# Aborting the birth of cancer

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Can cells sense and stop uncontrolled division driven by cancer-promoting stimuli? Perhaps so, given evidence that aberrant division can trigger the cellular response to DNA damage — blocking growth — at early stages in human cancer.

Why human cancer is not more frequent remains a mystery, given our trillions of susceptible cells, each with many genes subject to mutations that could ignite uncontrolled cell proliferation. One intuitive concept — which has been in the spotlight for decades — is that normal cells can somehow perceive and arrest aberrant cycles of cell division that are triggered by cancer-promoting (oncogenic) stimuli, such as the inappropriate activation of oncogenes. But how cells might do so remains elusive.

On pages 864 and 907 of this issue, Bartkova *et al.*[1] and Gorgoulis *et al.*[2] supply evidence that oncogene-driven cell-division cycles trigger DNA damage associated with DNA replication (the process that faithfully copies the genome in preparation for division). This DNA damage raises a barrier to sustained proliferation. From these findings, a fresh picture emerges, in which progression towards full-blown cancer requires the wayward cell to inactivate the mechanisms that monitor damage during DNA replication. This would help to explain the close link between genomic instability and cancer evolution, and extend our theoretical framework for understanding how cancers develop.

Early clues to the existence of mechanisms that prevent uncontrolled cell division came from the observation, more than 20 years ago, that viral oncogenes arrest the proliferation of normal cells in culture[3,4]. Later, the tumour-suppressor proteins p53 and ARF were found to be vital for constraining oncogene-driven proliferation[5,6]. Their activation was variously attributed to excessive stimulation to proliferate, oxidative stress, or the loss of appropriate signals from the tissue microenvironment[7] — all triggered by oncogenic stimuli. Activation of these tumour suppressors causes cells either to become dormant (senesce) or to commit suicide (by the process of 'apoptosis'). But evidence that these constraints on proliferation operate during human cancer development has been hard to find.

Enter Bartkova, Gorgoulis and their colleagues[1,2], who propose from studies of human cancer samples that another constraint limits aberrant cell division. They provide evidence that the cellular response to DNA damage — specifically, to double-strand breaks in DNA — is activated in early

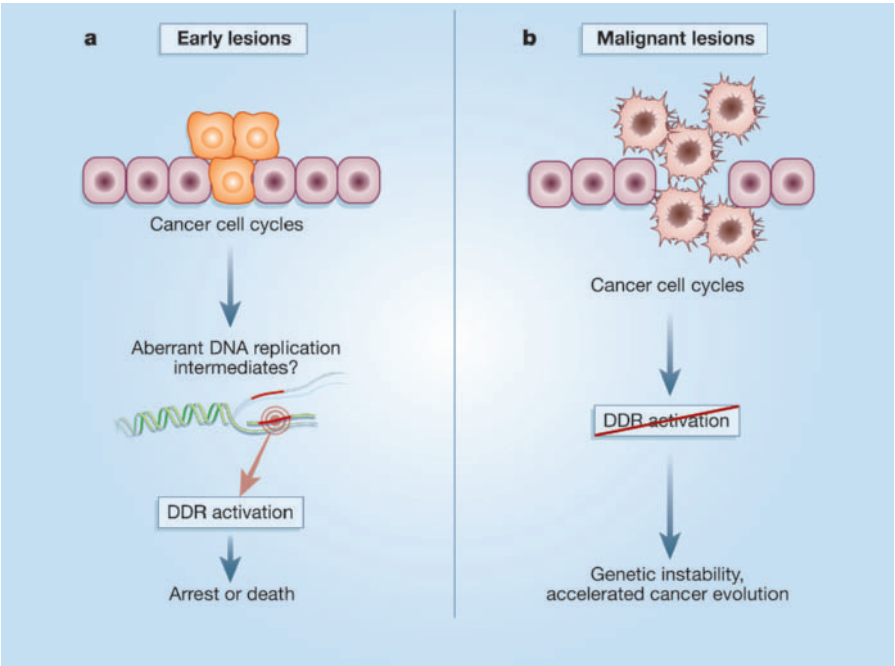


Figure 1 **Sensing and stopping wayward cell divisions.** a, **Bartkova *et al.*[1] and Gorgoulis *et al.*[2] provide evidence that, in early cancerous lesions, cell-division cycles driven by oncogenic stimuli ('cancer cell cycles') trigger the cellular DNA-damage response (DDR), as a result of aberrations in DNA replication. The nature of these aberrations is uncertain. The DDR then arrests cell proliferation or causes cell death. This might create a selection pressure for suppression of the DDR during carcinogenesis.** b, **Hence, the progression to malignant lesions might be accompanied by DDR inactivation, which would in turn create genetic instability and accelerate cancer evolution. What distinguishes cancer cell cycles from normal division at the level of DNA replication remains a key, unresolved question.**

lesions from lung or bladder tumours. This evidence includes the presence of active forms of ATM or Chk2, participants in the enzymatic cascade that responds to double-strand breaks[8]. Notably, these markers are detected in precancerous lesions — where there is evidence for oncogene-induced aberrant division, but not yet for the changes typical of full-blown cancers — suggesting that the DNA-damage response (DDR) is activated at the earliest stages in carcinogenesis (Fig. 1a). Moreover, the markers are absent from normal proliferating epithelial cells, and from inflammatory lesions, indicating that they discriminate normal from aberrant cell cycles.

To verify and extend these observations, the authors either overexpress oncogenes such as the cell-cycle regulator cyclin E in tissue-culture cells[1], or graft human skin sections onto the backs of immunodeficient mice and use growth factors to induce hyperproliferation of skin cells[2]. In both cases, the abnormal cell cycles elicit the DDR *in vitro*. This also occurs after inactivation of the tumour-suppressor protein Rb, which ordinarily serves as a gatekeeper for entry into the cell cycle — suggesting that the DDR can be initiated by numerous alterations that underlie the uncontrolled division of cancer cells.

The DDR arrests cell division, and can trigger apoptosis[9]. The authors propose[1,2] that the need for cells to surmount this barrier during carcinogenesis creates a selection pressure for the inactivation of p53 or other participants in the DDR (Fig. 1b). This, in turn, causes genetic instability — increasing the mutation rate, and accelerating cancer evolution. From this perspective, genetic instability is an unavoidable by-product of the breakdown of barriers to uncontrolled division during early stages of carcinogenesis.

This view raises several questions, the most important of which is how the abnormal

division cycles of precancerous cells — but not equally rapid divisions in normal tissues — can elicit the DDR. The authors argue[1,2] that the trigger involves DNA replication 'stress': the idea is that the replication machinery performs differently when activated by aberrant, rather than physiological, stimuli. In support of this, the authors offer evidence for abnormalities in replication when proliferation is driven by oncogenic stimuli *in vitro* or in tissues. Provocatively, for example, both groups find that allelic imbalances (signifying chromosomal translocations or deletions) in the genomes of incipient cancer cells occur frequently at 'fragile sites', believed to resist easy copying by the replication machinery.

Replication 'stress' conceived in this way is somewhat nebulous. A hard look at what could distinguish aberrant from physiological stimulation of DNA replication is now needed. Much thinking about the initiation of DNA replication is dominated by a simple 'on–off' concept, in which the replication machinery is loaded onto DNA when key enzymes (cyclin–CDK complexes) are 'off', and then activated when these enzymes are turned 'on'. Yet evidence is emerging[10] for more complex regulatory circuits. Here, the nature and intensity of growth-promoting stimuli are integrated by different levels of activity of cyclin–CDK complexes and of another crucial enzyme, the anaphase-promoting complex, to affect the assembly and operation of the replication machinery. Oncogenic stimuli could perturb these circuits, leading to aberrant replication[11,12].

But how aberrant replication might trigger a DDR is far from clear. Cancer cell cycles could generate excessive amounts of normal intermediates, such as single-stranded DNA, spawn abnormal structures, such as double-strand breaks, or even lower the threshold for DDR activation[13]. Identifying the triggering events will be vital to understanding what distinguishes normal from cancer cell cycles.

Alternative scenarios are also possible. In dividing cells, replication is frequently blocked[14] by problems such as oxidative changes to DNA bases. If such problems are unresolved, stalled replication creates abnormal DNA intermediates that trigger the DDR. So, could another difference between normal and cancer cell cycles relate to metabolic changes that augment DNA base lesions? For instance, overexpression of the oncogene *Myc* leads to the production of reactive oxygen species[15]. Bartkova *et al.*[1] find that antioxidants have little effect on oncogene-induced DDRs *in vitro*. But, given the high oxygen tensions under which tissue culture is performed relative to *in vivo* conditions, it would be premature to discard this possibility altogether.

Whatever its underlying mechanism, replication 'stress' as a trigger for DDR activation calls attention to the network of tumour-suppressor proteins that monitors genome integrity during DNA replication[16]. Besides ATM, ATR, Chk2 and p53, which enforce cell-cycle checkpoints during the DDR, the network includes Fanconi anaemia proteins and the breast-cancer-susceptibility proteins BRCA1 and BRCA2, which are more directly involved in processing replication-blocking lesions[17]. The proposals discussed here suggest that oncogenic stimuli will generate selective pressure for this network to be suppressed during carcinogenesis. Conversely, the proposals could also help to explain why inherited mutations that affect network components, and thereby potentially lower the barrier to uncontrolled division, predispose people to cancer. What we know about the involvement of these tumour suppressors in cancer is not fully consistent with the predictions, however, hinting that further nuances are yet to be discovered.

An interesting twist also reported in this issue is that BRCA2-deficient cells (which cannot deal with stalled replication[18]) can be killed by overloading them with replication-blocking DNA damage, using inhibitors of DNA repair[19,20] (pages 913, 917). Along similar lines, it has been suggested that DDR inhibitors might provide a means to sensitize cancers to therapeutic radiation. The work of Bartkova, Gourgolis and colleagues[1,2] suggests that there could be a long-term price to pay in either situation — in non-malignant cells — if these interventions also overburden, or stifle, the tumour-suppressor network that senses and stops cancer cell cycles. ■

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Climate change

# Water cycle shifts gear

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Various studies indicate that the hydrological cycle is speeding up at high northern latitudes. The resulting increase in freshwater flow into the Arctic Ocean is predicted to have long-range effects.

Discussions of global climate change tend to focus on increasing surface temperatures. By contrast, changes in the water cycle — precipitation, evaporation and river discharge — have received little attention. Yet water has profound effects on our planet's climate. The natural greenhouse effect is caused primarily by water vapour; the radiative balance at the Earth's surface is modified by snow and ice cover; the distribution of vegetation types is sensitive to the local water balance; and regional climate patterns are influenced by ocean currents.

Progress in modelling the many aspects of the water cycle is therefore essential to assess the changes that will result from rising levels of greenhouse gases in the atmosphere. A step forward has been made by Wu and co-workers[1], who, in a study published in *Geophysical Research Letters*, have investigated changes in the freshwater balance of the high northern latitudes.

Wu *et al.*[1] used a climate model that links the influences of the oceans, atmosphere and land surface on climate, and that, for example, has been used to demonstrate the contribution of rising greenhouse gases to warming during the twentieth century[2]. Four simulations modelling the climate over the past 140 years form an ensemble that shows large seasonal cycles and interannual variability. The ensemble gives a figure for mean discharge from Eurasian rivers of about 2.3 Berings (Be; see Fig. 1). This compares with an estimate of 1.9 Be based on observational measurements[3]. Given the complexity of the hydrological cycle, and the processes that need to be resolved, this discrepancy is remarkably small.

The ensemble suggests an average increase in Arctic river discharge since the mid-1930s of about $1.8 \pm 0.6$ mBe $yr^{-1}$, which compares well with the observation-based estimates of $2 \pm 0.7$ mBe $yr^{-1}$ (ref. 3).