Spermidine is a type of molecule called a polyamine. It is mainly produced from a metabolic pathway that converts the amino acid arginine to polyamines through intermediates that include the molecule ornithine (Fig. 1). Medina and colleagues traced the conversion of arginine to spermidine by this pathway, and found that cells induced to undergo apoptosis increased their synthesis of spermidine and its precursor, the molecule putrescine, before dying. The apoptotic cells released spermidine, but not putrescine. Spermidine release occurred in a PANX1-dependent manner.

Although this phenomenon was monitored using just one apoptosis-inducing condition (namely, ultraviolet radiation), the finding raises the possibility that activation of apoptosis drives this pathway, which synthesizes spermidine. The hint that suggests this is the authors' observation of the effects of administering a type of drug called a BH3 mimetic. This drug directly triggers a core step in apoptosis, the permeabilization of mitochondrial organelles in an event called mitochondrial outer membrane permeabilization (MOMP) — and its use led to spermidine release at levels comparable to those observed in apoptosis mediated by ultraviolet radiation. Perhaps MOMP prevents the transport of ornithine into mitochondria (where ornithine is converted to the molecule citrulline), and leads instead to ornithine being mobilized in cytoplasmic pathways leading to spermidine production. This model could be tested in cells engineered to lack components required for MOMP and exposed to BH3 mimetics.

The molecule urea is formed as a by-product of the conversion of arginine to ornithine. Urea is an inflammatory DAMP that is released from necrotic cells[6], but the authors did not determine whether urea is released through PANX1 during apoptosis. However, because Medina and colleagues observed a rise in arginine metabolism during apoptosis, if urea is not released through PANX1, this might provide a further reason why apoptosis is not inflammatory.

How do spermidine, guanosine monophosphate and inosine monophosphate induce responses in macrophages, and why do the three metabolites work only when given together? Guanosine monophosphate and inosine monophosphate are known to signal to G-protein-coupled adenosine receptors[9], and spermidine can participate in a broad range of activities. The molecule inosine (which can be derived from inosine monophosphate) has anti-inflammatory effects[9] and can prevent lethal inflammation in response to a bacterial toxin in mice[10]. It is possible that spermidine acts to increase such anti-inflammatory signalling from the adenosine receptors. Human cells are ten times less sensitive than mouse cells to the anti-inflammatory effects of inosine, probably owing to differences in adenosine-receptor expression and function between the species[8], and therefore efforts to use these metabolites to treat human disease might prove challenging.

Medina and colleagues' work opens rich possibilities for future investigations into how apoptosis triggers metabolic changes, and how the regulated release of metabolites influences tissues. In contrast to apoptosis, other forms of cell death, such as regulated forms of necrosis, have profoundly different effects on surrounding cells, and whether and how changes in metabolism triggered by those cell-death pathways influence their surroundings is unknown. Cells that die by a form of regulated necrosis termed necroptosis continue to synthesize and secrete molecules called cytokines that affect inflammation[11]. In these dead 'zombie' cells, this synthesis occurs in an organelle called the endoplasmic reticulum[11], raising the possibility that metabolites produced in the functioning endoplasmic reticulum of these zombie cells also signal to living cells in the surrounding tissue. Marley's ghost appears in chains that he said were forged in life; what other chains are forged in cell death?

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Nuclear physics

A broken nuclear mirror

Bertram Blank

The principle of mirror symmetry, which states that nuclear structure remains the same when protons are swapped for neutrons and vice versa, has been found to be broken in the lowest-energy forms of a mirror pair of nuclei. **See p.52**

Nature likes symmetry. Examples range across size scales from macroscopic objects, such as spiderwebs or honeycombs, to the microscopic world with its arrangement of atoms in molecules, or of electrons around an atomic nucleus. Symmetry also exists at the level of nuclei, but on page 52, Hoff *et al.*[1] report one way of breaking it.

Atomic nuclei are composed of two different types of particle — protons and neutrons — which, if we ignore the charge on the proton, resemble each other so much that they are often treated as a single particle, the nucleon. Mirror pairs of nuclei, in which the numbers of neutrons and protons have been exchanged, therefore have similar properties.

In particular, the sequence of energies of a mirror pair's nuclear states should be the same, from the ground state in which the nucleons are in the lowest possible energy level, to excited states of increasing energy[2]. A change in this sequence has, however, previously been observed for excited states of mirror partners[3]. Hoff and co-workers now report the breaking of mirror symmetry at the level of bound nuclear ground states (Fig. 1). They report that the ground states of the mirror partners bromine-73 and strontium-73 are not simply 'mirror images' in which protons and neutrons have been swapped, but have a different configuration of protons and neutrons.

How does this difference arise? The most basic building blocks of matter known today are quarks, of which there are six types. Protons and neutrons are both constructed from three quarks, and the most important difference between them is that their different quark combinations give the proton an electric charge of +1, whereas the neutron ends up neutral.

The strong nuclear interaction that binds nucleons together in an atomic nucleus is essentially the same between protons and neutrons. For protons, however, the electric repulsion between identically charged particles adds together. When building two mirror-symmetric atomic nuclei, one with

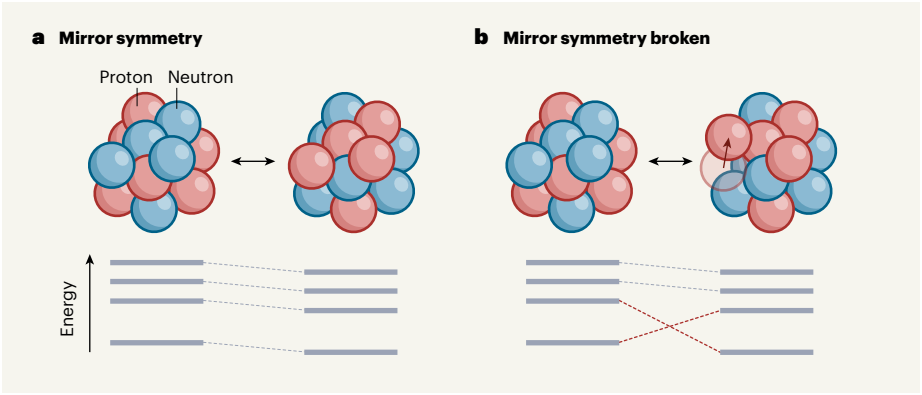

Figure 1 | Breaking nuclear mirror symmetry. a, In a pair of mirror nuclei, the number of protons in one nucleus equals the number of neutrons in the other, and vice versa. For perfect mirror symmetry, the nuclear structure and energy levels of the ground and excited states (shown schematically; dashed lines connect equivalent states) are essentially the same on swapping protons for neutrons, apart from a small overall shift caused by proton repulsion in the proton-rich nucleus. **b**, Hoff *et al.*[1] report that the lowest-energy states of a mirror pair can have a different configuration of protons and neutrons; red dashed lines indicate that the lowest energy levels in one nucleus have swapped places compared with **a**. The cartoon illustrates a simple example of mirror symmetry and how it might be broken.

Z protons and *N* neutrons and the other with *N* protons and *Z* neutrons, this repulsion adds an extra global energy (mass) to the nucleus that has the more protons, but does not modify the arrangement of protons and neutrons. This symmetry explains why several of the properties of mirror partners are nearly identical: in their shape; their behaviour when excited (that is, when energy is added); and the properties of the decay processes through which unstable nuclei lose energy by emitting particles or radiation.

To determine nuclear properties such as energy levels, energy is pumped into a nucleus (for instance, by colliding it with another nucleus), and the decay process in which γ-rays are emitted from the resulting excited nucleus is observed. The previously observed difference[3] in the sequence of energy levels for the excited states of mirror partners occurred particularly at higher excitation energies, in which the density of states increases (that is, the neighbouring states come closer to each other). This difference of energy levels is a sign that mirror symmetry is only approximate and can be broken in particular circumstances.

A different structure in nuclear ground states has been observed[4] previously for only one pair of mirror nuclei, nitrogen-16 and fluorine-16. In that case, however, one of the two partners (fluorine-16) is unbound – that is, the repulsion between protons outweighs the attraction from the strong nuclear force. It therefore decays rapidly by ejecting a proton in around 10^{-20} seconds (ref. 5), comparable to the time it takes a nucleon to travel across the nucleus. However, nitrogen-16 is much more stable, with a half-life of about 7 seconds (ref. 6). So the mirror difference there can be explained by the unbound nature of one partner.

Hoff *et al.* reveal that the situation is different for bromine-73 and strontium-73, because both are long-lived and quasi-stable. To break mirror symmetry, nature had to play a trick: the ground states of these two nuclei are very close in energy to their respective first excited states. Mirror symmetry, being only an approximate symmetry, can therefore be violated by exchanging the ground and the first excited states in one of the two nuclei.

The properties of bromine-73 have been well characterized for 50 years[7], whereas information about strontium-73 is limited: we have a rough value for its half-life[8], and know its strongest mode of decay[9]. The originality of Hoff and co-workers' study is that the authors did not study the properties of strontium-73 directly, but through its two consecutive radioactive decays: the first decay occurs through the emission of β-particles and produces a particular state in the daughter nucleus, rubidium-73, which immediately decays by proton emission to produce krypton-72. The observed properties of the proton emission allowed the authors to deduce the structure of the proton-emitting state in rubidium-73, and, from this, the structure of the ground state of strontium-73.

The results allowed a nuclear property known as spin to be characterized, and revealed something unexpected. The ground state of strontium-73 turns out not to have a spin of 1/2, as the ground state of bromine-73 does, but instead has a spin of 5/2, which corresponds to the first excited state of its mirror partner. Thus, mirror symmetry has now been shown to be broken in bound nuclear ground states.

Is this breaking of mirror symmetry a disaster for our understanding of the structure of the atomic nucleus? Not at all. Deviations from expectations challenge our knowledge of nuclear structure, and allow nuclear scientists to fine-tune their models to describe atomic nuclei. As Hoff *et al.* show, the observed mirror-symmetry breaking might be triggered by the existence of two competing nuclear shapes, a prolate (rugby-ball) shape and an oblate (disk) shape. Both structures give the nuclei approximately the same energy and mass. These two shapes can mix, and the symmetry breaking in bromine-73 and strontium-73 might arise because there is a different degree of mixing in the two nuclei.

It will be interesting to see whether other cases of ground-state mirror-symmetry breaking can be found. No other candidates seem to exist for nuclei that have similar numbers of nucleons to bromine-73 and strontium-73, because no nucleus is known for which the first excited state lies very close to the ground state. However, heavier nuclei are promising candidates. With more nucleons, more nuclear energy levels can be built, and the energy levels come closer together. By contrast, no mirror partners exist for nuclei whose mass number (the sum of the proton number and the neutron number) is greater than about 100 (ref. 10), because the nuclear interaction can no longer overcome the electrical repulsion associated with interactions between the protons in the 'proton-rich' mirror partner. The race is on to find more cases of broken mirror symmetry in nuclear ground states.

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