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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 in increased *Tert* expression. Using 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 binding events in adenomatous lesions 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 find 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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ORIGINAL RESEARCH PAPER Hoffmeyer, A. N. *et al.* Wnt/β-catenin signaling regulates telomerase in stem cells and cancer cells. *Science* **336**, 1549–1550 (2012)

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