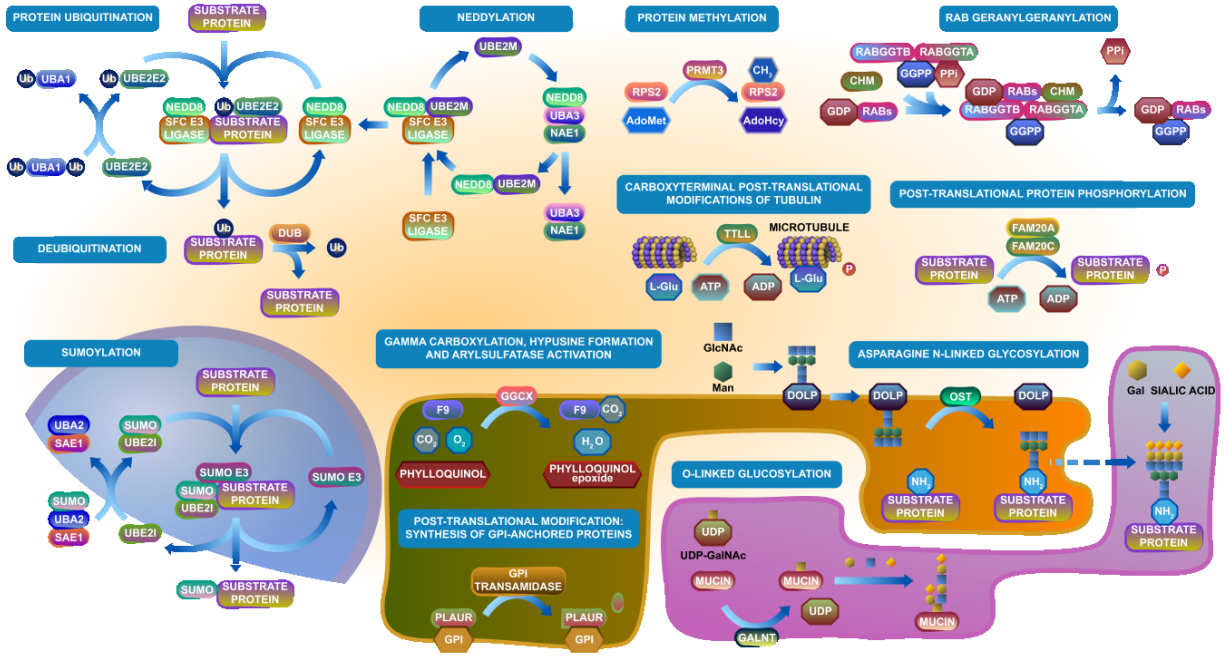
reactome

Post-translational protein modification



Azevedo, JE., D'Eustachio, P., Dall'Olio, GM., Falnes, PØ., Gagneux, P., Garg, AK., Jassal, B., Jupe, S., May, B., Meldal, BH., Orlean, P., Palsuledesai, CC., Pick, E., Rothfels, K., Stafford, DW., Wiley, SE.

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

14/09/2021

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.

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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. ↗

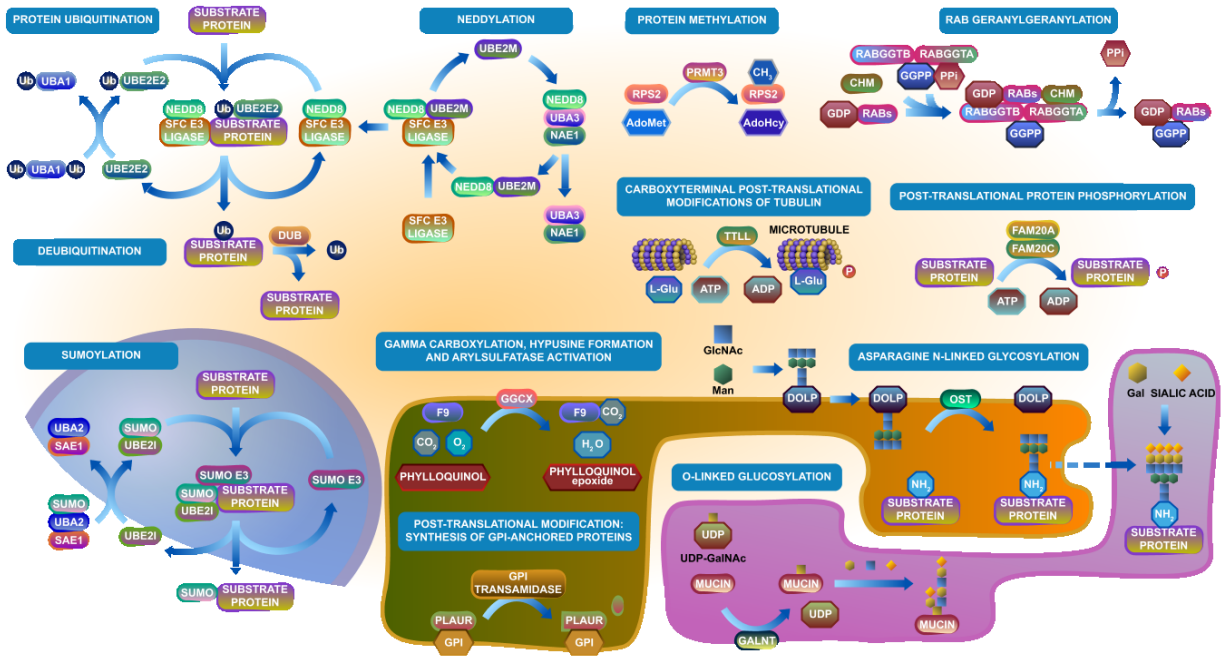
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 77

This document contains 13 pathways (see Table of Contents)

Post-translational protein modification ↗

Stable identifier: R-HSA-597592



After translation, many newly formed proteins undergo further covalent modifications that alter their functional properties. Modifications associated with protein localization include the attachment of oligosaccharide moieties to membrane-bound and secreted proteins (**N-linked** and **O-linked glycosylation**), the attachment of lipid (**RAB geranylgeranylation**) or glycolipid moieties (**GPI-anchored proteins**) that anchor proteins to cellular membranes, and the vitamin K-dependent attachment of carboxyl groups to glutamate residues. Modifications associated with functions of specific proteins include **gamma carboxylation** of clotting factors, **hypusine formation** on eukaryotic translation initiation factor 5A, conversion of a cysteine residue to formylglycine (**arylsulfatase activation**), methylation of lysine and arginine residues on non-histone proteins (**protein methylation**), **protein phosphorylation** by secretory pathway kinases, and **carboxyterminal modifications of tubulin** involving the addition of polyglutamate chains.

Protein ubiquitination and **deubiquitination** play a major role in regulating protein stability and, together with **SUMOylation** and **neddylation**, can modulate protein function as well.

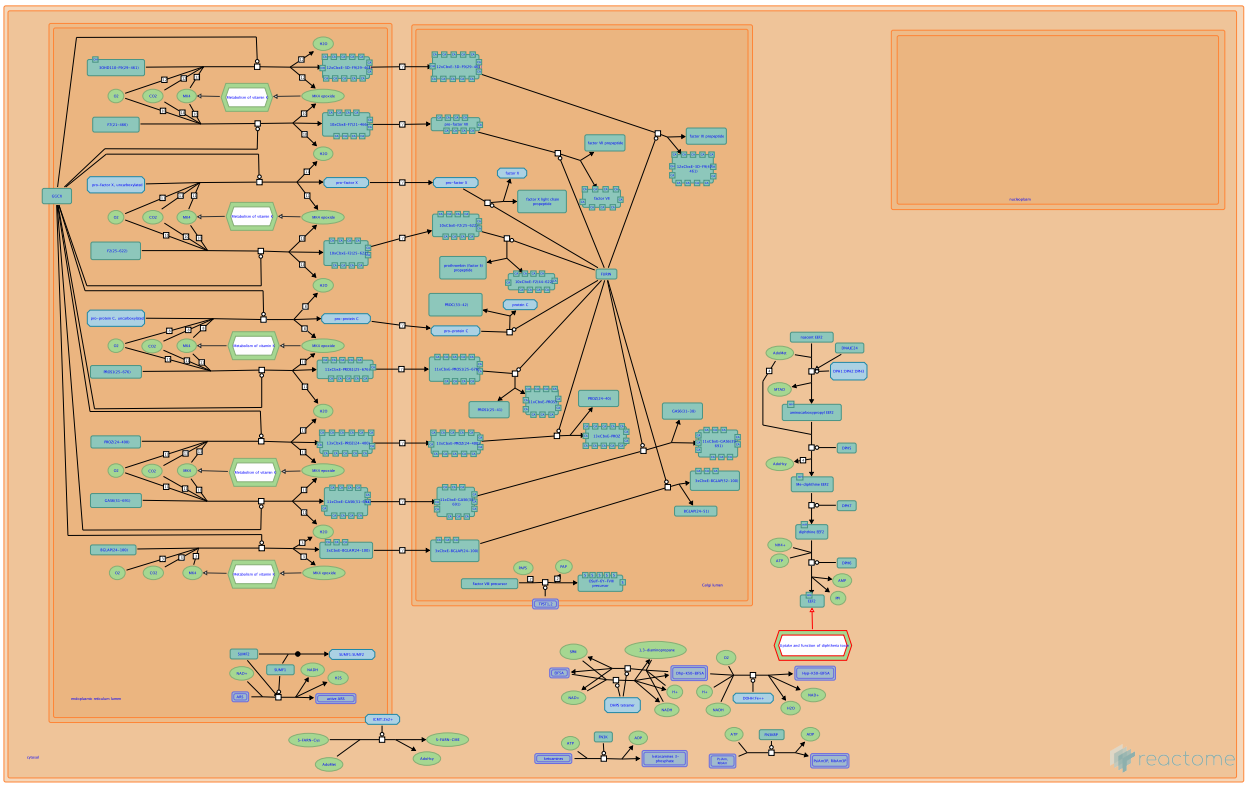
Editions

2005-04-18	Authored	D'Eustachio, P.
2021-05-18	Edited	D'Eustachio, P.
2021-05-18	Reviewed	Stafford, DW., Orlean, P.

Gamma carboxylation, hypusine formation and arylsulfatase activation ↗

Location: Post-translational protein modification

Stable identifier: R-HSA-163841



After translation, many newly formed proteins undergo further covalent modifications that alter their functional properties and that are essentially irreversible under physiological conditions in the body. These modifications include the vitamin K-dependent attachment of carboxyl groups to glutamate residues and the conversion of a lysine residue in eIF5A to hypusine, and the conversion of a histidine residue in EEF to diphthamide.

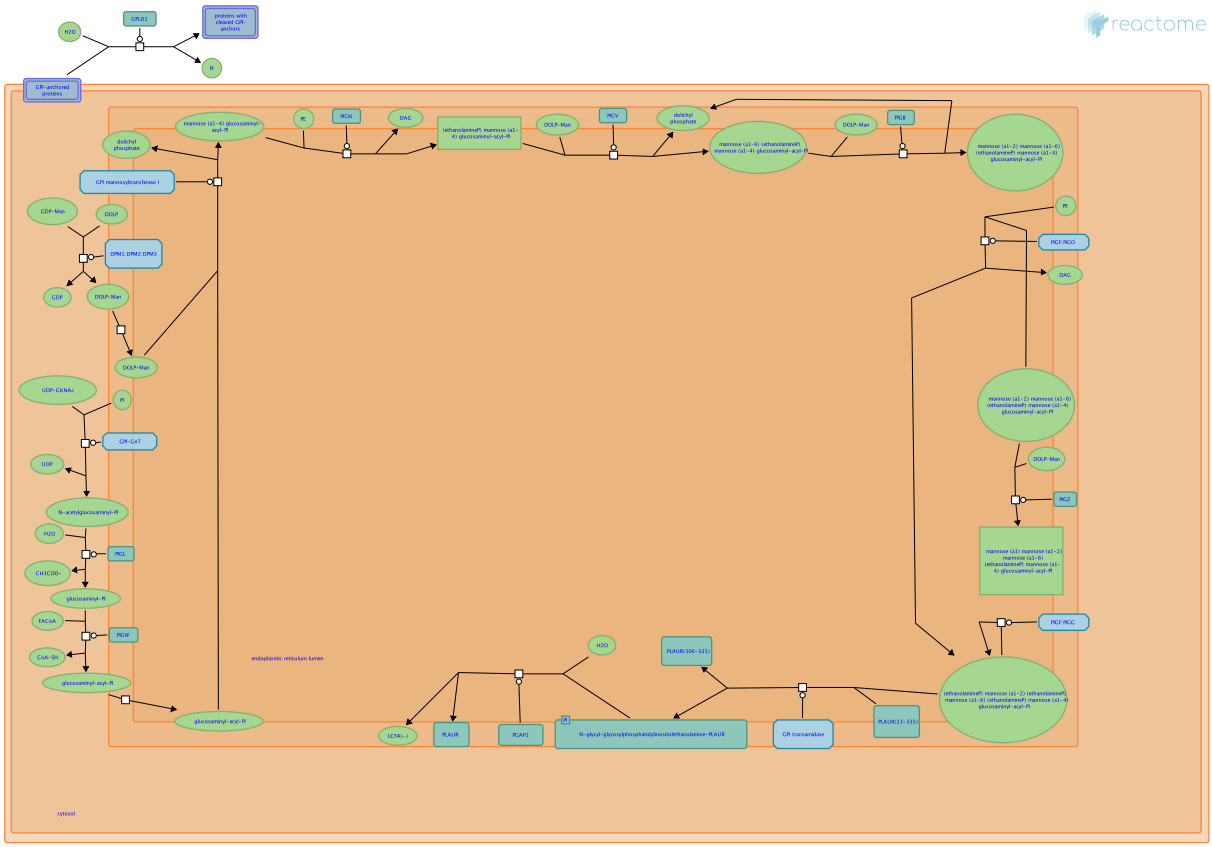
Editions

2005-05-08	Authored	D'Eustachio, P.
2021-05-18	Edited	D'Eustachio, P.
2021-05-18	Reviewed	Stafford, DW., Orlean, P.

Post-translational modification: synthesis of GPI-anchored proteins ↗

Location: Post-translational protein modification

Stable identifier: R-HSA-163125



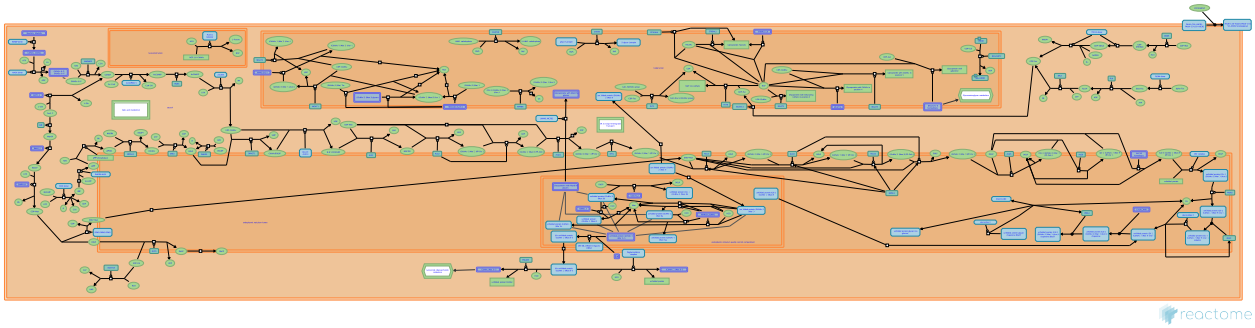
Glycosylphosphatidyl inositol (GPI) acts as a membrane anchor for many cell surface proteins. GPI is synthesized in the endoplasmic reticulum. In humans, a single pathway consisting of eleven reactions appears to be responsible for the synthesis of the major GPI species involved in membrane protein anchoring.

As a nascent protein fated to become GPI-anchored moves into the lumen of the endoplasmic reticulum, it is attacked by a transamidase complex that cleaves it near its carboxy terminus and attaches an acylated GPI moiety. The GPI moiety is deacylated, yielding a protein-GPI conjugate that can be efficiently transported to the Golgi apparatus.

Asparagine N-linked glycosylation ↗

Location: Post-translational protein modification

Stable identifier: R-HSA-446203



N-linked glycosylation is the most important form of post-translational modification for proteins synthesized and folded in the Endoplasmic Reticulum (Stanley et al. 2009). An early study in 1999 revealed that about 50% of the proteins in the Swiss-Prot database at the time were N-glycosylated (Apweiler et al. 1999). It is now established that the majority of the proteins in the secretory pathway require glycosylation in order to achieve proper folding.

The addition of an N-glycan to a protein can have several roles (Shental-Bechor & Levy 2009). First, glycans enhance the solubility and stability of the proteins in the ER, the golgi and on the outside of the cell membrane, where the composition of the medium is strongly hydrophilic and where proteins, that are mostly hydrophobic, have difficulty folding properly. Second, N-glycans are used as signal molecules during the folding and transport process of the protein: they have the role of labels to determine when a protein must interact with a chaperon, be transported to the golgi, or targeted for degradation in case of major folding defects. Third, and most importantly, N-glycans on completely folded proteins are involved in a wide range of processes: they help determine the specificity of membrane receptors in innate immunity or in cell-to-cell interactions, they can change the properties of hormones and secreted proteins, or of the proteins in the vesicular system inside the cell.

All N-linked glycans are derived from a common 14-sugar oligosaccharide synthesized in the ER, which is attached co-translationally to a protein while this is being translated inside the reticulum. The process of the synthesis of this glycan, known as Synthesis of the N-glycan precursor or LLO, constitutes one of the most conserved pathways in eukaryotes, and has been also observed in some eubacteria. The attachment usually happens on an asparagine residue within the consensus sequence asparagine-X-threonine by an complex called oligosaccharyl transferase (OST).

After being attached to an unfolded protein, the glycan is used as a label molecule in the folding process (also known as Calnexin/Calreticulin cycle) (Lederkremer 2009). The majority of the glycoproteins in the ER require at least one glycosylated residue in order to achieve proper folding, even if it has been shown that a smaller portion of the proteins in the ER can be folded without this modification.

Once the glycoprotein has achieved proper folding, it is transported via the cis-Golgi through all the Golgi compartments, where the glycan is further modified according to the properties of the glycoprotein. This process involves relatively few enzymes but due to its combinatorial nature, can lead to several millions of different possible modifications. The exact topography of this network of reactions has not been established yet, representing one of the major challenges after the sequencing of the human genome (Hossler et al. 2006).

Since N-glycosylation is involved in an great number of different processes, from cell-cell interaction to folding control, mutations in one of the genes involved in glycan assembly and/or modification can lead

to severe development problems (often affecting the central nervous system). All the diseases in genes involved in glycosylation are collectively known as Congenital Disorders of Glycosylation (CDG) (Sparks et al. 2003), and classified as CDG type I for the genes in the LLO synthesis pathway, and CDG type II for the others.

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Lederkremer, GZ. (2009). Glycoprotein folding, quality control and ER-associated degradation. *Curr Opin Struct Biol, 19*, 515-23. ↗

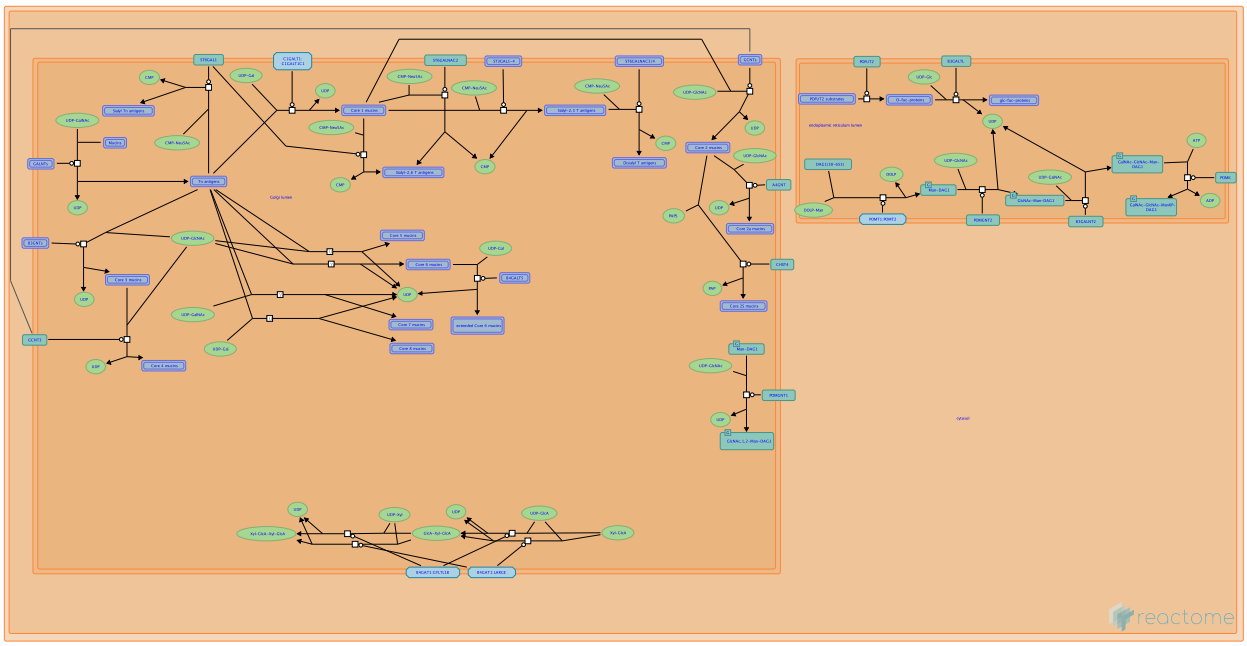
Editions

2009-11-10	Authored	Dall'Olio, GM.
2009-11-10	Edited	Jassal, B.
2010-04-16	Reviewed	Gagneux, P.

O-linked glycosylation ↗

Location: Post-translational protein modification

Stable identifier: R-HSA-5173105



O-glycosylation is an important post-translational modification (PTM) required for correct functioning of many proteins (Van den Steen et al. 1998, Moremen et al. 2012). The O-glycosylation of proteins containing thrombospondin type 1 repeat (TSR) domains and O-glycosylation of mucins are currently described here.

Literature references

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Editions

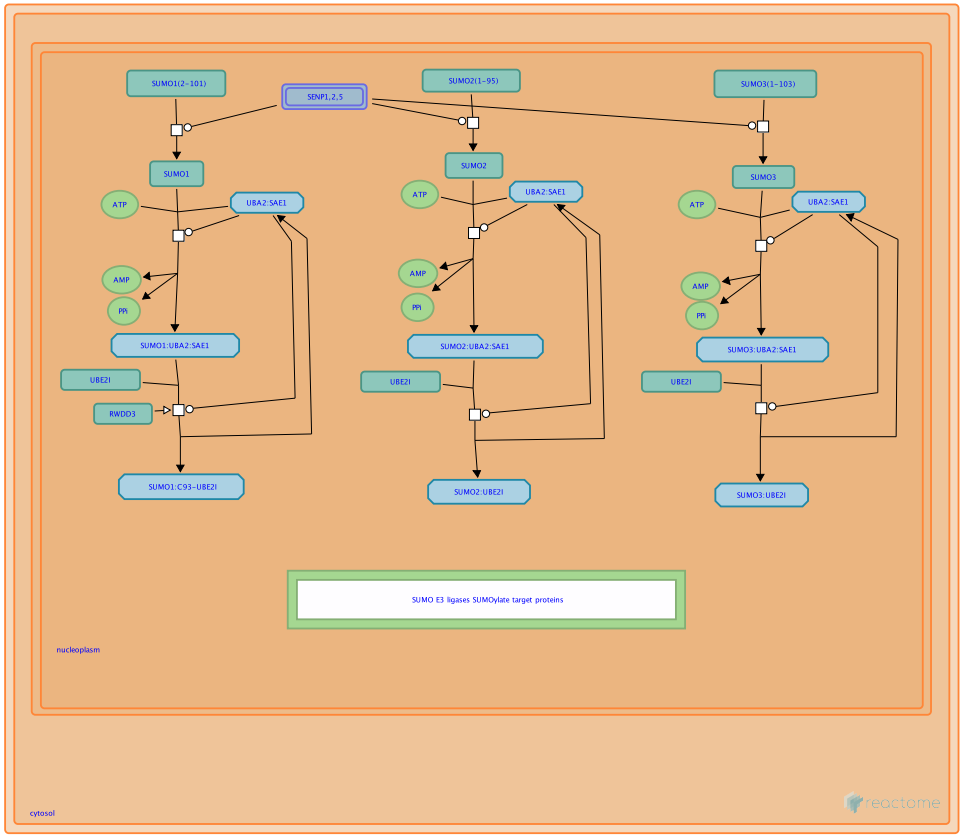
2013-11-25	Authored, Edited	Jassal, B.
2014-02-07	Reviewed	D'Eustachio, P.

SUMOylation ↗

Location: Post-translational protein modification

Stable identifier: R-HSA-2990846

Compartments: cytosol, nucleoplasm



Small Ubiquitin-like MOdifiers (SUMOs) are a family of 3 proteins (SUMO1,2,3) that are reversibly conjugated to lysine residues of target proteins via a glycine-lysine isopeptide bond (reviewed in Hay 2013, Hannoun et al. 2010, Gareau and Lima 2010, Wilkinson and Henley 2010, Wang and Dasso 2009). Proteomic methods have yielded estimates of hundreds of target proteins. Targets are mostly located in the nucleus and therefore SUMOylation disproportionately affects gene expression.

SUMOs are initially translated as proproteins possessing extra amino acid residues at the C-terminus which are removed by the SUMO processing endoproteases SENP1,2,5 (Hay 2007). Different SENPs have significantly different efficiencies with different SUMOs. The processing exposes a glycine residue at the C-terminus that is activated by ATP-dependent thiolation at cysteine-173 of UBA2 in a complex with SAE1, the E1 complex. The SUMO is transferred from E1 to cysteine-93 of a single E2 enzyme, UBC9 (UBE2I). UBC9 with or, in some cases, without an E3 ligase conjugates the glycine C-terminus of SUMO to an epsilon amino group of a lysine residue on the target protein. SUMO2 and SUMO3 may then be further polymerized, forming chains. SUMO1 is unable to form polymers.

Conjugated SUMO can act as a biinding site for proteins possessing SUMO interaction motifs (SIMs) and can also directly affect the formation of complexes between the target protein and other proteins.

Conjugated SUMOs are removed by cleavage of the isopeptide bond by processing enzymes SENP1,2,3,5. The processing enzymes SENP6 and SENP7 edit chains of SUMO2 and SUMO3.

Literature references

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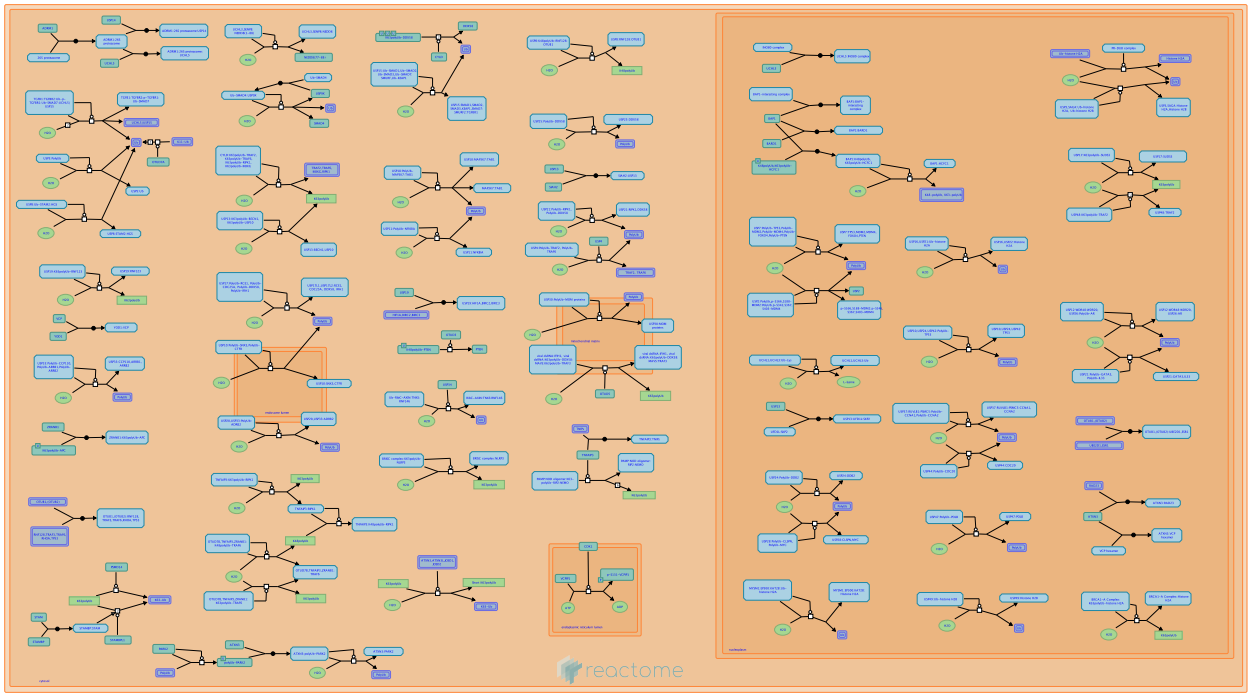
Editions

2013-01-16	Authored, Edited	May, B.
2013-05-16	Reviewed	Garg, AK.

Deubiquitination ↗

Location: Post-translational protein modification

Stable identifier: R-HSA-5688426



Ubiquitination, the modification of proteins by the covalent attachment of ubiquitin (Ub), is a key regulatory mechanism for many many cellular processes, including protein degradation by the 26S proteasome. Ub conjugates linked via lysine 48 (K48) target substrates to the proteasome, whereas those linked via any of the six other Ub lysines can alter the function of the modified protein without leading to degradation. Deubiquitination, the reversal of this modification, regulates the function of ubiquitin-conjugated proteins. Deubiquitinating enzymes (DUBs) catalyze the removal of Ub and regulate Ub-mediated pathways.

Given that Ub is covalently-linked to proteins destined to be degraded, it is a surprisingly long-lived protein in vivo (Haas & Bright 1987). This is due to the removal of Ub from its conjugates by DUBs prior to proteolysis. This may represent a quality control mechanism that prevents the degradation of proteins that were inappropriately tagged for degradation (Lam et al. 1997). DUBs are responsible for processing inactive Ub precursors and for keeping the 26S proteasome free of unanchored Ub chains that compete for Ub-binding sites.

DUBs can be grouped into five families based on their conserved catalytic domains (Amerik & Hochstrasser 2004). Four of these families are thiol proteases and comprise the bulk of DUBs, while the fifth family is a small group of Ub specific metalloproteases.

Thiol protease DUBs contain a Cys-His-Asp/Asn catalytic triad in which the Asp/Asn functions to polarize and orient the His, while the His serves as a general acid/base by both priming the catalytic Cys for nucleophilic attack on the (iso)peptide carbonyl carbon and by donating a proton to the lysine epsilon-amino leaving group. The nucleophilic attack of the catalytic Cys on the carbonyl carbon produces a negatively charged transition state that is stabilized by an oxyanion hole composed of hydrogen bond donors. A Cys-carbonyl acyl intermediate ensues and is then hydrolyzed by nucleophilic attack of a water molecule to liberate a protein C-terminal carboxylate and regenerate the enzyme. Ub binding often causes structural rearrangements necessary for catalysis. Many DUBs are inactivated by oxidation of the catalytic cysteine

to sulphenic acid (single bond SOH) (Cotto-Rios et al. 2012, Lee et al. 2013). This can be reversed by re duction with DTT or glutathione. The sulphenic acid can be irreversibly oxidized to sulphinic acid (single bond SO2H) or sulphonic acid (single bond SO3H).

Thiol proteases are reversibly inhibited by Ub C-terminal aldehyde, forming a thio-hemiacetal between the aldehyde group and the active site thiol.

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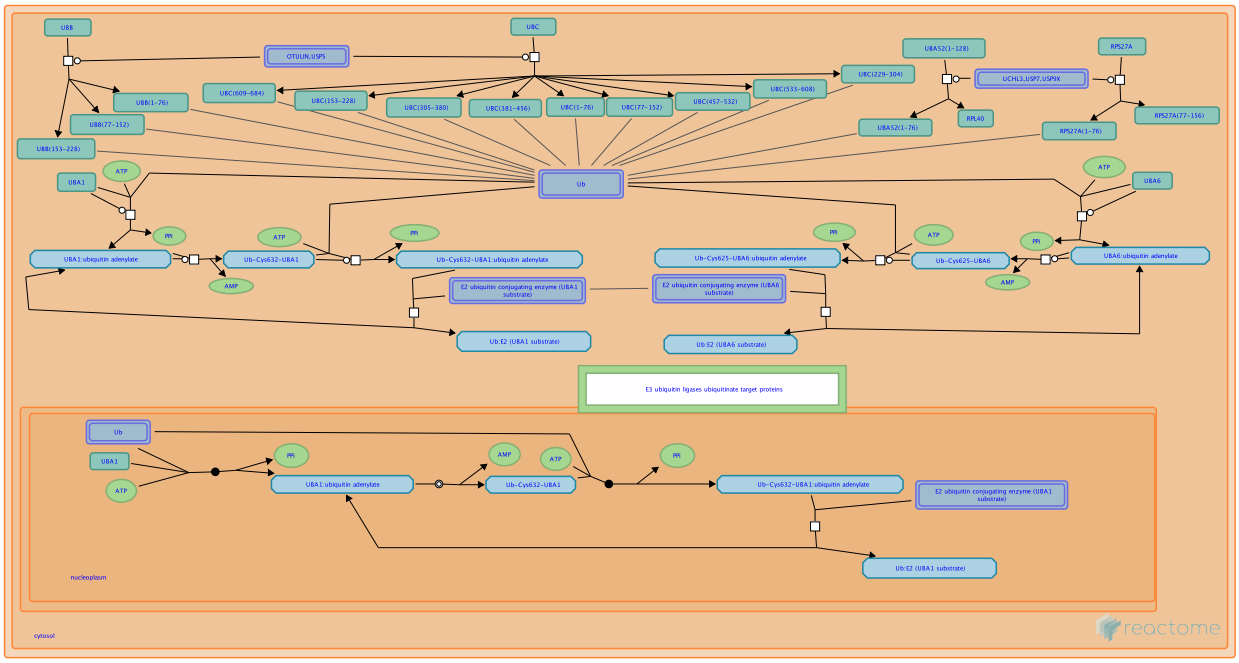
Editions

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

Protein ubiquitination ↗

Location: Post-translational protein modification

Stable identifier: R-HSA-8852135



Ubiquitin is a small, 76 amino acid residue protein that is conjugated by E3 ubiquitin ligases to other proteins in order to regulate their function or degradation (enzymatic cascade reviewed in Neutzner and Neutzner 2012, Kleiger and Mayor 2014, structures and mechanisms of conjugating enzymes reviewed in Lorenz et al. 2013). Ubiquitination of target proteins usually occurs between the C-terminal glycine residue of ubiquitin and a lysine residue of the target, although linkages with cysteine, serine, and threonine residues are also observed (reviewed in Wang et al. 2012, McDowell and Philpott 2013).

Ubiquitin must first be processed from larger precursors and then activated by formation of a thiol ester bond between ubiquitin and an E1 activating enzyme (UBA1 or UBA6) and transfer to an E2 conjugating enzyme before being transferred by an E3 ligase to a target protein. Precursor proteins containing multiple ubiquitin monomers (polyubiquitins) are produced from the UBB and UBC genes; precursors containing a single ubiquitin monomer and a ribosomal protein are produced from the UBA52 and RPS27A genes. Many proteases (deubiquitinases) may potentially process these precursors yielding monomeric ubiquitin. The proteases OTULIN and USP5 are particularly active in cleaving the polyubiquitin precursors, whereas the proteases UCHL3, USP7, and USP9X cleave the ubiquitin-ribosomal protein precursors yielding ubiquitin monomers (Grou et al. 2015). A resultant ubiquitin monomer is activated by adenylation of the C-terminal glycine followed by conjugation of the C-terminus to a cysteine residue of the E1 enzymes UBA1 or UBA6 via a thiol ester bond. The ubiquitin is then transferred from the E1 enzyme to a cysteine residue of one of several E2 enzymes (reviewed in van Wijk and Timmers 2010, Stewart et al. 2016). Through a less well characterized mechanism, E3 ubiquitin ligases then bring a target protein and the E2-ubiquitin conjugate into proximity so that the ubiquitin is transferred via formation of an amide bond to a particular lysine residue (or, in rarer cases, a thiol ester bond to a cysteine residue or an ester bond to a serine or threonine residue) of the target protein (reviewed in Berndsen and Wolberger 2014). Based on protein homologies, families of E3 ubiquitin ligases have been identified that include RING-type ligases (reviewed in Deshaies et al. 2009, Metzger et al. 2012, Metzger et al. 2014), HECT-type ligases (reviewed in Rotin et al. 2009, Metzger et al. 2012), and RBR-type ligases (reviewed in Dove et al. 2016). A subset of the RING-type ligases participate in CULLIN-RING ligase complexes (CRLs which include SCF

complexes, reviewed in Lee and Zhou 2007, Genschik et al. 2013, Skaar et al. 2013, Lee et al. 2014).

Some E3-E2 combinations catalyze mono-ubiquitination of the target protein (reviewed in Nakagawa and Nakayama 2015). Other E3-E2 combinations catalyze conjugation of further ubiquitin monomers to the initial ubiquitin, forming polyubiquitin chains. (It may also be possible for some E3-E2 combinations to preassemble polyubiquitin and transfer it as a unit to the target protein.) Ubiquitin contains several lysine (K) residues and a free alpha amino group to which further ubiquitin can be conjugated. Thus different types of polyubiquitin are possible: K11 linked polyubiquitin is observed in endoplasmic reticulum-associated degradation (ERAD), K29 linked polyubiquitin is observed in lysosomal degradation, K48 linked polyubiquitin directs target proteins to the proteasome for degradation, whereas K63 linked polyubiquitin generally acts as a scaffold to recruit other proteins in several cellular processes, notably DNA repair (reviewed in Komander et al. 2009). Ubiquitination is highly regulated (reviewed in Vittal et al. 2015) and affects all cellular processes including DNA damage response (reviewed in Brown and Jackson 2015), immune signaling (reviewed in Park et al. 2014, Lutz-Nicoladoni et al. 2015), and regulation of normal and cancerous cell growth (reviewed in Skaar and Pagano 2009, Yerlikaya and Yontem 2013, Strikoudis et al. 2014).

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Vittal, V., Stewart, MD., Brzovic, PS., Klevit, RE. (2015). Regulating the Regulators: Recent Revelations in the Control of E3 Ubiquitin Ligases. *J. Biol. Chem., 290*, 21244-51. ↗

Nakagawa, T., Nakayama, K. (2015). Protein monoubiquitylation: targets and diverse functions. *Genes Cells, 20*, 543-62 . ↗

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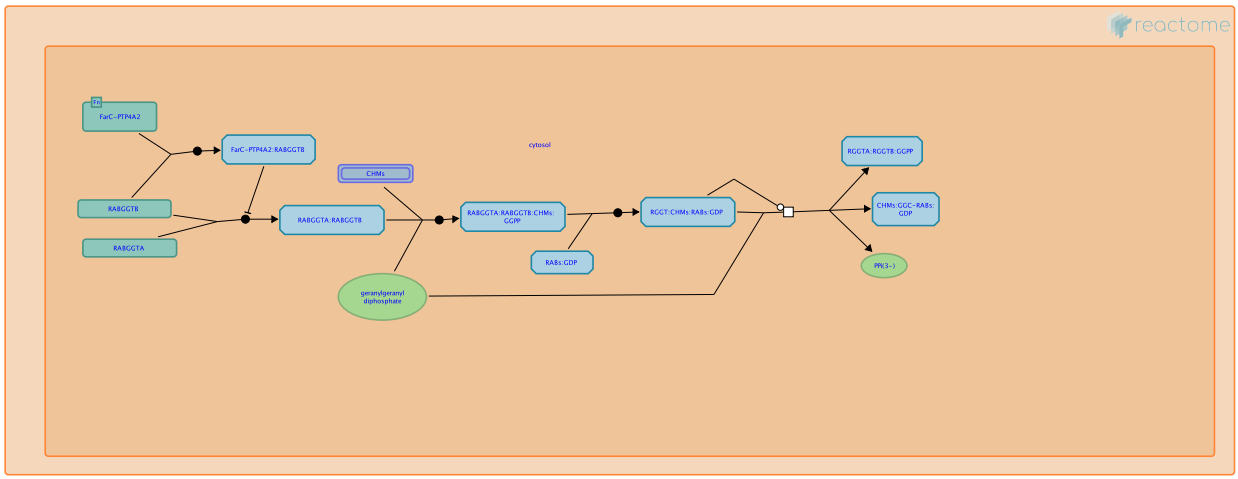
Editions

2016-01-12	Authored, Edited	May, B.
2016-08-11	Reviewed	Azevedo, JE.

RAB geranylgeranylation ↗

Location: Post-translational protein modification

Stable identifier: R-HSA-8873719



Human cells have more than 60 RAB proteins that are involved in trafficking of proteins in the endolysosomal system. These small GTPases contribute to trafficking specificity by localizing to the membranes of different endocytic compartments and interacting with effectors such as sorting adaptors, tethering factors, kinases, phosphatases and tubular-vesicular cargo (reviewed in Stenmark et al, 2009; Wandinger-Ness and Zerial, 2014). RAB localization depends on a number of factors including C-terminal prenylation, the sequence of an upstream hypervariable regions and what nucleotide is bound (Chavrier et al, 1991; Ullrich et al, 1993; Soldati et al, 1994; Farnsworth et al, 1994; Seabra, 1996; Wu et al, 2010; reviewed in Stenmark, 2009; Wandinger-Ness and Zerial, 2014). In the active, GTP-bound form, prenylated RAB proteins are membrane associated, while in the inactive GDP-bound form, RABs are extracted from the target membrane and exist in a soluble form in complex with GDP dissociation inhibitors (GDIs) (Ullrich et al, 1993; Soldati et al, 1994; Gavriljuk et al, 2103). Conversion between the inactive and active form relies on the activities of RAB guanine nucleotide exchange factors (GEFs) and GTPase activating proteins (GAPs) (Yoshimura et al, 2010; Wu et al, 2011; Pan et al, 2006; Frasa et al, 2012; reviewed in Stenmark, 2009; Wandinger-Ness and Zerial, 2014).

Newly synthesized RABs are bound by a RAB escort protein, CHM (also known as REP1) or CHML (REP2) (Alexandrov et al, 1994; Shen and Seabra, 1996). CHM/REP proteins are the substrate-binding component of the trimeric RAB geranylgeranyltransferase enzyme (GGTaseII) along with the two catalytic subunits RABGGTA and RABGGTB (reviewed in Gutkowska and Swiezewska, 2012; Palsuledesai and Distefano, 2015). REP proteins recruit the unmodified RAB in its GDP-bound state to the GGTase for sequential geranylgeranylation at one or two C-terminal cysteine residues (Alexandrov et al, 1994; Seabra et al 1996; Shen and Seabra, 1996; Baron and Seabra, 2008). After geranylgeranylation, CHM/REP proteins remain in complex with the geranylgeranylated RAB and escort it to its target membrane, where its activity is regulated by GAPs, GEFs, GDIs and membrane-bound GDI displacement factors (GDFs) (Sivars et al, 2003; reviewed in Stenmark, 2009; Wandinger-Ness and Zerial, 2014).

Literature references

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Wandinger-Ness, A., Zerial, M. (2014). Rab proteins and the compartmentalization of the endosomal system. *Cold Spring Harb Perspect Biol, 6*, a022616. ↗

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Soldati, T., Shapiro, AD., Svejstrup, AB., Pfeffer, SR. (1994). Membrane targeting of the small GTPase Rab9 is accompanied by nucleotide exchange. *Nature, 369*, 76-8. ↗

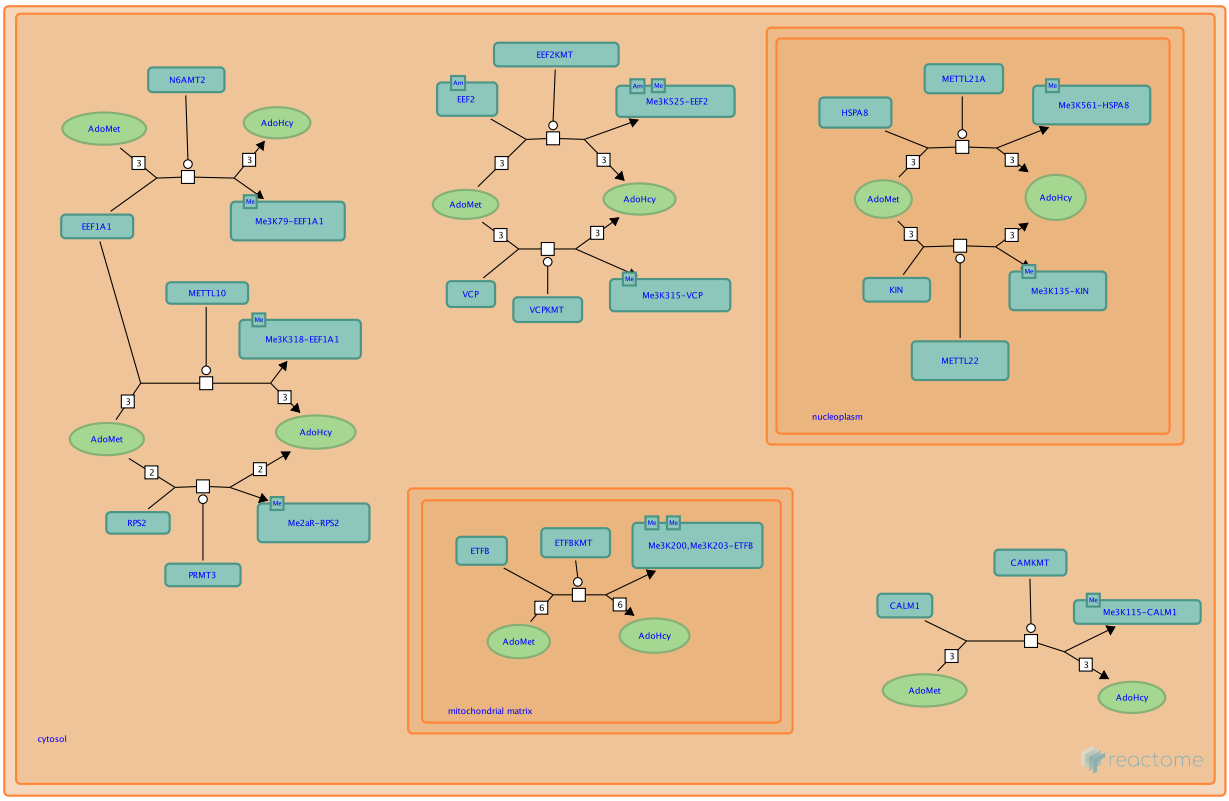
Editions

2016-06-03	Authored, Edited	Rothfels, K.
2016-08-04	Reviewed	Palsuledesai, CC.

Protein methylation ↗

Location: Post-translational protein modification

Stable identifier: R-HSA-8876725



Methylation of lysine (Lys) and arginine (Arg) residues on non-histone proteins is a prevalent post-translational modification and important regulator of cellular signal transduction pathways including MAPK, WNT, BMP, Hippo and JAK–STAT. Crosstalk between methylation and other types of post-translational modifications and between histone and non-histone protein methylation is frequent, affecting cellular functions such as chromatin remodelling, gene transcription, protein synthesis, signal transduction and DNA repair (Biggar & Li 2015).

Literature references

Biggar, KK., Li, SS. (2015). Non-histone protein methylation as a regulator of cellular signalling and function. *Nat. Rev. Mol. Cell Biol., 16*, 5-17. ↗

Editions

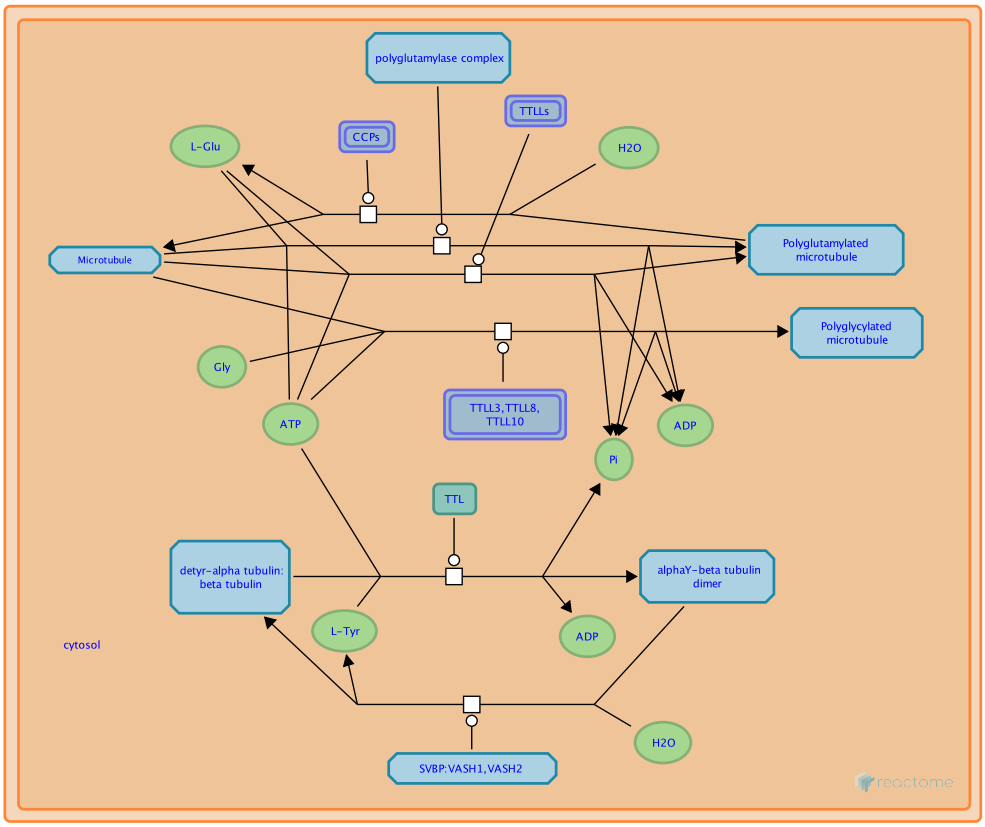
2016-06-16	Authored	Jupe, S.
2016-10-10	Reviewed	Falnes, PØ.
2016-10-10	Edited	Jupe, S.

Carboxyterminal post-translational modifications of tubulin ↗

Location: Post-translational protein modification

Stable identifier: R-HSA-8955332

Compartments: cytosol



Tubulins fold into compact globular domains with less structured carboxyterminal tails. These tails vary in sequence between tubulin isoforms and are exposed on the surfaces of microtubules. They can undergo a variety of posttranslational modifications, including the attachment and removal of polyglutamate chains and in the case of alpha-tunulins the loss and reattachment of a terminal tyrosine (Tyr) residue. These modifications are associated with changes in the rigidity and stability of microtubules (Song & Brady 2015; Yu et al. 2015).

Mutations affecting these modification processes can have severe effects on phenotype (e.g., Ikegami et al. 2007). Nevertheless, the precise molecular mechanisms by which these changes in tubulin structure modulate its functions remain unclear, so these modification processes are simply annotated here as a series of chemical transformations of tubulins.

Literature references

Ikegami, K., Heier, RL., Taruishi, M., Takagi, H., Mukai, M., Shimma, S. et al. (2007). Loss of alpha-tubulin polyglutamylation in ROSA22 mice is associated with abnormal targeting of KIF1A and modulated synaptic function. *Proc. Natl. Acad. Sci. U.S.A., 104*, 3213-8. ↗

Song, Y., Brady, ST. (2015). Post-translational modifications of tubulin: pathways to functional diversity of microtubules. *Trends Cell Biol., 25*, 125-36. ↗

Yu, I., Garnham, CP., Roll-Mecak, A. (2015). Writing and Reading the Tubulin Code. *J. Biol. Chem., 290*, 17163-72. ↗

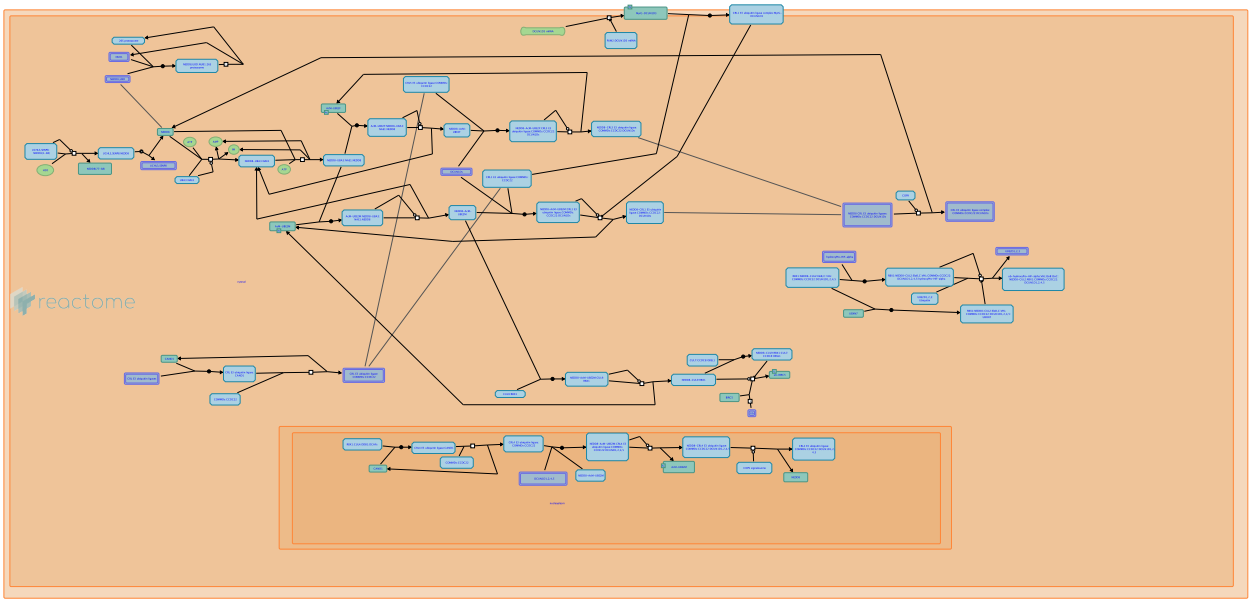
Editions

2017-01-13	Authored	D'Eustachio, P.
2017-01-19	Reviewed	Jassal, B.
2017-01-19	Edited	Jupe, S.

Neddylation ↗

Location: Post-translational protein modification

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).

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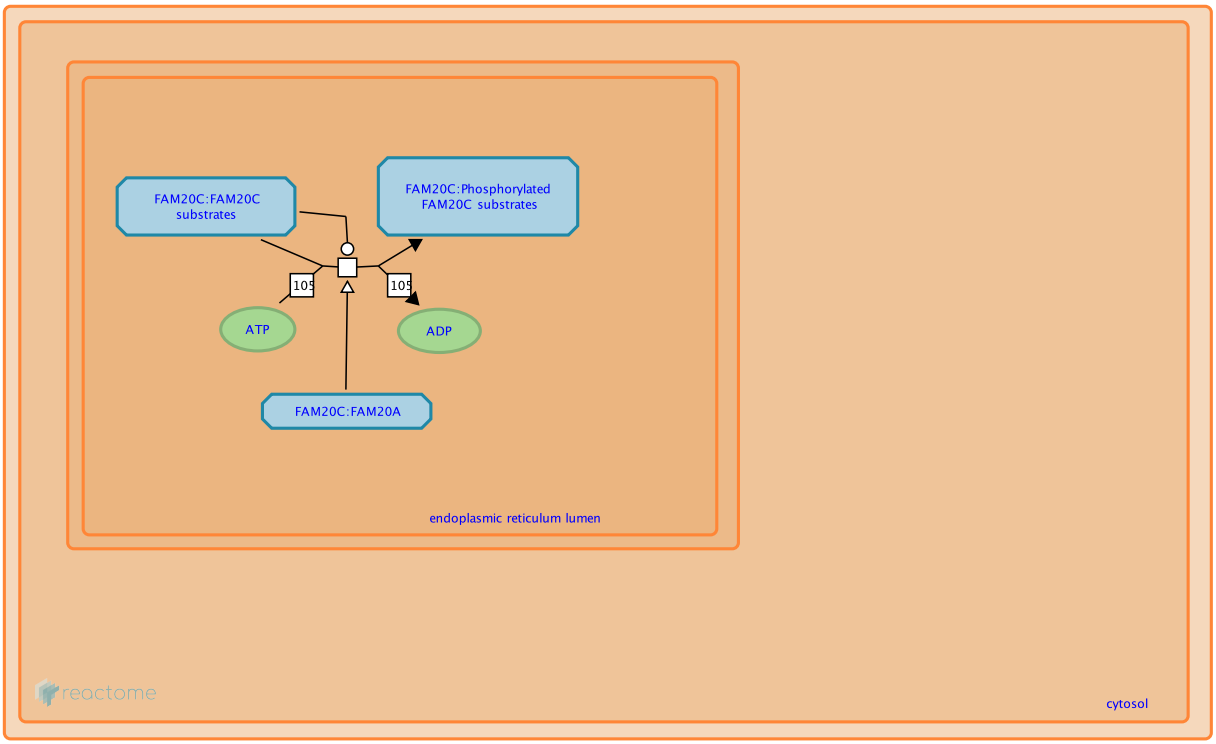
Editions

2017-02-07	Authored, Edited	Rothfels, K.
2017-02-22	Reviewed	Pick, E.

Post-translational protein phosphorylation ↗

Location: Post-translational protein modification

Stable identifier: R-HSA-8957275



Secretory pathway kinases phosphorylate a diverse array of substrates involved in many physiological processes.

Literature references

Sreelatha, A., Kinch, LN., Tagliabracci, VS. (2015). The secretory pathway kinases. *Biochim. Biophys. Acta, 1854*, 1687-93. ↗

Editions

2016-12-08	Authored	Jupe, S.
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