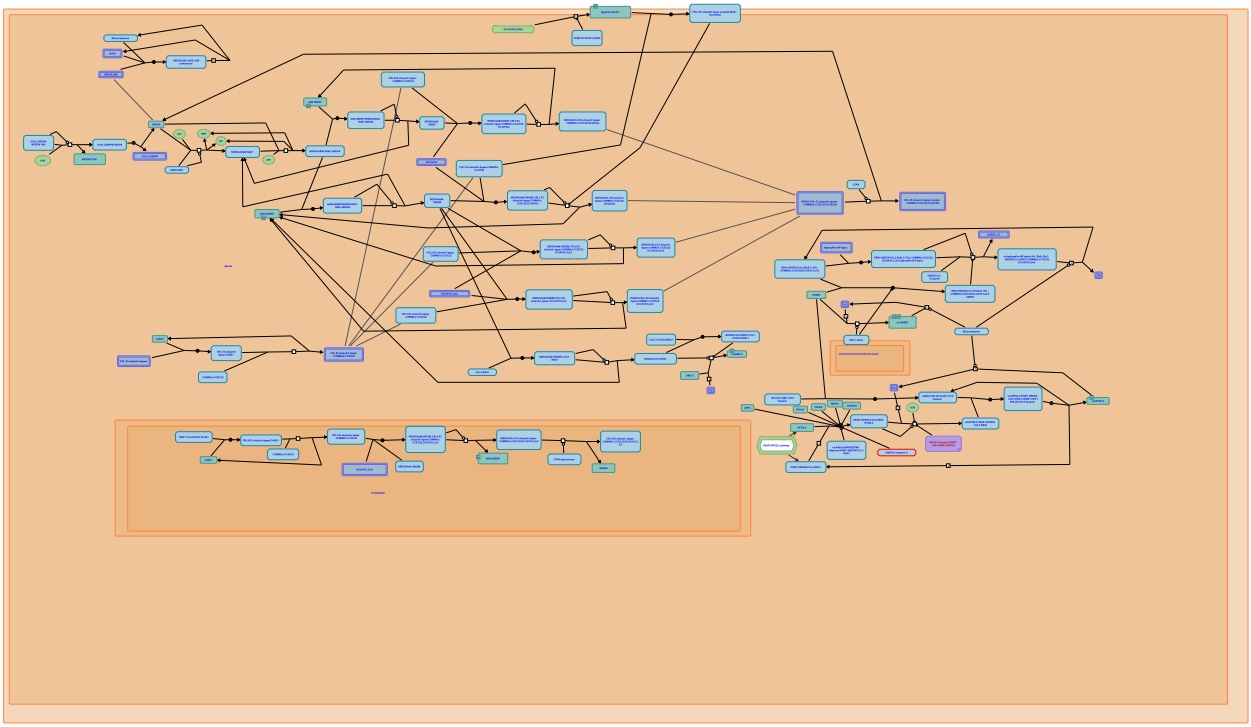
Neddylation



Cuadrado, A., Garapati, P V., Jupe, S., Meldal, BH., Pick, E., Rothfels, K., Somers, J.

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

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. ↗

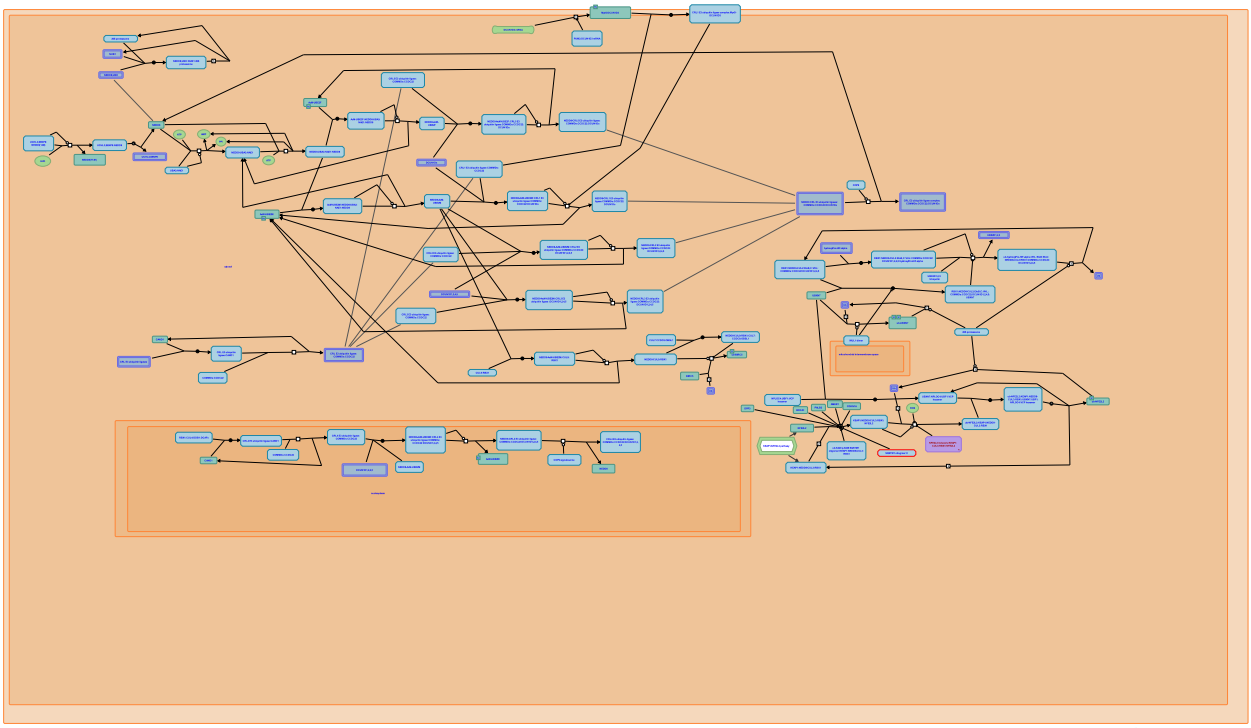
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Neddylation ↗

Stable identifier: R-HSA-8951664



NEDD8 is a small ubiquitin-like molecule that is conjugated to substrate proteins through an E1 to E3 enzyme cascade similar to that for ubiquitin. The best characterized target of neddylation is the cullin scaffold subunit of cullin-RING E3 ubiquitin ligases (CRLs), which themselves target numerous cellular proteins for degradation by the proteasome (Hori et al, 1999; reviewed in Soucy et al, 2010; Lyedeard et al, 2013). The multisubunit CRL complexes are compositionally diverse, but each contains a scaffolding cullin protein (CUL1, 2, 3, 4A, 4B, 5, 7 or 9) and a RING box-containing E3 ligase subunit RBX, along with other adaptor and substrate-interacting subunits. RBX2 (also known as RNF7) interacts preferentially with CUL5, while RBX1 is the primary E3 for most other cullin family members (reviewed in Mahon et al, 2014). Neddylation of the cullin subunit increases the ubiquitination activity of the CRL complex (Podust et al, 2000; Read et al, 2000; Wu et al, 2000; Kawakami et al, 2001; Ohh et al, 2002; Yu et al, 2015). In addition to CRL complexes, a number of other less-well characterized NEDD8 targets have been identified. These include other E3 ubiquitin ligases such as SMURF1 and MDM2, receptor tyrosine kinases such as EGFR and TGF beta RII, and proteins that contribute to transcriptional regulation, among others (Xie et al, 2014; Watson et al, 2010; Oved et al, 2006; Zuo et al, 2013; Xirodimas et al, 2004; Singh et al, 2007; Abida et al, 2007; Liu et al 2010; Watson et al, 2006; Loftus et al, 2012; Aoki et al, 2013; reviewed in Enchev et al, 2015).

Like ubiquitin, NEDD8 undergoes post-translational processing to generate the mature form. UCHL3- or SENP8-mediated proteolysis removes the C-terminal 5 amino acids of NEDD8, generating a novel C-terminal glycine residue for conjugation to the cysteine residues in the E1, E2 enzymes or lysine residues in the substrate protein, usually the E3 NEDD8 ligase itself (Wada et al, 1998; reviewed in Enchev et al, 2015). Most substrates in vivo appear to be singly neddylated on one or more lysine residues, but NEDD8 chains have been formed on cullin substrates in vitro and on histone H4 in cultured human cells after DNA damage (Jones et al, 2008; Ohki et al, 2009; Xirodimas et al, 2008; Jeram et al, 2010; Ma et al, 2013; reviewed in Enchev et al, 2015). The significance of NEDD8 chains is still not clear.

NEDD8 has a single heterodimeric E1 enzyme, consisting of NAE1 (also known as APPBP1) and UBA3, and two E2 enzymes, UBE2M and UBE2F, which are N-terminally acetylated (Walden et al, 2003; Bohnsack et al, 2003; Huang et al, 2004; Huang et al, 2005; Huang et al, 2009; Scott et al, 2011a; Monda et al, 2013; reviewed in Enchev et al, 2015). All NEDD8 E3 enzymes reported to date also function as E3 ubiquitin ligases, and most belong to the RING domain class. The best characterized NEDD8 E3 enzymes are the CRL complexes described above. RBX1-containing complexes interact preferentially with UBE2M, while UBE2F is the E2 for RBX2-containing complexes (Huang et al, 2009; Monda et al, 2013).

Neddylation is regulated in vivo by interaction with DCUN1D proteins (also called DCNLs). The 5 human DCUN1D proteins interact both with cullins and with the NEDD8 E2 proteins and thereby increase the kinetic efficiency of neddylation (Kurz et al, 2005; Kurz et al, 2008; Scott et al, 2010; Scott et al, 2011a; Scott et al, 2014; Monda et al, 2013). Glomulin (GLMN) is another regulator of CRL function that binds to the neddylated cullin and competitively inhibits interaction with the ubiquitin E2 enzyme (Arai et al, 2003; Tron et al, 2012; Duda et al, 2012;

reviewed in Mahon et al, 2014).
The multisubunit COP9 signalosome is the only cullin deneddylase, while SENP8 (also known as DEN1) contributes to deneddylation of other non-cullin NEDD8 targets (Cope et al, 2002; Emberley et al, 2012; Chan et al, 2008; Wu et al, 2003; reviewed in Wei et al, 2008; Enchev et al, 2015). In the deneddylated state, cullins bind to CAND1 (cullin associated NEDD8-dissociated protein1), which displaces the COP9 signalosome and promotes the exchange of the ubiquitin substrate-specific adaptor. This allows CRL complexes to be reconfigured to target other subtrates for ubiquitination (Liu et al, 2002; Schmidt et al, 2009; Pierce et al, 2013; reviewed in Mahon et al, 2014).

Literature references

Lane, DP., Saville, MK., Hay, RT., Xirodimas, DP., Bourdon, JC. (2004). Mdm2-mediated NEDD8 conjugation of p53 inhibits its transcriptional activity. *Cell, 118*, 83-97. ↗

Iyappan, S., Singh, RK., Scheffner, M. (2007). Hetero-oligomerization with MdmX rescues the ubiquitin/Nedd8 ligase activity of RING finger mutants of Mdm2. *J. Biol. Chem., 282*, 10901-7. ↗

Chou, YC., Willems, AR., Meyer-Schaller, N., Sicheri, F., Tyers, M., Peter, M. et al. (2008). Dcn1 functions as a scaffold-type E3 ligase for cullin neddylation. *Mol. Cell, 29*, 23-35. ↗

Gu, W., Abida, WM., Nikolaev, A., Zhang, W., Zhao, W. (2007). FBXO11 promotes the Neddylation of p53 and inhibits its transcriptional activity. *J. Biol. Chem., 282*, 1797-804. ↗

Chen, Y., Deng, H., Zuo, W., Zhang, T., Luo, S., Ding, Y. et al. (2013). c-Cbl-mediated neddylation antagonizes ubiquitination and degradation of the TGF-? type II receptor. *Mol. Cell, 49*, 499-510. ↗

Editions

2017-02-07	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.
2022-02-23	Reviewed	Cuadrado, A.
2022-03-04	Reviewed	Somers, J.

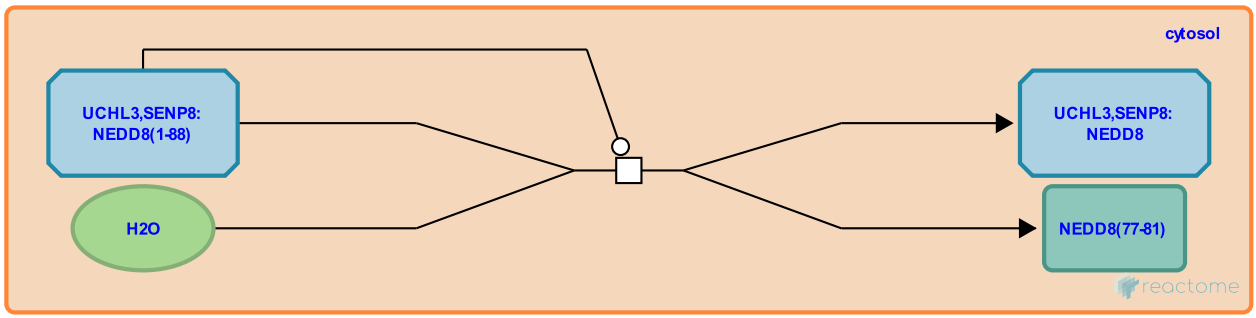
UCHL3, SENP8 cleave NEDD8 ↗

Location: Neddylation

Stable identifier: R-HSA-5690808

Type: transition

Compartments: cytosol



UCHL3 and SENP8 (DEN1) remove the C-terminal extension of NEDD8 propeptides, exposing a C-terminal Gly residue. UCHL3 can also process ubiquitin (Wada et al. 1998). UCHL3 and SENP8 are probably functionally redundant in NEDD8 processing as deletion of either enzyme does not lead to neddylation defects (Chan et al. 2008, Kurihara et al. 2000).

Followed by: Release of mature NEDD8

Literature references

Kamitani, T., Wada, H., Yeh, ET., Caskey, LS., Kito, K. (1998). Cleavage of the C-terminus of NEDD8 by UCH-L3. *Biochem. Biophys. Res. Commun., 251*, 688-92. ↗

Editions

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

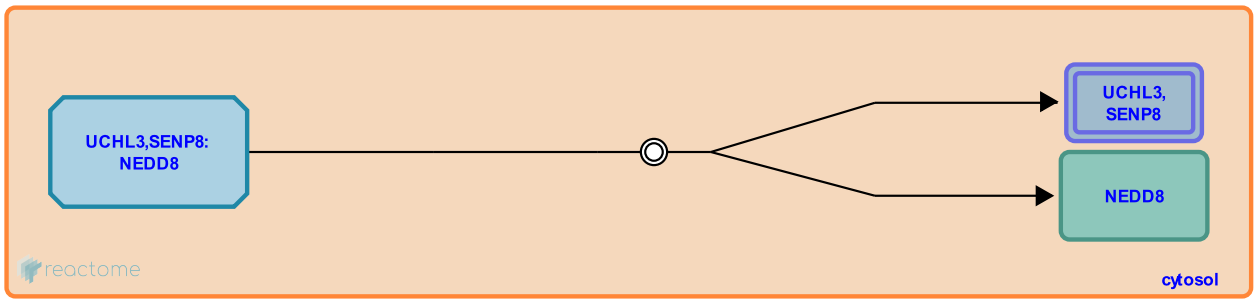
Release of mature NEDD8 ↗

Location: Neddylation

Stable identifier: R-HSA-8951644

Type: dissociation

Compartments: cytosol



After C-terminal processing by UCHL3 or SENP8, mature NEDD8 is released (Wada et al, 1998; Wu et al, 2003).

Preceded by: UCHL3, SENP8 cleave NEDD8

Followed by: NEDD8 and UBD bind NUB1 and the 26S proteasome, NEDD8 covalently binds catalytic cysteine of UBA3:NAE1

Literature references

Kamitani, T., Wada, H., Yeh, ET., Caskey, LS., Kito, K. (1998). Cleavage of the C-terminus of NEDD8 by UCH-L3. *Biochem. Biophys. Res. Commun., 251*, 688-92. ↗

Yamoah, K., Wu, K., Gan-Erdene, T., Wei, N., Wilkinson, KD., Wang, R. et al. (2003). DEN1 is a dual function protease capable of processing the C terminus of Nedd8 and deconjugating hyper-neddylated CUL1. *J. Biol. Chem., 278*, 28882-91. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

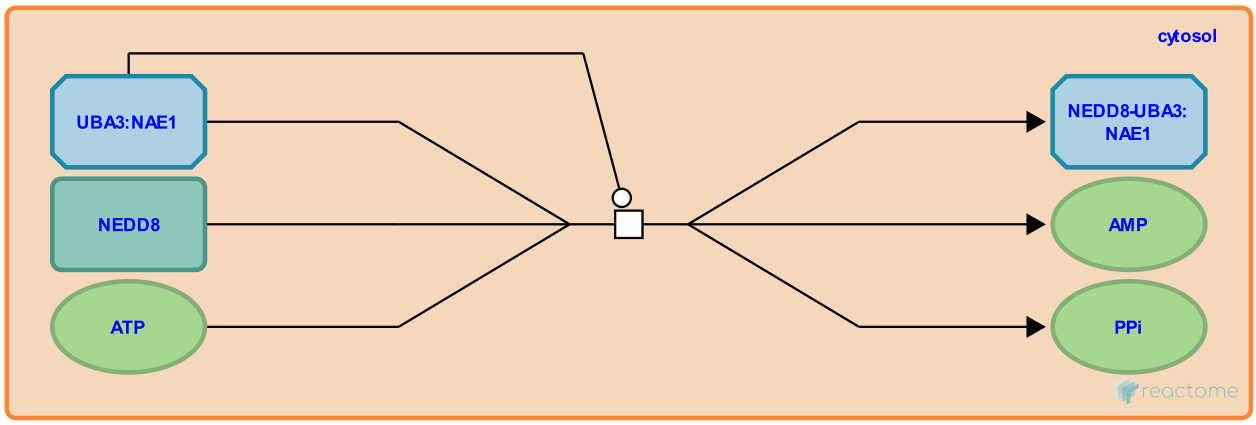
NEDD8 covalently binds catalytic cysteine of UBA3:NAE1 ↗

Location: Neddylation

Stable identifier: R-HSA-8951648

Type: transition

Compartments: cytosol



NEDD8 is attached via a thioester bond to the catalytic cysteine of its E1 as the first step in its transfer to substrates (Walden et al, 2003). The NEDD8 E1 is a heterodimer consisting of UBA3 and NAE1, and transfers NEDD8 to the E2 enzymes from a 'doubly loaded' state. In the first step, NEDD8 binds to the adenylation site on the NAE1 subunit in conjuction with ATP and Mg2+, generating a covalently modified NEDD8-adenylate conjugate. This conjugation activates the NEDD8 C-terminus for chemical attack by the thiol group of the catalytic cysteine of the UBA3 subunit. Catalysis is likely facilitated by a conformational change in the E1 enzyme. After catalysis, NEDD8 is covalently bound in the E1 catalytic site, leaving the adenylation site free to bind another NEDD8 molecule in the second step, prior to NEDD8 transfer to an E2 enzyme (Walden et al, 2003; Huang et al, 2004; Huang et al, 2005; Huang et al, 2007).

Preceded by: Release of mature NEDD8

Followed by: NEDD8-UBA3:NAE1 binds a second NEDD8

Literature references

Miller, DW., Huang, DT., Howard, RJ., Schulman, BA., Holton, JM., Minor, DL. et al. (2003). The structure of the APPBP1-UBA3-NEDD8-ATP complex reveals the basis for selective ubiquitin-like protein activation by an E1. *Mol. Cell, 12*, 1427-37. ↗

Huang, DT., Ohi, MD., Hunt, HW., Schulman, BA., Holton, JM., Zhuang, M. (2007). Basis for a ubiquitin-like protein thioester switch toggling E1-E2 affinity. *Nature, 445*, 394-8. ↗

Huang, DT., Schulman, BA., Holton, JM., Paydar, A., Waddell, MB., Zhuang, M. (2005). Structural basis for recruitment of Ubc12 by an E2 binding domain in NEDD8's E1. *Mol. Cell, 17*, 341-50. ↗

Miller, DW., Huang, DT., Cassell, R., Schulman, BA., Roussel, MF., Holton, JM. et al. (2004). A unique E1-E2 interaction required for optimal conjugation of the ubiquitin-like protein NEDD8. *Nat. Struct. Mol. Biol., 11*, 927-35. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

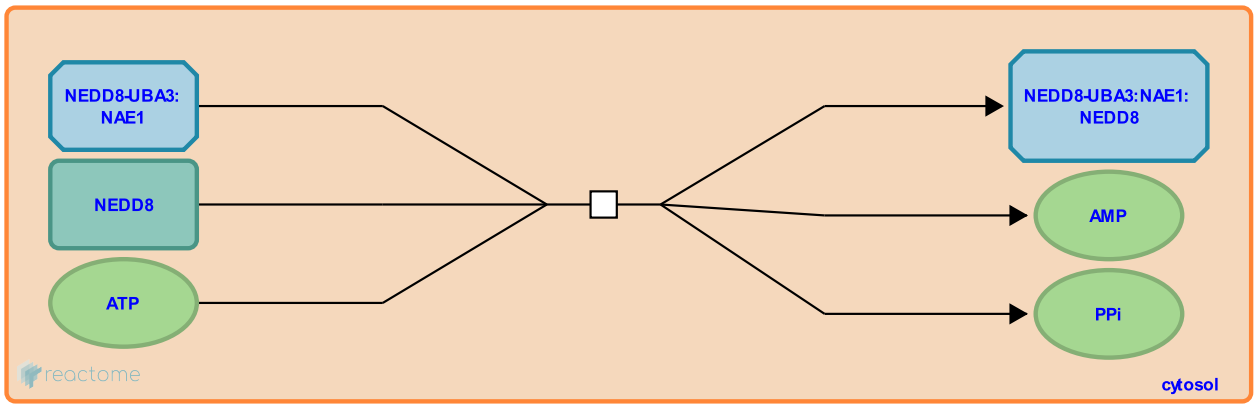
NEDD8-UBA3:NAE1 binds a second NEDD8 ↗

Location: Neddylation

Stable identifier: R-HSA-8951656

Type: transition

Compartments: cytosol



After covalent attachment of the first NEDD8 molecule to the catalytic cysteine, a second NEDD8 binds to the now-free adenylation site on the UBA3 subunit of UBA3:NAE1. This 'doubly-loaded' E1 enzyme is primed to transfer the covalently-bound NEDD8 to the downstream E2 enzyme (Huang et al, 2005; Huang et al, 2007; reviewed in Enchev et al, 2015). Note that although not depicted here, the second NEDD8 moiety is covalently adenylated at its C-terminal glycine residue at the end of this reaction.

Preceded by: NEDD8 covalently binds catalytic cysteine of UBA3:NAE1

Followed by: Doubly neddylated UBA3:NAE1 binds AcM-UBE2M, Doubly neddylated UBA3:NAE1 binds AcM-UBE2F

Literature references

Huang, DT., Ohi, MD., Hunt, HW., Schulman, BA., Holton, JM., Zhuang, M. (2007). Basis for a ubiquitin-like protein thioester switch toggling E1-E2 affinity. *Nature, 445*, 394-8. ↗

Huang, DT., Schulman, BA., Holton, JM., Paydar, A., Waddell, MB., Zhuang, M. (2005). Structural basis for recruitment of Ubc12 by an E2 binding domain in NEDD8's E1. *Mol. Cell, 17*, 341-50. ↗

Schulman, BA., Enchev, RI., Peter, M. (2015). Protein neddylation: beyond cullin-RING ligases. *Nat. Rev. Mol. Cell Biol., 16*, 30-44. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

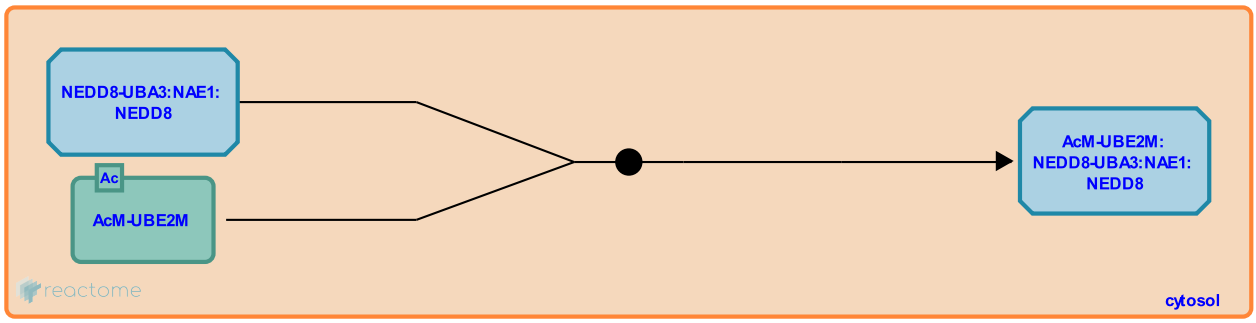
Doubly neddylated UBA3:NAE1 binds AcM-UBE2M ↗

Location: Neddylation

Stable identifier: R-HSA-8951751

Type: binding

Compartments: cytosol



When NAE1:UBA3 is doubly loaded with NEDD8 (one molecule covalently attached to the catalytic cysteine and the other bound in the adenylation site), the E1 enzyme is competent to interact with either of its E2 enzymes, UBE2F and UBE2M (also known as UBC12). Three binding interfaces contribute to the interaction of the E1 and E2 enzymes. When doubly neddylated, the "ubiquitin" folding domain of NAE1 reorients and, in conjunction with the adenylation domain, forms a cryptic E2-binding site. The adenylation domain also makes contact with the amino terminus of either E2 enzyme. UBE2M additionally interacts directly with the NEDD8 molecule covalently attached to the E1 catalytic cysteine (Huang et al, 2004; Huang et al, 2007; reviewed in Enchev et al, 2015). UBE2M is the E2 responsible for transfer of NEDD8 to RBX1-containing E3 ligase complexes, such as those formed with cullins 1, 2, 3 and 4. In contrast, UBE2F is the E2 for the CUL5:RBX2-containing E3 ligase (Huang et al, 2009).

Preceded by: NEDD8-UBA3:NAE1 binds a second NEDD8

Followed by: Transfer of NEDD8 to AcM-UBE2M

Literature references

Huang, DT., Ohi, MD., Hunt, HW., Schulman, BA., Holton, JM., Zhuang, M. (2007). Basis for a ubiquitin-like protein thioester switch toggling E1-E2 affinity. *Nature, 445*, 394-8. ↗

Miller, DW., Huang, DT., Cassell, R., Schulman, BA., Roussel, MF., Holton, JM. et al. (2004). A unique E1-E2 interaction required for optimal conjugation of the ubiquitin-like protein NEDD8. *Nat. Struct. Mol. Biol., 11*, 927-35. ↗

Schulman, BA., Enchev, RI., Peter, M. (2015). Protein neddylation: beyond cullin-RING ligases. *Nat. Rev. Mol. Cell Biol., 16*, 30-44. ↗

Borg, LA., Huang, DT., Duda, DM., Hunt, HW., Murray, PJ., Schulman, BA. et al. (2009). E2-RING expansion of the NEDD8 cascade confers specificity to cullin modification. *Mol. Cell, 33*, 483-95. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

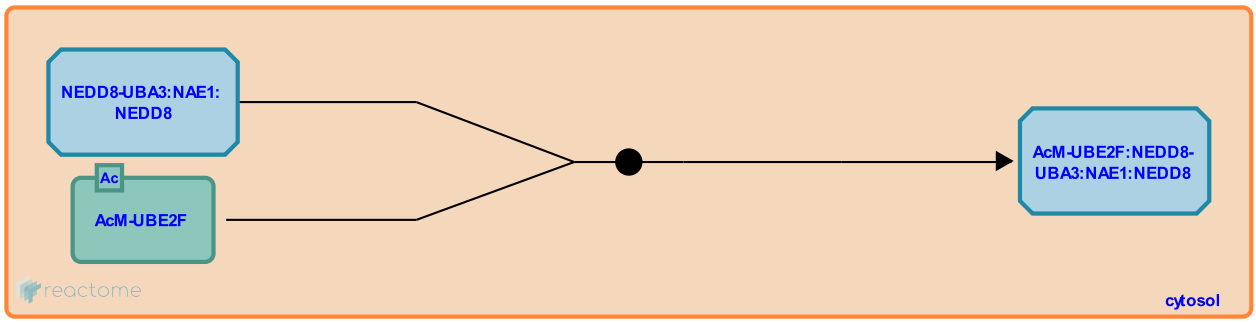
Doubly neddylated UBA3:NAE1 binds AcM-UBE2F ↗

Location: Neddylation

Stable identifier: R-HSA-8951766

Type: binding

Compartments: cytosol



When NAE1:UBA3 is doubly loaded with NEDD8 (one molecule covalently attached to the catalytic cysteine and the other bound in the adenylation site), the E1 enzyme is competent to interact with either of its E2 enzymes, UBE2F and UBE2M (also known as UBC12). Three binding interfaces contribute to the interaction of the E1 and E2 enzymes. When doubly neddylated, the ubiquitin fold domain of NAE1 reorients and, in conjunction with the adenylation domain, forms a cryptic E2-binding site. The adenylation domain also makes contact with the amino terminus of either E2 enzyme. UBE2M additionally interacts directly with the NEDD8 molecule covalently attached to the E1 catalytic cysteine (Huang et al, 2004; Huang et al, 2007; reviewed in Enchev et al, 2015).
UBE2F is the E2 responsible for the transfer of NEDD8 to the CUL5:RBX2 E3 ligase complex, while UBE2M is specific for RBX1-containing E3 ligase complexes formed with CUL1-4 (Huang et al, 2009; reviewed in Mahon et al, 2014).

Preceded by: NEDD8-UBA3:NAE1 binds a second NEDD8

Followed by: Transfer of NEDD8 to AcM-UBE2F

Literature references

Pick, E., Mahon, C., Krogan, NJ., Craik, CS. (2014). Cullin E3 ligases and their rewiring by viral factors. *Biomolecules, 4* , 897-930. ↗

Huang, DT., Ohi, MD., Hunt, HW., Schulman, BA., Holton, JM., Zhuang, M. (2007). Basis for a ubiquitin-like protein thioester switch toggling E1-E2 affinity. *Nature, 445*, 394-8. ↗

Miller, DW., Huang, DT., Cassell, R., Schulman, BA., Roussel, MF., Holton, JM. et al. (2004). A unique E1-E2 interaction required for optimal conjugation of the ubiquitin-like protein NEDD8. *Nat. Struct. Mol. Biol., 11*, 927-35. ↗

Schulman, BA., Enchev, RI., Peter, M. (2015). Protein neddylation: beyond cullin-RING ligases. *Nat. Rev. Mol. Cell Biol., 16*, 30-44. ↗

Borg, LA., Huang, DT., Duda, DM., Hunt, HW., Murray, PJ., Schulman, BA. et al. (2009). E2-RING expansion of the NEDD8 cascade confers specificity to cullin modification. *Mol. Cell, 33*, 483-95. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

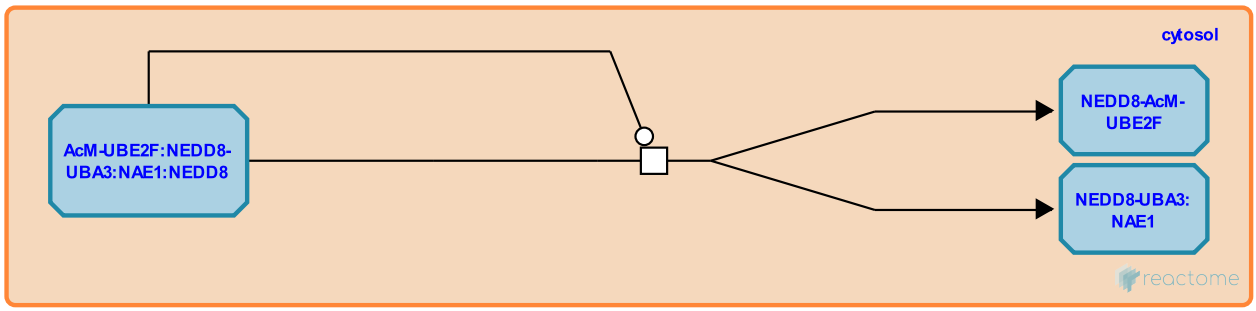
Transfer of NEDD8 to AcM-UBE2F ↗

Location: Neddylation

Stable identifier: R-HSA-8951764

Type: transition

Compartments: cytosol



UBA3:NAE1 transfers NEDD8 to the catalytic cysteine residue of UBE2F. Because two of the three E1-E2 interaction interfaces are created by conformational states present in the doubly-NEDDylated NAE1, transfer of NEDD8 to UBE2M is thought to weaken the interaction between UBA3:NAE1 and UBE2F, contributing to UBE2F release (Walden et al, 2003; Huang et al, 2004; Hunag et al, 2005; Huang et al, 2007).

Preceded by: Doubly neddylated UBA3:NAE1 binds AcM-UBE2F

Followed by: NEDD8:AcM-UBE2F binds CRL5 E3 ubiquitin ligase complex

Literature references

Miller, DW., Huang, DT., Howard, RJ., Schulman, BA., Holton, JM., Minor, DL. et al. (2003). The structure of the APPBP1-UBA3-NEDD8-ATP complex reveals the basis for selective ubiquitin-like protein activation by an E1. *Mol. Cell, 12*, 1427-37. ↗

Huang, DT., Ohi, MD., Hunt, HW., Schulman, BA., Holton, JM., Zhuang, M. (2007). Basis for a ubiquitin-like protein thioester switch toggling E1-E2 affinity. *Nature, 445*, 394-8. ↗

Huang, DT., Schulman, BA., Holton, JM., Paydar, A., Waddell, MB., Zhuang, M. (2005). Structural basis for recruitment of Ubc12 by an E2 binding domain in NEDD8's E1. *Mol. Cell, 17*, 341-50. ↗

Miller, DW., Huang, DT., Cassell, R., Schulman, BA., Roussel, MF., Holton, JM. et al. (2004). A unique E1-E2 interaction required for optimal conjugation of the ubiquitin-like protein NEDD8. *Nat. Struct. Mol. Biol., 11*, 927-35. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

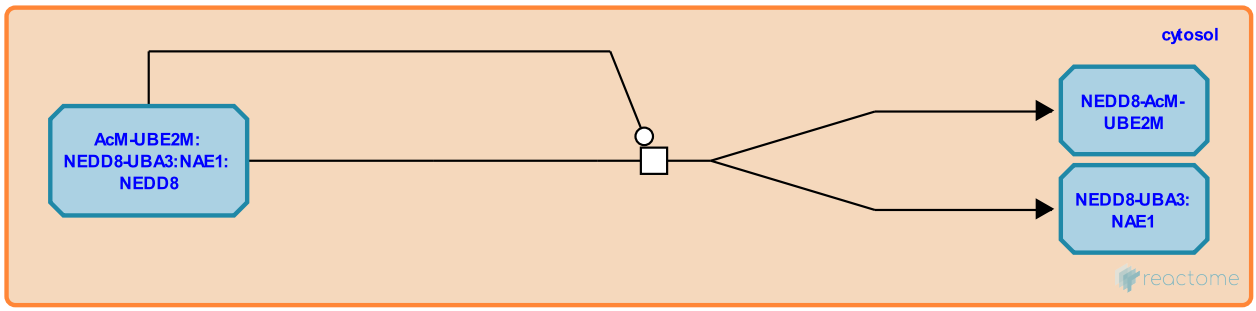
Transfer of NEDD8 to AcM-UBE2M ↗

Location: Neddylation

Stable identifier: R-HSA-8951661

Type: transition

Compartments: cytosol



UBA3:NAE1 transfers NEDD8 to the catalytic cysteine residue of UBE2M. Because two of the three E1-E2 interaction interfaces are created by conformational states present in the doubly-NEDDylated NAE1, transfer of NEDD8 to UBE2M is thought to weaken the interaction between UBA3:NAE1 and UBE2M, contributing to UBE2M release (Walden et al, 2003; Huang et al, 2004; Hunag et al, 2005; Huang et al, 2007).

Preceded by: Doubly neddylated UBA3:NAE1 binds AcM-UBE2M

Followed by: NEDD8:AcM-UBE2M binds CRL4 E3 ubiquitin ligase complex, NEDD8:AcM-UBE2M binds CRL1 E3 ubiquitin ligase complex, NEDD8:AcM-UBE2M binds CUL9:RBX1 ubiquitin ligase complex, NEDD8:AcM-UBE2M binds CRL3 E3 ubiquitin ligase complex, NEDD8:AcM-UBE2M binds CRL2 E3 ubiquitin ligase complex

Literature references

Miller, DW., Huang, DT., Howard, RJ., Schulman, BA., Holton, JM., Minor, DL. et al. (2003). The structure of the APPBP1-UBA3-NEDD8-ATP complex reveals the basis for selective ubiquitin-like protein activation by an E1. *Mol. Cell, 12*, 1427-37. ↗

Huang, DT., Ohi, MD., Hunt, HW., Schulman, BA., Holton, JM., Zhuang, M. (2007). Basis for a ubiquitin-like protein thioester switch toggling E1-E2 affinity. *Nature, 445*, 394-8. ↗

Huang, DT., Schulman, BA., Holton, JM., Paydar, A., Waddell, MB., Zhuang, M. (2005). Structural basis for recruitment of Ubc12 by an E2 binding domain in NEDD8's E1. *Mol. Cell, 17*, 341-50. ↗

Miller, DW., Huang, DT., Cassell, R., Schulman, BA., Roussel, MF., Holton, JM. et al. (2004). A unique E1-E2 interaction required for optimal conjugation of the ubiquitin-like protein NEDD8. *Nat. Struct. Mol. Biol., 11*, 927-35. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

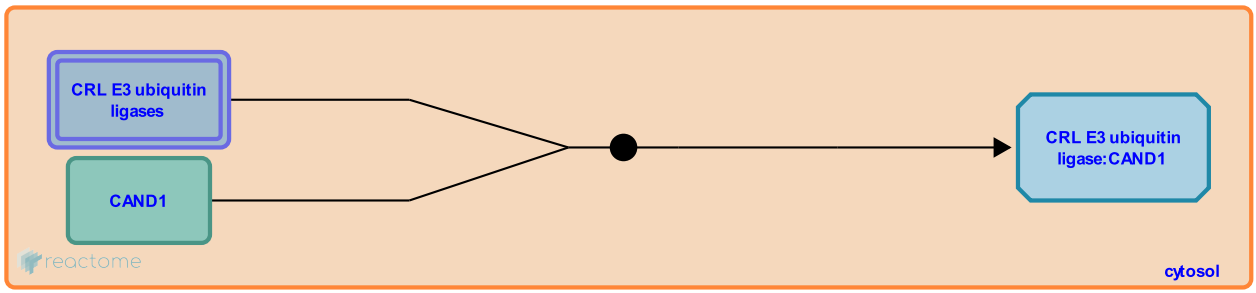
CAND1 binds cytosolic CRL E3 ubiquitin ligases ↗

Location: Neddylation

Stable identifier: R-HSA-8955241

Type: binding

Compartments: cytosol



CRL complexes consist of a cullin protein (CUL1, 2, 3, 4A, 4B, 5, 7 and 9 in humans) and a RING box protein (RBX1 or 2) in addition to one or more substrate binding proteins that confer substrate specificity to the complex (reviewed in Petroski and Deshaies, 2005; Lipkowitz and Weismann, 2011). CRL complexes can be classes according to their cullin proteins: CRL1 complexes (also called SCF complexes) contain CUL1, CRL2 complexes contain CUL2, CLR complexes contain CUL3, and CLR5 complexes contain CUL5. Cullin-associated NEDD8-dissociated protein 1 (CAND1, TIP120) is a key assembly factor of Cullin E3 RING ubiquitin ligase (CRL) complexes, acting as a substrate receptor exchange factor. CAND1 binds to the inactive, deneddylated CRL complex through the conserved amino-terminal 3 Cullin repeats of the cullin subunit, which are also required for binding of the substrate binding proteins (Zheng et al, 2002a, b; Liu et al 2002; Min et al, 2003; Goldenberg et al, 2004). By disrupting the substrate binding protein interaction interface on the cullin proteins, CAND1 binding destabilizes the CRL complex, allowing exchange of the substrate binding protein (Schmidt et al, 2009; Pierce et al, 2013; Zemla et al, 2013; Wu et al, 2013). Neddylation of the CRL complex results in a conformational change that eliminates the CAND1 binding site, thereby promoting the active CRL ubiquitin ligase complex (Duda et al, 2008; Saha and Deshaies, 2008; Boh et al, 2011; Yu et al, 2015).

Followed by: COMMDs displace CAND1 from cytosolic CRL E3 ubiquitin ligase complexes

Literature references

Boh, BK., Hagen, T., Smith, PG. (2011). Neddylation-induced conformational control regulates cullin RING ligase activity in vivo. *J. Mol. Biol., 409*, 136-45. ↗

Saha, A., Deshaies, RJ. (2008). Multimodal activation of the ubiquitin ligase SCF by Nedd8 conjugation. *Mol. Cell, 32*, 21-31. ↗

Petroski, MD., Deshaies, RJ. (2005). Function and regulation of cullin-RING ubiquitin ligases. *Nat. Rev. Mol. Cell Biol., 6*, 9-20. ↗

Furukawa, M., Liu, J., Xiong, Y., Matsumoto, T. (2002). NEDD8 modification of CUL1 dissociates p120(CAND1), an inhibitor of CUL1-SKP1 binding and SCF ligases. *Mol. Cell, 10*, 1511-8. ↗

Lipkowitz, S., Weissman, AM. (2011). RINGs of good and evil: RING finger ubiquitin ligases at the crossroads of tumour suppression and oncogenesis. *Nat. Rev. Cancer, 11*, 629-43. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

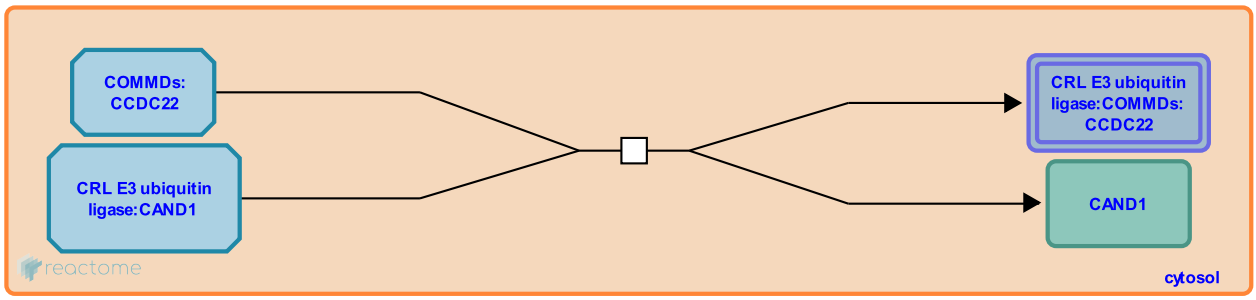
COMMDs displace CAND1 from cytosolic CRL E3 ubiquitin ligase complexes ↗

Location: Neddylation

Stable identifier: R-HSA-8955289

Type: transition

Compartments: cytosol



COMMD1 is a member of a family of 10 copper metabolism MURR1 domain-containing proteins that have pleiotropic roles in copper metabolism, NF kappa beta-mediated transcription, the hypoxic response and electrolyte transport (Burstein et al, 2005; reviewed in Maine and Burstein, 2007). COMMD proteins have differential tissue and expression levels, but appear to have partially overlapping function and form homo- and heterodimers through the shared COMM domain (Burstein et al, 2005). COMMD1 and other family members interact with the cullin subunit of CRL E3 ubiquitin ligase complexes, as well as with CCDC22, a protein implicated in X-linked intellectual disability that may regulate COMMD localization. Together, COMMD proteins and CCDC22 activate the ubiquitin ligase activity of CRL complexes by displacing the CAND1 inhibitor (Burstein et al, 2005; Maine et al, 2007; Mao et al, 2011; Starokadomskyy et al, 2013;Phillips-Krawczak et al, 2015). The specificity of interaction between various COMMD and CUL family members may serve to fine tune the regulation of CRL activation, although these details remain to be determined.

Preceded by: CAND1 binds cytosolic CRL E3 ubiquitin ligases

Followed by: MyrG-DCUN1D3 binds CRL1 E3 ubiquitin ligase complex, NEDD8:AcM-UBE2M binds CRL3 E3 ubiquitin ligase complex, NEDD8:AcM-UBE2M binds CRL2 E3 ubiquitin ligase complex, NEDD8:AcM-UBE2F binds CRL5 E3 ubiquitin ligase complex, NEDD8:AcM-UBE2M binds CRL1 E3 ubiquitin ligase complex

Literature references

Maine, GN., Mao, X., Komarck, CM., Burstein, E. (2007). COMMD1 promotes the ubiquitination of NF-kappaB subunits through a cullin-containing ubiquitin ligase. *EMBO J., 26*, 436-47. ↗

Gluck, N., Maine, GN., Li, H., Starokadomskyy, P., Chen, B., Mao, X. et al. (2011). COMMD1 (copper metabolism MURR1 domain-containing protein 1) regulates Cullin RING ligases by preventing CAND1 (Cullin-associated Nedd8-dissociated protein 1) binding. *J. Biol. Chem., 286*, 32355-65. ↗

Gluck, N., Zecha, A., Maine, GN., Li, H., Wallis, M., Ropers, HH. et al. (2013). CCDC22 deficiency in humans blunts activation of proinflammatory NF-κB signaling. *J. Clin. Invest., 123*, 2244-56. ↗

Maine, GN., Burstein, E. (2007). COMMD proteins: COMMing to the scene. *Cell. Mol. Life Sci., 64*, 1997-2005. ↗

Hoberg, JE., Maine, GN., Duckett, CS., Wilkinson, AS., Wilkinson, JC., Rumble, JM. et al. (2005). COMMD proteins, a novel family of structural and functional homologs of MURR1. *J. Biol. Chem., 280*, 22222-32. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

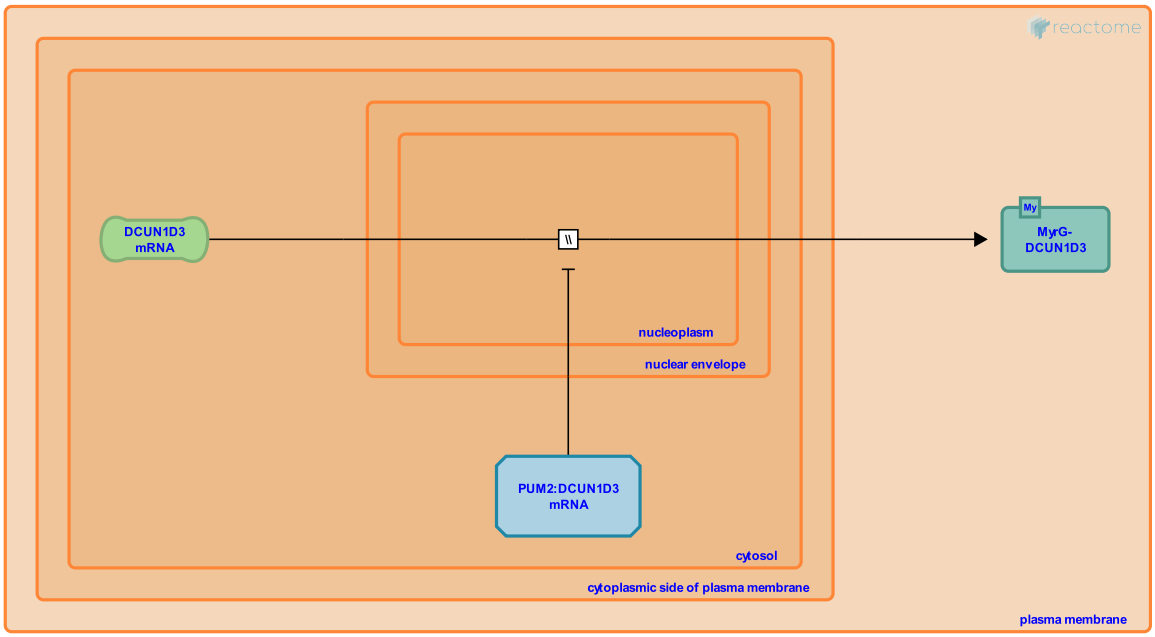
Translation of DCUN1D3 is inhibited by PUM2 ↗

Location: Neddylation

Stable identifier: R-HSA-8956234

Type: omitted

Compartments: nucleoplasm



PUM2 is a sequence-specific RNA binding protein that binds DCUN1D3 mRNA and decreases levels of mature DCUN1D3 protein, likely by promoting mRNA degradation (Galgano et al, 2008; Huang et al, 2014).

Followed by: MyrG-DCUN1D3 binds CRL1 E3 ubiquitin ligase complex

Literature references

Zavolan, M., Galgano, A., Gerber, AP., Forrer, M., Jaskiewicz, L., Kanitz, A. (2008). Comparative analysis of mRNA targets for human PUF-family proteins suggests extensive interaction with the miRNA regulatory system. *PLoS ONE, 3*, e3164. ↗

Bommeljé, CC., Rechler, W., Shaha, M., Shah, K., Buss, E., Weeda, VB. et al. (2014). SCCRO3 (DCUN1D3) antagonizes the neddylation and oncogenic activity of SCCRO (DCUN1D1). *J. Biol. Chem., 289*, 34728-42. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

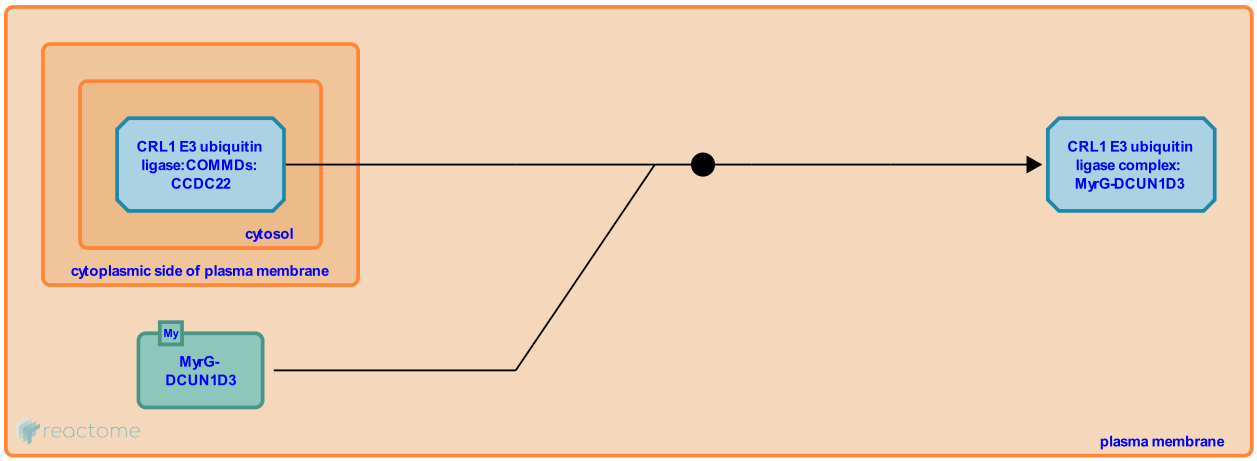
MyrG-DCUN1D3 binds CRL1 E3 ubiquitin ligase complex ↗

Location: Neddylation

Stable identifier: R-HSA-8956200

Type: binding

Compartments: plasma membrane



DCUN1D3 binds to CRL1 ligase complexes to antagonize their neddylation and activation. DCUN1D3 is unique among the DCUN1D family members in that is N-terminally myristolyated, resulting in plasma membrane localization. Binding of DCUN1D3 to CUL1-containing E3 ligase complexes sequesters the cullin complexes at the plasma membrane, inhibiting their DCUN1D1-mediated neddylation (Huang et al, 2014). Although in this reaction DCUN1D3 is shown binding to cullin E3 ligases in complex with COMMD proteins and CCDC22, DCUN1D3 has also been shown to interact with CAND1 and the precise timing of this sequestration binding event remains to be clarified.

Preceded by: Translation of DCUN1D3 is inhibited by PUM2, COMMDs displace CAND1 from cytosolic CRL E3 ubiquitin ligase complexes

Literature references

Bommeljé, CC., Rechler, W., Shaha, M., Shah, K., Buss, E., Weeda, VB. et al. (2014). SCCRO3 (DCUN1D3) antagonizes the neddylation and oncogenic activity of SCCRO (DCUN1D1). *J. Biol. Chem., 289*, 34728-42. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

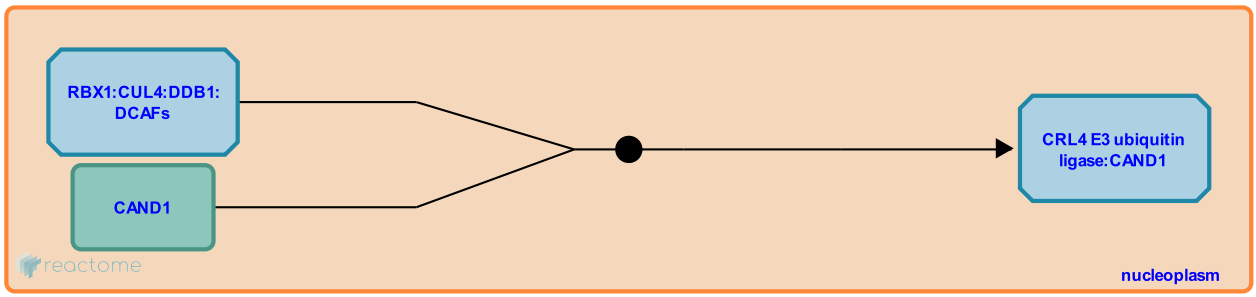
CAND1 binds CRL4 E3 ubiquitin ligase in the nucleus ↗

Location: Neddylation

Stable identifier: R-HSA-8955245

Type: binding

Compartments: nucleoplasm



CRL complexes consist of a cullin protein (CUL1, 2, 3, 4A, 4B, 5, 7 and 9 in humans) and a RING box protein (RBX1 or 2) in addition to one or more substrate binding proteins that confer substrate specificity to the complex (reviewed in Petroski and Deshaies, 2005; Lipkowitz and Weismann, 2011). CRL4 complexes contain CUL4A or CUL4B. Cullin-associated NEDD8-dissociated protein 1 (CAND1, TIP120) is a key assembly factor of Cullin E3 RING ubiquitin ligase (CRL) complexes, acting as a substrate receptor exchange factor. CAND1 binds to the inactive, deneddylated CRL complex through the conserved amino-terminal 3 Cullin repeats of the cullin subunit, which are also required for binding of the substrate binding proteins (Zheng et al, 2002a, b; Liu et al 2002; Min et al, 2003; Goldenberg et al, 2004). In this way, CAND1 binding destabilizes the CRL complex, allowing exchange of the substrate binding protein (Schmidt et al, 2009; Pierce et al, 2013). Neddylation of the CRL complex results in a conformational change that eliminates the CAND1 binding site (Duda et al, 2008; Saha and Deshaies, 2008; Boh et al, 2011).

Followed by: COMMDs displace CAND1 from CRL4 E3 ubiquitin ligase complex

Literature references

Boh, BK., Hagen, T., Smith, PG. (2011). Neddylation-induced conformational control regulates cullin RING ligase activity in vivo. *J. Mol. Biol., 409*, 136-45. ↗

Saha, A., Deshaies, RJ. (2008). Multimodal activation of the ubiquitin ligase SCF by Nedd8 conjugation. *Mol. Cell, 32*, 21-31. ↗

Petroski, MD., Deshaies, RJ. (2005). Function and regulation of cullin-RING ubiquitin ligases. *Nat. Rev. Mol. Cell Biol., 6*, 9-20. ↗

Furukawa, M., Liu, J., Xiong, Y., Matsumoto, T. (2002). NEDD8 modification of CUL1 dissociates p120(CAND1), an inhibitor of CUL1-SKP1 binding and SCF ligases. *Mol. Cell, 10*, 1511-8. ↗

Lipkowitz, S., Weissman, AM. (2011). RINGs of good and evil: RING finger ubiquitin ligases at the crossroads of tumour suppression and oncogenesis. *Nat. Rev. Cancer, 11*, 629-43. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

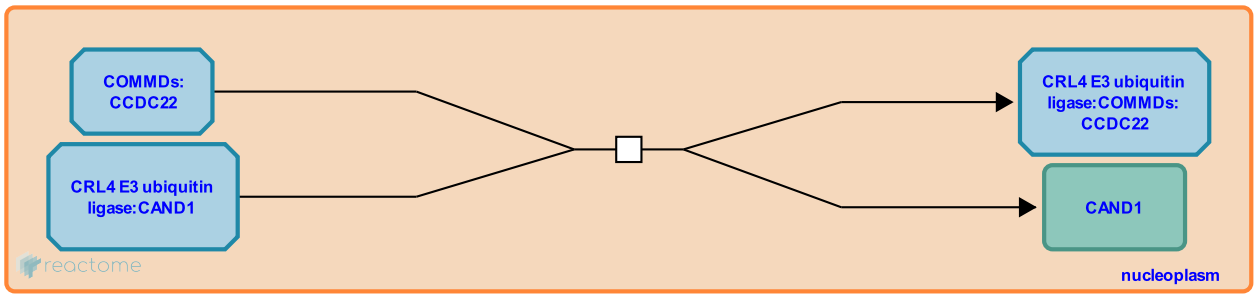
COMMDs displace CAND1 from CRL4 E3 ubiquitin ligase complex ↗

Location: Neddylation

Stable identifier: R-HSA-8955285

Type: transition

Compartments: nucleoplasm



COMMD1 is a member of a family of 10 copper metabolism MURR1 domain-containing proteins that have pleiotropic roles in copper metabolism, NF kappa beta-mediated transcription, the hypoxic response and electrolyte transport (Burstein et al, 2005; reviewed in Maine and Burstein, 2007). COMMD proteins have differential tissue and expression levels, but appear to have partially overlapping function and form homo- and heterodimers through the shared COMM domain (Burstein et al, 2005). COMMD1 and other family members interact with the cullin subunit of CRL E3 ubiquitin ligase complexes, as well as with CCDC22, a protein implicated in X-linked intellectual disability that may regulate COMMD localization. Together, COMMD proteins and CCDC22 activate the ubiquitin ligase activity of CRL complexes by displacing the CAND1 inhibitor (Burstein et al, 2005; Maine et al, 2007; Mao et al, 2011; Starokadomskyy et al, 2013;Phillips-Krawczak et al, 2015). The specificity of interaction between various COMMD and CUL family members may serve to fine tune the regulation of CRL activation, although these details remain to be determined.

Preceded by: CAND1 binds CRL4 E3 ubiquitin ligase in the nucleus

Followed by: NEDD8:AcM-UBE2M binds CRL4 E3 ubiquitin ligase complex

Literature references

Maine, GN., Mao, X., Komarck, CM., Burstein, E. (2007). COMMD1 promotes the ubiquitination of NF-kappaB subunits through a cullin-containing ubiquitin ligase. *EMBO J., 26*, 436-47. ↗

Gluck, N., Maine, GN., Li, H., Starokadomskyy, P., Chen, B., Mao, X. et al. (2011). COMMD1 (copper metabolism MURR1 domain-containing protein 1) regulates Cullin RING ligases by preventing CAND1 (Cullin-associated Nedd8-dissociated protein 1) binding. *J. Biol. Chem., 286*, 32355-65. ↗

Gluck, N., Zecha, A., Maine, GN., Li, H., Wallis, M., Ropers, HH. et al. (2013). CCDC22 deficiency in humans blunts activation of proinflammatory NF-κB signaling. *J. Clin. Invest., 123*, 2244-56. ↗

Maine, GN., Burstein, E. (2007). COMMD proteins: COMMing to the scene. *Cell. Mol. Life Sci., 64*, 1997-2005. ↗

Hoberg, JE., Maine, GN., Duckett, CS., Wilkinson, AS., Wilkinson, JC., Rumble, JM. et al. (2005). COMMD proteins, a novel family of structural and functional homologs of MURR1. *J. Biol. Chem., 280*, 22222-32. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

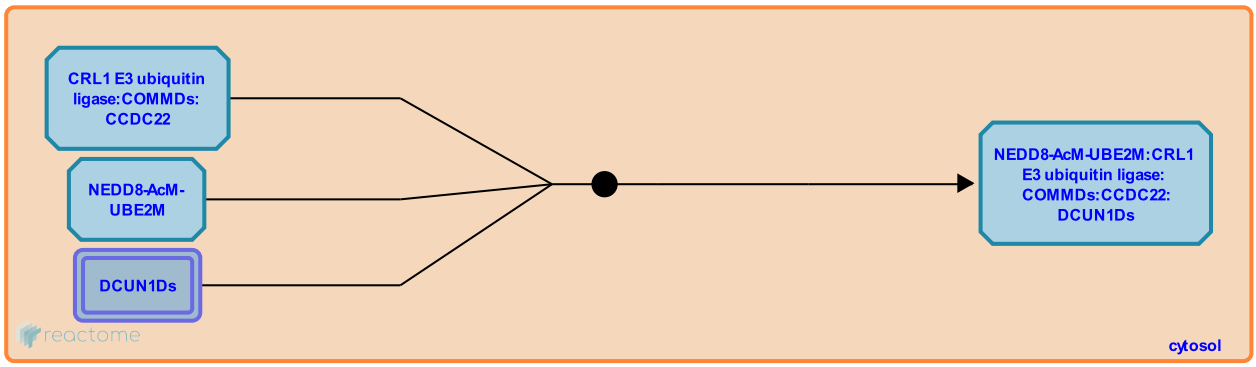
NEDD8:AcM-UBE2M binds CRL1 E3 ubiquitin ligase complex ↗

Location: Neddylation

Stable identifier: R-HSA-8952620

Type: binding

Compartments: cytosol



UBE2M is the E2 for CRL complexes containing cullin 1, 2, 3 and 4 (Huang et al, 2009; Monda et al, 2013). Interaction between UBE2M and the CUL1 E3 complex is facilitated by a DCUN1D (also known as DCNL) scaffold protein, of which there are 5 in human cells (Kim et al, 2008; Kurz et al, 2008; Meyer-Schaller et al, 2009; Monda et al, 2013; Keuss et al, 2016). DCUN1D proteins interact with higher affinity to the N-terminally acetylated forms of UBE2F and UBE2M (Scott et al, 2011; Monda et al, 2013). Although each of the 5 DCUN1D proteins appears to interact with most cullin subtypes, specificity may arise through differences in expression and localization, and DCUN1D3 may play a specialized role in sequestering CRL E3 ligase complexes at the cell membrane (Monda et al, 2013; Keuss et al, 2016; Meyer-Schaller et al, 2009; Huang et al, 2014; reviewed in Enchev et al, 2103). Although in this pathway, COMMD proteins and DCUN1D are shown acting sequentially in the activation of the CRL E3 ligase complex, the relationship between these protein families is not totally clear, as DCUN1D proteins have been identified in complexes that also contain the inhibitor CAND1 (Kim et al, 2008; Huang et al, 2014). Target specificity of the CRL1 complex is directed by the nature of the F box substrate recognition protein, of which there are more than 60 in humans. Identified targets of CRL1-containing complexes include signaling molecules, transcriptional regulators and regulators of cell cycle progression, among others (reviewed in Gutierrez and Ronai, 2006; Lipkowitz and Weissman, 2011). CRL1 complexes are also hijacked by a number of viruses, redirecting the ubiquitin ligase complex to target host proteins and in this way promoting viral propagation (reveiwed in Mahon et al, 2014).

Preceded by: Transfer of NEDD8 to AcM-UBE2M, COMMDs displace CAND1 from cytosolic CRL E3 ubiquitin ligase complexes

Followed by: AcM-UBE2M transfers NEDD8 to CRL1 E3 ubiquitin ligase complex

Literature references

Bennett, EJ., Miller, DJ., Schulman, BA., Harper, JW., King, D., Lydeard, J. et al. (2013). Structural conservation of distinctive N-terminal acetylation-dependent interactions across a family of mammalian NEDD8 ligation enzymes. *Structure, 21*, 42-53. ↗

Pick, E., Mahon, C., Krogan, NJ., Craik, CS. (2014). Cullin E3 ligases and their rewiring by viral factors. *Biomolecules, 4* , 897-930. ↗

Gutierrez, GJ., Ronai, Z. (2006). Ubiquitin and SUMO systems in the regulation of mitotic checkpoints. *Trends Biochem. Sci., 31*, 324-32. ↗

Chou, YC., Willems, AR., Meyer-Schaller, N., Sicheri, F., Tyers, M., Peter, M. et al. (2008). Dcn1 functions as a scaffold-type E3 ligase for cullin neddylation. *Mol. Cell, 29*, 23-35. ↗

Hofmann, K., Chou, YC., Sumara, I., Meyer-Schaller, N., Sicheri, F., Berthiaume, LG. et al. (2009). The human Dcn1-like protein DCNL3 promotes Cul3 neddylation at membranes. *Proc. Natl. Acad. Sci. U.S.A., 106*, 12365-70. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

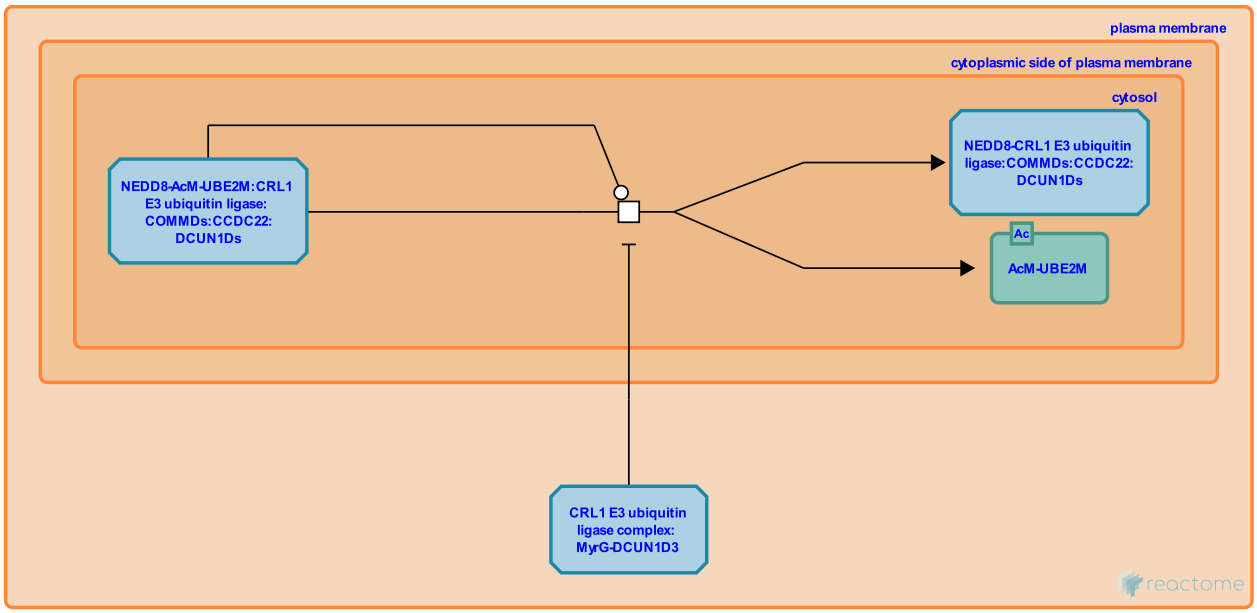
AcM-UBE2M transfers NEDD8 to CRL1 E3 ubiquitin ligase complex ↗

Location: Neddylation

Stable identifier: R-HSA-8952618

Type: transition

Compartments: cytosol



UBE2M transfers NEDD8 to lysine 720 of CUL1 in the CRL E3 ubiquitin ligase complex (Hori et al, 1999; Duda et al, 2008). Neddylation increases the ubiquitination activity of the E3 complex towards its targets, and prevents binding of the CUL1 complex with the CAND1 inhibitor (Hori et al, 1999; Goldenberg et al, 2004; Duda et al, 2008; Kelsall et al, 2013; Scott et al, 2016). Targets of CUL1 RING complexes include a variety of cellular proteins including regulators of transcription and cell cycle progression, among others (reviewed in Lipkowitz and Weissman, 2011). CRL1 complexes are also hijacked by viruses, redirecting the ubiquitin ligase complex to target host proteins (reviewed in Mahon et al, 2014).

Preceded by: NEDD8:AcM-UBE2M binds CRL1 E3 ubiquitin ligase complex

Followed by: COP9 signalosome deneddylates cytosolic CRL E3 ubiquitin ligase complexes

Literature references

Pick, E., Mahon, C., Krogan, NJ., Craik, CS. (2014). Cullin E3 ligases and their rewiring by viral factors. *Biomolecules, 4* , 897-930. ↗

Kato, S., Shimbara, N., Miyamoto, C., Osaka, F., Okabayashi, K., Chiba, T. et al. (1999). Covalent modification of all members of human cullin family proteins by NEDD8. *Oncogene, 18*, 6829-34. ↗

Alpi, AF., Duda, DM., Paulo, JA., Schulman, BA., Ovaa, H., Rhee, DY. et al. (2016). Two Distinct Types of E3 Ligases Work in Unison to Regulate Substrate Ubiquitylation. *Cell, 166*, 1198-1214.e24. ↗

Lipkowitz, S., Weissman, AM. (2011). RINGs of good and evil: RING finger ubiquitin ligases at the crossroads of tumour suppression and oncogenesis. *Nat. Rev. Cancer, 11*, 629-43. ↗

Hofmann, K., Alpi, AF., Duda, DM., Schulman, BA., Knebel, A., Wood, N. et al. (2013). TRIAD1 and HHARI bind to and are activated by distinct neddylated Cullin-RING ligase complexes. *EMBO J., 32*, 2848-60. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

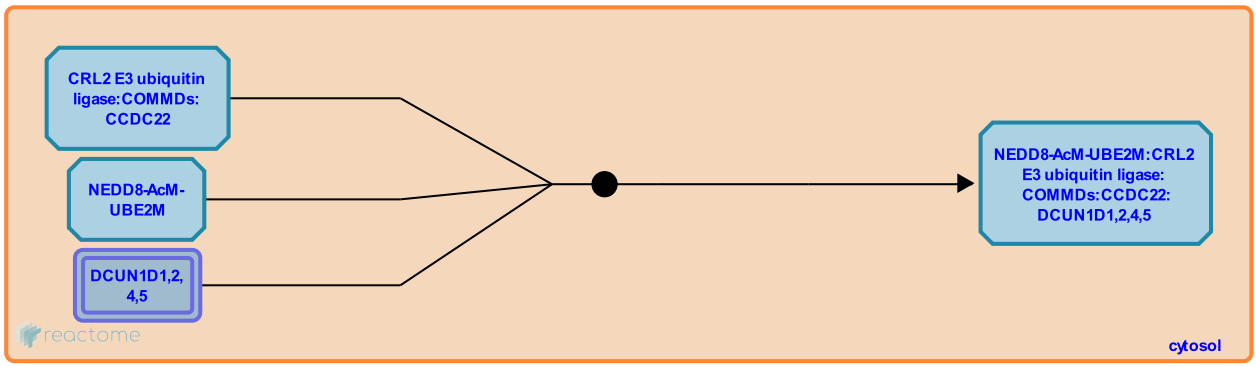
NEDD8:AcM-UBE2M binds CRL2 E3 ubiquitin ligase complex ↗

Location: Neddylation

Stable identifier: R-HSA-8952625

Type: binding

Compartments: cytosol



UBE2M is the E2 ubiquitin ligase for CRL complexes containing cullin 1, 2, 3 and 4 (Huang et al, 2009; Monda et al, 2013). Interaction between UBE2M and the CUL2 E3 complex is facilitated by a DCUN1D (also known as DCNL) scaffold protein, of which there are 5 in human cells (Kim et al, 2008; Kurz et al, 2008; Meyer-Schaller et al, 2009; Monda et al, 2013; Keuss et al, 2016). DCUN1D proteins interact with higher affinity to the N-terminally acetylated forms of UBE2F and UBE2M (Scott et al, 2011; Monda et al, 2013). Although each of the 5 DCUN1D proteins appears to interact with most cullin subtypes, specificity may arise through differences in expression and localization, and DCUN1D3 may play a specialized role in sequestering CRL E3 ligase complexes at the cell membrane (Monda et al, 2013; Keuss et al, 2016; Meyer-Schaller et al, 2009; Huang et al, 2014; reviewed in Enchev et al, 2103). Although in this pathway, COMMD proteins and DCUN1D are shown acting sequentially in the activation of the CRL E3 ligase complex, the relationship between these protein families is not totally clear, as DCUN1D proteins have been identified in complexes that also contain the inhibitor CAND1 (Kim et al, 2008; Huang et al, 2014).
Target specificity of the CRL2 complex is directed by the nature of the F box substrate recognition protein. The best characterized CRL2 F-box protein is the von Hippel-Lindau (VHL) tumor suppressor, which targets the alpha subunit of hypoxia inducible factor (HIFalpha), among other substrates (reviewed in Cai and Yang, 2016). Another example is CRL1/HRD1 that has been reported to target NFE2L2 for degradation in liver (Wu et al, 2014). CRL2 complexes are hijacked by a number of viruses, including adenovirus, Epstein-Barr virus and HPV, among others. This redirects the ubiquitin ligase complex to target host proteins and in this way promotes viral propagation (reviewed in Mahon et al, 2014).

Preceded by: Transfer of NEDD8 to AcM-UBE2M, COMMDs displace CAND1 from cytosolic CRL E3 ubiquitin ligase complexes

Followed by: AcM-UBE2M transfers NEDD8 to CRL2 E3 ubiquitin ligase complex

Literature references

Gao, B., Tan, C., Zhang, DD., Chapman, E., Yagishita, N., Zhao, F. et al. (2014). Hrd1 suppresses Nrf2-mediated cellular protection during liver cirrhosis. *Genes Dev, 28*, 708-22. ↗

Chou, YC., Willems, AR., Meyer-Schaller, N., Sicheri, F., Tyers, M., Peter, M. et al. (2008). Dcn1 functions as a scaffold-type E3 ligase for cullin neddylation. *Mol. Cell, 29*, 23-35. ↗

Hofmann, K., Chou, YC., Sumara, I., Meyer-Schaller, N., Sicheri, F., Berthiaume, LG. et al. (2009). The human Dcn1-like protein DCNL3 promotes Cul3 neddylation at membranes. *Proc. Natl. Acad. Sci. U.S.A., 106*, 12365-70. ↗

Bommeljé, CC., Ramanathan, Y., Ryan, RJ., Lee, BE., Yonekawa, Y., Choi, L. et al. (2008). SCCRO (DCUN1D1) is an essential component of the E3 complex for neddylation. *J. Biol. Chem., 283*, 33211-20. ↗

Bennett, EJ., Schulman, BA., Harper, JW., Scott, DC., Monda, JK. (2011). N-terminal acetylation acts as an avidity enhancer within an interconnected multiprotein complex. *Science, 334*, 674-8. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2022-03-04	Reviewed	Somers, J.

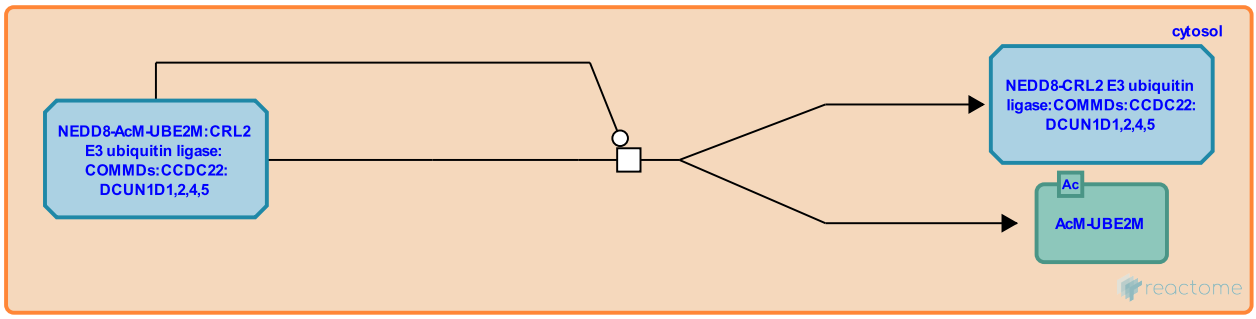
AcM-UBE2M transfers NEDD8 to CRL2 E3 ubiquitin ligase complex ↗

Location: Neddylation

Stable identifier: R-HSA-8952626

Type: transition

Compartments: cytosol



UBE2M transfers NEDD8 to lysine 689 of CUL2 in the E3 ligase complex (Hori et al, 1999; Duda et al, 2008). Neddylation increases the ubiquitin ligase activity of the E3 complex towards its targets, and prevents binding of the CUL2 complex with the CAND1 inhibitor (Hori et al, 1999; Duda et al, 2008).
Target specificity of the CRL2 complex is directed by the nature of the F box substrate recognition protein. The best characterized CRL2 F-box protein is the von Hippel- Lindau (VHL) tumor suppressor, which targets the alpha subunit of hypoxia inducible factor (HIFalpha), among other substrates (reviewed in Cai and Yang, 2016). Another example if CRL2/HRD1 that has been reported to target NFE2L2 for degradation in liver (Wu et al, 2014). CRL2 complexes are hijacked by a number of viruses, including adenovirus, Epstein-Barr virus and HPV, among others. This redirects the ubiquitin ligase complex to target host proteins and in this way promotes viral propagation (reviewed in Mahon et al, 2014).

Preceded by: NEDD8:AcM-UBE2M binds CRL2 E3 ubiquitin ligase complex

Followed by: VHL:EloB,C:NEDD8-CUL2:RBX1 complex binds UBXN7, VHL:EloB,C:NEDD8-CUL2:RBX1 complex binds hydroxyprolyl-HIF-alpha, COP9 signalosome deneddylates cytosolic CRL E3 ubiquitin ligase complexes

Literature references

Pick, E., Mahon, C., Krogan, NJ., Craik, CS. (2014). Cullin E3 ligases and their rewiring by viral factors. *Biomolecules, 4* , 897-930. ↗

Kato, S., Shimbara, N., Miyamoto, C., Osaka, F., Okabayashi, K., Chiba, T. et al. (1999). Covalent modification of all members of human cullin family proteins by NEDD8. *Oncogene, 18*, 6829-34. ↗

Gao, B., Tan, C., Zhang, DD., Chapman, E., Yagishita, N., Zhao, F. et al. (2014). Hrd1 suppresses Nrf2-mediated cellular protection during liver cirrhosis. *Genes Dev, 28*, 708-22. ↗

Cai, W., Yang, H. (2016). The structure and regulation of Cullin 2 based E3 ubiquitin ligases and their biological functions. *Cell Div, 11*, 7. ↗

Borg, LA., Hunt, HW., Duda, DM., Schulman, BA., Hammel, M., Scott, DC. (2008). Structural insights into NEDD8 activation of cullin-RING ligases: conformational control of conjugation. *Cell, 134*, 995-1006. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2022-03-04	Reviewed	Somers, J.

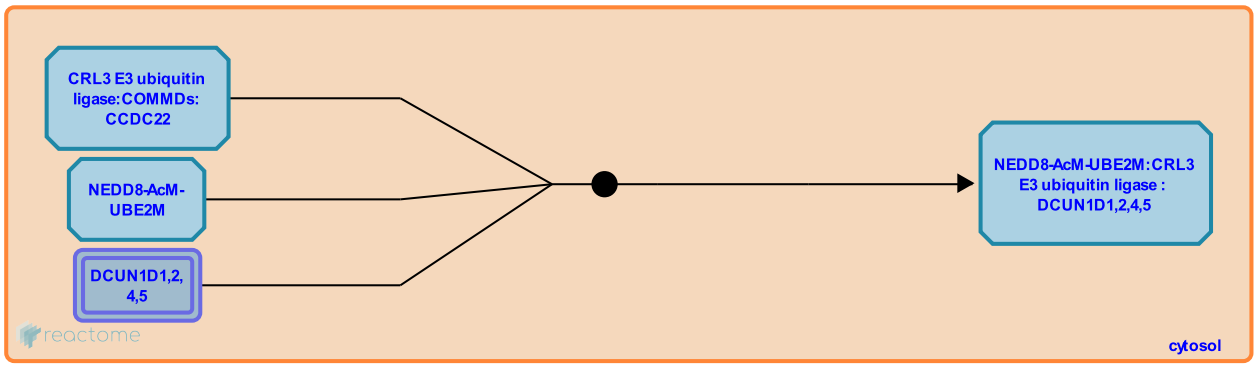
NEDD8:AcM-UBE2M binds CRL3 E3 ubiquitin ligase complex ↗

Location: Neddylation

Stable identifier: R-HSA-8952630

Type: binding

Compartments: cytosol



UBE2M is the E2 for CRL complexes containing cullin 1, 2, 3 and 4 (Huang et al, 2009; Monda et al, 2013). Interaction between UBE2M and the CUL3 E3 complex is facilitated by a DCUN1D (also known as DCNL) scaffold protein, of which there are 5 in human cells (Kim et al, 2008; Kurz et al, 2008; Meyer-Schaller et al, 2009; Monda et al, 2013; Keuss et al, 2016). DCUN1D proteins interact with higher affinity to the N-terminally acetylated forms of UBE2F and UBE2M (Scott et al, 2011; Monda et al, 2013). Although each of the 5 DCUN1D proteins appears to interact with most cullin subtypes, specificity may arise through differences in expression and localization, and DCUN1D3 may play a specialized role in sequestering CRL E3 ligase complexes at the cell membrane (Monda et al, 2013; Keuss et al, 2016; Meyer-Schaller et al, 2009; Huang et al, 2014; reviewed in Enchev et al, 2103). Although in this pathway, COMMD proteins and DCUN1D are shown acting sequentially in the activation of the CRL E3 ligase complex, the relationship between these protein families is not totally clear, as DCUN1D proteins have been identified in complexes that also contain the inhibitor CAND1 (Kim et al, 2008; Huang et al, 2014).
Target specificity of the CRL3 complex is directed by the nature of the BTB substrate recognition protein. For instance, BTB protein KEAP1 is the main controller of NFE2L2 stability (Cuadrado et al, 2019). CRL3 complexes target proteins involved in processes such as development and stress response (reviewed in Genschik et al, 2013). CRL3 complexes are also hijacked by a number of viruses, redirecting the ubiquitin ligase complex to target host proteins and in this way promoting viral propagation (reviewed in Mahon et al, 2014).

Preceded by: Transfer of NEDD8 to AcM-UBE2M, COMMDs displace CAND1 from cytosolic CRL E3 ubiquitin ligase complexes

Followed by: AcM-UBE2M transfers NEDD8 to CRL3 E3 ubiquitin ligase complex

Literature references

Bennett, EJ., Miller, DJ., Schulman, BA., Harper, JW., King, D., Lydeard, J. et al. (2013). Structural conservation of distinctive N-terminal acetylation-dependent interactions across a family of mammalian NEDD8 ligation enzymes. *Structure, 21*, 42-53. ↗

Pick, E., Mahon, C., Krogan, NJ., Craik, CS. (2014). Cullin E3 ligases and their rewiring by viral factors. *Biomolecules, 4* , 897-930. ↗

Chou, YC., Willems, AR., Meyer-Schaller, N., Sicheri, F., Tyers, M., Peter, M. et al. (2008). Dcn1 functions as a scaffold-type E3 ligase for cullin neddylation. *Mol. Cell, 29*, 23-35. ↗

Hofmann, K., Chou, YC., Sumara, I., Meyer-Schaller, N., Sicheri, F., Berthiaume, LG. et al. (2009). The human Dcn1-like protein DCNL3 promotes Cul3 neddylation at membranes. *Proc. Natl. Acad. Sci. U.S.A., 106*, 12365-70. ↗

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. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2022-02-23	Reviewed	Cuadrado, A.
2022-02-23	Revised	Rothfels, K.

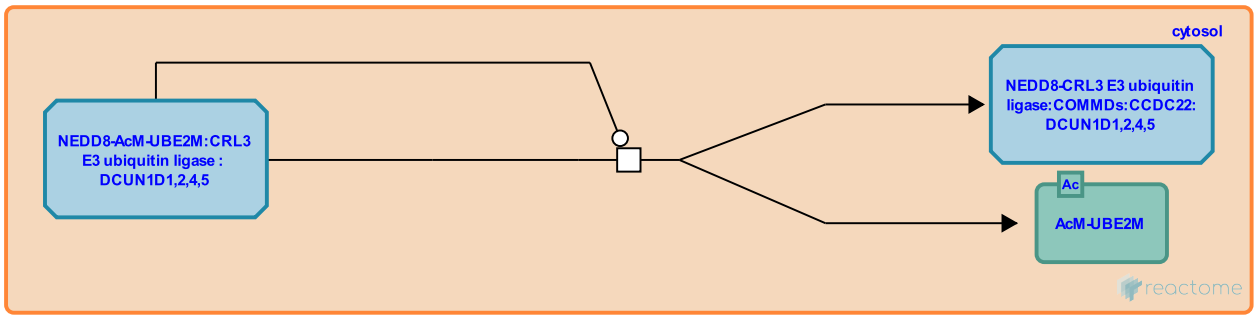
AcM-UBE2M transfers NEDD8 to CRL3 E3 ubiquitin ligase complex ↗

Location: Neddylation

Stable identifier: R-HSA-8952631

Type: transition

Compartments: cytosol



UBE2M transfers NEDD8 to lysine 712 of CUL3 in the E3 ligase complex (Hori et al, 1999; Duda et al, 2008). Neddylation increases the ubiquitin ligase activity of the E3 complex towards its targets, and prevents binding of the CUL3 complex with the CAND1 inhibitor (Hori et al, 1999; Duda et al, 2008). CRL3 ubiquitin ligase complexes target substrates through a BTB substrate recognition protein, and regulate processes such as development and stress response, as well as viral replication (reviewed in Genschik et al, 2013; Mahon et al, 2014).

Preceded by: NEDD8:AcM-UBE2M binds CRL3 E3 ubiquitin ligase complex

Followed by: COP9 signalosome deneddylates cytosolic CRL E3 ubiquitin ligase complexes

Literature references

Pick, E., Mahon, C., Krogan, NJ., Craik, CS. (2014). Cullin E3 ligases and their rewiring by viral factors. *Biomolecules, 4* , 897-930. ↗

Kato, S., Shimbara, N., Miyamoto, C., Osaka, F., Okabayashi, K., Chiba, T. et al. (1999). Covalent modification of all members of human cullin family proteins by NEDD8. *Oncogene, 18*, 6829-34. ↗

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. ↗

Borg, LA., Hunt, HW., Duda, DM., Schulman, BA., Hammel, M., Scott, DC. (2008). Structural insights into NEDD8 activation of cullin-RING ligases: conformational control of conjugation. *Cell, 134*, 995-1006. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2022-02-23	Reviewed	Cuadrado, A.
2022-02-23	Revised	Rothfels, K.

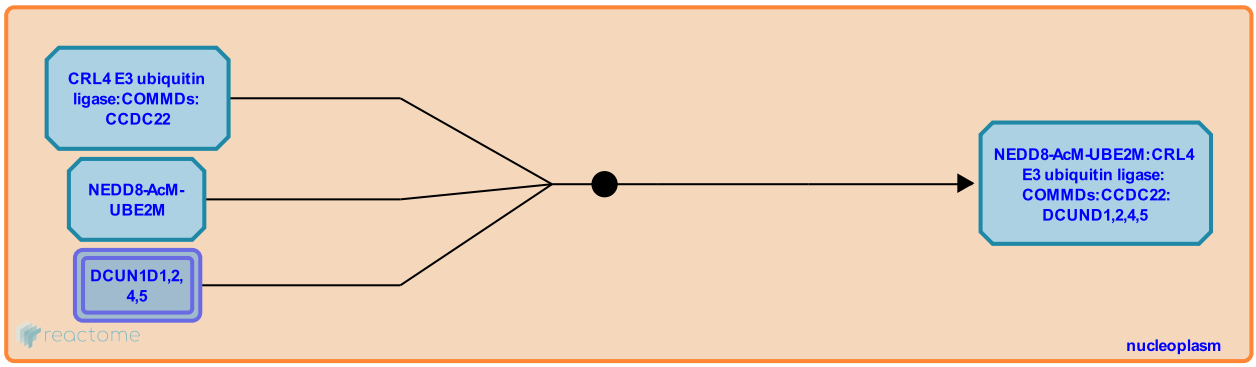
NEDD8:AcM-UBE2M binds CRL4 E3 ubiquitin ligase complex ↗

Location: Neddylation

Stable identifier: R-HSA-8952639

Type: binding

Compartments: nucleoplasm



UBE2M is the E2 for CRL complexes containing cullin 1, 2, 3 and 4 (Huang et al, 2009; Monda et al, 2013). Interaction between UBE2M and the CUL4A and 4B E3 complex is facilitated by a DCUN1D (also known as DCNL) scaffold protein, of which there are 5 in human cells (Kim et al, 2008; Kurz et al, 2008; Meyer-Schaller et al, 2009; Monda et al, 2013; Keuss et al, 2016). DCUN1D proteins interact with higher affinity to the N-terminally acetylated forms of UBE2F and UBE2M (Scott et al, 2011; Monda et al, 2013). Although each of the 5 DCUN1D proteins appears to interact with most cullin subtypes, specificity may arise through differences in expression and localization, and DCUN1D3 may play a specialized role in sequestering CRL E3 ligase complexes at the cell membrane (Monda et al, 2013; Keuss et al, 2016; Meyer-Schaller et al, 2009; Huang et al, 2014; reviewed in Enchev et al, 2103). Although in this pathway, COMMD proteins and DCUN1D are shown acting sequentially in the activation of the CRL E3 ligase complex, the relationship between these protein families is not totally clear, as DCUN1D proteins have been identified in complexes that also contain the inhibitor CAND1 (Kim et al, 2008; Huang et al, 2014).
CRL4 complexes ubiquitinate target proteins involved in processes such as cell cycle progression, DNA repair and replication, cell growth and metabolism (reviewed in Hannah and Zhou, 2015; Sang et al, 2015). CRL4 complexes are also hijacked by a number of viruses, redirecting the ubiquitin ligase complex to target host proteins and in this way promoting viral propagation (reviewed in Mahon et al, 2014). Note that because many of the key CRL4 ubiquitin targets are nuclear, these complexes are depicted in the nucleus. Cytoplasmic targets have also been identified, however (reviewed in Hannah and Zhou, 2015).

Preceded by: COMMDs displace CAND1 from CRL4 E3 ubiquitin ligase complex, Transfer of NEDD8 to AcM-UBE2M

Followed by: AcM-UBE2M transfers NEDD8 to CRL4 E3 ubiquitin ligase complex

Literature references

Bennett, EJ., Miller, DJ., Schulman, BA., Harper, JW., King, D., Lydeard, J. et al. (2013). Structural conservation of distinctive N-terminal acetylation-dependent interactions across a family of mammalian NEDD8 ligation enzymes. *Structure, 21*, 42-53. ↗

Pick, E., Mahon, C., Krogan, NJ., Craik, CS. (2014). Cullin E3 ligases and their rewiring by viral factors. *Biomolecules, 4* , 897-930. ↗

Ren, X., Sang, Y., Yan, F. (2015). The role and mechanism of CRL4 E3 ubiquitin ligase in cancer and its potential therapy implications. *Oncotarget, 6*, 42590-602. ↗

Chou, YC., Willems, AR., Meyer-Schaller, N., Sicheri, F., Tyers, M., Peter, M. et al. (2008). Dcn1 functions as a scaffold-type E3 ligase for cullin neddylation. *Mol. Cell, 29*, 23-35. ↗

Hofmann, K., Chou, YC., Sumara, I., Meyer-Schaller, N., Sicheri, F., Berthiaume, LG. et al. (2009). The human Dcn1-like protein DCNL3 promotes Cul3 neddylation at membranes. *Proc. Natl. Acad. Sci. U.S.A., 106*, 12365-70. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

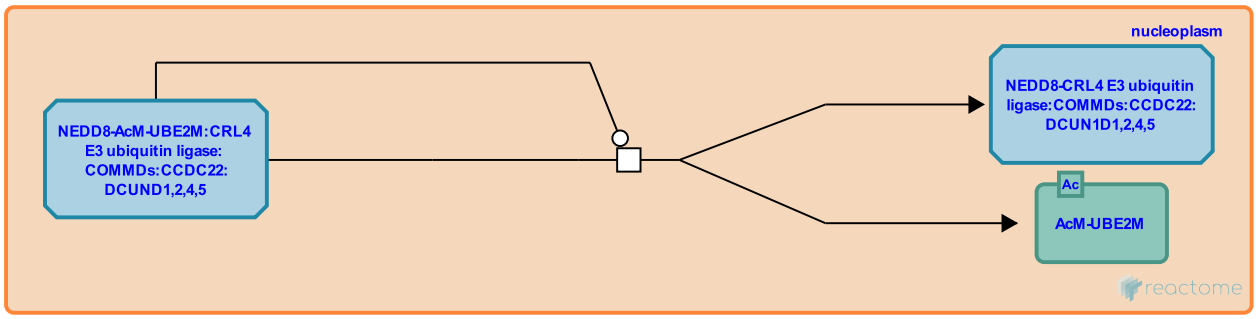
AcM-UBE2M transfers NEDD8 to CRL4 E3 ubiquitin ligase complex ↗

Location: Neddylation

Stable identifier: R-HSA-8952638

Type: transition

Compartments: nucleoplasm



UBE2M transfers NEDD8 to lysine 705 of CUL4A and lysine 859 of CUL4B (Hori et al, 1999; Duda et al, 2008). Neddylation increases the ubiquitination activity of the E3 complex towards its targets, and prevents binding of the CUL4 complex with the CAND1 inhibitor (Hori et al, 1999; Duda et al, 2008). CRL4 complexes ubiquitinate target proteins involved in processes such as cell cycle progression, DNA repair and replication, cell growth and metabolism (reviewed in Hannah and Zhou, 2015; Sang et al, 2015). CRL4 complexes are also hijacked by a number of viruses, redirecting the ubiquitin ligase complex to target host proteins and in this way promoting viral propagation (reveiwed in Mahon et al, 2014). Note that because many of the key CRL4 ubiquitin targets are nuclear, these complexes are depicted in the nucleus. Cytoplasmic targets have also been identified, however (reviewed in Hannah and Zhou, 2015).

Preceded by: NEDD8:AcM-UBE2M binds CRL4 E3 ubiquitin ligase complex

Followed by: COP9 signalosome deneddylates nuclear CRL4 E3 ubiquitin ligase complex

Literature references

Pick, E., Mahon, C., Krogan, NJ., Craik, CS. (2014). Cullin E3 ligases and their rewiring by viral factors. *Biomolecules, 4* , 897-930. ↗

Kato, S., Shimbara, N., Miyamoto, C., Osaka, F., Okabayashi, K., Chiba, T. et al. (1999). Covalent modification of all members of human cullin family proteins by NEDD8. *Oncogene, 18*, 6829-34. ↗

Ren, X., Sang, Y., Yan, F. (2015). The role and mechanism of CRL4 E3 ubiquitin ligase in cancer and its potential therapy implications. *Oncotarget, 6*, 42590-602. ↗

Zhou, P., Hannah, J. (2015). Distinct and overlapping functions of the cullin E3 ligase scaffolding proteins CUL4A and CUL4B. *Gene, 573*, 33-45. ↗

Borg, LA., Hunt, HW., Duda, DM., Schulman, BA., Hammel, M., Scott, DC. (2008). Structural insights into NEDD8 activation of cullin-RING ligases: conformational control of conjugation. *Cell, 134*, 995-1006. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

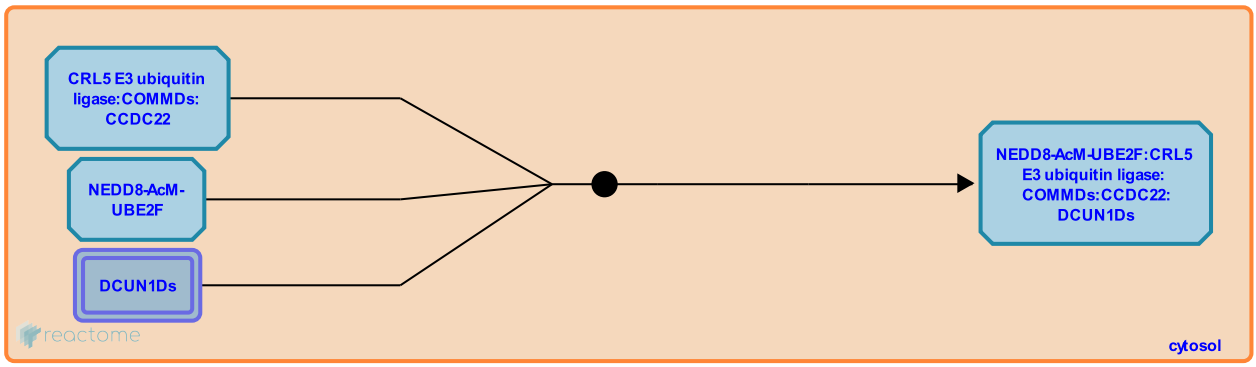
NEDD8:AcM-UBE2F binds CRL5 E3 ubiquitin ligase complex ↗

Location: Neddylation

Stable identifier: R-HSA-8952039

Type: binding

Compartments: cytosol



UBE2F is specific for the CUL5:RBX2-containing E3 ligase complex (Huang et al, 2009; Monda et al, 2013). Interaction between UBE2F and the CUL5 E3 complex is facilitated by a DCUN1D (also known as DCNL) scaffold protein, of which there are 5 in human cells (Kim et al, 2008; Kurz et al, 2008; Meyer-Schaller et al, 2009; Monda et al, 2013; Keuss et al, 2016). DCUN1D proteins interact with higher affinity to the N-terminally acetylated forms of UBE2F and UBE2M (Scott et al, 2011; Monda et al, 2013). Although each of the 5 DCUN1D proteins appears to interact with most cullin subtypes, specificity may arise through differences in expression and localization, and DCUN1D3 may play a specialized role in sequestering CRL E3 ligase complexes at the cell membrane (Monda et al, 2013; Keuss et al, 2016; Meyer-Schaller et al, 2009; Huang et al, 2014; reviewed in Enchev et al, 2103). Although in this pathway, COMMD proteins and DCUN1D are shown acting sequentially in the activation of the CRL E3 ligase complex, the relationship between these protein families is not totally clear, as DCUN1D proteins have been identified in complexes that also contain the inhibitor CAND1 (Kim et al, 2008; Huang et al, 2014).
CUL5 RING complexes target a variety of cellular proteins for ubiquitination and degradation, including receptor and non-receptor tyrosine kinases, signaling molecules transcriptional regulators (reviewed in Okumura et al, 2016). CRL5 complexes are also hijacked by viruses such as HIV and HPV, among others. Interaction with viral proteins redirects the ubiquitin ligase complex, targeting host proteins such as immune factors and in this way promoting viral propagation (reveiwed in Mahon et al, 2014).

Preceded by: Transfer of NEDD8 to AcM-UBE2F, COMMDs displace CAND1 from cytosolic CRL E3 ubiquitin ligase complexes

Followed by: AcM-UBE2F transfers NEDD8 to CRL5 E3 ubiquitin ligase complex

Literature references

Bennett, EJ., Miller, DJ., Schulman, BA., Harper, JW., King, D., Lydeard, J. et al. (2013). Structural conservation of distinctive N-terminal acetylation-dependent interactions across a family of mammalian NEDD8 ligation enzymes. *Structure, 21*, 42-53. ↗

Pick, E., Mahon, C., Krogan, NJ., Craik, CS. (2014). Cullin E3 ligases and their rewiring by viral factors. *Biomolecules, 4* , 897-930. ↗

Chou, YC., Willems, AR., Meyer-Schaller, N., Sicheri, F., Tyers, M., Peter, M. et al. (2008). Dcn1 functions as a scaffold-type E3 ligase for cullin neddylation. *Mol. Cell, 29*, 23-35. ↗

Hofmann, K., Chou, YC., Sumara, I., Meyer-Schaller, N., Sicheri, F., Berthiaume, LG. et al. (2009). The human Dcn1-like protein DCNL3 promotes Cul3 neddylation at membranes. *Proc. Natl. Acad. Sci. U.S.A., 106*, 12365-70. ↗

Bommeljé, CC., Ramanathan, Y., Ryan, RJ., Lee, BE., Yonekawa, Y., Choi, L. et al. (2008). SCCRO (DCUN1D1) is an essential component of the E3 complex for neddylation. *J. Biol. Chem., 283*, 33211-20. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

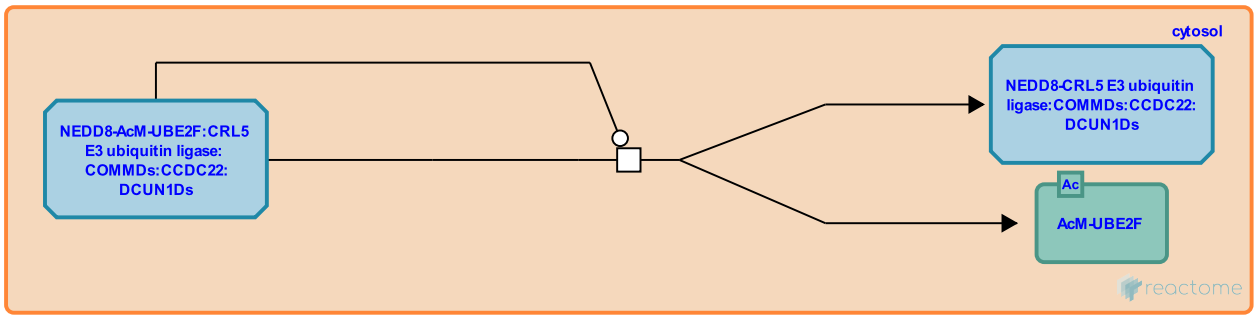
AcM-UBE2F transfers NEDD8 to CRL5 E3 ubiquitin ligase complex ↗

Location: Neddylation

Stable identifier: R-HSA-8952044

Type: transition

Compartments: cytosol



UBE2F transfers NEDD8 to lysine 724 of CUL5 in the E3 ligase complex (Duda et al, 2008). Neddylation increases the ubiquitination activity of the E3 complex towards its target, and prevents binding of the CUL5 complex with the CAND1 inhibitor (Hori et al, 1999; Duda et al, 2008; Kelsall et al, 2013). Targets of CUL5 RING complexes include a variety of cellular proteins including receptor and non-receptor tyrosine kinases, signaling molecules transcriptional regulators (reviewed in Okamura et al, 2016). CRL5 complexes are also hijacked by viruses such as HIV, HPV and adenovirus among others. Interaction with viral proteins redirects the ubiquitin ligase complex to target host proteins to promote conditions that favor viral propagation (Harada et al, 2002; Mehle et al, 2004; reviewed in Mahon et al, 2014).

Preceded by: NEDD8:AcM-UBE2F binds CRL5 E3 ubiquitin ligase complex

Followed by: COP9 signalosome deneddylates cytosolic CRL E3 ubiquitin ligase complexes

Literature references

Santa-Marta, M., Goncalves, J., Gabuzda, D., McPike, M., Mehle, A. (2004). Phosphorylation of a novel SOCS-box regulates assembly of the HIV-1 Vif-Cul5 complex that promotes APOBEC3G degradation. *Genes Dev, 18*, 2861-6. ↗

Pick, E., Mahon, C., Krogan, NJ., Craik, CS. (2014). Cullin E3 ligases and their rewiring by viral factors. *Biomolecules, 4* , 897-930. ↗

Berk, AJ., Pallas, DC., Harada, JN., Shevchenko, A., Shevchenko, A. (2002). Analysis of the adenovirus E1B-55K-anchored proteome reveals its link to ubiquitination machinery. *J. Virol., 76*, 9194-206. ↗

Kato, S., Shimbara, N., Miyamoto, C., Osaka, F., Okabayashi, K., Chiba, T. et al. (1999). Covalent modification of all members of human cullin family proteins by NEDD8. *Oncogene, 18*, 6829-34. ↗

Hofmann, K., Alpi, AF., Duda, DM., Schulman, BA., Knebel, A., Wood, N. et al. (2013). TRIAD1 and HHARI bind to and are activated by distinct neddylated Cullin-RING ligase complexes. *EMBO J., 32*, 2848-60. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

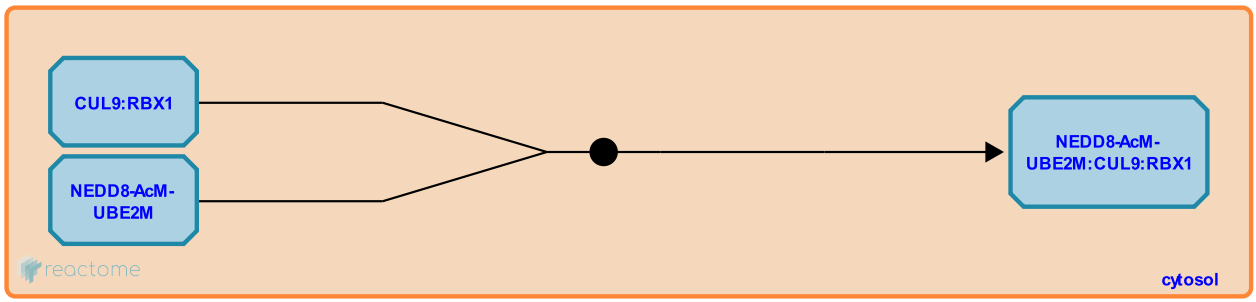
NEDD8:AcM-UBE2M binds CUL9:RBX1 ubiquitin ligase complex ↗

Location: Neddylation

Stable identifier: R-HSA-8956031

Type: binding

Compartments: cytosol



CUL9 (also known as PARC for p53-associated PARkin-like cytoplasmic protein) is an atypical cullin that has been shown to form a ubiquitin ligase complex with RBX1, although other components of the putative CRL9 complex have not yet been identified (Skaar et al, 2007; Li et al, 2014). CUL9:RBX1 is neddylated in vivo, likely through the UBE2M E2 although this hasn't been directly demonstrated (Skaar et al, 2007).
CUL9 is 60% identical to CUL7, another atypical mammalian cullin family member, but more distantly related to CUL1, 2, 3, 4A,4B and 5. CUL9 and CUL7 have been shown to form a heterodimer in vivo, and both interact with p53 (Skaar et al, 2007; Andrews et al, 2006; Nikolaev et al, 2003). CUL9 ubiquitinates BIRC5 (also known as Survivin), a protein with roles in cellular proliferation and inhibition of apoptosis. CUL9-mediated ubiquitination of BIRC5 is inhibited by the 3M complex, which consists of CUL7, CCDC8 and OBSL1 (Li et al, 2014).

Preceded by: Transfer of NEDD8 to AcM-UBE2M

Followed by: AcM-UBE2M transfers NEDD8 to CUL9:RBX1

Literature references

Gu, W., Nikolaev, AY., Qin, J., Puskas, N., Li, M. (2003). Parc: a cytoplasmic anchor for p53. *Cell, 112*, 29-40. ↗

Tron, A., Florens, L., Tsutsumi, T., Skaar, JR., Swanson, SK., Arai, T. et al. (2007). PARC and CUL7 form atypical cullin RING ligase complexes. *Cancer Res., 67*, 2006-14. ↗

He, YJ., Andrews, P., Xiong, Y. (2006). Cytoplasmic localized ubiquitin ligase cullin 7 binds to p53 and promotes cell growth by antagonizing p53 function. *Oncogene, 25*, 4534-48. ↗

Pei, XH., Yan, J., Li, Z., Xiong, Y., Yan, F., Cappell, KM. et al. (2014). CUL9 mediates the functions of the 3M complex and ubiquitylates survivin to maintain genome integrity. *Mol. Cell, 54*, 805-19. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

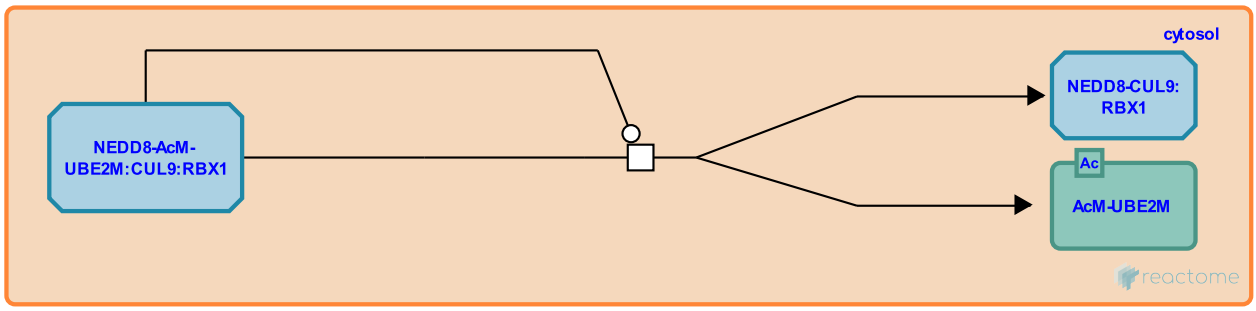
AcM-UBE2M transfers NEDD8 to CUL9:RBX1 ↗

Location: Neddylation

Stable identifier: R-HSA-8956025

Type: transition

Compartments: cytosol



UBE2M transfers NEDD8 to lysine 1881 of CUL9 (Skaar et al, 2007; Li et al, 2014). Neddylation increases the ubiquitination activity of the E3 complex towards its targets (Hori et al, 1999; Duda et al, 2008). One defined target of CUL9 is BIRC5 (also known as Survivin), which has roles in cellular proliferation, inhibition of apoptosis and maintenance of genome stability (Zhao et al, 2000; Watanabe, 2010). CUL9-mediated ubiquitination of BIRC5 is negatively regulated by the 3M complex, consisting of CUL7, CCDC8 and OBSL1 (Li et al, 2014).

Preceded by: NEDD8:AcM-UBE2M binds CUL9:RBX1 ubiquitin ligase complex

Followed by: CUL9:RBX1 ubiquitinates BIRC5, NEDD8-CUL9:RBX1 binds CUL7:CCDC8:OBSL1

Literature references

Tron, A., Florens, L., Tsutsumi, T., Skaar, JR., Swanson, SK., Arai, T. et al. (2007). PARC and CUL7 form atypical cullin RING ligase complexes. *Cancer Res., 67*, 2006-14. ↗

Kato, S., Shimbara, N., Miyamoto, C., Osaka, F., Okabayashi, K., Chiba, T. et al. (1999). Covalent modification of all members of human cullin family proteins by NEDD8. *Oncogene, 18*, 6829-34. ↗

Pei, XH., Yan, J., Li, Z., Xiong, Y., Yan, F., Cappell, KM. et al. (2014). CUL9 mediates the functions of the 3M complex and ubiquitylates survivin to maintain genome integrity. *Mol. Cell, 54*, 805-19. ↗

Watanabe, Y. (2010). Temporal and spatial regulation of targeting aurora B to the inner centromere. *Cold Spring Harb. Symp. Quant. Biol., 75*, 419-23. ↗

Downward, J., Lemoine, NR., Martins, LM., Tenev, T., Zhao, J. (2000). The ubiquitin-proteasome pathway regulates survivin degradation in a cell cycle-dependent manner. *J. Cell. Sci., 113*, 4363-71. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

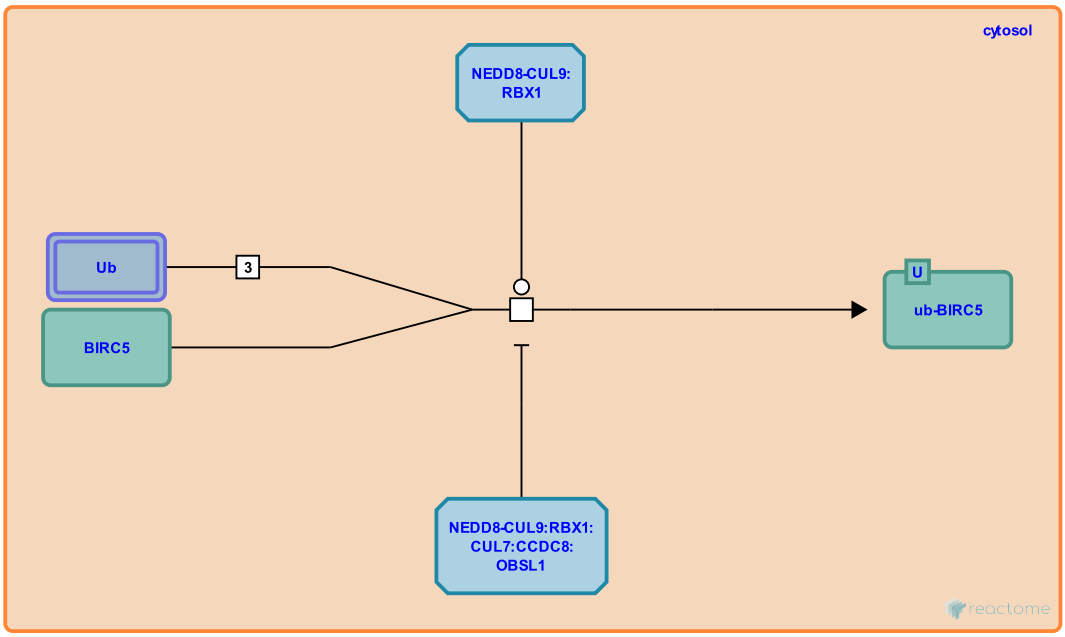
CUL9:RBX1 ubiquitinates BIRC5 ↗

Location: Neddylation

Stable identifier: R-HSA-8956026

Type: transition

Compartments: cytosol



One defined target of CUL9 ubiquitin ligase is BIRC5 (also known as Survivin), which has roles in cellular proliferation, inhibition of apoptosis and maintenance of genome stability (Zhao et al, 2000; Watanabe, 2010). Deletion of CUL9 leads to polyploidy, abnormal nuclear morphology and DNA damage and is accompanied by an increase in survivin protein levels (Li et al, 2014). CUL9-mediated ubiquitination of BIRC5 is negatively regulated by the 3M complex, consisting of CUL7, CCDC8 and OBSL1 (Li et al, 2014; Yan et al, 2014). This CUL7-dependent inhibition of CUL9 ubiquitin ligase activity is promoted by heterodimerization between CUL7 and CUL9 (Li et al, 2014).

Preceded by: AcM-UBE2M transfers NEDD8 to CUL9:RBX1

Literature references

Yu, Y., Chen, X., Sinnott, B., Yan, J., Li, Z., Xiong, Y. et al. (2014). The 3M complex maintains microtubule and genome integrity. *Mol. Cell, 54*, 791-804. ↗

Pei, XH., Yan, J., Li, Z., Xiong, Y., Yan, F., Cappell, KM. et al. (2014). CUL9 mediates the functions of the 3M complex and ubiquitylates survivin to maintain genome integrity. *Mol. Cell, 54*, 805-19. ↗

Watanabe, Y. (2010). Temporal and spatial regulation of targeting aurora B to the inner centromere. *Cold Spring Harb. Symp. Quant. Biol., 75*, 419-23. ↗

Downward, J., Lemoine, NR., Martins, LM., Tenev, T., Zhao, J. (2000). The ubiquitin-proteasome pathway regulates survivin degradation in a cell cycle-dependent manner. *J. Cell. Sci., 113*, 4363-71. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

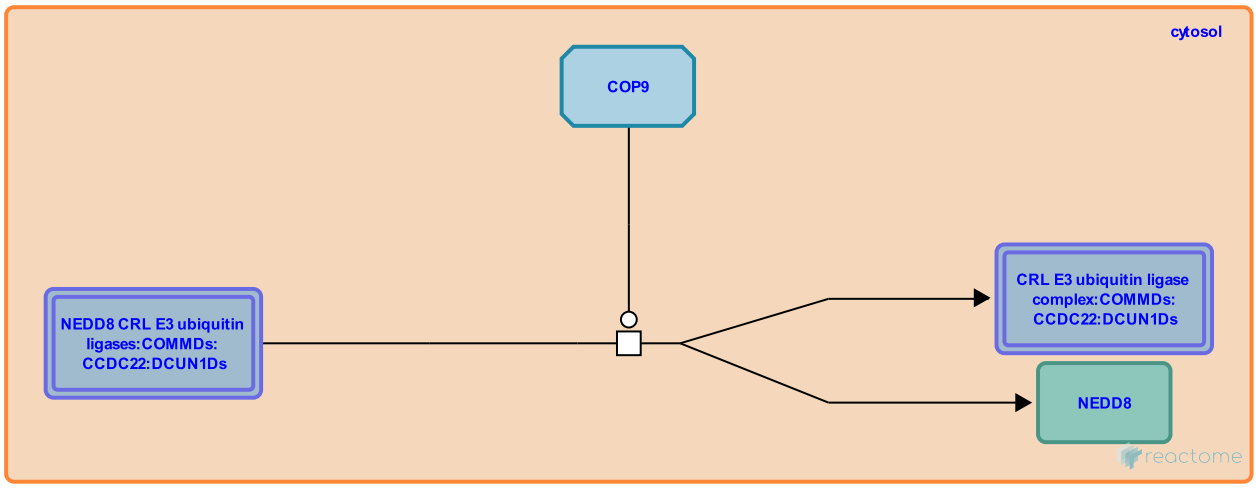
COP9 signalosome deneddylates cytosolic CRL E3 ubiquitin ligase complexes ↗

Location: Neddylation

Stable identifier: R-HSA-8956040

Type: transition

Compartments: cytosol



The COP9 signalosome (also known as CSN) is a highly conserved multi-subunit enzymatic complex that plays a role as the sole CRL ubiquitin ligase deneddylase. Deneddylation decreases ubiquitin ligase activity of CRL complexes, and is required for the sCAND1 binding to the cullin subunit. The CSN is required for stabilization of CRL substrate receptors: without the CSN, CRL complexes are "hyper-active" and promote their own degradation through autoubiquitination. Both the CSN and CAND1 allow remodeling of the ubiquitin ligase complex through exchange of the ubiquitin substrate specific receptors (Cope et al, 2006; Denti et al, 2006; Peth et al, 2007; Schmidt et al, 2009; Enchev et al, 2012; Pierce et al, 2013; Zemla et al, 2013; Wu et al, 2013, reviewed in Wei et al, 2008). Deregulation of the CRL-CSN pathway causes misregulation of numerous important cellular targets and has been implicated in the development of some cancers (reviewed in Gummlich et al, 2013).

Preceded by: AcM-UBE2M transfers NEDD8 to CRL3 E3 ubiquitin ligase complex, AcM-UBE2M transfers NEDD8 to CRL2 E3 ubiquitin ligase complex, AcM-UBE2F transfers NEDD8 to CRL5 E3 ubiquitin ligase complex, AcM-UBE2M transfers NEDD8 to CRL1 E3 ubiquitin ligase complex

Followed by: NEDD8 and UBD bind NUB1 and the 26S proteasome

Literature references

Wood, NT., Knebel, A., Rabut, G., Kedziora, S., Thomas, Y., Kurz, T. et al. (2013). CSN- and CAND1-dependent remodelling of the budding yeast SCF complex. *Nat Commun, 4*, 1641. ↗

Maine, GN., Mao, X., Komarck, CM., Burstein, E. (2007). COMMD1 promotes the ubiquitination of NF-kappaB subunits through a cullin-containing ubiquitin ligase. *EMBO J., 26*, 436-47. ↗

Cope, GA., Deshaies, RJ. (2006). Targeted silencing of Jab1/Csn5 in human cells downregulates SCF activity through reduction of F-box protein levels. *BMC Biochem., 7*, 1. ↗

Wei, N., Serino, G., Deng, XW. (2008). The COP9 signalosome: more than a protease. *Trends Biochem. Sci., 33*, 592-600. ↗

Wu, S., Petroski, MD., Nhan, T., Wolf, DA., Toth, JI., Zhu, W. (2013). CAND1 controls in vivo dynamics of the cullin 1-RING ubiquitin ligase repertoire. *Nat Commun, 4*, 1642. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

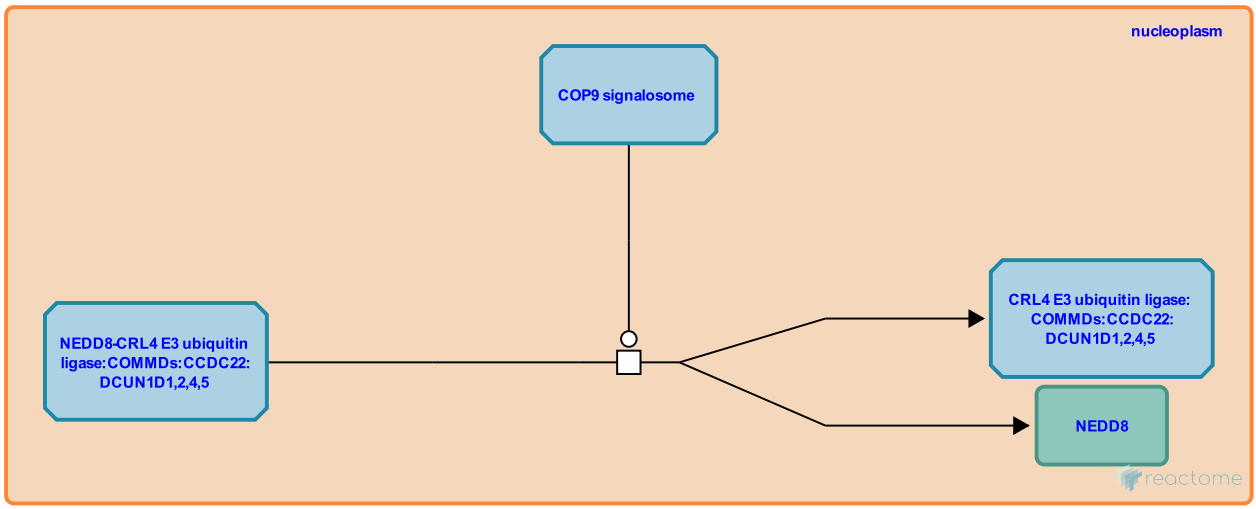
COP9 signalosome deneddylates nuclear CRL4 E3 ubiquitin ligase complex ↗

Location: Neddylation

Stable identifier: R-HSA-8956045

Type: transition

Compartments: nucleoplasm



The COP9 signalosome (also known as CSN) is a highly conserved multi-subunit enzymatic complex that plays a role as the sole CRL ubiquitin ligase deneddylase. Deneddylation decreases ubiquitin ligase activity of CRL complexes, and is required for the subsequent binding of CAND1 to the cullin subunit. The CSN is required for stabilization of CRL substrate receptors: without the CSN, CRL complexes are "hyper-active" and promote their own degradation through autoubiquitination. Both the CSN and CAND1 allow remodeling of the ubiquitin ligase complex through exchange of the ubiquitin substrate specific receptors (Cope et al, 2006; Denti et al, 2006; Peth et al, 2007; Schmidt et al, 2009; Enchev et al, 2012; Pierce et al, 2013; Zemla et al, 2013; Wu et al, 2013, reviewed in Wei et al, 2008). Deregulation of the CRL-CSN pathway causes misregulation of numerous important cellular targets and has been implicated in the development of some cancers (reviewed in Gummlich et al, 2013).

Preceded by: AcM-UBE2M transfers NEDD8 to CRL4 E3 ubiquitin ligase complex

Literature references

Wood, NT., Knebel, A., Rabut, G., Kedziora, S., Thomas, Y., Kurz, T. et al. (2013). CSN- and CAND1-dependent re-modelling of the budding yeast SCF complex. *Nat Commun, 4*, 1641. ↗

Cope, GA., Deshaies, RJ. (2006). Targeted silencing of Jab1/Csn5 in human cells downregulates SCF activity through reduction of F-box protein levels. *BMC Biochem., 7*, 1. ↗

Wei, N., Serino, G., Deng, XW. (2008). The COP9 signalosome: more than a protease. *Trends Biochem. Sci., 33*, 592-600. ↗

Wu, S., Petroski, MD., Nhan, T., Wolf, DA., Toth, JI., Zhu, W. (2013). CAND1 controls in vivo dynamics of the cullin 1-RING ubiquitin ligase repertoire. *Nat Commun, 4*, 1642. ↗

Hofmann, K., Wee, S., Schmidt, MW., McQuary, PR., Wolf, DA. (2009). F-box-directed CRL complex assembly and regulation by the CSN and CAND1. *Mol. Cell, 35*, 586-97. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

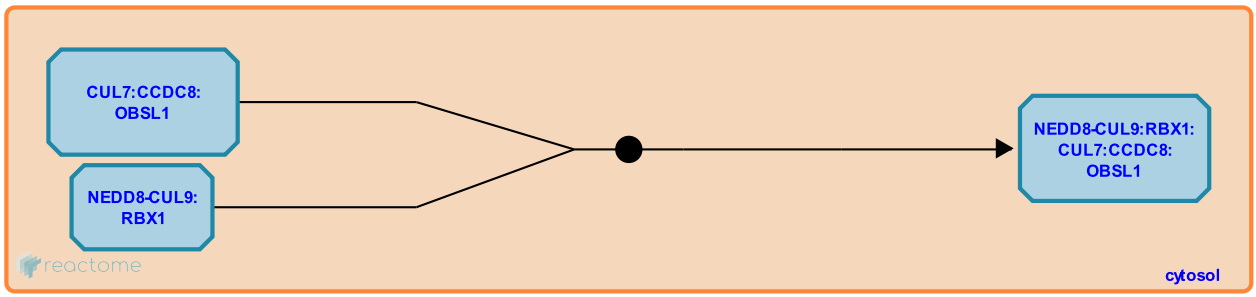
NEDD8-CUL9:RBX1 binds CUL7:CCDC8:OBSL1 ↗

Location: Neddylation

Stable identifier: R-HSA-8956050

Type: binding

Compartments: cytosol



CUL7, CCDC8 and OBSL1 are part of a 3M complex that has roles in maintenace of genome stability and microtubule dynamics (Li et al, 2014; Yan et al, 2014). The 3M complex inhibits CUL9-mediated ubiquitination of BIRC5 through the formation of a CUL9:CUL7 heterodimer (Skaar et al, 2007; Li et al, 2014)

Preceded by: AcM-UBE2M transfers NEDD8 to CUL9:RBX1

Literature references

Tron, A., Florens, L., Tsutsumi, T., Skaar, JR., Swanson, SK., Arai, T. et al. (2007). PARC and CUL7 form atypical cullin RING ligase complexes. *Cancer Res., 67*, 2006-14. ↗

Yu, Y., Chen, X., Sinnott, B., Yan, J., Li, Z., Xiong, Y. et al. (2014). The 3M complex maintains microtubule and genome integrity. *Mol. Cell, 54*, 791-804. ↗

Pei, XH., Yan, J., Li, Z., Xiong, Y., Yan, F., Cappell, KM. et al. (2014). CUL9 mediates the functions of the 3M complex and ubiquitylates survivin to maintain genome integrity. *Mol. Cell, 54*, 805-19. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

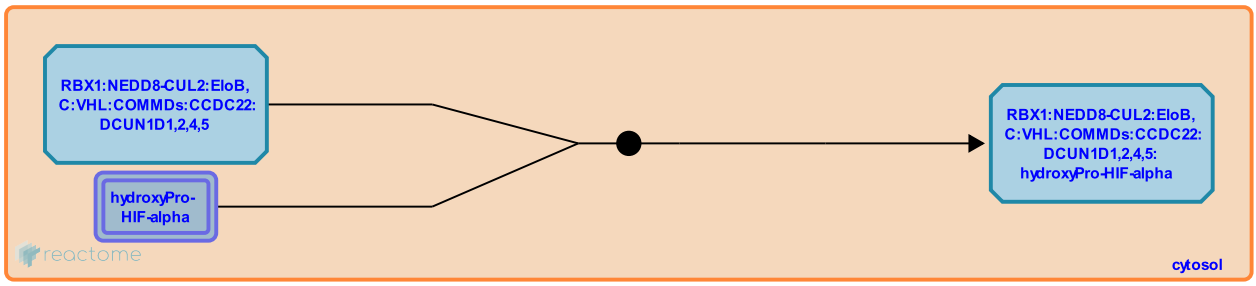
VHL:EloB,C:NEDD8-CUL2:RBX1 complex binds hydroxyprolyl-HIF-alpha ↗

Location: Neddylation

Stable identifier: R-HSA-8956103

Type: binding

Compartments: cytosol



The best characterized CRL2 substrate binding F-box protein is the von Hippel- Lindau (VHL) tumor suppressor, which targets the alpha subunit of hypoxia inducible factor (HIFalpha) for ubiquitination and degradation through VCP/p97 and the 26 S proteasome (Sufan and Ohh, 2006; Heir et al, 2013; reviewed in Cai and Yang, 2016). UBXN7 is an adapter that binds to neddylated CUL2 and interferes with the ability of the CUL2:EloB:EloC:VHL E3 ubiquitin ligase complex to ubiquitinate HIF alpha, in this way causing accumulation of HIF alpha (Bandau et al, 2012; Den Besten et al, 2012). MUL1 is an E3 ligase located in the outer mitochondrial membrane with its RING domain facing the cytosol. MUL1 ubiquitinates the cullin scaffold/adaptor protein UBXN7 at lysine residues K14 and K412, promoting its 26S proteasome-dependent degradation (Cilenti et al, 2020, DiGregorio et al, 2021). By inactivating UBXN7, MUL1 activity promotes the CUL2:RBX1-mediated degradation of HIF1 alpha (Di Gregorio et al, 2021).

Preceded by: AcM-UBE2M transfers NEDD8 to CRL2 E3 ubiquitin ligase complex

Followed by: VHL:EloB,C:NEDD8-CUL2:RBX1 complex ubiquitinylates HIF-alpha

Literature references

Sufan, RI., Ohh, M., Lee, JE., Poon, BP., Greer, SN., Heir, P. (2013). DCNL1 functions as a substrate sensor and activator of cullin 2-RING ligase. *Mol. Cell. Biol., 33*, 1621-31. ↗

Sufan, RI., Ohh, M. (2006). Role of the NEDD8 modification of Cul2 in the sequential activation of ECV complex. *Neoplasia, 8*, 956-63. ↗

Verma, R., Oania, RS., Kleiger, G., Deshaies, RJ., den Besten, W. (2012). NEDD8 links cullin-RING ubiquitin ligase function to the p97 pathway. *Nat. Struct. Mol. Biol., 19*, 511-6, S1. ↗

Cai, W., Yang, H. (2016). The structure and regulation of Cullin 2 based E3 ubiquitin ligases and their biological functions. *Cell Div, 11*, 7. ↗

Wood, NT., Knebel, A., Alexandru, G., Gage, ZO., Bandau, S. (2012). UBXN7 docks on neddylated cullin complexes using its UIM motif and causes HIF1α accumulation. *BMC Biol., 10*, 36. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

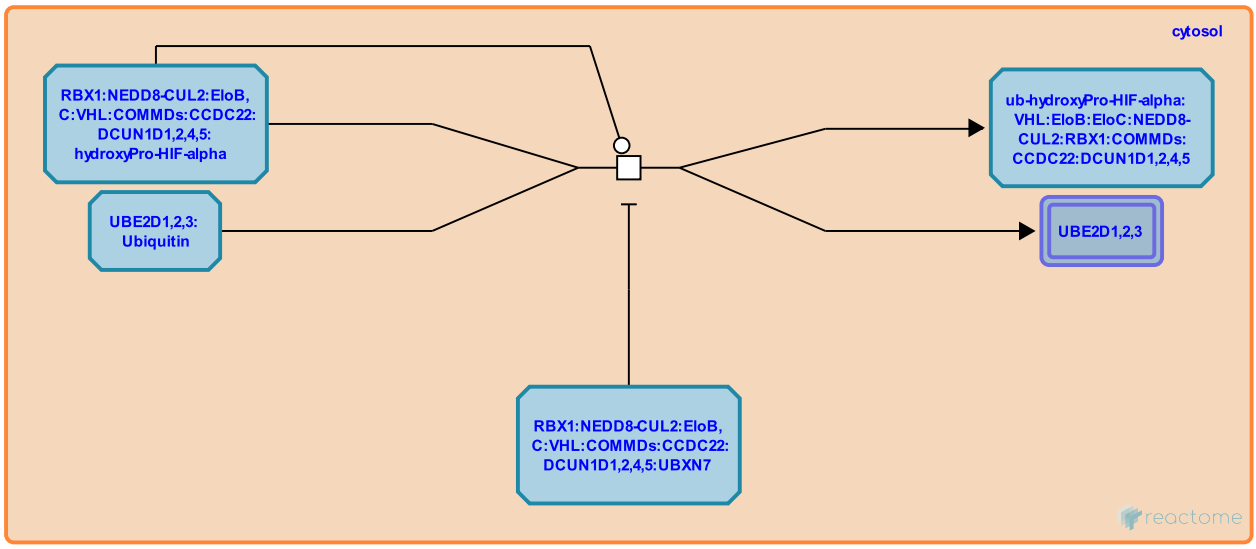
VHL:EloB,C:NEDD8-CUL2:RBX1 complex ubiquitinylates HIF-alpha ↗

Location: Neddylation

Stable identifier: R-HSA-8956106

Type: transition

Compartments: cytosol



VHL is the substrate binding protein of a CUL2-based E3 ubiquitin ligase complex that conjugates ubiquitin to hydroxylated HIF-alpha (Iwai et al. 1999, Kamura et al. 2000, Ohh et al. 2000, Groulx and Lee 2002, Maynard et al. 2003). VHL is predominantly cytosolic and shuttles between the cytosol and the nucleus (Lee et al. 1999, Groulx and Lee 2002). Ubiquitination and degradation of HIF-alpha can occur in both the cytosol and the nucleus (Berra et al. 2001). Upon return to normoxia from hypoxia most ubiquitinated HIF-alpha is nuclear (Groulx and Lee 2002).

Preceded by: VHL:EloB,C:NEDD8-CUL2:RBX1 complex binds hydroxyprolyl-HIF-alpha

Followed by: 26S proteasome degrades HIFalpha

Literature references

Lee, EH., Chung, J., Maynard, MA., Qi, H., Ohh, M., Conaway, JW. et al. (2003). Multiple splice variants of the human HIF-3 alpha locus are targets of the von Hippel-Lindau E3 ubiquitin ligase complex. *J Biol Chem, 278*, 11032-40. ↗

Pouysségur, J., Roux, D., Richard, DE., Berra, E. (2001). Hypoxia-inducible factor-1 alpha (HIF-1 alpha) escapes O(2)-driven proteasomal degradation irrespective of its subcellular localization: nucleus or cytoplasm. *EMBO Rep, 2*, 615-20. ↗

Kamura, T., Sato, S., Czyzyk-Krzeska, M., Conaway, JW., Iwai, K., Conaway, RC. (2000). Activation of HIF1alpha ubiquitination by a reconstituted von Hippel-Lindau (VHL) tumor suppressor complex. *Proc Natl Acad Sci U S A, 97*, 10430-5. ↗

Stearman, R., Pavlakis, GN., Stauber, R., Neumann, M., Klausner, RD., Lee, S. et al. (1999). Transcription-dependent nuclear-cytoplasmic trafficking is required for the function of the von Hippel-Lindau tumor suppressor protein. *Mol Cell Biol, 19*, 1486-97. ↗

Pavletich, N., Kim, TY., Park, CW., Ivan, M., Kaelin, WG., Ohh, M. et al. (2000). Ubiquitination of hypoxia-inducible factor requires direct binding to the beta-domain of the von Hippel-Lindau protein. *Nat Cell Biol, 2*, 423-7. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

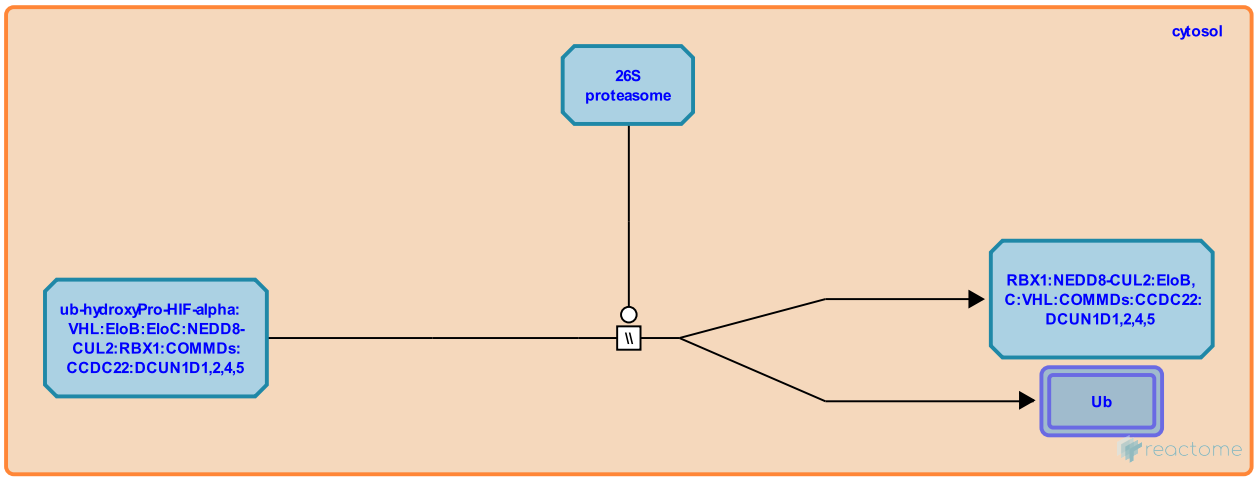
26S proteasome degrades HIFalpha ↗

Location: Neddylation

Stable identifier: R-HSA-9755303

Type: omitted

Compartments: cytosol



Destruction of ubiquitinated HIF-alpha can occur in both the cytosol and nucleus (Berra et al. 2001). Upon reoxygenation of hypoxic cells HIF-alpha is ubiquitinated in the nucleus and transported to the cytosol in a complex with VHL:ElonginB:ElonginC:CUL2:RBX1 where it is destroyed (Groulx and Lee 2002, Jaakkola et al. 2001, Ivan et al. 2001)

Preceded by: VHL:EloB,C:NEDD8-CUL2:RBX1 complex ubiquitinylates HIF-alpha

Literature references

Pouysségur, J., Roux, D., Richard, DE., Berra, E. (2001). Hypoxia-inducible factor-1 alpha (HIF-1 alpha) escapes O(2)-driven proteasomal degradation irrespective of its subcellular localization: nucleus or cytoplasm. *EMBO Rep, 2*, 615-20. ↗

Lane, WS., Asara, JM., Kim, W., Salic, A., Valiando, J., Ivan, M. et al. (2001). HIFalpha targeted for VHL-mediated destruction by proline hydroxylation: implications for O2 sensing. *Science, 292*, 464-8. ↗

Gielbert, J., Gaskell, SJ., Maxwell, PH., Mukherji, M., Pugh, CW., Mole, DR. et al. (2001). Targeting of HIF-alpha to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. *Science, 292*, 468-72. ↗

Lee, S., Groulx, I. (2002). Oxygen-dependent ubiquitination and degradation of hypoxia-inducible factor requires nuclear-cytoplasmic trafficking of the von Hippel-Lindau tumor suppressor protein. *Mol Cell Biol, 22*, 5319-36. ↗

Editions

2022-01-16	Authored, Edited	Rothfels, K.
2022-03-04	Reviewed	Somers, J.

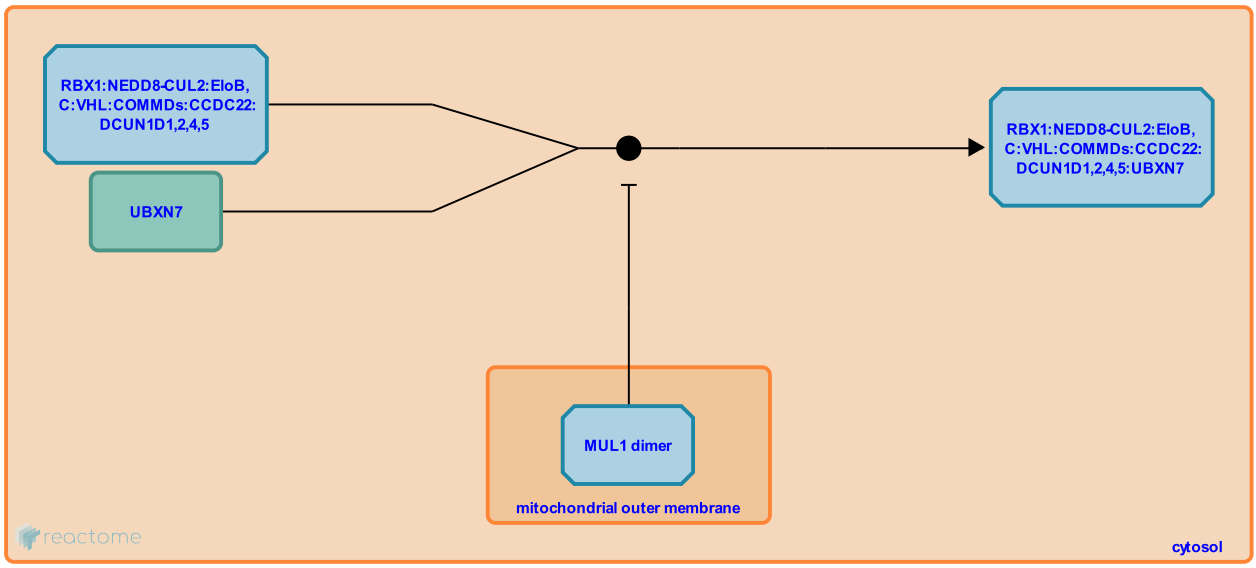
VHL:EloB,C:NEDD8-CUL2:RBX1 complex binds UBXN7 ↗

Location: Neddylation

Stable identifier: R-HSA-8956099

Type: binding

Compartments: cytosol



The best characterized CRL2 substrate binding F-box protein is the von Hippel- Lindau (VHL) tumor suppressor, which targets the alpha subunit of hypoxia inducible factor (HIFalpha) for ubiquitination and degradation through VCP/p97 and the 26 S proteasome (Sufan and Ohh, 2006; Heir et al, 2013; reviewed in Cai and Yang, 2016). UBXN7 is an adapter that binds to neddylated CUL2 and interferes with the ability of the CUL2:EloB:EloC:VHL E3 ubiquitin ligase complex to ubiquitinate HIF alpha, in this way causing accumulation of HIF alpha (Bandau et al, 2012; Den Besten et al, 2012). MUL1 is an E3 ligase located in the outer mitochondrial membrane with its RING domain facing the cytosol. MUL1 ubiquitinates the cullin scaffold/adaptor protein UBXN7 at lysine residues K14 and K412, promoting its 26S proteasome-dependent degradation (Cilenti et al, 2020, DiGregorio et al, 2021). By inactivating UBXN7, MUL1 activity promotes the CUL2:RBX1-mediated degradation of HIF1 alpha (Di Gregorio et al, 2021).

Preceded by: AcM-UBE2M transfers NEDD8 to CRL2 E3 ubiquitin ligase complex

Literature references

Sufan, RI., Ohh, M., Lee, JE., Poon, BP., Greer, SN., Heir, P. (2013). DCNL1 functions as a substrate sensor and activator of cullin 2-RING ligase. *Mol. Cell. Biol., 33*, 1621-31. ↗

Sufan, RI., Ohh, M. (2006). Role of the NEDD8 modification of Cul2 in the sequential activation of ECV complex. *Neoplasia, 8*, 956-63. ↗

Verma, R., Oania, RS., Kleiger, G., Deshaies, RJ., den Besten, W. (2012). NEDD8 links cullin-RING ubiquitin ligase function to the p97 pathway. *Nat. Struct. Mol. Biol., 19*, 511-6, S1. ↗

Di Gregorio, J., Zervos, AS., Liao, R., Andl, T., Ambivero, CT., Cilenti, L. (2020). Mitochondrial MUL1 E3 ubiquitin ligase regulates Hypoxia Inducible Factor (HIF-1α) and metabolic reprogramming by modulating the UBXN7 cofactor protein. *Sci Rep, 10*, 1609. ↗

Cai, W., Yang, H. (2016). The structure and regulation of Cullin 2 based E3 ubiquitin ligases and their biological functions. *Cell Div, 11*, 7. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.
2022-02-23	Reviewed	Cuadrado, A.
2022-02-28	Revised	Rothfels, K.

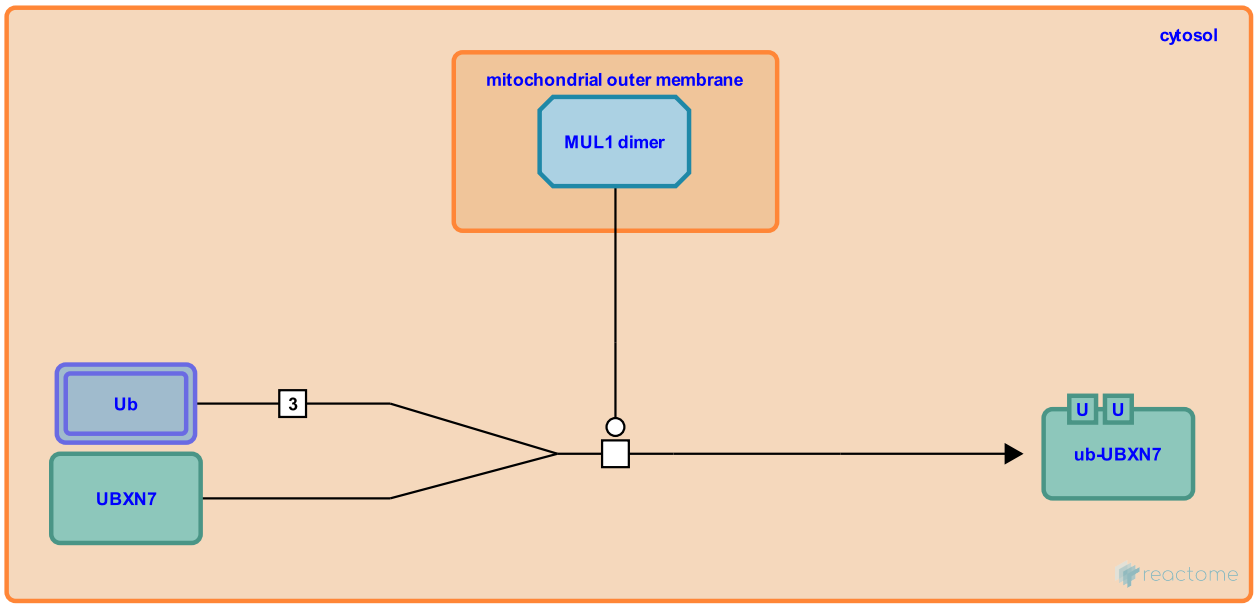
MUL1 ubiquitinates UBXN7 ↗

Location: Neddylation

Stable identifier: R-HSA-9755304

Type: transition

Compartments: cytosol, mitochondrial outer membrane



MUL1 is an E3 ligase located in the outer mitochondrial membrane with its RING domain facing the cytosol. MUL1 ubiquitinates the cullin scaffold/adaptor protein UBXN7 at lysine residues K14 and K412, promoting its 26S proteasome-dependent degradation (Cilenti et al, 2020, DiGregorio et al, 2021).
Protein levels of UBXN7, in turn, govern the stability and and activity of various cullin E3 ligase complexes, including the VHL:CUL2 ligase complex and the KEAP1:CUL3 ligase complex. Ubiquitination by these CRL cullin ligase complexes promote the degradation of transcription factors such as HIF1alpha and NFE2L2, which play roles in the response to hypoxia and oxidative stress (Iwai et al. 1999, Kamura et al. 2000, Ohh et al. 2000, Groulx and Lee 2002, Maynard et al. 2003; Tao et al, 2017; Itoh et al. 1999, Cullinan et al. 2004, Kobayashi et al. 2004, Zhang et al. 2004, Furukawa & Xiong 2005). High levels of UBXN7 lead to HIF1alpha accumulation, whereas low levels of UBXN7 correlate with an increase in NFE2L2 protein.
By regulating UBXN7 levels in response to reactive oxygen species and hypoxic stress, MUL1 affects the protein levels of HIF1alpha and NFE2L2 and ultimately their targets and may contribute to a switch between glycolysis and oxidative phosphorylation. The role of MUL1 in regulating these factors through UBXN7 protein levels may contribute to the Warburg effect, common in many cancers, where cells switch to glycolysis even in the presence of adequate oxygen. Consistent with this, downregulation of UBXN7 is associated with increased oxidative phosphorylation while high levels of UBXN7 promote glycolysis (Cilenti et al, 2020; Di Gregorio et al, 2021).

Followed by: ub UBXN7 is degraded by the 26S proteasome

Literature references

Lee, EH., Chung, J., Maynard, MA., Qi, H., Ohh, M., Conaway, JW. et al. (2003). Multiple splice variants of the human HIF-3 alpha locus are targets of the von Hippel-Lindau E3 ubiquitin ligase complex. *J Biol Chem, 278*, 11032-40. ↗

Pavletich, N., Kim, TY., Park, CW., Ivan, M., Kaelin, WG., Ohh, M. et al. (2000). Ubiquitination of hypoxia-inducible factor requires direct binding to the beta-domain of the von Hippel-Lindau protein. *Nat Cell Biol, 2*, 423-7. ↗

Di Gregorio, J., Zervos, AS., Liao, R., Andl, T., Ambivero, CT., Cilenti, L. (2020). Mitochondrial MUL1 E3 ubiquitin ligase regulates Hypoxia Inducible Factor (HIF-1α) and metabolic reprogramming by modulating the UBXN7 cofactor protein. *Sci Rep, 10*, 1609. ↗

Furukawa, M., Xiong, Y. (2005). BTB protein Keap1 targets antioxidant transcription factor Nrf2 for ubiquitination by the Cullin 3-Roc1 ligase. *Mol. Cell. Biol., 25*, 162-71. ↗

Jin, J., Harper, JW., Gordan, JD., Diehl, JA., Cullinan, SB. (2004). The Keap1-BTB protein is an adaptor that bridges Nrf2 to a Cul3-based E3 ligase: oxidative stress sensing by a Cul3-Keap1 ligase. *Mol. Cell. Biol., 24*, 8477-86. ↗

Editions

2022-02-23	Reviewed	Cuadrado, A.
2022-02-23	Authored, Edited	Rothfels, K.

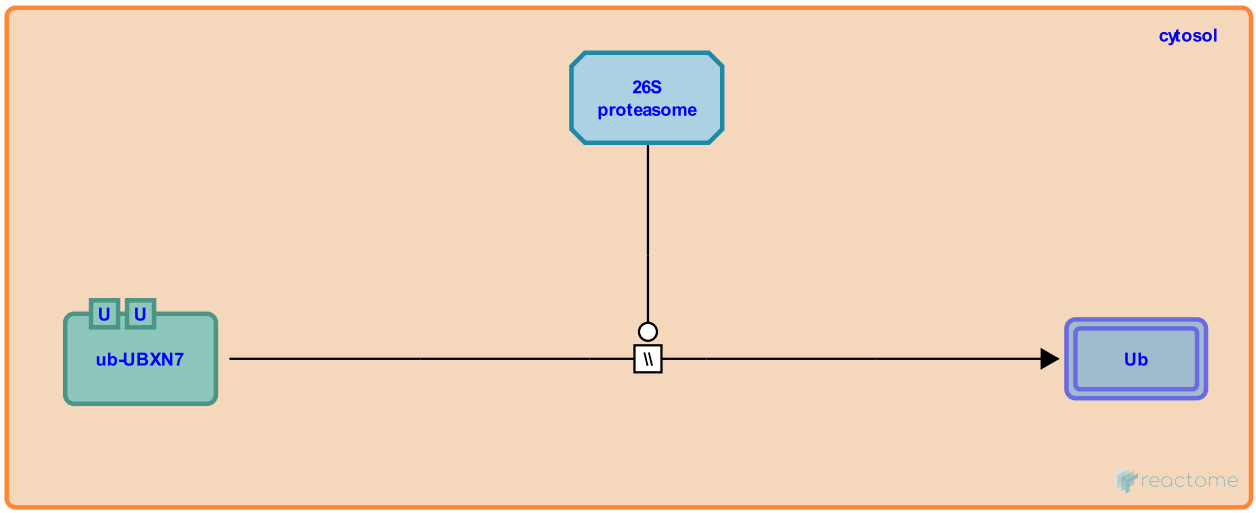
ub UBXN7 is degraded by the 26S proteasome ↗

Location: Neddylation

Stable identifier: R-HSA-9755306

Type: omitted

Compartments: cytosol



After MUL1-dependent ubiquitination, UBXN7 is degraded by the 26 S proteasome. This results in increased levels of NFE2L2 and corresponding decreased levels in HIF1alpha (Cilenti et al, 2020; Di Gregorio et al, 2021).

Preceded by: MUL1 ubiquitinates UBXN7

Literature references

Di Gregorio, J., Zervos, AS., Liao, R., Andl, T., Ambivero, CT., Cilenti, L. (2020). Mitochondrial MUL1 E3 ubiquitin ligase regulates Hypoxia Inducible Factor (HIF-1α) and metabolic reprogramming by modulating the UBXN7 cofactor protein. *Sci Rep, 10*, 1609. ↗

Di Gregorio, J., Zervos, AS., Liao, R., Andl, T., Ambivero, CT., Cilenti, L. (2021). UBXN7 cofactor of CRL3^{KEAP1} and CRL2^{VHL} ubiquitin ligase complexes mediates reciprocal regulation of NRF2 and HIF-1α proteins. *Biochim Biophys Acta Mol Cell Res, 1868*, 118963. ↗

Editions

2021-10-08	Edited	Rothfels, K.
2022-02-23	Reviewed	Cuadrado, A.
2022-02-23	Authored	Rothfels, K.

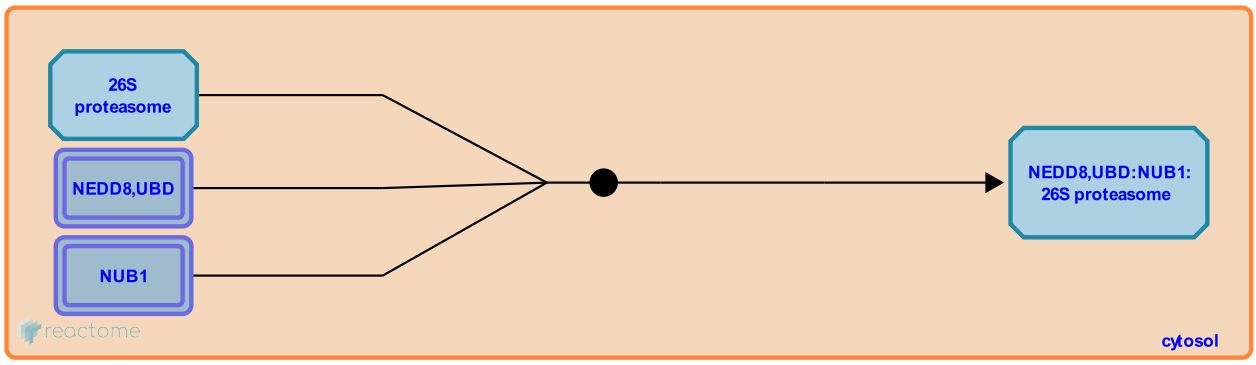
NEDD8 and UBD bind NUB1 and the 26S proteasome ↗

Location: Neddylation

Stable identifier: R-HSA-8956140

Type: binding

Compartments: cytosol



NEDD8 ultimate buster 1 (NUB1) is a negative regulator of the NEDD8 conjugation system. NUB1 interacts with NEDD8 and another ubiquitin-like modifier, UBD (also known as FAT10) to promote their degradation and that of their conjugated proteins (Kito et al, 2001; Kamitani et al, 2001; Hipp et al, 2004; Schmidtke et al, 2006). NUB1 interacts directly with both NEDD8/UBD and with PMSD4, a subunit of the 19S cap of the 26S proteasome, through a ubiquitin-like domain (UBL), and in this way promotes the contact between the proteasome and its substrate (Kito et al, 2001; Kamitani et al, 2001; Hipp et al, 2004; Tanji et al, 2005; Schmidtke et al, 2006; reviewed in Tanaka et al, 2012; Schmidtke et al, 2014). There are two isoforms of NUB1 in human cells that differ by the presence of a 14 amino acid insertion in the NUB1L. NUB1L promotes the degradation of NEDD8 more efficiently than the short isoform (Tanaka et al, 2003).

Preceded by: Release of mature NEDD8, COP9 signalosome deneddylates cytosolic CRL E3 ubiquitin ligase complexes

Followed by: 26S- and NUB1-mediated degradation of NEDD8, UBD and their conjugates

Literature references

Kito, K., Fukuda-Kamitani, T., Yeh, ET., Kamitani, T. (2001). Targeting of NEDD8 and its conjugates for proteasomal degradation by NUB1. *J. Biol. Chem., 276*, 46655-60. ↗

Kito, K., Kamitani, T., Yeh, ET. (2001). NUB1, a NEDD8-interacting protein, is induced by interferon and down-regulates the NEDD8 expression. *J. Biol. Chem., 276*, 20603-9. ↗

Groettrup, M., Raasi, S., Hipp, MS., Schmidtke, G. (2004). NEDD8 ultimate buster-1L interacts with the ubiquitin-like protein FAT10 and accelerates its degradation. *J. Biol. Chem., 279*, 16503-10. ↗

Yeh, ET., Tanaka, T., Kawashima, H., Kamitani, T. (2003). Regulation of the NEDD8 conjugation system by a splicing variant, NUB1L. *J. Biol. Chem., 278*, 32905-13. ↗

Tanaka, T., Tanji, K., Kamitani, T. (2005). Interaction of NUB1 with the proteasome subunit S5a. *Biochem. Biophys. Res. Commun., 337*, 116-20. ↗

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

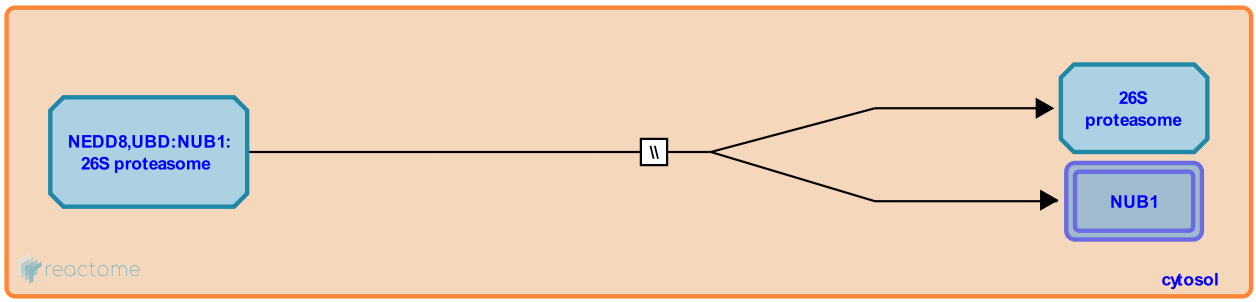
26S- and NUB1-mediated degradation of NEDD8, UBD and their conjugates

Location: Neddylation

Stable identifier: R-HSA-8956184

Type: omitted

Compartments: cytosol



NUB1 mediates the 26S proteasome-dependent degradation of NEDD8, UBN (also known as FAT10) and their protein conjugates (Kamitani et al, 2001; Tanji et al, 2005;Schmidtke et al, 2006; reviewed in Tanaka et al, 2012; Schmidtke et al, 2014). Unlike the case for ubiquitin, the NEDD8 moiety also seems to be subject to degradation along with its conjugated proteins.

Preceded by: NEDD8 and UBD bind NUB1 and the 26S proteasome

Literature references

Kito, K., Fukuda-Kamitani, T., Yeh, ET., Kamitani, T. (2001). Targeting of NEDD8 and its conjugates for proteasomal degradation by NUB1. *J. Biol. Chem., 276*, 46655-60.

Tanaka, T., Tanji, K., Kamitani, T. (2005). Interaction of NUB1 with the proteasome subunit S5a. *Biochem. Biophys. Res. Commun., 337*, 116-20.

Groettrup, M., Hipp, MS., Schmidtke, G., Kalveram, B., Lukasiak, S., Bochtler, P. et al. (2006). The UBA domains of NUB1L are required for binding but not for accelerated degradation of the ubiquitin-like modifier FAT10. *J. Biol. Chem., 281*, 20045-54.

Tanaka, T., Nakatani, T., Kamitani, T. (2012). Inhibition of NEDD8-conjugation pathway by novel molecules: potential approaches to anticancer therapy. *Mol Oncol, 6*, 267-75.

Aichem, A., Groettrup, M., Schmidtke, G. (2014). FAT10ylation as a signal for proteasomal degradation. *Biochim. Biophys. Acta, 1843*, 97-102.

Editions

2016-12-13	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

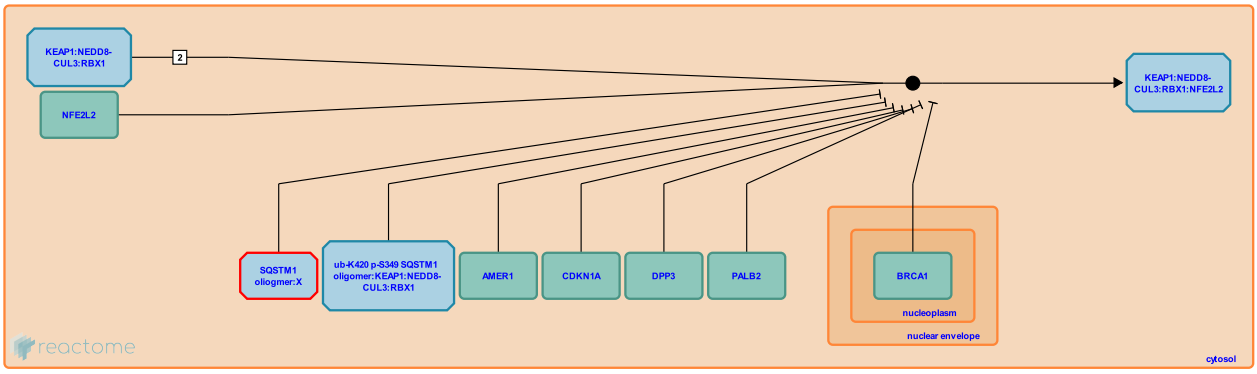
NFE2L2 binds KEAP1:NEDD8-CUL3:RBX1 ↗

Location: Neddylation

Stable identifier: R-HSA-8932327

Type: binding

Compartments: cytosol



Under the basal resting conditions, cytosolic Nuclear factor erythroid 2-related NFE2L2 (NRF2) is maintained at low basal levels by constitutive proteasomal degradation. Kelch-like ECH associated protein 1 (KEAP1), which is a substrate adaptor protein for the Cullin 3 (CUL3)-dependent E3 ubiquitin ligase complex binds with and represses NFE2L2 by promoting its ubiquitination and subsequent proteasomal degradation (Itoh et al. 1999, Cullinan et al. 2004, Kobayashi et al. 2004, Zhang et al. 2004, Furukawa & Xiong 2005). Therefore, the KEAP1–CUL3–E3 ubiquitin ligase complex tightly regulates NFE2L2 protein to maintain it at a low level. NFE2L2 contains seven functional domains, known as Neh1-Neh7. Neh2 domain contains two motifs termed ETGE and DLG that are involved in interacting with KEAP1. The ETGE and the DLG motifs have overlapping binding sites on KEAP1, with the ETGE motif mediating a higher affinity interaction with KEAP1 than the DLG motif. One molecule of NFE2L2 interacts simultaneously with two KEAP1 molecules, with the DLG motif and the ETGE motif on NFE2L2 contacting similar sites on each member of the KEAP1 dimer (Tong et al, 2006; McMahon et al, 2006; Baird et al, 2013; Fukutomi et al, 2014). This complex assembly positions NFE2L2 appropriately to be ubiquitinated by the CUL3/RBX1 ubiquitin ligase, targeting it for degradation. In the presence of electrophiles or other NFE2L2 inducers, conformational changes within KEAP1 occur as inducers interact with KEAP1 'sensor cysteines'. These conformational changes disrupt the KEAP1-DLG motif interaction, repositioning NFE2L2 within the KEAP1 complex in such a way as to prevent its ubiquitination. In this 'hinge and latch model', saturation of the KEAP1:CUL3:RBX1 complex with mal-positioned and thus not degradable NFE2L2 allows newly translated NFE2L2 to accumulate and translocate into the nucleus to stimulate transcription (Tong et al, 2006; Tong et al, 2007; reviewed in Baird and Yamamoto, 2020). This NFE2L2-KEAP1 interaction is also known to be regulated negatively by multiple proteins like PALB2, DPP3 and AMER(WTX1) which competitively bind with NFE2L2/KEAP1 and allow NFE2L2 nuclear translocation. They play an important role in NFE2L2 regulation to other pathways (Mizukami et al, 2012; Lu et al, 2017; Camp et al, 2012). In addition to that, this NFE2L2-KEAP1 binding is also regulated by succinylation of KEAP1 as cysteine residue and inhibits KEAP1 binding with NRF2 in FH mutant (LOF) condition (Ooi et al, 2011).
KEAP1 and NFE2L2 mutations occur in several tumor types and KEAP1 and NFE2L2 mutations occur at a frequency of around 25% in lung cancer. The NFE2L2 pathway has multiple pro-tumorigenic functions, and NFE2L2 levels are increased in head and neck squamous cell carcinoma (HNSCC). KEAP1 somatic mutant C23Y is observed in tumors from approximately 15% of patients with lung cancer (Hayes & McMahon 2009).

Followed by: KEAP1:NEDD8-CUL3:RBX1 complex ubiquitinates NFE2L2

Literature references

Zhang, DD., Cross, JV., Hannink, M., Templeton, DJ., Lo, SC. (2004). Keap1 is a redox-regulated substrate adaptor protein for a Cul3-dependent ubiquitin ligase complex. *Mol. Cell. Biol., 24*, 10941-53. ↗

Yamamoto, M., Itoh, K., Hayes, JD., McMahon, M., Thomas, N. (2006). Dimerization of substrate adaptors can facilitate cullin-mediated ubiquitylation of proteins by a "tethering" mechanism: a two-site interaction model for the Nrf2-Keap1 complex. *J Biol Chem, 281*, 24756-68. ↗

Yamamoto, M., Kobayashi, A., Katsuoka, F., Tong, KI. (2006). Two-site substrate recognition model for the Keap1-Nrf2 system: a hinge and latch mechanism. *Biol Chem, 387*, 1311-20. ↗

Yamamoto, M., Baird, L. (2020). The Molecular Mechanisms Regulating the KEAP1-NRF2 Pathway. *Mol Cell Biol, 40*. ↗

Yamamoto, M., Takagi, K., Ohuchi, N., Fukutomi, T., Mizushima, T. (2014). Kinetic, thermodynamic, and structural characterizations of the association between Nrf2-DLGex degron and Keap1. *Mol Cell Biol, 34*, 832-46. ↗

Editions

2016-07-22	Authored, Edited	Garapati, P V.
2021-01-23	Reviewed	Somers, J.
2022-02-23	Reviewed	Cuadrado, A.
2022-02-23	Revised	Rothfels, K.

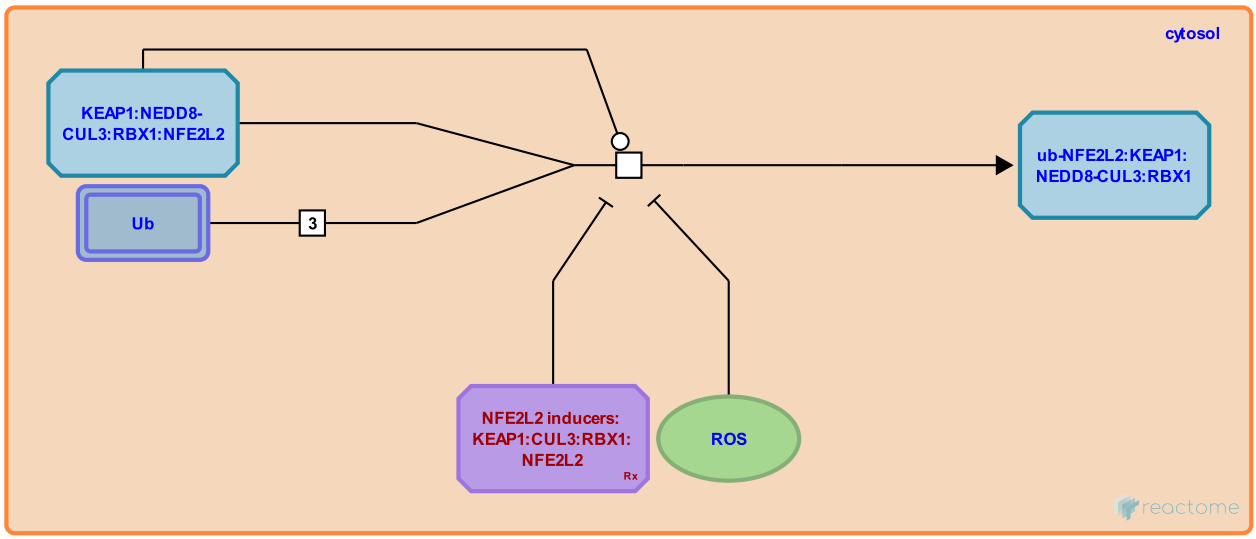
KEAP1:NEDD8-CUL3:RBX1 complex ubiquitinates NFE2L2 ↗

Location: Neddylation

Stable identifier: R-HSA-9755505

Type: transition

Compartments: cytosol



The KEAP1:CUL3:RBX1 E3-ubiquitin ligase complex is a negative regulator of Nuclear factor erythroid 2-related (NFE2L2). In the absence of oxidative alterations this E3-ubiquitin ligase complex is bound to NFE2L2 and targets it for ubiquitination (Cullinan et al, 2004; Kobayashi et al, 2004; reviewed in Baird and Yamamoto, 2020).

Preceded by: NFE2L2 binds KEAP1:NEDD8-CUL3:RBX1

Followed by: UBXN7:UBF1:NPLOC4:VCP hexamer binds NFE2L2:CRL3 complex

Literature references

Yamamoto, M., Baird, L. (2020). The Molecular Mechanisms Regulating the KEAP1-NRF2 Pathway. *Mol Cell Biol, 40*. ↗

Yamamoto, M., Kang, MI., Kobayashi, A., Igarashi, K., Chiba, T., Okawa, H. et al. (2004). Oxidative stress sensor Keap1 functions as an adaptor for Cul3-based E3 ligase to regulate proteasomal degradation of Nrf2. *Mol. Cell. Biol., 24*, 7130-9. ↗

Jin, J., Harper, JW., Gordan, JD., Diehl, JA., Cullinan, SB. (2004). The Keap1-BTB protein is an adaptor that bridges Nrf2 to a Cul3-based E3 ligase: oxidative stress sensing by a Cul3-Keap1 ligase. *Mol. Cell. Biol., 24*, 8477-86. ↗

Editions

2021-10-08	Authored, Edited	Rothfels, K.
2022-02-23	Reviewed	Cuadrado, A.

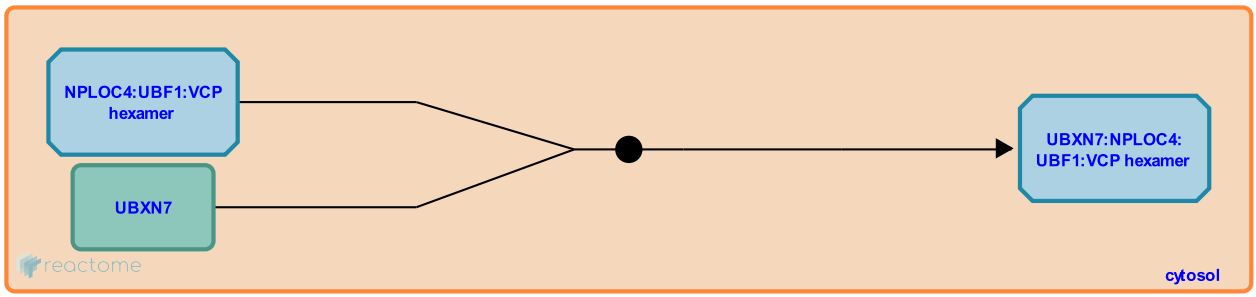
UBXN7 binds VCP hexamer:UBF1:NPLOC4 ↗

Location: Neddylation

Stable identifier: R-HSA-9758088

Type: binding

Compartments: cytosol



UBXN7 interacts with a complex of VCP, UBF1 and NPLOC4 to promote the CRL3- and 26 S proteasome-mediated degradation of factors such as NFE2L2 (Alexandru et al, 2008; Tao et al, 2017).

Followed by: UBXN7:UBF1:NPLOC4:VCP hexamer binds NFE2L2:CRL3 complex

Literature references

Fang, R., Kolawa, NJ., Graumann, J., Smith, GT., Alexandru, G., Deshaies, RJ. (2008). UBXD7 binds multiple ubiquitin ligases and implicates p97 in HIF1alpha turnover. *Cell, 134*, 804-16. ↗

Rojo de la Vega, M., Chen, H., Zhang, DD., Luo, G., Tao, S., Chapman, E. et al. (2017). p97 Negatively Regulates NRF2 by Extracting Ubiquitylated NRF2 from the KEAP1-CUL3 E3 Complex. *Mol Cell Biol, 37*. ↗

Editions

2021-10-08	Authored, Edited	Rothfels, K.
2022-02-23	Reviewed	Cuadrado, A.

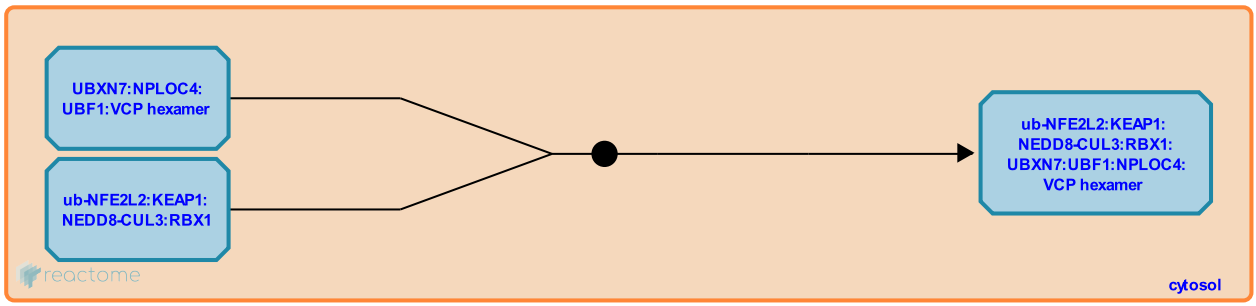
UBXN7:UBF1:NPLOC4:VCP hexamer binds NFE2L2:CRL3 complex ↗

Location: Neddylation

Stable identifier: R-HSA-9755507

Type: binding

Compartments: cytosol



VCP (also known as p97) is a hexameric ATPase with known roles in extracting ubiquinated substrates from multimeric E3 ligase complexes to promote their degradation by the 26S proteasome (Richly et al, 2005; Meyer et al, 2000; Rape et al, 2001; Tao et al, 2017; reviewed in van den Boom and Meyer, 2018). VCP has been shown to promote the extraction of ubiquitinated NFE2L2 from the KEAP1:CUL3:RBX1 complex in association with co-factors UBF1 and NPLOC4. UBXN7 also plays a role in the regulation of NFE2L2 protein levels, and interacts with VCP, UBF1 and NPLOC4 (Tao et al, 2017; Di Gregario et al, 2021).

Preceded by: UBXN7 binds VCP hexamer:UBF1:NPLOC4, KEAP1:NEDD8-CUL3:RBX1 complex ubiquitinates NFE2L2

Followed by: Ubiquitinated NFE2L2 is extracted from CRL3 complex for degradation

Literature references

Richly, H., Rape, M., Gorr, I., Jentsch, S., Hoppe, T., Kalocay, M. (2001). Mobilization of processed, membrane-tethered SPT23 transcription factor by CDC48(UFD1/NPL4), a ubiquitin-selective chaperone. *Cell, 107*, 667-77. ↗

Warren, G., Shorter, JG., Seemann, J., Meyer, HH., Pappin, D. (2000). A complex of mammalian ufd1 and npl4 links the AAA-ATPase, p97, to ubiquitin and nuclear transport pathways. *EMBO J, 19*, 2181-92. ↗

van den Boom, J., Meyer, H. (2018). VCP/p97-Mediated Unfolding as a Principle in Protein Homeostasis and Signaling. *Mol Cell, 69*, 182-194. ↗

Di Gregorio, J., Zervos, AS., Liao, R., Andl, T., Ambivero, CT., Cilenti, L. (2021). UBXN7 cofactor of CRL3^{KEAP1} and CRL2^{VHL} ubiquitin ligase complexes mediates reciprocal regulation of NRF2 and HIF-1α proteins. *Biochim Biophys Acta Mol Cell Res, 1868*, 118963. ↗

Hoege, C., Rape, M., Richly, H., Jentsch, S., Braun, S., Rumpf, S. (2005). A series of ubiquitin binding factors connects CDC48/p97 to substrate multiubiquitylation and proteasomal targeting. *Cell, 120*, 73-84. ↗

Editions

2021-10-08	Authored, Edited	Rothfels, K.
2022-02-23	Reviewed	Cuadrado, A.

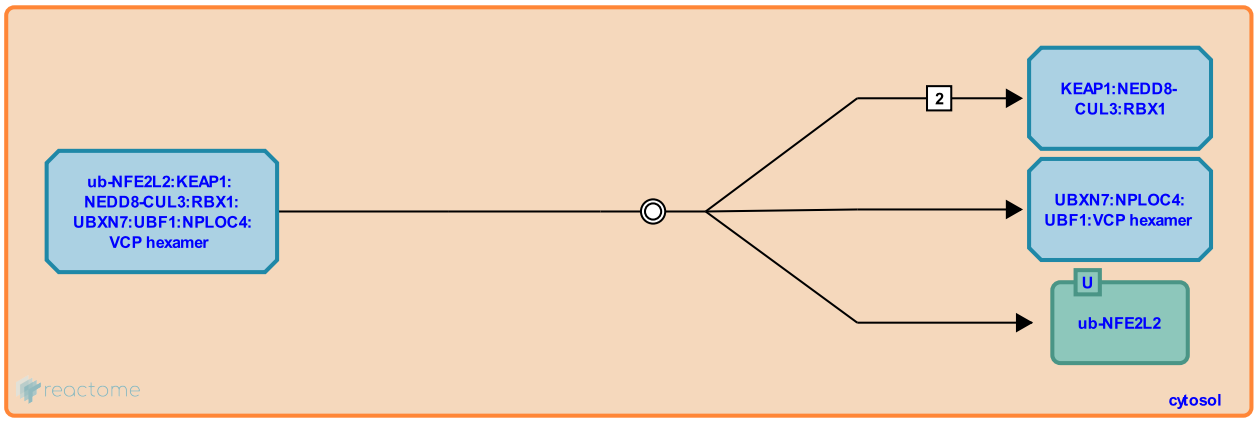
Ubiquitinated NFE2L2 is extracted from CRL3 complex for degradation ↗

Location: Neddylation

Stable identifier: R-HSA-9758090

Type: dissociation

Compartments: cytosol



The complex of VCP/p97 with cofactors UFD1, NPLOC4 and UBXN7 extract ubiquitinated NFE2L2 from the KEAP1-CUL3 ubiquitin ligase complex prior to its 26S proteasome-mediated degradation (Tao et al, 2017; Di Gregorio et al, 2021; reviewed in van den Boom and Meyer, 2020).

Preceded by: UBXN7:UBF1:NPLOC4:VCP hexamer binds NFE2L2:CRL3 complex

Followed by: 26S proteasome degrades Ub-NFE2L2

Literature references

van den Boom, J., Meyer, H. (2018). VCP/p97-Mediated Unfolding as a Principle in Protein Homeostasis and Signaling. *Mol Cell, 69*, 182-194. ↗

Di Gregorio, J., Zervos, AS., Liao, R., Andl, T., Ambivero, CT., Cilenti, L. (2021). UBXN7 cofactor of CRL3^{KEAP1} and CRL2^{VHL} ubiquitin ligase complexes mediates reciprocal regulation of NRF2 and HIF-1α proteins. *Biochim Biophys Acta Mol Cell Res, 1868*, 118963. ↗

Rojo de la Vega, M., Chen, H., Zhang, DD., Luo, G., Tao, S., Chapman, E. et al. (2017). p97 Negatively Regulates NRF2 by Extracting Ubiquitylated NRF2 from the KEAP1-CUL3 E3 Complex. *Mol Cell Biol, 37*. ↗

Editions

2021-10-08	Authored, Edited	Rothfels, K.
2022-02-23	Reviewed	Cuadrado, A.

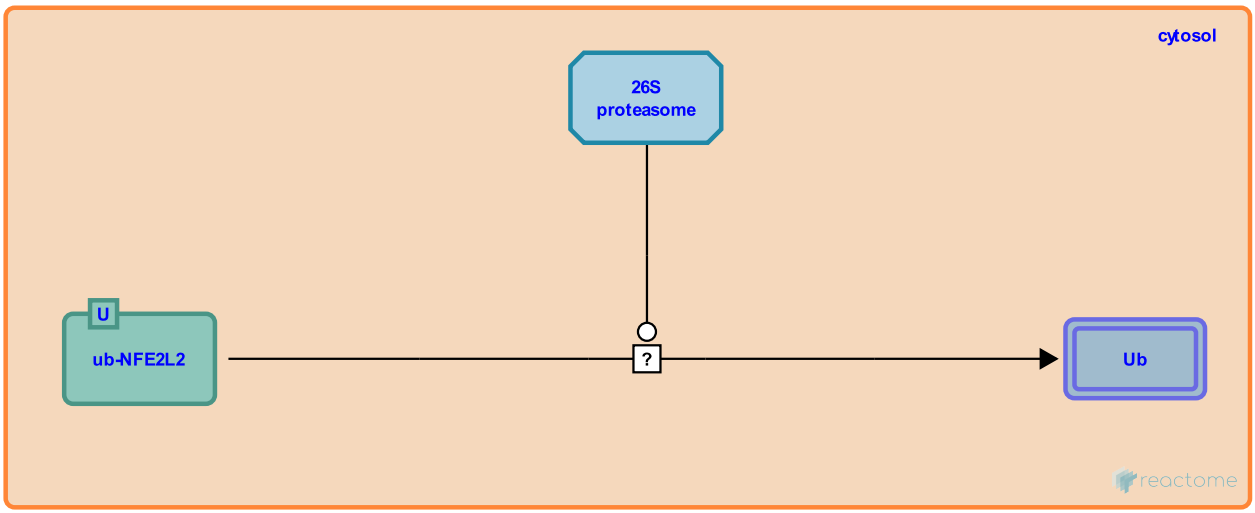
26S proteasome degrades Ub-NFE2L2 ↗

Location: Neddylation

Stable identifier: R-HSA-8932355

Type: uncertain

Compartments: cytosol



Ubiquitinated Nuclear factor erythroid 2-related (NFE2L2) undergoes proteasomal degradation and this maintains the protein level and activity at low levels. (Kobayashi et al, 2004; McMahon et al, 2003)

Preceded by: Ubiquitinated NFE2L2 is extracted from CRL3 complex for degradation

Literature references

Yamamoto, M., Kang, MI., Kobayashi, A., Igarashi, K., Chiba, T., Okawa, H. et al. (2004). Oxidative stress sensor Keap1 functions as an adaptor for Cul3-based E3 ligase to regulate proteasomal degradation of Nrf2. *Mol. Cell. Biol., 24*, 7130-9. ↗

Yamamoto, M., Itoh, K., Hayes, JD., McMahon, M. (2003). Keap1-dependent proteasomal degradation of transcription factor Nrf2 contributes to the negative regulation of antioxidant response element-driven gene expression. *J Biol Chem, 278*, 21592-600. ↗

Editions

2016-07-22	Authored, Edited	Garapati, P V.
2021-01-23	Reviewed	Somers, J.
2022-02-23	Reviewed	Cuadrado, A.
2022-02-23	Revised	Rothfels, K.

Table of Contents