cells without affecting other regulatory systems such as those that control differentiation.

But the work of Kiyono *et al.*[1] now indicates that it may not be so easy to avoid senescence, at least in certain cell types. Their work with two human epithelial cell types — keratinocytes and mammary epithelial cells — indicates that immortalization of these cells requires expression of the *hTERT* gene and inactivation of the retinoblastoma (Rb)/p16^{INK4a} tumour-suppressor pathway. This pathway halts cells in the G1 phase of the cell cycle in response to a range of physiological signals known to inhibit growth (Fig. 1).

These results highlight the complexity of the senescence phenotype. The very name is misleading, because senescence is provoked by many stimuli that have nothing to do with cell ageing. For example, activation of oncogenes can induce a cell to senesce rapidly[6]. Hence, telomere shortening cannot be the only stimulus to provoke senescence. This conclusion is made obvious by the observation that when primary cells are placed into culture they often senesce within a small number of generations — long before their telomeres have eroded significantly.

Such observations might indicate that the senescence phenotype signals the difficulties that cells experience when they are explanted from living tissue into the artificial environment of the culture dish. Physiological stress may, for example, activate the p16^{INK4a} cyclin-dependent kinase inhibitor, which in turn shuts down growth by blocking phosphorylation of Rb. Hence, senescence provoked by difficulties in adapting to a culture medium may be avoided only by neutralizing the p16^{INK4a}/Rb braking system. Kiyono *et al.*[1] exploit human papillomavirus oncoproteins to do so, but the SV40 large T oncoprotein used by others seems to achieve the same result[5].

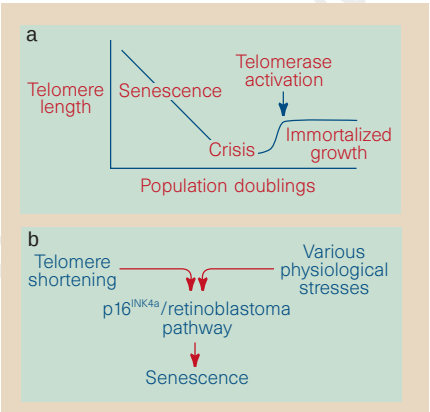

Figure 1 **Models for the role of telomeres in cell immortalization.** a, **Standard model. With each cell division, the telomeres at the end of the chromosomes become shortened. In normal cells this leads to senescence and eventually to crisis. But activation of telomerase, in cancer cells for example, allows the telomeres to be regenerated indefinitely, immortalizing these cells.** b, **Revised model, according to the results of Kiyono *et al.*[1]. They show that activation of telomerase alone is not enough to immortalize certain epithelial cells, and that inactivation of the p16^{INK4a}/retinoblastoma pathway is also needed. Because this pathway is activated by many other physiological stresses, immortalizing cells may not be as simple as was previously thought.**

All this converges on the idea that the epithelial cells studied by Kiyono *et al.* — and, perhaps, all epithelial cells — may need to overcome the senescence induced by explantation into culture before they confront the barrier to unlimited proliferation of telomere shortening. Such a sequence of events might explain why inactivation of the Rb pathway and ectopic expression of telomerase are both required for immortalization of epithelial cells. For those intent on using *hTERT* to immortalize primary epithelial cells and study their differentiation phenotypes, this model, if extended and validated, will have unfortunate consequences because inactivation of the Rb pathway often affects differentiation programmes[7].

This work may also affect our view of how tumours progress in the 90% of human cancers that derive from epithelia. Cell immortalization may be a two-step process at the least. The first step, inactivation of the p16^{INK4a}/Rb pathway, may occur relatively early, enabling cells to avoid the senescence provoked by, for example, oncogene activation[6]. Only later in tumour progression, when clones of premalignant cells have begun to exhaust their endowment of telomeres, will activation of telomerase through derepression of *hTERT* become advantageous for further proliferation.

Moreover, the apparent separation between oncogenes, tumour-suppressor genes and *hTERT* may be an illusion. A recent study[8] indicates that the *myc* oncogene upregulates telomerase expression, and the work of Kiyono *et al.*[1] and earlier work of others[9] shows that the E6 oncogene of the human papillomavirus can induce expression of *hTERT*. Accordingly, the circuitry that governs the cell-cycle clock may be tightly linked to that governing the telomere-based generational clock. Thus, oncogene activation may yield both short-term advantages in deregulating advance of the cell cycle and long-term advantages by stabilizing telomeres. □

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Daedalus

Smokeless microwaves

A flame keeps burning by thermal feedback. The heat it gives out vaporizes incoming fuel, and raises it to combustion temperature. Sadly, the process is not particularly efficient. Vaporized fuel is never completely burnt in its passage through the flame. A little unburnt fuel, and a variety of partly burnt combustion products, always escape into the cooling flue gases. The result is soot, smoke, and frequently the need for a costly catalytic converter downstream, to oxidize the pollutants before they get away.

So Daedalus is planning an alternative form of energetic feedback. His idea is to beam intense microwaves into the burner or furnace. The hot, ionized combustion gases should be conducting enough to absorb the energy, which will make them hotter still. The beam should be concentrated just above or beyond the flames, to heat and oxidize the partially burnt gases before they can cool down. Visible smoke, in the form of carbonaceous particles, will be particularly well suppressed. Carbon is such a good conductor that the microwaves will keep it glowing until it has burnt completely. But microwaves seem to encourage chemical reactions not merely by heating, but also by direct molecular agitation. Nasties such as carbon monoxide and nitric oxide absorb them strongly, and should be rapidly reacted away.

The obvious application is to big power-stations. They could well afford to boost their combustion efficiency by feeding a bit of power back into their furnaces. Old, polluting coal-fired stations, and ecologically virtuous ones heroically trying to burn rubbish, would benefit the most. Indeed, even the Greens might applaud a guaranteed pollution-free, microwave-augmented incinerator.

The internal-combustion engine is a more daring challenge. DREADCO engineers are now plumbing microwave waveguides into the cylinders of a test diesel engine. A dynamo on the engine will power a klystron. At each moment of ignition, it will beam an intense microwave pulse into the firing cylinder, which will act as a frequency-swept resonant cavity. Smoke and partial-combustion products should vanish. They will be burned, not in a wasteful exhaust catalyser, but in the engine itself, thus raising its efficiency. Even the microwave energy beamed into the cylinders will boost the engine's power, and be partly returned to the dynamo generating it.

David Jones