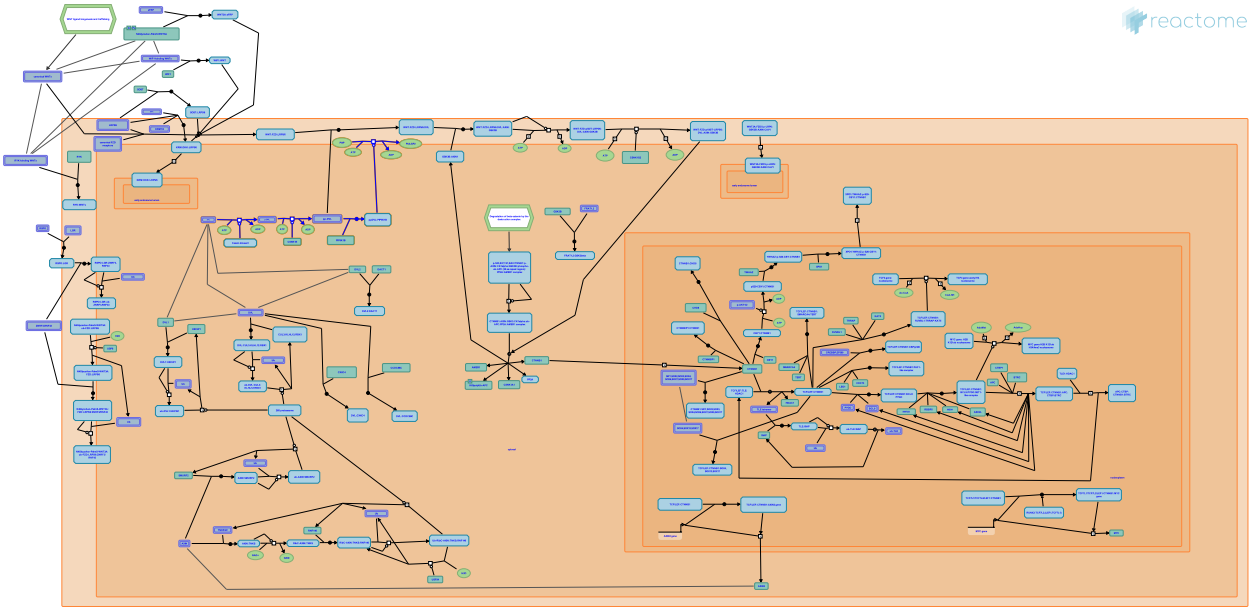
WNT mediated activation of DVL



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.

16/01/2021

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.

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. ↗

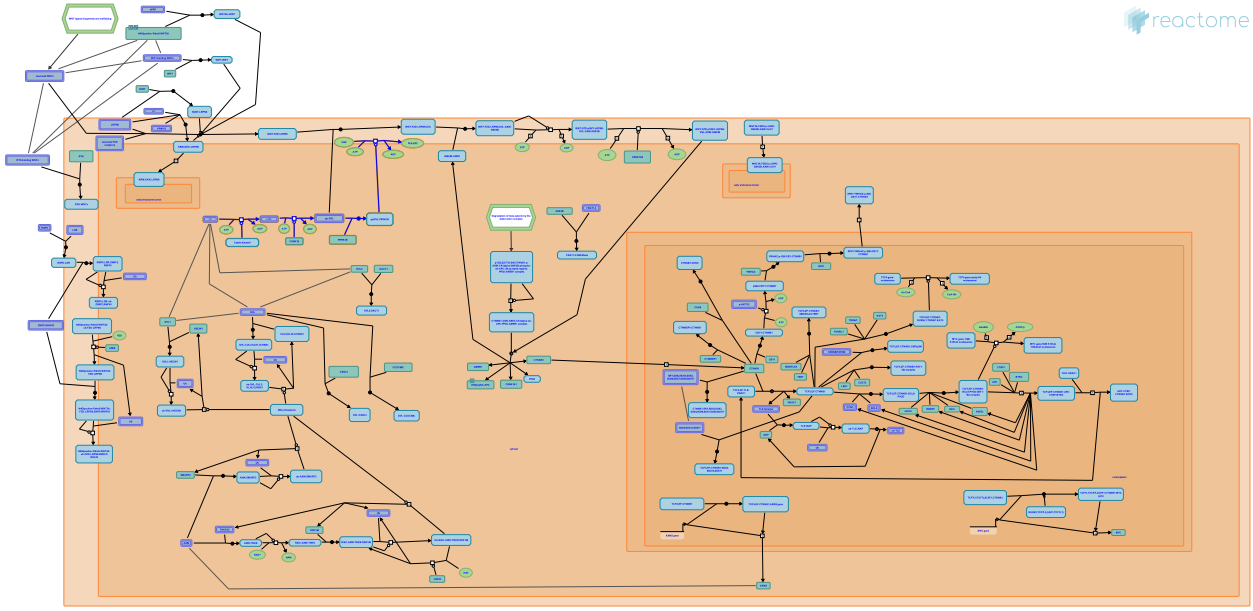
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

WNT mediated activation of DVL ↗

Stable identifier: R-HSA-201688



The three human Dishevelled (DVL) proteins play a central and overlapping role in the transduction of the WNT signaling cascade (Lee et al, 2008; reviewed in Gao and Chen 2010). DVL activity is regulated by phosphorylation, although the details are not completely worked out. DVL likely exists as a phosphoprotein even in the absence of WNT stimulation, and is further phosphorylated upon ligand binding. Casein kinase 1epsilon (CSNK1E), casein kinase 2 (CSNK2) and PAR1 have all been reported to phosphorylate DVL (Willert et al, 1997; Sun et al, 2001; Cong et al, 2004; Ossipova et al, 2005). Upon pathway activation, phosphorylated DVL translocates to the plasma membrane through an interaction between the DVL PDZ domain and the FZD KTxxxW motif (Wong et al, 2003; Umbhauer et al, 2000; Kikuchi et al, 2011). At the plasma membrane, DVL is believed to oligomerize through its DIX domain, providing a platform for AXIN recruitment; recruitment of AXIN is also facilitated by interaction with LRP (Schwarz-Romond et al, 2007; Mao et al, 2001). DVL interacts with phosphatidylinositol-4-kinase type II (PI4KII) and phosphatidylinositol-4-phosphate 5-kinase type I (PIP5KI) to promote formation of phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) in the membrane, which is required for the clustering and phosphorylation of LRP6 and the recruitment of AXIN (Pan et al, 2008; Qin et al, 2009).

Literature references

Pan, W., Choi, SC., Wang, H., Qin, Y., Volpicelli-Daley, L., Swan, L. et al. (2008). Wnt3a-mediated formation of phosphatidylinositol 4,5-bisphosphate regulates LRP6 phosphorylation. *Science, 321*, 1350-3. ↗

Wong, HC., Bourdelas, A., Krauss, A., Lee, HJ., Shao, Y., Wu, D. et al. (2003). Direct binding of the PDZ domain of Dishevelled to a conserved internal sequence in the C-terminal region of Frizzled. *Mol Cell, 12*, 1251-60. ↗

Cong, F., Schweizer, L., Varmus, H. (2004). Wnt signals across the plasma membrane to activate the beta-catenin pathway by forming oligomers containing its receptors, Frizzled and LRP. *Development, 131*, 5103-15. ↗

Schwarz-Romond, T., Fiedler, M., Shibata, N., Butler, PJ., Kikuchi, A., Higuchi, Y. et al. (2007). The DIX domain of Dishevelled confers Wnt signaling by dynamic polymerization. *Nat. Struct. Mol. Biol., 14*, 484-92. ↗

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

Editions

2007-09-04	Edited	Matthews, L.
2013-08-24	Authored	Rothfels, K.
2013-10-03	Edited	Gillespie, ME.
2014-01-22	Reviewed	Rajakulendran, N.
2014-02-15	Reviewed	van Amerongen, R.
2014-04-22	Reviewed	Kikuchi, A.

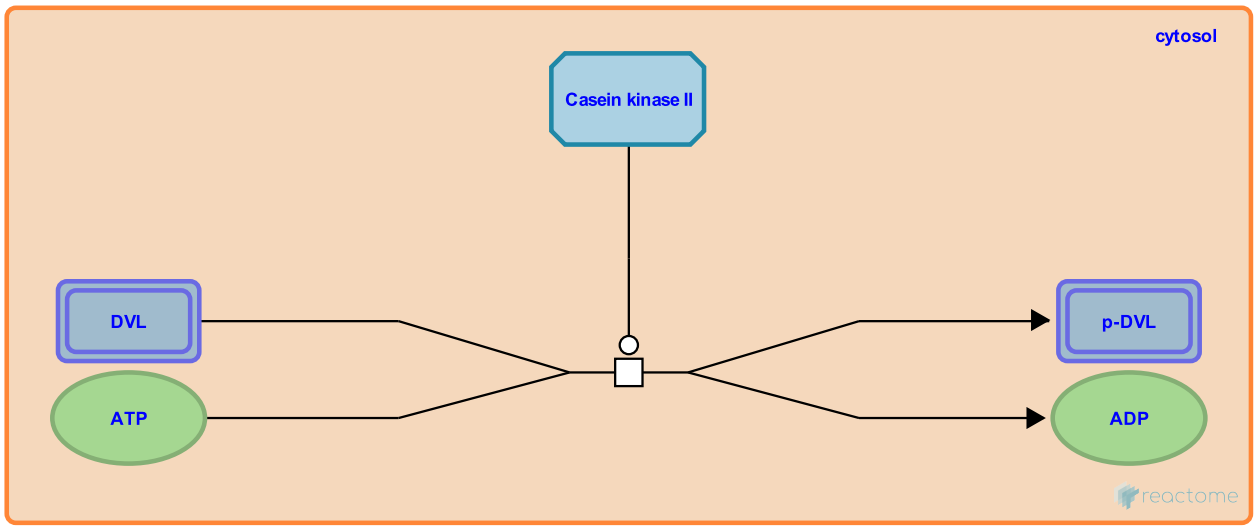
CSNK2-mediated phosphorylation of DVL ↗

Location: WNT mediated activation of DVL

Stable identifier: R-HSA-201717

Type: transition

Compartments: cytosol



DVL proteins from Drosophila, Xenopus, mouse and human cells have been shown to be phosphorylated, however the role of phosphorylation remains incompletely understood (Willert et al, 1997; Semenov and Synder, 1997; Yanagawa et al, 1995; Rothbächer et al, 2000). CSNK2 was identified as a DVL-associated kinase in Drosophila cells, and was shown to mediate the phosphorylation of serine and threonine residues in vitro (Willert et al, 1997). CSNK2-mediated phosphorylation of DVL may be constitutive, as DVL exists as a phosphoprotein even in the absence of WNT signaling (Bernatik et al, 2011). The association between DVL and CSNK2 may be enhanced upon WNT signaling, leading to increased levels of DVL phosphorylation (Willert et al, 2007).

Followed by: WNT signaling stimulates CSNK1-dependent phosphorylation of DVL

Literature references

Rothbächer, U., Laurent, MN., Deardorff, MA., Klein, PS., Cho, KW., Fraser, SE. (2000). Dishevelled phosphorylation, subcellular localization and multimerization regulate its role in early embryogenesis. *EMBO J., 19*, 1010-22. ↗

Bernatik, O., Ganji, RS., Dijksterhuis, JP., Konik, P., Cervenka, I., Polonio, T. et al. (2011). Sequential activation and inactivation of Dishevelled in the Wnt/beta-catenin pathway by casein kinases. *J. Biol. Chem., 286*, 10396-410. ↗

Willert, K., Brink, M., Wodarz, A., Varmus, H., Nusse, R. (1997). Casein kinase 2 associates with and phosphorylates dishevelled. *EMBO J., 16*, 3089-96. ↗

Yanagawa, S., van Leeuwen, F., Wodarz, A., Klingensmith, J., Nusse, R. (1995). The dishevelled protein is modified by wingless signaling in Drosophila. *Genes Dev., 9*, 1087-97. ↗

Semënov, MV., Snyder, M. (1997). Human dishevelled genes constitute a DHR-containing multigene family. *Genomics , 42*, 302-10. ↗

Editions

2007-09-04	Edited	Matthews, L.
2013-08-24	Authored	Rothfels, K.
2013-10-03	Edited	Gillespie, ME.
2014-01-22	Reviewed	Rajakulendran, N.
2014-02-15	Reviewed	van Amerongen, R.
2014-04-22	Reviewed	Kikuchi, A.

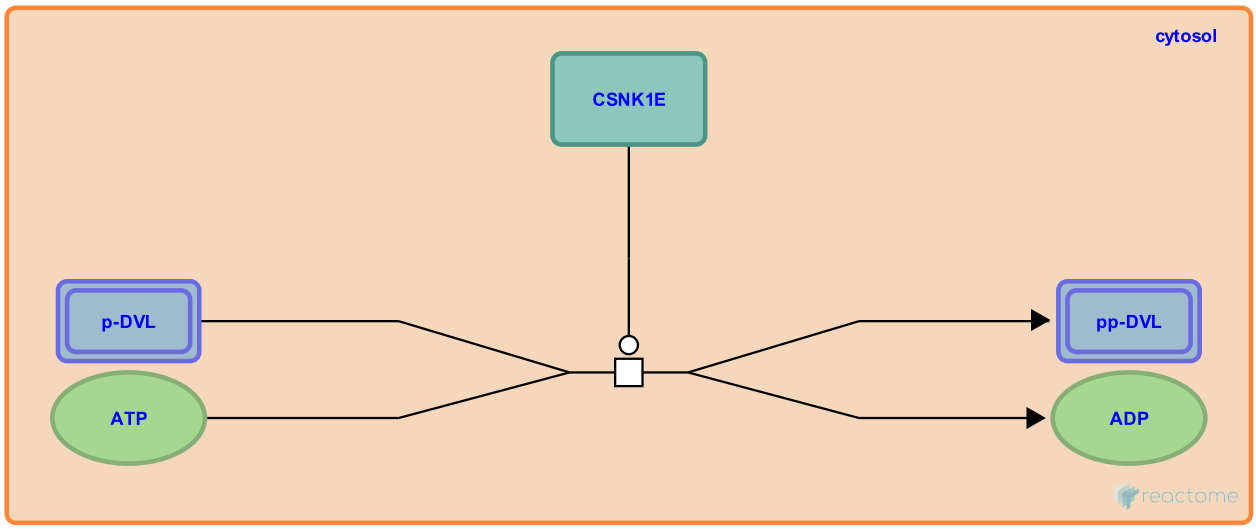
WNT signaling stimulates CSNK1-dependent phosphorylation of DVL ↗

Location: WNT mediated activation of DVL

Stable identifier: R-HSA-3772435

Type: transition

Compartments: cytosol



CSNK1E and DVL physically interact in vivo and CSNK1E phosphorylates DVL in response to WNT signaling (Peters et al, 1999; Sakanaka et al, 1999; Kishida et al, 2001; Gao et al, 2002; Hino et al, 2003; Klimowski et al, 2006; Bernatik et al, 2011). Phosphorylation by CSNK1E in the PDZ domain of DVL appears to be required for the recruitment of AXIN and the subsequent phosphorylation of LRP6 (Bernatik et al, 2011).

Preceded by: CSNK2-mediated phosphorylation of DVL

Followed by: Phosphorylated DVL recruits PIP5K1B to the plasma membrane

Literature references

Bernatik, O., Ganji, RS., Dijksterhuis, JP., Konik, P., Cervenka, I., Polonio, T. et al. (2011). Sequential activation and inactivation of Dishevelled in the Wnt/beta-catenin pathway by casein kinases. *J. Biol. Chem., 286*, 10396-410. ↗

Klimowski, LK., Garcia, BA., Shabanowitz, J., Hunt, DF., Virshup, DM. (2006). Site-specific casein kinase 1epsilon-dependent phosphorylation of Dishevelled modulates beta-catenin signaling. *FEBS J., 273*, 4594-602. ↗

Peters, JM., McKay, RM., McKay, JP., Graff, JM. (1999). Casein kinase I transduces Wnt signals. *Nature, 401*, 345-50. ↗

Gao, ZH., Seeling, JM., Hill, V., Yochum, A., Virshup, DM. (2002). Casein kinase I phosphorylates and destabilizes the beta-catenin degradation complex. *Proc Natl Acad Sci U S A, 99*, 1182-7. ↗

Hino, S., Michiue, T., Asashima, M., Kikuchi, A. (2003). Casein kinase I epsilon enhances the binding of Dvl-1 to Frat-1 and is essential for Wnt-3a-induced accumulation of beta-catenin. *J. Biol. Chem., 278*, 14066-73. ↗

Editions

2013-05-30	Authored	Rothfels, K.
2013-10-03	Edited	Gillespie, ME.
2014-01-22	Reviewed	Rajakulendran, N.
2014-02-15	Reviewed	van Amerongen, R.
2014-04-22	Reviewed	Kikuchi, A.

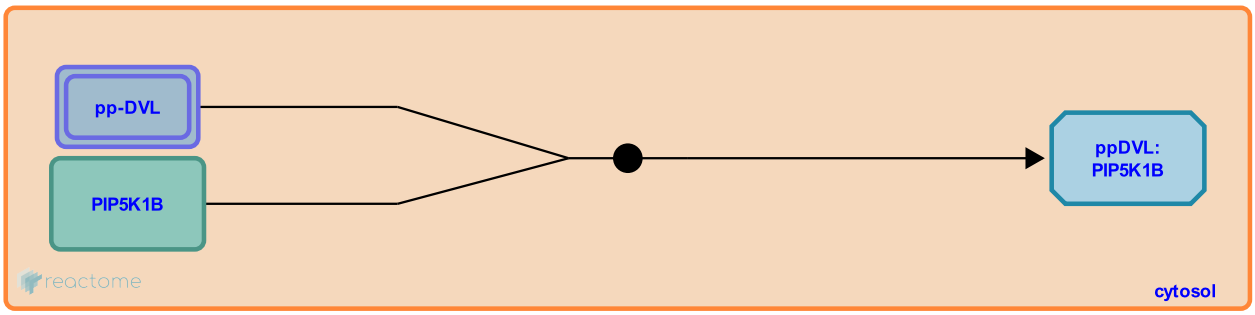
Phosphorylated DVL recruits PIP5K1B to the plasma membrane ↗

Location: WNT mediated activation of DVL

Stable identifier: R-HSA-3772434

Type: binding

Compartments: cytosol



DVL1 and 3 have been shown to co-immunoprecipitate with PIP5KB in HEK293 cells. This interaction is mediated by the N-terminal half of the kinase and the PDZ and DIX domain of DVL and recruits PIPK5B to the receptor complex. The interaction of DVL and PIP5KB is required for the WNT3A-dependent phosphorylation of LRP6 at serine 1490 and threonine 1479, as well as and the subsequent formation of the signalosome and recruitment of AXIN (Pan et al, 2008).

Preceded by: WNT signaling stimulates CSNK1-dependent phosphorylation of DVL

Followed by: DVL-associated PIP5K1B phosphorylates PI4P to PI(4,5)P2

Literature references

Pan, W., Choi, SC., Wang, H., Qin, Y., Volpicelli-Daley, L., Swan, L. et al. (2008). Wnt3a-mediated formation of phosphatidylinositol 4,5-bisphosphate regulates LRP6 phosphorylation. *Science, 321*, 1350-3. ↗

Editions

2013-05-30	Authored	Rothfels, K.
2013-10-03	Edited	Gillespie, ME.
2014-01-22	Reviewed	Rajakulendran, N.
2014-02-15	Reviewed	van Amerongen, R.
2014-04-22	Reviewed	Kikuchi, A.

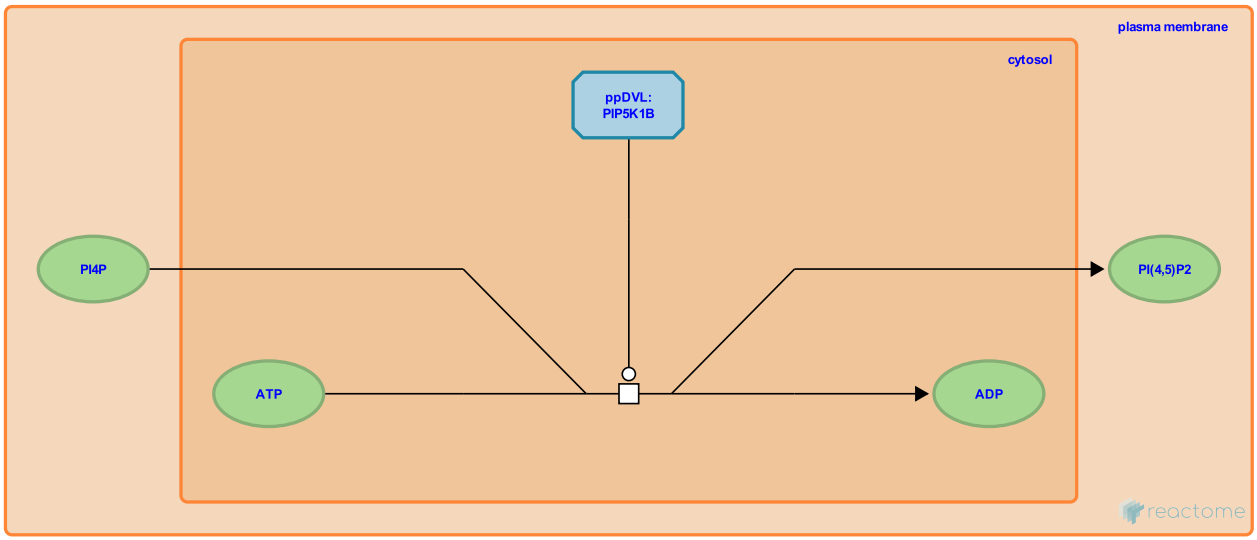
DVL-associated PIP5K1B phosphorylates PI4P to PI(4,5)P2 ↗

Location: WNT mediated activation of DVL

Stable identifier: R-HSA-3772436

Type: transition

Compartments: cytosol, plasma membrane



Stimulation of the WNT pathway controls the activity of PIP5KB in a FZD- and DVL-dependent manner (Pan et al, 2008; Bilic et al, 2007; Cong et al, 2004; Qin et al, 2009). Activation of PIP5KB results in the formation of PI(4,5)P2 at the plasma membrane, which is required through an unclear mechanism for the phosphorylation of LRP6 at serine 1490, LRP6 aggregation into 'signalosomes' and LRP6 phosphorylation at threonine 1479. These events are required for the recruitment of AXIN to the plasma membrane (Pan et al, 2008; Qin et al, 2009).

Preceded by: Phosphorylated DVL recruits PIP5K1B to the plasma membrane

Literature references

Pan, W., Choi, SC., Wang, H., Qin, Y., Volpicelli-Daley, L., Swan, L. et al. (2008). Wnt3a-mediated formation of phosphatidylinositol 4,5-bisphosphate regulates LRP6 phosphorylation. *Science, 321*, 1350-3. ↗

Bilic, J., Huang, YL., Davidson, G., Zimmermann, T., Cruciat, CM., Bienz, M. et al. (2007). Wnt induces LRP6 signalosomes and promotes dishevelled-dependent LRP6 phosphorylation. *Science, 316*, 1619-22. ↗

Cong, F., Schweizer, L., Varmus, H. (2004). Wnt signals across the plasma membrane to activate the beta-catenin pathway by forming oligomers containing its receptors, Frizzled and LRP. *Development, 131*, 5103-15. ↗

Qin, Y., Li, L., Pan, W., Wu, D. (2009). Regulation of phosphatidylinositol kinases and metabolism by Wnt3a and Dvl. *J. Biol. Chem., 284*, 22544-8. ↗

Editions

2013-05-30	Authored	Rothfels, K.
2013-10-03	Edited	Gillespie, ME.
2014-01-22	Reviewed	Rajakulendran, N.
2014-02-15	Reviewed	van Amerongen, R.
2014-04-22	Reviewed	Kikuchi, A.

Table of Contents