sequences might be the key. The authors moved a specific regulatory sequence from the *Hoxb1* locus into an equivalent position in the *Hoxa1* locus and then deleted *Hoxb1*. These mice developed normally despite having only two copies of a Hox1 gene. The authors had therefore reconstructed the ancestral state and found it functionally indistinguishable from having two separate Hox1 loci. This implies that the two loci have drifted to have complementary functions — subfunctionalization — rather than being selected for new and diverse functions — neofunctionalization. Similar studies with other paralogous genes will give insight into the relative importance of these two processes.

Patrick Goymer

ORIGINAL RESEARCH PAPER Tvrdik, P. & Capecchi, M. R. Reversal of *Hox1* gene subfunctionalization in the mouse. *Dev. Cell* **11**, 239–250 (2006)
FURTHER READING Garcia-Fernàndez, J. The genesis and evolution of homeobox gene clusters. *Nature Rev. Genet.* **6**, 881–892 (2005)

and the effect was also seen *in vivo* by exposing zebrafish embryos to the 7-DHC derivative vitamin D3. The fact that PTCH1 looks like a pump means that the pieces of the puzzle can be put into place. PTCH1 normally pumps out vitamin D3 (or its precursor) from the cell, which then inhibits SMO in cells nearby. When HH comes along and binds to PTCH1, the pump shuts down, and SMO is free to activate the intracellular HH pathway.

This neat story has ramifications beyond the understanding of animal development. By acting non-cell-autonomously, PTCH1 could exert a tumour-suppressor function on surrounding PTCH1-inactivated (that is, HH-pathway hyperactive) cells, and so manipulating the expression of wild-type PTCH1 could represent a fruitful avenue for cancer therapy.

Tanita Casci

ORIGINAL RESEARCH PAPER Bijlsma, M. F. *et al.* Repression of Smoothened by Patched-dependent (pro-)vitamin D3 secretion. *PLoS Biol.* **4**, e232 (2006)
WEB SITE
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CHROMOSOME BIOLOGY

POT-tering about the telomere

The ends of linear chromosomes are protected from DNA repair by a number of protein factors, six of which form a multiprotein complex dubbed Shelterin. Among Shelterin's constituents is POT1 (protection of telomeres 1) — a DNA-binding protein — which interacts with a single-stranded, G-rich overhang. Two groups have knocked out POT1 in mice to show that it is required for telomere integrity and genome stability, contributing to our understanding of the distinct roles of Shelterin components.

Hockemeyer *et al.* and Wu *et al.* found that, unlike most organisms, the mouse has two *Pot1* paralogues: *Pot1a* and *Pot1b*. Whereas Wu *et al.* focused on generating a *Pot1a* knockout mouse, Hockemeyer *et al.* created a knockout for each of the paralogues and discovered that each has a distinct function. This finding has implications for using the mouse as a model of human telomere biology because the human genome contains a single *Pot1* locus.

So what are the functions of POT1a and POT1b? *Pot1a* knockout results in embryonic lethality, but *Pot1b* knockout mice are viable and fertile. The role of POT1 in telomere protection from DNA repair was assessed by looking at the formation of cytologically visible foci of DNA response factors at the telomeres of knockout mice. In the absence of both proteins, telomere protection is lost in 70–80% of nuclei; this proportion falls to 30% when only *Pot1a* is deleted, whereas *Pot1b* does not have an effect on its own (which is surprising in view of the telomere structure in this strain; see below). The relationship between POT1a and POT1b in repressing the DNA damage signal is not simple, because overexpressing POT1a or POT1b in *Pot1a*$^{-/-}$ cells results in different protection levels.

Hockemeyer *et al.* found that, unlike the loss of *Pot1a*, loss of *Pot1b* resulted in excessively long G-strand overhangs. By crossing *Pot1b* knockout mice with those that lack functional telomerase, the authors showed that POT1b functions at the telomere independently of the telomerase. Wu *et al.* found that deleting *Pot1a* resulted in an increase in telomere length.

Both groups report interesting genome integrity phenotypes associated with *Pot1* deletion. Hockemeyer *et al.* showed that *Pot1a* alone can prevent telomeric fusions, for which *Pot1b* can only partially compensate. Loss of *Pot1a* also leads to endoreduplication. Wu *et al.* saw numerous chromosome breaks, fusions and fragments in cells lacking *Pot1a*. Their data also indicate that POT1a has an important role in repressing homologous recombination at telomeres.

Interestingly, the two groups reported different proliferation phenotypes for cells that lack *Pot1a*: whereas Hockemeyer *et al.* saw no apparent growth defects, *Pot1a* loss led to p53-dependent replicative senescence in the hands of Wu *et al.* In the absence of p53, *Pot1a*$^{-/-}$ cells bypass this growth defect. These differences remain to be reconciled. Nevertheless, by dissecting POT1 function, both studies demonstrate that different components of Shelterin have distinct functions in protecting chromosome ends. By showing that the functions of the mouse POT1 paralogues seem to have diverged, Hockemeyer *et al.* also raise the possibility that evolution might have tinkered with the solution to a fundamental problem in chromosome biology more than had been expected.

Magdalena Skipper

ORIGINAL RESEARCH PAPERS Wu, L. & Multani, A. S. *et al. Pot1* deficiency initiates DNA damage checkpoint activation and aberrant homologous recombination at telomeres. *Cell* **126**, 49–62 (2006) | Hockemeyer, D. *et al.* Recent expansion of the telomeric complex in rodents: two distinct POT1 proteins protect mouse telomeres. *Cell* **126**, 63–77 (2006)
FURTHER READING Baumann, P. Are mouse telomeres going to Pot? *Cell* **126**, 33–36 (2006) | Blasco, M. A. Telomeres and human disease: ageing, cancer and beyond. *Nature Rev. Genet.* **6**, 611–622 (2005)