Nature Reviews Molecular Cell Biology | AOP, published online 17 May 2006; doi:10.1038/nrm1950

SIGNAL TRANSDUCTION

Adding a piece to the puzzle

DOI:
10.1038/nrm1950

URLs

Wnt signalling is involved in fundamental cellular processes and regulates gene expression through β-catenin. Mosimann and colleagues now add a piece to the puzzle of Wnt-mediated transcriptional regulation by identifying a novel component of the Wnt pathway that directly associates with β-catenin to control Wnt target-gene expression.

In the cytoplasm, β-catenin is constitutively marked for proteasomal degradation. However, upon activation of the Wnt signalling pathway, β-catenin translocates to the nucleus, where it interacts with the TCF/LEF DNA-binding proteins and induces the transcription of Wnt target genes. Recent studies have revealed some of the nuclear partners of β-catenin and shed light on the mechanism of Wnt transcriptional regulation. For example, β-catenin interacts with the BCL9/Legless (LGS; the *Drosophilia melanogaster* homologue) coactivator, which links β-catenin to the PhD-finger protein Pygopus (PYGO), to form a complex with TCF/LEF.

In an attempt to identify further factors that mediate the transcriptional output of this complex, Mosimann *et al.* performed a genetic screen in *D. melanogaster* and identified a new gene, *Hyrax* (*Hyx*), which functions as a positive-regulatory component of the Wnt signalling pathway. Mutational and RNA interference (RNAi) analysis showed that the inactivation of *Hyx* expression reduces the activity of the Wnt pathway — the reduction of HYX *in vivo*, as well as the knockdown of HYX in cultured cells, abrogated Armadillo (the *D. melanogaster* β-catenin homologue)-mediated transduction of Wnt signals.

Interestingly, HYX and its human orthologue, parafibromin (a known tumour suppressor in parathyroid cancer), are homologous to *Saccharomyces cerevisiae* Cdc73. Cdc73 is a component of the polymerase-associated factor-1 (PAF1) complex, which is involved in the regulation of transcription initiation and elongation. This finding led the authors to postulate that HYX and parafibromin are nuclear factors of a metazoan PAF1 complex, which mediates Wnt target-gene activation.

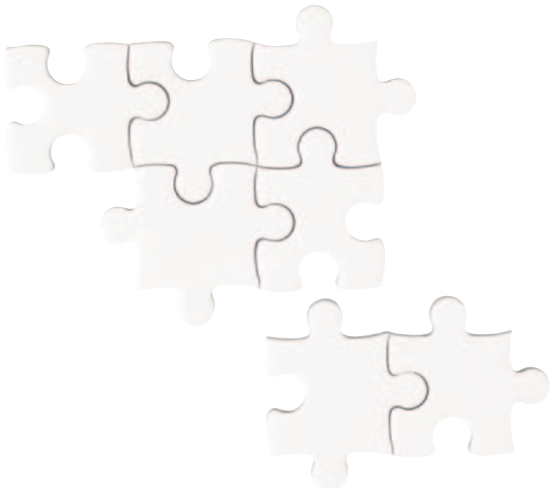
But, how does HYX promote Wnt target-gene expression? And could HYX provide the missing link between the β-catenin complex and trancription initiation and elongation by RNA polymerase II? Mosimann and colleagues showed that a stable complex exists between parafibromin and β-catenin. Fine-mapping of the regions in parafibromin and β-catenin that are involved in this direct interaction revealed that the C-terminal domain of β-catenin interacts with a β-catenin interaction domain in the N terminus of parafibromin. These results were also confirmed with the *D. melanogaster* homologues.

As both BCL9/LGS–PYGO and parafibromin are recruited to β-catenin, the authors reasoned that parafibromin functions in parallel with BCL9/LGS–PYGO. Biochemical analysis showed that the parafibromin–β-catenin complex also contains BCL9 and PYGO. Therefore, β-catenin functions as a scaffold protein that assembles a nuclear complex that consists of BCL9/LGS–PYGO and parafibromin.

These findings delineate a new regulatory component of the Wnt signal-transduction pathway. However, many pieces in the puzzle of Wnt signalling-mediated gene expression are still missing, including many transcriptional targets of this complex.

Ekat Kritikou

> “Mosimann and colleagues now add a piece to the puzzle of Wnt-mediated transcriptional regulation by identifying a novel component of the Wnt pathway…”



ORIGINAL RESEARCH PAPER Mosimann, C. *et al.* Parafibromin/Hyrax activates Wnt/Wg target gene transcription by direct association with β-catenin/Armadillo. *Cell* **125**, 327–341 (2006)