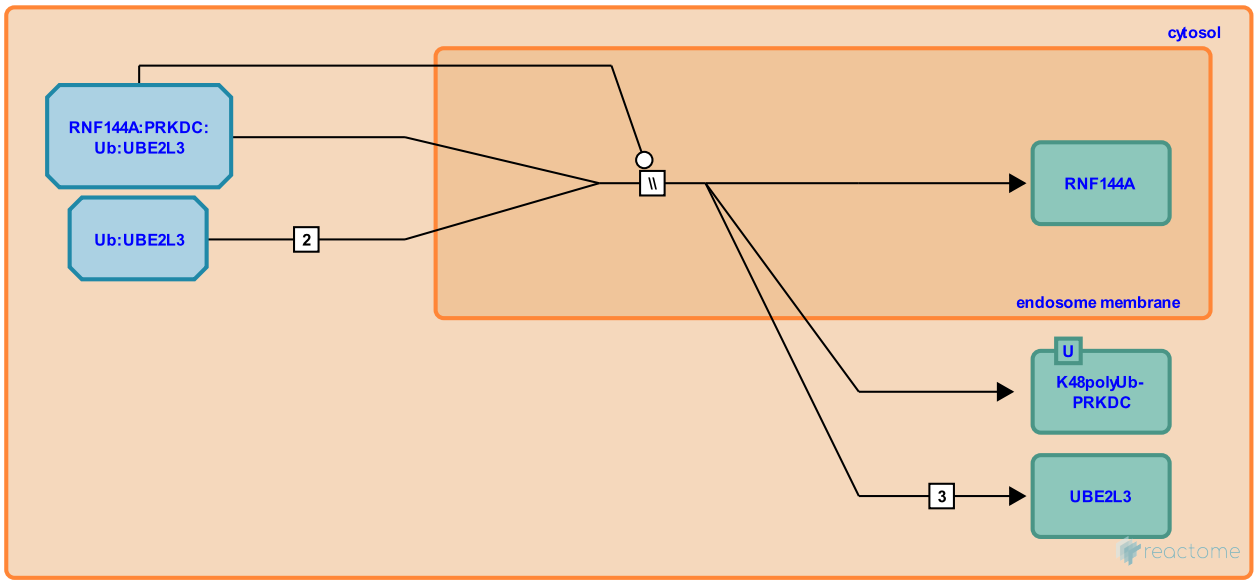
RNF144A polyubiquitinates PRKDC ↗

Location: E3 ubiquitin ligases ubiquitinate target proteins

Stable identifier: R-HSA-8938773

Type: omitted

Compartments: endosome membrane, cytosol



The ubiquitin E3 ligase RNF144A transfers ubiquitin from the E2-ubiquitin conjugate UBE2L3:Ubiquitin to an unknown residue of PRKDC (DNA-PKcs, the catalytic subunit of DNA-dependent protein kinase) (Ho et al. 2014). RNF144A polyubiquitinates PRKDC with lysine-48 linked ubiquitin, leading to proteasomal degradation of PRKDC. Expression of RNF144A is activated by TP53 (p53) and the degradation of PRKDC caused by RNF144A may be pro-apoptotic (Ho et al. 2014). RNF144A contains a transmembrane domain that localizes RNF144A to endosomal membranes (Ho et al. 2015).

Preceded by: RNF144A binds PRKDC and Ubiquitin:UBE2L3

Literature references

Lin, WC., Mahanic, CS., Ho, SR., Lee, YJ. (2014). RNF144A, an E3 ubiquitin ligase for DNA-PKcs, promotes apoptosis during DNA damage. *Proc. Natl. Acad. Sci. U.S.A., 111,* E2646-55. ↗

Lin, WC., Ho, SR., Lee, YJ. (2015). Regulation of RNF144A E3 Ubiquitin Ligase Activity by Self-association through Its Transmembrane Domain. *J. Biol. Chem., 290,* 23026-38. ↗

Editions

2016-09-11	Authored, Edited	May, B.
2016-10-18	Reviewed	Lin, WC.

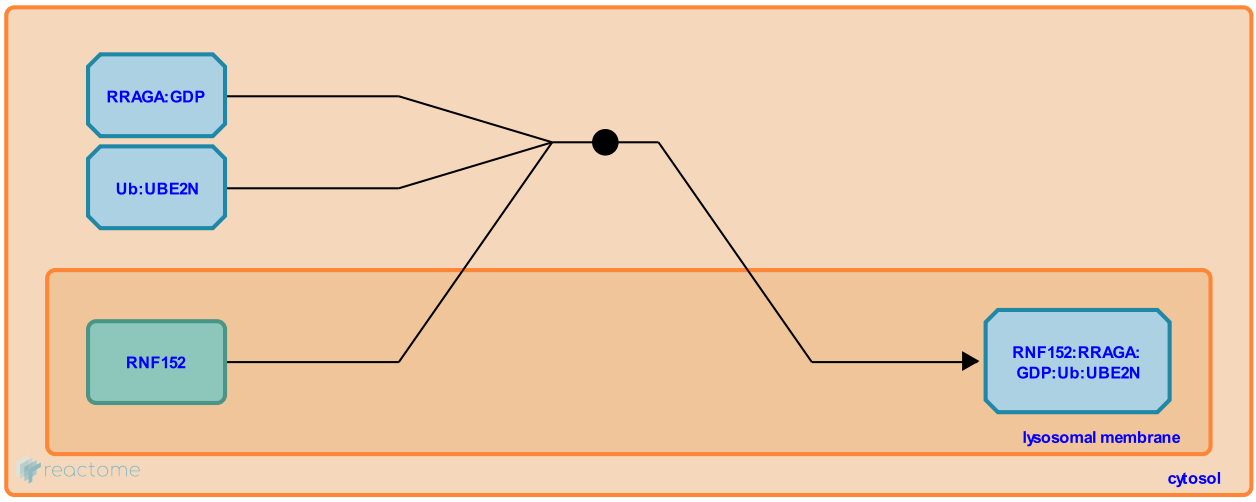
RNF152 binds RRAGA:GDP and Ubiquitin:UBE2D3 ↗

Location: E3 ubiquitin ligases ubiquitinate target proteins

Stable identifier: R-HSA-8938829

Type: binding

Compartments: cytosol, lysosomal membrane



The ubiquitin E3 ligase RNF152 located in the lysosomal membrane (Zhang et al. 2010) binds GDP-bound RRAGA and the E2-ubiquitin conjugate UBE2N:Ubiquitin prior to ubiquitinating RRAGA (Deng et al. 2015), RNF152, like many E3 ligases, can also autoubiquitinate (Zhang et al. 2010).

Followed by: RNF152 polyubiquitinates RRAGA

Literature references

Wu, W., Zheng, J., Tang, H., Wu, Y., Suo, T., Zhang, S. et al. (2010). RNF152, a novel lysosome localized E3 ligase with pro-apoptotic activities. *Protein Cell, 1*, 656-63. ↗

Chen, L., Li, D., Jin, J., Chen, M., Xu, Y., Wang, P. et al. (2015). The ubiquitination of rag A GTPase by RNF152 negatively regulates mTORC1 activation. *Mol. Cell, 58*, 804-18. ↗

Editions

2016-09-11	Authored, Edited	May, B.
2016-10-19	Reviewed	Deng, L.

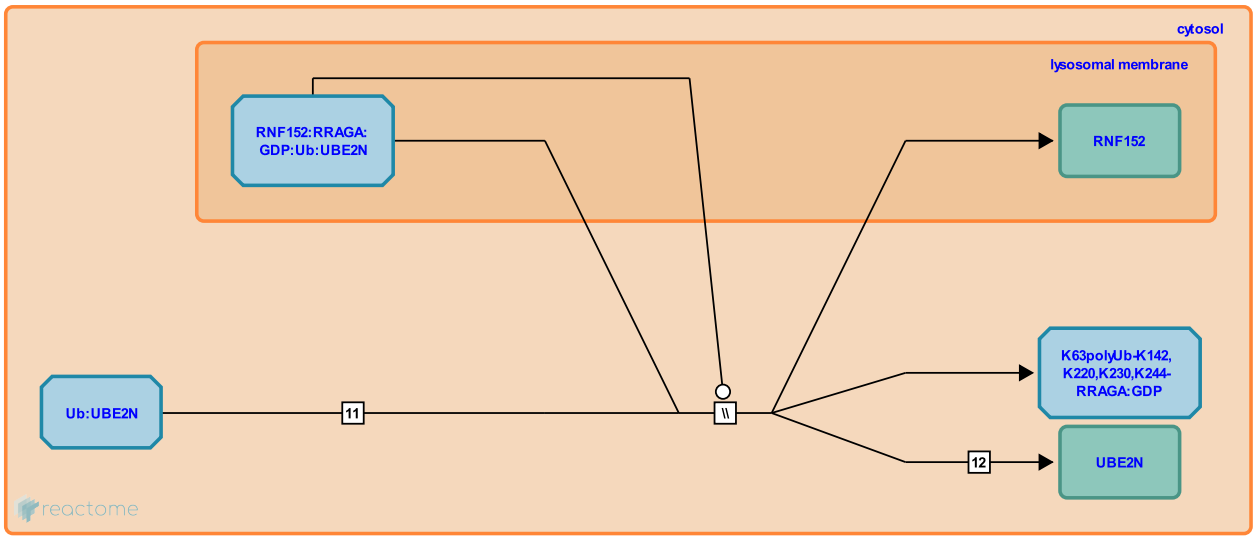
RNF152 polyubiquitinates RRAGA ↗

Location: E3 ubiquitin ligases ubiquitinate target proteins

Stable identifier: R-HSA-8938815

Type: omitted

Compartments: cytosol, lysosomal membrane



When the cellular concentration of amino acids is low, the ubiquitin E3 ligase RNF152 (Zhang et al. 2010) transfers ubiquitin from the E2-ubiquitin conjugate UBE2N:Ubiquitin to RRAGA (RagA GTPase) (Deng et al. 2015). RNF152 polyubiquitinates RRAGA with lysine-63 linked ubiquitin, which recruits GATOR1, an inhibitor of RRAGA. The inhibition of RRAGA, in turn, inhibits mTORC1 thereby regulating activity of mTORC1 in response to amino acids (Deng et al. 2015). RNF152 is located in the lysosomal membrane and can autoubiquitinate (Zhang et al. 2010).

Preceded by: RNF152 binds RRAGA:GDP and Ubiquitin:UBE2D3

Literature references

Wu, W., Zheng, J., Tang, H., Wu, Y., Suo, T., Zhang, S. et al. (2010). RNF152, a novel lysosome localized E3 ligase with pro-apoptotic activities. *Protein Cell, 1*, 656-63. ↗

Chen, L., Li, D., Jin, J., Chen, M., Xu, Y., Wang, P. et al. (2015). The ubiquitination of rag A GTPase by RNF152 negatively regulates mTORC1 activation. *Mol. Cell, 58*, 804-18. ↗

Editions

2016-09-11	Authored, Edited	May, B.
2016-10-19	Reviewed	Deng, L.

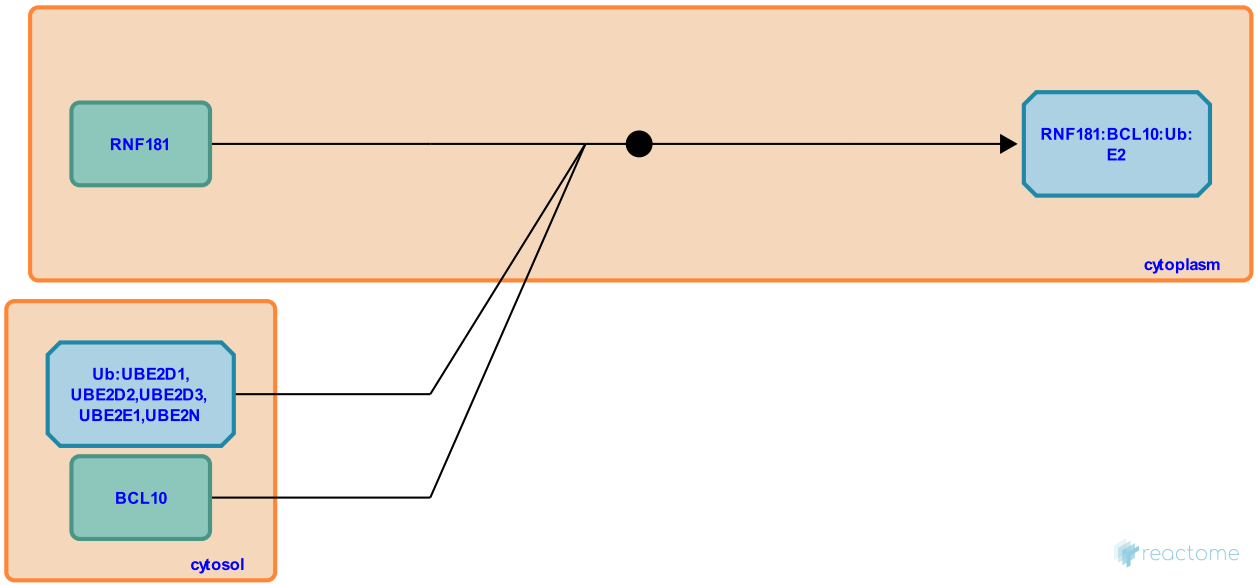
RNF181 binds BCL10 and Ubiquitin:E2 ↗

Location: E3 ubiquitin ligases ubiquitinate target proteins

Stable identifier: R-HSA-8939323

Type: binding

Compartments: cytoplasm



The ubiquitin E3 ligase RNF181 interacts with activated (phosphorylated) CARD11, BCL10, and the E2-ubiquitin conjugate (UBE2D1, UBE2D2, UBE2D3, UBE2B, UBE2E1, or UBE2N) (Pedersen et al. 2015).

Followed by: RNF181 polyubiquinates BCL10

Literature references

Pomerantz, JL., Mackie, dS., Chan, W., Pedersen, SM., Jattani, RP. (2016). Negative Regulation of CARD11 Signaling and Lymphoma Cell Survival by the E3 Ubiquitin Ligase RNF181. *Mol. Cell. Biol., 36*, 794-808. ↗

Editions

2016-09-17	Authored, Edited	May, B.
2016-10-18	Reviewed	Pomerantz, JL.

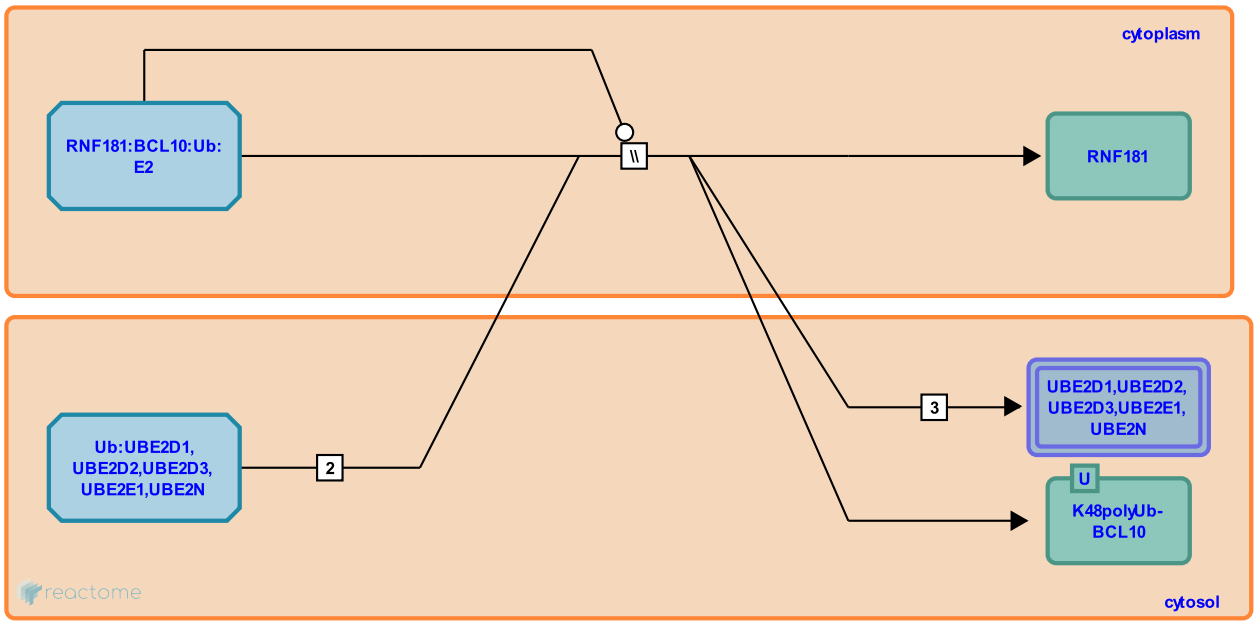
RNF181 polyubiquinates BCL10 ↗

Location: E3 ubiquitin ligases ubiquitinate target proteins

Stable identifier: R-HSA-8939335

Type: omitted

Compartments: cytoplasm



The ubiquitin E3 ligase RNF181 transfers ubiquitin from the E2-ubiquitin conjugate (UBE2D1, UBE2D2, UBE2D3, UBE2E1, UBE2B, or UBE2N) to BCL10 (Pedersen et al. 2015). RNF181, which can interact with CARD11, appears to act on BCL10 before BCL10 is recruited to activated (phosphorylated) CARD11. The resulting lysine-48 polyubiquitinated BCL10 is degraded by the proteasome, resulting in attenuation of T cell receptor signaling downstream of CARD11 (Pedersen et al. 2015).

Preceded by: RNF181 binds BCL10 and Ubiquitin:E2

Literature references

Pomerantz, JL., Mackie, dS., Chan, W., Pedersen, SM., Jattani, RP. (2016). Negative Regulation of CARD11 Signaling and Lymphoma Cell Survival by the E3 Ubiquitin Ligase RNF181. *Mol. Cell. Biol., 36*, 794-808. ↗

Editions

2016-09-17	Authored, Edited	May, B.
2016-10-18	Reviewed	Pomerantz, JL.

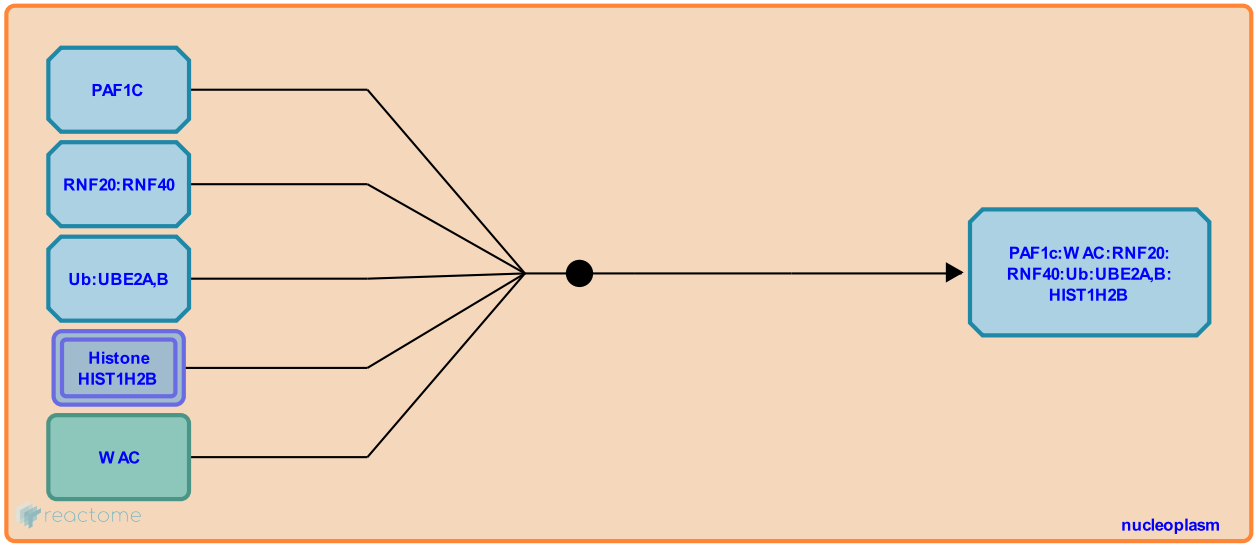
RNF20:RNF40 binds PAF complex, Ubiquitin:UBE2A,B (Ubiquitin:RAD6), WAC and Histone H2B ↗

Location: E3 ubiquitin ligases ubiquitinate target proteins

Stable identifier: R-HSA-8942099

Type: binding

Compartments: nucleoplasm



The ubiquitin E3 ligase complex RNF20:RNF40 (also known as Bre1 in Saccharomyces cerevisiae) interacts with the PAF complex and the E2-ubiquitin conjugate UBE2A,B:Ubiquitin (RAD6:Ubiquitin in Saccharomyces cerevisiae) (Zhu et al. 2005, Kim et al. 2009, Hahn et al. 2012, Foglizzo et al. 2016). The complex binds nucleosomal histone H2B after which RNF20:RNF40 monoubiquitinates histone H2B (Zhu et al. 2005, Kim et al. 2009). RNF20:RNF40 also binds WAC, which targets RNF20:RNF40 to the RNA polymerase II complex and promotes monoubiquitination of histone H2B (Zhang and Yu 2011).

Followed by: RNF20:RNF40 monoubiquitinates Histone H2B

Literature references

Kim, J., Shilatifard, A., Tang, Z., Roeder, RG., Guermah, M., Milne, TA. et al. (2009). RAD6-Mediated transcription-coupled H2B ubiquitylation directly stimulates H3K4 methylation in human cells. *Cell, 137*, 459-71. ↗

Pham, AD., Zheng, Y., Reinberg, D., Mandal, SS., Tempst, P., Erdjument-Bromage, H. et al. (2005). Monoubiquitination of human histone H2B: the factors involved and their roles in HOX gene regulation. *Mol. Cell, 20*, 601-11. ↗

Marsh, DJ., Jackson, S., Clarkson, A., Dickson, KA., Gill, AJ., Hahn, MA. (2012). The tumor suppressor CDC73 interacts with the ring finger proteins RNF20 and RNF40 and is required for the maintenance of histone 2B monoubiquitination. *Hum. Mol. Genet., 21*, 559-68. ↗

Yu, X., Zhang, F. (2011). WAC, a functional partner of RNF20/40, regulates histone H2B ubiquitination and gene transcription. *Mol. Cell, 41*, 384-97. ↗

Foglizzo, M., Day, CL., Middleton, AJ. (2016). Structure and Function of the RING Domains of RNF20 and RNF40, Dimeric E3 Ligases that Monoubiquitylate Histone H2B. *J. Mol. Biol., 428*, 4073-4086. ↗

Editions

2016-10-02	Authored, Edited	May, B.
2016-10-18	Edited, Reviewed	Yu, X.
2017-01-11	Edited, Reviewed	Zhu, B.

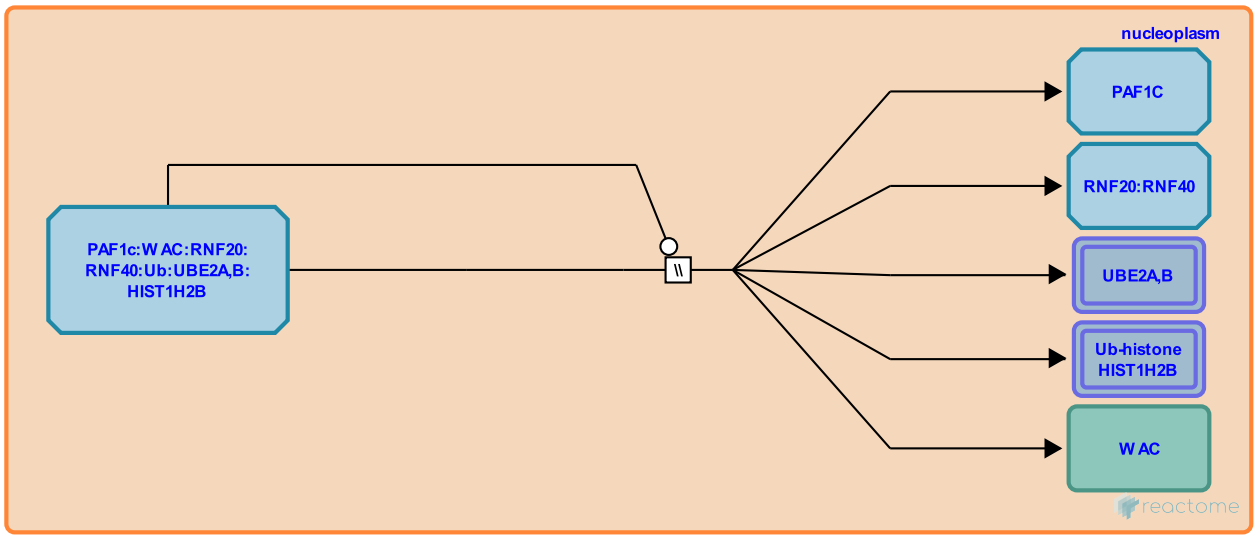
RNF20:RNF40 monoubiquitinates Histone H2B ↗

Location: E3 ubiquitin ligases ubiquitinate target proteins

Stable identifier: R-HSA-8942101

Type: omitted

Compartments: nucleoplasm



The ubiquitin E3 ligase complex RNF20:RNF40 interacts with the PAF complex (Kim et al. 2009) that is associated with RNA polymerase II via WAC (Zhang and Yu 2011) at transcriptionally active genes (Zhe et al. 2005). RNF20:RNF40 monoubiquitinates nucleosomal histone H2B on lysine-120 (lysine-121 of the unprocessed histone H2B) using UBE2A,B:Ubiquitin as the ubiquitin donor (Zhu et al. 2005, Kim et al. 2009, Zhang and Yu 2011, Zhang et al. 2014, Dickson et al. 2016). Monoubiquitination of histone H2B leads to methylation of lysine-4 and lysine-79 of histone H3, marks of active chromatin (Zhu et al. 2005). Arsenite binds the RING domains of RNF20 and RNF40 and inhibits the ubiquitination of histone H2B (Zhang et al. 2014).

Preceded by: RNF20:RNF40 binds PAF complex, Ubiquitin:UBE2A,B (Ubiquitin:RAD6), WAC and Histone H2B

Literature references

Kim, J., Shilatifard, A., Tang, Z., Roeder, RG., Guermah, M., Milne, TA. et al. (2009). RAD6-Mediated transcription-coupled H2B ubiquitylation directly stimulates H3K4 methylation in human cells. *Cell, 137*, 459-71. ↗

Pham, AD., Zheng, Y., Reinberg, D., Mandal, SS., Tempst, P., Erdjument-Bromage, H. et al. (2005). Monoubiquitination of human histone H2B: the factors involved and their roles in HOX gene regulation. *Mol. Cell, 20*, 601-11. ↗

Chou, A., Cole, AJ., Clarkson, A., Kennedy, CJ., Dickson, KA., Gill, AJ. et al. (2016). The RING finger domain E3 ubiquitin ligases BRCA1 and the RNF20/RNF40 complex in global loss of the chromatin mark histone H2B monoubiquitination (H2Bub1) in cell line models and primary high-grade serous ovarian cancer. *Hum. Mol. Genet.*. ↗

Dai, X., Zhang, F., Wang, P., Cai, Q., Song, J., Wang, Y. et al. (2014). Arsenite binds to the RING finger domains of RNF20-RNF40 histone E3 ubiquitin ligase and inhibits DNA double-strand break repair. *J. Am. Chem. Soc., 136*, 12884-7. ↗

Yu, X., Zhang, F. (2011). WAC, a functional partner of RNF20/40, regulates histone H2B ubiquitination and gene transcription. *Mol. Cell, 41*, 384-97. ↗

Editions

2016-10-02	Authored, Edited	May, B.
2016-10-18	Reviewed	Yu, X.
2017-01-11	Reviewed	Zhu, B.

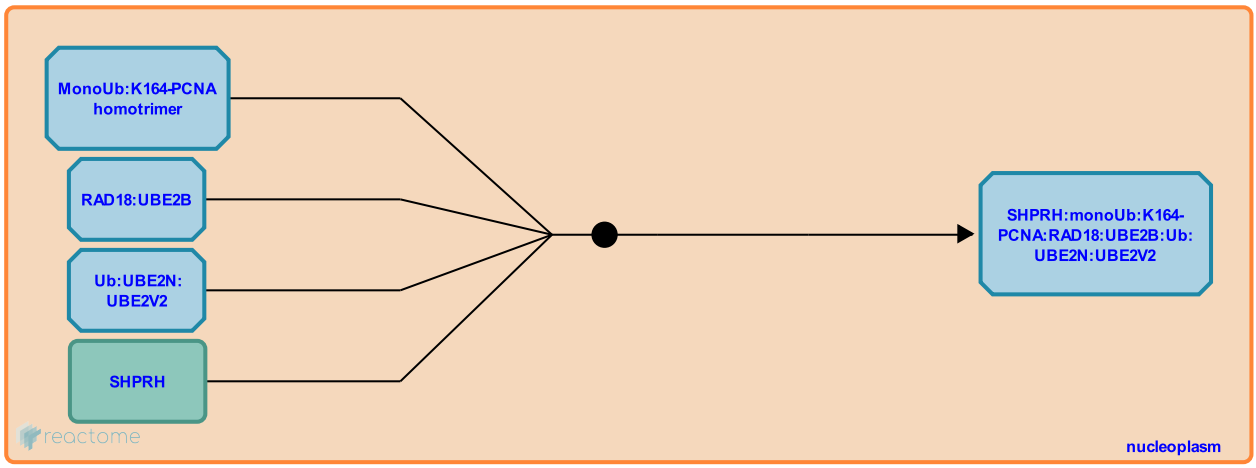
SHPRH binds monoUb-K164-PCNA, RAD6:RAD18, UBE2V2:Ub:UBE2N ↗

Location: E3 ubiquitin ligases ubiquitinate target proteins

Stable identifier: R-HSA-8943007

Type: binding

Compartments: nucleoplasm



At stalled replication forks, the E3 ubiquitin ligase SHPRH interacts with PCNA monoubiquitinated at lysine-164 (monoUb-K164-PCNA), the RAD18:UBE2B complex (RAD18:RAD6 complex), and the Ub:UBE2N:UBE2V2 complex (UBC13:MMS2 complex with ubiquitin conjugated to UBC13) (Unk et al. 2006, Motegi et al. 2006, Motegi et al. 2008).

Followed by: SHPRH polyubiquitinates monoubiquitinated PCNA

Literature references

Roest, HP., Ding, H., Motegi, A., Myung, K., Markowitz, SD., Wu, X. et al. (2008). Polyubiquitination of proliferating cell nuclear antigen by HLTF and SHPRH prevents genomic instability from stalled replication forks. *Proc. Natl. Acad. Sci. U.S.A., 105*, 12411-6. ↗

Haracska, L., Hurwitz, J., Blastyák, A., Bermudez, V., Prakash, L., Fatyol, K. et al. (2006). Human SHPRH is a ubiquitin ligase for Mms2-Ubc13-dependent polyubiquitylation of proliferating cell nuclear antigen. *Proc. Natl. Acad. Sci. U.S.A., 103*, 18107-12. ↗

Motegi, A., Myung, K., Markowitz, SD., Sood, R., Liu, PP., Moinova, H. (2006). Human SHPRH suppresses genomic instability through proliferating cell nuclear antigen polyubiquitination. *J. Cell Biol., 175*, 703-8. ↗

Editions

2016-10-22	Authored, Edited	May, B.
2017-01-11	Edited, Reviewed	Myung, K.

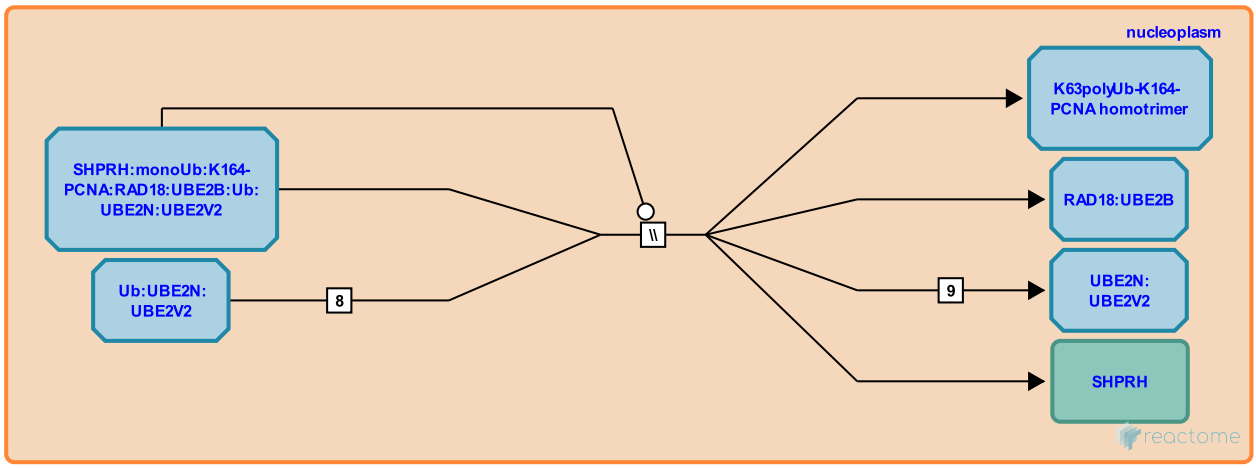
SHPRH polyubiquitinates monoubiquitinated PCNA ↗

Location: E3 ubiquitin ligases ubiquitinate target proteins

Stable identifier: R-HSA-8943003

Type: omitted

Compartments: nucleoplasm



In response to a stalled replication fork, SHPRH polyubiquitinates lysine-164 of PCNA that has already been monoubiquitinated on lysine-164 by RAD18:UBE2B (RAD18:RAD6) (Unk et al. 2006, Motegi et al. 2006, Motegi et al. 2008). The ubiquitin donor is the E2 complex UBE2N:UBE2V2 (UBC13:MMS2) containing ubiquitin conjugated to UBE2N. The resulting polyubiquitin chain contains lysine-63 (K63) linkages and appears to change the repair process from translesion synthesis (TLS) to template switching (TS). SHPRH interacts directly with PCNA, RAD18:UBE2B, and UBE2N:UBE2V2.

Preceded by: SHPRH binds monoUb-K164-PCNA, RAD6:RAD18, UBE2V2:Ub:UBE2N

Literature references

Roest, HP., Ding, H., Motegi, A., Myung, K., Markowitz, SD., Wu, X. et al. (2008). Polyubiquitination of proliferating cell nuclear antigen by HLTF and SHPRH prevents genomic instability from stalled replication forks. *Proc. Natl. Acad. Sci. U.S.A., 105*, 12411-6. ↗

Haracska, L., Hurwitz, J., Blastyák, A., Bermudez, V., Prakash, L., Fatyol, K. et al. (2006). Human SHPRH is a ubiquitin ligase for Mms2-Ubc13-dependent polyubiquitylation of proliferating cell nuclear antigen. *Proc. Natl. Acad. Sci. U.S.A., 103*, 18107-12. ↗

Motegi, A., Myung, K., Markowitz, SD., Sood, R., Liu, PP., Moinova, H. (2006). Human SHPRH suppresses genomic instability through proliferating cell nuclear antigen polyubiquitination. *J. Cell Biol., 175*, 703-8. ↗

Editions

2016-10-22	Authored, Edited	May, B.
2017-01-11	Edited, Reviewed	Myung, K.

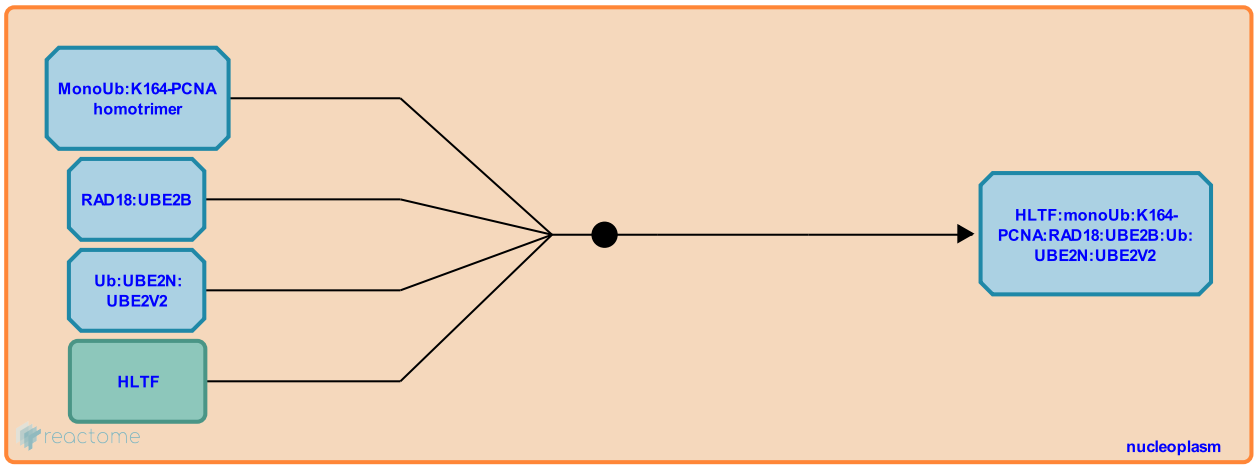
HLTF binds monoUb-K164-PCNA, RAD6:RAD18, UBE2V2:Ub:UBE2N

Location: E3 ubiquitin ligases ubiquitinate target proteins

Stable identifier: R-HSA-8943041

Type: binding

Compartments: nucleoplasm



At stalled replication forks, the E3 ubiquitin ligase HLTF interacts with PCNA monoubiquitinated at lysine-164 (monoUb-K164-PCNA), the RAD18:UBE2B complex (RAD18:RAD6 complex), and the Ub:UBE2N:UBE2V2 complex (UBC13:MMS2 complex with ubiquitin conjugated to UBC13) (Unk et al. 2008, Motegi et al. 2008, MacKay et al. 2009).

Followed by: HLTF polyubiquitinates monoubiquitinated PCNA

Literature references

Roest, HP., Ding, H., Motegi, A., Myung, K., Markowitz, SD., Wu, X. et al. (2008). Polyubiquitination of proliferating cell nuclear antigen by HLTF and SHPRH prevents genomic instability from stalled replication forks. *Proc. Natl. Acad. Sci. U.S.A., 105*, 12411-6.

Toth, R., Rouse, J., MacKay, C. (2009). Biochemical characterisation of the SWI/SNF family member HLTF. *Biochem. Biophys. Res. Commun., 390*, 187-91.

Haracska, L., Hurwitz, J., Prakash, L., Fatyol, K., Yoon, JH., Hajdu, I. et al. (2008). Human HLTF functions as a ubiquitin ligase for proliferating cell nuclear antigen polyubiquitination. *Proc. Natl. Acad. Sci. U.S.A., 105*, 3768-73.

Editions

2016-10-22	Authored, Edited	May, B.
2017-01-11	Edited, Reviewed	Myung, K.

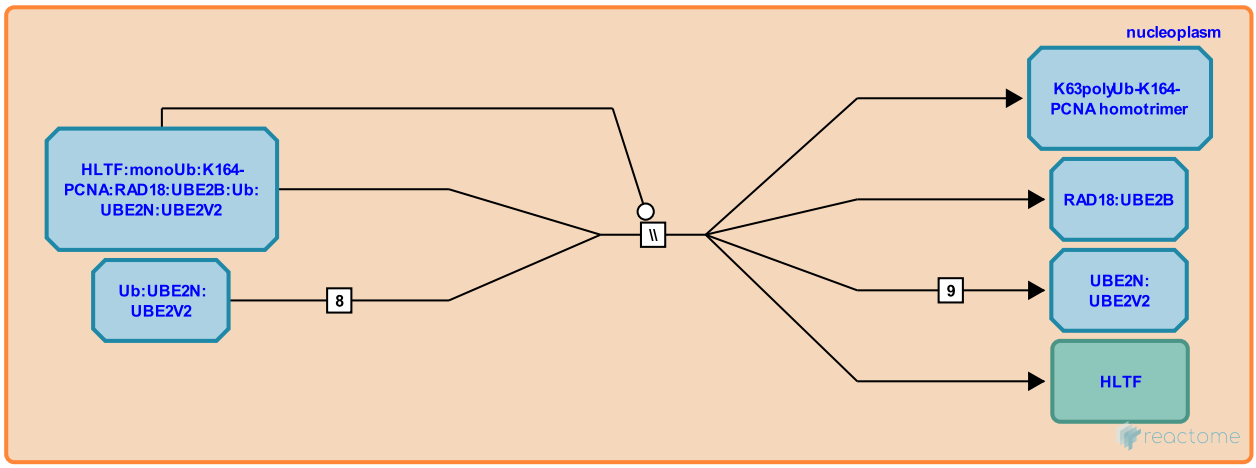
HLTF polyubiquitinates monoubiquitinated PCNA ↗

Location: E3 ubiquitin ligases ubiquitinate target proteins

Stable identifier: R-HSA-8943040

Type: omitted

Compartments: nucleoplasm



In response to a stalled replication fork, HLTF polyubiquitinates lysine-164 of PCNA that has already been monoubiquitinated on lysine-164 by RAD18:UBE2B (RAD18:RAD6) (Unk et al. 2008, Motegi et al. 2008, MacKay et al. 2009, Achar et al. 2015). The ubiquitin donor is the E2 complex UBE2N:UBE2V2 (UBC13:MMS2) containing ubiquitin conjugated to UBE2N. The resulting polyubiquitin chain contains lysine-63 (K63) linkages and appears to change the repair process from translesion synthesis (TLS) to template switching (TS). HLTF interacts directly with PCNA, RAD18:UBE2B, and UBE2N:UBE2V2. HLTF and SHPRH are not completely redundant: HLTF is involved in repair of DNA lesions created by ultraviolet light while SHPRH is involved in repair of lesions created by methylmethane sulfonate (Lin et al. 2011). Despite the polyubiquitination activity of HLTF, in vivo HLTF appears to increase monoubiquitination of PCNA (Lin et al. 2011).

Preceded by: HLTF binds monoUb-K164-PCNA, RAD6:RAD18, UBE2V2:Ub:UBE2N

Literature references

Chen, JY., Zeman, MK., Yee, MC., Cimprich, KA., Lin, JR. (2011). SHPRH and HLTF act in a damage-specific manner to coordinate different forms of postreplication repair and prevent mutagenesis. *Mol. Cell, 42*, 237-49. ↗

Roest, HP., Ding, H., Motegi, A., Myung, K., Markowitz, SD., Wu, X. et al. (2008). Polyubiquitination of proliferating cell nuclear antigen by HLTF and SHPRH prevents genomic instability from stalled replication forks. *Proc. Natl. Acad. Sci. U.S.A., 105*, 12411-6. ↗

Toth, R., Rouse, J., MacKay, C. (2009). Biochemical characterisation of the SWI/SNF family member HLTF. *Biochem. Biophys. Res. Commun., 390*, 187-91. ↗

Haracska, L., Venclovas, Č., Gali, H., Balogh, D., Neculai, D., Dhe-Paganon, S. et al. (2015). Human HLTF mediates postreplication repair by its HIRAN domain-dependent replication fork remodelling. *Nucleic Acids Res., 43*, 10277-91. ↗

Haracska, L., Hurwitz, J., Prakash, L., Fatyol, K., Yoon, JH., Hajdu, I. et al. (2008). Human HLTF functions as a ubiquitin ligase for proliferating cell nuclear antigen polyubiquitination. *Proc. Natl. Acad. Sci. U.S.A., 105*, 3768-73. ↗

Editions

2016-10-22	Authored, Edited	May, B.
2017-01-11	Edited, Reviewed	Myung, K.
2017-02-12	Reviewed	Cimprich, KA.

US11:HLA binds DERL1:TMEM129:Ub:UBE2J2,UBE2K:VIMP:VCP ↗

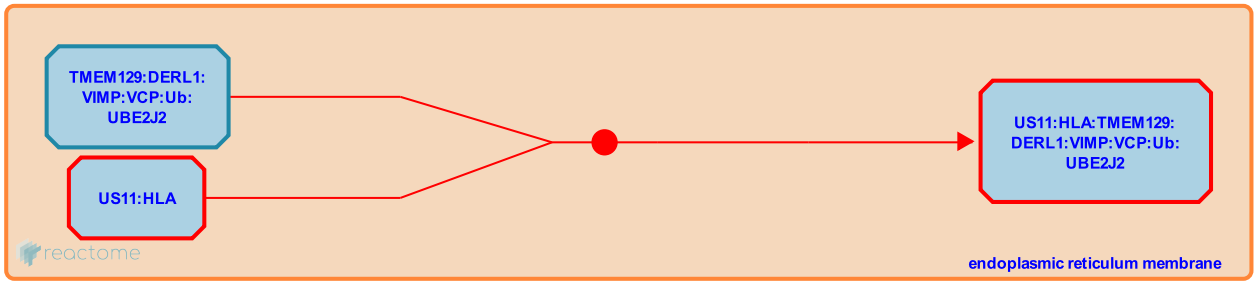
Location: E3 ubiquitin ligases ubiquitinate target proteins

Stable identifier: R-HSA-8943083

Type: binding

Compartments: endoplasmic reticulum membrane

Diseases: human cytomegalovirus infection



The human cytomegalovirus US11 protein interacts with a MHC class I heavy chain and recruits the heavy chain to the TMEM129 E3 ubiquitin ligase complex comprising TMEM129, its cognate E2 conjugases UBE2J2 and UBE2K, and the VCP complex (VCP:VIMP) via the rhomboid pseudo-protease DERL1 (van de Weijer et al. 2014, van den Boomen et al. 2014, Flierman 2006, Lilley et al. 2004, Ye et al. 2004, Ye et al. 2001).

Literature references

Nathan, JA., Dougan, G., Stagg, HR., Skødt, K., Timms, RT., van den Boomen, DJ. et al. (2014). TMEM129 is a Derlin-1 associated ERAD E3 ligase essential for virus-induced degradation of MHC-I. *Proc. Natl. Acad. Sci. U.S.A., 111*, 11425-30. ↗

Lilley, BN., Ploegh, HL. (2004). A membrane protein required for dislocation of misfolded proteins from the ER. *Nature, 429*, 834-40. ↗

Coleman, CS., Rapoport, TA., Pickart, CM., Flierman, D., Chau, V. (2006). E2-25K mediates US11-triggered retrotranslocation of MHC class I heavy chains in a permeabilized cell system. *Proc. Natl. Acad. Sci. U.S.A., 103*, 11589-94. ↗

van de Weijer, ML., Hoelen, H., Lebbink, RJ., Voorburg, CM., Chen, S., Ressing, ME. et al. (2014). A high-coverage shRNA screen identifies TMEM129 as an E3 ligase involved in ER-associated protein degradation. *Nat Commun, 5*, 3832. ↗

Meyer, HH., Ye, Y., Rapoport, TA. (2001). The AAA ATPase Cdc48/p97 and its partners transport proteins from the ER into the cytosol. *Nature, 414*, 652-6. ↗

Editions

2016-10-24	Authored, Edited	May, B.
2017-01-12	Edited, Reviewed	Lehner, PJ.
2017-01-12	Edited, Reviewed	van den Boomen, DJ.

TMEM129 polyubiquitinates HLA (MHC class I heavy chain) bound to cytomegalovirus US11 ↗

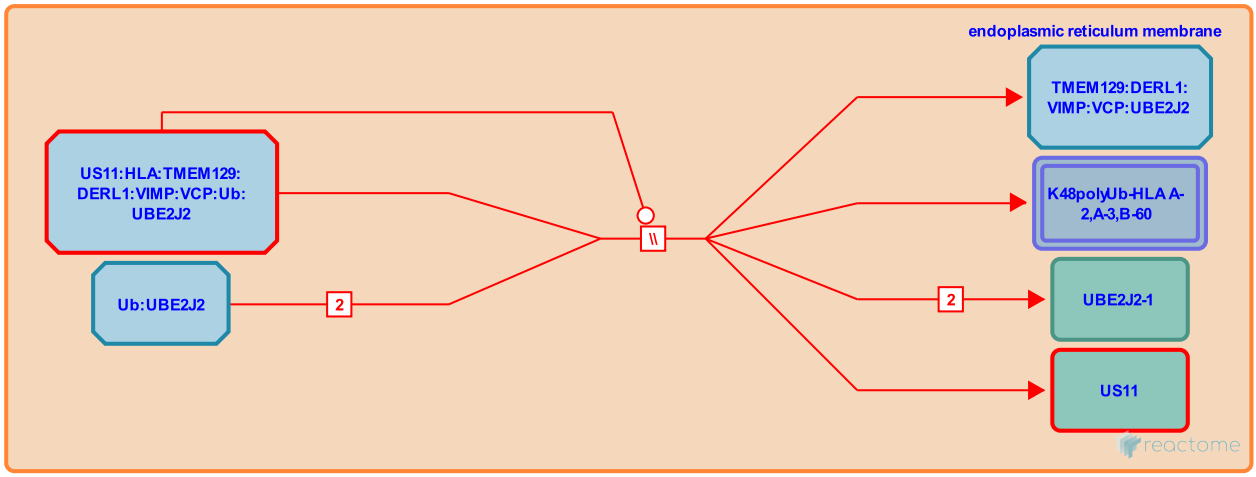
Location: E3 ubiquitin ligases ubiquitinate target proteins

Stable identifier: R-HSA-8943080

Type: omitted

Compartments: endoplasmic reticulum membrane

Diseases: human cytomegalovirus infection



The E3 ubiquitin ligase TMEM129 transfers ubiquitin from the E2 ubiquitin conjugases UBE2J2 and UBE2K to a MHC class I heavy chain bound by the human cytomegalovirus US11 protein (van de Weijer et al. 2014, van den Boomen et al. 2014, Flierman et al. 2006, reviewed in van den Boomen and Lehner 2015). TMEM129 is located in the endoplasmic reticulum membrane in a complex containing DERL1, UBE2J2 and UBE2K, VIMP and VCP. After polyubiquitination, MHC class I heavy chain is retrotranslocated by the AAA ATPase VCP to the cytosol (Ye et al. 2001) where it is deglycosylated by NGLYI and degraded by the proteasome (Wiertz et al. 1996). US11 is released after the reaction and, if unable to bind another MHC I heavy chain, US11 is ubiquitinated by the HRD1-SEL1L E3 ubiquitin ligase complex and itself degraded by the proteasome (van den Boomen et al. 2014). This self-regulatory loop allows the amount of US11 in the cell to be buffered against the amount of MHC I molecules.

Literature references

Nathan, JA., Dougan, G., Stagg, HR., Skødt, K., Timms, RT., van den Boomen, DJ. et al. (2014). TMEM129 is a Derlin-1 associated ERAD E3 ligase essential for virus-induced degradation of MHC-I. *Proc. Natl. Acad. Sci. U.S.A., 111*, 11425-30. ↗

Lilley, BN., Ploegh, HL. (2004). A membrane protein required for dislocation of misfolded proteins from the ER. *Nature, 429*, 834-40. ↗

Sun, L., Ploegh, HL., Bogyo, M., Wiertz, EJ., Geuze, HJ., Jones, TR. (1996). The human cytomegalovirus US11 gene product dislocates MHC class I heavy chains from the endoplasmic reticulum to the cytosol. *Cell, 84*, 769-79. ↗

van de Weijer, ML., Hoelen, H., Lebbink, RJ., Voorburg, CM., Chen, S., Ressing, ME. et al. (2014). A high-coverage shRNA screen identifies TMEM129 as an E3 ligase involved in ER-associated protein degradation. *Nat Commun, 5*, 3832. ↗

Meyer, HH., Ye, Y., Rapoport, TA. (2001). The AAA ATPase Cdc48/p97 and its partners transport proteins from the ER into the cytosol. *Nature, 414*, 652-6. ↗

Editions

2016-10-24	Authored, Edited	May, B.
2017-01-12	Edited, Reviewed	Lehner, PJ.
2017-01-12	Edited, Reviewed	van den Boomen, DJ.

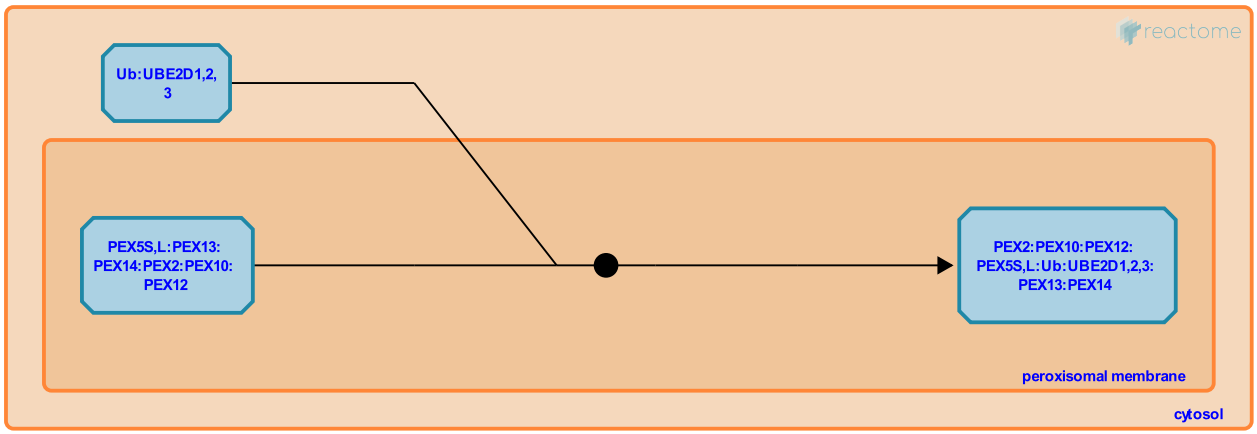
PEX2:PEX10:PEX12 binds PEX5S,L (in PEX5S:PEX13:PEX14) and Ub:UBE2D1,2,3 ↗

Location: E3 ubiquitin ligases ubiquitinate target proteins

Stable identifier: R-HSA-8953917

Type: binding

Compartments: peroxisomal membrane



A RING E3 ubiquitin ligase complex containing PEX10, PEX12, and PEX2 ubiquitinates PEX5L. The PEX2:PEX10:PEX12 complex is believed to bind an activated E2-ubiquitin conjugate (one of Ub:UBE2D1, Ub:UBE2D2, Ub:UBE2D3) and PEX5L in a complex that also contains PEX13 and PEX14 (Chang et al. 1999, Carvalho et al. 2007, Grou et al. 2008, Grou et al. 2009, Okumoto et al. 2011). The short isoform of PEX5, PEX5S, is inferred to undergo the same reaction.

Followed by: PEX2:PEX10:PEX12 monoubiquitinates PEX5S,L at cysteine-11

Literature references

Gould, SJ., Chang, CC., Warren, DS., Sacksteder, KA. (1999). PEX12 interacts with PEX5 and PEX10 and acts downstream of receptor docking in peroxisomal matrix protein import. *J. Cell Biol., 147*, 761-74. ↗

Wiese, S., Sá-Miranda, C., Piechura, H., Grou, CP., Meyer, HE., Carvalho, AF. et al. (2008). Members of the E2D (UbcH5) family mediate the ubiquitination of the conserved cysteine of Pex5p, the peroxisomal import receptor. *J. Biol. Chem., 283*, 14190-7. ↗

Huybrechts, SJ., Sá-Miranda, C., Grou, CP., Carvalho, AF., Azevedo, JE., Pinto, MP. et al. (2009). Properties of the ubiquitin-pex5p thiol ester conjugate. *J. Biol. Chem., 284*, 10504-13. ↗

Miyata, N., Mukai, S., Okumoto, K., Misono, S., Matsumoto, Y., Fujiki, Y. (2011). Cysteine ubiquitination of PTS1 receptor Pex5p regulates Pex5p recycling. *Traffic, 12*, 1067-83. ↗

Sá-Miranda, C., Grou, CP., Carvalho, AF., Alencastre, IS., Azevedo, JE., Pinto, MP. et al. (2007). Ubiquitination of mammalian Pex5p, the peroxisomal import receptor. *J. Biol. Chem., 282*, 31267-72. ↗

Editions

2017-01-01	Authored, Edited	May, B.
2018-02-13	Reviewed	Van Veldhoven, PP., Fransen, M.
2018-03-12	Reviewed	Azevedo, JE.

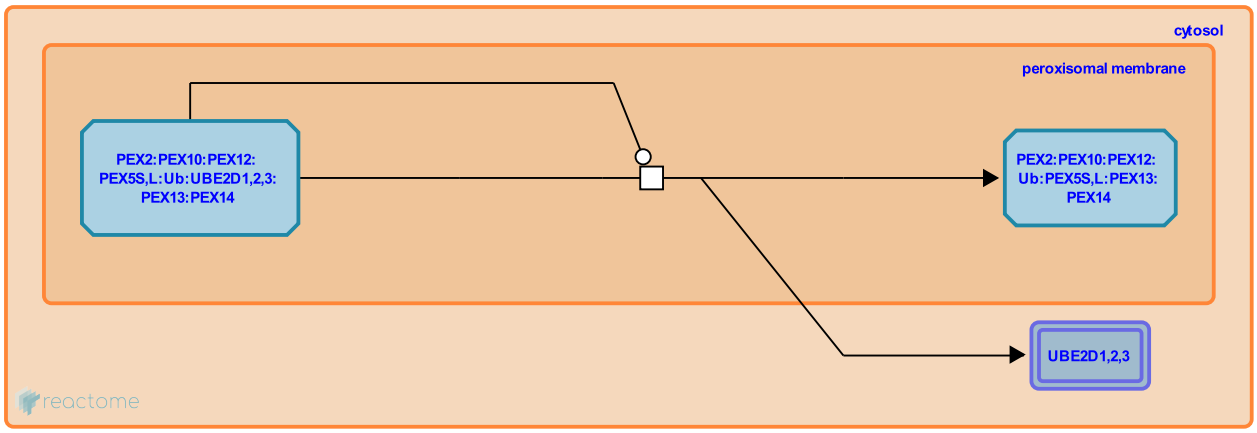
PEX2:PEX10:PEX12 monoubiquitinates PEX5S,L at cysteine-11 ↗

Location: E3 ubiquitin ligases ubiquitinate target proteins

Stable identifier: R-HSA-8953946

Type: transition

Compartments: peroxisomal membrane



The RING-type E3 ubiquitin ligase sub-complex PEX2:PEX10:PEX12 catalyzes the transfer of ubiquitin from an E2-ubiquitin conjugate (one of Ub:UBE2D1, Ub:UBE2D2, or Ub:UBE2D3) to the cysteine-11 residue of the substrate PEX5L, the peroxisomal matrix protein shuttling receptor (Carvalho et al. 2007; Grou et al. 2008, Okumoto et al. 2011, Sargent et al. 2016, inferred from yeast in Dodt and Gould 1996). The thiol ester bond between ubiquitin and the cysteine residue of PEX5 is unusual among ubiquitin substrates, which usually have isopeptide bonds between ubiquitin and a lysine residue. Monoubiquitination of PEX5 at cysteine-11 is an integral and mandatory step in the PEX5-mediated peroxisomal protein transport pathway; in its absence, PEX5 cannot be extracted from the peroxisomal membrane docking/translocation machinery (the peroxisomal protein translocon), and thus transport of newly synthesized peroxisomal matrix proteins to the organelle matrix stops (Grou et al. 2009). In addition to monoubiquitinating PEX5 during peroxisomal protein import, the PEX2:PEX10:PEX12 complex has also been implicated in pexophagy, a type of selective autophagy targeting peroxisomes. Pexophagy seems to be triggered mainly by ubiquitination of PEX5, which, in this case, can occur either at its cysteine-11 or lysine-209 residues, but ubiquitination of ABCD3 (also known as PMP70) and other peroxisomal membrane proteins may also be involved (Zhang et al. 2015, inferred from mouse in Nordgren et al. 2015, Sargent et al. 2016).

Preceded by: PEX2:PEX10:PEX12 binds PEX5S,L (in PEX5S:PEX13:PEX14) and Ub:UBE2D1,2,3

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Gould, SJ., Dodt, G. (1996). Multiple PEX genes are required for proper subcellular distribution and stability of Pex5p, the PTS1 receptor: evidence that PTS1 protein import is mediated by a cycling receptor. *J. Cell Biol., 135*, 1763-74. ↗

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Wiese, S., Sá-Miranda, C., Piechura, H., Grou, CP., Meyer, HE., Carvalho, AF. et al. (2008). Members of the E2D (UbcH5) family mediate the ubiquitination of the conserved cysteine of Pex5p, the peroxisomal import receptor. *J. Biol. Chem., 283*, 14190-7. ↗

Okumoto, K., Noda, H., Fujiki, Y. (2014). Distinct modes of ubiquitination of peroxisome-targeting signal type 1 (PTS1) receptor Pex5p regulate PTS1 protein import. *J. Biol. Chem., 289*, 14089-108. ↗

Di Giovanni, V., Zhang, L., Sargent, G., van Zutphen, T., Kim, PK., Shatseva, T. et al. (2016). PEX2 is the E3 ubiquitin ligase required for pexophagy during starvation. *J. Cell Biol., 214*, 677-90. ↗

Editions

2017-01-01	Authored, Edited	May, B.
2018-02-13	Reviewed	Van Veldhoven, PP., Fransen, M.
2018-03-12	Reviewed	Azevedo, JE.

Table of Contents