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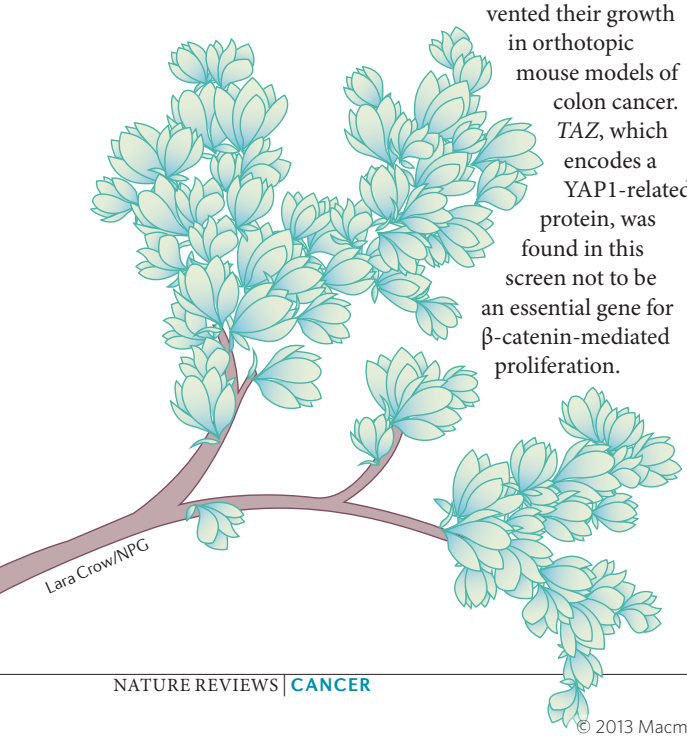
TUMORIGENESIS

# WNT branches out

WNT signalling can be mediated by β-catenin, a protein that regulates gene transcription through binding to the TCF family of transcription factors. Recent studies by William Hahn and colleagues have added to the evidence that WNT signalling through β-catenin also involves the transcriptional co-activator YES-associated protein 1 (YAP1).

The authors determined which of 85 cancer cell lines had high levels of β-catenin activity. They then compared β-catenin-active and β-catenin-inactive cell lines to identify genes that are essential for β-catenin-mediated cell proliferation and survival, one of which was *YAP1*. *YAP1*-targeted short hairpin RNAs (shRNAs) were used to show that YAP1 is required for proliferation and anchorage-independent growth in the cell lines with active β-catenin and that this does not require the β-catenin–TCF4 transcriptional complex. Loss of YAP1 activity in these cell lines also prevented their growth in orthotopic mouse models of colon cancer. *TAZ*, which encodes a YAP1-related protein, was found in this screen not to be an essential gene for β-catenin-mediated proliferation.

> “deregulated β-catenin activity can contribute to tumorigenesis by forming two different transcriptional complexes”



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As β-catenin and YAP1 have previously been shown to regulate cardiac development, the authors used immunoprecipitation to show that these two proteins are found in the same complex. Neither *TEAD* (the transcriptional binding partner of YAP1) nor *TCF4* were present in the list of essential genes required for proliferation in cells with active β-catenin. However, another transcription factor, *TBX5*, was present, and shRNAs that targeted *TBX5* reduced the growth of cancer cells with active β-catenin. Moreover, co-immunoprecipitation using TBX5 antibodies also pulled down a complex that contained both β-catenin and YAP1. How is this complex activated? The authors showed that YAP1 is phosphorylated by the tyrosine kinase YES1, but that the tyrosine kinase activity of YES1 is not required to promote the association between YAP1 and β-catenin. However, the kinase activity of YES1 is required for this transcriptional complex to be active and to bind the promoters of the pro-survival genes *BIRC5* and *BCL2L2*, which also appear in the list of genes that are essential for the proliferation of cells with active β-catenin. YES1 is a member of the SRC family of tyrosine kinases and as such can be inhibited by the tyrosine kinase inhibitor dasatinib. The *in vitro* and *in vivo* proliferation of colon cancer cell lines that have activated β-catenin signalling was reduced by dasatinib.

These results indicate that deregulated β-catenin activity can contribute to tumorigenesis by forming two different transcriptional complexes, one of which might be amenable to inhibition with tyrosine kinase inhibitors that target members of the SRC family.

Interestingly, in the same issue of *Cell*, Stefano Piccolo and colleagues show that TAZ functions downstream of WNT signalling. Gene expression profiles indicate that TAZ is responsible for a substantial proportion of the genes expressed in colorectal cancer cells with mutant adenomatous polyposis coli (*APC*). Piccolo and colleagues also show that the interaction between TAZ and β-catenin leads to the degradation of TAZ, and therefore that both β-catenin and TAZ are regulated by the same ubiquitin-mediated destruction complex that involves APC. These findings indicate that, in the absence of WNT signalling, β-catenin regulates TAZ by promoting its degradation.

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**ORIGINAL RESEARCH PAPER** Rosenbluh, J. *et al.* β-catenin-driven cancers require a YAP1 transcriptional complex for survival and tumorigenesis. *Cell* 21 Dec 2012 (doi:10.1016/j.cell.2012.11.026)

**FURTHER READING** Azzolin, L. *et al.* Role of TAZ as a mediator of Wnt signalling. *Cell* 21 Dec 2012 (doi:10.1016/j.cell.2012.11.027)