McCauley and colleagues' findings also raise the exciting possibility that pharmacologically inhibiting STING could decrease the risk of autoimmunity in people who have ALS. Indeed, small-molecule inhibitors of STING have been developed, and seem safe and effective in preclinical models of autoinflammatory disease[12].

With many studies suggesting that toxic RNAs or proteins are produced by the *C9orf72* repeat expansion, considerable work has focused on reducing the levels of these products. For instance, antisense oligonucleotides (short nucleic acids that bind to RNAs containing the *C9orf72* repeat and trigger their degradation) have shown promising results in preclinical studies[7,13]. A clinical trial of one such molecule is under way in people who have ALS (see go.nature.com/3g0cpat). If the trial is successful, it will be exciting to see whether boosting levels of normal C9orf72 or mitigating the effects of reduced C9orf72 function — perhaps by targeting the STING pathway — will have added benefits.

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Atomic physics

The deuteron weighs in

Jeroen C. J. Koelemeij

Contradictory values for the masses of atomic nuclei have cast doubt on the reliability of these widely used quantities. A new mass measurement of the deuteron, the second-simplest atomic nucleus, clarifies the situation. **See p.43**

Precise values for the masses of the nuclei of the simplest atoms, such as hydrogen and helium, are crucial for experiments targeting big unsolved problems in physics. A technique known as Penning-trap mass spectrometry has produced some of the most precise nuclear-mass values obtained so far, but the various results do not seem to be consistent with each other. On page 43, Rau *et al.*[1] report an astonishingly precise measurement of the mass of the deuteron — the nucleus of a hydrogen isotope called deuterium. Remarkably, this result also deviates widely from previous values. The authors therefore carried out a clever auxiliary measurement revealing that their findings back up those parts of the 'nuclear-mass puzzle' that initially seemed to be discrepant.

The mass values for atomic nuclei represent a rich source of information for research in physics and chemistry. For example, atoms can bind together to form molecules, and when they do, their bonds resemble vibrating springs rather than stiff rods (Fig. 1a). Molecular vibrations drive biological processes in cells and define properties of solids, but the frequencies of these vibrations ultimately depend on the masses of the atomic nuclei.

Nuclear masses also provide information through Einstein's famous energy–mass relationship, $E = mc^2$, where c is the speed of light in a vacuum. Some nuclei are radioactive, meaning that they will decay into a lighter atomic nucleus while producing a few lightweight (and highly energetic) elementary particles, such as electrons and the ghostly neutrinos. If the mass difference between the parent and daughter nuclei, Δm, is precisely known, the total energy and mass available for the elementary particles produced can be predicted by computing Δmc^2. This principle underpins experiments aimed at answering one of today's biggest questions in physics[2]: what is the mass of the elusive neutrino?

Clearly, precise nuclear-mass values are useful, but how can they be measured? An atomic nucleus is a charged particle, which implies that its motional path can be deflected by a magnetic field. An extreme version of this principle forms the basis of devices known as Penning traps, as used by Rau and colleagues. A Penning trap consists of an extremely strong magnet, which can capture a single deuteron in perpetual orbital motion, together with a vacuum chamber containing a stack of ring-shaped electrodes, all placed inside the magnetic field generated by the magnet.

The measurement principle makes use of tiny alternating currents, called image currents, that are induced at the inner surfaces of the electrodes by the charge of the moving deuteron. From these image currents, the orbital frequency of the deuteron is determined, which scales inversely with its mass. Next, the deuteron is replaced with a carbon nucleus, the orbital frequency of which is also measured. The key step now involves taking the ratio of the two measured frequencies so that the common magnetic-field dependence cancels out. The deuteron mass, m_d, is then found in atomic mass units, where one atomic mass unit is defined as one-twelfth the mass of the carbon atom.

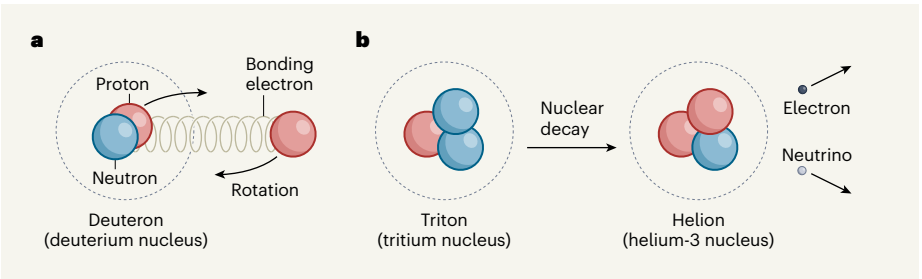

Figure 1 | The importance of nuclear masses for physics research. a, The rotating molecule HD^+ comprises a deuteron — the nucleus of a hydrogen isotope called deuterium — and a proton. These two particles are bound by an electron, which acts like a vibrating spring. The rotational and vibrational frequencies of HD^+ reflect the deuteron and proton masses, as well as fundamental laws of physics[7,8]. But the interpretation of these laws has been hampered by inconsistent mass measurements. **b**, A triton (the nucleus of a hydrogen isotope known as tritium) decays into a helion (the nucleus of a helium-3 atom), an electron and an elementary particle called a neutrino. The unknown neutrino mass could, in principle, be determined from the energy of the decay products[2]. However, doubt could be cast on the outcome of this approach if the helion mass is not known precisely — and measurements of the helion mass have been contradictory[6]. Rau *et al.*[1] have obtained ultraprecise measurements of the deuteron and HD^+ masses that will help to resolve these issues.

In previous such mass measurements, the precision was limited by deviations of the magnetic field from its ideal form, resulting in imperfect magnetic-field cancellation. Rau *et al.* therefore used an adjustable superconducting electromagnetic coil to measure these deviations and suppress them by a factor of 100. This suppression enabled m_d to be determined at a remarkable precision of eight parts per trillion (p.p.t.), making it the most precisely known particle mass so far. However, the deuteron mass measured by Rau and colleagues is smaller than the previous state-of-the-art value of m_d by about 100 p.p.t. – five times its specified precision[3] of 20 p.p.t. This situation is reminiscent of similar large discrepancies in observed values of the proton mass[4,5], m_p, and the mass of the helium-3 nucleus, also known as the helion[6], m_h.

This unfolding nuclear-mass puzzle seriously hinders experiments at the forefront of physics and chemistry. For example, the simplest molecules in nature are the molecular hydrogen ions H_2^+ and HD^+ (a proton and a deuteron, bound by an electron). Studies of these ions attempt to verify whether quantum electrodynamics – a theory that has been extremely successful at explaining the behaviour of particles and atoms – is also valid for molecules. However, the precision of this theory's predictions of rotational and vibrational frequencies of molecular hydrogen ions is severely hampered by the observed mass discrepancies[7,8]. Likewise, the contradictory mass values could impair the outcome of an experiment to determine the neutrino mass by studying the nuclear decay of tritium[2], a radioactive isotope of hydrogen (Fig. 1b).

To remedy this situation, Rau and colleagues also measured the mass of the HD^+ ion using their Penning-trap set-up. From this measurement, the authors extracted the value of the sum $m_p + m_d$, and found it to be in excellent agreement with their values of m_p and m_d obtained from single protons[4,5] and deuterons, respectively. In addition, all the results were consistent with a recent and precise measurement of the deuteron–proton mass ratio[9], m_d/m_p, as well as with experimental results from rotational[7] and vibrational[8] spectroscopy of HD^+. These successful consistency checks suggest that the authors' precise value of m_p and the current value of m_d, both of which might have seemed discrepant at first, are reliable, after all.

Despite Rau and colleagues' major advance, one piece of the mass puzzle still stands. Multiple ways of determining the mass difference $m_p + m_d - m_h$ have produced inconsistent results depending on whether the newer mass values or older reference values are used. The authors' work suggests that the mass of the helion, m_h, might be the source of this remaining inconsistency, and it provides strong motivation for new mass measurements of this particle. But perhaps the most valuable lesson to be learnt from this work is that, in the art of precision measurement, no result stands completely on its own.

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Tumour biology

Cancer cells stock up in lymph vessels to survive

Barbara M. Grüner & Sarah-Maria Fendt

A cellular condition called oxidative stress can kill cancer cells. The finding that skin cancer cells evade such destruction using lipids acquired while passing through lymphatic vessels reveals a mechanism that boosts cancer spread. **See p.113**

The spread of cancer to distant parts of the body, such as to a compartment of the lymphatic system called a lymph node, indicates a poor prognosis for many types of the disease. However, for certain tumours, such as the skin cancer melanoma, lymph-node removal to prevent this spread does not increase survival time[1,2]. This finding might be explained by observations suggesting that the lymphatic system (which helps to maintain fluid balance and provides immune cells with a route for their movement) supplies vessels that offer an entry point through which spreading cancer cells can reach blood vessels[3,4] on their way to distant organs. Once they have travelled there, the cancer cells seed and form secondary tumours called metastases. Thus, lymph-node infiltration is not necessarily an endpoint, but rather a stopover on the cells' journey elsewhere. Yet the advantage of this detour has been unclear. Ubellacker *et al.*[5] reveal on page 113 the boost that cancer cells receive in transit through the lymphatic system.

Cancer spread, or metastasis, is an inefficient process[6,7], and many cancer cells die in the bloodstream. A major contributory factor is oxidative stress in tumour cells. Studies have found that antioxidant treatment to block such stress causes an increase in the number of tumour cells in the bloodstream, and a rise in cancer spread to distant sites[8,9]. Oxidative stress can induce several types of cell death, but Ubellacker and colleagues show in mice that human or mouse melanoma cells in the bloodstream are killed by ferroptosis (Fig. 1), a cell-death mechanism that depends on lipid oxidation[10].

The authors report that pretreating melanoma cells with the ferroptosis-inhibitor molecule liproxstatin-1 resulted in more metastases when the cells were injected into the animals' bloodstream than when cells were not pretreated. By contrast, melanoma cells that disseminated through the lymphatic system produced the same degree of metastasis irrespective of liproxstatin-1 treatment, suggesting that such cells did not undergo ferroptosis. This finding indicates that, while in the lymphatic system, cancer cells acquire the ability to thwart a cell-death mechanism that usually impedes their progress if they move directly into the bloodstream. Moreover, Ubellacker *et al.* found that the number of melanoma cells in the animals' lymph fluid was higher than the number in the bloodstream, and that cells that disseminated through the lymphatic system were more likely to form metastases than were those that did not. This finding is remarkable, because it shows that only particular environments induce ferroptosis, and it suggests that melanoma cells that move through the lymph system and then exit into the bloodstream are more likely to survive than are cells that do not pass through the lymph.

Ferroptosis requires phospholipids in the cancer-cell membranes to be unsaturated (meaning that the molecules contain carbon–carbon double bonds that can be oxidized), and this type of cell death also requires iron[10].