agonist binding or with the conformational changes that accompany receptor activation[7]. Intense, micro-focused X-ray beams produced by synchrotrons were required to tease out the diffraction data from which the crystal structures were derived.

Cherezov *et al.*[5] used an alternative approach. They replaced the IC3 loop of β_2AR with a small, stable protein known as T4 phage lysozyme (T4L). The T4L protein promotes crystal-lattice formation in the same way as the antibody fragment used by Rasmussen *et al.*[4]. The modified receptor, bound to carazolol, was crystallized in a semi-solid lipid medium that provided an artificial, membrane-like environment for the receptor. Synchroton X-rays were also required in this case to obtain good-quality diffraction data. The results of these investigations are described by Rosenbaum *et al.*[6].

A surprise finding from the crystal structures[4,5] is that the ionic lock is broken (as expected in an active state) despite the presence of an inverse agonist (which promotes the inactive state). Had only one crystal form of β_2AR been available, it could have been argued that this was an artefact of the experimental conditions — either a consequence of the artificial lipid environments, or because of perturbation of IC3. But because the lipid supports and IC3 region are different in each structure, it is unlikely that the same misleading result could have occurred in both cases. Moreover, the TM regions in both structures align well with each other, further corroborating the results.

Thus, the weak constitutive activity of β_2AR might be attributed to the breaking of the ionic lock; this can be compared with rhodopsin, which retains the lock and shows no such activity. In contrast, the toggle is intact in the two β_2AR structures, just as it is in inactivated rhodopsin, despite considerable differences in the binding modes adopted by the ligand molecules for these two GPCRs. Perhaps stronger inverse agonists than carazolol would stabilize the ionic lock and fully inactivate β_2AR, whereas agonists would release both lock and toggle. But these speculations have yet to be confirmed.

The crystal structures[4,5] reveal several other interesting clues to β_2AR behaviour. For example, many of the amino acids that produce constitutive activity are known to respond to agonist binding, but are not directly connected to the agonist binding site. It can now be seen that these residues are linked to the binding site via packing interactions[6], so that movement of amino acids in the binding site could affect the packing of others throughout the structure (Fig. 1). Furthermore, a water-filled channel in the core of the receptor offers space for structural rearrangement, which could enable the receptor to adopt several different active states. Finally, the capacious agonist binding site is compatible with the existence of several molecular binding modes, each with the potential to trigger a different state in the receptor.

To learn how structural changes are conveyed from the agonist pocket to the G-protein binding site, the structure of the fully active, agonist-bound β_2AR must be determined. The instability of the activated receptor will make this difficult — in fact, it may be possible to resolve the structure of a receptor only if it is bound to a G protein. Nevertheless, with the structures[4–6] of β_2AR in hand, we can expect those of other GPCRs to follow, so that the conformational complexities common to the members of this family of receptors might finally be revealed. ■

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PLANETARY SCIENCE

Isotopic lunacy

Alex N. Halliday

The Moon could have been derived from a well-mixed disk of rock vapour that was produced after the early Earth collided with another planet. This persuasive idea offers a fresh perspective on the history of both bodies.

"It is the very error of the moon; She comes more nearer earth than she was wont; And makes men mad." Thus spoke Othello, who was talking of a murderous madness. For 30 years scientists have been gripped, albeit with less deadly consequences, by a maddening paradox to do with the Moon: how near its oxygen-isotope composition is to that of Earth.

It is generally agreed that the Moon formed in a giant impact between Earth and another, smaller body. But previous simulations of that event show that, dynamically, the Moon should be largely derived from the smaller body, in which case its oxygen isotopic composition should be different from that of Earth. Writing in *Earth and Planetary Science Letters*, Pahlevan and Stevenson[1] put forward an explanation for the oxygen-isotope paradox: they propose that the giant impact produced a disk of rock vapour within which the atoms were able to mix before the lunar component condensed out.

The scientific context of this story goes back to the discovery of large variations in the isotopic composition of oxygen in meteorites[2], which occurred at about the same time as lunar samples were being returned by Apollo astronauts. These variations are so large that they can readily be used to identify which meteorites come from the same planet or asteroid. Lunar samples were found to have a terrestrial isotopic composition[2], which was taken as evidence that the Moon was derived from Earth[3]. But the evidence from dynamic simulations is that most of the mass of the Moon came from another planet, Theia, that hit the early Earth with a glancing blow[4].

The isotopic composition of every element studied so far is the same in lunar samples as it is in samples from Earth, apart from elements that would change because of radioactive decay, or through the effects of cosmic rays or the charged particles of the solar wind. But the background Solar System heterogeneity is far bigger for oxygen than for most other elements[2]. So, with the development of more precise techniques, a further analysis of lunar samples aimed to resolve an Earth–Moon oxygen-isotope difference that it was thought must surely exist at some finite level[5]. Far from doing that, however, samples from the two bodies were found to be identical to within better than five parts per million. One explanation was that Theia must have formed from the same mix of material as Earth.

Pahlevan and Stevenson's dynamic simulations[1] of Solar System formation build on previous work in assuming that, based on the measured difference between Earth and Mars, an oxygen-isotopic gradient existed within the early planetesimals of the circumstellar disk. This is a reasonable assumption, but might not be easy to test at the required precision until samples are returned from sizeable bodies such as Mercury and Venus. The obvious test at present involves a class of meteorites that were probably derived from the asteroid 4 Vesta. The oxygen-isotope data for these meteorites do not fit with the proposed radial-gradient model. But this can be explained if, as seems likely, Vesta has migrated outwards from the innermost Solar System.

Based on this putative gradient, the new calculations[1] show that it is unlikely for two bodies such as Theia and Earth to have had the same bulk isotopic composition. Indeed, it is hard to imagine how they could have formed from the same mix of primordial matter unless they grew at exactly the same distance from the Sun, which in turn raises the question of why it took them so long to collide. Tungsten-

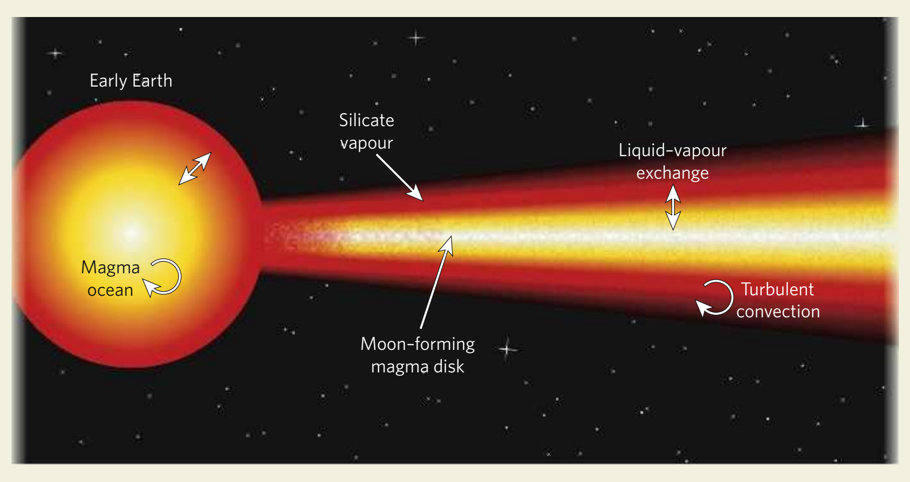

Figure 1 | The big mix-up. According to Pahlevan and Stevenson's model[1], the immense energy released in the collision between the early Earth and another body vaporized Earth's outer, silicate portion and created an internal ocean of liquid magma. The material from which the Moon eventually formed was a disk of magma created in the impact, and derived from the impacting body, which was connected to Earth by a shared atmosphere of silicate vapour. Through the processes of turbulent convection and exchanges between the different phases driven by heat loss, matter from the two bodies became well mixed on a timescale of 10^2–10^3 years. This scheme can account for the fact that although the oxygen-isotope content of both the proto-Earth and the impactor were probably dissimilar, those of today's Earth and Moon are virtually identical. (Derived from Fig. 3 of ref. 1.)

isotope measurements indicate that the Moon did not form until about 4.5 billion years ago, more than 40 million years after the birth of the Solar System[6].

The energy released when sizeable worlds collide is astonishing by geological standards. The giant impact would almost certainly have melted most of the Earth and produced a magma ocean[7]. Much of the Earth and Theia may have been vaporized. Pahlevan and Stevenson[1] calculate that over the time required for the disk of vapour to cool and condense, the atoms of the silicate portion of Earth — that is, everything but the metal core — would have been vigorously and repeatedly stirred, mixing with the atoms of the disk and eliminating isotopic variations (Fig. 1).

Support for Pahlevan and Stevenson's theory comes from a study[8] of silicon isotopic compositions, which differ in meteorites and samples from the silicate Earth. The latter are fractionated to heavier isotopic compositions, and this is thought to have been caused by equilibration with silicon that was incorporated into Earth's core under very high pressures and temperatures. Theia was a small (Mars-sized) planet that should have had a silicon isotopic composition like that of meteorites and Mars. However, the Moon's composition is heavy, like that of the silicate Earth[8] — which is hard to explain unless Pahlevan and Stevenson are correct and there was large-scale equilibration.

If they are indeed right, it means that certain features of the Moon's composition reflect those of the early Earth. So, since the first lunar samples were returned, we have, without realizing it, been analysing a unique archive about our own planet — a body that has lost almost all traces of its early development with 4.5 billion years of subsequent bombardment, mantle convection and geological reprocessing.

The new theory raises lots of questions. For example, it is unclear whether all isotopic systems would have been efficiently mixed. Mixing is related to volatilization, so highly refractory elements might still show differences. Exploring this possibility will probably require improvements in mass spectrometry to resolve tiny isotopic differences — unlike oxygen, most elements in the periodic table have an almost identical proportion of isotopes, whether measured on a lump of the Empire State Building or a meteorite from the asteroid belt.

Another issue is that, although the Moon is isotopically identical to Earth, it is chemically different. In particular, it is far more depleted in volatile elements such as alkalis, even though these elements should have mixed especially efficiently. This can be explained if volatiles were somehow lost from the hot disk from which the Moon condensed. But other differences are harder to account for. The iron content of lunar basalt rocks is higher than that of Earth's and more like those of Mars' and Vesta's. This is thought to reflect a higher iron content in the lunar mantle. The lower iron content of Earth's mantle was thought to reflect an early, less-oxidized stage in the growth of the Earth[9]. However, if the Moon is essentially a sample of Earth at the time of the giant impact, it may indicate that Earth's mantle originally had a higher iron content that was subsequently depleted by formation of the core.

The ramifications of Pahlevan and Stevenson's model[1] extend well beyond these issues. Testing and developing this exciting new theory will be priorities over the coming years — the maddening paradox may well be about to generate a new wave of highly creative science. ■

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EPIGENETICS

Reversing the 'irreversible'

Richard S. Jones

"Do not speak — unless it improves on silence" is generally wise advice, and is even vital for a subset of essential genes. New studies describe how, when appropriate, the silence of these genes is broken.

In cellular tissues, it is essential that certain genes are turned on in appropriate cells but remain silent in others. For years, the dogma has been that some forms of gene silencing are irreversible, or at least extremely stable. One such form of silencing is mediated by the Polycomb group of proteins, which repress gene expression partly by altering the structure of chromatin — complexes of DNA and histone proteins. Such repression can be achieved by, for example, adding a specific molecular tag to a histone. Five papers[1–5], including one by Jepsen *et al.*[1] on page 415 of this issue, now describe how enzymatic removal of one molecular tag reverses the silencing of gene expression that is mediated by the Polycomb group.

It has long been known that the way genes are packaged inside the nucleus of a cell can determine their expression (transcription). Molecular tags on histones have crucial roles