analogous to Bloch functions can be applied to quasicrystals.

Rotenberg *et al.* do not, however, rule out the possibility of critical states co-existing alongside the extended states. In this vein, we note that the existence of extended states in decagonal Al-Ni-Co is not too surprising, as it is among the most 'metallic' of the quasicrystals. Icosahedral Al-Pd-Re is at the other extreme, showing extremely high resistivity, and perhaps should even be classified as an insulator rather than as a metal at low temperatures[6]. The next step is to test whether extended states exist in other alloys. ■

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Cancer

Benefits of bad telomeres

Douglas Hanahan

Tumour cells can be considered in terms of their acquisition of capabilities that enable cancerous growth[1]. One property involves the ability to go through countless cycles of chromosome replication followed by cell division. This is achieved largely through activation of the enzyme telomerase[2], which protects the ends (telomeres) of linear chromosomes by capping them with short repetitive DNA elements called telomere repeats. Without telomerase, each chromosome loses a few telomere repeats — and so is shortened — every time it is duplicated. This makes the chromosomes unstable, which can lead to the death of the cell or its inability to continue multiplying. So it is not surprising that telomerase is activated in most human cancers, often around the stage when progression from contained lesions to invasive cancer occurs[3]. But the results of Artandi and colleagues[4], reported on page 641 of this issue, come as a surprise. The authors look at mice engineered to lack functional telomerase and a well-known tumour-suppressor protein, p53. They find that epithelial cancers develop that would not have emerged in mice lacking only p53.

Genome instability can reprogramme a nascent tumour cell, endowing it with the capabilities it needs to develop further[1]. The integrity of the genome in normal cells is preserved by a specialized system, a key component of which is p53. A signalling circuit centred on p53 detects DNA damage and limits the emergence of cells with mutant genomes, either by arresting the cell-division cycle to allow DNA repair or by inducing cell death[5]. This DNA-damage sensor is often disrupted in tumour cells, allowing genomic instability.

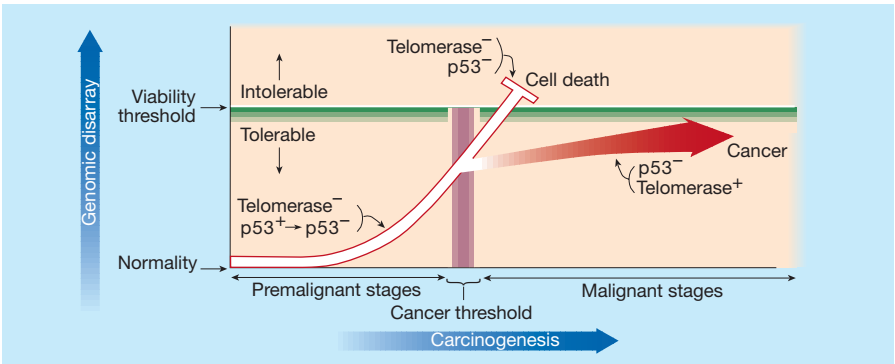

Figure 1 **How the absence and presence of the enzyme telomerase might benefit human cancer cells. This model is suggested by both present[4] and previous[2,3,10,11] results. Cancer development (carcinogenesis) occurs in several stages, and can be considered in terms of accumulating disarray of the genome, produced by genomic instability. There are two thresholds: a viability threshold, above which genomic disarray is incompatible with the survival of the cell; and a cancer threshold, after which developing tumours grow expansively. In the early (premalignant) stages, continuing cell proliferation in the absence of telomerase results in progressive shortening of telomeres, which eventually become so short that they can no longer protect chromosome ends. This causes chromosome fusions, translocations and other rearrangements. Combined with the loss of DNA-damage sensors (such as p53), the scrambled genomes persist and acquire mutations that enhance the capabilities of the tumour. If unchecked, the accumulating genomic disarray will reach intolerable proportions, resulting in cell death. But in many developing cancers, telomerase is activated around the time of the cancer threshold, restoring telomere function, reducing further genomic instability and allowing expansive proliferation.**

Mice lacking p53 alone rapidly develop sarcomas (tumours of connective tissue) or lymphomas (cancers of white blood cells)[6]. Only rarely are epithelial cancers, such as those of the gut lining, seen in these p53-deficient mice[6], despite the fact that 90% of human cancers are epithelial in origin, and most show malfunctioning of the p53 damage-sensing pathway[5,7]. The absence of telomerase alone, however, has no immediate effect on mice[8], as they have much longer telomeres than humans. But if telomerase-deficient mice are bred with each other, and so too are their progeny, then progressive shortening of the telomeres occurs. After six generations the telomeres are almost non-functional, and the mice begin to show a plethora of abnormalities, including sterility and rare cancers[8].

Artandi *et al.*[4] made their unexpected discovery by analysing mice with inactivating mutations in the genes encoding p53 and the essential RNA subunit of telomerase. The authors crossbred these mice, and again found that rapidly developing sarcomas and lymphomas were prevalent in the offspring. Reasoning that the early onset of such tumours might be masking other, more slowly developing cancers, the authors sought to limit the sarcomas and lymphomas, by using telomerase-deficient mice that carried one normal and one mutant p53 gene (that is, they were 'heterozygous' for p53). Mice heterozygous for p53 (but with normal telomerase) develop sarcomas and lymphomas later than mice with two mutant versions of the p53 gene[6]. This probably reflects incomplete tumour suppression by the single intact copy of p53 and the relative ease with which it can be lost in tumours.

Artandi *et al.* inbred their telomerase-deficient, p53-heterozygous mice for five to seven generations. The resulting mice had short telomeres. As they aged, about half of the mice still developed sarcomas and lymphomas. But the remainder developed epithelial carcinomas, mainly of the breast, skin or intestines. Intriguingly, all the mice analysed had microscopic cancerous lesions in the large intestine, indicating a marked effect on this self-renewing epithelium. What caused the shift in tumour spectrum?

The data indicate[4] that the already short telomeres may have become critically short in these epithelial tissues, presumably during cell proliferation, with the malfunctioning telomeres catalysing genomic rearrangements that initiated and sustained the development of cancer. The tumours showed marked disarray in their genomes, presum-

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ably allowed by the observed loss of the one functional p53 gene. The disarray included chromosomal end-to-end fusions and translocations, as well as changes in chromosome number. It seems that these genomic rearrangements allowed the development of epithelial cancers in particular. But how can one relate this result — that the absence of telomerase can lead to epithelial cancers in mice — with extensive evidence that telomerase activity is common to, and important for, those very epithelial cancers in humans? The answer may lie in the timing of telomerase activation, and in the nature of cancer progression (Fig. 1).

Cancers develop in several distinct steps, with cells of increasing aggressiveness and capability emerging over time. In most cancers, disease progression is accompanied by an accumulation of genomic abnormalities[9]; in some, the disarray arises mainly at a characteristic stage. In the absence of telomerase, as telomeres become too short to function, sudden episodes of widespread genomic disarray can occur — a conclusion supported by previous work[10,11]. This might enable cells to acquire the capabilities they need to become tumour cells. But genome disarray can reach a point (a 'viability threshold') beyond which cells can no longer live. So the eventual activation of telomerase could be seen as necessary for the survival of a human tumour cell (Fig. 1). Early on, the normal absence of telomerase allows critical telomere shortening in the proliferating cells. This shortening, combined with defects in a DNA-damage sensor (such as p53), produces genome rearrangements that allow the cancer to develop. But then, before the damage becomes so extensive as to preclude cell viability, telomerase is activated, adding telomere repeats and stabilizing the ends of both normal and mutant chromosomes. This enables continuing proliferation, progression and dissemination of the cancer.

One testable prediction of this hypothesis is that the genome rearrangements produced by malfunctioning telomeres alter the expression or function of critical genes, allowing the genesis of epithelial cancers. High-resolution genome mapping and studying candidate genes would address this possibility. But why do the genome rearrangements produced by telomere malfunction fuel epithelial cancers specifically? Perhaps the growth-regulatory genes in epithelial cells are, coincidentally, located in regions prone to being altered by genome rearrangements induced by malfunctional telomeres. Or perhaps the regulation of transitory proliferation in self-renewing epithelial sheets is more easily disrupted by chromosomal imbalances. The answer may shed light on the bias towards epithelial cancer in humans.

A challenge to the theory comes, however, from the observation that the mouse tumours seem to violate the viability threshold by their very emergence in the telomerase-deficient mice. This result might be explained by the presence in mice of an alternative, DNA-recombination-based mechanism of preserving telomeres[12]. Also, when two chromosomes are fused end to end, burying malfunctional telomeres, the hybrid chromosomes in one orientation seem to be better tolerated in mice than in humans.

The theory (Fig. 1) does fit, though, with the patterns of telomerase activity seen in many human cancer types[3]. If progression through the early stages of cancer is indeed fuelled in part by the absence of telomerase, there may be implications for treatments that seek to interfere with telomerase activity. Pharmacological inhibitors of telomerase are likely to cause advanced cancers to breach the viability threshold and die. But they may also enhance the progression of telomerase-expressing cancers that are still far from the threshold. So telomerase inhibitors may prove most effective when used in combination with traditional chemotherapeutic drugs that damage DNA, together accelerating the accumulation of intolerable disarray in the genome of a cancer cell. ■

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Oceanography

The giant diatom dump

Victor Smetacek

Diatoms, single-celled algae with silica cell walls, are a major component of oceanic phytoplankton. They are a motley lot. There are about 1,000 species, ranging across three orders of magnitude in size (about as much as land plants) and exhibiting a remarkable variety of shapes. The biggest species take the form of flat discs, squat cylinders or slender rods, and can reach 2–5 millimetres in diameter or length.

These giants among diatoms occur in all of the oceans and are prominent in the sediments on the ocean floor. Their ecology is not well understood, but they are widely believed to have only a marginal influence in marine ecosystems. In a paper in *Deep-Sea Research II*, however, Kemp *et al.*[1] show that giant diatoms can make a large contribution to the rain of particles settling out of the ocean surface layer, and so are serious players in ocean biogeochemistry.

In contrast, the small-celled, long-chained diatoms, which form dense blooms along ocean margins and across the North Atlantic, are well studied. They occur in spring after deep winter mixing introduces new nutrients to the surface layer, and also in freshly upwelled, nutrient-rich water. Given their high growth rates, these small-celled species (5–50 micrometres) accumulate biomass rapidly following warming and stabilization of a shallow, nutrient-rich surface layer. They tend to aggregate into flocs that sink quickly when nutrients run out. Particles sinking in the aftermath of these blooms fuel the 'biological carbon pump' that draws down carbon dioxide from the atmosphere and exports it to the ocean interior[2]. Kemp *et al.* now report that the springtime and upwelling blooms leave less of a trace in the sediments than the large diatoms that settle out later in the year.

This new perspective comes from detailed analysis of the annual sequence of settling particles preserved in layered sediments from sites in the Gulf of California and the Mediterranean. Such layered sediments are rare in the ocean (in contrast to lakes) because the burrowing activity of the deep-sea fauna tends to blend seasonal signals over many years. In the sediments painstakingly examined by Kemp *et al.*, however, discrete bands representing seasonal settling events have been preserved. Layers of large diatoms were prominent at both sites. The layers were dominated by single species (Fig. 1), which i n each case had settled during the summer and autumn months. Kemp *et al.* argue convincingly that these layers reflect a different type of event to that producing the blooms. They propose that the layers are the outcome of a 'fall dump' of large diatoms, as opposed to that of the 'spring bloom' of their smaller relatives.

The prominence of the fall dumps is surprising because the large-celled diatoms must have accumulated substantial biomass in stratified, nutrient-depleted water columns. Stratification arises when the surface layer warms, becomes less dense and is thus sealed off from the rest of the upper ocean by the thermocline, a barrier created by an abrupt change in temperature. Under

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