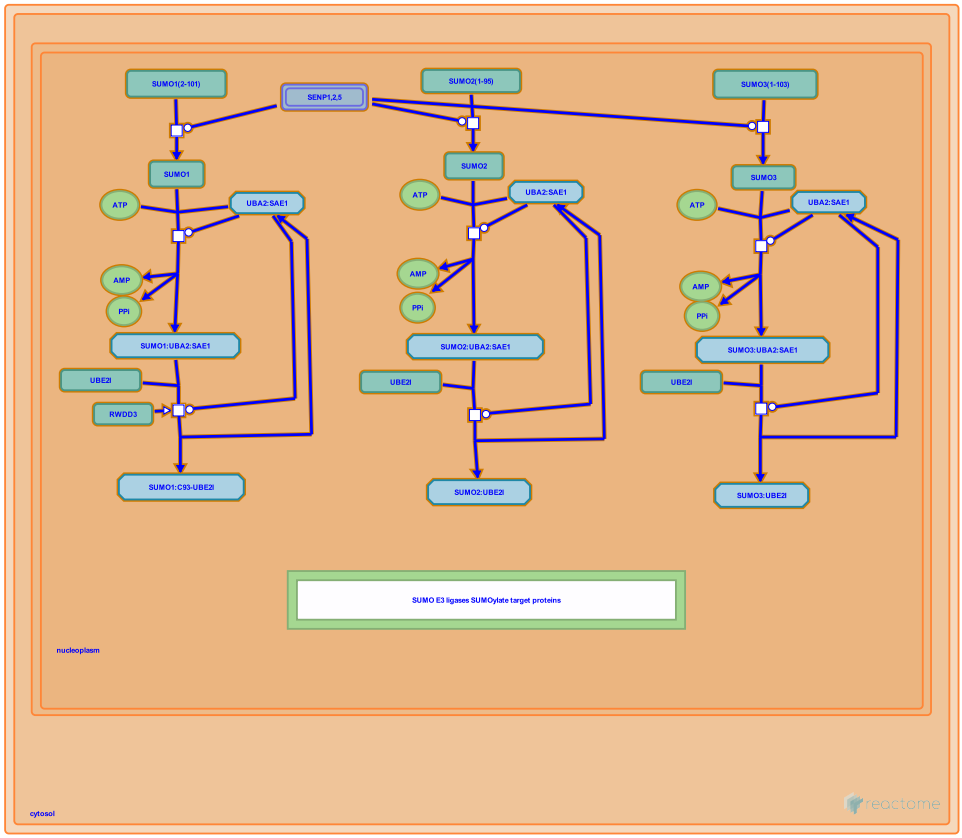
Processing and activation of SUMO



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26/06/2019

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. ↗

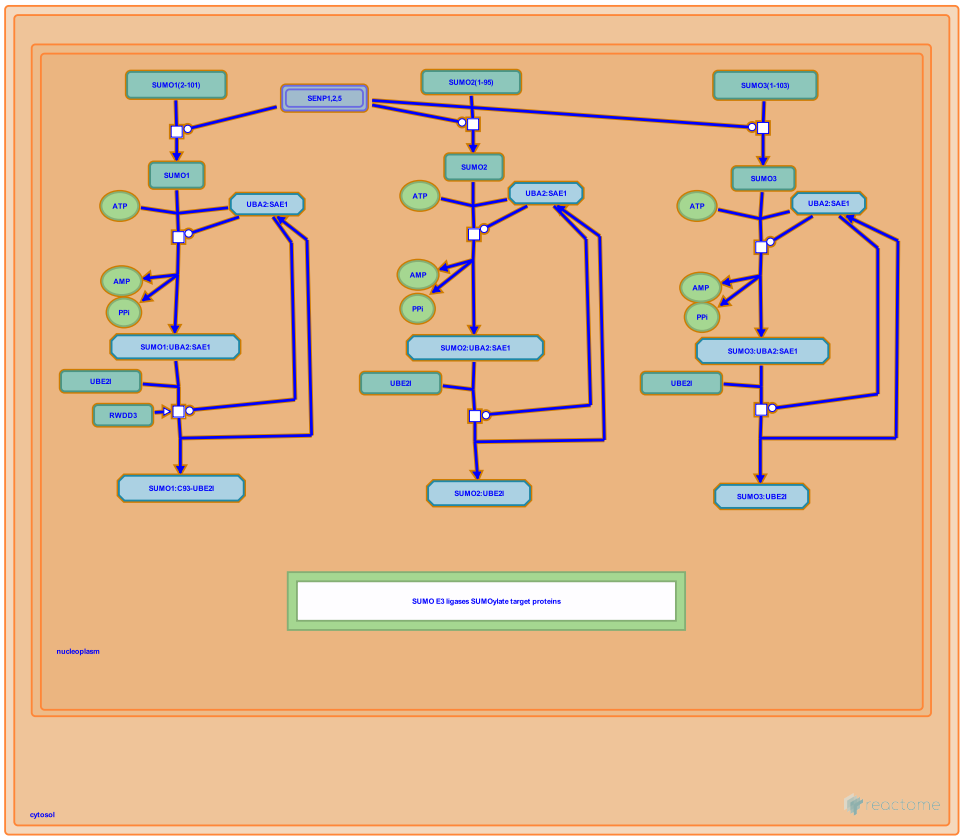
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

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. ↗

Processing and activation of SUMO ↗

Stable identifier: R-HSA-3215018

Compartments: nucleoplasm



The initial translation products of SUMO1, SUMO2, and SUMO3 are precursors that have extra amino acid residues at the C-terminus (reviewed in Wang and Dasso 2009, Wilkinson and Henley 2010, Hannoun et al. 2010, Gareau and Lima 2010, Hay 2007). SUMO1 has 4 extra residues, SUMO2 has 2 extra residues, and SUMO3 has 11 extra residues. Proteolytic cleavage by SUMO peptidases (SENPs) removes the propeptide and leaves diglycine residues at the C-terminus. Each SENP has distinct preferences for certain SUMOs. SENP1 has highest activity on SUMO1; SENP2 and SENP5 have highest activity on SUMO2 (Shen et al. 2006, Reverter and Lima 2006, Mikolajczyk et al. 2007). SENP1 and SENP2 are predominantly nucleoplasmic (Bailey and O'Hare 2004, Kim et al. 2005, Zhang et al. 2002, Hang and Dasso 2002, Itahana et al. 2006) and SENP5 is predominantly nucleolar (Di Bacco et al. 2006, Gong and Yeh 2006), therefore the processing reactions are believed to occur in the nucleus. The processed SUMO is then activated by formation of a thioester bond with a cysteine residue of an E1 enzyme, UBA2 (SAE2) in a complex with SAE1. SUMO is then transferred from the E1 enzyme to an E2 enzyme, UBC9 (UBE2I).

Literature references

Zhang, H., Saitoh, H., Matunis, MJ. (2002). Enzymes of the SUMO modification pathway localize to filaments of the nuclear pore complex. *Mol. Cell. Biol., 22*, 6498-508. ↗

Wang, Y., Dasso, M. (2009). SUMOylation and deSUMOylation at a glance. *J. Cell. Sci., 122*, 4249-52. ↗

Hay, RT. (2007). SUMO-specific proteases: a twist in the tail. *Trends Cell Biol., 17*, 370-6. ↗

Bailey, D., O'Hare, P. (2004). Characterization of the localization and proteolytic activity of the SUMO-specific protease, SENP1. *J. Biol. Chem., 279*, 692-703. ↗

Reverter, D., Lima, CD. (2006). Structural basis for SENP2 protease interactions with SUMO precursors and conjugated substrates. *Nat. Struct. Mol. Biol., 13*, 1060-8. ↗

Editions

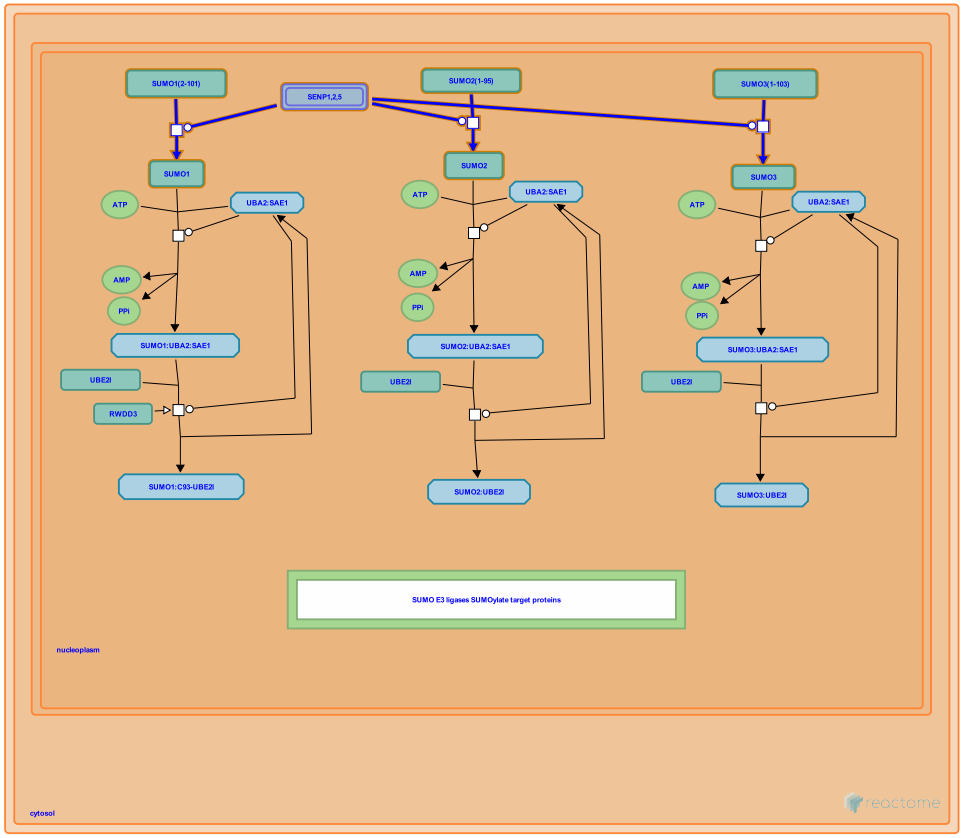
2013-03-10	Authored, Edited	May, B.
2013-05-16	Reviewed	Garg, AK.

SUMO is proteolytically processed ↗

Location: Processing and activation of SUMO

Stable identifier: R-HSA-3065679

Compartments: nucleoplasm



SUMO1, 2, and 3 are initially expressed as propeptides containing extra residues at the C-terminus. (SUMO1 has 4 residues, SUMO2 has 2 residues, and SUMO3 has 11 residues,) SENP1, 2, and 5 are endoproteases that process the precursors to produce the mature peptides (reviewed in Wang and Dasso 2009, Wilkinson and Henley 2010, Hannoun et al. 2010, Gareau and Lima 2010). SENP1 processes SUMO1 with greater efficiency than SUMO2 or SUMO3. SENP2 and SENP5 process SUMO2 with greater efficiency than SUMO1 or SUMO3 (Gong and Yeh 2006, Mikolajczyk et al. 2007). SENP1 shuttles between the cytosol and nuceoplasm and is predominantly nuclear (Bailey and O'hare 2004, Kim et al. 2005). SENP2 also shuttles (Itahana et al. 2006) and is mainly located on nucleoplasmic filaments of the nuclear pore complex (Hang and Dasso 2002, Zhang et al. 2002). SENP5 is located mostly in the nucleolus (Di Bacco et al. 2006, Gong and Yeh 2006).

Literature references

Wilkinson, KA., Henley, JM. (2010). Mechanisms, regulation and consequences of protein SUMOylation. *Biochem. J., 428*, 133-45. ↗

Hannoun, Z., Greenhough, S., Jaffray, E., Hay, RT., Hay, DC. (2010). Post-translational modification by SUMO. *Toxicology, 278*, 288-93. ↗

Wang, Y., Dasso, M. (2009). SUMOylation and deSUMOylation at a glance. *J. Cell. Sci., 122*, 4249-52. ↗

Gareau, JR., Lima, CD. (2010). The SUMO pathway: emerging mechanisms that shape specificity, conjugation and recognition. *Nat. Rev. Mol. Cell Biol., 11*, 861-71. ↗

Bailey, D., O'Hare, P. (2004). Characterization of the localization and proteolytic activity of the SUMO-specific protease, SENP1. *J. Biol. Chem., 279*, 692-703. ↗

Editions

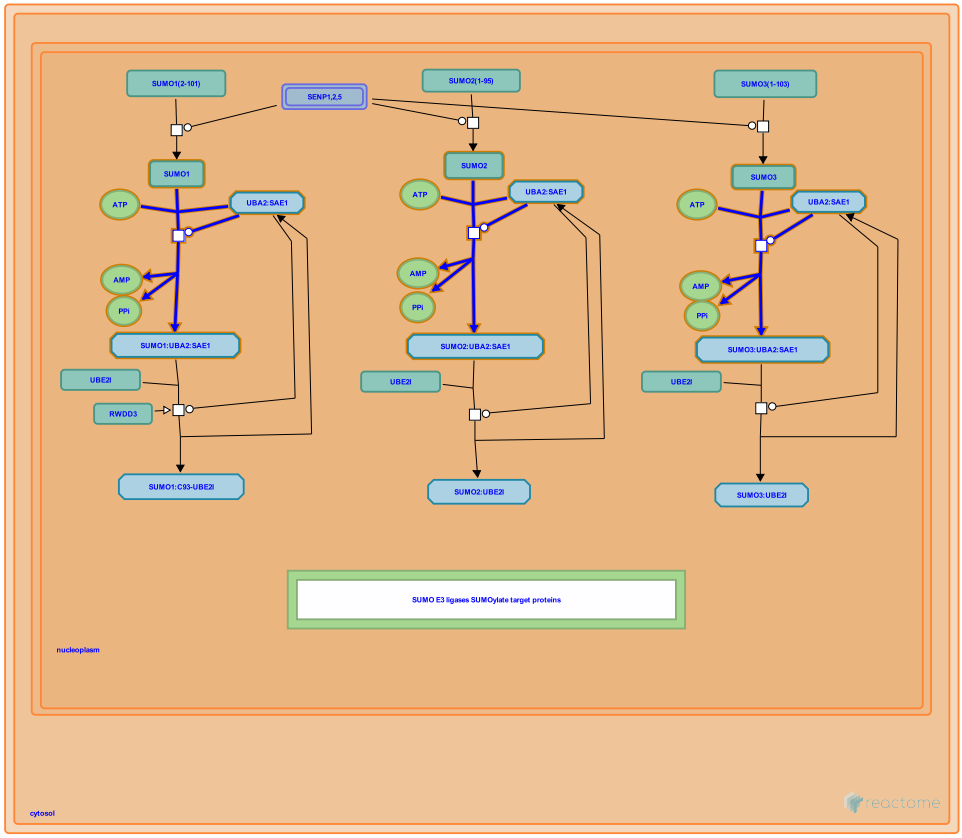
2013-02-06	Authored, Edited	May, B.
2013-05-16	Reviewed	Garg, AK.

SUMO is conjugated to E1 (UBA2:SAE1) ↗

Location: Processing and activation of SUMO

Stable identifier: R-HSA-3065676

Compartments: nucleoplasm



The UBA2:SAE1 complex catalyzes the formation of a thioester linkage between the C-terminal glycine of the mature SUMO and a cysteine residue (cysteine-173) in UBA2 (SAE2) (reviewed in Wang and Dasso 2009, Wilkinson and Henley 2010, Hannoun et al. 2010, Gareau and Lima 2010). During the process the C-terminal glycine residue of SUMO is reacted with ATP to yield pyrophosphate and a transient intermediate, SUMO adenylate. The SUMO adenylate then reacts with the thiol group of the cysteine residue of UBA2 (Olsen et al. 2010).

Literature references

Hannoun, Z., Greenhough, S., Jaffray, E., Hay, RT., Hay, DC. (2010). Post-translational modification by SUMO. *Toxicology, 278*, 288-93. ↗

Wang, Y., Dasso, M. (2009). SUMOylation and deSUMOylation at a glance. *J. Cell. Sci., 122*, 4249-52. ↗

Gareau, JR., Lima, CD. (2010). The SUMO pathway: emerging mechanisms that shape specificity, conjugation and recognition. *Nat. Rev. Mol. Cell Biol., 11*, 861-71. ↗

Olsen, SK., Capili, AD., Lu, X., Tan, DS., Lima, CD. (2010). Active site remodelling accompanies thioester bond formation in the SUMO E1. *Nature, 463*, 906-12. ↗

Editions

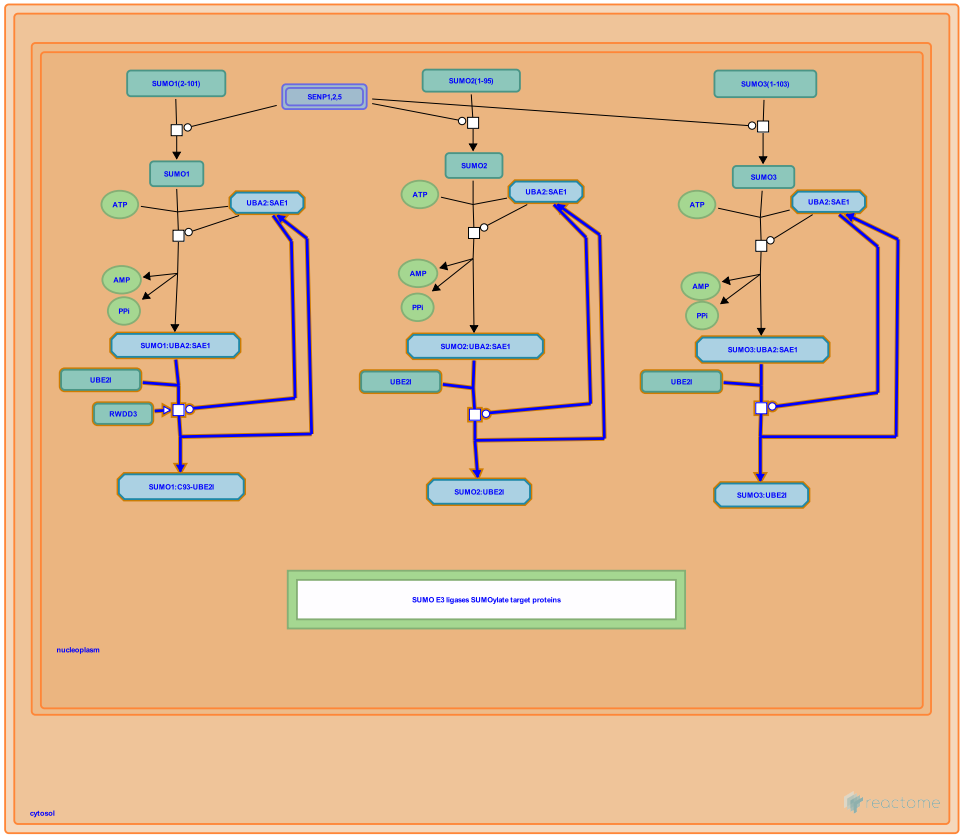
2013-02-06	Authored, Edited	May, B.
2013-05-16	Reviewed	Garg, AK.

SUMO is transferred from E1 to E2 (UBE2I, UBC9) ↗

Location: Processing and activation of SUMO

Stable identifier: R-HSA-3065678

Compartments: nucleoplasm



SUMO is transferred from cysteine-173 of UBA2 to cysteine-93 of UBC9 (UBE2I) in a transthiolation reaction (reviewed in Wang and Dasso 2009, Wilkinson and Henley 2010, Hannoun et al. 2010, Gareau and Lima 2010). UBC9 is the only known E2 enzyme for SUMO and on certain substrates such as RanGAP1 may act without the requirement of an E3 ligase.

Literature references

Wilkinson, KA., Henley, JM. (2010). Mechanisms, regulation and consequences of protein SUMOylation. *Biochem. J., 428*, 133-45. ↗

Hannoun, Z., Greenhough, S., Jaffray, E., Hay, RT., Hay, DC. (2010). Post-translational modification by SUMO. *Toxicology, 278*, 288-93. ↗

Wang, Y., Dasso, M. (2009). SUMOylation and deSUMOylation at a glance. *J. Cell. Sci., 122*, 4249-52. ↗

Gareau, JR., Lima, CD. (2010). The SUMO pathway: emerging mechanisms that shape specificity, conjugation and recognition. *Nat. Rev. Mol. Cell Biol., 11*, 861-71. ↗

Editions

2013-02-06	Authored, Edited	May, B.
2013-05-16	Reviewed	Garg, AK.

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