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CELL BIOLOGY

The not-so-odd couple

Sarah E. Millar

Actively dividing cells do so at a risk — with each division, chromosome ends tend to shorten. Pairing proteins that promote cell division with a chromosome-end repair factor is a smart way to solve this problem.

Embryonic development and homeostasis of adult tissues are regulated by a relatively small number of signalling pathways with astoundingly diverse functions. These include controlling the rate of cell division, regulating the differentiation of cells into organs with complex structures, and activating adult stem cells. The functional complexity of signalling pathways is achieved in part by the interaction of proteins in specific cell types with core components of signalling pathways, which modulates pathway activity and confers cell-type-specific functions. A study by Park *et al.*[1] on page 66 of this issue identifies one such protein that functions in tissue-progenitor cells to increase the transcription of genes activated by the Wnt–β-catenin signalling pathway. Unexpectedly, this protein turns out to be an essential component of telomerase, a protein–RNA complex that has an apparently unrelated role in protecting the ends of chromosomes (telomeres) from shortening during DNA replication[2]. Park *et al.* propose an intriguing functional connection.

The Wnt–β-catenin signalling pathway stimulates proliferation of embryonic progenitor cells and adult stem cells in self-renewing tissues such as the intestine, the haematopoietic system and hair follicles[3]. Wnt proteins bind to membrane-bound Frizzled receptors and LRP co-receptors, and this binding prevents degradation of cytoplasmic β-catenin. β-catenin translocates to the nucleus, where it activates target genes by binding to LEF/TCF transcription factors[3].

The first inklings of a link between β-catenin and telomerase came from studies of adult stem cells in the hair follicle. Throughout adult life, hair follicles undergo cycles of growth and regression that are dependent on stem cells located in a region of the follicle known as the bulge. Expression of stable, active β-catenin protein in skin epithelial cells causes proliferation of bulge stem cells and initiation of a new phase of hair growth[4]. Previous work[5] had created mice in which extra copies of the gene encoding TERT, the protein component of telomerase, can be switched on in adult life in skin epithelial cells. Surprisingly, this study[5] revealed that extra TERT mimics the proliferative and hair-growth-promoting effects of β-catenin. Another group[6], working independently, found that continuous expression of TERT in skin epithelial cells enhances stem-cell proliferation in response to hair plucking or topical treatment with a tumour-promoting chemical. Subsequent experiments in hair follicles showed that extra TERT enhances the expression of genes targeted by β-catenin[7]. However, exactly how TERT affects gene activity was unclear. TERT provides the reverse transcriptase enzyme activity of telomerase — it synthesizes DNA at the ends of chromosomes, transcribing from an RNA template provided by the telomerase RNA component, TERC. Interestingly, the effects of TERT on hair-follicle growth are independent of its reverse transcriptase activity and of TERC, suggesting that, in this context, TERT has an atypical function[5,7].

Park *et al.*[1] provide a molecular basis for these unexpected observations. They purified TERT protein complexes from mammalian cells to identify any novel components, and were surprised to discover that these complexes contained BRG1. BRG1 is a subunit of a complex of proteins that alters the conformation of chromatin to facilitate transcription. β-catenin is known to bind directly to BRG1, resulting in enhanced expression of β-catenin target genes[8]. Thus, the existence of TERT–BRG1 complexes provided a possible molecular link between TERT and β-catenin. Subsequent experiments showed that TERT interacts directly with BRG1, and that complexes of TERT, β-catenin and a TCF protein bind to β-catenin target genes in cells from mouse small intestine.

The authors[1] found that, in several cell types, TERT is required for expression of Wnt-regulated genes. In mouse embryonic stem (ES) cells, deletion of TERT reduces expression of Wnt target genes. This inhibition is overcome by the addition of enzymatically inactive TERT, indicating that, similarly to its effects on hair growth, the effect of TERT on Wnt target genes in ES cells is independent of telomerase's reverse transcriptase activity. Strikingly, depletion of TERT in embryos of the frog *Xenopus laevis* produces developmental defects similar to those seen in mouse embryos that lack β-catenin[9]. Excess Wnt signalling in *X. laevis* embryos causes duplication of the embryo's anterior–posterior axis, resulting in the development of two-headed tadpoles[10]. Park and colleagues[1] discovered that TERT overexpression in *X. laevis* embryos synergizes with β-catenin to promote expression of Wnt reporter genes and axis duplication. Taken together, these findings provide convincing evidence for TERT as a key component of β-catenin transcriptional complexes in various contexts.

Telomerase activity is particularly important in stem cells and other progenitor cells to maintain their extensive proliferative capacity and to prevent cellular senescence — a form of cell-cycle arrest that can be triggered by shortened telomeres[11,12].

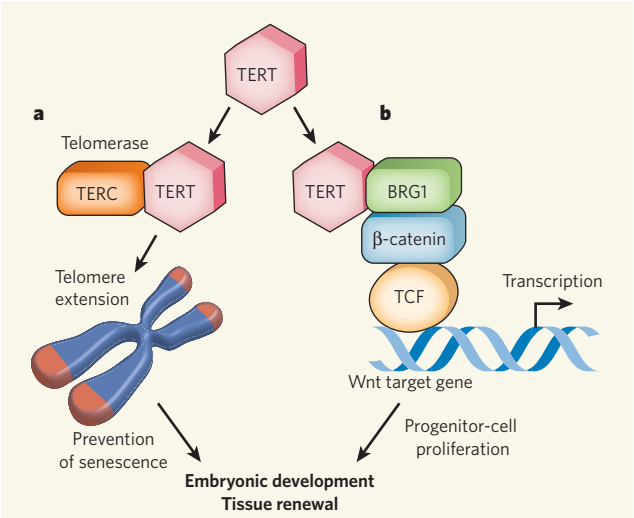

Figure 1 | The TERT–β-catenin connection. a, The telomerase complex functions in progenitor cells to repair chromosome ends, known as telomeres, during cell division. TERT provides reverse transcriptase activity to the complex, and uses TERC, the RNA component of telomerase, as a template. **b**, Park *et al.*[1] find that TERT also increases the transcriptional activity of β-catenin/TCF complexes through interaction with BRG1, a factor that binds the Wnt signalling molecule β-catenin and alters the conformation of chromatin. These two separate functions of TERT may simultaneously prevent cellular senescence and increase proliferation of progenitor cells, permitting embryonic development and renewal of adult tissues.

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Thus the link between β-catenin and TERT may not be so surprising after all. Park *et al.*[1] argue that the functional interaction between β-catenin and TERT may have evolved to coordinate mechanisms regulating progenitor-cell proliferation and chromosome integrity (Fig. 1), permitting embryonic development and renewal of adult tissues.

Given the identification of this exciting new partnership, and the significant effects of TERT deletion on Wnt-target-gene expression in mouse ES cells, it is perhaps surprising that first-generation knockout mice lacking TERT look normal[12]. In these mice, and in mice lacking TERC, obvious defects in self-renewing tissues become apparent only after continued breeding, and are associated with progressive telomere shortening, reflecting the absence of a mechanism to protect chromosome ends[11,12].

Park and colleagues wondered whether subtle developmental defects resulting from decreased Wnt signalling in TERT-knockout mice might have been overlooked in previous studies. As *X. laevis* embryos that were depleted of TERT showed abnormal development of embryonic structures that give rise to vertebrae, a process known to require the Wnt protein Wnt3a[13], the authors examined vertebral development in TERT-deficient mice. A significant proportion of these mice showed abnormalities of the vertebrae similar to those seen in mice with reduced Wnt3a expression. Thus mammals also seem to require TERT for normal Wnt signalling during embryonic development. Notwithstanding these findings, the limited developmental defects found in TERT-deficient mice remain puzzling.

It is possible that the modulating effects of TERT on activity of the Wnt pathway are relatively small in mice *in vivo*, and only become significant during cellular stress (for instance, when ES cells are removed from their embryonic environment and grown on a plastic dish). Alternatively, TERT may function semi-redundantly with factors that are yet to be discovered, or TERT-deleted embryos may compensate for lack of TERT by activating other pathways. The latter hypothesis could be tested by generating embryos that have a mix of labelled TERT-deficient cells and normal cells. If true, TERT-deficient cells should be out-competed by the normal cells during development. Similarly, the extent to which the Wnt-promoting functions of TERT are required in adult stem cells *in vivo* remains unclear. This central issue could be addressed by deleting TERT in specific adult tissues. The molecular tools for such an experiment are readily available for tissues such as the hair follicle, which can be counted on once again to release more of its treasure trove of secrets[14]. ■

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APPLIED PHYSICS

A leak of information

Pavlo Zubko and Jean-Marc Triscone

As capacitors, the ubiquitous components of electronic circuitry, get smaller, keeping them insulating is a challenge. But that's not necessarily bad news — some conductivity might be just the thing for data storage.

A general problem in the electronics industry is that the insulating materials used in the continually shrinking capacitors and transistors start to leak charge when they become too thin. This leads to large power consumption and, in the case of memory, to difficulties in storing and retrieving information. But on page 81 of this issue, Garcia *et al.*[1] show that this generally undesirable leakage current can in fact be very useful. They find that the leakage current flowing through ultrathin (1–3 nanometres) ferroelectric films of barium titanate ($BaTiO_3$) is strongly dependent on their electric polarization states — that is, on whether the net electric dipole of the material is in one or the other of the two possible orientations. The authors' result, which allows direct reading of the polarization state through a simple measurement of the material's electrical resistance, may be just what is needed to put ferroelectric random access memories (FeRAMs) — those based on storing information in the polarization states of ferroelectric materials — back on track in the race for faster and better memory.

The ability of ferroelectrics to retain a permanent dipole in the absence of an electric field, and the possibility of reversing its direction with a modest voltage, has been a driving force behind decades of intense research in ferroelectric memory, where the 'up' and 'down' polarization states are used to code the 'ones' and 'zeros' of binary information[2]. Offering the non-volatility — the ability to retain information even when power is switched off — of hard disks, combined with speeds at which data are read and written comparable to those of 'dynamic random access memories' (DRAMs), FeRAMs were touted as the potential replacement for the flash memories found in today's mobile phones and digital cameras.

But despite huge technological advances and the successful commercialization of FeRAMs by several leading electronics manufacturers, the dream of the ultimate memory is at present still beyond reach, and FeRAMs remain competitive only in a number of niche applications. Industrial forecasts for the role of FeRAMs in the memory market have become more mixed. Whereas Samsung has recently presented its new vision of a FeRAM as part of a fusion memory[3], rather than as a stand-alone solution, and subsequently shelved its FeRAM programme altogether, other manufacturers remain optimistic. For example, Toshiba has just announced a new 128-megabit prototype with writing speeds of 1.6 gigabytes per second (ref. 4).

The obstacles encountered by FeRAMs in the memory race are as much financial as technical. One of the main disadvantages of current FeRAMs is that they are charge-sensing devices. The information is stored in the dipole orientation of the ferroelectric, the insulating layer that is sandwiched between two metallic electrodes to make a tiny capacitor. To determine this orientation, a voltage is applied that, depending on the dipole's original direction, either reverses it or leaves it unchanged. A reversal of the polarization is accompanied by a current pulse that can be detected and so allows the dipole's orientation to be determined. The magnitude of this current pulse depends on the charge stored on the capacitor plates, and therefore on the area of the capacitor. With lateral dimensions approaching 100 nm, the charge available for sensing during the read operation is reduced. A concomitant increase in parasitic conduction (leakage) currents associated with downscaling of the capacitors further complicates the memory readout. What's more, the read process is destructive, in that each bit must be rewritten after being read. Achieving non-destructive readout is a major quest, and NASA's Jet Propulsion Laboratory in the 1990s[5], and more recently Tonouchi's group[6], have investigated various optical routes.

In their experiment, Garcia *et al.*[1] explore another promising non-destructive readout technique. They use the conducting tip of

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