lar lattice of defects is melted and entangled by thermal fluctuations. A rapid quench to low temperatures and a regime of high line-crossing barriers might then produce an entangled, polymer-like glassy state. Another is to inject splayed columnar defects of some sort into the sample, which can produce entangled ground states even at fairly high temperatures[4]. Finally, one could cool the lines in the presence of a current parallel to the average vortex direction, braiding the lines as in the new experiment[1].

A microscopic vortex configuration which might result from a constant current is shown in Fig. 1. Here, a regular hexagonal array of screw dislocation lines[5,6] has been superimposed on a conventional flux lattice to produce a configuration that is simultaneously crystalline in cross-section and entangled, while carrying a net current parallel to the lines. The structure is a compromise between the crystalline close packing favoured by inter-vortex interactions and the braiding induced by the current. Although this braided 'moiré state' was originally proposed[7] for chiral polymer crystals like DNA, it could also arise in type-II superconductors with currents parallel to the field direction.

The transition from the Bronze Age to the Iron Age was produced by trial and error, a process that took millennia. The metallurgical principles involved were only completely understood in the second half of this century. Superconductivity has been with us for only 86 years. It would be refreshing if ideas sketched above from basic research and fundamental science allow us to compress the time required to improve the electrical properties of superconductors. □

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Telomeres

# Different means to common ends

**David Shore**

Telomeres — the structures that are found at the ends of eukaryotic chromosomes — have evolved to solve two problems: they ensure the complete replication of chromosome ends (which cannot be accomplished by known DNA polymerases), and they protect those ends from degradation or fusion[1]. In most organisms, telomeres are composed of variable numbers of simple repeat sequences (TTAGGG in vertebrates) that are produced by a special ribonucleoprotein called telomerase[2].

Cells must somehow monitor telomere length and use this information to regulate telomerase, which could otherwise add repeats to the end of the chromosome in an uncontrolled manner. How might such a process work? One hint has come from studies on the budding yeast *Saccharomyces cerevisiae*, which show that a telomere-repeat binding protein, Rap1p, negatively regulates telomere elongation[3]. Now, two reports on pages 740 and 744 of this issue, by van Steensel and de Lange[4] and by Cooper *et al.*[5], show that a newly discovered repeat-binding protein from a distantly related yeast, *Schizosaccharomyces pombe*, and the analogous human factor, also block the elongation of telomeres. The new work indicates that the mechanisms of telomere length regulation are highly conserved, and it provides a fresh perspective on the relationships between telomere length and both ageing and cancer.

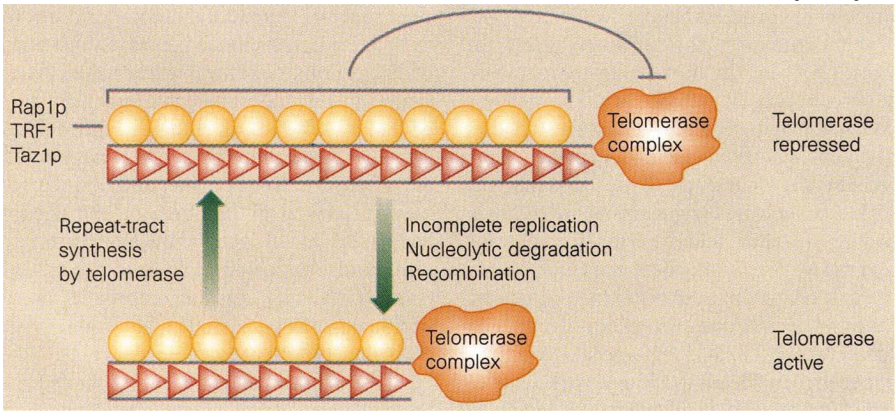


Figure 1 **The stabilization of telomere repeat tracts by the enzyme telomerase has been implicated in cancer, and the shortening of these tracts may be associated with ageing — but how is telomere length regulated? van Steensel and de Lange[4] have identified a human protein (TRF1) that binds to telomeres, and Cooper *et al.*[5] have isolated its analogue (Taz1p) in the yeast *S. pombe*. These proteins may prevent the elongation of telomere-repeat tracts by inhibiting telomerase.**

The variable length of telomere-repeat tracts has attracted considerable attention for two reasons. First, telomere tract shortening in somatic cells is associated with senescence, and it has been proposed to act as a molecular clock to prevent oncogenesis[6]. Second, telomerase is undetectable in most somatic cells, but it seems to be reactivated in many tumours, suggesting that telomere elongation might be an important — or even essential — step in tumour formation[7]. What is important to keep in mind is that telomere length in telomerase-containing tumour cells does not increase without bound, but is instead regulated at a constant average value. The same is true in germline cells, which also contain telomerase, and which regulate telomere length at a species-specific average value.

van Steensel and de Lange[4] report the first functional studies of a human telomere-repeat binding protein, TRF1 (ref. 8), and they suggest how it might work to regulate telomere length. They have stably overexpressed both full-length TRF1 and a dominant-negative mutant that reduces the binding of TRF1 to telomeres. Prolonged overexpression of wild-type TRF1 results in gradual telomere shortening, whereas the dominant-negative mutant abolishes detectable telomeric TRF1 staining (by indirect immunofluorescence), and causes pronounced telomere elongation. Both of these results point to the direct involvement of TRF1 in determining the length of telomeres in human cells. The authors suggest a simple model in which the amount of TRF1 that is bound to telomeric repeat tracts acts to regulate telomerase. The addition of wild-type protein increases the amount of TRF1 at telomeres — creating a negative signal for telomerase — whereas the depletion of functional TRF1 by the dominant-negative mutant leads to telomerase activation and telomere elongation.

Cooper *et al.*[5] have used a 'one-hybrid' approach to clone the *S. pombe* gene that encodes Taz1p (for telomere associated in *Schizosaccharomyces pombe*), a protein that binds to double-stranded DNA at telomeres. Remarkably, although the telomere-repeat sequences of *S. pombe*, *S. cerevisiae* and humans differ, all three repeat-binding proteins (Taz1p, Rap1p and TRF1, respectively) share similar (Myb-like) DNA-binding domains. Outside the DNA-binding domain, Taz1p has little homology with human TRF1, and no homology at all with Rap1p. Nonetheless, mutation of the *taz1*$^+$ gene creates two phenotypes that are strikingly similar to those seen in Rap1p carboxy-terminal truncation mutants — massive

elongation of the telomere-repeat tracts, and a complete loss of telomeric gene silencing or telomere positional effects[3,9]. So despite the absence of any clear sequence homology between these yeast proteins, they share two telomeric functions. But whereas the *taz1*$^+$ gene is not absolutely necessary for growth in *S. pombe*, Rap1p also works as an apparently essential transcriptional activator in *S. cerevisiae*[10].

A general theme to emerge from these studies is that proteins that bind to double-stranded telomere repeats negatively regulate telomere elongation. This concept was first suggested for Rap1p and its homologue in the related yeast *Kluyveromyces lactis*[11], and it may provide the key to understanding two central questions: how does the cell 'measure' telomere length, and how is this information used to regulate the length of telomeres?

One possibility is that a mechanism exists to sense the number of telomere-repeat binding proteins on the end of the chromosome. When this number exceeds a certain threshold, a signal is generated that blocks elongation by telomerase (Fig. 1). Alternatively, this signal might activate nucleolytic or recombinational processes that shorten telomere-repeat tracts. Incomplete replication or degradation events that remove repeat-tract binding sites would relieve the repression of telomerase, allowing subsequent elongation. This, in turn, would lead once again to the repression of telomerase.

Such a simple negative-feedback model could explain how germline cells or cancer cells (which contain active telomerase) can maintain a constant average telomere tract length. One prediction of the model is that telomere length is sensed by a mechanism that can discern the precise number of molecules that are bound to the telomere repeats. Direct evidence for such a mechanism has just been described for *S. cerevisiae*[12], and the experiments by van Steensel and de Lange[4] indicate that a similar protein 'counting' mechanism may be at work in human cells. So it is likely that TRF1 is directly involved in determining telomere length in germline cells, as well as in tumours.

With the outlines of a plausible model for the regulation of telomere length in view, the challenge will now be to understand the process in molecular detail. In *S. cerevisiae*, there is mounting evidence that length regulation by Rap1p is mediated by a pair of proteins called Rif1 and Rif2 (for Rap1-interacting factor)[13]. Are similar factors at work in *S. pombe* and mammalian cells? Although the principle of length regulation by a negative-feedback mechanism that involves repeat-binding proteins may be generally applicable, we should not be surprised to find that the details vary in different systems, or that additional mechanisms exist. Even in yeast, there seems to be an alternative pathway that can rapidly reduce an extremely elongated telomere to the size of its normal cohorts[14].

Finally, the putative target for regulation by telomere-tract binding proteins remains elusive, although attractive candidates have been identified in several systems — for example, telomerase subunits and proteins that bind specifically to the single-stranded protrusions at the very ends of telomeres. We can anticipate that a more detailed picture of telomere length regulation will emerge in the coming years, and this new perspective will certainly affect our view of the role of telomeres in senescence and tumorigenesis — the two problems that generated all of the excitement in the first place. □

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**Olfactory adaptation**

# The nose leads the eye

**Geoffrey H. Gold and Edward N. Pugh Jr**

Stimuli such as light, odours, hormones and other chemical signals, generate an intracellular response by altering the levels of intracellular second messengers. This type of signal transduction involves three components — a receptor protein that interacts directly with the stimulus; a guanine-nucleotide-binding (G) protein that is activated by the receptor; and an intracellular enzyme that is activated or inhibited by the G protein. Because a single receptor protein can activate a large number of G-protein molecules (each of which can interact with an intracellular enzyme molecule), this enzymatic cascade can provide enormous amplification. For example, vertebrate rods and certain invertebrate photoreceptors can respond reliably to as little as one photon of light.

But high transduction gain has a cost: a relatively weak stimulus can drive the signal-transduction mechanism into saturation. So G-protein-coupled mechanisms have evolved a variety of ways in which to desensitize (or adapt) to strong stimuli, allowing the cell to respond to stimuli over a wider range of magnitudes than would be possible with fixed, high gain. On page 725 of this issue, Kurahashi and Menini[1] show that of the many adaptation mechanisms that have been suggested, one seems to be dominant in newt olfactory receptor cells.

Odorants are detected by olfactory receptor cells in the nasal cavity. These cells

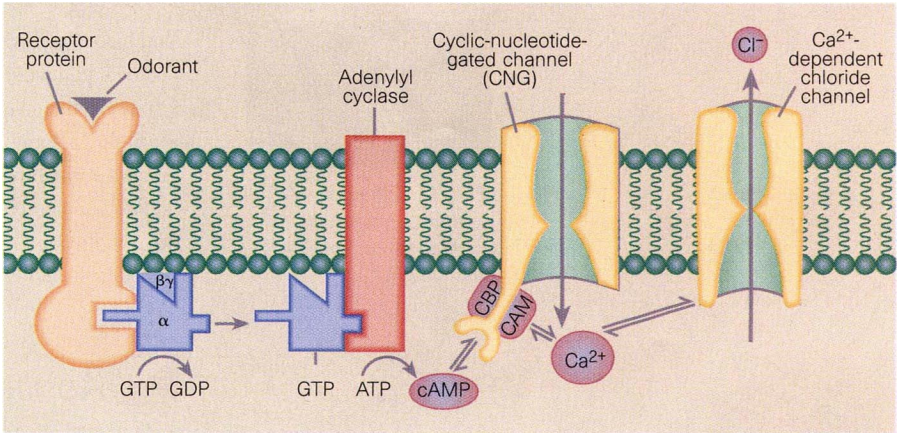


Figure 1 **To avoid becoming saturated by weak stimuli, sensory cells desensitize (or adapt). By studying olfactory receptor cells, Kurahashi and Menini[1] have explained exactly how adaptation occurs in response to odorant molecules. Following binding of the odorant to its receptor, G-protein-mediated activation of adenylyl cyclase leads to the production of cyclic AMP (cAMP), which activates a cyclic-nucleotide-gated (CNG) cation channel. Activation — and subsequent opening — of the channel allows an influx of $Ca^{2+}$, which evokes a response to the odorant by activating a $Ca^{2+}$-dependent chloride channel. But $Ca^{2+}$ also mediates adaptation, by desensitizing the CNG channel through which it entered the cell. Desensitization is thought to be mediated by calmodulin (CAM) and possibly also by a new calcium-binding protein (CBP). (Figure adapted from ref. 10.)**