Beta-catenin:TCF associates with BCL9 and PYGO

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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

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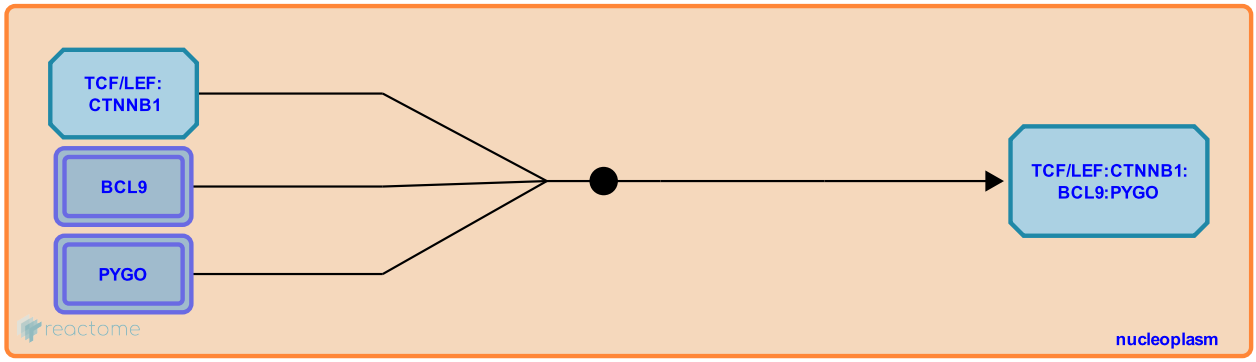
Stable identifier: R-HSA-201712

Type: binding

Compartments: nucleoplasm



Once tethered at WNT promoters, beta-catenin is a scaffold for the recruitment of a variety of transcriptional activators. The C-terminal end of beta-catenin interacts with a wide range of general transcriptional activators and chromatin remodelers, while the N-terminal region recruits more WNT-specific activators including BCL9 and Pygopus (reviewed in Jessen et al, 2008). BCL9 proteins (2 in vertebrates, BCL9 and BCL9L) interact with both beta-catenin and the putative activator Pygo (also 2 in vertebrates, Pygo1 and Pygo2) and in this way function as a bridging molecule to promote WNT-dependent transcription (reviewed in Valenta et al, 2012).
BCL9 was identified as the gene overexpressed in a B cell acute lymphoblastic leukemia cell line (Willis et al, 1998) and was subsequently found to be homologous to Legless (Lgs), a Drosophila gene identified in a number of screens for components of the WNT signalling pathway (Kramps et al, 2002; Belenkaya et al, 2002; Thompson et al, 2002). Lgs and BCL9 have no recognizable protein motifs and share sequence similarity only in three short stretches of 30 amino acids termed homology domains (HD) 1-3 (Kramps et al, 2002; reviewed in Valenta et al, 2012). HD1 mediates the interaction with the N-terminal ARM domain of beta-catenin while HD2 is required for the recruitment of Pygo through its C-terminal plant homology domain (PHD) (Kramps et al, 2002; Sampietro et al, 2006, Sierra et al, 2006). Replacement of the PHD domain of Pygo with the beta-catenin-interacting HD2 domain of Lgs rescues the phenotype of both lgs and pygo deletion in Drosophila suggesting that the primary role of Lgs is the recruitment of Pygo (Kramps et al, 2002). Transcriptional activation by Pygo depends on the conserved tripeptide NPF in the N-terminal homology domain (NHD) (Kramps et al, 2002; Hoffmans and Basler, 2004; Hoffmans et al, 2005; Städeli and Basler, 2005).
In Drosophila, Lgs is essential for Wg signalling, and deletion of either Lgs or Pygo phenocopies armadillo (the Drosophila beta-catenin homologue) null mutants (Kramps et al, 2002; Thompson et al, 2002). In mammals, the requirement and roles for BCL9 and Pygo are both less strict and less completely understood. Unlike in Drosophila, disruption of the BCL9/Pygo branch in mammals has less impact on transcriptional activation than abrogation of beta-catenin-dependent signalling through the C-terminal tail (Valenta et al, 2011). Ablation of pygopus genes in mice does not phenocopy with loss of Wnt signaling (Song et al, 2007; Schwab et al, 2007; Li et al, 2007), and disruption of the BCL9/BCL9L beta-catenin interaction results in embryonic lethality three days later than in the case of complete disruption of beta-catenin-dependent transcription (Valenta et al, 2011). Mammalian BCL9 also has Pygo-independent roles in WNT signaling and has been shown to interact directly with other transcriptional co-activators such as CBP/p300 or TRRAP/GCN5 through its C-terminus (Sustmann et al, 2008). Finally, the PHD of Pygo is able to bind methylated histones, which may contribute to context-specific roles of the protein (Gu et al, 2009; Fielder et al, 2008; Kessler et al, 2009; Gu et al, 2012).

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