to enable recombination-based immune diversification might drive a type of chromosomal abnormality known as a chromosomal translocation, which could lead to cancer. Much like the DNA loops themselves, these insights into the role of chromosomal architecture might help to reveal connections between areas that were previously considered to be separate.

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High-energy physics

Link between antimatter and dark matter probed

Gianpaolo Carosi

Ultrasensitive experiments on trapped antiprotons provide a window onto possible differences between matter and antimatter. Now they could also shed light on the identity of dark matter — the 'missing' mass in the Universe. **See p.310**

Two of the most intriguing mysteries in modern cosmology are the apparent preponderance of ordinary matter over antimatter and the nature of dark matter, which accounts for about 85% of the mass in the Universe[1]. Dark matter has made its presence known only through its gravitational effects on astrophysical objects. Therefore, whatever type of particle it is made of must have feeble interactions with other matter. One leading candidate is the axion — a light neutral particle that was originally postulated to explain why the neutron lacks a measurable electric dipole moment[2]. Until now, researchers have looked for evidence of couplings between axion dark matter and only ordinary particles such as photons, electrons and nuclei[3,4]. On page 310, Smorra *et al.*[5] report a search for a coupling between axion dark matter and antimatter (specifically, antiprotons).

Every known particle can be classified as either a boson or a fermion. Bosons have integer spin (intrinsic angular momentum), and include the (spin-1) photon and the (spin-0) Higgs boson. By contrast, fermions have half-integer spin, and include the (spin-1/2) electron. The axion is expected to be a spin-0 boson that has odd parity, which means that its wavefunction changes sign if spatial coordinates are flipped.

Unlike fermionic dark matter (such as dark-matter candidates called weakly interacting massive particles, WIMPs), there is no limit to the number of axions that can exist in a certain volume of space. As a result, axion dark matter has an extremely wide range of potential masses. Astrophysical measurements place an upper limit[6] on the mass of about 10^{-2} electronvolts (eV). This value is expressed in units of energy, in which the electron mass is 511 kiloelectronvolts and the proton mass is 938 megaelectronvolts (see go.nature.com/2bwkrqz). And a lower limit[7] of about 10^{-22} eV comes from the fact that, when these particles are described as waves in quantum mechanics, their wavelengths cannot be larger than the size of a dwarf galaxy — otherwise, such galaxies would show deviations from their observed structure.

The particles associated with axion dark matter can be thought of as classical waves that have an oscillation frequency directly proportional to the axion mass. There are several techniques that can be used to look for such waves, and the most appropriate one depends mainly on the frequency range that is being considered. For axions that have masses below 10^{-17} eV (corresponding to a frequency of tens of millihertz), the waves oscillate extremely slowly. If antiprotons are held in the strong magnetic field of a device known as a Penning trap, these waves will produce changes in the frequency at which the spins of the antiprotons precess.

The Baryon Antibaryon Symmetry Experiment[8] (BASE) at the European particle-physics laboratory CERN near Geneva, Switzerland, uses this technique. The BASE collaboration relies on ultrasensitive Penning traps, which use specialized configurations of magnetic and electric fields to trap antiprotons in a high-vacuum environment. This set-up allows the antiprotons to be measured continuously for long periods of time, and to be shuttled back and forth between different measurement chambers without running into ordinary matter and being annihilated. One of the main

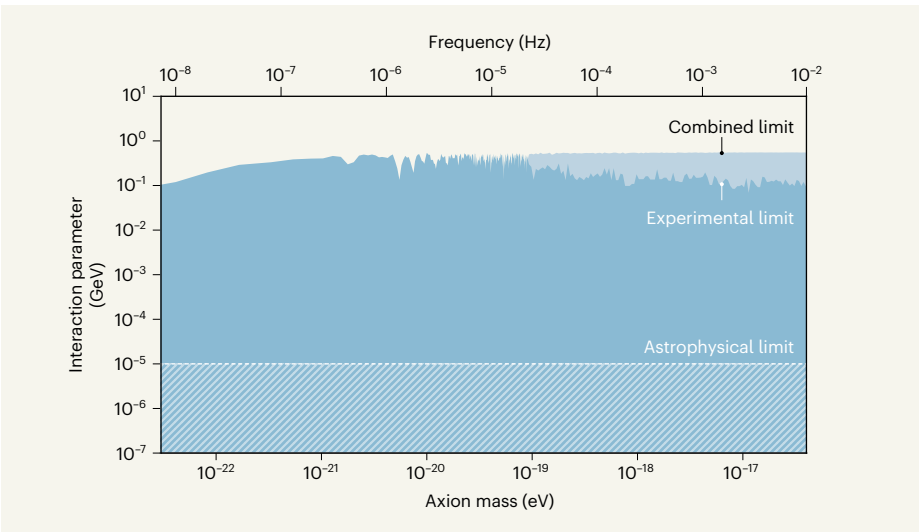

Figure 1 | Constraining axion–antiproton interactions. Particles called axions could account for the elusive dark matter that pervades the Universe. Smorra *et al.*[5] present experimental limits on the coupling between axion dark matter and antiprotons. These bounds are expressed in terms of an axion–antiproton interaction parameter and vary with the axion mass or the frequency of the axion if the particle is represented as a wave (eV, electronvolts; GeV, gigaelectronvolts; Hz, hertz). The combined limit represents the strongest constraint that could be set by the experimental data. An astrophysical limit, as estimated by the authors, is included for comparison. The coloured and hatched areas show the parameter space that is excluded.

goals of the collaboration is to determine the intrinsic magnetic moment of the antiproton. This quantity can be calculated to extremely high precision using the standard model of particle physics — the current explanation of the Universe's particles and forces.

In 2017, Smorra *et al.* made an ultraprecise measurement of the antiproton's magnetic moment (to one part in a billion)[9], constraining many theories of physics beyond the standard model. The key to their method was the simultaneous measurement of the spin precession and a quantity called the cyclotron frequency, which describes the cyclical motion of an antiproton in a trap. This task was challenging, because it required meticulous control of a device known as a magnetic bottle to non-destructively determine the spin state of the antiproton. The group's measurement required hundreds of experiments, each of which lasted for almost an hour, taking place over several months.

In the current paper, Smorra and colleagues, who include members of the BASE collaboration, analysed the data from these experiments. They proposed that waves corresponding to axion dark matter that oscillated at frequencies between 10^{-8} and 10^{-2} hertz would shift the spin-precession frequency in a small but measurable way if the axion coupling to antiprotons was sufficiently strong. Although no axion signal was detected, Smorra *et al.* constrained the parameter that quantifies axion–antiproton interactions to values greater than 0.1–0.6 gigaelectronvolts in the axion mass range from 2×10^{-23} eV to 4×10^{-17} eV (Fig. 1). These limits are as much as 10^5 times stronger than astrophysical constraints (as estimated by the authors), which consider how axions might have been produced by antiprotons in the supernova 1987A.

Future work should aim to further constrain the axion–antiproton coupling and to look for evidence of interactions between axion dark matter and other forms of antimatter, such as positrons (the antiparticles of electrons). One key finding from these studies could be the observation that dark matter couples to antimatter in different ways from its couplings to ordinary matter — a result that might help to explain why there is a predominance of matter over antimatter in the Universe.

Smorra and colleagues have highlighted a growing trend in high-energy physics, whereby exquisitely precise measurements are used to nail down fundamental particle parameters and to look for evidence of physics beyond that of the standard model. Axion dark matter, which has a vast potential mass range and extraordinarily weak predicted couplings, has gone through a renaissance in terms of innovative detection techniques. The search for a preferred coupling of axion dark matter to antimatter (as opposed to ordinary matter) is an exciting prospect, and could prove to be the key to unlocking several mysteries in cosmology as technology improves.

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Medical research

'Undruggable' cancer protein targeted

Roy S. Herbst & Joseph Schlessinger

A molecule has now been characterized that acts to inhibit a cancer-causing form of KRAS protein and stimulate the immune system. The inhibitor is one of the first of its kind to show anticancer activity in the clinic.

Mutations in the gene *KRAS* are the most frequent drivers of tumour development across the spectrum of human cancers[1]. Despite this prevalence, mutant KRAS protein has remained an intractable therapeutic target. Writing in *Nature*, Canon *et al.*[2] describe a small molecule that binds one form of mutant KRAS with high specificity and sensitivity, inhibiting the protein. The authors use animal models to analyse how the inhibitor works, and show that it can shrink tumours in patients. This is among the first evidence of a clinical response to a specific KRAS inhibitor.

KRAS is an enzyme that controls a signalling pathway crucial for cell growth, differentiation and survival. The inactive protein is bound by a guanosine diphosphate (GDP) molecule — replacement of GDP by guanosine triphosphate (GTP) facilitates conformational changes in KRAS that allow the enzyme to bind and activate downstream effector molecules (Fig. 1a). Nearly all cancer-promoting KRAS mutations prevent GTP breakdown, leaving KRAS in a permanently active state[3] (Fig. 1b). One such mutation involves substitution of a glycine amino-acid residue for a cysteine residue. The resulting mutant protein, $KRAS^{G12C}$, is found infrequently in various cancers. It is most prevalent in lung cancer, and is responsible for approximately 12% of non-small cell lung cancers[4,5].

In the past few years, several irreversible small-molecule inhibitors have been developed[6–8] that bind covalently to a pocket in GDP-bound $KRAS^{G12C}$ to inhibit GTP binding. These inhibitors successfully prevent activation of the protein in animal models, but none has had any effect on tumours in patients. Canon *et al.* characterized another small-molecule inhibitor, AMG 510, that forms a covalent bond with GDP-bound $KRAS^{G12C}$ (Fig. 1c). AMG 510 has similar structural properties to one of the previous inhibitors, ARS-1620, but has one key difference — it binds a structure called a cryptic surface groove that forms in $KRAS^{G12C}$, and so recognizes the mutant protein with high specificity.

The authors showed that AMG 510 inhibits the exchange of GDP for GTP more potently than does ARS-1620. Moreover, AMG 510 strongly inhibits phosphorylation of the protein ERK (a known effector of KRAS activity) in cells harbouring $KRAS^{G12C}$, and impairs cell proliferation.

Next, Canon and colleagues turned to mice carrying $KRAS^{G12C}$ tumour cells taken from patients. Treatment with AMG 510 at a concentration of 100 milligrams per kilogram of body weight resulted in tumour regression, but the cancer subsequently returned. At 200 mg kg^{-1}, however, AMG 510 triggered permanent tumour regression in eight out of ten mice. Of note, the robust potency with which AMG 510 triggers cell death raises the possibility that it becomes covalently attached to other cysteine-containing proteins, in addition to $KRAS^{G12C}$ — something that should be investigated in future, if the molecule is to be regularly used in patients.

Interestingly, mice showed a durable