Signaling by WNT

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

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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: 82

This document contains 5 pathways (see Table of Contents)
WNT signaling pathways control a wide range of developmental and adult process in metazoans including cell proliferation, cell fate decisions, cell polarity and stem cell maintenance (reviewed in Saito-Diaz et al, 2013; MacDonald et al, 2009). The pathway is named for the WNT ligands, a large family of secreted cysteine-rich glycoproteins. At least 19 WNT members have been identified in humans and mice with distinct expression patterns during development (reviewed in Willert and Nusse, 2012). These ligands can activate at least three different downstream signaling cascades depending on which receptors they engage.

In the so-called 'canonical' WNT signaling pathway, WNT ligands bind one of the 10 human Frizzled (FZD) receptors in conjunction with the LRP5/6 co-receptors to activate a transcriptional cascade that controls processes such as cell fate, proliferation and self-renewal of stem cells. Engagement of the FZD-LRP receptor by WNT ligand results in the stabilization and translocation of cytosolic beta-catenin to the nucleus where it is a co-activator for LEF (lymphoid enhancer-binding factor)- and TCF (T cell factor) -dependent transcription. In the absence of WNT ligand, cytosolic beta-catenin is phosphorylated by a degradation complex consisting of glycogen synthase kinase 3 (GSK3), casein kinase 1 (CK1), Axin and Adenomatous polyposis coli (APC), and subsequently ubiquitinated and degraded by the 26S proteasome (reviewed in Saito-Diaz et al, 2013; Kimmelman and Xu, 2006).

In addition to the beta-catenin-dependent transcriptional response, WNT signaling can also activate distinct non-transcriptional pathways that regulate cell migration and polarity. These beta-catenin-independent 'non-canonical' pathways signal through Frizzled receptors independently of LRP5/6, or occur through the tyrosine kinase receptors ROR and RYK (reviewed in Veeman et al, 2003; James et al, 2009). Non-canonical WNT pathways are best studied in Drosophila where the planar cell polarity (PCP) pathway controls the orientation of wing hairs and eye facets, but are also involved in processes such as convergent extension, neural tube closure, inner ear development and hair orientation in vertebrates and mammals(reviewed in Seifert and Mlodzik, 2007; Simons and Mlodzik, 2008). In the PCP pathway, binding of WNT ligand to the FZD receptor leads to activation of small Rho GTPases and JNK, which regulate the cytoskeleton and coordinate cell migration and polarity (reviewed in Lai et al, 2009; Schlessinger et
al, 2009). In some cases, a FZD-WNT interaction increases intracellular calcium concentration and activates CaMK II and PKC; this WNT calcium pathway promotes cell migration and inhibits the canonical beta-catenin dependent transcriptional pathway (reviewed in Kuhl et al, 2000; Kohn and Moon, 2005; Rao et al 2010). Binding of WNT to ROR or RYK receptors also regulates cell migration, apparently through activation of JNK or SRC kinases, respectively, however the details of these pathways remain to be worked out (reviewed in Minami et al, 2010).

Although the WNT signaling pathways were originally viewed as discrete, linear pathways controlled by defined subsets of 'canonical' or 'non-canonical' ligands and receptors, the emerging evidence is challenging this notion. Instead, the specificity and the downstream response appear to depend on the particular cellular context and vary with species, tissue and stage of development (reviewed in van Amerongen and Nusse, 2009; Rao et al, 2010).

**Literature references**


**Editions**

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19 WNT proteins have been identified in human cells. The WNTs are members of a conserved metazoan family of secreted morphogens that activate several signaling pathways in the responding cell: the canonical (beta-catenin) WNT signaling cascade and several non-canonical pathways, including the planar cell polarity (PCP), the regulation of intracellular calcium signaling and activation of JNK kinases. WNT proteins exist in a gradient outside the secreting cell and are able to act over both short and long ranges to promote proliferation, changes in cell migration and polarity and tissue homeostasis, among others (reviewed in Saito-Diaz et al, 2012; Willert and Nusse, 2012).

The WNTs are ~40kDa proteins with 23 conserved cysteine residues in the N-terminal that may form intramolecular disulphide bonds. They also contain an N-terminal signal sequence and a number of N-linked glycosylation sites (Janda et al, 2012). In addition to being glycosylated, WNTs are also lipid-modified in the endoplasmic reticulum by a WNT-specific O-acyl-transferase, Porcupine (PORCN), contributing to their characteristic hydrophobicity. PORCN-dependent palmitoylation is required for the secretion of WNT as well as its signaling activity, as either depletion of PORCN or mutation of the conserved serine acylation site results in the intracellular accumulation of WNT ligand (Takada et al, 2006; Barrott et al, 2011; Biechele et al, 2011; reviewed in Willert and Nusse, 2012).

Secretion of WNT requires a number of other dedicated factors including the sorting receptor Wntless (WLS) (also known as Evi, Sprinter, and GPR177), which binds WNT and escorts it to the cell surface (Banzerger et al, 2006; Bartscherer et al, 2006; Goodman et al, 2006). A WNT-specific retromer containing SNX3 is subsequently required for the recycling of WLS back to the Golgi (reviewed in Herr et al, 2012; Johannes and Wunder, 2011). Once at the cell surface, WNT makes extensive contacts with components of the extracellular matrix such as heparan sulphate proteoglycans (HSPGs) and may be bound by any of the WNT signaling receptors. For a detailed overview of WNT protein biogenesis and trafficking, see the Reactome pathway descriptions at https://reactome.org.
a number of regulatory proteins, including WIFs and SFRPs. The diffusion of the WNT ligand may be aided by its packing either into WNT multimers, exosomes or onto lipoprotein particles to shield the hydrophobic lipid adducts from the aqueous extracellular environment (Gross et al, 2012; Luga et al, 2012, Korkut et al, 2009; reviewed in Willert and Nusse, 2012).

**Literature references**


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Degradation of beta-catenin by the destruction complex

Location: Signaling by WNT

Stable identifier: R-HSA-195253

The beta-catenin destruction complex plays a key role in the canonical Wnt signaling pathway. In the absence of Wnt signaling, this complex controls the levels of cytoplasmic beta-catenin. Beta-catenin associates with and is phosphorylated by the destruction complex. Phosphorylated beta-catenin is recognized and ubiquitinated by the SCF-beta TrCP ubiquitin ligase complex and is subsequently degraded by the proteasome (reviewed in Kimelman and Xu, 2006).

Literature references


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19 WNT ligands and 10 FZD receptors have been identified in human cells; interactions amongst these ligands and receptors vary in a developmental and tissue-specific manner and lead to activation of so-called 'canonical' and 'non-canonical' WNT signaling. In the canonical WNT signaling pathway, binding of a WNT ligand to the Frizzled (FZD) and lipoprotein receptor-related protein (LRP) receptors results in the inactivation of the destruction complex, the stabilization and nuclear translocation of beta-catenin and subsequent activation of T-cell factor/lymphoid enhancing factor (TCF/LEF)-dependent transcription. Transcriptional activation in response to canonical WNT signaling controls processes such as cell fate, proliferation and self renewal of stem cells, as well as contributing to oncogenesis (reviewed in MacDonald et al, 2009; Saito-Diaz et al, 2013; Kim et al, 2013).

Literature references


Humans and mice have 19 identified WNT proteins that were originally classified as either 'canonical' or 'non-canonical' depending upon whether they were able to transform the mouse mammary epithelial cell line C57MG and to induce secondary axis formation in Xenopus (Wong et al, 1994; Du et al, 1995). So-called canonical WNTs, including Wnt1, 3, 3a and 7, initiate signaling pathways that destabilize the destruction complex and allow beta-catenin to accumulate and translocate to the nucleus where it promotes transcription (reviewed in Saito-Diaz et al, 2013). Non-canonical WNTs, including Wnt 2, 4, 5a, 5b, 6, 7b, and Wnt11 activate beta-catenin-independent responses that regulate many aspects of morphogenesis and development, often by impinging on the cytoskeleton (reviewed in van Amerongen, 2012). Two of the main beta-catenin-independent pathways are the Planar Cell Polarity (PCP) pathway, which controls the establishment of polarity in the plane of a field of cells, and the WNT/Ca2+ pathway, which promotes the release of intracellular calcium and regulates numerous downstream effectors (reviewed in Gao, 2012; De, 2011).

**Literature references**


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