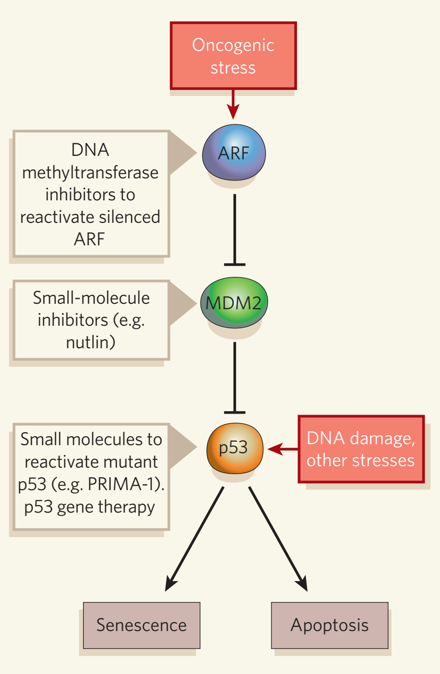

Figure 1 | Approaches to reactivating the p53 pathway. In the cell, p53 is usually degraded by the MDM2 protein. Various cellular stresses, including DNA damage, can activate p53, and once triggered, p53 can initiate programmed cell death (apoptosis) or permanent growth arrest (senescence). The p53 pathway is probably compromised to various extents in all human cancers. There are several potential approaches to reactivating the pathway in human cancers, depending on the type of lesion in the p53 pathway. Mutant p53 could be targeted directly with drugs or gene therapy. Or p53 signalling could be reactivated in tumours that overexpress MDM2 by using MDM2 inhibitors such as the nutlin molecules[12] that are in preclinical development. Likewise, the ARF tumour suppressor, which inhibits MDM2, is sometimes switched off in cancer by 'epigenetic' silencing, and agents that reverse such silencing are already well into human testing (for example, DNA methyltransferase inhibitors).

of tumour shrinkage: a rapid, non-apoptotic clearance of senescent tumour cells by an exuberant immune-mediated mechanism. As this tumour clearance takes place in 'nude' mice, which lack functional B and T immune cells, the authors argue that it represents activation of an innate immune response as a result of the production of proinflammatory molecules (for example, CSF1 and IL-15) by the senescent cells. It is worth noting, however, that markers of senescence accumulate in many tissues with age[8,9] and that senescent cells in precancerous tissue can persist for decades or more in humans[10,11]. Thus, some senescent cells seem to be impervious to this clearance mechanism. A better understanding of how this phenomenon works may make it possible to unleash the process on cancerous cells, while sparing normal ageing tissues.

These three papers[3–5] provide reason for cautious optimism that reactivation of p53, and possibly of other tumour-suppressor genes, might be useful in treating certain cancers. Reinstating p53 will no doubt be difficult in practice, but may be simplest in tumours with normal p53 that lack tumour-suppressor activity because of other mutations in the p53 pathway (Fig. 1). Moreover, the more rigorous determination of which factors are involved in tumour maintenance and the precise genetic and biological context in which they work will pave the way for further therapeutic possibilities.

The unwelcome finding in human patients, however, has been that although therapies that target tumour-maintaining oncogenes are initially effective, secondary genetic events occur all too often that render the tumours resistant to such treatment. Indeed, Martins *et al.*[5] inject a dose of clinical realism into the possibility of exploiting p53 reactivation for therapeutic ends. They found that although reactivation of p53 did induce widespread tumour-cell apoptosis, this was followed by the rapid appearance of tumours that progressed despite p53 expression. In many cases, these tumours harboured secondary lesions in regulators of the p53 pathway that rendered them resistant to p53. So, even under experimental conditions designed for near-optimal p53 reactivation, secondary resistance can limit the long-term benefit of the approach. Despite this cautionary observation, the three papers establish that resurrecting p53 can be of therapeutic benefit even in established, fully formed cancers. ■

Norman E. Sharpless is in the Department of Medicine and Genetics, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina 27599, USA.
Ronald A. DePinho is in the Center for Applied Cancer Science and Departments of Medical Oncology, Medicine and Genetics, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115, USA.
e-mails: nes@med.unc.edu; ron_depinho@dfci.harvard.edu

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PALAEOCLIMATE

When the world turned cold

Gabriel J. Bowen

As massive ice sheets grew on Antarctica during the first major glaciation of the Cenozoic era, the northern continents cooled and dried. The coincidence in timing implies that the cause was global rather than regional.

It has been nearly 34 million years since Earth was last free of large continental ice sheets. Before the beginning of the Oligocene epoch, 33.7 million years ago, Antarctica had been a lush, green continent for several tens of millions of years, and the only significant concentrations of ice on Earth probably occurred on the Antarctic highlands and in and around the Arctic Ocean. Then, in two short pulses spanning the first 300,000 years of the Oligocene, ice sheets grew over most of Antarctica[1]. The continent has been largely ice-covered ever since (Fig. 1, overleaf). But did the severe event at high southern latitudes affect the rest of the globe? And if so, how? Elsewhere in this issue, Dupont-Nivet *et al.*[2] and Zanazzi *et al.*[3] describe climatic and biotic changes in central Asia and North America during the early Oligocene that implicate declining levels of atmospheric carbon dioxide as a driver for changes in both hemispheres.

Given the importance of the early Oligocene event to the evolution of polar climate, it may be surprising that we have an imperfect understanding of its global consequences. In fact, records preserved in the veneer of sedimentary rock that coats the continents suggest a variety of changes in the climate, and in plant and animal communities, during the transition from the warm Eocene world to the cool Oligocene. But owing to inaccuracies in the dating of continental rocks and conflicting results generated using different methodologies, the interpretation of these records has been in question. Moreover, evidence for climate change in the Northern Hemisphere seemed to clash with the prevailing explanation for the cause of Antarctic glaciation in the early Oligocene: the tectonic rifting of Australia and South America from Antarctica, which was argued to have initiated the Antarctic Circumpolar Current and thus climatically isolated Antarctica[4]. Computer models suggest that such a change in ocean circulation would warm, rather than cool, the northern continents[5].

Dupont-Nivet *et al.*[2] (page 635) apply precision dating techniques to demonstrate that climate change in central Asia occurred at the

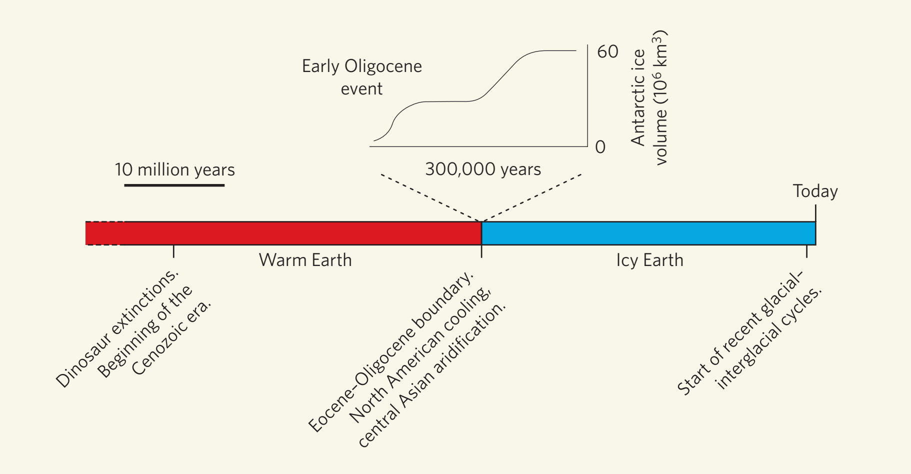

Figure 1 | The Eocene–Oligocene boundary in context. This timeline shows the transition from the warm pre-Oligocene Earth to today's icy planet that occurred at the Eocene–Oligocene boundary (33.7 million years ago), approximately midway between the extinction of the dinosaurs and today. The drying in central Asia and cooling of North America described by Dupont-Nivet *et al.*[2] and Zanazzi *et al.*[3] coincided with an abrupt, 300,000-year build-up of continental-scale ice sheets on Antarctica. (Graphic after ref. 1.)

same time as the early Oligocene glaciation of Antarctica. Their data come from the Xining basin on the northeastern margin of the Tibetan plateau, where a thick stack of sedimentary rocks records the abrupt disappearance of lakes that had episodically flooded the basin prior to the Oligocene epoch. Using a detailed record of changes in Earth's magnetic field as these rocks were deposited, the authors temporally link the rock layers in the Xining basin to seafloor records documenting ice build-up in the Antarctic.

The magnetic records also demonstrate that the flooding and drying of the basin before the Oligocene drying event was episodic, and occurred in step with the same 100,000-year cyclic change in the shape of Earth's orbit that has been the pacemaker of recent ice ages. Counting these flood cycles gives the authors a precise assessment of the age of Xining basin drying relative to the marine records. The increase in Asian aridity was essentially synchronous with Antarctic glaciation. Furthermore, a major turnover of mammals is associated with the aridification of central Asia at this time[6], and Dupont-Nivet and colleagues' chronology provides the first solid link between this change and the global early Oligocene event.

In the second paper, Zanazzi *et al.*[3] (page 639) report new North American climate-change records produced using an innovative twist on a common geochemical technique. They measure the relative abundance of the stable isotopes of oxygen (^{18}O/^{16}O) in ancient minerals. This is determined by two factors: the ^{18}O/^{16}O of the water from which the mineral was derived, and the temperature at the time of formation. If one of these two values is known, the other can be estimated. The challenge for workers studying continental palaeoclimate is that usually neither parameter is known.

Zanazzi *et al.* overcome this limitation by analysing two materials that have different chemical histories. They use ^{18}O/^{16}O measurements of dense, chemically resilient tooth enamel from mammal fossils to estimate the ^{18}O/^{16}O of ancient water at their study sites in the northern Great Plains of the United States. Because the tooth mineral grew at the near-constant temperature of the mammal's body and — given its density — is unlikely to change in isotopic composition after deposition, the authors can estimate the ^{18}O/^{16}O of the animal's body water, which is closely related to that of its drinking water. Once the isotopic composition of water is known, they use ^{18}O/^{16}O from fossil bone, which is porous and obtains most of its oxygen at ambient temperatures after it is buried in soils, to reconstruct temperatures.

Zanazzi and colleagues' data[3] present a mixed picture relative to previous studies. They provide robust evidence for a substantial drop in average annual temperatures of about 8 °C. This is near the high end of values obtained in previous studies, and implies that the authors' continental site cooled much more than did the mid-latitude oceans[7]. The authors also relate this temperature change to a burst of faunal turnover in North America in the early Oligocene, noting that the wave of extinctions occurred primarily among cool-blooded animals that might have been most sensitive to a rapid decline in temperature. In further analysing their data using other isotope–climate relationships, however, the authors find no evidence for the changes in seasonal temperature range or aridity that have been inferred in other studies[8,9].

Together, these two studies[2,3] convincingly demonstrate the global nature of climate and biotic change during the early Oligocene. They strongly support challenges to the ocean-circulation hypothesis for the early Oligocene event[10,11], and imply that a global forcing agent, such as declining concentrations of atmospheric greenhouse gases[12], played a role in triggering the build-up of Antarctic ice. But the detailed links between the observed climate changes and global forcing remain unresolved.

For example, Zanazzi and colleagues' lack of evidence for changes in aridity accompanying the major cooling of the North American continent is puzzling, both because of the range of existing evidence for aridification[8], and because continental cooling should have decreased the atmosphere's capacity to carry water to continental interiors. However, although their data offer no obvious support for Northern Hemisphere aridification, the interpretation of these data is less well constrained than for their coupled tooth/bone isotope measurements, and they may not be entirely inconsistent with the changes noted in earlier studies.

In Asia, climate-model simulations are needed to test whether climate cooling resulting from reduced CO_2 levels can indeed explain drying in this region. If they cannot, it is possible that Asian drying and early Oligocene climate change elsewhere are indirectly linked. One possibility, which remains to be tested, is that regional tectonic events (that is, uplift of the Himalayas) caused both the observed aridification in central Asia and far-afield climate change in Antarctica and North America. A pulse of Himalayan uplift near the Eocene–Oligocene boundary could have caused drying in central Asia by creating a rain shadow or increasing the seasonality of precipitation in the region. It might simultaneously have triggered a global reduction in atmospheric CO_2 concentrations through increased weathering of the mountains, which pulls CO_2 from the atmosphere.

What is clear is that these two studies[2,3] show that the early Oligocene was a turning point not just for Antarctica, but for Earth as a whole. If that event can serve as a guide, more than just polar ice is at stake as atmospheric CO_2 levels push the planet's climate towards an increasingly warm, potentially ice-free state. ■

Gabriel J. Bowen is in the Department of Earth and Atmospheric Sciences, Purdue University, West Lafayette, Indiana 47907, USA.
e-mail: gjbowen@purdue.edu

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Editor's Summary

8 February 2007

Local climate goes global

The Eocene–Oligocene transition, about 33.5 million years ago, was a major global climate event. The end of the Eocene was unusually warm with no significant ice on Antarctica but the Oligocene saw the arrival of a permanent Antarctic ice-sheet. Two papers this week relate to the continental effects of this global change. Dupont-Nivet *et al*. examined sedimentary records from the Tibetan plateau and find a drop in atmospheric water, which caused cooling and aridification coincident with Antarctic cooling. Previous studies attributed this phenomenon to the rapid uplift of the Tibetan plateau, but this new work suggests that regional Tibetan climate was influenced by global events. In an unrelated paper on the same climate transition, Zanazzi *et al*. explore the cooling in North America at the time. Using stable isotope measurements from fossil teeth and bones to create a proxy temperature record, they find a large drop in mean annual temperature of 8.2 °C — a greater fall than seen in the oceans. This continental transition may explain why many cold-blooded reptiles and amphibians became extinct whereas mammals — able to regulate their body temperature — escaped relatively unscathed.

News and Views : Palaeoclimate: When the world turned cold

As massive ice sheets grew on Antarctica during the first major glaciation of the Cenozoic era, the northern continents cooled and dried. The coincidence in timing implies that the cause was global rather than regional.

Gabriel J. Bowen

doi:10.1038/445607a

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Letter: Tibetan plateau aridification linked to global cooling at the Eocene–Oligocene transition

Guillaume Dupont-Nivet, Wout Krijgsman, Cor G. Langereis, Hemmo A. Abels, Shuang Dai and Xiaomin Fang

doi:10.1038/nature05516

First paragraph | Full Text | PDF (0) | Supplementary information

Letter: Large temperature drop across the Eocene–Oligocene transition in central North America

Alessandro Zanazzi, Matthew J. Kohn, Bruce J. MacFadden and Dennis O. Terry

doi:10.1038/nature05551

First paragraph | Full Text | PDF (0) | Supplementary information