Of ice and elephants

Daniel P. Schrag

What caused the great ice ages? Accurate dating of the end of one of these ice ages makes us reconsider which part of the climate system drives severe glaciation.

For over a century, geologists have turned to astronomy for explanations of the cause of ice ages during the Pleistocene epoch (the past 1.6 million years). In the 1870s, James Croll[1] first suggested that ice ages were caused by changes in the amount of solar irradiance received at the poles as a result of changes in the shape (with a frequency of about 100,000 years), tilt and wobble (with frequencies of about 40,000 and 20,000 years) of the Earth's orbit around the Sun. Despite the success of this astronomical theory, some fundamental questions remain. We still don't know how subtle changes in the pattern of solar irradiance are amplified to produce such spectacular changes in climate — cooling the deep ocean almost to the freezing point and extending ice sheets thousands of kilometres towards the Equator. And we don't understand why ice ages occur in both hemispheres simultaneously when the changes in solar irradiance from orbital variations have opposite effects in the north and south.

Many theories for the origin of ice ages have centred on the Northern Hemisphere as the connection between orbital variations and climate. In the 1930s, Milankovitch[2] suggested that orbitally induced variations in solar irradiance at 60° N drove the waxing and waning of ice sheets in North America and Europe. This was a reasonable hypothesis as most of the volume of ice during the glacial maximum was located in the Northern Hemisphere. Recently, the 'ocean conveyor belt' in the North Atlantic has been proposed as an important amplifier of climate variation, magnifying subtle temperature and precipitation changes near Greenland. But is the North Atlantic, or even the Northern Hemisphere, really running the show?

One reason for concentrating on the North Atlantic is that many of the highest-quality, best-dated records originate from this region. But, like the story of the wise men and the elephant, could we be seeing only part of the climate system? The story tells of an emperor who sends his wise men to investigate a gift from a foreign land, an exotic animal called an elephant. But the wise men have grown blind from reading their books, and after each feels a different part of the strange beast, they return to the emperor in total confusion.

On page 61 of this issue, Henderson and Slowey[3] provide an accurate date for the end of the second-to-last ice age, calling into question the Northern Hemisphere connection between orbital variations and climate. If we think of the climate as an elephant, Henderson and Slowey's finding is a reminder of how vast the elephant is, or at least it should make us re-examine which end might be the head.

Since the 1950s, the ratio of oxygen isotopes in marine microfossils has been the standard measure of Pleistocene climate change as it reflects, in part, the size of continental ice sheets. But precise dating of the oxygen isotope records has not been possible beyond the range of radiocarbon dating (30,000 years or so), making it difficult to compare these records with astronomical data. Imbrie and colleagues[4] proposed that complex ice-sheet dynamics, paced by orbital variations, forced the ending of ice ages, and they created a timescale (SPECMAP) for the oxygen isotope record based on this theory (Fig. 1). This timescale predicts that the end of the second-to-last ice age occurred 127,000 years ago.

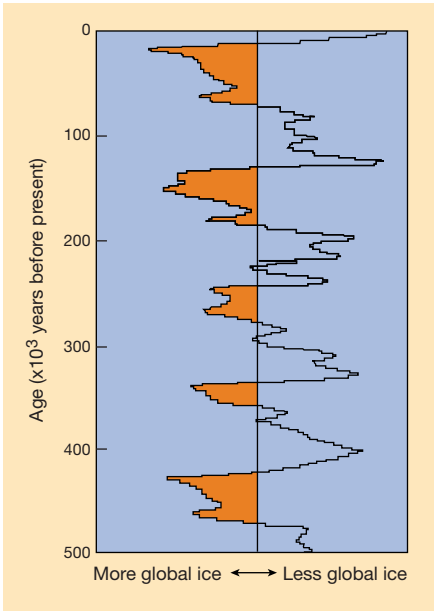

Figure 1 **Timescale of ice ages during the late Pleistocene. The Spectral Mapping Project (SPECMAP) record is based on oxygen isotope data from marine fossils that reflect the size of continental ice sheets. The record for the past 500,000 years indicates that ten major ice ages and warm periods occurred during this time. Together these make up five ice-age cycles, which occur at essentially the same frequency (every 100,000 years or so) as changes in the shape of the Earth's orbit around the Sun. The Earth has been experiencing a warm period (or deglaciation) for the past 10,000 years or so. Henderson and Slowey[3] now provide an accurate date for the midpoint of the previous deglaciation (135,000 years ago). This is significantly different from that predicted by SPECMAP (127,000 years ago), suggesting that we may need to rethink our picture of what drives the ice ages.**

Henderson and Slowey used an improved method of uranium–thorium dating, which allows accurate dating of much older sediments, to show that the midpoint of the end of this ice age was much older, at 135,000 ± 2,000 years ago. To achieve this level of precision the authors overcame many technical obstacles. This work represents a huge improvement in the absolute dating of the oxygen isotope record, and may redeem previous estimates of an even earlier date for this deglaciation[5]. But the real significance of this result is their claim that the new date is consistent with deglaciation driven by orbital variations in solar irradiance, either in the Southern Hemisphere or in the tropics, but not in the Northern Hemisphere.

Henderson and Slowey are not alone in suggesting that the Southern Hemisphere may drive the ice-age cycles. Data from the Vostok ice core — near the centre of Antarctica — shows a warming at the end of the last glacial maximum that appeared 1,000 to 2,500 years before the first major warming in Greenland[6]. Climate models have suggested a possible connection between orbital variations and changes in sea ice around Antarctica[7], including a link to atmospheric carbon dioxide[8]. But the story from Antarctica has been complicated by results from an ice core from Taylor Dome, close to the Pacific margin of Antarctica, which has a history more like Greenland than Vostok[9]. And we still don't know how climatic change in the Southern Hemisphere could cause ice sheets in North America to melt.

So what about the tropics? Some wise men (and wise women) who study the Pacific argue that the vast amount of warm water in the Pacific Ocean is the dominant force affecting global climate, and that the Pacific is relatively insensitive to climate in other parts of the world[10]. Last year, Clement and colleagues[11] suggested that ice-age cycles

might be related to the direct effects of orbital cycles on the tropical Pacific, through changes in the frequency and intensity of El Niño. Unfortunately, appropriate sites in the tropical Pacific are difficult to find, so high-resolution, well-dated records that rival those from Greenland or the North Atlantic do not yet exist.

Henderson and Slowey's dating of the second-to-last deglaciation allows us to match climate changes and orbital cycles with new confidence, and forces us to think about how the many parts of the climate system interact. If the link between orbital and ice-age cycles does lie in the Southern Hemisphere, then we must explain how changes in the south are communicated to the north, perhaps by way of the tropics. An interesting idea proposed by Broecker[12] suggests a seesaw relationship between north and south, whereby Greenland and Antarctica are out of step during rapid climate changes (over timescales of less than 1,000 years). Although it is not yet clear how such rapid climate changes are related to the larger cycles of ice ages, if at all, such ideas are a step in the right direction. Progress in this area depends on obtaining well-dated records from the tropical Pacific, as well as resolving the spatial and temporal pattern of climate changes over Antarctica. Without direct observations of the whole climate system, we may forever argue, like the wise men, about the exact nature of this climate beast. ■

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1. Croll, J. *Climate and Time* (Appleton, New York, 1875).
2. Milankovitch, M. in *Handbuch der Klimatologie* (eds Koppen, W. & Geiger, R.) 1–176 (Gebruder Borntraeger, Berlin, 1930).
3. Henderson, G. M. & Slowey, N. C. *Nature* **404,** 61–66 (2000).
4. Imbrie, J. *et al. Paleoceanography* **7,** 701–738 (1992).
5. Winograd, I. J. *et al. Science* **258,** 255–260 (1992).
6. Blunier, T. *et al. Nature* **394,** 739–743 (1998).
7. Kim, S.-J., Crowley, T. J. & Stossel, A. *Science* **280,** 728–730 (1998).
8. Stephens, B. B. & Keeling, R. F. *Nature* (in the press).
9. Steig, E. J. *et al. Science* **282,** 92–95 (1998).
10. Cane, M. A. *Science* **282,** 59–61 (1998).
11. Clement, A., Seager, R. & Cane, M. A. *Paleoceanography* **14,** 441–456 (1999).
12. Broecker, W. S. *Paleoceanography* **13,** 119–121 (1998).

Cancer

p53 sends nucleotides to repair DNA

Guillermina Lozano and Stephen J. Elledge

The p53 protein actively suppresses tumour formation; when it is mutated, the road is open for the development of several forms of cancer. Mutations in p53 or the pathway that directly regulates it have been found in over 80% of human tumours, so there has been intense research into the *p53* gene and its product. Several roles for the p53 protein have been identified, to which Tanaka *et al.*[1] (on page 42 of this issue) now add another. It is one, moreover, that may offer a fresh strategy for antitumour drug development.

The initial discovery that p53 is a tightly regulated transcription factor that is activated in response to DNA damage provided a biological basis for understanding its involvement in maintaining the integrity of the genome[2]. One of p53's functions in the damage response is the activation of genes that initiate apoptosis — programmed cell death[3]. Selective removal of severely damaged cells is thought to protect an organism from cancer. p53 has also been shown to arrest the cell cycle in response to DNA damage, thus preventing the replication of damaged DNA[4]. Some experiments suggest that cells arrested in the G1 phase of the cell cycle by p53 remain arrested permanently, so preventing damaged cells from ever proliferating[5].

Both of these mechanisms prevent cells, once damaged, from contributing to tumorigenesis. But does p53 contribute to damage repair in the first place? From the work of Tanaka *et al.*[1], the answer seems to be yes. The authors have identified a new p53-regulated gene, *p53R2*, which turns out to encode a subunit of the enzyme ribonucleotide reductase (RNR).

Ribonucleotide reductase catalyses the rate-limiting step in the production of deoxyribonucleotide triphosphates (dNTPs) required for DNA replication and repair[6]. It is an $\alpha 2\beta 2$ tetramer composed of two dissimilar subunits. The large subunit, R1, contains the allosteric regulatory sites that maintain and balance dNTP pools; the small subunit, R2, contains a binuclear iron centre and a tyrosyl free radical that is essential for the enzymatic conversion of ribonucleotides to deoxyribonucleotides. Mammalian ribonucleotide reductase is regulated by the cell cycle[7]. The R2 subunit is made in the late G1 phase before DNA replication, and disappears in late S or early G2. In contrast, the R1 subunit is produced throughout the cell cycle. Paradoxically, ribonucleotide reductase is in the cell cytoplasm, presumably producing dNTPs that diffuse into the nucleus for DNA replication[8].

The product of the *p53R2* gene is an R2 subunit that was identified by screening a p53-inducible colon-cancer cell line for differentially expressed genes. p53 binds a DNA sequence in the first intron of *p53R2* that is required for directly activating its transcription. The p53R2 protein is highly related to the normal R2 subunit, but it differs in one crucial aspect: it is found in the nucleus (Fig. 1).

This change in venue led Tanaka *et al.* to speculate that replication requires the previously known cytoplasmically synthesized source of dNTPs, whereas repair needs concentrated nuclear sources near the sites of damage. To test whether *p53R2* has a role in repair, the investigators inhibited it with antisense DNA and observed a sharp decrease in incorporation of dNTPs into

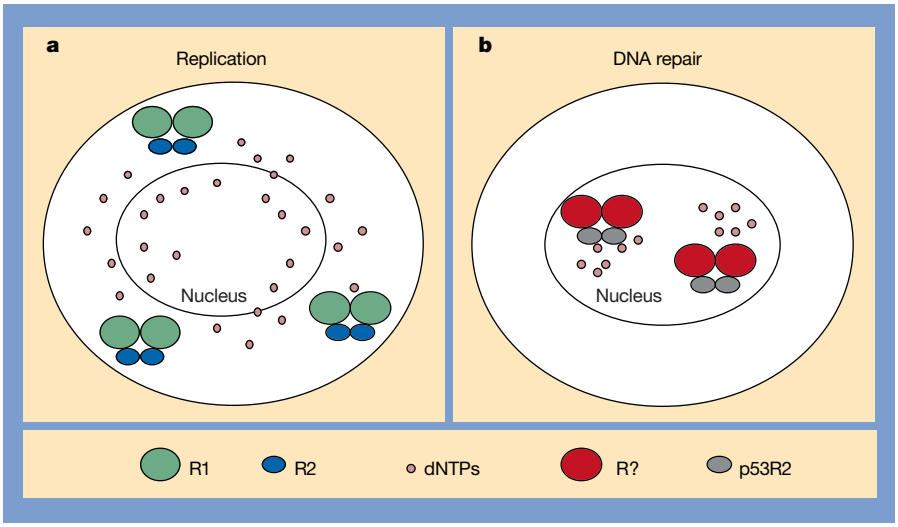

Figure 1 **Differential composition and localization of ribonucleotide reductase (RNR) during DNA replication and repair.** a, **During the S phase in the cell cycle, the cytoplasmically localized RNR causes the production of deoxyribonucleotide triphosphates (dNTPs) in the cytoplasm which diffuse into the nucleus for DNA replication. R1 and R2 are the two subunits of the RNR tetramer.** b, **Tanaka *et al.*[1] show that, in the presence of DNA damage, the *p53R2* gene is induced and, together with an unknown large subunit protein, its product causes dNTP production in the nucleus to facilitate DNA repair. A cell in the G1 or G2 phase is shown.**