

TELOMERES

Stem cells, cancer and telomerase linked by WNT

The WNT signalling pathway has a crucial role in regulating pluripotency in stem cells, and its misregulation is common in cancers. Telomerase regulates telomere length, and it too has a role in stem cell biology and cancer. Here, the authors identify a direct link between the two: the WNT pathway component β -catenin can regulate the expression of the telomerase catalytic subunit TERT.

First, the authors showed that β -catenin-deficient mouse embryonic stem cells display decreased expression of *Tert* mRNA and TERT protein compared with wild-type cells. In β -catenin-deficient cells, reduced telomerase activity results in shorter telomeres. Conversely, stimulation of wild-type cells with WNT3A results

chromatin immunoprecipitation (ChIP) and luciferase reporter experiments, the authors then confirmed that *Tert* is a direct target of β -catenin and showed that β -catenin binds at *Tert* in concert with the transcription factor KLF4.

To confirm that the WNT pathway and telomerase also interact in adult stem cells, the authors analysed β -catenin binding by ChIP in the mouse intestinal crypt, which is rich in stem cells. They showed that it bound at the *Tert* transcription start site (TSS) in these cells and also in primary neurospheres.

An attractive hypothesis is that this interaction may be relevant to cancer cells. The authors thus developed a mouse model to analyse the β -catenin

by conditionally activating a β -catenin gain-of-function allele in the villus. Here they were able to observe hyperproliferative tissue in a region of the villus in the same region as they found β -catenin binding at *Tert*. The authors also showed that β -catenin binds to the TSS of human *Tert* in two human cancer cell lines, the embryonal carcinoma cell line NTERA2 and the human colorectal carcinoma cell line SW480. Furthermore, small interfering RNA knockdown of β -catenin in these cells reduced the expression levels of *Tert* mRNA.

The authors thus propose a model in which mutations in β -catenin in cancers result in increased telomerase activity — a potential line of investigation for therapy.

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Nature Reviews Genetics

This article is modified from the original in *Nature Reviews Genetics* (doi:10.1038/nrg3286).

ORIGINAL RESEARCH PAPER

Hoffmeyer, A. N. et al. Wnt/ β -catenin signaling regulates telomerase in stem cells and cancer



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