**Targeted Therapy**

**Major finding:** Phase II studies show that vismodegib induces BCC regression and blocks new lesion growth.

**Mechanism:** Vismodegib is a small-molecule Smoothened inhibitor that blocks Hedgehog pathway activation.

**Impact:** Vismodegib has been approved by the FDA for treatment of locally advanced and metastatic BCC.

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**VISMODEGIB IS EFFECTIVE IN THE TREATMENT AND PREVENTION OF BCC**

The vast majority of basal-cell carcinomas (BCC), the most common human cancer, harbor genetic alterations that cause Hedgehog pathway upregulation. Most BCCs are treated surgically, but no effective therapy exists for metastatic or locally advanced BCC. Two phase II trials evaluated the safety and efficacy of vismodegib, an oral small-molecule inhibitor of Smoothened (a Hedgehog pathway activator). In the nonrandomized study by Sekulic and colleagues, 33 patients with metastatic BCC and 63 patients with inoperable locally advanced BCC took vismodegib daily. Strikingly, the majority of patients had visible tumor shrinkage with improved appearance. Decreases in tumor burden of 30% or more were observed in 30% of patients with metastatic BCC and 43% of patients with locally advanced BCC, 13 of whom had complete responses, and the median duration of response was 7.6 months. Tang and colleagues conducted a randomized, double-blind, placebo-controlled study of vismodegib in 41 patients with basal-cell nevus syndrome, a BCC predisposition syndrome in which the discovery of germline mutations in the Hedgehog pathway inhibitor PTCH1 provided the original evidence of overactive Hedgehog signaling in BCC. No tumors progressed on vismodegib, and compared with the placebo, vismodegib significantly reduced the size of existing BCCs (−65% vs. −11%) as well as the per-patient rate of new lesions (2 vs. 25 per year). Notably, 1 month of vismodegib treatment reduced expression of the Hedgehog target gene GLI1 by 90% in BCC biopsy specimens. In both trials, vismodegib frequently caused adverse effects such as hair loss, muscle cramps, taste disturbances, and weight loss that often led to drug discontinuation. However, these results established the efficacy of targeting the Hedgehog pathway in BCC and led to FDA approval of vismodegib for patients with locally advanced and metastatic BCC.


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**Stem Cells**

**Major finding:** β-catenin activates telomerase in stem cells and cancer cells.

**Mechanism:** Recruitment of β-catenin to the Tert promoter by KLF4 leads to increased Tert expression.

**Impact:** β-catenin mutations in human cancers may increase TERT expression and telomere stabilization.

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**β-CATENIN DIRECTLY REGULATES TERT**

Telomeres are regions of repetitive nucleotides that protect the ends of chromosomes from degradation and shorten with each round of DNA replication. Self-renewing cells, such as stem cells and cancer cells, express telomerase, a ribonucleoprotein that extends telomere length, to allow cell division to continue indefinitely. Hoffmeyer and colleagues observed that deletion of β-catenin in murine embryonic stem (ES) cells led to a significant reduction in the expression of the gene encoding the enzymatic subunit of telomerase, Tert. β-catenin-deficient ES cells also had significantly shorter telomeres than wild-type ES cells and ES cells with constitutive β-catenin activity. β-catenin immunoprecipitated at the Tert transcriptional start site, indicating that β-catenin mediates telomere length by directly regulating Tert expression. β-catenin recruitment was dependent on the transcription factor KLF4 and led to the localization of histone methyltransferases and the acquisition of activating histone modifications at the Tert promoter. β-catenin also selectively bound to the Tert promoter in the adult stem cells of the intestinal crypt but not in the differentiated epithelial cells of the villi, which was associated with higher Tert expression in the crypt cells compared with the villi. Tert expression could be induced in the villi by conditional activation of β-catenin, providing further in vivo evidence for transcriptional regulation of Tert by β-catenin. TERT was also regulated by β-catenin in human colorectal cancer cells, and high β-catenin levels were significantly correlated with high TERT expression in colorectal cancer expression datasets. These findings suggest that mutational activation of the WNT pathway, which occurs in most human colorectal cancers and in many other malignancies, directly leads to telomerase activation to promote cellular immortalization.

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