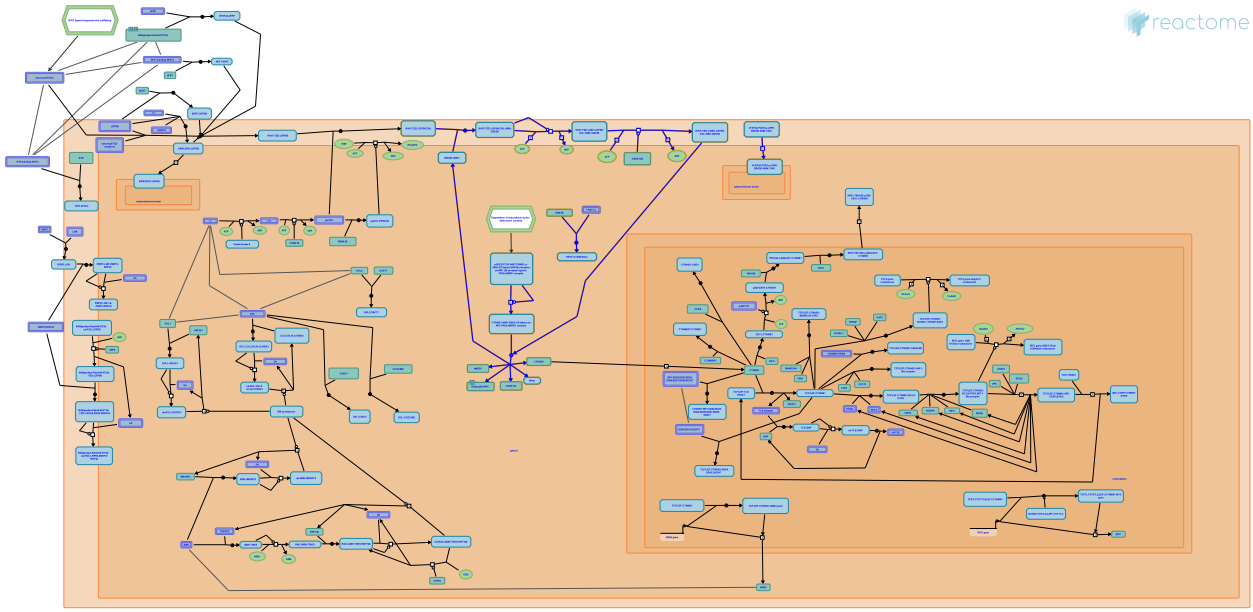
Disassembly of the destruction complex and recruitment of AXIN to the membrane



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

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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).

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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. ↗

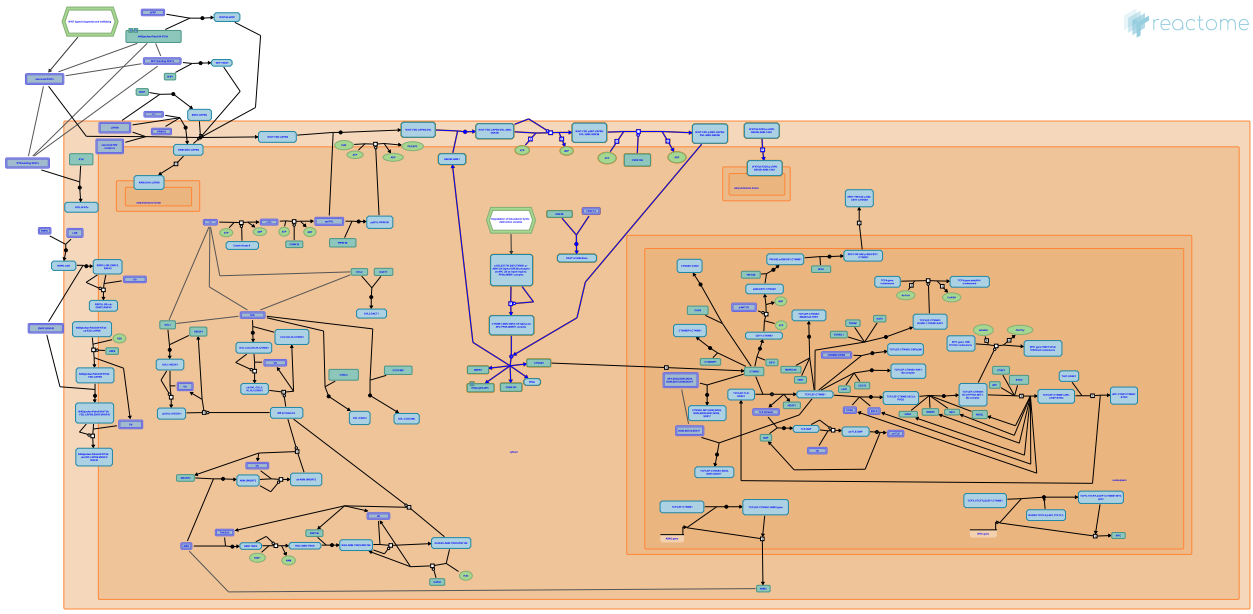
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Disassembly of the destruction complex and recruitment of AXIN to the membrane ↗

Stable identifier: R-HSA-4641262



Upon stimulation with WNT ligand, AXIN and GSK3beta are recruited to the plasma membrane through interaction with DVL (Tamai et al, 2004; Mao et al, 2001; reviewed in He et al, 2004). Polymerization of membrane-associated DVL and GSK3beta- and CSNK1-mediated phosphorylation of LRP5/6 establish a feed-forward mechanism for enhanced membrane recruitment of AXIN upon WNT signaling (Tamai et al, 2004; Cong et al, 2004; Zeng et al, 2005; Bilic et al, 2007). In Xenopus oocytes, but not necessarily all sytems, AXIN is present in limiting concentrations and is considered rate limiting for the assembly of the destruction complex (Lee et al, 2003; Benchabane et al, 2008; Tan et al, 2012; reviewed in MacDonald et al, 2009). The recruitment of AXIN away from the destruction complex upon WNT stimulation effectively destabilizes the destruction complex and contributes to the accumulation of free beta-catenin (Kikuchi, 1999; Lee et al, 2003). AXIN association with the destruction complex is also regulated by phosphorylation. In the active destruction complex, AXIN is phosphorylated by GSK3beta; dephosphorylation by protein phosphatase 1 (PP1) or protein phosphatase 2A (PP2A) destabilizes the interaction of AXIN with the other components of the destruction complex and promotes its disassembly (Luo et al, 2007; Willert et al, 1999; Jho et al, 1999). Free AXIN is also subject to degradation by the 26S proteasome in a manner that depends on the poly-ADP-ribosylating enzymes tankyrase 1 and 2 (Huang et al, 2009).

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MacDonald, BT., Tamai, K., He, X. (2009). Wnt/beta-catenin signaling: components, mechanisms, and diseases. *Dev Cell, 17*, 9-26. ↗

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Tamai, K., Zeng, X., Semenov, M., He, X. (2004). LDL receptor-related proteins 5 and 6 in Wnt/beta-catenin signaling: arrows point the way. *Development, 131*, 1663-77. ↗

Editions

2007-09-04	Edited	Matthews, L.
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2014-04-22	Reviewed	Kikuchi, A.

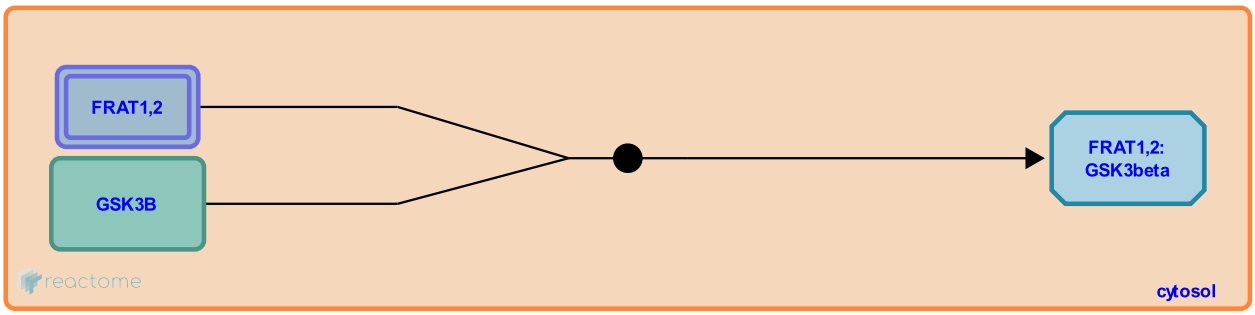
FRAT proteins bind GSK3beta ↗

Location: Disassembly of the destruction complex and recruitment of AXIN to the membrane

Stable identifier: R-HSA-5323526

Type: binding

Compartments: cytosol



The FRAT genes, which were initially identified as a target of Frequent Rearrangement in Advanced T-cell lymphoma, encode potent activators of canonical WNT signaling and are highly conserved in vertebrates. Xenopus and zebrafish each have one FRAT gene, while the human and mouse genomes contains two and three, respectively (Jonkers et al, 1997; reviewed in van Amerongen and Berns, 2005). Frat proteins activate WNT signaling by binding to GSK3beta and inhibiting its phosphorylation of beta-catenin (Yost et al, 1998; van Amerongen et al, 2004). The interaction with GSK3beta is mediated by a highly conserved IKEA box in the C-terminal domain of FRAT (Yost et al, 1998; van Amerongen et al, 2004; Thomas et al, 1999). This region of FRAT is able to compete with AXIN for binding to GSK3beta, suggesting a model where FRAT is able to destabilize the destruction complex by abrogating the GSK3beta-AXIN interaction (Farr et al, 2000; Thomas et al, 1999; Fraser at el, 2002; Ferkey et al, 2002). This model is supported by structural studies showing that AXIN and FRAT bind to the same region on the surface of GSK3beta (Bax et al, 2001; Dajani et al, 2003). Endogenous FRAT1 has also been shown to interact with DVL3, and this reaction persists in a FRAT1 mutant lacking the GSK3beta-interacting domain (Li et al, 1999). FRAT proteins may thus help bridge between GSK3beta's role in the destruction complex and its role in activating signaling in response to WNT.

Despite the apparent importance of FRAT proteins in beta-catenin-dependent signaling, a triple FRAT knockout mouse shows no readily evident defects in canonical signaling and, unlike the GBP knockout in Xenopus, no overt phenotypic defects (van Amerongen et al, 2005; Yost et al, 1989). The in vivo role and significance of the FRAT proteins in WNT signaling remains to be resolved; it is worth noting, however, that FRAT proteins have also recently been shown to be involved in non-canonical WNT signaling in a GSK3beta-independent manner. It is possible that it is through this non-canonical role that FRAT proteins contribute to oncogenesis (van Amerongen et al, 2010; Walf-Vorderwülbecke et al, 2012).

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Webster, MT., Smalley, MJ., Dale, TC., Harwood, A., Franca-Koh, J., Ryves, J. et al. (2002). Identification of the Axin and Frat binding region of glycogen synthase kinase-3. *J. Biol. Chem., 277*, 2176-85. ↗

Kimelman, D., Ferkey, DM. (2002). Glycogen synthase kinase-3 beta mutagenesis identifies a common binding domain for GBP and Axin. *J. Biol. Chem., 277*, 16147-52. ↗

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2014-02-10	Authored	Rothfels, K.
2014-02-15	Edited	Rothfels, K.
2014-02-15	Reviewed	van Amerongen, R.

PP2A dephosphorylates AXIN, APC and CTNNB1 in the destruction complex ↗

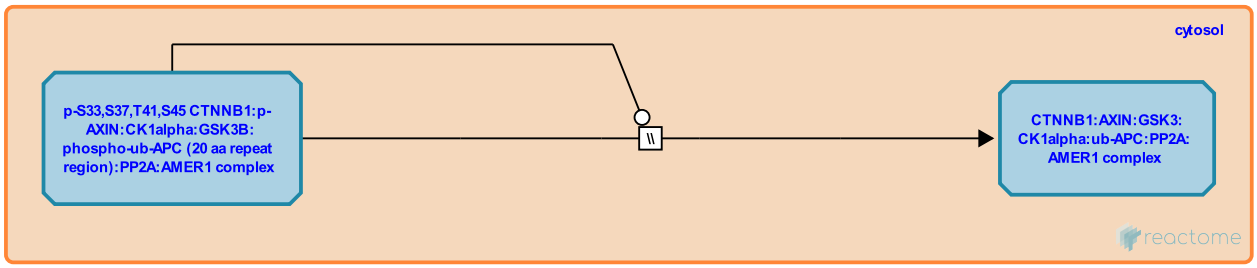
Location: Disassembly of the destruction complex and recruitment of AXIN to the membrane

Stable identifier: R-HSA-3601585

Type: omitted

Compartments: cytosol

Inferred from: Murine Axin1 is dephosphorylated by PP2A leading to reduced binding affinity with beta-catenin (Mus musculus)



AXIN is believed to be dephosphorylated upon WNT pathway stimulation, decreasing its affinity for beta-catenin (Willert et al, 1999; Jho et al 1999). AXIN has been shown to be a direct target of GSK3beta in vitro (Ikeda et al, 1998; Jho et al, 1999). In the absence of a WNT signal AXIN is phosphorylated at Thr519 and Ser524 by GSK3beta and at Ser531 by an unknown kinase. Mutation of these sites decreases the binding to beta-catenin and results in increased TCF-dependent signaling (Jho et al, 1999).

The destruction complex phosphatase PP2A has been implicated as both a positive and negative regulator of WNT and is a candidate for the WNT-dependent dephosphorylation of AXIN (Willert et al, 1999; reviewed in Kimelman and Xu, 2006; MacDonald et al, 2009). Stimulation of the WNT pathway leads to changes in AXIN mobility that are reproduced in vitro by dephosphorylation of immunoprecipitated AXIN by PP2A. Consistent with this, treatment of cells with the PP2A inhibitor okadaic acid blocks the dephosphorylation of AXIN upon treatment with WNT3A (Willert et al, 1999). Stimulation of the WNT pathway results in the recovery of less AXIN in a beta-catenin pulldown, and the AXIN that is isolated in this way is exclusively the phosphorylated form (Willert et al, 1999). In addition to dephosphorylating AXIN, PP2A has also been shown to dephosphorylate beta-catenin itself, as well as APC (Su et al, 2008; Ikeda et al, 2000).

Another candidate for the dephosphorylation of AXIN is PP1. PP1 interacts with AXIN and PP1-dependent dephosphorylation of AXIN decreases the AXIN-GSK3beta interaction and inhibits beta-catenin phosphorylation (Luo et al, 2007).

Followed by: Beta-catenin is released from the destruction complex

Literature references

Stella, A., Liu, B., Su, Y., Ishikawa, S., Kojima, M., Schreiber, EM. et al. (2008). APC is essential for targeting phosphorylated beta-catenin to the SCFbeta-TrCP ubiquitin ligase. *Mol. Cell, 32*, 652-61. ↗

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Editions

2013-05-27	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.

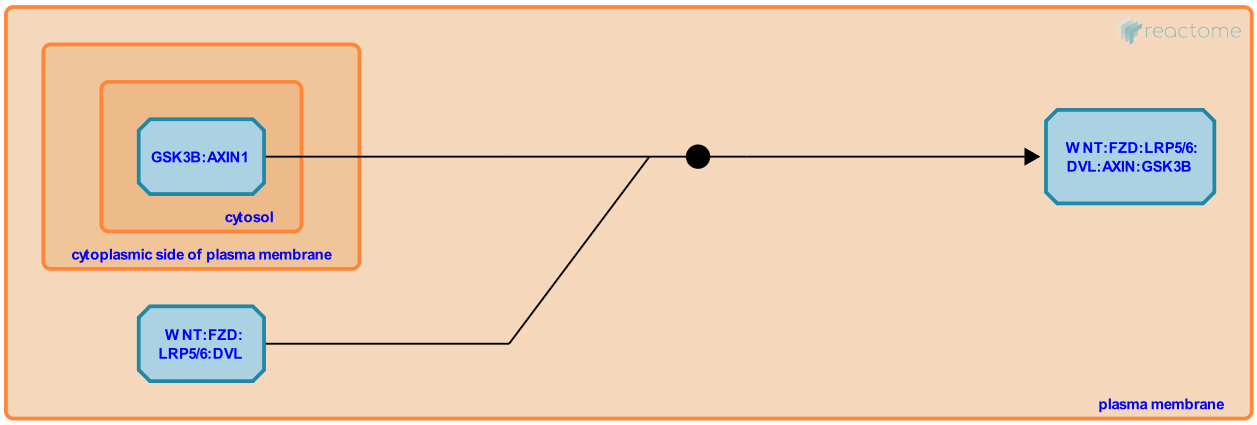
DVL recruits GSK3beta:AXIN1 to the receptor complex ↗

Location: Disassembly of the destruction complex and recruitment of AXIN to the membrane

Stable identifier: R-HSA-1504186

Type: binding

Compartments: plasma membrane, cytosol



The DIX domains of DVL and AXIN interact and this interaction brings GSK3beta:AXIN1 to the receptor complex (Schwarz-Romond et al, 2007). Subsequently, sequential phosphorylation of LRP5/6 by GSK3beta and CSNK1 generates high affinity AXIN binding sites and functions to amplify recruitment to the membrane (Mao et al, 2001; Zeng et al, 2008). In some models, this recruitment of AXIN to the membrane is facilitated by clustering of DVL and/or LRP5/6 into a 'signalosome' (Bilic et al, 2007).

Preceded by: Beta-catenin is released from the destruction complex

Followed by: Phosphorylation of LRP5/6 cytoplasmic domain by membrane-associated GSK3beta

Literature references

Li, L., Kimelman, D., Takada, S., Wu, D., Yuan, H., Farr GH, 3rd. et al. (2001). Low-density lipoprotein receptor-related protein-5 binds to Axin and regulates the canonical Wnt signaling pathway. *Mol Cell, 7*, 801-9. ↗

Almeida, K., Woodgett, J., Hsieh, JC., Harada, Y., Tamai, K., Huang, H. et al. (2008). Initiation of Wnt signaling: control of Wnt coreceptor Lrp6 phosphorylation/activation via frizzled, dishevelled and axin functions. *Development, 135*, 367-75. ↗

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

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

Editions

2013-05-30	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.

Phosphorylation of LRP5/6 cytoplasmic domain by membrane-associated GSK3beta

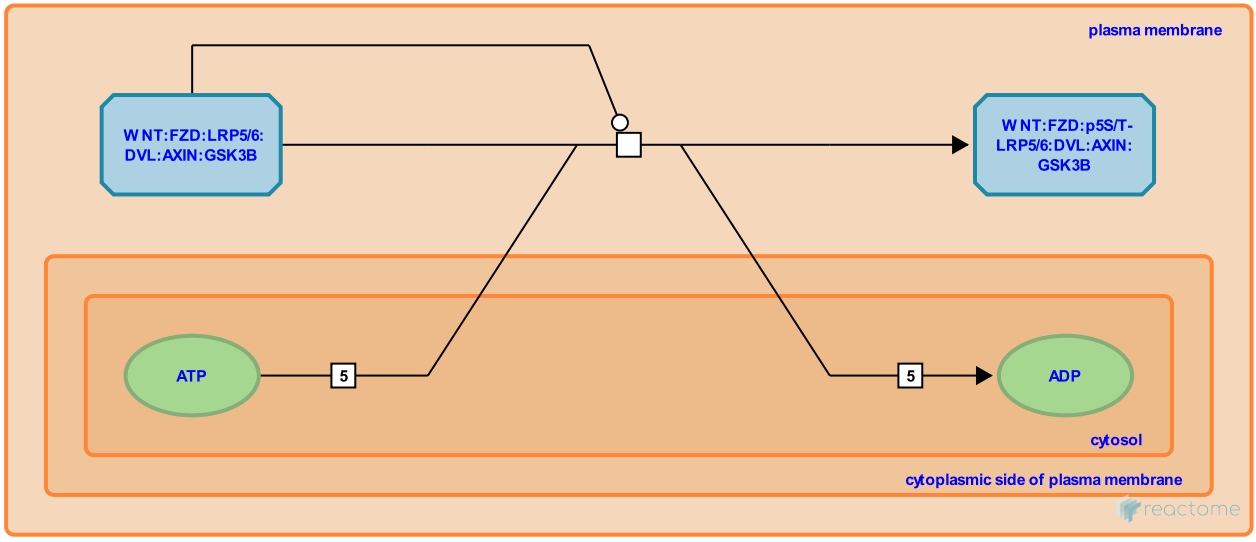
↗

Location: Disassembly of the destruction complex and recruitment of AXIN to the membrane

Stable identifier: R-HSA-201677

Type: transition

Compartments: plasma membrane, extracellular region, cytosol



LRP5/6 contains 5 PPP(S/T)PxS motifs in its intracellular domain which have been shown to be phosphorylated by a membrane-associated pool of GSK3beta. Individual phosphorylation of each of these motifs promotes interaction with AXIN and stimulates WNT signaling as assessed by activation of a TCF/beta-catenin responsive reporter (Tamai et al, 2004; Zeng et al, 2005; MacDonald et al, 2008). In the context of full length LRP6, phosphorylation of the five motifs shows cooperative stimulation of AXIN binding and WNT signaling. GSK3beta-mediated phosphorylation of LRP6 is thought to prime the receptor for subsequent phosphorylation by CSNK1 (Zeng et al, 2005; reviewed in He et al, 2004).

Preceded by: DVL recruits GSK3beta:AXIN1 to the receptor complex

Followed by: Phosphorylation of LRP5/6 cytoplasmic domain by CSNKI

Literature references

Tamai, K., Zeng, X., Semenov, M., He, X. (2004). LDL receptor-related proteins 5 and 6 in Wnt/beta-catenin signaling: arrows point the way. *Development, 131*, 1663-77. ↗

MacDonald, BT., Tamai, K., Yokota, C., Zeng, X., He, X. (2008). Wnt signal amplification via activity, cooperativity, and regulation of multiple intracellular PPPSP motifs in the Wnt co-receptor LRP6. *J Biol Chem, 283*, 16115-23. ↗

Tamai, K., Woodgett, J., Okamura, H., Doble, B., Li, S., Huang, H. et al. (2005). A dual-kinase mechanism for Wnt co-receptor phosphorylation and activation. *Nature, 438*, 873-7. ↗

Zhang, X., Tamai, K., Chang, Z., Harada, Y., Zeng, X., He, X. et al. (2004). A mechanism for Wnt coreceptor activation . *Mol Cell, 13*, 149-56. ↗

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2014-04-22	Reviewed	Kikuchi, A.

Phosphorylation of LRP5/6 cytoplasmic domain by CSNKI ↗

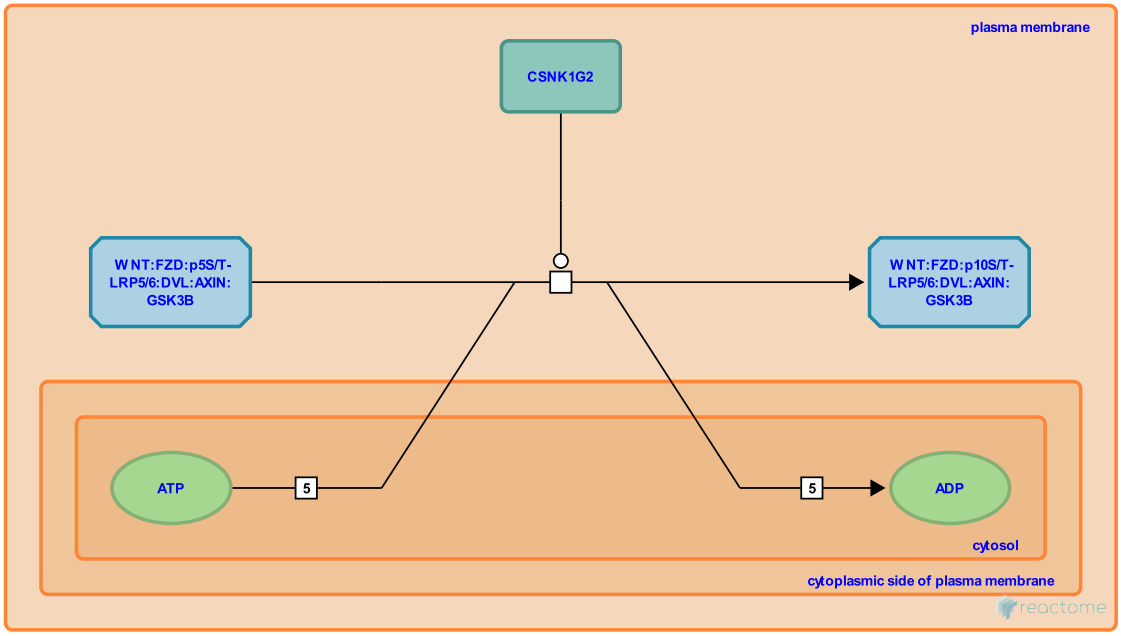
Location: Disassembly of the destruction complex and recruitment of AXIN to the membrane

Stable identifier: R-HSA-201691

Type: transition

Compartments: plasma membrane, extracellular region, cytosol

Inferred from: frog CK1gamma phosphorylates LRP5/6 (Homo sapiens)



After being phosphorylated by GSK3beta on the PPPSP motifs, LRP6 (and by extension LRP5) is phosphorylated at up to 5 sites by a member of the CSNK1 family (Davidson et al, 2005). One screen identified CSNK1gamma as a candidate kinase, while another study showed that CSNK1alpha, delta and epsilon contribute to this phosphorylation step (Davidson et al, 2005; Zeng et al, 2005). This sequential phosphorylation of LRP5/6 by GSK3beta and CSNK1 generates a high affinity binding site for AXIN, thereby amplifying the recruitment of AXIN to the membrane. This is thought to promote the disassembly of the destruction complex, and the activation of WNT signaling (Mao et al, 2001; Tamai et al, 2004; Bilic et al, 2007; reviewed in He et al, 2004).

Preceded by: Phosphorylation of LRP5/6 cytoplasmic domain by membrane-associated GSK3beta

Followed by: Beta-catenin is released from the destruction complex

Literature references

Li, L., Kimelman, D., Takada, S., Wu, D., Yuan, H., Farr GH, 3rd. et al. (2001). Low-density lipoprotein receptor-related protein-5 binds to Axin and regulates the canonical Wnt signaling pathway. *Mol Cell, 7*, 801-9. ↗

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

Tamai, K., Zeng, X., Semenov, M., He, X. (2004). LDL receptor-related proteins 5 and 6 in Wnt/beta-catenin signaling: arrows point the way. *Development, 131*, 1663-77. ↗

Tamai, K., Woodgett, J., Okamura, H., Doble, B., Li, S., Huang, H. et al. (2005). A dual-kinase mechanism for Wnt co-receptor phosphorylation and activation. *Nature, 438*, 873-7. ↗

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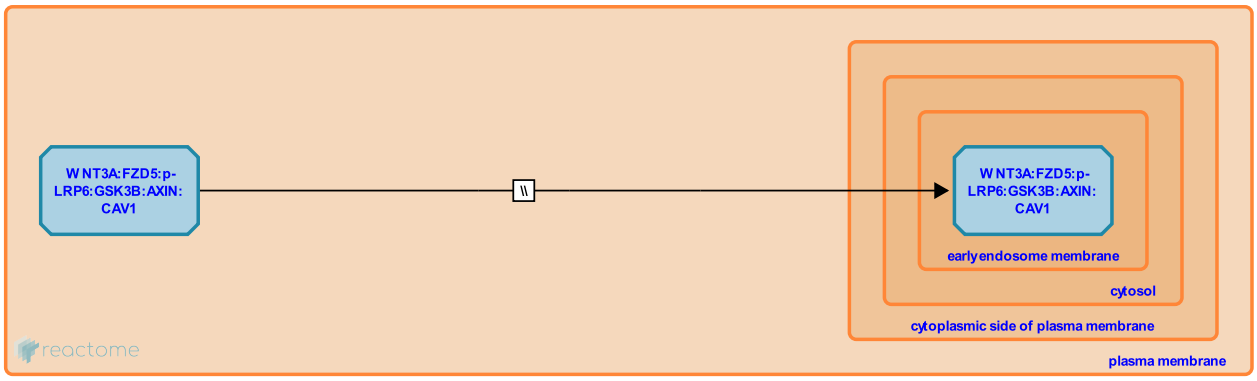
WNT3A stimulates the caveolin-dependent internalization of FZD5:p-LRP6 ↗

Location: Disassembly of the destruction complex and recruitment of AXIN to the membrane

Stable identifier: R-HSA-5368596

Type: omitted

Compartments: plasma membrane, early endosome membrane



After stimulation by WNT3A, FZD5 and phosphorylated LRP6 are internalized from lipid rafts in a caveolin- and RAB5-dependent manner (Yamamoto et al, 2006; Yamamoto et al, 2008). Recruitment of CAV1 to the activated receptor complex inhibits the binding of beta-catenin to AXIN in the destruction complex, resulting in the accumulation of cytosolic beta-catenin and the induction of WNT-dependent signaling (Yamamoto et al, 2006; Yamamoto et al, 2008).

Literature references

Kikuchi, A., Michiue, T., Yamamoto, H., Yamamoto, H., Sakane, H. (2008). Wnt3a and Dkk1 regulate distinct internalization pathways of LRP6 to tune the activation of beta-catenin signaling. *Dev. Cell, 15*, 37-48. ↗

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Editions

2014-04-22	Authored	Kikuchi, A.
2014-05-07	Edited	Matthews, L.

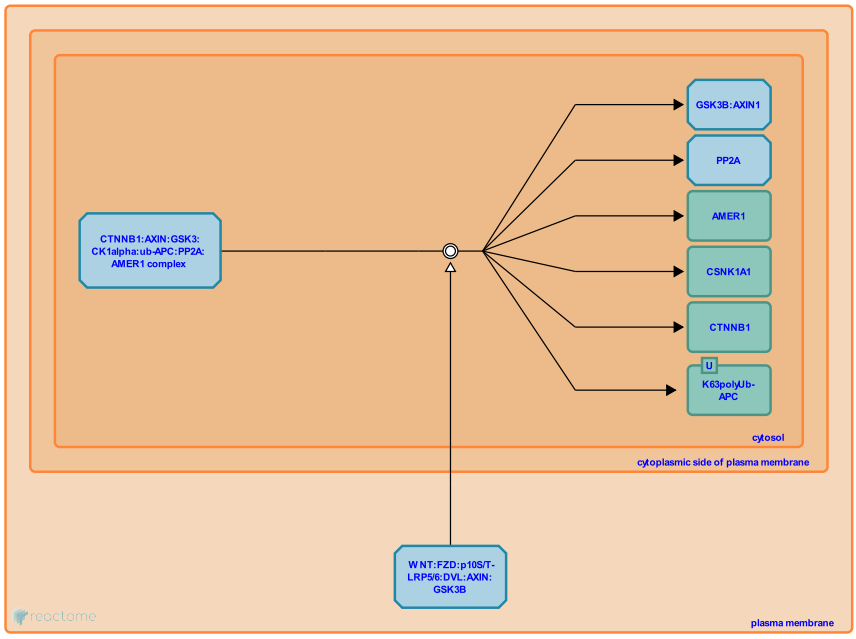
Beta-catenin is released from the destruction complex ↗

Location: Disassembly of the destruction complex and recruitment of AXIN to the membrane

Stable identifier: R-HSA-201685

Type: dissociation

Compartments: cytosol



Stimulation of the WNT pathway results in the recruitment of the GSK3beta:AXIN complex to the membrane (Willert et al, 1999; Schwarz Romond et al, 2007; Bilic et al, 2007; reviewed in Saito-Diaz et al, 2013). Activation of WNT signaling is believed to transiently inhibit GSK3beta kinase activity preventing its phosphorylation of beta-catenin (described in detail in the pathway "Degradation of beta-catenin by the destruction complex"; Piao et al, 2008; reviewed in Saito-Diaz et al, 2013). Inhibition of GSK3beta activity also prevents phosphorylation of AXIN allowing the constitutive dephosphorylation of AXIN at GSK3beta-dependent phosphorylation sites by PP2A predominate. This is believed to weaken the interaction between AXIN and beta-catenin (Willert et al, 1999). AXIN has also been shown to be dephosphorylated by PP1 at several serinve residues initially phosphorylated by CSNK1. The dephosphorylation by PP1 weakens the interaction between AXIN-GSK3beta and inhibits beta-catenin phosphorylation/degradation (Luo et al, 2007; reviewed in Huang et al, 2008). A recent study suggests that sustained inactivation of GSK3beta may result from its sequestration in multivesicular bodies (Taelman et al, 2010; reviewed in Niehrs and Acebon, 2010; Schuldt, 2011). Together, these changes destabilize the destruction complex and allow beta-catenin to accumulate.

Preceded by: Phosphorylation of LRP5/6 cytoplasmic domain by CSNKI, PP2A dephosphorylates AXIN, APC and CTNNB1 in the destruction complex

Followed by: DVL recruits GSK3beta:AXIN1 to the receptor complex

Literature references

Park, BJ., Lee, SH., Ha, NC., Oh, S., Lee, SJ., Lee, J. et al. (2008). Direct inhibition of GSK3beta by the phosphorylated cytoplasmic domain of LRP6 in Wnt/beta-catenin signaling. *PLoS ONE, 3*, e4046. ↗

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2007-09-04	Edited	Matthews, L.
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2014-01-22	Reviewed	Rajakulendran, N.
2014-02-15	Reviewed	van Amerongen, R.
2014-04-22	Reviewed	Kikuchi, A.

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