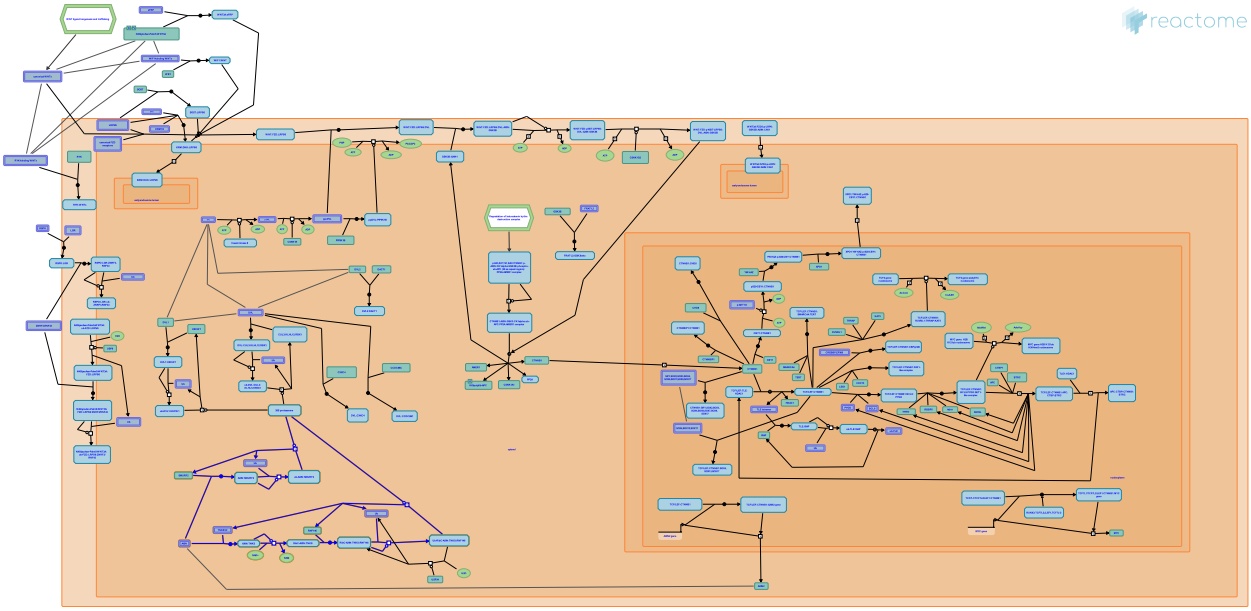
Degradation of AXIN



Gillespie, ME., Kikuchi, A., Matthews, L., Rajakulendran, N., Rothfels, K., van Amerongen, R.

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

03/05/2024

Introduction

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

Literature references

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

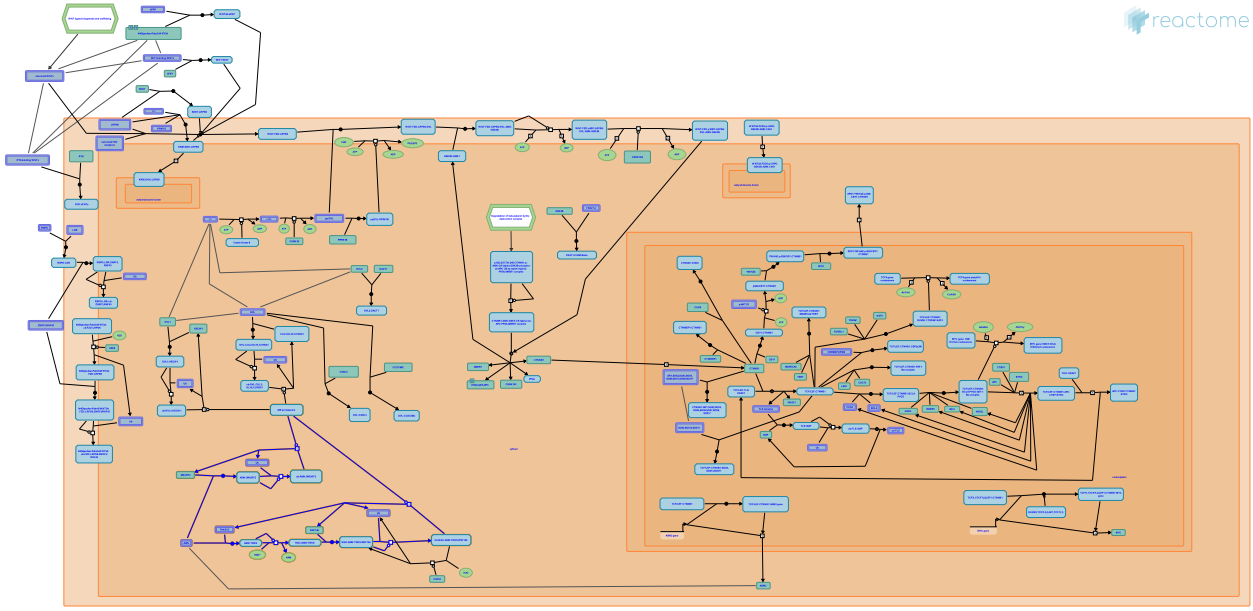
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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

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

Degradation of AXIN ↗

Stable identifier: R-HSA-4641257



AXIN is present in low concentrations in the cell and is considered to be the limiting component of the beta-catenin destruction complex in Xenopus; this may not be the case in mammalian cells, however (Lee et al, 2003; Tan et al, 2012). Cellular levels of AXIN are regulated in part through ubiquitin-mediated turnover. E3 ligases SMURF2 and RNF146 have both been shown to play a role in promoting the degradation of AXIN by the 26S proteasome (Kim and Jho, 2010; Callow et al, 2011; Zhang et al, 2011).

Literature references

Mickanin, C., Zhang, Y., Shi, X., Charlat, O., Feng, Y., Cong, F. et al. (2011). RNF146 is a poly(ADP-ribose)-directed E3 ligase that regulates axin degradation and Wnt signalling. *Nat. Cell Biol., 13*, 623-9. ↗

Jho, EH., Kim, S. (2010). The protein stability of Axin, a negative regulator of Wnt signaling, is regulated by Smad ubiquitination regulatory factor 2 (Smurf2). *J. Biol. Chem., 285*, 36420-6. ↗

Kruger, R., Salic, A., Kirschner, MW., Lee, E., Heinrich, R. (2003). The roles of APC and Axin derived from experimental and theoretical analysis of the Wnt pathway. *PLoS Biol, 1*, E10. ↗

Kirkpatrick, DS., Bheddah, S., Lau, T., Callow, MG., Lee, J., Davis, D. et al. (2011). Ubiquitin ligase RNF146 regulates tankyrase and Axin to promote Wnt signaling. *PLoS ONE, 6*, e22595. ↗

Hirokawa, Y., Tan, CW., Layton, MJ., Burgess, AW., Smith, DW., Gardiner, BS. (2012). Wnt signalling pathway parameters for mammalian cells. *PLoS ONE, 7*, e31882. ↗

Editions

2007-09-04	Edited	Matthews, L.
2013-06-25	Authored	Rothfels, K.
2013-10-03	Edited	Gillespie, ME.
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2014-02-15	Reviewed	van Amerongen, R.
2014-04-22	Reviewed	Kikuchi, A.

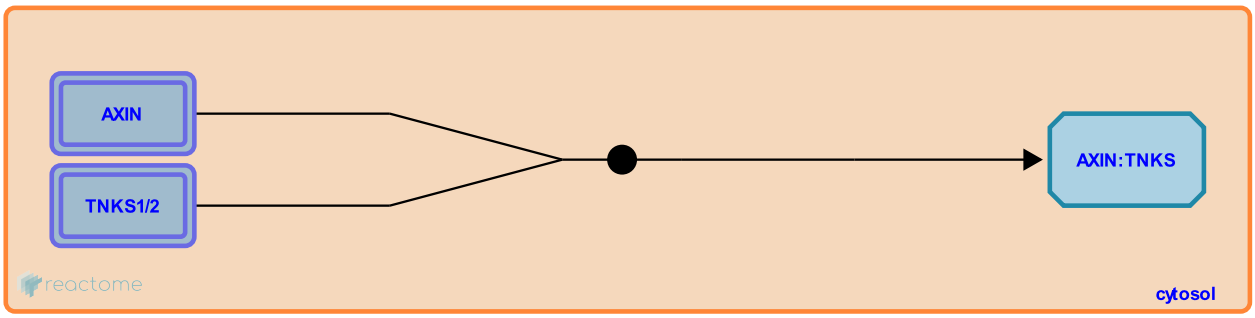
Tankyrase binds AXIN ↗

Location: Degradation of AXIN

Stable identifier: R-HSA-3640862

Type: binding

Compartments: cytosol



Several recent chemical screens have identified inhibitors of the poly-ADP ribosylation enzymes tankyrase (TNKS) 1 and 2 as regulators of WNT signalling (Huang et al, 2009; Chen et al, 2009; Waaler et al, 2012). Endogenous TNKS1 and 2 associate with AXIN2 in SW480 cells as assessed by co-immunoprecipitation. Both AXIN1 and AXIN2 interact strongly with TNKS1/2 by two-hybrid, and deletion analysis shows that amino acids 19-30 of AXIN1 are necessary and sufficient for binding to TNKS1. This region, termed the tankyrase-binding-domain (TBD) is necessary and sufficient for the interaction in GST-pulldown and co-immunoprecipitation studies (Huang et al, 2009).

Followed by: Tankyrase ADP-ribosylates AXIN

Literature references

Williams, NS., Fan, CW., Chen, C., Kilgore, J., Amatruda, JF., Wei, S. et al. (2009). Small molecule-mediated disruption of Wnt-dependent signaling in tissue regeneration and cancer. *Nat. Chem. Biol., 5*, 100-7. ↗

Mickanin, C., Zhang, Y., Fawell, S., Mishina, YM., Fazal, A., Myer, V. et al. (2009). Tankyrase inhibition stabilizes axin and antagonizes Wnt signalling. *Nature, 461*, 614-20. ↗

Wilson, SR., Machon, O., Korinek, V., Waaler, J., Dinh, H., Machonova, O. et al. (2012). A novel tankyrase inhibitor decreases canonical Wnt signaling in colon carcinoma cells and reduces tumor growth in conditional APC mutant mice. *Cancer Res., 72*, 2822-32. ↗

Editions

2013-05-27	Authored	Rothfels, K.
2013-10-03	Edited	Gillespie, ME.
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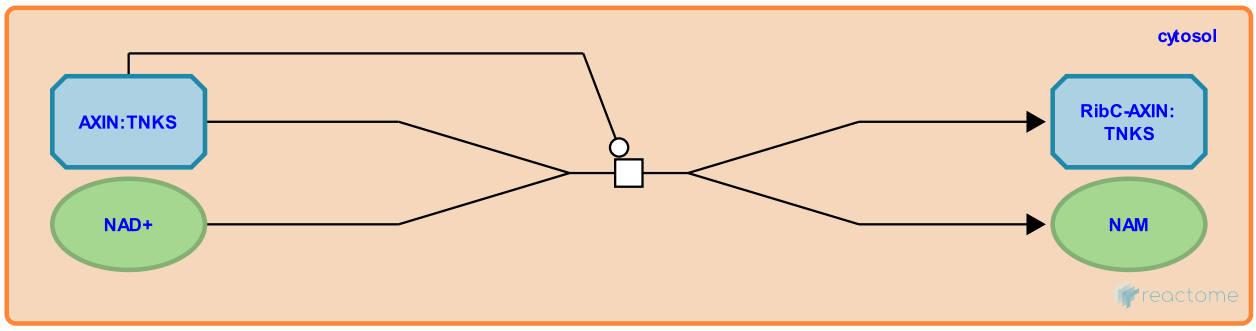
Tankyrase ADP-ribosylates AXIN ↗

Location: Degradation of AXIN

Stable identifier: R-HSA-3640858

Type: transition

Compartments: cytosol



TNKS1 and 2 function redundantly to control AXIN protein levels through the addition of poly-ADP-ribosyl groups (PARSylation), which may lead to subsequent ubiquitination and degradation by the proteasome. In HEK293, SW480 and breast cancer cell lines, depletion of TNKS1 and 2 increases the protein levels of AXIN1 and AXIN2 resulting in increased beta-catenin phosphorylation, decreased beta-catenin abundance and decreased expression of WNT targets and WNT-responsive reporters (Huang et al, 2009; Callow et al, 2011; Waaler et al, 2012; Bao et al, 2012). In vitro, TNKS2 catalyzes the addition of ADP-ribosyl groups to the TBD fragment of AXIN1, while in vivo, both exogenous GST-AXIN1 and endogenous AXIN1 are PARSylated in a TNKS-dependent manner (Huang et al, 2009; Callow et al, 2011; Zhang et al, 2011). PARSylation is likely required for the subsequent proteasome-mediated degradation of AXIN, as the increase in levels of polyubiquitinated AXIN1 and 2 seen upon treatment of cells with the proteasome inhibitor MG132 is lost if cells are simultaneously treated with an inhibitor of TNKS1 and 2 (Huang et al, 2009). Although in this reaction, TNKS is shown PARSylating unbound AXIN, it is likely that this regulation occurs at the level of the destruction complex. Also not shown in this reaction is the ability of TNKS to catalyze autoPARSylation reactions, which ultimately lead to its own degradation (Yeh et al, 2006; Huang et al, 2009; Zhang et al, 2011).

Preceded by: Tankyrase binds AXIN

Followed by: RNF146 binds RibC-AXIN:TNKS complex

Literature references

Mickanin, C., Zhang, Y., Shi, X., Charlat, O., Feng, Y., Cong, F. et al. (2011). RNF146 is a poly(ADP-ribose)-directed E3 ligase that regulates axin degradation and Wnt signalling. *Nat. Cell Biol., 13*, 623-9. ↗

Mickanin, C., Zhang, Y., Fawell, S., Mishina, YM., Fazal, A., Myer, V. et al. (2009). Tankyrase inhibition stabilizes axin and antagonizes Wnt signalling. *Nature, 461*, 614-20. ↗

Tsun, ZY., Yeh, TY., Lee, RM., Meyer, TN., Schwesinger, C., Chi, NW. (2006). Tankyrase recruitment to the lateral membrane in polarized epithelial cells: regulation by cell-cell contact and protein poly(ADP-ribosyl)ation. *Biochem. J., 399*, 415-25. ↗

Wilson, SR., Machon, O., Korinek, V., Waaler, J., Dinh, H., Machonova, O. et al. (2012). A novel tankyrase inhibitor decreases canonical Wnt signaling in colon carcinoma cells and reduces tumor growth in conditional APC mutant mice. *Cancer Res., 72*, 2822-32. ↗

Kirkpatrick, DS., Bheddah, S., Lau, T., Callow, MG., Lee, J., Davis, D. et al. (2011). Ubiquitin ligase RNF146 regulates tankyrase and Axin to promote Wnt signaling. *PLoS ONE, 6*, e22595. ↗

Editions

2013-05-27	Authored	Rothfels, K.
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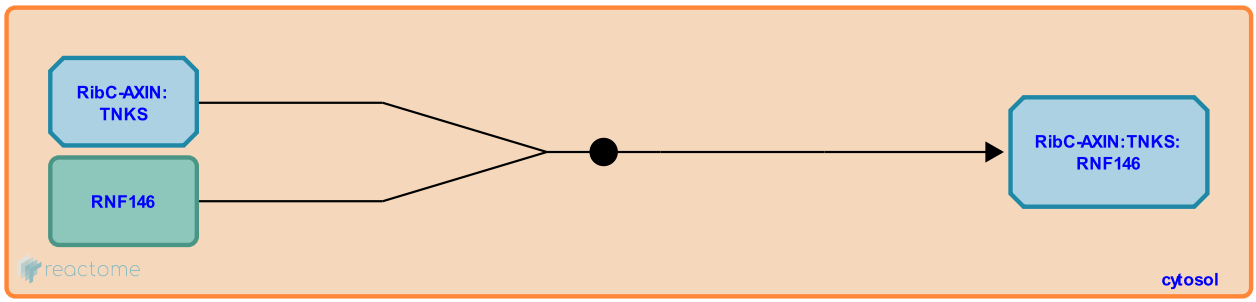
RNF146 binds RibC-AXIN:TNKS complex ↗

Location: Degradation of AXIN

Stable identifier: R-HSA-3640844

Type: binding

Compartments: cytosol



RNF146 is an E3 RING ubiquitin ligase that was identified as a positive regulator of WNT signalling (Callow et al, 2011; Zhang et al, 2011). Depletion of RNF146 increases the levels of AXIN and decreases expression of WNT target genes and WNT-responsive reporters in a WNT-independent manner (Zhang et al, 2011; Callow et al, 2011). RNF146 binds directly to poly-ADP-ribose groups through its WWE domain and ubiquitinates substrates in a tankyrase-dependent manner (Zhang et al, 2011). AXIN, Tankyrase and RNF146 are thought to exist in a complex (Callow et al, 2011) and RNF146 mediates the tankyrase-dependent ubiquitination of all three proteins to promote their degradation (Callow et al, 2011; Zhang et al, 2011). In this reaction, only the targeted degradation of AXIN is depicted.

Preceded by: Tankyrase ADP-ribosylates AXIN

Followed by: RNF146 ubiquitinates ADP-ribosylated AXIN

Literature references

Mickanin, C., Zhang, Y., Shi, X., Charlat, O., Feng, Y., Cong, F. et al. (2011). RNF146 is a poly(ADP-ribose)-directed E3 ligase that regulates axin degradation and Wnt signalling. *Nat. Cell Biol., 13*, 623-9. ↗

Kirkpatrick, DS., Bheddah, S., Lau, T., Callow, MG., Lee, J., Davis, D. et al. (2011). Ubiquitin ligase RNF146 regulates tankyrase and Axin to promote Wnt signaling. *PLoS ONE, 6*, e22595. ↗

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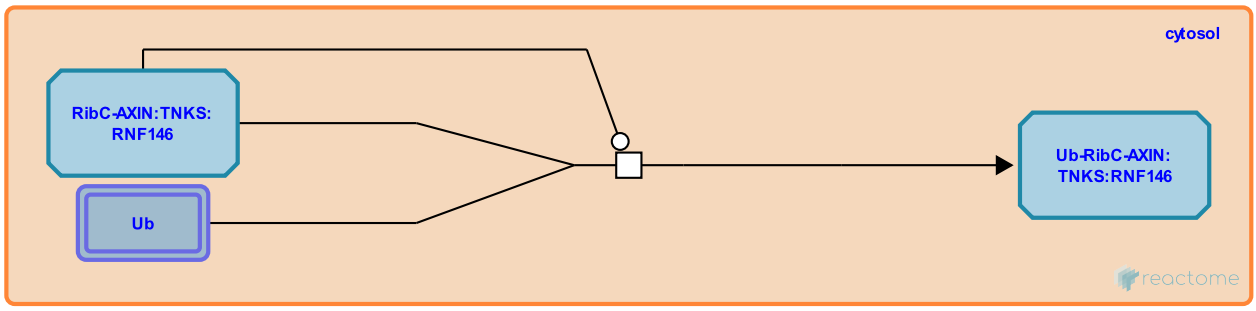
RNF146 ubiquitinates ADP-ribosylated AXIN ↗

Location: Degradation of AXIN

Stable identifier: R-HSA-3640861

Type: transition

Compartments: cytosol



RNF146 has in vitro and in vivo ubiquitination activity against AXIN, Tankyrase and itself (Callow et al, 2011; Zhang et al, 2011).

Preceded by: RNF146 binds RibC-AXIN:TNKS complex

Followed by: Ub-RibC-AXIN is degraded by the proteasome

Literature references

Mickanin, C., Zhang, Y., Shi, X., Charlat, O., Feng, Y., Cong, F. et al. (2011). RNF146 is a poly(ADP-ribose)-directed E3 ligase that regulates axin degradation and Wnt signalling. *Nat. Cell Biol., 13*, 623-9. ↗

Kirkpatrick, DS., Bheddah, S., Lau, T., Callow, MG., Lee, J., Davis, D. et al. (2011). Ubiquitin ligase RNF146 regulates tankyrase and Axin to promote Wnt signaling. *PLoS ONE, 6*, e22595. ↗

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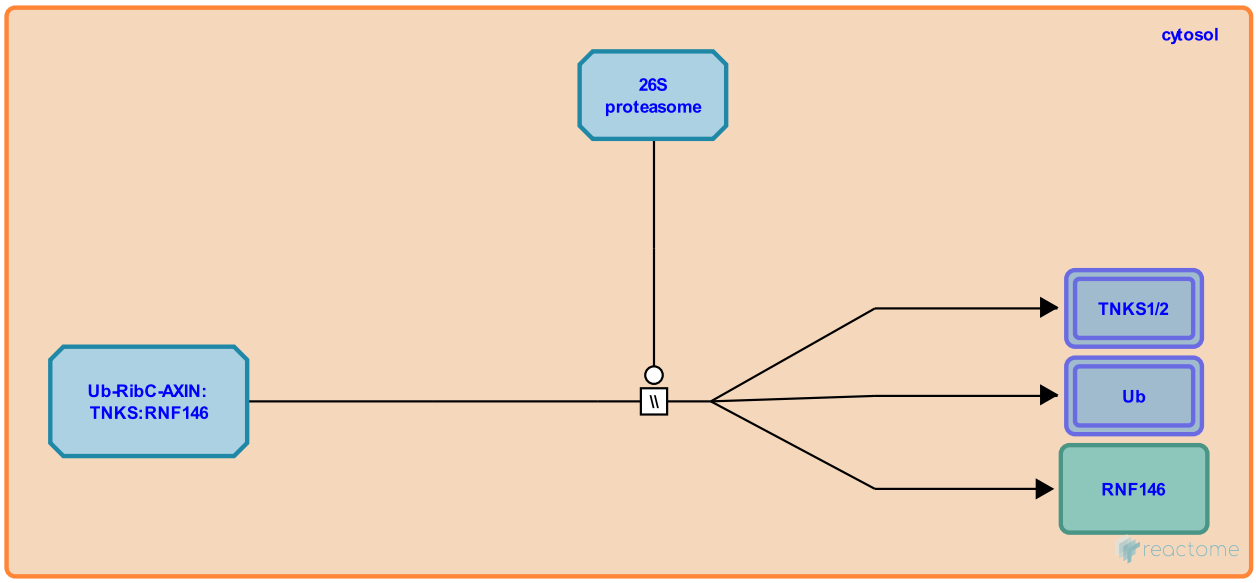
Ub-RibC-AXIN is degraded by the proteasome ↗

Location: Degradation of AXIN

Stable identifier: R-HSA-3640874

Type: omitted

Compartments: cytosol



In the presence of the proteasome inhibitor MG132, polyubiquitinated forms of AXIN accumulate (Huang et al, 2009; Zhang et al, 2011; Callow et al, 2011). This effect is abrogated by co-treatment of cells with both MG132 and inhibitors of tankyrase activity, suggesting that both PARSylation and ubiquitination are required for AXIN degradation (Huang et al, 2009).

Preceded by: RNF146 ubiquitinates ADP-ribosylated AXIN

Literature references

Mickanin, C., Zhang, Y., Shi, X., Charlat, O., Feng, Y., Cong, F. et al. (2011). RNF146 is a poly(ADP-ribose)-directed E3 ligase that regulates axin degradation and Wnt signalling. *Nat. Cell Biol., 13*, 623-9. ↗

Mickanin, C., Zhang, Y., Fawell, S., Mishina, YM., Fazal, A., Myer, V. et al. (2009). Tankyrase inhibition stabilizes axin and antagonizes Wnt signalling. *Nature, 461*, 614-20. ↗

Kirkpatrick, DS., Bheddah, S., Lau, T., Callow, MG., Lee, J., Davis, D. et al. (2011). Ubiquitin ligase RNF146 regulates tankyrase and Axin to promote Wnt signaling. *PLoS ONE, 6*, e22595. ↗

Editions

2013-05-30	Authored	Rothfels, K.
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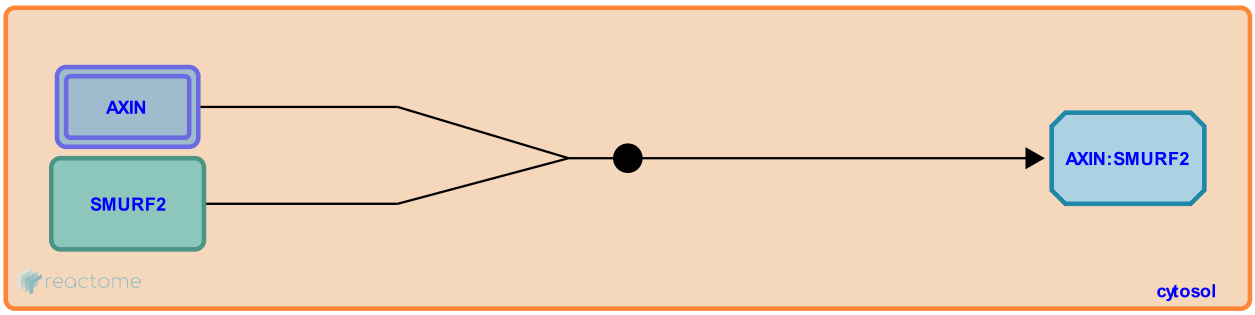
SMURF2 binds AXIN ↗

Location: Degradation of AXIN

Stable identifier: R-HSA-4641134

Type: binding

Compartments: cytosol



SMURF2 is an E3 ubiquitin ligase for AXIN and promotes its ubiquitin-mediated degradation. Ectopic SMURF2 immunoprecipitates both exogenously expressed and endogenous AXIN. AXIN is polyubiquitinated by SMURF2 at lysine 505 both in vitro and in vivo (Kim and Jho, 2012).

Followed by: AXIN is ubiquitinated by SMURF2

Literature references

Jho, EH., Kim, S. (2010). The protein stability of Axin, a negative regulator of Wnt signaling, is regulated by Smad ubiquitination regulatory factor 2 (Smurf2). *J. Biol. Chem., 285*, 36420-6. ↗

Editions

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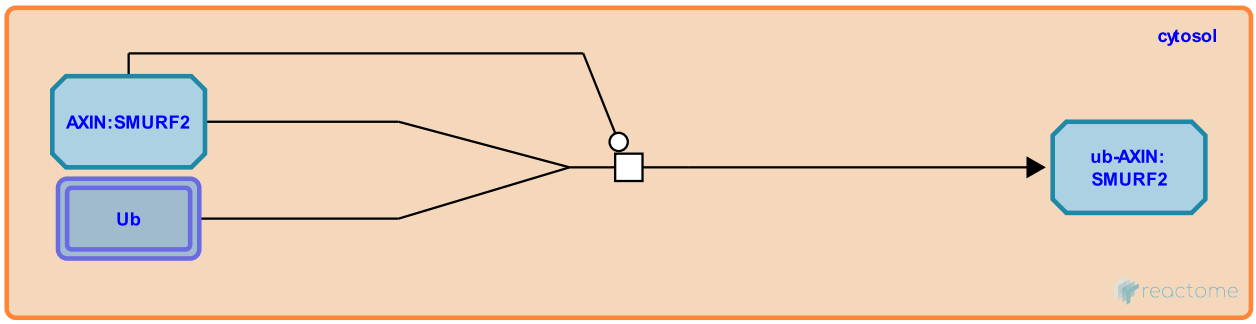
AXIN is ubiquitinated by SMURF2

Location: Degradation of AXIN

Stable identifier: R-HSA-4641129

Type: transition

Compartments: cytosol



SMURF2 has been shown to ubiquitinate AXIN at lysine 505 both in vitro and in vivo in a manner that depends on the interaction between the two proteins (Kim and Jho, 2012).

Preceded by: SMURF2 binds AXIN

Followed by: Ubiquitinated AXIN is degraded by the proteasome

Literature references

Jho, EH., Kim, S. (2010). The protein stability of Axin, a negative regulator of Wnt signaling, is regulated by Smad ubiquitination regulatory factor 2 (Smurf2). *J. Biol. Chem., 285*, 36420-6.

Editions

2013-09-23	Authored	Rothfels, K.
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2014-02-15	Reviewed	van Amerongen, R.
2014-04-22	Reviewed	Kikuchi, A.

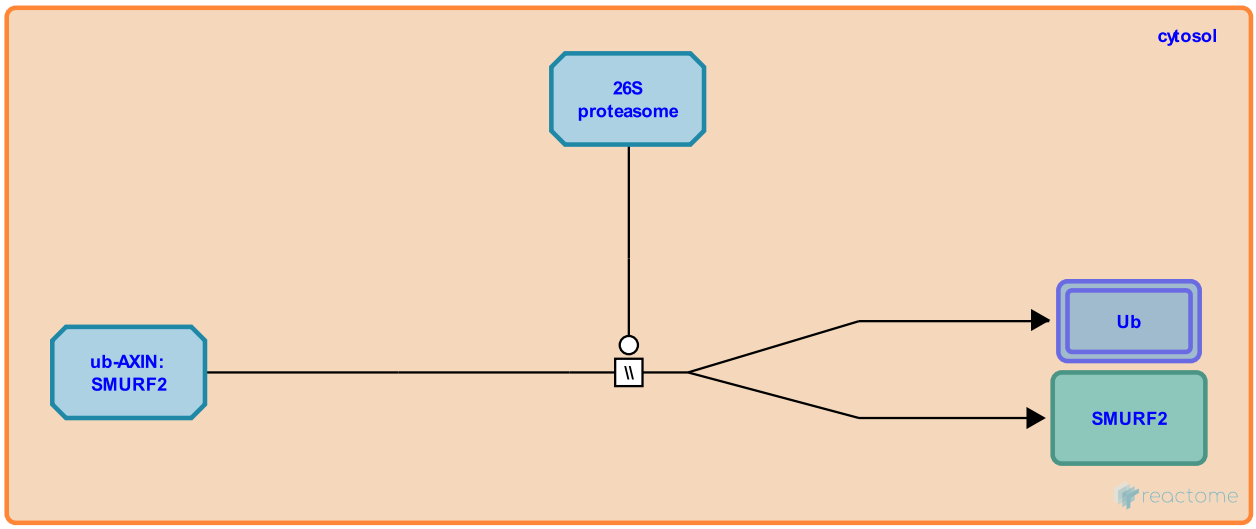
Ubiquitinated AXIN is degraded by the proteasome ↗

Location: Degradation of AXIN

Stable identifier: R-HSA-4641256

Type: omitted

Compartments: cytosol



After ubiquitination by SMURF2, AXIN is degraded by the proteasome.

Preceded by: AXIN is ubiquitinated by SMURF2

Literature references

Jho, EH., Kim, S. (2010). The protein stability of Axin, a negative regulator of Wnt signaling, is regulated by Smad ubiquitination regulatory factor 2 (Smurf2). *J. Biol. Chem., 285,* 36420-6. ↗

Editions

2013-09-23	Authored	Rothfels, K.
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2014-01-22	Reviewed	Rajakulendran, N.
2014-02-15	Reviewed	van Amerongen, R.
2014-04-22	Reviewed	Kikuchi, A.

Table of Contents