realizing such unusual thermalization is confining the light in one direction, so that every photon is forced to have a frequency at least as high as that of a standing wave. Because the separation between the mirrors is only a few micrometres, this minimum photon frequency is high — crucially, much higher than the frequency corresponding to the temperature of the dye.

This large frequency difference makes the energy budget of the system resemble the finances of a peculiar commercial firm that sells both skateboards and satellites. In the firm's ledgers, the billions column and the millions column must always be balanced separately, because the total volume of the skateboard business never amounts to a single satellite. In the Weitz group's system of dye and light, the thermal energy and the energy of excitations at the standing-wave frequency are similarly each conserved separately, because their scale discrepancy prevents one from balancing the other. And this means that the number of photons between the mirrors changes as photons are absorbed and re-emitted by the dye, but only in the same way that the number of atoms in a gas changes, locally, as the atoms drift around. In technical terms, the light in the Weitz group's experiment reaches thermal equilibrium with a chemical potential as well as a temperature, just like gases cooled to nanokelvin temperatures in magnetic traps. The textbook example of what this can allow is Bose–Einstein condensation, which confers the properties of classical wave physics on a gas of conserved quantum particles below a critical temperature, and is intimately related to the phenomena of superfluidity and superconductivity. The Weitz group has observed Bose–Einstein condensation of light, in remarkably close analogy to that of atoms.

As well as being a landmark achievement in itself, making photons behave thermodynamically as atoms, even to the point of Bose–Einstein condensation, illustrates a broader theme in current physics. Atomic gases have been made to behave as laser light[4], and even as black holes[5]. The 'holes' left when electrons in graphene sheets are energetically displaced reproduce the behaviour of relativistic positrons[6]. Quantized spin-wave excitations in magnetic films have been made to behave as quantum gases[7], and atomic gases have been made to behave as ferromagnets[8]. The discernible trend is that everything is becoming everything else. Physics is the art of the interchangeable.

The purely scientific merit in this trend is that demonstrating the interchangeability of physical details clarifies the few universal patterns and principles that really are conserved — the atoms, as it were, not of matter or of light, but of reality. In this sense, the reductionist progress of science proceeds at full tilt. But in the proliferation of startling masquerades, physical science is also taking on more than ever the aspect of a creative art, in a medium that, with the advances of modern technology, is proving far less constraining than it once seemed. Light is unlimited — or not, as we choose. Blake spoke too soon. ■

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MECHANOREGULATION

Cellular seat belts

Accurate cell division depends on proper attachment of chromosomes to the microtubule-based division apparatus. An impressive *in vitro* study shows how applied force plays a pivotal part in regulating such attachment. SEE LETTER P.576

YUTA SHIMAMOTO & TARUN M. KAPOOR

The main safety feature of seat belts is that if the vehicle jolts, an abrupt pull locks the belt, keeping the passenger in place. Cells also seem to carry a nanoscale version of seat belts: the kinetochores — macromolecular machines that consist of more than 50 different proteins and connect chromosomes to dynamic microtubules of the cell-division apparatus — keep the chromosomes from accidentally ending up in the wrong daughter cell (Akiyoshi *et al.*[1], page 576 of this issue).

Stable propagation of genomes through mitotic cell division depends on the equal partitioning of replicated DNA, which is packaged into sister chromatids. Equal division depends on chromosome bi-orientation — that is, attachment of sister chromatids to microtubules that extend from opposite ends of the bipolar spindle (Fig. 1a). Failure of bi-orientation is common, but the improper attachments that emerge somehow get corrected[2]. Classic studies in grasshopper cells indicated[3] that differences in physical forces acting on a chromosome could be crucial for distinguishing between correct and incorrect attachments. But how force-based regulation may work has remained largely mysterious. A major barrier to progress has been the biochemical complexity of the kinetochores[4] and, therefore, the tremendous difficulty in isolating them in a functional form.

Enter Akiyoshi and co-workers[1]. The authors tagged different kinetochore proteins and developed conditions to isolate functional kinetochores from dividing yeast cells. Budding yeast is an ideal model system for such studies: not only can it be easily manipulated genetically, but also its kinetochore binds only one microtubule — unlike a human kinetochore, which can bind more than 20 microtubules. Nonetheless, the kinetochore architecture is essentially conserved across

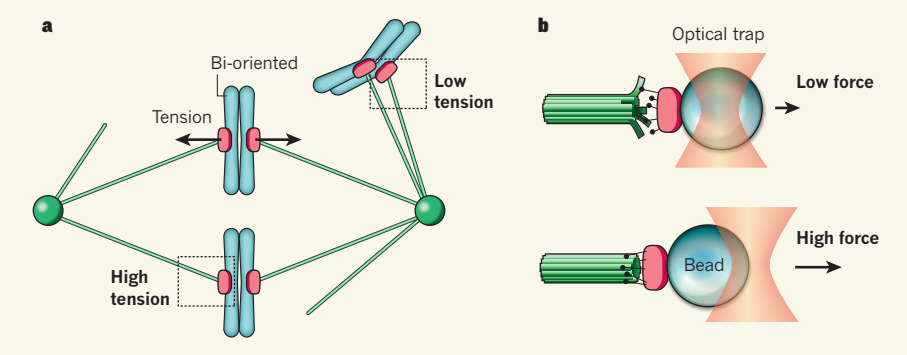

Figure 1 | Tension and chromosome-attachment state. **a**, Spindle microtubules (green) capture sister chromatids (blue) through kinetochores (pink). Tension across bi-oriented chromosomes is higher than across improperly attached chromosomes (dashed boxes). **b**, To investigate how force affects chromosome–microtubule attachment, Akiyoshi *et al.*[1] isolate minimal kinetochores, attach them to a bead and pull the bead with optical tweezers. They find that the reconstituted kinetochores attach to microtubules *in vitro* and that high tensile force enhances the lifetime of the attachment.

eukaryotes (organisms with nucleated cells), with microtubule-binding capacity increasing largely as a result of juxtaposing multiple copies of the core unit of the yeast kinetochore[5].

A key feature of kinetochores *in vivo* is that they can remain attached to the ends of disassembling microtubules. The kinetochores Akiyoshi and colleagues isolate can also do this. What's more, although many of the typical structural proteins are present in the isolated kinetochores, key proteins — such as the enzyme Aurora kinase[6] — that regulate chromosome attachment to the mitotic spindle are absent. These 'minimal' kinetochores therefore allow tests of how forces might regulate microtubule binding, independently of any potential regulation through protein phosphorylation.

Akiyoshi *et al.* attach the minimal kinetochores to a bead that they can manipulate with optical tweezers[7] (Fig. 1b). A bead 'trapped' by optical tweezers behaves as if it is attached to a mechanical spring, such that a force restoring its position is proportional to the change in displacement. The authors examine interactions of the kinetochores with polymerizing and depolymerizing microtubules under different forces. This *in vitro* experiment recapitulates the pulling force that a kinetochore of a bi-oriented chromosome experiences within a cell.

It is reasonable to expect that the lifetime of the attachment between any two interacting partners, such as a ligand and its receptor, decreases as an applied force increases; this is because the mechanical work helps to overcome the detachment energy barrier[8]. Remarkably, however, Akiyoshi *et al.* reveal that force — in the range relevant to physiological forces that act on chromosomes — increases the lifetime of kinetochore–microtubule attachment twofold. The authors' further analysis reveals that the kinetochore–microtubule attachment behaves like a 'catch bond' — similar to a seat belt that locks in place when pulled abruptly[9].

A catch bond can be modelled as a system with both a strongly bound state and a weakly bound state; force favours the strongly bound state. The minimal kinetochores are weakly bound to microtubules that are disassembling, and strongly bound to growing microtubules. Notably, applied force suppresses microtubule disassembly and can therefore favour the strongly bound state. On the basis of direct measurements and simple assumptions, Akiyoshi *et al.* develop a quantitative catch-bond model that accounts for the observed kinetochore–microtubule-attachment behaviour.

The catch-bond mechanism may be considered as a mechanical extension of biochemical allosteric regulation. Force can be considered to be the equivalent of a molecule binding a protein's regulatory site and inducing a conformational change that modulates activity. Evidence from other cellular components with catch-bond behaviour, such as the bacterial adhesion protein FimH, is consistent with this idea[10]. In the case of the kinetochore–microtubule interaction, it is possible that force directly induces a conformational change in microtubule tips[11]. The strongly bound state could involve kinetochore interactions with microtubule protofilaments that are relatively straight, as seen in growing microtubules *in vitro*[12]. The weakly bound state could have protofilaments splaying outwards, as seen in disassembling filaments[12].

Examining the structure of the minimal kinetochores and how they bind different microtubule-tip structures are essential next steps. Combining these structural studies with mutagenesis analysis should allow the design of experiments to test the catch-bond mechanism in dividing cells. Aurora kinases, or other proteins that correct errors in chromosome–spindle attachments, could have a role in fine-tuning the catch-bond mechanism. Experiments with purified kinetochores will also no doubt be useful in dissecting the interplay between these chemical and mechanical regulatory mechanisms.

In vitro studies of isolated kinetochores might help to settle another outstanding question regarding the regulation of chromosome segregation. If chromosomes are improperly attached to the spindle, a signalling network called the spindle-assembly checkpoint blocks mitotic cell division before its anaphase step. It is unclear whether the spindle-assembly checkpoint directly responds to force (or tension)[13]. As the purified kinetochores contain proteins required for the spindle-assembly checkpoint, these kinetochores can be used to investigate whether the recruitment of checkpoint proteins — an early step in the signalling — is sensitive to force. Keep your seat belts fastened for the next phase of this exciting journey. ■

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CANCER

The blind spot of p53

It is hoped that reactivating the tumour-suppressor protein p53 will help to combat cancer. However, fresh evidence suggests it is unlikely that all cells in a tumour will respond to such treatment. SEE LETTERS P.567 & P.572

ANTON BERNS

The tumour suppressor that is most frequently mutated in human cancers is p53. Reactivation of this protein in tumours, which induces programmed cell death or cell-cycle arrest, is therefore an appealing therapeutic strategy. In this issue, however, Feldser *et al.*[1] and Junttila *et al.*[2] report work in mouse models of cancer showing that restoring p53 activity affects only advanced tumours, leaving untouched early lesions that are likely to one day become cancerous.

Earlier work[3–5] suggested that restoring p53 function in several independent oncogene-driven mouse tumours elicits a potent anti-tumour response. The outcome was either programmed tumour-cell death by the process of apoptosis, or tumour-cell senescence. In fact, in two of the three animal models[3–5], even temporary p53 reactivation led to prolonged survival. These data enhanced the appeal of p53 reactivation as a means of treating cancer.

Feldser *et al.* (page 572) and Junttila *et al.* (page 567) add a new twist to these observations. Both groups used variants of a mouse model of non-small-cell lung cancer (NSCLC) characterized by sporadic expression of a mutant *Kras* oncogene; this model closely resembles human NSCLC. Sporadic expression of physiological levels of mutant Kras in mice causes lung tumours that progress through different stages — from hyperplasia to adenoma to carcinoma. The advanced stages of the disease are marked by increased signalling flux through the RAS–MAPK pathway (the pathway in which Kras functions), probably due to additional alterations in this pathway. If sporadic tumour lesions associated with Kras mutations are also p53 deficient, they progress faster and become more malignant.