time transfer. To avoid reducing the accuracy of the timing in transfer, these transmission systems need to be more stable than the clocks themselves, but their stability is degraded by vibration and temperature changes near the fibre, or by turbulence in the air.

Members of the same team as that of Caldwell and colleagues previously demonstrated optical time transfer by pairing atomic clocks with optical frequency combs, which are lasers that produce extremely short, precise pulses of light[1]. One of the reasons these combs are so useful for precision measurements is that the pulses are generated at a very regular rate. By measuring the difference in the arrival time of pulses sent from two clock–comb pairs at either end of an optical link, the time difference between the clocks can be calculated, revealing how close they are to being synchronized. And because both combs send pulses simultaneously through the link, any degradation in timing precision caused by vibration or by air turbulence is eliminated.

Last year, such combs were used to transmit stable clock signals over a 113-kilometre link between two mountains[3]. However, the demonstration relied on high-power optical frequency combs to transmit and receive the signals, using telescopes that were fitted with complex optics systems to correct for the distortion of the comb signal caused by turbulence on the link. By contrast, Caldwell *et al.* transmitted such signals across 300 km using combs that require 200 times less power, and so were able to use smaller telescopes that didn't need corrective optics.

The authors showed that this system worked by sending signals between the Hawaiian volcanoes Mauna Loa and Haleakala, which are around 150 km apart (Fig. 1). The clocks were both stationed on Mauna Loa so that the accuracy and precision of the time transfer could be easily verified, and the signals were reflected from Haleakala to maximize the distance traversed. The authors optimized the optical time transfer so that it reached the quantum limit, at which the highest stability and precision possible is fundamentally limited by the number of photons being received from the combs.

To achieve this, Caldwell *et al.* used a device they had developed previously, known as a time-programmable frequency comb[4]. In research carried out before this innovation[1,3], the combs at either end of the link were set to pulse at different rates. Every so often, the pulses from each comb would align, allowing the time difference between the clocks to be measured. This enabled the time-transfer system to scan over a range of possible time differences between the two clocks, but because the rates were fixed, it also meant that most pulses from the combs were out of sync, so the majority of photons went unused.

The authors' time-programmable comb allowed them to precisely adjust the pulse rate so that the two combs could be brought in sync after an initial scan of the possible time differences. But despite this advance, photons were still lost as they traversed the 300 km of air between the transmitter and receiver — only around one in every 100 pulses from the combs resulted in a photon being detected at the other end of the link. However, by digital filtering and careful optimization of the comb's control system, the authors were able to use the few photons that were detected to enable efficient time transfer in spite of these losses.

One of the most promising aspects of Caldwell and colleagues' work is that it shows that the system could be used to span the distance between the ground and geostationary satellites, which orbit Earth at an altitude that allows them to stay over the same spot on Earth as the planet turns. And the combs required to transmit time signals successfully across this distance need only 4 milliwatts of power (a typical laser pointer emits 1 mW). The findings therefore open up the exciting prospect of performing fundamental-physics experiments with much higher precision than is possible with existing systems (see, for example, ref. 5). In particular, the efficiency of the authors' system makes it ideal for use on satellites, because its low power and small telescope apertures minimize its size and weight, and therefore the cost of the satellite.

However, major challenges remain in designing an optical time-transfer system capable of linking to satellites that are in close orbit around Earth. These satellites move at several kilometres per second relative to the ground station, resulting in frequency changes, known as Doppler shifts, that are large and rapidly varying. It will be extremely difficult to compensate for these effects at the precision needed for effective time transfer. And although optical links to geostationary satellites will open up a range of scientific experiments, many applications will require satellites in closer orbits.

More broadly, Caldwell and colleagues' feat represents the highest time-transfer precision that can be achieved at the 'standard' quantum limit. However, a technique called quantum squeezing, which reduces quantum uncertainty in one measurement by increasing uncertainty in another[6], could be used to push the limits of achievable precision further to keep up with developments in atomic-clock technology. For now, the team's work provides the most convincing demonstration so far that time signals from optical clocks could feasibly be transmitted between the ground and satellites — a prospect that will have far-reaching impacts on the use of satellites for fundamental and applied science.

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Tumour biology

Ultraviolet light affects cancer evolution

Elli Papaemmanuil

Much remains to be discovered about how premalignant cells become cancer cells. An analysis of the development of a type of human leukaemia implicates ultraviolet light in triggering a rare form of cancer. **See p.834**

The factors that cause cancer to develop from premalignant cells at a single anatomical site are becoming clearer. However, the role of tissue-specific environmental pressures that drive these cellular lineages (clones) to cause the disease to spread is less well understood. On page 834, Griffin *et al.*[1] investigate the development of an aggressive form of leukaemia called blastic plasmacytoid dendritic cell neoplasm (BPDCN), which is often diagnosed by the presence of malignant cells in the skin. The authors' data show that the migration of a type of immune cell through the skin leads to the accumulation of DNA damage associated with exposure to ultraviolet (UV) light. This damage precedes

the acquisition of mutations associated with the transformation to malignancy, indicating that movement of pre-leukaemic cells to the skin is involved in the early stages of BPDCN.

In the past decade, scientists have discovered that the growth (expansion) of cellular clones that have mutations is common in normal tissues — a phenomenon referred to as somatic mosaicism[2]. Although most clones do not progress to malignant disease, some rare cells might acquire further alterations that promote their survival in the local tissue environment.

In the context of blood cancers, blood-cell lineages that harbour gene mutations implicated in certain types of cancer (myeloid and lymphoid neoplasia) can arise from stem cells or populations of progenitor cells. This is known as clonal haematopoiesis. The transition from clonal haematopoiesis to leukaemia is typically thought to occur in the bone marrow when cells acquire further, collaborative mutations that might target particular versions of genes. This could affect the number of copies of the gene that a cell has, result in loss of tumour-suppressor genes or produce combinations of mutations that increase cell survival[3,4]. Cell-extrinsic factors, such as cancer therapies or tobacco smoke, might enhance the growth of clones that carry specific mutations[5], such as those in the genes *TP53* and *ASXL1*. There is also evidence that such clones can become established early in the developing embryo, but do not lead to cancer until later in life[6].

Clinical models of disease progression have suggested that BPDCN might originate in both the skin and bone marrow. Clonal haematopoiesis occurs frequently in people with BPDCN, and it has been demonstrated that cells arising from clonal haematopoiesis can progress to form the BPDCN clone. Understanding the evolutionary path that leads to BPDCN transformation will be crucial for the development of early diagnosis and surveillance strategies.

Griffin and colleagues examined a data set from 16 people with BPDCN, and investigated the disease's evolution (Fig. 1) using a range of genomic analyses (including whole-genome sequencing, single-cell RNA sequencing and single-cell DNA sequencing). Seven of the individuals had cancer growths (lesions) in the skin and bone marrow, whereas the others showed no signs of bone-marrow involvement. The model that emerges is one in which the most recent common ancestor (the ancestral lineage giving rise to the cancer) is a clone that developed during clonal haematopoiesis in the bone marrow. The mutations most frequently implicated (for 79% of the individuals) targeted cellular signalling pathways involving the proteins TET2 and IDH2.

Integration of single-cell RNA- and DNA-sequencing results showed that mutations associated with clonal haematopoiesis were acquired by cells called multi-potent progenitors, which have few other somatic mutations (mutations that are not inherited but are acquired later in life). Single-cell gene-expression analysis reveals that in cancers with bone-marrow involvement, the differentiation of immune cells was skewed towards the production of a type of cell called a plasmacytoid dendritic cell (pDC). After migration of these cells to the skin, there was an increase in their number of mutations (the mutation burden). There was also recurring evidence of mutational events that targeted the proteins CDKN2A, SETD2, TP53 and RAS, and these mutations were observed in the skin but not the bone marrow.

Similarly, the evolution of some cell lineages was confined to the bone marrow, with the cells accumulating specific mutations not shared with the skin cancer. Single-cell DNA sequencing and gene-expression analyses by RNA sequencing showed that the pDCs carried mutations associated with both the initiation (founder mutations) and progression (secondary-progression mutations) of the disease. The cells also showed distinct signatures of BPDCN that involved increased expression of *TCL1A* and *BCL2*, as well as other genes.

By contrast, pDCs in samples without bone-marrow involvement had a low mutation burden. Also, they typically carried founder but not secondary-progression mutations, and did not have a prominent BPDCN gene-expression signature, although they still showed increased expression of *TCL1A*. This gene was previously identified[7] as having a key role in the survival of haematopoietic stem and progenitor cells in clonal haematopoiesis, a finding that has potential therapeutic implications, and thus is in keeping with Griffin and colleagues' results.

The authors' analysis of UV-associated mutation signatures and clonality demonstrated that UV-induced damage precedes the acquisition of secondary-progression mutations and malignant transformation. Tracking of UV-associated mutational signatures showed that BPDCN cells in the skin could then seed other anatomical sites (including previously unaffected bone marrow), and could cause relapse of cancer in the skin.

Notably, UV-induced DNA damage did not lead directly to mutations implicated in BPDCN. Griffin and colleagues explored an alternative hypothesis for how exposure to UV radiation might boost the growth of premalignant pDCs. Using a technique for culturing cancer cells in the laboratory, the authors exposed differentiating cells to UV radiation and observed a dose-dependent increase in cell death. However, pDCs with *TET2* mutations were more resistant to UV-induced death than were cells with normal *TET2*, suggesting a tumour-suppressor role for *TET2* in UV-exposed pDCs. The evidence indicates a strong association between *TET2* inactivation, skin localization and the acquisition by cells of UV-associated mutations in

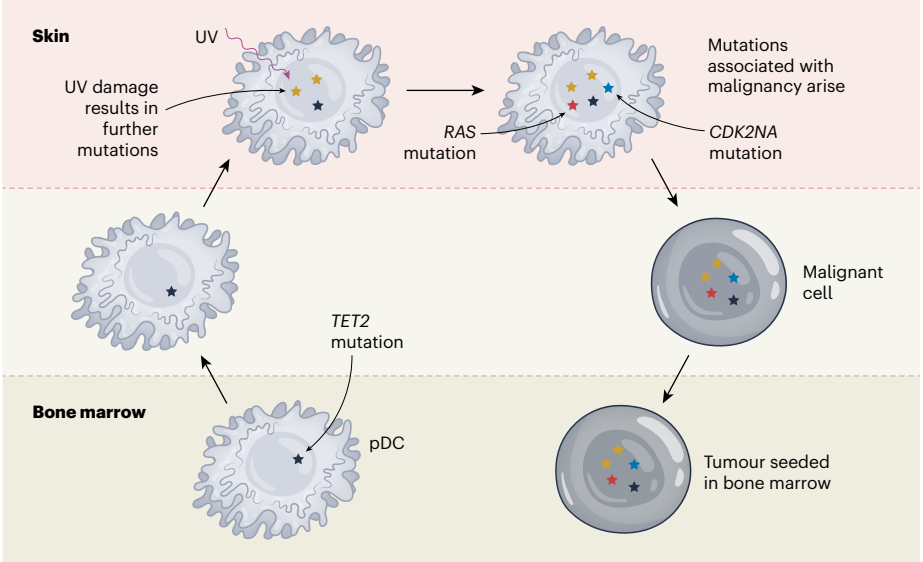

Figure 1 | Ultraviolet light shapes the development of a form of leukaemia. Griffin *et al.*[1] studied the patterns of mutational change found in people with a type of rare and aggressive blood cancer called blastic plasmacytoid dendritic cell neoplasm. This cancer can affect other organs, such as the skin. The authors report that premalignant cells migrate from the bone marrow to the skin. Immune cells implicated in this disease, called plasmacytoid dendritic cells (pDCs), often have a mutation in the gene *TET2*, which boosts survival after exposure to ultraviolet (UV) light. These cells move from the bone marrow to the skin, where exposure to UV light causes them to acquire UV-radiation-induced mutations. The cells subsequently acquire mutations that are associated with malignancy, such as those in the genes *CDK2NA* and *RAS*. Malignant cells can migrate back to the bone marrow, causing tumour spread to this distant site.

BPDCN. This observation probably explains, at least in part, why mutations in the *TET2* pathway are associated with BPDCN.

The authors' findings demonstrate how tissue-specific environmental pressures can drive the evolution of premalignant clones to form a cancer that can affect local (such as skin) and distant (bone marrow) sites. The Darwinian model of cancer evolution is in itself complex and branching in this study across anatomical sites. As evidence grows for the pervasive nature of somatic mosaicism, further investigation is warranted into the interplay between inherited mutations, somatic mosaicism, factors that shape cell survival and, as highlighted by Griffin *et al.*, the role of organ-specific mutations involved in the evolution of disorders arising from clonal-cell lineages.

Given the rise in technologies that can gather data from single cells, it is increasingly possible to find ways of linking diverse measurements of tumour growth. Careful study design, together with the collection of biological samples and the development of disease models representing each stage of disease evolution, could deepen our understanding of cancer initiation and progression, and also guide the development of surveillance and interception strategies that target the key factors of malignant transformation.

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Organic chemistry

Strain equals gain for organic synthesis

Fahima I. M. Idiris & Christopher R. Jones

Energy released from molecules under strain can promote difficult chemical reactions. A practical method has been developed that uses an overlooked, highly strained compound to rapidly construct complex organic products. **See p. 748**

Organic chemists continually strive to develop methods that enable the preparation of molecules that cannot currently be synthesized, or that allow synthesizable compounds to be made more efficiently. One approach to this is to find ways of promoting reactions that must overcome a large energy barrier to proceed. As with a child trying to scale a high wall to retrieve a ball from a neighbouring garden, there are different options for overcoming the barrier. One option is for the child to start from a point above ground level, such as a nearby tree, and then to drop down over the wall. In a chemical reaction, this equates to starting from a molecule that is much higher in energy than the desired products, and on page 748, Kelleghan *et al.*[1] report an ingenious form of this strategy. They use the high levels of energy stored in a rarely used type of strained organic molecule, known as a 1,2,3-cyclohexatriene, to drive reactions that enable complex chemical synthesis.

Organic compounds known as benzynes, cyclic alkynes and cyclic allenes (Fig. 1) contain a ring of carbon atoms that incorporates either a carbon–carbon triple bond (in the case of benzynes and cyclic alkynes) or two consecutive double bonds (in cyclic allenes). Such double- and triple-bonded systems preferentially adopt linear structures when unconstrained, but are forced to adopt bent structures when accommodated in a ring; the rings, in turn, are also distorted out of a regular arrangement by these bonded systems. The molecules are therefore strained and have high internal energies — much like a rubber quoit becomes strained when one side is pressed flat against a table. Such ring systems react swiftly with other molecules to release strain and generate lower-energy products. These reactions involve the formation of several bonds in a single step, which makes benzynes, cyclic alkynes and cyclic allenes valuable building blocks for the efficient synthesis

From the archive

The architect Christopher Wren uses his astronomy skills to assess an observatory proposal, and questions about cyclones.

100 years ago

"Tom Tower," Christ Church, Oxford. Some Letters of S' Christopher Wren to John Fell, Bishop of Oxford — This book was published in honour of the bicentenary of Wren's death ... [T]here are seven ... letters written by Wren ... [T]he sixth and most interesting one ... is a reply to a proposal on the part of the bishop, that the tower should be converted into an observatory. Wren is too polite to reject the proposal altogether, but gives good reasons why it should not be hastily adopted. It would involve a change in the whole design; the bell would have to be lowered so as to heighten the loft, and it might then not be well heard. The Gothic roof, agreeing with the rest of the College buildings, would have to be abandoned ... In addition to these objections from the point of view of an architect, Wren next produces others from the point of view of an astronomer, and here also he could speak with authority, having held the office of Savilian professor of astronomy for twelve years (1661–73) until pressure of other work obliged him to relinquish it ... Oxford did not get an observatory on this occasion (there were only two University Observatories in existence at that time, at Copenhagen and at Leyden), and nearly a hundred years had to pass, before the Radcliffe Observatory was built.
From *Nature* 23 June 1923

150 years ago

We have now reached a point where we can properly and intelligently consider a question that has always baffled meteorologists — the origin of cyclones. The diagnosis of the phenomenon necessarily precedes its explanation. This subject has engrossed many minds, and various have been the ingenious devices for unravelling its mystery. Mr Redfield — the father of storm physics — in his modesty and diffidence ... so keenly felt the need of a more enlarged induction of facts, that he has scarcely left us his opinion.
From *Nature* 19 June 1873