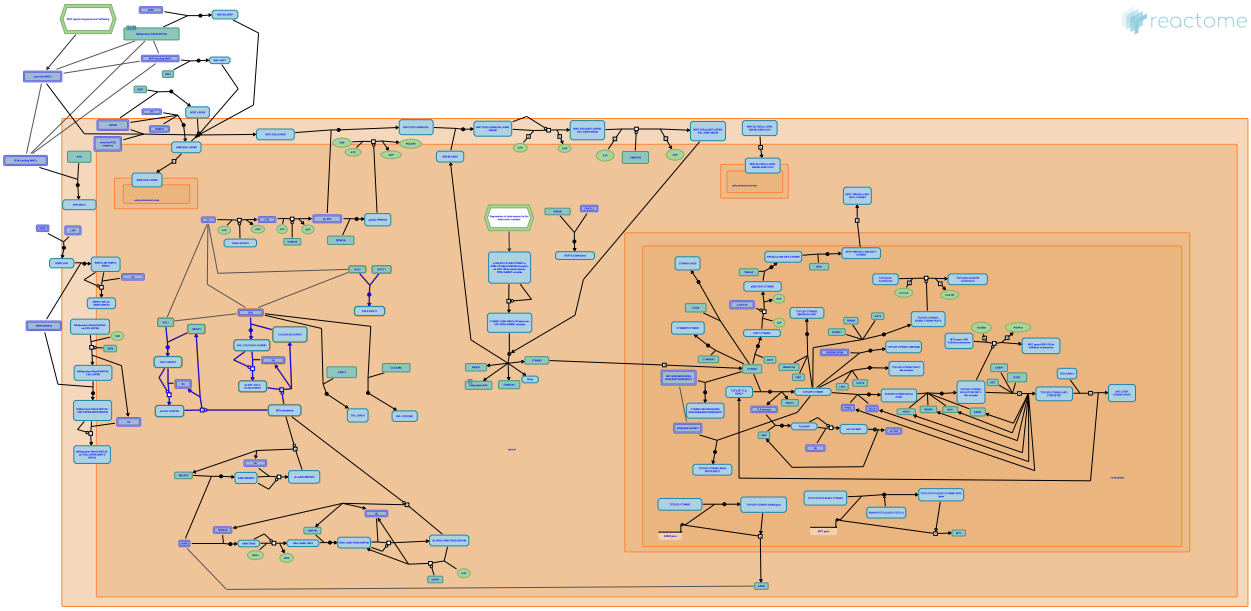
Degradation of DVL



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

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20/11/2019

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. ↗

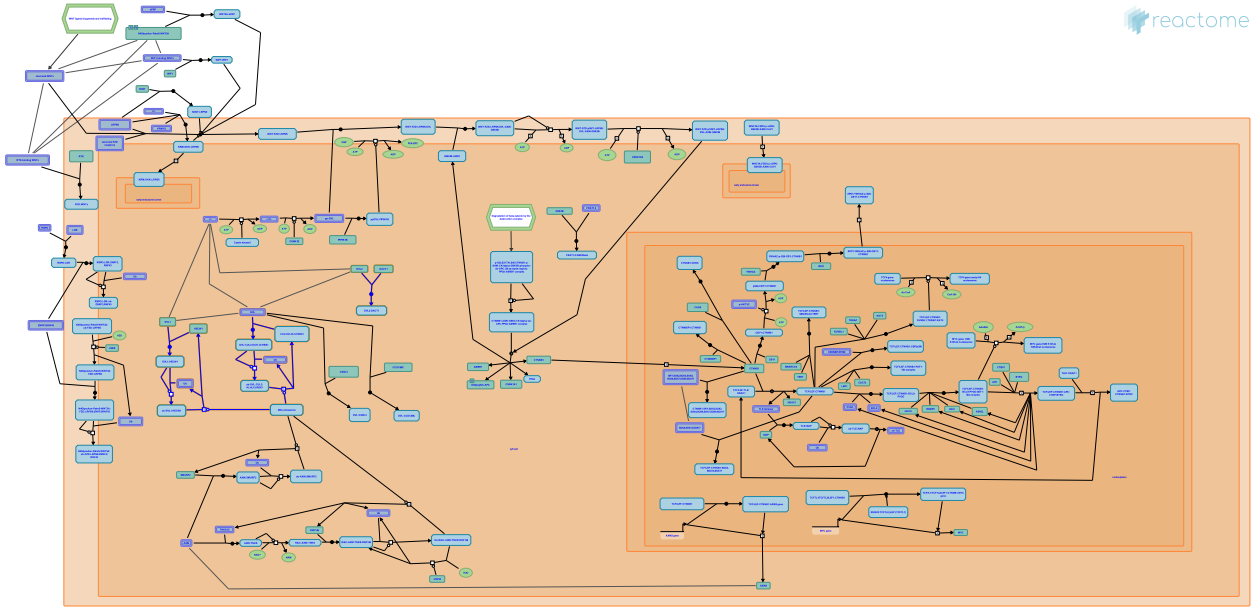
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Degradation of DVL ↗

Stable identifier: R-HSA-4641258



DVL protein levels are regulated by both proteasomal and lysosomal degradation (reviewed in Gao and Chen, 2010). The E3 ligases HECF1, ITCH and KLHL12:CUL3 have all been shown to contribute to the polyubiquitination and subsequent degradation of DVL (Angers et al, 2006; Miyazaki et al, 2004; Wei et al, 2012). DVL stability is also regulated by its interaction with DACT1, which promotes degradation of DVL in the lysosome (Cheyette et al, 2002; Zhang et al, 2006).

Literature references

Wei, W., Li, M., Wang, J., Nie, F., Li, L. (2012). The E3 ubiquitin ligase ITCH negatively regulates canonical Wnt signaling by targeting dishevelled protein. *Mol. Cell. Biol., 32*, 3903-12. ↗

Angers, S., Thorpe, CJ., Biechele, TL., Goldenberg, SJ., Zheng, N., Maccoss, MJ. et al. (2006). The KLHL12-Cullin-3 ubiquitin ligase negatively regulates the Wnt-beta-catenin pathway by targeting Dishevelled for degradation. *Nat Cell Biol, 8*, 348-57. ↗

Gao, C., Chen, YG. (2010). Dishevelled: The hub of Wnt signaling. *Cell. Signal., 22*, 717-27. ↗

Cheyette, BN., Waxman, JS., Miller, JR., Takemaru, K., Sheldahl, LC., Khlebtsova, N. et al. (2002). Dapper, a Dishevelled-associated antagonist of beta-catenin and JNK signaling, is required for notochord formation. *Dev. Cell, 2*, 449-61. ↗

Miyazaki, K., Fujita, T., Ozaki, T., Kato, C., Kurose, Y., Sakamoto, M. et al. (2004). NEDL1, a novel ubiquitin-protein isopeptide ligase for dishevelled-1, targets mutant superoxide dismutase-1. *J. Biol. Chem., 279*, 11327-35. ↗

Editions

2007-09-04	Edited	Matthews, L.
2013-06-24	Authored	Rothfels, K.
2013-10-02	Edited	Gillespie, ME.
2014-01-22	Reviewed	Rajakulendran, N.
2014-02-14	Reviewed	van Amerongen, R.
2014-04-22	Reviewed	Kikuchi, A.

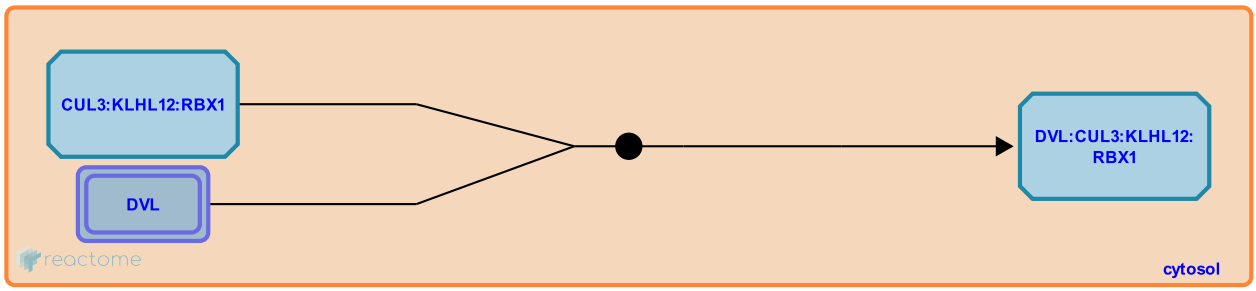
DVL is bound by the CUL3:KLHL12:RBX1 ubiquitin ligase complex ↗

Location: Degradation of DVL

Stable identifier: R-HSA-1504213

Type: binding

Compartments: cytosol



In response to WNT signaling, DVL is recruited to the CUL3:KLHL12:RBX1 ubiquitin ligase complex and is subsequently polyubiquitinated and degraded. The BTB domains of the adaptor protein KLHL12 bind constitutively to CUL3 while its Kelch domains mediate a WNT-dependent interaction with the C-terminus of DVL (Angers et al, 2006).

Followed by: DVL is ubiquitinated by CUL3:KLHL12:RBX1

Literature references

Angers, S., Thorpe, CJ., Biechele, TL., Goldenberg, SJ., Zheng, N., Maccoss, MJ. et al. (2006). The KLHL12-Cullin-3 ubiquitin ligase negatively regulates the Wnt-beta-catenin pathway by targeting Dishevelled for degradation. *Nat Cell Biol, 8*, 348-57. ↗

Editions

2013-05-29	Authored	Rothfels, K.
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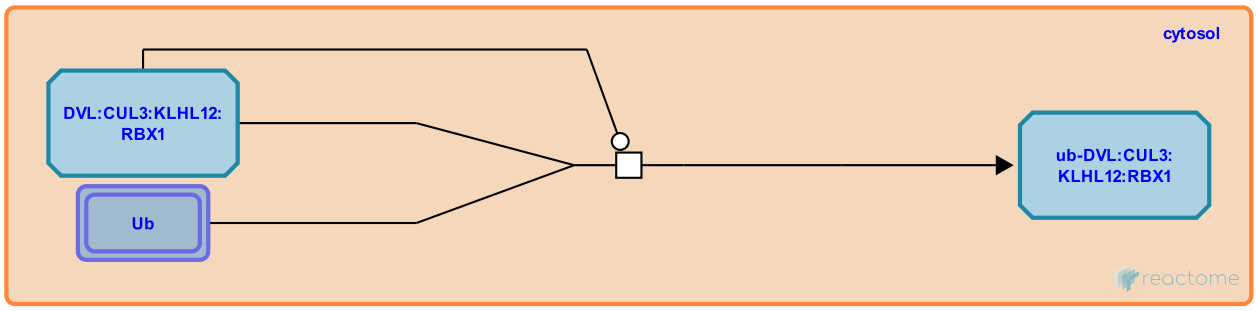
DVL is ubiquitinated by CUL3:KLHL12:RBX1 ↗

Location: Degradation of DVL

Stable identifier: R-HSA-1504190

Type: transition

Compartments: cytosol



CUL3:KLHL12:RBX1 polyubiquitinates Dishevelled, targeting it for degradation by the proteasome (Angers et al, 2006).

Preceded by: DVL is bound by the CUL3:KLHL12:RBX1 ubiquitin ligase complex

Followed by: Ubiquitinated DVL is degraded by the proteasome

Literature references

Angers, S., Thorpe, CJ., Biechele, TL., Goldenberg, SJ., Zheng, N., Maccoss, MJ. et al. (2006). The KLHL12-Cullin-3 ubiquitin ligase negatively regulates the Wnt-beta-catenin pathway by targeting Dishevelled for degradation. *Nat Cell Biol, 8*, 348-57. ↗

Editions

2013-05-29	Authored	Rothfels, K.
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2014-04-22	Reviewed	Kikuchi, A.

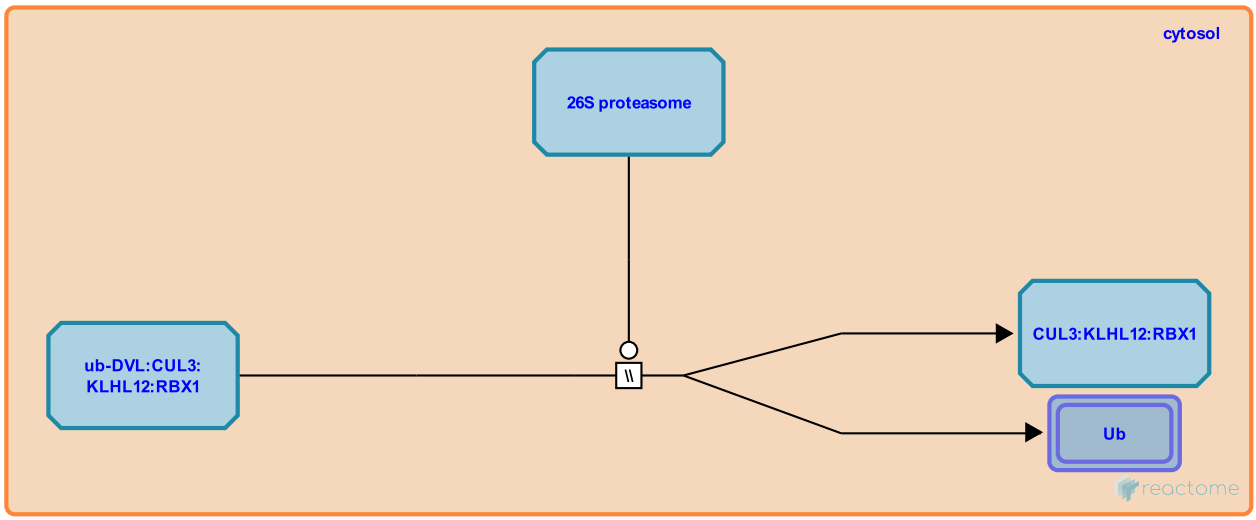
Ubiquitinated DVL is degraded by the proteasome ↗

Location: Degradation of DVL

Stable identifier: R-HSA-1504193

Type: omitted

Compartments: cytosol



Ubiquitinated Dishevelled is degraded by the proteasome.

Preceded by: DVL is ubiquitinated by CUL3:KLHL12:RBX1

Literature references

Angers, S., Thorpe, CJ., Biechele, TL., Goldenberg, SJ., Zheng, N., Maccoss, MJ. et al. (2006). The KLHL12-Cullin-3 ubiquitin ligase negatively regulates the Wnt-beta-catenin pathway by targeting Dishevelled for degradation. *Nat Cell Biol, 8*, 348-57. ↗

Editions

2013-05-29	Authored	Rothfels, K.
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2014-04-22	Reviewed	Kikuchi, A.

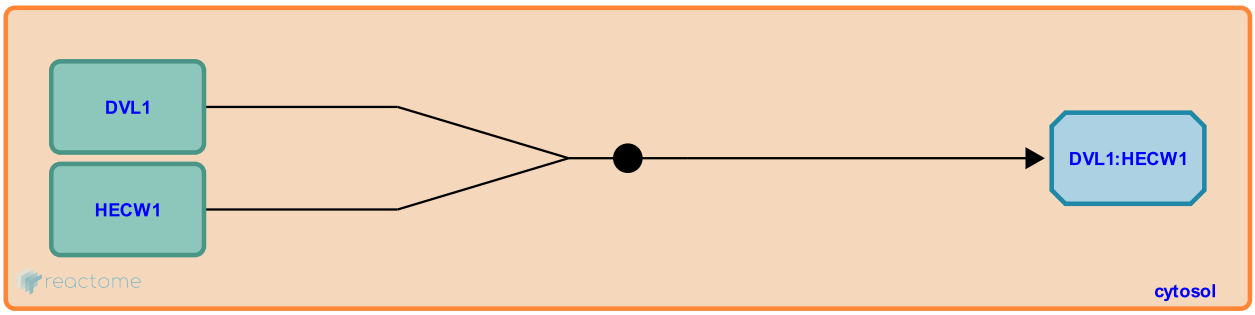
DVL1 is bound by the HECT ubiquitin ligase HECW1 ↗

Location: Degradation of DVL

Stable identifier: R-HSA-4641155

Type: binding

Compartments: cytosol



HECW1, also known as NEDL1, is an HECT E3 ligase that co-immunoprecipitates with DVL1 upon co-transfection in Neuro2 cells and targets it for proteasomal degradation (Miyazaki et al, 2004).

Followed by: DVL1 is ubiquitinated by HECW1

Literature references

Miyazaki, K., Fujita, T., Ozaki, T., Kato, C., Kurose, Y., Sakamoto, M. et al. (2004). NEDL1, a novel ubiquitin-protein isopeptide ligase for dishevelled-1, targets mutant superoxide dismutase-1. *J. Biol. Chem., 279*, 11327-35. ↗

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2013-09-23	Authored	Rothfels, K.
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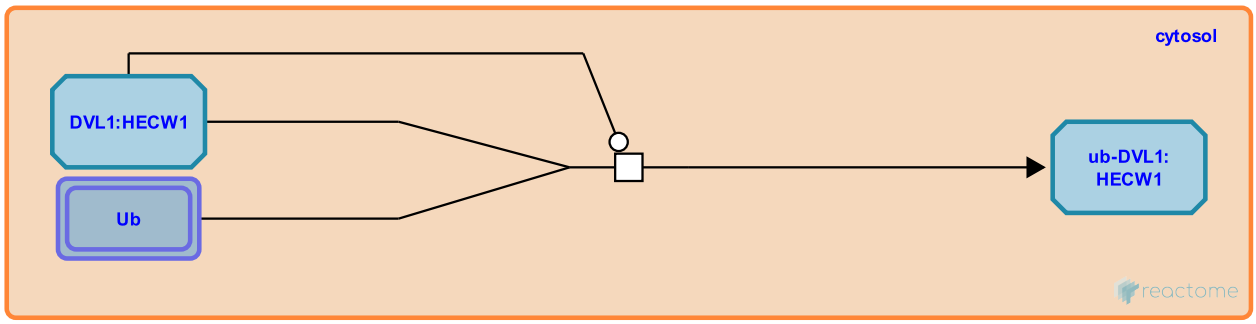
DVL1 is ubiquitinated by HECW1 ↗

Location: Degradation of DVL

Stable identifier: R-HSA-4641159

Type: transition

Compartments: cytosol



DVL1 is ubiquitinated by HECW1 in Neuro2 cells.

Preceded by: DVL1 is bound by the HECT ubiquitin ligase HECW1

Followed by: Ubiquitinated DVL1 is degraded by the proteasome

Literature references

Miyazaki, K., Fujita, T., Ozaki, T., Kato, C., Kurose, Y., Sakamoto, M. et al. (2004). NEDL1, a novel ubiquitin-protein isopeptide ligase for dishevelled-1, targets mutant superoxide dismutase-1. *J. Biol. Chem., 279*, 11327-35. ↗

Editions

2013-09-23	Authored	Rothfels, K.
2013-10-02	Edited	Gillespie, ME.
2014-01-22	Reviewed	Rajakulendran, N.
2014-02-14	Reviewed	van Amerongen, R.
2014-04-22	Reviewed	Kikuchi, A.

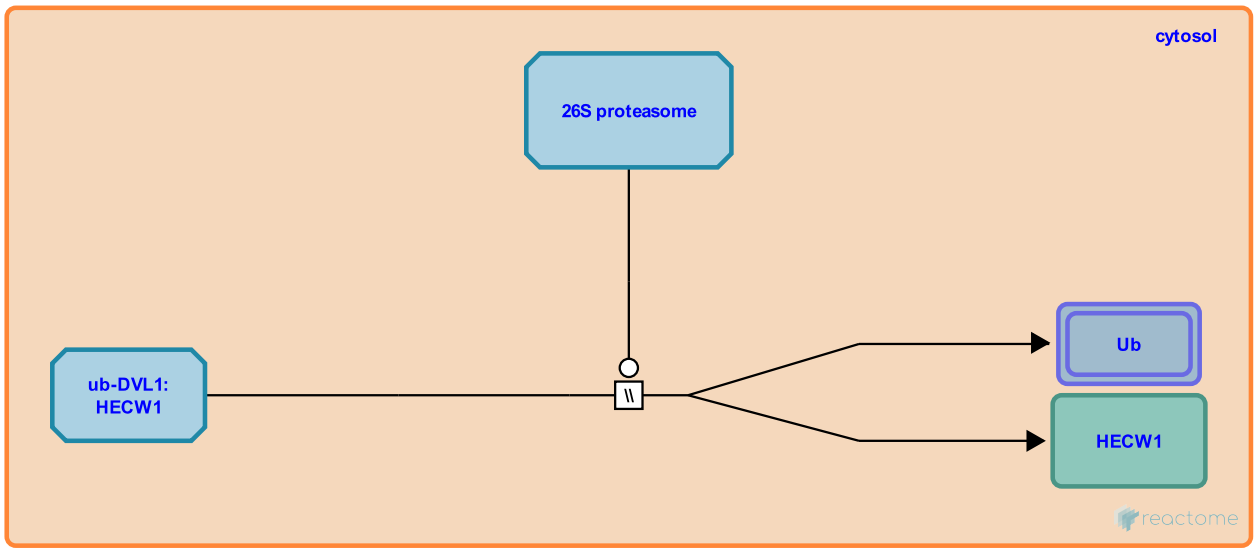
Ubiquitinated DVL1 is degraded by the proteasome ↗

Location: Degradation of DVL

Stable identifier: R-HSA-4641260

Type: omitted

Compartments: cytosol



After ubiquitination by HECW1, DVL1 is degraded by the proteasome.

Preceded by: DVL1 is ubiquitinated by HECW1

Literature references

Miyazaki, K., Fujita, T., Ozaki, T., Kato, C., Kurose, Y., Sakamoto, M. et al. (2004). NEDL1, a novel ubiquitin-protein isopeptide ligase for dishevelled-1, targets mutant superoxide dismutase-1. *J. Biol. Chem., 279*, 11327-35. ↗

Editions

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2014-02-14	Reviewed	van Amerongen, R.
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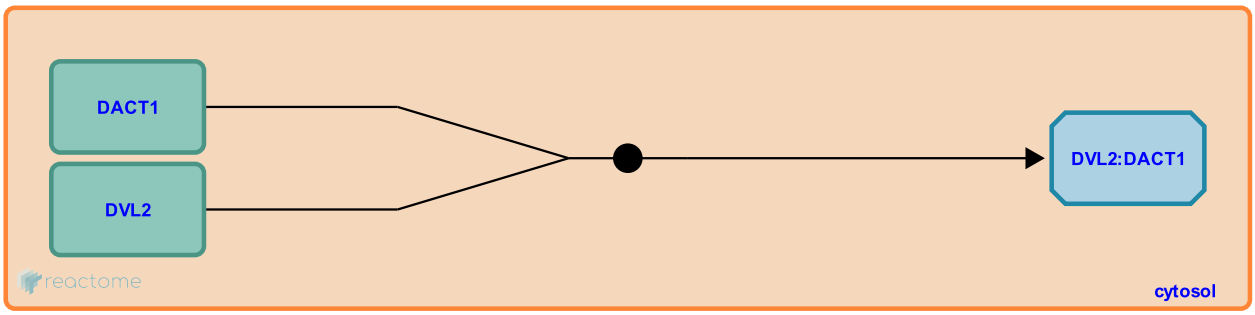
DACT1 binds DVL2 ↗

Location: Degradation of DVL

Stable identifier: R-HSA-4641147

Type: binding

Compartments: cytosol



DACT1, also known as DAPPER1, was identified in Xenopus as a negative regulator of WNT canonical and non-canonical signaling. In Xenopus, DACT1 has been shown to form a complex with GSK3beta, AXIN, CSNK1 and beta-catenin when co-expressed in HEK293 cells with DVL, and expression of DACT1 negatively regulates expression of beta-catenin target genes (Cheyette et al, 2002). In human cells, DACT1 co-precipitates with DVL2, an interaction mediated by the DIX domain of DVL2 and the C-terminal region of DACT1. siRNA depletion of DACT1 results in higher expression of beta-catenin dependent reporters and increased protein levels of DVL2, suggesting that DACT1 restricts beta-catenin-dependent signaling by promoting the degradation of DVL2. Consistent with this, lysosome inhibitors block DACT1-induced degradation of DVL2 (Zhang et al, 2006).

Literature references

Zhang, L., Gao, X., Wen, J., Ning, Y., Chen, YG. (2006). Dapper 1 antagonizes Wnt signaling by promoting dishevelled degradation. *J. Biol. Chem., 281*, 8607-12. ↗

Cheyette, BN., Waxman, JS., Miller, JR., Takemaru, K., Sheldahl, LC., Khlebtsova, N. et al. (2002). Dapper, a Dishevelled-associated antagonist of beta-catenin and JNK signaling, is required for notochord formation. *Dev. Cell, 2*, 449-61. ↗

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2014-04-22	Reviewed	Kikuchi, A.

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