computers[6], in which trapped ions must be held nearly stationary before they can be manipulated with lasers to store quantum bits of information.

Metastable antiprotonic helium atoms, in which one of the two electrons of a helium atom has been replaced by an antiproton, have been slowed down simply by immersing them in a gas of colder matter[7]. But this approach would not be practical for antihydrogen atoms because they would immediately annihilate in a matter–antimatter reaction. By contrast, a beam of light can exert a mechanical force on both matter[8–13] and antimatter, without causing the latter to annihilate. A handheld red or green laser pointer typically emits between 10^{15} and 10^{16} laser photons per second, but the momentum that each photon can impart is so minuscule that it is hard to detect the pressure exerted by this light on everyday objects. The mass of a single antihydrogen atom, however, is so small (1.7×10^{-24} grams) that its velocity can be changed by about 12 kilometres per hour each time it absorbs a laser photon that has an ultraviolet wavelength of 121.6 nanometres.

In their current study, Baker *et al.* used a laser carefully tuned to a wavelength that causes only trapped antihydrogen atoms that move towards the laser to absorb photons and slow down (Fig. 1). The absorption selectivity arose from a type of Doppler effect[8,9] experienced by the atoms — an effect that caused the light of the laser beam to seem to shift towards shorter wavelengths. The shifted wavelength exactly matched the photon energy needed to be absorbed by the atoms, and this absorption promoted the atoms from their ground state to an excited state. The atoms then spontaneously returned to the ground state by emitting another photon in a random direction. The authors observed that a few dozen such absorptions slowed down a fraction of the atoms in the sample to below 50 kilometres per hour. This reduction in speed corresponds to a cooling of the atoms.

Conversely, the atoms that moved away from the laser experienced the opposite Doppler effect: the wavelength of the light apparently shifted further away from that needed for photon absorption. The light therefore passed right through the receding atoms, thus avoiding their undesirable acceleration. Once the antihydrogen atoms had been properly cooled, the authors irradiated them with a pair of counter-propagating laser beams to excite a characteristic atomic transition. Because of the low velocity of the atoms, the line that corresponds to this transition in the atomic spectrum was four times sharper than had been observed for atoms without laser cooling. This will allow researchers to carry out future comparisons of the characteristic atomic transitions of hydrogen and antihydrogen at a higher precision than was previously possible.

One limitation of the reported method is that it is difficult to generate 121.6-nm laser light of sufficient intensity to cool the antihydrogen atoms efficiently. Baker and colleagues used a train of laser pulses of nanowatt-scale average power, which meant that many hours were required for each atom to absorb the dozens of photons needed for substantial cooling. The authors plan to increase the laser power in future experiments to speed up the process. Another approach might be to use continuous, rather than pulsed, laser beams[14].

Finally, because laser cooling leads to a greater concentration of slower atoms at the magnetic-field minimum of the neutral atom trap, it might allow denser clouds of antihydrogen to be produced than is currently possible. This would further improve the precision of measurements in future experiments.

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Cancer immunology

Bacterial peptides reveal tumours to T cells

Angelika B. Riemer

Protein fragments from bacteria that invade tumour cells can be presented on the tumour-cell surface and recognized by the immune system. This discovery could have implications for cancer immunotherapies. **See p.138**

Human tumours are colonized by microorganisms[1], collectively called the tumour microbiota, that can affect the microenvironment of the tumour — for example, by causing inflammation or local immune suppression[2]. This can lead to changes in how the body's immune system responds to the tumour, and can alter responses to therapy[3]. But are intratumoral bacteria themselves recognized by the immune system? Kalaora *et al.*[4] show on page 138 that bacterial protein fragments called peptides are presented to the immune system on the surface of tumour cells, and are recognized by immune cells called T cells. This discovery might be exploited for cancer immunotherapeutics.

Molecules called tumour antigens enable the immune system to differentiate tumour cells from healthy cells. Every cell contains antigen-processing machinery, which enables antigen-derived peptides to be presented to the immune system by specialized molecules called human leukocyte antigens (HLAs) on the cell surface. HLA-presented peptides that are recognized by immune cells are called epitopes.

Tumour antigens come in two main categories: tumour-associated and tumour-specific[5]. Tumour-associated antigens are expressed in normal tissues as well as in tumours, and so do not readily activate immune responses. But if immune responses are mounted, there is a risk of harmful autoimmune reactions against the normal tissues that express the antigen. Nonetheless, because tumour-associated antigens are often found in multiple types of tumour and in many people who have cancer, they can be good targets for broadly applicable immunotherapies. By contrast, tumour-specific antigens are expressed solely on tumour cells and so are ideal targets for mounting a specific immune attack against tumours. One subtype, neoantigens, arises from tumour-specific gene mutations, and so neoantigens are typically tumour- and patient-specific. Targeting neoantigen-derived peptides (called neoepitopes) therefore necessitates truly personalized immunotherapies.

A skin cancer called melanoma has three known classes of tumour-associated antigen, and its cells typically carry many genetic mutations, resulting in a high likelihood of neoantigens[6]. It has therefore been at the

forefront of tumour-antigen discovery and cancer-immunotherapy development[7–9]. It is thus fitting that Kalaora *et al.* use melanoma samples to describe another potential class of tumour antigen.

The authors set out to investigate the bacterial composition of 17 melanoma metastases (tumours formed when a cancer spreads from its original site to other regions of the body) from 9 people. They found that the composition of bacteria was highly similar in different metastases from the same individual, and sometimes in samples from different people. This finding indicates that particular bacterial species are common to melanoma, in line with a previous study reporting tumour microbiota specific to different types of cancer[1]. The authors also confirmed that these bacteria were present in melanoma cells, rather than in the surrounding extracellular microenvironment.

Kalaora and colleagues went on to investigate whether peptides from these intracellular bacteria are presented to the immune system in the same way as are other intracellular antigens. To this end, they used an approach based on mass spectrometry called immunopeptidomics, which allows direct detection of HLA-presented peptides. They found close to 300 peptides in their samples, from 33 bacterial species. Several peptides were found in more than one tumour from the same person and in tumours from different people.

The authors next asked whether the bacterial peptides are truly presented by melanoma cells, rather than by immune cells called antigen-presenting cells (APCs) that detect, take up and present pathogens to other cells of the immune system. The authors used an immune-cell marker protein to separate cells from two melanoma samples into APCs and tumour cells. Immunopeptidomics revealed that both groups of cell presented bacterial peptides. A subset of the peptides was presented by both APCs and tumour cells, indicating that the same peptide can both initiate an immune response through presentation on APCs and be a target for immune attack on tumour cells. The researchers then showed that T cells (which recognize HLA-presented peptides) isolated from the melanomas reacted to the identified bacterial peptides, including some of the peptides shared between tumours and individuals.

Taken together, Kalaora and colleagues' results point to the possibility that tumour-displayed bacterial peptides are a previously unidentified class of tumour antigen (Fig. 1). However, several questions remain. To be bona fide tumour antigens, the identified bacterial species should not invade non-tumour tissue and their peptides should not be presented on HLAs on non-tumour cells. If this presentation were detected, the peptides would not qualify as immunotherapy targets. In addition, the bacterial peptides seem to be quite abundant (at least, compared with the numbers of identified melanoma neoepitopes[7]), so why does the body not mount an effective immune response against melanomas? Further studies of tumour-displayed bacterial peptides in combination with patient information will be needed to elucidate the potential clinical role of the peptides. Such data might help researchers to select suitable bacterial targets for cancer-immunotherapy approaches.

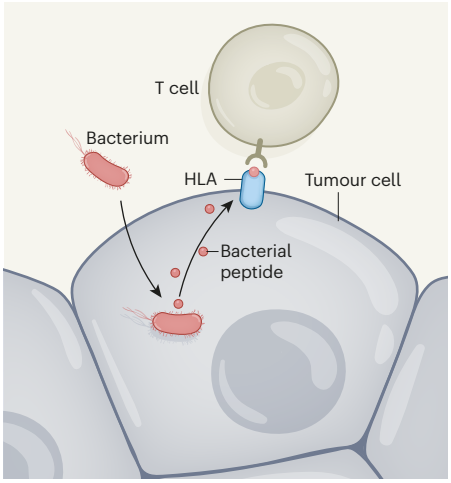

Figure 1 | A route to antitumour immunity triggered by bacteria. Kalaora *et al.*[4] report that certain bacteria can invade cells from a type of tumour called melanoma. Peptide fragments from bacterium-derived molecules are presented on the tumour cell surface by proteins called human leukocyte antigens (HLAs). Immune cells called T cells recognize and are activated against these presented peptides. Thus, bacterial peptides might be a previously unidentified class of tumour antigen – a type of molecule that enables T cells to distinguish tumour cells from normal tissue.

In conclusion, the bacterial peptides identified by Kalaora *et al.* could be attractive targets for immunotherapy. As bacterial peptides are 'non-self', it should be comparatively easy to elicit strong immune responses against them, and there would be no concerns about autoimmunity if it could be ascertained that they are not presented on any normal tissue. Thus, tumour-displayed bacterial peptides could serve as tumour-specific antigens shared between people – a rare and useful combination for therapeutics, so far seen only in virally induced tumours, in which epitopes can be derived from viral cancer-causing proteins[5]. Recent data indicate that tumour-invading bacteria might be a common phenomenon[1,2]. Kalaora and colleagues' work could therefore lay the foundation for identifying shared tumour-specific antigens in a wide range of tumour types.

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Microbiology

Gut microbes regroup to aid defence after infection

Melissa M. Kendall & Vanessa Sperandio

Resident gut microbes can help to block infection, but the mechanisms involved are not fully understood. It has now been found that changes in the microbial community after infection boost the level of a molecule that combats harmful bacteria.

Complex interactions between a mammalian host and its intestinal microbiota (the community of microorganisms that reside in the small and large intestines) influence host health and disease susceptibility. A major challenge in delving into the mechanistic relationships driving such interactions is the high diversity of species in the microbiota, which gives rise to a microbial profile that is unique to each individual[1], much as a fingerprint is. There is a growing appreciation that the gut microbiota is implicated in generating resistance to gut colonization by disease-causing microorganisms (pathogens). However, many