PARTICLE PHYSICS

Exotic nuclear decay detected

A detector that was designed to probe dark matter, the 'missing' mass in the Universe, has seen an elusive nuclear decay called two-neutrino double electron capture — with implications for nuclear and particle physics. SEE LETTER P.532

JOUNI SUHONEN

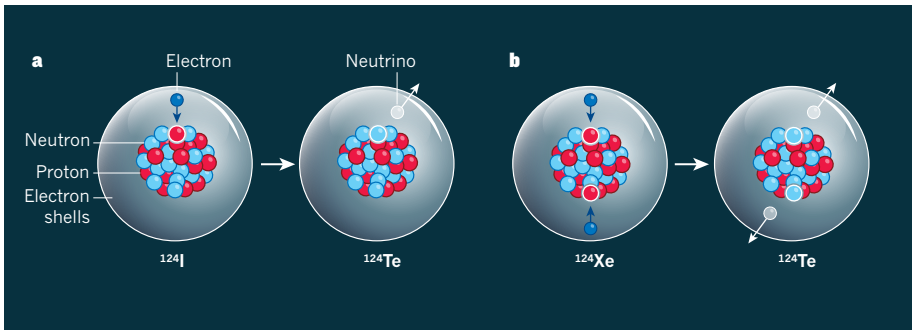

Figure 1 | Electron capture and two-neutrino double electron capture. a, An iodine-124 atom can decay with a half-life of 4.2 days to an atom of tellurium-124, through a process called electron capture. The nucleus of the iodine-124 atom captures an electron from the electron shells that surround it. A proton (circled) in the nucleus is converted into a neutron, and a neutrino is emitted. **b**, A xenon-124 atom cannot decay by electron capture, because of the law of energy conservation. However, it can decay with an extremely long half-life to a tellurium-124 atom, through a process known as two-neutrino double electron capture. The xenon-124 nucleus captures two electrons from the surrounding electron shells, which results in the conversion of two protons (circled) into neutrons, and the emission of two neutrinos. The XENON Collaboration[2] has measured the half-life of this process to be 1.8×10^{22} years — about one trillion times the age of the Universe.

For half a century, our view of the world has been based on the standard model of particle physics. However, this view has been challenged by theories[1] that can overcome some of the limitations of the standard model. These theories allow neutrinos to be Majorana particles (that is, they are indistinguishable from their own antiparticles) and predict the existence of weakly interacting massive particles (WIMPs) as the constituents of invisible 'dark matter' in the Universe. Majorana neutrinos mediate a type of nuclear decay called neutrinoless double-β decay, an example of which is neutrinoless double electron capture. A crucial step towards observing this decay is to detect its standard-model equivalent: two-neutrino double electron capture. On page 532, the XENON Collaboration[2] reports the first direct observation of this process in xenon-124 nuclei, using a detector that was built to detect WIMPs.

All known interactions in the Universe are mediated by one of four forces: electromagnetic, gravitational, strong or weak. The electromagnetic force and gravitational force, which we encounter in daily life, are long-range and can act over large distances. The strong force acts over short distances and binds together elementary particles known as quarks to form nucleons (protons and neutrons) on the femtometre scale (1 fm is 10^{-15} m). The weaker long-range residue of the strong force, in turn, binds nucleons into atomic nuclei. For example, this residue binds together the 124 nucleons (54 protons and 70 neutrons) of a xenon-124 nucleus. Last, the weak force is extremely short-range and causes atomic nuclei to disintegrate through a process called nuclear β-decay.

One type of β-decay is nuclear electron capture, in which a nucleus, embedded in an atom, captures an electron from the electron shells that surround it (Fig. 1a). As a result, one proton in the nucleus is converted into a neutron, and a neutrino is emitted. Electron capture, or any other form of β-decay, is known as a lowest-order weak interaction. For such processes, the decay rate of a nucleus, which is inversely proportional to the half-life of the nucleus, is proportional to the square of the weak coupling constant — a parameter that quantifies the strength of the weak force. Because this constant is small, the resulting half-life is long. For example, in the case of the electron-capture-mediated decay of iodine-124 to tellurium-124, the half-life is 4.2 days.

In some instances, electron capture (or any other lowest-order weak interaction) is forbidden by the law of energy conservation. Then, the nuclear decay can proceed through a weak-interaction process of the second order, for which the decay rate is proportional to the fourth power of the weak coupling constant, and the associated half-life is extremely long. An example of a second-order weak interaction is two-neutrino double electron capture, in which a nucleus captures two electrons from the electron shells that surround it, resulting in the conversion of two protons into neutrons and the emission of two neutrinos (Fig. 1b).

This process can be viewed as two simultaneous electron-capture decays that directly convert an atomic nucleus into one that has two fewer protons and two more neutrons. Each captured electron leaves a hole in the electron shell from which it came. These holes are filled by other atomic electrons, leading to the emission of X-rays and electrons called Auger electrons. Such emissions pave the way for the direct observation of two-neutrino double electron capture in a nucleus. The first experimental indications of this process were obtained for krypton-78 in direct counting experiments[3,4], in which the double electron captures are registered one by one, and for barium-130 in geochemical studies[5,6].

The XENON Collaboration looked for the decay of xenon-124 to tellurium-124, which occurs through two-neutrino double electron capture, using the XENON1T dark-matter detector. This instrument contains about 3 tonnes of ultra-pure liquid xenon and was designed to search for the scattering of WIMPs off xenon nuclei[7]. The detector is at the Gran Sasso National Laboratory, which is located under the Gran Sasso massif in central Italy, roughly 120 km from Rome. The researchers carried out a direct counting experiment in which emissions of X-rays and Auger electrons were measured to pin down the rare decay. The data were collected over one year (between 2017 and 2018) as part of the hunt for WIMPs.

Thanks to the huge amount of xenon in the detector, the authors achieved the first direct observation of two-neutrino double electron capture in xenon-124 nuclei. They measured the half-life of the process to be 1.8×10^{22} years, which is about one trillion times the age of the Universe. The successful measurement of this half-life lays the foundations for experiments that aim to detect these rare decays in other nuclei. Moreover, the researchers' use of a

WIMP-searching liquid-xenon instrument provides striking evidence of the power and versatility of such detectors. However, only four types of double-β decay can be probed by these instruments — namely, the decays of xenon-124, xenon-126, xenon-134 and xenon-136.

From the point of view of nuclear theory, the decay rates of both two-neutrino and neutrinoless double electron capture can be connected to quantities called nuclear matrix elements. Such quantities contain information about nuclear structure that is extracted from nuclear models and can be applied by researchers in the field of nuclear-structure theory. The measured two-neutrino double electron capture will help to test the various nuclear models[8] that are used to calculate rates of double-β decay. Moreover, the acquired half-life data will enable model parameters to be fine-tuned, allowing scientists to more accurately predict the values of the nuclear matrix elements that are associated with neutrinoless double electron capture, as well as neutrinoless double-β decays in general. Finally, all of these factors will contribute to the accurate extraction of neutrino parameters from the data gathered by present and future neutrino experiments. ■

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MEDICAL RESEARCH

Lethal clues reveal tumour vulnerability

Cancer cells often have mutations in anticancer genes that make their survival dependent on other genes. The gene-editing approach CRISPR–Cas9 offers a way to identify such vulnerabilities. SEE ARTICLE P.511 & LETTER P.551

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Suitable protein targets are needed to develop new anticancer drug-based treatments. Writing in *Nature*, Behan *et al.*[1] (page 511) and Chan *et al.*[2] (page 551), and, in *eLife*, Lieb *et al.*[3], report that certain tumours that have deficiencies in a type of DNA-repair process require an enzyme called Werner syndrome ATP-dependent helicase (WRN) for their survival. If inhibitors of WRN are found, such molecules might be promising drug candidates for further testing.

Imagine a scenario in which scientists could perform an experiment that reveals how almost every gene in the human genome is dysregulated in cancer. Even better, what if such an investigation also offered a road map for how to select a target when trying to develop treatments that take aim at cancer cells, but are non-toxic to normal cells? A type of gene-editing technology called CRISPR–Cas9 enables just that in an approach termed functional genomics. Using this technique, the function of almost every gene in cell-based models of cancer (comprising human cells grown *in vitro* or *in vivo* animal models) can be perturbed, and the effect of each perturbation on cancer-cell survival can be measured.

CRISPR can be used to mutate, repress or activate any targeted human gene[4,5]. In functional genomics, gene function is assessed in a single experiment by growing a large number of cells and then perturbing one gene in each of the cells. The approach is aided by measuring the concentration in each sample of the DNA sequence that encodes an engineered RNA molecule (termed a single-guide RNA; sgRNA) that is needed for the CRISPR gene-editing process. When the DNA that encodes a particular sgRNA is present in a sample of cancer cells in such an experiment, this means that the gene that the sgRNA targets is not required for cell survival. However, if the sgRNA-encoding DNA sequence is not detected, this indicates that the gene targeted by the sgRNA is required for cancer-cell viability, and those cells containing it died, thereby eliminating the sgRNA-encoding sequence from the sample. This approach offers the possibility of systematically searching for genes that are crucial to tumour-cell survival in large collections of cancer cells that are representative of the diversity of tumour types in humans.

Behan *et al.* report their development of an online database that they call Project Score. It is a platform for cancer researchers that amalgamates Behan and colleagues' large-scale data for genome-wide gene editing by CRISPR with previously published genomics information about the cancer models used. The resource consists of data for more than 5 million CRISPR-mediated perturbations undertaken to prevent the expression of individual genes (generating what are known as gene knockouts) in 324 cell-based models of cancer, representing 30 types of cancer in humans. This systematic effort has enabled the identification of genes on which cancer cells depend for survival, as well as those that drive cancer-cell proliferation.

In the database, the authors' integrated analysis of this functional-genomics data is provided together with other data about the samples. For example, there is information about tumour-cell genomes, such as the sequence of the whole genome or that of the genome's protein-coding regions. Also available are the gene-expression profiles for each cell-based cancer model, which reveal vulnerabilities in cancer cells that are associated with the specific tumour-driving alterations that exist naturally in each model. These include mutations in types of gene known as oncogenes and tumour suppressors that, respectively, are associated with promoting or blocking cancer formation. The platform developed by Behan *et al.* complements a similar effort called the Cancer Dependency Map[6,7], and together these resources should accelerate cancer research. For example, these approaches could guide target prioritization for the development of treatments that might be effective in multiple types of cancer.

Many cancers in humans are driven by genetic mutations known as loss-of-function mutations, which inactivate genes so that they no longer encode functional proteins. In cancers, such mutations commonly occur in tumour-suppressor genes. Because these mutations result in the absence of a protein, they do not offer an opportunity for directly targeting an abnormal protein with drugs. However, loss-of-function mutations can render cancer cells dependent on specific genes through a principle known as synthetic lethality[8,9]. Synthetic lethality is a relationship between two genes in which the loss of both gene *A* and gene *B* is lethal, whereas the loss of either gene can be tolerated by cells. If we could understand how the inactivation of tumour-suppressor genes rewires cancer cells to drive tumour progression, this knowledge could be used to implement strategies that enable the specific killing of such mutated cancer cells.

The possibility of synthetic lethality pointing the way to fresh therapeutic approaches is exemplified by studies that demonstrate that combining loss-of-function mutations in the tumour-suppressor genes *BRCA1* or *BRCA2* with the inhibition of a type of enzyme called PARP imparts synthetic lethality[9]. *BRCA1* and *BRCA2* are often mutated in breast, ovarian and prostate cancers, and clinical trials that