

**Figure 1 | Roughness on a simulated gold surface.** Hinkle *et al.*<sup>1</sup> carried out molecular-dynamics simulations of tens of millions of atoms in smooth blocks of three materials, including gold (shown here), and observed how surface roughness develops when the blocks are compressed. Colours represent atomic positions perpendicular to the surface, measured relative to the surface's mean height: red indicates high topography; blue, low. The highest features are 8.8 nanometres above the lowest point on the surface. The authors found that roughness emerges that is similar across nearly two orders of magnitude of length scales. Similar triangular features and variation of topography are visible in **a** (a region 80 nm across) and **b** (a region of **a** expanded to four times its original size). The same is also true at magnifications of 8 and 64 (not shown).

simulation 'box', which was approximately 70–100 nm; Fig. 1).

In addition to simulating millions of atoms, the authors simulated a continuum model of compressive deformation in which the material is not treated as being composed of individual atoms, but as a continuous medium. In these simulations, there is no sign of self-affine roughness. The authors therefore conclude that the development of self-affine roughness is related to atomic-scale fluctuations in plastic flow that are missing from the continuum model.

Hinkle and colleagues' results are convincing across the observed length scales, but the scaling behaviour of the roughness will need to be demonstrated across three orders of magnitude to confirm that it truly obeys a power law. This will require the atomic simulations to be extended to even larger scales. Modelling techniques (see ref. 3, for example) are available at mesoscale lengths (which range from a few nanometres to several hundred micrometres), and provide a link between atomistic and continuum simulations. These approaches take flow into account in more detail than does the continuum model used by Hinkle *et al.*, and would allow for increased atomistic detail and fluctuations in simulations. This could help to provide the extra order of magnitude needed to convincingly show the power-law statistics of the roughness.

It remains to be seen how universal the reported behaviour is. All of the materials investigated by Hinkle and co-workers are based on metals. After undergoing plastic deformation, they are all homogeneous (there is only one type of solid phase in the material) but disordered, and the dynamics and energy

scales involved in atom displacement are all comparable. It would be interesting to see whether similar scaling behaviour emerges from the compression of other types of material that have different mechanisms of plasticity and deformation, such as polymers. If so, are the scaling exponents – the key scaling parameters in the power-law equation – the same for all materials? If roughness profiles can be extended to include one or more extra orders of magnitude, it would enable a reliable comparison of the scaling exponents.

## Cancer

# Loss of p53 protein strikes a nerve for tumour growth

Marco Napoli & Elsa R. Flores

Tumours often grow entangled among neurons, which makes the cancer difficult to treat. The finding that cancer cells hijack neighbouring neurons to promote tumour growth suggests new therapeutic targets. **See p.449**

Malignant tumours are a complex, yet organized, diverse ensemble of cells. Tumour cells are surrounded by other types of cell, which collectively form the tumour microenvironment. Components of this microenvironment include fibroblast cells, which can promote the growth and spread of tumours to distant sites, and immune cells. The latter have antitumour functions that are often suppressed

This, in turn, would help to determine whether these exponents vary with strain, deformation mechanisms, or even time.

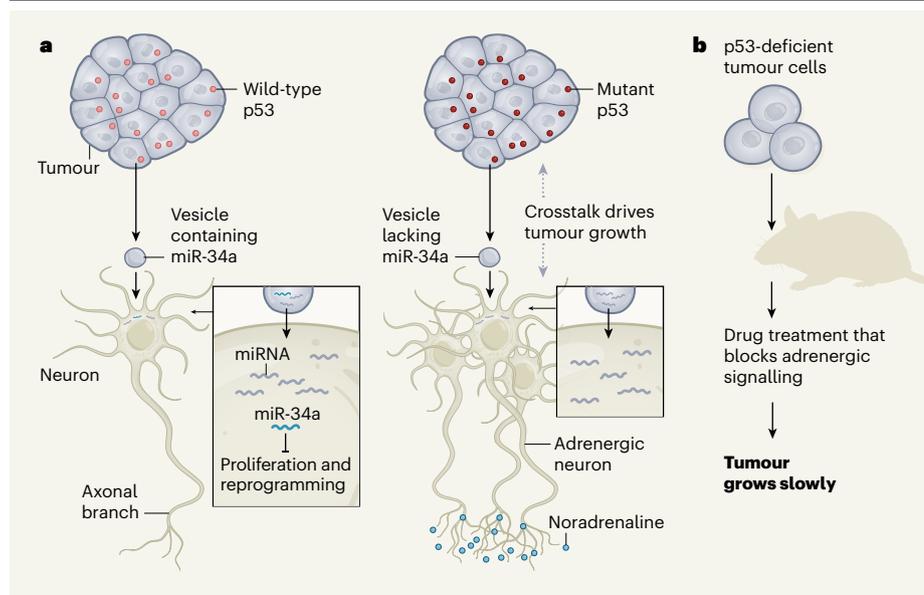
Power-law behaviour is common in plastic deformation. For example, 'avalanches' of plastic deformation occur in metals<sup>4</sup>, and in fibrous materials a power law describes the size distribution of avalanches when these materials deform plastically under tensile stress<sup>5</sup>. Given that Hinkle *et al.* simulate the formation of rough surfaces in response to plastic deformation, and also observe scale-free roughness in the bulk of the modelled materials, it seems likely that there is a link between the development of self-affine roughness and the power-law behaviour of plastic deformation events – as the authors also note. It would therefore now be interesting to study the emergence of roughness in a more dynamic way, by investigating the formation of roughness features during compression, and relating the changes in the surface profile to plastic events.

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by cancer cells; indeed, therapies that boost such immune cells are revolutionizing the treatment of certain cancers. By contrast, the interactions between cancer cells and neurons in the tumour microenvironment are less well understood. On page 449, Amit *et al.*<sup>1</sup> reveal how tumours influence neurons to promote tumour growth, and show how this discovery might lead to new anticancer therapies.



**Figure 1 | Tumours manipulate neighbouring neurons to boost cancer growth.** Amit *et al.*<sup>1</sup> analysed head and neck cancers using clinical data and mouse models. **a**, Tumour cells that expressed wild-type p53 protein released vesicles containing small RNA molecules called microRNAs (miRNAs) that were taken up by neighbouring neurons. An miRNA known as miR-34a blocks neuronal proliferation, and the neurons were maintained in their current state. By contrast, tumours that had a mutant version of p53 released vesicles that lacked miR-34a. In this case, neurons increased in number in the vicinity of the tumour, and these cells were reprogrammed as adrenergic neurons that express the molecule noradrenaline. These neurons had more axonal branches than did those near tumours that expressed wild-type p53. Interactions between adrenergic neurons and the tumour aided cancer growth. **b**, When mice received a transplant of p53-deficient tumour cells, treatment with a drug (carvedilol) that blocks adrenergic signalling pathways slowed tumour growth. This might provide a new therapeutic tool for targeting tumours that need neighbouring adrenergic neurons for their growth.

The interplay between cancer and neurons has negative clinical consequences for people with prostate tumours<sup>2</sup>. Individuals who have a higher number of new neurons (in structures called nerve fibres) in the tumour microenvironment tend to have more-aggressive tumour features, such as further tumour growth and migration to distant sites, and a decrease in survival time<sup>2</sup>.

Studies last year found that cancer cells and neurons can interact directly with each other through connections called synapses, that these connections aid the growth of brain tumours<sup>3–5</sup> called gliomas, and that this interaction is associated with lethal cancer spread<sup>5</sup>. These and other findings<sup>3–6</sup> contribute to a growing body of evidence that neurons are crucial components of the tumour microenvironment. However, what prompts the formation of neurons in the microenvironment had not been understood until now.

Amit and colleagues took on this challenge by focusing on tumours known as head and neck cancers, which can arise in the oral cavity. In humans, these tumours are often characterized by mutations that inactivate the gene *TP53*. This gene encodes a protein (p53) that functions as a tumour suppressor and that can modulate the tumour microenvironment<sup>7</sup>. By analysing four different mouse models of this

disease and data obtained from biopsies of people with head and neck cancer, the authors found that tumours with mutant versions of p53 have a higher number of associated newly formed neurons than do those with wild-type p53. Moreover, an increased number of such neurons correlated with a shorter survival time.

To try to determine whether cancer cells with mutant p53 might stimulate neurons to form, Amit *et al.* analysed the factors released

**“The authors’ findings might have repercussions that reach beyond the field of cancer research.”**

by human cancer cells that have mutant or wild-type p53. Both types of cell secreted vesicles that contained small RNA molecules called microRNAs (miRNAs). The vesicles in the two cell types were of a comparable number and size, but their contents differed (Fig. 1). Only the vesicles secreted from tumours with mutant p53 were devoid of an miRNA termed miR-34a, which is a tumour suppressor. When vesicles from tumours lacking p53 were injected into mice with tumours that had wild-type p53, the tumours with wild-type

p53 grew larger and had more surrounding neurons than normal, indicating that the contents of these vesicles drive the formation of new neurons. This is the first report showing that miR-34a, the main function of which is to keep in check the proliferation of normal and cancer cells<sup>8</sup>, is important in counteracting the formation of neurons in the tumour microenvironment.

Amit and colleagues analysed how these newly formed neurons promote tumour growth. The authors examined the neurons present in tumours with mutant and wild-type p53. Intriguingly, in the former set, the neurons (presumably including those already present in the area where the tumour formed) had undergone a functional change to become a type of neuron known as an adrenergic neuron – which uses the adrenergic signalling pathway and is activated in the ‘fight-or-flight’ response. This adrenergic feature (which has hallmarks including expression of the molecule noradrenaline) was crucial for sustaining cancer growth.

Interestingly, previous epidemiological analysis<sup>9</sup> revealed that the use of the drug carvedilol, which blocks adrenergic signalling and is prescribed for conditions such as high blood pressure, is associated with a reduced risk of cancer onset. Now, Amit *et al.* raise the question of whether carvedilol’s anticancer properties might be due to its ability to target adrenergic neurons, given the effectiveness of the drug in treating mice with p53-deficient tumours (Fig. 1). The authors’ findings are of particular interest because these insights might offer a way to combat the tumour-driven formation of adrenergic neurons and to counteract their tumour-promoting effects. It will be important to establish whether adrenergic neurons’ contribution to tumour growth is limited to just head and neck cancers that have mutant p53, or whether this phenomenon could also be a feature of other types of tumour, as suggested by the epidemiological evidence for carvedilol use<sup>9</sup>.

Mutant versions of the gene encoding p53 are among the most common alterations in certain human cancers, occurring in approximately 60% of colon cancers, 50–80% of lung cancers and 95% of ovarian tumours<sup>10</sup>. Given the high prevalence of p53 abnormalities in cancer, numerous efforts have been made to design compounds that target mutant p53 to force it to act like wild-type p53, and promising results have been obtained in early-phase clinical trials of such drugs<sup>11</sup>. It would be worth testing whether using both carvedilol and a drug that targets mutant p53 is more effective than either compound alone in treating these lethal forms of cancer.

Amit and colleagues’ discovery that the absence of functional p53 influences the formation of neighbouring neurons might have relevance for interpreting reports showing

that fluctuations in the levels of wild-type p53 are observed in nerve regeneration<sup>12</sup>. Thus, the authors' findings might have repercussions that reach beyond the field of cancer research to regenerative medicine. Perhaps therapies that modulate the activity of p53 will have a future role in aiding the repair or regeneration of neurons, an outcome that would make a profound difference to the lives of people who have neurodegenerative diseases or other types of nerve injury.

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## Atomic physics

# Fundamental symmetry tested using antihydrogen

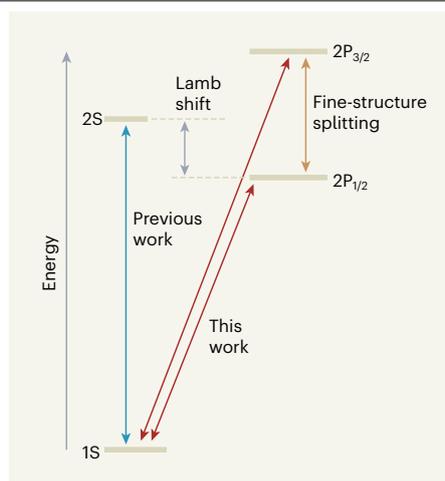
Randolf Pohl

The breaking of a property of nature called charge–parity–time symmetry might explain the observed lack of antimatter in the Universe. Scientists have now hunted for such symmetry breaking using the antimatter atom antihydrogen. **See p.375**

One of the greatest mysteries in modern physics is why the Universe seems to contain mostly matter and almost no antimatter. This observation could be explained if a property of nature called charge–parity–time (CPT) symmetry is violated. Under CPT symmetry, the physics of particles and their antiparticles is identical. A tiny violation of CPT symmetry during the Big Bang could, in principle, be responsible for the lack of antiparticles in the Universe. On page 375, the ALPHA Collaboration<sup>1</sup> reports high-precision spectroscopic measurements of antihydrogen – an atom comprising an antiproton and a positron (the antiparticle of an electron). The authors find that the gaps between energy levels in antihydrogen are in excellent agreement with those measured previously in ordinary hydrogen<sup>2–4</sup>, placing strong constraints on potential CPT violation.

Tests of CPT symmetry using individual particles – such as neutral kaons<sup>5</sup>, positrons<sup>6</sup> and antiprotons<sup>7,8</sup> – have shown no sign of CPT violation. However, studies of antihydrogen might probe the influence of factors that were not explored in previous tests.

Hydrogen is the simplest atom, and its properties can be calculated with impressive precision. For more than a century, the study of this atom has been the driving force behind groundbreaking ideas about the structure of matter. The optical spectrum of hydrogen was



**Figure 1 | Lowest-energy states of antihydrogen.**

The ALPHA Collaboration<sup>1</sup> carried out high-precision spectroscopic measurements of antihydrogen – the antimatter counterpart of hydrogen. Specifically, the team determined the energy differences between the 1S ground state and the 2P<sub>1/2</sub> and 2P<sub>3/2</sub> excited states of antihydrogen. They used these results to estimate the fine-structure splitting (the 2P<sub>1/2</sub>–2P<sub>3/2</sub> energy gap). They also combined their previous determination<sup>11</sup> of the energy gap between the 1S and 2S states with their current measurement of the 1S–2P<sub>1/2</sub> energy difference to infer the Lamb shift (the 2S–2P<sub>1/2</sub> energy gap). The authors found that all of these results are in agreement with the corresponding ones for ordinary hydrogen. (Drawing not to scale.)

measured with great accuracy in the 1880s, before being quantitatively explained in the 1910s. The structure of the atom was then at the heart of the formulation of quantum mechanics and in the generalization of this theory to relativistic (fast-moving) particles in the 1920s. And it was the unexpected discovery<sup>9</sup> of an energy gap between the 2S and 2P<sub>1/2</sub> excited states of hydrogen by the physicist Willis Lamb in 1947 that motivated the development of quantum electrodynamics – the theory that describes the interactions between particles and light.

This energy gap, known as the Lamb shift, exists in both hydrogen and antihydrogen. It originates mostly from quantum fluctuations, whereby particle–antiparticle pairs spontaneously emerge in empty space and then instantly annihilate each other. However, its magnitude is subtly affected by, for example, the charge radius (the spatial extent of the charge distribution) of the proton or antiproton, the weak nuclear force and, potentially, currently unknown phenomena that could be the source of the matter–antimatter asymmetry in the Universe.

The current work was carried out using the ALPHA experiment at CERN, Europe's particle-physics laboratory near Geneva, Switzerland. A facility called the Antiproton Decelerator delivers antiprotons to this experiment, with a source of radioactive sodium providing positrons. Every few minutes, 90,000 cold trapped antiprotons and 3 million positrons are mixed in a sophisticated charged-particle trap. This process yields about 20 cold antihydrogen atoms that are then confined to a neutral-atom trap made from superconducting magnets. These antihydrogen atoms can be stored<sup>10</sup> for at least 60 hours, and production cycles can be repeated to obtain hundreds of such atoms.

The aim of the present study was to measure the energy differences between the 1S ground state and the 2P<sub>1/2</sub> and 2P<sub>3/2</sub> excited states of antihydrogen (Fig. 1). The ALPHA Collaboration used an approach called laser spectroscopy, which involved injecting pulses of laser light into the antihydrogen trap. This injection caused atoms to transition from the 1S state to the 2P<sub>1/2</sub> or 2P<sub>3/2</sub> state and to subsequently decay back to the 1S state. Atoms that ended up in a different magnetic substate of the 1S state from the one in which they started were expelled from the magnetic neutral-atom trap. These antihydrogen atoms then annihilated on contact with regular atoms in the walls of the ALPHA apparatus to produce particles called charged pions.

The ALPHA Collaboration plotted the number of observed charged pions as a function of the frequency of the laser light. They then used the positions of the two peaks in these plots to infer the 1S–2P<sub>1/2</sub> and 1S–2P<sub>3/2</sub> energy differences in antihydrogen.