an independent group working on the genetic basis of anxiety has implicated ROS metabolism in this complex trait[6]. Are the behavioural changes in the PGC-1α-deficient mice also due to an absence of antioxidant defences? If so, does this imply that what cell biologists call oxidative stress and what social scientists call psychological stress might ultimately share a common mechanism? Further study is necessary, but people who fear public speaking may take some comfort in the notion that the problem might not be in their head but rather, more specifically, in their mitochondria.

The work of Spiegelman and colleagues[1] brings up another interesting aspect of mitochondrial biology. It is well known that these organelles, whether they come from simple organisms or complex mammals, all leak measurable amounts of ROS. Experimental systems that simply increase the production of antioxidant proteins seem to be quite effective at reducing this leakage. If ROS synthesis is so bad, and a molecular solution so apparently straightforward, why has this 'design flaw' not been eradicated during the billions of years of evolution? There are many possible answers, but one is that the notion that ROS from the mitochondria are solely harmful could be incorrect. Indeed, substantial evidence exists that ROS generated in the cytoplasm could have vital signalling functions[7], and this might also be true for oxidants derived from mitochondria[8,9]. The new study[1] strengthens this possibility and suggests that a homeostatic loop exists between mitochondria and ROS and that this loop is, at least in part, orchestrated by PGC-1α (Fig. 1).

Previous reports have suggested that certain life-extending strategies, such as calorie restriction, might work through the PGC-1α-induced mitochondrial biogenesis programme[10]. Spiegelman and colleagues' study suggests that PGC-1α could also alter our susceptibility to neurodegenerative conditions that are linked to mitochondrial dysfunction and oxidative stress, such as Parkinson's disease. Therefore, fine-tuning the activity of this resourceful coactivator might have a wide range of clinical benefits, including potentially allowing us to live longer and think more clearly. Not a bad set of objectives, especially if we are ultimately going to need to tackle really tricky problems like global warming. ■

Toren Finkel is in the Cardiology Branch, NHLBI, National Institutes of Health, 10/CRC 5-3330, 10 Center Drive, Bethesda, Maryland 20892, USA.
e-mail: finkelt@nih.gov

1. St-Pierre, J. *et al. Cell* **127,** 397–408 (2006).
2. Finck, B. N. & Kelly, D. P. *J. Clin. Invest.* **116,** 615–622 (2006).
3. Puigserver, P. *et al. Cell* **92,** 829–839 (1998).
4. Lin, J. *et al. Cell* **119,** 121–135 (2004).
5. Leone, T. C. *et al. PLoS Biol.* **3,** e101 (2005).
6. Hovatta, I. *et al. Nature* **438,** 662–666 (2005).
7. Finkel, T. *Curr. Opin. Cell Biol.* **15,** 247–254 (2003).
8. Nemoto, S., Takeda, K., Yu, Z. X., Ferrans, V. J. & Finkel, T. *Mol. Cell Biol.* **20,** 7311–7318 (2000).
9. Werner, E. & Werb, Z. *J. Cell Biol.* **158,** 357–368 (2002).
10. Lopez-Lluch, G. *et al. Proc. Natl Acad. Sci. USA* **103,** 1768–1773 (2006).

CLIMATE CHANGE

The south–north connection

Eric J. Steig

A new ice-core record from Antarctica provides the best evidence yet of a link between climate in the northern and southern polar regions that operates through changes in ocean circulation.

Over the past 20 years, the analysis of ice cores has been transforming our understanding of past climate. Most notably, the Vostok core from Antarctica[1] provided remarkable evidence of the correspondence between temperature and atmospheric carbon dioxide concentrations over the past 420,000 years. And the GISP2, GRIP and NGRIP cores from Greenland[2,3] offered a view in unprecedented detail of climate change over the past 100,000 years (including the revelation that abrupt warming events of 10 °C or more have taken place in Greenland).

More recently, the European Project for Ice Coring in Antarctica (EPICA) obtained the longest ice-core record yet[4], one spanning 800,000 years of climate history, from Dome C, in the same sector of Antarctica as Vostok. The EPICA team has now pulled off another feat. As it reports on page 195 of this issue[5], it has completed analysis of 2,500 metres of an ice core from Dronning Maud Land in the Atlantic sector of Antarctica (Fig. 1).

The significance of this 'EDML' core is not its sheer length; at the site concerned, 2,500 m takes us back 150,000 years. Rather, it is its resolution: this is the highest-resolution record obtained outside Greenland that extends well beyond the last glacial maximum (about 20,000 years ago). In consequence, the EPICA team has been able to place the EDML record with high precision on the same timescale as the records from Greenland. This allows us to compare the Greenland and Antarctic records over time intervals as short as a few centuries.

At this point, an analogy may help. On a year-to-year basis, much global climate variability is dominated by the El Niño–Southern Oscillation (ENSO). Understanding ENSO has required comparison of climate records in the main ENSO region (the tropical Pacific) with records elsewhere. This could not have been achieved without placing different time-series data on the same timescale. We would otherwise have little confidence, for example, in the observed correspondence between ENSO and rainfall variations in southern California. Nor would it be meaningful to try to understand the ocean and atmospheric dynamics that give rise to that relationship, because we could not reject the null hypothesis that it was merely due to chance. The Greenland and Antarctic ice-core records are likewise measures of climate variability, but on timescales of centuries, millennia and longer. Indeed, the high-resolution measures of climate afforded by ice-core records show unambiguously that climate varies on these longer timescales much more widely than one would expect from simple extrapolation of the power spectrum of observed (modern) climate[6].

The usual explanation for the millennial-scale variability is that it is due to changes in the deep meridional overturning circulation (MOC) in the Atlantic Ocean. Put simply, a vigorous MOC is thought to deliver heat to the North Atlantic at the expense of the Southern Ocean. Increases and decreases in MOC strength should thus result in a climate 'see-saw' between the Southern and Northern

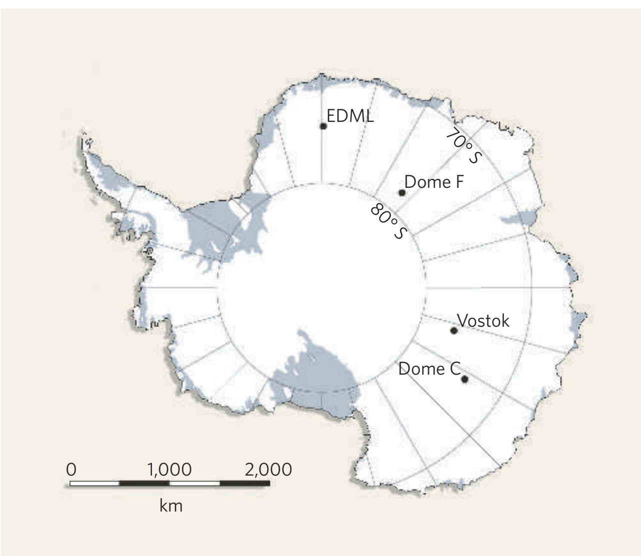

Figure 1 | Core sites. Locations of deep ice-core drilling projects in Antarctica where records longer than 100,000 years have been obtained. The new EDML core[5] in Dronning Maud Land has the highest time resolution of these cores.

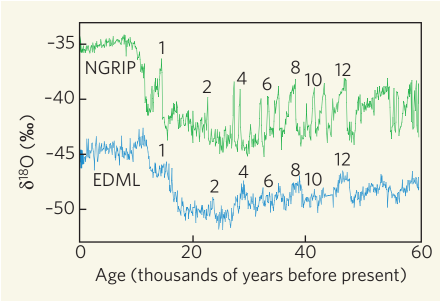

Figure 2 | Core data. Comparison of records from the EDML ice core from Antarctica[5] and the NGRIP core from Greenland[3]; oxygen-isotope ($\delta^{18}O$) ratios are a measure of temperature. Temperatures increase gradually in Antarctica, reaching a maximum at about the same time that Greenland warms rapidly. The numbers refer to designated warming events in Greenland and the corresponding Antarctic temperature maxima. Statistically, the records are largely coherent for time periods down to around 800 years, which is similar to the relative dating uncertainty. Thus, the Greenland and Antarctic climates are meaningfully related on timescales as short as measurement precision allows.

Hemispheres[7]. An observation cited in support of this idea is that there is an out-of-phase relationship between Antarctic and Greenland ice-core records of temperature (or rather, of oxygen and deuterium isotope ratios, which are well-established proxies for temperature)[8]. The problem has been that — unlike in the ENSO analogy — there is considerable uncertainty in the dating. Analyses of the existing records have generally shown that the relationship between the Greenland and Antarctic records is weak and not statistically significant, except on the very longest timescales associated with well-understood astronomical factors (the Milankovich forcing of ice ages)[9]. So it has been difficult to rule out the null hypothesis that the variability in these records largely reflects regional phenomena such as variations in wind patterns or sea-ice extent.

This is where the EDML results come in. They show that the Antarctic and Greenland ice-core records are meaningfully related, and on quite short timescales. In particular, comparison of the oxygen-isotope records shows that one can make a direct link between the distinctive temperature maxima in the Antarctic record (at least going back 60,000 years) and the unambiguous abrupt warmings in Greenland (Fig. 2). Not every Antarctic temperature maximum is as distinct as the Greenland warmings; for example, it is not clear why the small maxima labelled 6 and 10 in Fig. 2 should count as 'events', but the similarly sized bumps between maxima 1 and 2 should not. But the relationship is too strong to be due to chance.

In fact, for the interval 20,000 to 90,000 years ago a remarkable 40% of the variance in the Greenland records can be explained by the EDML time series. A more rigorous estimate of the spectral coherence between the records shows that this significant relationship extends to timescales as short as a few centuries. Furthermore, there is a consistent out-of-phase relationship between the records. They are not strictly 'antiphased', as the term see-saw would imply. Rather, the average phase relationship is about 90°. Although cold conditions in Greenland tend to be associated with warming in Antarctica, and vice versa, the peak warmth in both records actually occurs at about the same time.

Does the EDML record demonstrate the dominant influence of the MOC on climate variability? This is not just an academic question. Variations in this circulation have been invoked to explain everything from the abrupt climate changes observed in the Greenland records to the Little Ice Age (a period of cooling between about AD 1400 and 1900 in the North Atlantic region). And the possibility of a sensitive MOC has been proposed as a 'tipping point' in future human-influenced climate change[10].

One objection to these ideas is that the MOC plays a minor role in the heat budget of the polar regions[11]. Heat transport in the atmosphere is much more important, and the atmosphere might simply compensate for any changes in MOC[12]. Furthermore, the causes of the purported changes in MOC are not understood. The conventional answer — flooding of the North Atlantic Ocean by ice and meltwater from the Laurentide ice sheet in northern North America (so-called Heinrich events) — is not very convincingly supported by the evidence[13].

The EDML data do not directly address these concerns. But they are nonetheless compatible with the idea that the MOC has a central role in millennial-scale variability. What is particularly compelling is that there is a strong linear relationship between the magnitude of warming in Antarctica and the duration of the warm period that follows each abrupt event in Greenland (see Fig. 3 of the paper[5] on page 197). The authors' explanation is simple: the duration of the warm periods in Greenland reflects the duration of reduced MOC, and hence the amount of heat retained in the Southern Ocean. This is consistent with a model[14], proposed a few years ago, in which the magnitude of Antarctic temperature change is controlled by the effective size of the Southern Ocean heat reservoir (including both dynamic and thermodynamic effects). We may have to wait some time before we see whether these results can be reproduced by more sophisticated ocean–atmosphere climate models, because realistically encapsulating the dynamics of the Southern Ocean in such models remains a problem. But we can hope that these new results[5] will inspire the relevant work to be done. ■

Eric J. Steig is in the Department of Earth and Space Sciences, 70 Johnson Hall, University of Washington, Seattle, Washington 98195, USA.
e-mail: steig@ess.washington.edu

1. Barnola, J. M., Raynaud, D., Korotkevich, Y. S. & Lorius, C. *Nature* **329,** 408–414 (1987).
2. Grootes, P. M., Stuiver, M., White, J. W. C., Johnsen, S. & Jouzel, J. *Nature* **366,** 552–554 (1993).
3. North Greenland Ice Core Project members *Nature* **431,** 147–151 (2004).
4. EPICA Community Members *Nature* **429,** 623–628 (2004).
5. EPICA Community Members *Nature* **444,** 195–198 (2006).
6. Huybers, P. & Currey, W. *Nature* **441,** 329–332 (2006).
7. Crowley, T. J. *Paleoceanography* **7,** 489–497 (1992).
8. Blunier, T. *et al. Nature* **394,** 739–743 (1998).
9. Roe, G. H. & Steig, E. J. *J. Clim.* **17,** 1929–1944 (2004).
10. Rahmstorf, S. in *Encyclopedia of Quaternary Sciences* (ed. Elias, S. A.) (Elsevier, Amsterdam, in the press).
11. Seager, R. & Battisti, D. S. in *Global Circulation of the Atmosphere* (eds Schneider, T. & Sobel, A. H.) (Princeton Univ. Press, in the press).
12. Wunsch, C. *Quat. Res.* **65,** 191–203 (2006).
13. Steig, E. *Nature* **439,** 660 (2006).
14. Stocker, T. F. & Johnsen, S. J. *Paleoceanography* **18,** 1087 (2003).

STRUCTURAL BIOLOGY

Enzyme theory holds water

Matthew Freeman

Intramembrane proteases have attracted much attention because of their biological and medical value. The first crystal structure of one of these enzymes begins to solve the mystery of how they work.

Proteases are some of the most potent tools to which a cell has access, because, unlike most other protein-modifying enzymes, they catalyse an essentially irreversible reaction — the breaking of peptide bonds. This can obviously be used to degrade unwanted proteins, but proteases also have many vital regulatory functions[1]. In the past few years, a class of proteases called intramembrane proteases has been discovered. These comprise diverse families, but all have multiple transmembrane domains and an active site apparently embedded within the hydrophobic region of cell membranes.

All intramembrane proteases share the curious property of cutting their membrane-spanning protein targets in the transmembrane regions — that is, they are thought to perform the peptide-cleaving reaction (which requires water) within the lipid bilayer of cellular membranes[2]. As this is an environment where water is traditionally assumed to be in short supply, this is a somewhat heretical idea. This