Figure 1 Synthesis of telomeric DNA by telomerase. **a**, A short region of the upper strand of the telomere (composed of TTAGGG repeats) cannot be copied by normal DNA replication (see box) and is indicated by asterisks. **b**, Telomerase circumvents this by synthesizing new TTAGGG repeats (blue), allowing the ends to be copied by conventional DNA replication (**c**). Mouse telomerase carries an RNA molecule that acts as a template for synthesis of the TTAGGG sequence. Blasco *et al.*⁴ have deleted the *mTR* gene (which encodes this RNA molecule) in the mouse germ line. The resultant knockout mice have no telomerase activity, and their telomeres become shorter with continuing cell division.

that interference with chromosome function may need to be more widespread to compromise cell proliferation severely. It seems improbable that the observed telomere erosion could continue unabated without eventually stopping growth. For example, viral-oncogene-transformed human cells eventually undergo 'crisis' (cell death) during continuous culture, unless telomere erosion is halted by activation of either telomerase³ or of an alternative pathway⁶. A remarkable counterpart *in vivo* may be the spontaneous tumour regression that occurs in a subset of childhood neuroblastomas (so-called stage IV-S), which apparently fail to up-regulate telomerase⁷. So, if telomere erosion continues, oncogene-transformed *mTR*^{-/-} cells might be expected, eventually, to lose their ability to generate tumours, once they have undergone enough cell divisions.

It is also risky to extrapolate from the mouse with regard to the timing of telomerase up-regulation in tumour development — not least because telomerase seems to be more tightly regulated in man. Many (but not all) human cancers possess very short telomeres, consistent with the classic model of telomere erosion followed by selection for telomerase reactivation during an *in vivo* equivalent of crisis. Of course, some tumours may acquire telomerase ahead of critical telomere erosion; for example, if telomerase is reactivated as part of a 'package' of changes in gene expression that occurs after some other genetic event (the 'co-selection' hypothesis^{4,8}). But such anticipatory up-regulation does not mean that telomerase is not required at a later stage, so this should not dampen enthusiasm for anti-telomerase therapies.

We may also need to revise our ideas about how cells distinguish between unnatural genomic breaks such as those caused by ionizing radiation (which usually lead to immediate cell-cycle arrest or programmed

cell death), and natural chromosome ends (which do not). It has been assumed that in mammalian cells, specific terminal DNA sequences and associated proteins somehow 'shield' the natural end of the chromosome and prevent it from activating genome-damage-monitoring systems. The later-generation *mTR*^{-/-} cells show an apparent loss of telomere-protective function (as judged by end-to-end fusions in metaphase chromosome preparations). But the fact that such cells have reached metaphase suggests that they have passed through at least one damage-sensing checkpoint (at G2-M), despite having critically eroded telomeres.

If the absence of telomere-specific DNA sequences and proteins does not activate cell-cycle arrest, then what does? It is possible that the physical structure of the DNA-end itself is differentially recognized — a break caused by ionizing radiation is not only physiologically abnormal, but it is chemically very different from a natural chromosome terminus formed by DNA replication.

We now await with interest the phenotype of later generations of these mice (if they remain fertile), and later passages of cell cultures derived from them. Whatever the outcome, it is certain that interest in telomeres has not come to an end. □

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Daedalus

Smooth ascent

A solid-fuel rocket is simply an enormous firework. Once lit, it cannot be stopped or controlled. Furthermore, it burns in massively turbulent flow, generating extreme vibration. Everything that has to fly in a rocket must pass a searching vibration test. Daedalus is now devising a less vibrant way to climb into space.

A typical solid fuel is a mixture of aluminium powder and ammonium perchlorate, formed into a resilient solid by a polymeric binder. DREADCO chemists are replacing the aluminium powder by fine aluminium wire, and the binder by a water-based gel. The product is just damp enough so that ignition cannot spread through it spontaneously; but each element can be ignited by passing a current through the local aluminium wire. The charge will be fired controllably, element by element, by passing a programmed sequence of current pulses through the wires.

In this simple form, the idea is clearly impractical. A big rocket motor could have millions of ignitable elements, far too many for each to have its own electrical leads. But Daedalus recalls the old flashbar units for small cameras, which carried ten separate flash-bulbs. As each bulb fired, it carbonized and caused a lead to the next bulb to become conducting. Each time the shutter was depressed, the trigger current set off the next live bulb. This trick, suitably developed, would allow thousands of elements in the motor to be set off controllably by a single set of leads. A few thousand sets of such leads could command the complete motor.

The resulting rocket will be a masterpiece of smooth power. Its thrust will be controlled from instant to instant by the rate at which its elements are fired. Its vibration will be damped by fast-acting acceleration sensors feeding its control computer, which will stagger the firing sequence to the next elements so as to cancel or minimize the instantaneous fluctuations of thrust. If required, the whole motor can be shut off instantly, and started again later; once in space, it can be operated on command at very low thrust for orientation or course correction.

The technology could even be adapted for other purposes, such as blasting, demolition and explosive forming. Instead of many explosives for different jobs, one all-purpose DREADCO product will do. It can be programmed to act as a propellant, a low, medium or high explosive, or even a subtle combination of each.

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