Neurodegenerative disease

It's not all about those bases

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A mutation in the *C9orf72* gene is the most common genetic cause of two neurodegenerative diseases. A newly identified immunological function for the C9orf72 protein points to a potential therapeutic strategy for these diseases. **See p.96**

The most common genetic cause of two neurodegenerative disorders, amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), is the mutation of a gene called *C9orf72* (ref. 1). The mutation involves expansion of a section of DNA in which six bases — four guanine bases followed by two cytosine — are repeated many times. Much research has focused on the hypothesis that this alteration produces rogue RNAs or proteins that are toxic to cells. However, the mutation also lowers the amount of normal C9orf72 protein, which might contribute to disease. On page 96, McCauley *et al.*[2] report a mechanism by which reduced C9orf72 function causes defects in the immune system. Their findings might explain why people with ALS and FTD who harbour the *C9orf72* mutation seem to be susceptible to autoimmune disorders[3].

There are several mouse strains that lack the C9orf72 protein. These mice do not develop ALS- or FTD-like traits, but instead exhibit enlarged spleens and lymph nodes, as well as other defects related to the immune system[4–7]. McCauley *et al.* hypothesized that these immune defects might be caused by loss of C9orf72 function in a subset of immune cells called myeloid cells. They confirmed this idea by generating a strain of mouse in which *C9orf72* is deleted in myeloid cells, but remains intact in other cells. These mice exhibited similar defects to those of the original C9orf72-deficient animals.

McCauley and colleagues went on to ask exactly how loss of *C9orf72* caused these immune defects. The authors measured RNA levels from immune cells of mice that completely lacked *C9orf72*. They found a striking increase in messenger RNAs encoding both type I interferon-β protein and interferon-stimulated genes (expression of which is activated by interferon proteins) in the mutant cells, compared with controls. Type I interferons are normally secreted in the body to help ward off infection by modifying the activity of the immune system. These findings therefore pinpoint the specific immune defect caused by loss of C9orf72 — an increased type I interferon response.

Next, McCauley *et al.* cultured immune cells from the bone marrow of wild-type and *C9orf72*-mutant mice and stimulated them with several known activators of the type I interferon response. Almost all of the molecules they tested elicited similar responses in both mutant and control cells. But one, cyclic GAMP (cGAMP), induced a hyperactive type I interferon response in the mutant cells. cGAMP is an activator of the cGAS–STING signalling pathway, which senses double-stranded DNA in the cell cytoplasm as part of the immune system's first line of defence against viral infection[8].

Why would loss of C9orf72 function result in increased STING protein activity? STING is normally degraded by a cellular process called autophagy[9], and the regulation of this process is one of the functions of C9orf72 (ref. 10). The researchers therefore reasoned that STING degradation might be impaired in the *C9orf72*-mutant immune cells (Fig. 1). In support of this idea, they showed that the breakdown of STING was delayed in the bone-marrow cells of *C9orf72* mutants, compared with those from wild-type animals.

These findings raise the possibility that reducing STING activity could eradicate the defects associated with C9orf72 deficiency. McCauley *et al.* inhibited STING activity in mice and cells lacking *C9orf72*, using drugs or by introducing a mutation in the gene that encodes STING. These approaches restored normal type I interferon responses and spleen sizes in the mutant mice. McCauley and colleagues' work therefore identifies STING as a potential therapeutic target.

Finally, the authors applied their findings to ALS in humans. When they performed RNA sequencing on cells from people with ALS who harbour *C9orf72* mutations, they again found an enhanced type I interferon signature. The researchers also showed that this response is, at least partly, mediated by STING, because treatment with a chemical STING inhibitor suppressed this enhanced interferon response. These findings might help to explain why *C9orf72* mutations are over-represented in the few people who have a combination of ALS and the autoimmune disorder multiple sclerosis, compared with the population of people with ALS as a whole[11].

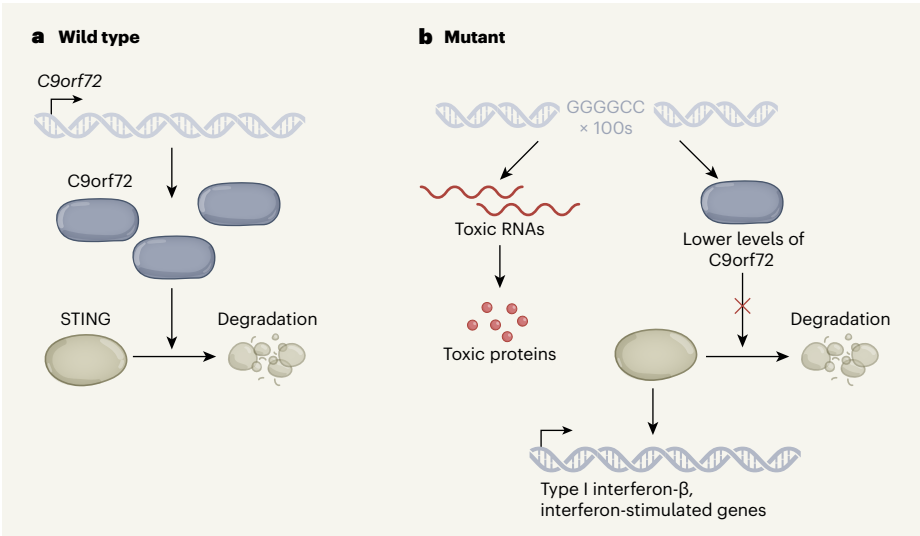

Figure 1 | How a neurodegenerative disease protein affects immune cells. a, McCauley *et al.*[2] show that the protein C9orf72 normally functions to promote degradation of another protein, STING, in immune cells called myeloid cells. **b**, Some neurodegenerative diseases are caused by a mutation in the *C9orf72* gene that involves abnormal repetition of a sequence of six bases (dubbed GGGGCC). The mutation produces potentially toxic RNAs and proteins, and reduces levels of C9orf72. The authors demonstrate that reduced C9orf72 levels delay STING degradation, leading to enhanced STING activity. STING promotes expression of the gene that encodes type I interferon-β protein, which activates interferon-stimulated genes that are involved in an immune response. Therapeutic strategies to inhibit STING might be effective against the immune-related abnormalities caused by *C9orf72* mutations (not shown).

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

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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.

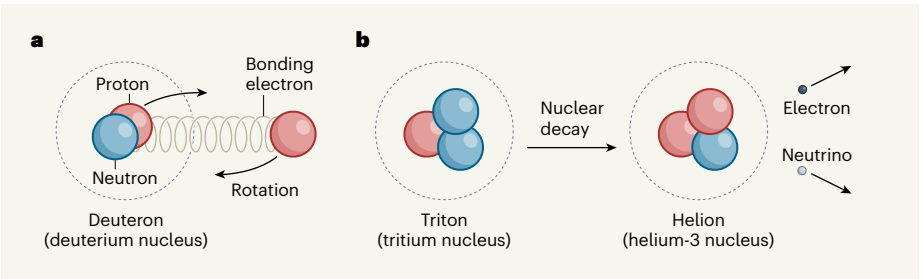

Figure 1 | The importance of nuclear masses for physics research. a, The rotating molecule HD^+ comprises a deuteron — the nucleus of a hydrogen isotope called deuterium — and a proton. These two particles are bound by an electron, which acts like a vibrating spring. The rotational and vibrational frequencies 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.