Negative regulation of TCF-dependent signaling by WNT ligand antagonists

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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.

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Literature references


Reactome database release: 78

This document contains 1 pathway and 5 reactions (see Table of Contents)
Several unrelated families of secreted proteins antagonize WNT signaling. Secreted frizzled-related proteins (sFRPs) have a cysteine rich domain (CRD) that is also found in FZD and ROR receptors, while WNT inhibitory factor (WIF) proteins contain a WIF domain also present in the WNT-receptor RYK. Both these classes of secreted WNT antagonists inhibit signaling by binding to WNTs and preventing their interaction with the FZD receptors. sFRPs may also able to bind the receptors, blocking ligand binding (Bafico et al, 1999; reviewed in Kawano and Kypta, 2003). The interaction of WIF and sFRPs with WNT ligand may also play a role in regulating WNT diffusion and gradient formation (reviewed in Boloventa et al, 2008).

Dickkopf (DKK) and Sclerostin (SOST) family members, in contrast, antagonize WNT signaling by binding to LRP5/6. There are four DKK family members in vertebrates; the closely related DKK1, 2 and 4 proteins have been shown to have roles in WNT signaling, while the more divergent DKK3 appears not to (Glinka et al, 1998; Fedi et al, 1999; Mao et al, 2001; Semenov et al, 2001; reviewed in Niehrs, 2006). Secreted DKK proteins bind to LRP6 in conjunction with the single-pass transmembrane proteins Kremen 1 and 2, and this interaction is thought to disrupt the WNT-induced FZD-LRP5/6 complex. In some cases, DKK2 has also been shown to function as a WNT agonist (reviewed in Niehrs, 2006).

Like DKK proteins, SOST binds LRP5/6 and disrupts WNT-dependent receptor activation (Semenov et al, 2005).

**Literature references**


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DKK and KRM bind LRP5/6

**Location:** Negative regulation of TCF-dependent signaling by WNT ligand antagonists

**Stable identifier:** R-HSA-3769401

**Type:** binding

**Compartments:** plasma membrane, extracellular region

DKK1, 2 and 4 are secreted antagonists of WNT signaling that act by binding to LRP5/6 and preventing the formation of an LRP:FZD receptor complex (Semenov et al, 2001; Mao et al, 2001; Bafico et al, 2001; reviewed in Niehrs, 2006). LRP6 has multiple independent WNT binding sites on its surface that are bound by different subsets of WNT proteins (Bourhis et al, 2010; Bourhis et al, 2011). Structural studies show that full length DKK1 binds to an LRP6 site that overlaps with both of these regions, suggesting that WNT and DKK proteins compete for receptor binding (Chen et al, 2011; Ahn et al, 2011; Cheng et al, 2011). Binding of DKK1 is postulated to stabilize LRP6 in an autoinhibited conformation that is relieved upon WNT-binding (Liu et al, 2003; Ahn et al, 2011). In some instances, DKK-mediated inhibition of WNT signaling may be enhanced by the concurrent binding of the single pass transmembrane proteins Kre- men1 and 2, although their presence is not absolutely required (Mao et al, 2002; Mao and Niehrs, 2003; Wang et al, 2008). In some cases, DKK2 may also function as a WNT agonist (Brott and Sokol, 2002; Wu et al, 2000; Mao and Niehrs, 2003; Li et al, 2007).

**Followed by:** DKK promotes clathrin-dependent internalization of LRP6

**Literature references**


### Editions

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DKK promotes clathrin-dependent internalization of LRP6

**Location:** Negative regulation of TCF-dependent signaling by WNT ligand antagonists

**Stable identifier:** R-HSA-5368586

**Type:** omitted

**Compartments:** plasma membrane, early endosome membrane

Binding of DKK1 to LRP6 induces the clathrin-mediated endocytosis of LRP6, preventing the WNT3-dependent phosphorylation of LRP and thereby attenuating WNT signaling (Sakane et al, 2010; Yamamoto et al, 2008). The DKK:LRP:KRM complex traffics to the early endosome in a RAB5-dependent manner. The LRP receptor can subsequently recycle back to the plasma membrane in a RAB11-dependent manner, while DKK may be degraded in the lysosome (Sakane et al, 2010)

**Preceded by:** DKK and KRM bind LRP5/6

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SOST binds LRP5/6

**Location:** Negative regulation of TCF-dependent signaling by WNT ligand antagonists

**Stable identifier:** R-HSA-3769397

**Type:** binding

**Compartments:** plasma membrane, extracellular region

SOST is a secreted antagonist of WNT signaling that acts by binding to LRP5/6 (Li et al, 2005; Semenov et al, 2005; Veverka et al, 2005). Binding of SOST requires the first two YWTD EGF repeats of LRP5/6 and appears to inhibit WNT signaling by preventing the formation of the LRP5/6:FZD receptor complex (Li et al, 2005; Semenov et al, 2005).

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WIF1 binds WNTs

**Location:** Negative regulation of TCF-dependent signaling by WNT ligand antagonists

**Stable identifier:** R-HSA-3769370

**Type:** binding

**Compartments:** extracellular region

**Inferred from:** Wif1 binds Wnts (Mus musculus)

WNT Inhibitory factor 1 (WIF1) is a secreted antagonist of WNT signaling that acts by binding to WNTs in the extracellular space and inhibiting their interaction with the FZD receptor complex (Hsieh et al, 1999; Surmann-Schmitt et al, 2009; Malinauskas et al, 2011; Banyai et al, 2012). WIF1 consists of a WIF domain (WD; also present in RYK receptors) and 5 EGF domains (Pathy 2000; Hsieh et al, 1999). Functional studies show that the WD contributes most of the WNT-binding activity while the EGF repeats make contact with components of the extracellular matrix such as HSPGs and glypicans (Hsieh et al, 1999; Malinauskas et al, 2011; Sanchez-Hernandez et al, 2012). WIF1 is downregulated in some cancers, and overexpression of human WIF1 has been shown to inhibit growth of lung and bladder cancer cells (Mazieres et al, 2004; Kansara et al, 2009; Lin et al, 2006; Tang et al, 2009)

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sFRP binds WNT3A and inhibits WNT:FZD binding

**Location:** Negative regulation of TCF-dependent signaling by WNT ligand antagonists

**Stable identifier:** R-HSA-3772441

**Type:** binding

**Compartments:** extracellular region

**Inferred from:** sFrp binds Wnt3a and inhibits WNT-FZD binding (Homo sapiens)

Mammalian genomes encode 5 secreted Frizzled related proteins (sFRPs) that are proposed to antagonize WNT signaling by binding directly to WNT ligands. Binding is mediated by a cysteine-rich-domain in the N-terminal that is homologous to the one found in FZD receptors and which is also found in the alternative WNT receptors ROR1 and ROR2 (reviewed in Kawano and Kupta, 2003; Boloventa et al, 2008). Direct binding of sFRP1, 2, 3 and 4 to Wnt3a has been demonstrated by surface plasmon resonance, but only sFRP1 and 2 were shown to inhibit Wnt3a-dependent signaling in mouse ES cells (Wawrzak et al, 2007). In addition to binding to WNT ligands, sFRPs are proposed to antagonize WNT signaling in a number of other ways. sFRPs have been shown to bind directly to FZD proteins by virtue of the CRDs: this interaction is postulated to block WNT signaling by inhibiting the WNT:FZD interaction (Bafico et al, 1999; Rodriguez et al, 2005).

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