contain degradative enzymes, allowing the P_i to be released and used by the cell.

Phospholipid-rich multilamellar organelles similar to PXo bodies, known as lamellar bodies (LBs), have been described in several mammalian cell types[4]. LBs secrete specialized mixtures of lipids and proteins that maintain protective barriers in the skin, lung and stomach[4]. However, Xu and colleagues showed that *PXo* deletion in flies does not affect the integrity of the gut barrier. Moreover, mass spectrometry of PXo bodies showed that the fly equivalents of the proteins required to make LBs are not present, and revealed that the phospholipids present in PXo bodies are different from those in LBs. The authors therefore conclude that PXo bodies are distinct from LBs.

In a final set of experiments, the authors revisited their initial observation, to determine what mediates gut proliferation in the absence of P_i. They looked for PXo-interacting proteins and identified STRIPAK, a protein complex involved in communication between organelles[5]. Deletion of *PXo* in absorptive cells caused large increases in levels of the STRIPAK-complex component Cka, which accumulates in the cells' nuclei. Cka then recruits the stress-induced protein kinase enzyme JNK, which is known[6] to induce proliferation of nearby progenitor cells.

It seems counter-intuitive that the gut activates cell proliferation in times of nutrient starvation, but the authors suggest that this might be a compensatory mechanism to produce more absorptive cells, thus maximizing absorption of scarce dietary P_i. Response to starvation of different micronutrients is understudied, and these scarce nutrients might require specialized mechanisms to ensure enough is acquired from the diet. Other micronutrients, such as zinc, are stored in vesicles in flies[7], nematode worms (*Caenorhabditis elegans*)[8] and rodents[9]. In flies, these zinc-storage granules are found in the Malpighian tubules, the insect equivalent of the kidney[7]. However, zinc deficiency might not trigger gut-cell proliferation[10], and it remains to be seen whether the authors' suggestion in the context of P_i is borne out.

An alternative hypothesis is that P_i scarcity increases proliferation to give rise to different absorptive cells that have reduced phospholipid content, which could affect their membrane properties. By modulating the membrane composition of its absorptive cells, the gut might be able to handle nutrients differently, perhaps allowing the fly to cope better with the nutritional challenge.

Xu and colleagues' work is an excellent example of how the complex physiology of fruit flies, and the ease with which genetic mutations can be induced, can be applied to analysis of fundamental cell-biological processes, revealing links between diet, organelle physiology and tissue homeostasis. The findings also add to an increasing body of work pointing to roles for micronutrients in physiology. Another case in point is the intestinal protein Hodor, which drives zinc-induced changes in appetite and food preference in fly larvae[11]. It would be interesting to know whether P_i starvation also leads to a change in feeding behaviour. Conversely, possible links between zinc availability, Hodor and intestinal epithelial renewal, such as those described for PXo, deserve further investigation.

The gut, alongside the kidneys and bone, is thought to be one of the key organs in regulation of P_i levels in the body, but mammalian P_i sensing is not fully understood[12]. It will be crucial to see whether multilamellar organelles similar to PXo bodies can be found in mammalian cells, especially in the gut. The ability of PXo organelles to dynamically change their phospholipid content is of particular interest, given that membrane composition is known to change with age[13] and disease[14].

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Metrology

Photon lights a path towards a nuclear clock

Adriana Pálffy

A long-sought photon that is emitted by the nucleus of a thorium isotope has now been observed. The feat is a key step in efforts to build a nuclear clock, a device that is precise enough to probe the Universe's best-kept secrets. **See p.706**

The most precise timekeepers today are atomic clocks, which measure time using the frequency associated with transitions that electrons make between the different energy levels of an atom. But atomic nuclei make similar transitions, and these jumps could potentially offer an even better way of keeping time. In particular, the nucleus of the isotope thorium-229 undergoes a transition with an energy and a frequency that make it uniquely suitable for very precise timekeeping. But observing this transition and identifying its energy precisely are difficult tasks. On page 706, Kraemer *et al.*[1] have detected the photon that is emitted in this transition, an advance that is crucial for the development of nuclear clocks.

Originally discovered in a mineral found off the Norwegian coast in 1828, thorium is named after Thor, the Norse god of thunder. It would take another century and a half for scientists to determine that one specific thorium isotope displays an anomaly that sets it apart from the rest[2] – and perhaps makes the element worthy of its other-worldly name. The thorium nucleus in question has 229 nucleons (protons and neutrons), and can transition to an excited state that is only around 8 electronvolts more energetic than its lowest energy (ground) state. This difference is so tiny by nuclear-physics standards that the two states could barely be distinguished when they were first reported[2]. And it is the transition between these states that could make extraordinary nuclear timekeeping possible.

The working principle behind the nuclear clock closely resembles that of its atomic siblings[3]. The idea is that a light wave can induce a nucleus to jump between energy levels; the light's frequency simply must precisely match that corresponding to the energy difference between the levels. This

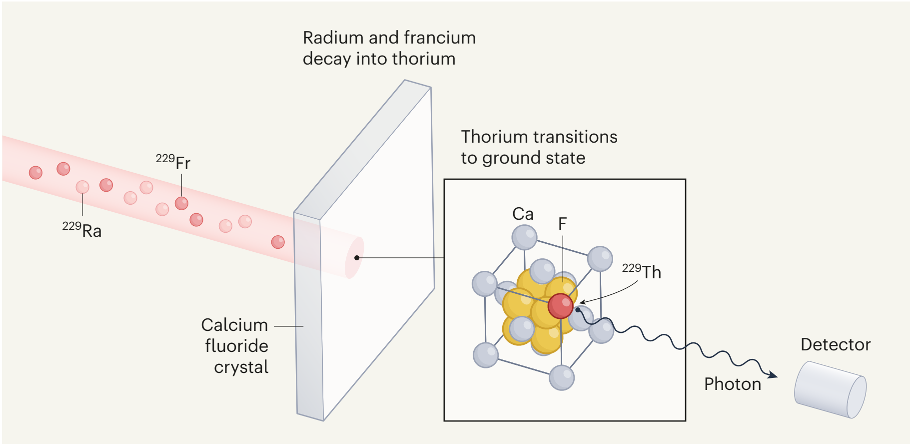

Figure 1 | An elusive photon captured at last. Monitoring the frequency corresponding to the energy generated when atomic nuclei of a thorium isotope (^{229}Th) transition between energy levels could be the basis for an extremely precise clock. Kraemer *et al.*[1] report an observation of the photon emitted during this transition. The authors fired a beam containing nuclei of francium and radium isotopes (^{229}Fr and ^{229}Ra) into a calcium fluoride crystal, which is transparent to light at frequencies corresponding to the nuclear transition. The beam decayed into thorium nuclei, some of which were in an excited state that is around 8 electronvolts more energetic than the lowest energy (ground) state. The thorium replaced ions in the crystal lattice and decayed to the ground state mostly by emitting a photon, which exited the crystal undisturbed and was recorded at a detector.

can be achieved with a laser, and – for optimal timekeeping – the ratio between the tuning range (the band of frequencies that can drive the jump) and the transition frequency itself should be very small. For thorium-229, this ratio is minuscule, and the transition is also better protected against stray photons that could affect the signal than are atomic transitions. Unfortunately, the laser required to drive the thorium-229 transition is yet to be built, in part because the exact value of the nuclear-transition energy was, for a long time, not known[4–6].

Two other hurdles have complicated the task of building a nuclear clock. First, in the absence of a suitable laser, thorium-229 has been excited only through uncontrolled and inefficient mechanisms – for instance, through the radioactive decay of elements that neighbour thorium in the periodic table. So far, physicists have mainly used a radioactive process known as the α-decay of uranium-233, which populates the 8-eV excited state of thorium-229 with a 2% probability (ref. 7).

Second, one possible signature of the nuclear transition is the emission of a photon, but this photon has remained elusive, mostly because its emission is one billion times less likely[8] than is another process that occurs when neutral thorium-229 atoms decay[5,9]. This mechanism is known as internal conversion, and it transfers the energy gained from the nuclear transition to the atomic shell, kicking out the outermost electron and thereby forming an ion.

Internal conversion is forbidden for thorium-229 ions, because 8 eV is not a high enough energy to eject another electron from the atomic shell. This makes the chances of detecting the photon emitted from thorium-229 ions higher than those for neutral atoms. And observing this photon enables the nuclear-transition energy to be measured with better accuracy than that associated with measuring internal-conversion electrons.

Kraemer *et al.* have now captured the elusive photon on camera, and they owe this success to two key innovations. Instead of inducing the decay of uranium-233, they used a different process, the β-decay of actinium-229, to populate the nuclear excited state more efficiently. The actinium nuclei were generated at the ISOLDE facility at CERN, Europe's particle-physics laboratory near Geneva, Switzerland, and were themselves β-decay products of the isotopes francium-229 and radium-229. The authors also fired their beams of radioactive nuclei into calcium fluoride or magnesium fluoride crystals, thereby replacing some of the atoms in the crystals with the nuclei from the beams. Crucially, these crystals are transparent to light at frequencies around that of the elusive nuclear-clock transition photon (Fig. 1).

This combination proved advantageous in many ways. The crystal environment allowed the authors to collect many thorium-229 nuclei[10], leading to a signal that was finally strong enough to be observed. It seems that when thorium was implanted in the crystal, it took over a crystal-lattice site in an ionic state, which strongly suppressed mechanisms other than the emission of the missing photon. Crucially, the damage to the crystal and corresponding background radiation caused by the β-decay were much suppressed compared with those resulting from the α-decay of uranium-233. This enabled Kraemer *et al.* to observe the photon, and also to determine its energy with seven times less uncertainty than obtained in previous attempts[5,6]. They also inferred the half-life of the nuclear decay through photon emission.

Kraemer and colleagues' results are undoubtedly an important step towards developing a nuclear clock, but many steps must yet follow. The authors deduced properties of the photon using approximations, and some values retain many uncertainties, such as in the half-life, which is crucial to the clock design. Other details are similarly uncertain, including the depth at which the thorium is implanted in the crystal, the probabilities with which radioactive decay products are formed, and how the crystal environment influences the decay of the nuclear excited state. These details could have a considerable impact on the understanding of the nuclear-clock transition. Given the complexity of the crystal environment, and the consequent lack of control, it is likely that future nuclear-clock designs will instead focus on mimicking established atomic-clock set-ups[11], by trapping and cooling thorium-229 ions.

Will nuclear clocks one day outperform existing atomic clocks? This remains a matter of speculation. As the accuracy of atomic clocks continues to improve, there might well be a timekeeping race, the outcome of which could depend on the development of a laser capable of driving the nuclear transition in thorium-229. A nuclear clock would not only provide an alternative to the atomic clock, but also enable investigations of concepts that are typically taken for granted, for example whether fundamental physical constants really are constant. A nuclear clock could also help to tackle open questions, such as what makes up the cosmic material known as dark matter. The fundamental interactions at play in nuclear transitions make the nuclear clock uniquely positioned to answer such questions[12], which, in turn, makes Kraemer and colleagues' feat a cause for much excitement.

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