Signaling by WNT in cancer

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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).

Literature references


Reactome database release: 69

This document contains 11 pathways (see Table of Contents)
The WNT signaling pathway has been linked with cancer ever since the identification of the first WNT as a gene activated by integration of mouse mammary tumor virus proviral DNA in virally-induced breast tumors (Nusse et al, 1984). The most well known example of aberrant WNT signaling in cancer is in colorectal cancer, where an activating mutation in a WNT pathway component is seen in 90% of sporadic cases. Inappropriate WNT pathway activation has also been implicated in most other solid human cancers but is not always associated with mutations in WNT pathway components (reviewed in Polakis, 2012).

Both tumor suppressors and oncogenes have been identified in the so-called canonical WNT pathway, which regulates WNT-dependent transcription by promoting the degradation of beta-catenin in the absence of ligand (reviewed in Polakis, 2012). Loss-of-function mutations in the destruction complex components APC, Axin and AMER1 and gain-of-function mutations in beta-catenin itself cause constitutive signaling and are found in cancers of the intestine, kidney, liver and stomach, among others (Polakis, 1995; Segiditsas and Tomlinson, 2006; Peifer and Polakis, 2000; Laurent-Puig et al, 2001; Liu et al, 2000; Satoh et al, 2000; Major et al, 2007; Ruteshouser et al, 2008). WNTs and WNT pathway components are also frequently over- or under-expressed in various cancers, and these changes are correlated with epigenetic regulation of promoter activity. In some contexts, both the canonical and non-canonical WNT signaling, which governs processes such as cell polarity and morphogenesis, may also contribute to tumor formation by promoting cell migration, invasiveness and metastasis.
Literature references


Editions

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https://reactome.org
truncated APC mutants destabilize the destruction complex

Location: Signaling by WNT in cancer

Stable identifier: R-HSA-4839744

Compartments: cytosol

Diseases: cancer

APC is a large and central component of the destruction complex, which limits signaling in the absence of WNT ligand by promoting the ubiquitin-mediated degradation of beta-catenin. APC interacts with numerous components of the destruction complex, including AXINs (AXIN1 and AXIN2), GSK3s (GSK3alpha and GSK3beta), CK1, PP2A and beta-catenin, and these interactions are critical for the phosphorylation and degradation of beta-catenin (reviewed in Saito-Diaz et al, 2013). APC is itself the target of phosphorylation and K63 ubiquitination in the absence of WNT signaling and these modifications are required for its interactions with other components of the destruction complex (Tran and Polakis, 2012; Ha et al, 2004; reviewed in Stamos and Weis, 2013).

More than 85% of sporadic and hereditary colorectal tumors carry loss-of-function mutations in APC. Most of the mutations are frameshifts and result in truncated proteins that lack the SAMP motifs and the 15 and 20 aa repeats that are implicated in binding AXIN and regulating beta-catenin binding and degradation (Miyoshi et al, 1992; Nagase and Nakamura, 1993; reviewed in Segditsas and Tomlinson, 2006). Cancers expressing truncated APC have high levels of cytoplasmic beta-catenin and deregulated expression of WNT target genes (Korinek et al, 1997). Approximately 15% of the colorectal tumors with wild-type APC harbor phosphodegron mutations of beta-catenin; interestingly, mutations in APC and beta-catenin are mutually exclusive events. Similar to APC-mutant tumors, beta-catenin is stabilized in these tumors and constitutive WNT target activation is detected (Morin et al, 1997; reviewed in Polakis, 2000).

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AXIN mutants destabilize the destruction complex, activating WNT signaling

Location: Signaling by WNT in cancer

Stable identifier: R-HSA-4839735

Compartments: cytosol

Diseases: cancer

AXIN1 and AXIN2 are critical scaffolding proteins of the beta-catenin destruction complex and make protein-protein interactions with several of the other complex components including APC, GSK3, CK1 and beta-catenin itself through specific domains (reviewed in Saito-Diaz et al, 2013). Because of its role in promoting the degradation of beta-catenin and thereby restricting WNT signaling, AXIN1 is regarded as a tumor suppressor; consistent with this, biallelic mutations in AXIN1 that abrogate its expression or result in the production of truncated proteins have been identified in some human cancers, notably in hepatocellular and colorectal carcinomas and medulloblastoma (Satoh et al, 2000; Taniguchi et al, 2002; Shimizu et al, 2002; Dahmen et al, 2001; reviewed in Salahshor and Woodgett, 2005).

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AMER1 mutants destabilize the destruction complex

**Location:** Signaling by WNT in cancer

**Stable identifier:** R-HSA-4839748

**Compartments:** cytosol

**Diseases:** cancer, kidney cancer, nephroblastoma

AMER1/WTX is a component of the destruction complex that interacts directly with beta-catenin through its C-terminal half. Depletion of AMER1 through siRNA stabilizes cellular beta-catenin levels and increases transcriptional activity in a reporter assay consistent with a role for AMER1 in the degradation of beta-catenin (Major et al, 2007). Deletions of the entire AMER1 gene have been reported in Wilms tumor, as have nonsense and missense mutations that truncate the protein before the beta-catenin interaction domain. These mutations are predicted to stabilize beta-catenin and increase WNT signaling (reviewed in Saito-Diaz et al, 2013; Huff, 2011).

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phosphorylation site mutants of CTNNB1 are not targeted to the proteasome by the destruction complex

**Location:** Signaling by WNT in cancer

**Stable identifier:** R-HSA-4839743

**Compartments:** cytosol

**Diseases:** cancer

Mutations in exon 3 of the beta-catenin gene have been identified in a number of human cancers (Morin et al, 1997; Rubinfeld et al, 1997; reviewed in Polakis, 2000; Polakis, 2007). These mutations generally affect serine and threonine residues (S33, S37, T41, S45) that are the sites of phosphorylation by CK1 and GSK3; phosphorylation of these residues is required for the ubiquitin-mediated degradation of beta-catenin. Hence mutation of these phospho-acceptor sites stabilizes beta-catenin, allowing it to accumulate, translocate to the nucleus and activate WNT signaling through association with LEF1/TCF DNA binding partners (Hart et al, 1999; Peifer and Polakis, 2000; Laurent-Puig et al, 2001; reviewed in Saito-Diaz et al, 2013).

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GSK3beta is subject to in-frame missplicing in CML stem cells resulting in the production of mutant protein that lacks the AXIN and FRAT binding domains. Cells containing this mutant GSK3beta show elevated levels of nuclear beta-catenin and enhanced TCF-dependent reporter activity (Jamieson et al, 2008; Abrahamsson et al, 2009).

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TCF7L2 mutants don't bind CTBP

Location: Signaling by WNT in cancer

Stable identifier: R-HSA-5339700

Compartments: nucleoplasm

Diseases: colorectal cancer

~50% of colorectal cancers with microsatellite instability show frameshift mutations in TCF7L2 that result in the loss of the CTBP-binding region (Duval et al, 1999; Cuilliere-Dartigues et al, 2006). These cancer cells show decreased colocalization of CTBP and TCF7L2 and have increased expression of a TCF-dependent reporter gene (Cuilliere-Dartigues et al, 2006).

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Misspliced LRP5 mutants have enhanced beta-catenin-dependent signaling

**Location:** Signaling by WNT in cancer

**Stable identifier:** R-HSA-5339717

**Compartments:** cytosol

**Diseases:** breast cancer, parathyroid carcinoma

LRP5 is subject to an in-frame missplicing event in breast and parathyroid cancers that renders the protein insensitive to inhibition by the WNT antagonist DKK1. Expression of the mutant protein results in elevated levels of active, unphosphorylated beta-catenin and enhanced TCF-dependent WNT-signaling, promoting cellular proliferation (Bjorklund et al 2007a, b; Bjorklund et al, 2009).

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RNF mutants show enhanced WNT signaling and proliferation

Location: Signaling by WNT in cancer

Stable identifier: R-HSA-5340588

Compartments: plasma membrane

Diseases: cancer

RNF43 and related protein ZNRF3 are E3 ubiquitin ligases that negatively regulate WNT signaling by downregulating FZD receptors at the cell surface (Mukai et al, 2010; Hao et al, 2012). Frameshift loss-of-function mutations in RNF43 that enhance WNT signaling have been identified in pancreatic and colorectal cancers; the proliferation of these cells is dependent on the presence of secreted WNT, as their growth is abrogated by treatment of cells with the Porcupine inhibitor LGK974 (Koo et al, 2012; Jiang et al, 2013).

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XAV939 inhibits tankyrase, stabilizing AXIN

**Location:** Signaling by WNT in cancer

**Stable identifier:** R-HSA-5545619

**Diseases:** cancer

XAV939 binds to the catalytic sites of tankyrase 1 and 2 and inhibits the ADP-ribosylation of AXIN1 and 2. Treatment of cells with XAV939 significantly increases the protein, but not the mRNA levels of AXIN1 and 2 and supports a strong increase in the level of GSK3beta-AXIN complexes. These cells also show increased phosphorylation of beta-catenin, decreased beta-catenin protein levels and a corresponding decrease in beta-catenin dependent transcription. Treatment of DLD-1 cells with XAV939 has also been shown to inhibit proliferation (Huang et al, 2009). XAV939 has not been tested in a clinical setting.

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WNT ligand secretion is abrogated by the PORCN inhibitor LGK974

Location: Signaling by WNT in cancer

Stable identifier: R-HSA-5340573

Compartments: endoplasmic reticulum membrane

Diseases: cancer

Aberrant WNT signaling is associated with the development of numerous cancers, and strategies for targeting this pathway are under intense investigation (reviewed in Polakis, 2012; Polakis, 2000; Yao et al, 2011). Secretion of WNT ligand depends on its PORCN-dependent palmitoleoylation in the ER, making PORCN an attractive therapeutic target in cases where WNT is aberrantly over-expressed (reviewed in MacDonald et al, 2009). LGK974 is a PORCN-inhibitor that was identified in a screen for compounds that abrogate the secretion of WNT ligands, and is in Phase I clinical trials for the treatment of WNT-dependent cancers (Liu et al, 2013)

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