with sensory organs. It had chemosensory nuchal organs and palpae; a pair of two-celled larval eyes for phototaxis[2]; and possibly a pair of more elaborate, multicellular adult eyes with an alternating arrangement of rhabdomeric photoreceptors and shading pigment cells. The latter combination is found in extant errantians[8] and in the sipunculans[9], which represent an outgroup to both errantians and sedentarians (see Fig. 1 of the paper[1]).

The urannelid was segmented, a detail that is clear from the nested position of two unsegmented taxa, the echiurans and sipunculans, within segmented groups[10]. This ancestor probably lived on the sea floor, using its relatively complex lateral appendages for undulatory crawling (as seen in today's Errantia and for example in the Spionidae, which lie in the basal part of the Sedentaria branch of the tree). Given the power of phylogenomics, we might soon know what the urannelid mollusc- or flatworm-like relatives looked like in the ancient oceans. ■

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CLIMATE CHANGE

Another Antarctic rhythm

A novel explanation for the long-term temperature record in Antarctic ice cores invokes local solar radiation as the driving agent. This proposal will prompt palaeoclimate scientists to pause and to go back to basics. SEE LETTER P.91

KOJI FUJITA

Analysis of ice cores retrieved from the Antarctic and Greenland ice sheets is one of the main sources of our understanding of past climate. A component of that understanding is that, on timescales of 20,000 years and more, climate change in Antarctica is determined by the amount of solar radiation (insolation) reaching high northern latitudes in summer. On page 91 of this issue, Laepple *et al.*[1] call into question some of the evidence for that view.

Precisely dated polar ice cores have allowed examination of the 'bipolar see-saw' relationship of air temperatures between the hemispheres on millennial timescales[2], as well as of longer-term, glacial–interglacial climate change paced by variations in Earth's orbit — the Milankovitch forcing of ice ages[3]. In these studies, the use of isotopes that are stable in water, in the form of the ratios of oxygen and deuterium isotopes, is well established. These ratios constitute the fundamental proxy measurements for estimating past temperatures from ice cores at both poles[2–4].

Because ice cores consist of ice, the stable-isotope ratios in the ice stem from those contained in precipitation (snow, which becomes compacted to ice). In other words, if there is no precipitation, no isotopic signal remains in the ice core. This simple principle has been acknowledged in interpreting the Greenland ice-core record[5]. Subsequent studies[6,7] have described how changes in the seasonal pattern of precipitation during glacial–interglacial cycles have significantly biased the isotopic temperature record in Greenland. But it was thought that the effect in Antarctica was probably minor because of its comparatively stable precipitation seasonality.

Laepple and co-authors[1] apply this idea of precipitation seasonality to the Antarctic ice-core record. However, they do not deal with changes in seasonal patterns, as the previous studies did, but instead consider the situation in which seasonality is itself unchanging and in which snow accumulation over inland Antarctica is maximal in winter and minimal in summer. This seasonality in snowfall has various causes, such as the strong radiative cooling that induces clear-sky precipitation and increased moisture transport in winter, and sublimation of ice into water vapour in summer.

By assuming that this seasonal pattern of snow accumulation has persisted throughout glacial–interglacial cycles, and that the local air temperature has fluctuated according to the present-day relationship between temperature and insolation, the authors[1] produce an accumulation-weighted insolation signal as a record of temperatures in Antarctic ice cores. They find that it has the opposite phase to the orbital-precession component (determined by long-term changes in the orientation of Earth's rotational axis) of the local summer-insolation signal — and so, surprisingly, that it is in phase with summer-insolation intensity in the Northern Hemisphere.

If the Antarctic local temperature is determined by local insolation, the precession component in the ice-core temperature signal should be out of phase with Northern Hemisphere insolation, because the precession component is out of phase between the two hemispheres. However, the precession component filtered from the isotopic temperature record in the Antarctic ice cores is coherent and in phase with the Northern Hemisphere insolation intensity[3] — seemingly supporting the Milankovitch theory, according to which southern climate is driven by insolation changes at high northern latitudes.

But does the close phasing necessarily support a causal relationship? Perhaps not. Laepple and co-authors[1] have rethought how the signals of temperature change are produced. Their accumulation-weighted insolation record suggests that a precession rhythm synchronized with — but not caused by — the Northern Hemisphere could be generated if the local temperature fluctuated in line with local insolation conditions in the Southern Hemisphere. The unveiling of this 'pseudo-rhythm' strikes at the foundation of temperature estimates gleaned by analysing isotope ratios in ice cores. Does it mean, as Laepple *et al.* suggest, that the evidence from Antarctic ice cores cannot be used to support or refute the Milankovitch theory?

This theory is supported not just by temperatures inferred from Antarctic ice cores, but also by sea surface temperatures recorded in sediment cores from the Southern Ocean. In these cores, the orbital-precession rhythm is often found to be in phase with summer insolation in the Northern Hemisphere and therefore opposing the local summer insolation[8]. The seasonality of snow accumulation does not affect sediment processes in the ocean. Furthermore, the existence of shorter (millennial timescale) but strong bipolar see-saw connections between the two hemispheres implies that there are indeed mechanisms for the inter-hemispheric propagation of climate signals through the ocean and/or atmosphere[2]. There is no reason to believe that such mechanisms have not operated over longer timescales.

A caveat regarding the results themselves is that Laepple and colleagues' insolation-based air-temperature estimate shows a rather small amplitude (around 0.7 °C peak to peak) compared with that derived from ice cores (3 °C peak to peak). This is probably because the authors' use of local insolation as the temperature proxy means that they

assume zero insolation during winter (polar night) throughout glacial–interglacial cycles. They themselves acknowledge this point, and suggest that other factors not accounted for in their approach may explain the discrepancy.

Nevertheless, we must now consider that the orbital-precession rhythm in Antarctic ice cores can partly be attributed to local conditions. In the same way that an ill-fitting piece of a jigsaw puzzle can be disconcerting, this pseudo-rhythm will be discomfiting to those who study palaeoclimate and climate dynamics. 'Is the signal I see really created by climate change?', is a question they will have to ask themselves. And they will need to take a hard look at the principles on which their data are founded. The relationship between the isotopes in water and air temperature, for instance, is based on geographical (spatial) observations only. But its temporal variability has not been confirmed at any ice-core drilling sites in inland Antarctica, even by observations on an annual timescale. Sometimes, in science as in life, it is necessary to pause in order to make progress. ■

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STEM CELLS

The dark side of induced pluripotency

Induced pluripotent stem cells have great therapeutic potential. But genomic and epigenomic analyses of these cells generated using current technology reveal abnormalities that may affect their safe use. SEE ARTICLES P.58, P.63 & P.68

MARTIN F. PERA

Induced pluripotent stem cells (iPSCs) are generated through the reprogramming of differentiated adult cells and can be coaxed to develop into a wide range of cell types. They therefore have far-reaching potential for use in research and in regenerative medicine. But the ultimate value of these cells as disease models or as sources for transplantation therapy will depend on the fidelity of their reprogramming to the pluripotent state, and on their maintenance of a normal genetic and epigenetic (involving aspects other than DNA sequence) status. Five recent surveys[1–5], including three in this issue[1–3], show that the reprogramming process and subsequent culture of iPSCs *in vitro* can induce genetic and epigenetic abnormalities in these cells. The studies raise concerns over the implications of such aberrations for future applications of iPSCs.

It has long been known[6] that, during cultivation *in vitro*, human embryonic stem cells (ESCs) can become aneuploid; that is, they acquire an abnormal number of chromosomes. The new papers have applied various state-of-the-art genomic technologies to assess in detail the occurrence and frequency of genetic and epigenetic defects in both human iPSCs and ESCs.

Hussein *et al.*[1] (page 58) studied copy number variation (CNV) across the genome during iPSC generation, whereas Gore and colleagues[2] (page 63) looked for point mutations in iPSCs using genome-wide sequencing of protein-coding regions. Lister *et al.*[3] (page 68) examined DNA methylation — an epigenetic mark — across the genomes of ESCs and iPSCs at the single-base level. These studies, along with other investigations into changes in chromosome numbers[4] and CNV[5] in the two kinds of stem cell, lead to the conclusion that reprogramming and subsequent expansion of iPSCs in culture can lead to the accumulation of diverse abnormalities at the chromosomal, subchromosomal and single-base levels. Specifically, three common themes, regarding the genetic and epigenetic stability of ESCs and iPSCs, emerge.

First, by several measures, iPSCs display more genetic and epigenetic abnormalities than do ESCs or fibroblasts — the cells from which they originated. Chromosomal abnormalities appear early during the culturing of iPSCs[5], a phenomenon not generally observed in ESCs. Also, the frequency of mutations in iPSCs is estimated to be ten times higher than in fibroblasts[2]. And there are greater numbers of novel CNVs (CNVs not found in the cell of origin or in human genomes of comparable background) in iPSCs than in ESCs[1,5]. Similarly, the epigenome of iPSCs features incomplete reprogramming (with cells retaining epigenetic marks of the cell of origin), aberrant methylation of CG dinucleotides, and abnormalities in non-CG methylation — an epigenetic feature seen only in pluripotent cells[3].

Second, the studies show that genetic abnormalities can arise at different stages of iPSC generation. Some lesions are inherited from the cell used for reprogramming. Gore *et al.*[2] employ a particularly sensitive approach to demonstrate that a subset of point mutations found in iPSC lines pre-existed in a small minority of fibroblasts used for reprogramming. Other lesions seem to arise early on in reprogramming, as mentioned previously. For example, Hussein *et al.*[1] found large numbers of new CNVs during early passages (subcultures) following reprogramming, but noted that subsequent growth *in vitro* seemingly selected against most of the changes, which implies that they are deleterious for the cells that bear them. The studies also report changes that apparently relate to long-term adaptation to cell culture. These include over-representation either of the short arm of chromosome 12 (12p) or of this entire chromosome[4,5], and of a subregion in the long arm of chromosome 20 (ref. 5). Both of these changes have been observed[6] in ESC lines, with an increased number of 12p being a hallmark of testicular germ-cell tumours — the malignant prototype of human pluripotent stem cells.

Third, several of the groups[2,4,5] report clues to the potential function of the genetic lesions that arise in ESCs and iPSCs. For example, regions prone to amplification, deletion or point mutation seem to be enriched in genes involved in cell-cycle regulation and cancer. Although the changes observed do not strongly implicate any particular gene functionally as a target for change during the amplification of iPSCs or during their adaptation to culture conditions, the frequent association of the affected genes with cancer gives cause for concern.

This highly significant body of data[1–5] provides a revealing, in-depth portrait of the status of the genome and the epigenome during cellular reprogramming. But it also leaves open some fairly challenging questions.

The studies provide little insight into the crucial question of what aspects of the reprogramming methods might predispose the cells to the accumulation of recurrent genetic or epigenetic lesions. Although recurrence of change in specific genomic regions across a number of cell lines strongly implies a selective process, in several studies the researchers noted that there was no obvious correlation between the extent of genetic damage in a