genomes derived from sperm and eggs immediately after the cells fuse during fertilization showed that maternal chromatin has loops and TADs, but lacks compartments, implying that these features arise independently.

Single-cell Hi-C studies are of great value. But even if cells can be arranged in pseudotime, as achieved by Nagano and colleagues, they can provide only static snapshots of chromosome conformation. Unlocking the temporal dynamics of chromatin folding will require the analysis of live cells over time using microscopy.

An open question that could be resolved using live imaging is whether specific TADs inferred by Hi-C maps really exist in individual cells. TADs were first identified in Hi-C maps generated by averaging the contacts found in millions of cells. As such, they could arise from weak preferences summed across many cells, with real contacts in individual cells frequently crossing TAD boundaries. Single-cell Hi-C (which does measure contacts in individual cells) has not yet given a definitive answer: the current study provides evidence that TADs do indeed exist in individual cells, whereas other recent analyses[12,13] have reached the opposite conclusion.

Single-cell Hi-C data sets yield the most information if computational modelling is used to infer full models of 3D chromosome structure for whole, individual cells. Nagano *et al.* are only the second group to achieve this, and do so for cells exiting mitosis[13]. A major technical hurdle has prevented the wider adoption of this potentially powerful computational modelling — cells normally contain maternal and paternal copies of each chromosome, and these have similar DNA sequences but are folded differently. Because most of the contacts identified by single-cell Hi-C cannot be unambiguously attributed to either parental genome, only a few contacts are left available for modelling approaches. The two studies that inferred full models avoided this issue by using specific mouse embryonic stem cells containing only one copy of each chromosome, and by examining only cells in which the DNA had not yet replicated.

There is much research into whether changes in chromatin folding can explain why thousands of variants in regions of the genome that do not encode proteins are linked to human disease. Using single-cell Hi-C in combination with 3D chromatin modelling could be a powerful way to unpick the variation between individual healthy and diseased cells. It remains to be seen whether improvements in sequencing technology or in the efficiency of single-cell Hi-C will eventually allow 3D modelling of human cells that have two copies of each chromosome. This advance would be invaluable in the study of medically relevant patient samples. ■

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PALAEOCLIMATOLOGY

Ice-sheet history revealed by fossils

Microscopic fossils show that, from 10,400 to 7,500 years ago, upwelling of a water mass called Circumpolar Deep Water destabilized Antarctic ice shelves — a finding that advances our understanding of ice-sheet retreat. SEE ARTICLE P.43

JENNIFER HERTZBERG

Understanding the past drivers of Antarctic ice-sheet retreat is key to recognizing the constraints on present and future ice-sheet stability. The Amundsen Sea Embayment (ASE) region of West Antarctica is a dominant contributor to the present mass loss from the West Antarctic Ice Sheet[1], containing enough ice to raise the global sea level[2] by 1.2 metres. In the ASE, ocean-driven melting of the undersides of ice shelves, which restrain the flow of ice from the ice sheet, is mainly caused by the inflow of a relatively warm water mass, Circumpolar Deep Water (CDW), onto the continental shelf beneath the ice shelf[3] (Fig. 1). This inflow is thought to have led to ice-sheet retreat in the past. On page 43, Hillenbrand *et al.*[4] provide the first definitive evidence that enhanced upwelling

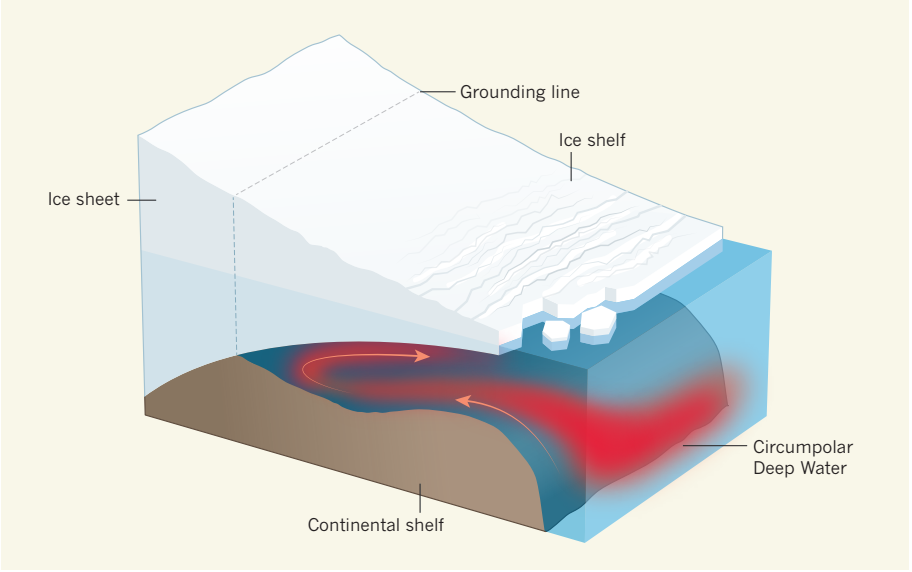

Figure 1 | A mechanism for ice-sheet retreat. Hillenbrand *et al.*[4] report evidence that a relatively warm water mass called Circumpolar Deep Water (CDW) led to past deglaciation of the Amundsen Sea Embayment (ASE) region of West Antarctica. In this process, CDW flows onto the continental shelf beneath the ASE ice shelf. This causes melting of the underside of the shelf, leading to ice-shelf collapse and possible ice-sheet retreat. The grounding line marks the transition from the grounded ice sheet to the floating ice shelf. Arrows indicate the direction of travel of CDW.

of CDW forced deglaciation of the ASE from at least 10,400 years ago until 7,500 years ago, when ice-shelf collapse could have caused rapid ice-sheet thinning. The authors also suggest that this process has been responsible for ice loss in the region since the 1940s.

The persistence of the modern West Antarctic Ice Sheet relies on the stabilizing influence of its ice shelves[5]. During the last glacial period (between 110,000 and 11,700 years ago), cooling or decreased presence of CDW, or both, would have reduced melting beneath the Antarctic ice shelves, contributing to ice-sheet growth and stability[6]. One study has suggested that the postglacial retreat of the ice sheet to modern levels in the ASE occurred about 8,000 years ago, and its authors speculated that the inflow of warmer ocean waters led to ice-shelf instability, which in turn drove ice-sheet retreat[7].

Although scientists can use satellites and other instrumentation to investigate the modern West Antarctic Ice Sheet, ice shelves and surrounding seas, they must rely on proxy measurements from archives to reconstruct past changes. Hillenbrand and colleagues studied sediment cores recovered from the Amundsen Sea to reconstruct CDW upwelling onto the ASE continental shelf and to determine the role of CDW upwelling in driving ice-sheet retreat over the past 11,000 years. The authors analysed the chemical composition and assemblage of the microscopic fossil shells of organisms known as planktic and benthic foraminifera, which live in the upper ocean and on the sea floor, respectively.

Hillenbrand *et al.* used the ratios of chemical elements in benthic foraminifera as a proxy to show that relatively warm bottom water persisted on the ASE continental shelf before 7,500 years ago, suggesting that warm CDW flooded the region until that time. Subsequently cooler temperatures indicate that CDW inflow was reduced until modern times. The authors confirmed these findings using measurements of a water-mass tracer on planktic and benthic foraminifera — CDW has a distinct chemical signature, and the authors found that its presence on the ASE continental shelf is recorded until about 8,000 years ago, after which the pure CDW signature is reduced as a result of the mixing of CDW with other water masses.

The authors then used variations in the assemblage (species composition) of benthic foraminifera to infer the presence or absence of an ice shelf covering the ASE. They found that species indicative of a sub-ice-shelf environment dominate the assemblage until 7,500 years ago, when a distinct change — to an assemblage dominated by species attributed to an ice-shelf edge environment — occurred.

Taken together, these lines of evidence provide strong support for an oceanic driver of ice-shelf collapse in the ASE between about 8,000 and 7,500 years ago. Specifically, the enhanced inflow of warm CDW onto the ASE continental shelf, beginning at least 10,400 years ago, probably contributed to the melting of the undersides of ice shelves, leading to their collapse. Hillenbrand *et al.* attribute the intensification of CDW inflow before 7,500 years ago to a southerly position of the Southern Hemisphere westerly wind belt[8]. A major strength of the authors' study is the multi-proxy approach taken, because it allows independent validation of data.

Hillenbrand and colleagues' findings provide a crucial oceanic link to a previous study that found that Pine Island Glacier, one of two main glaciers that drain the West Antarctic Ice Sheet into the ASE, experienced rapid thinning about 8,000 years ago[7]. This ice-sheet retreat coincided with the strengthened CDW inflow on the ASE continental shelf found by Hillenbrand and collaborators. Such inflow probably caused the ice shelf to collapse, reducing its stabilizing effect on the ice sheet and leading to increased rates of ice-sheet retreat.

The authors also reconstructed CDW inflow to the ASE over the past century, and although their work is based on limited data, they found a renewed strengthening of CDW inflow onto the ASE continental shelf since the 1940s. If that is the case, it would confirm oceanic forcing and CDW inflow as the main drivers of ice-shelf collapse[9] and ice-sheet retreat in the ASE region[7] in the past few decades.

Hillenbrand and colleagues' findings are limited by the length of the sediment records and the low resolution of the bottom-water temperature data. Because the sediment records extend back about 11,000 years, when CDW was already present on the ASE continental shelf, it is difficult to determine when the enhanced CDW inflow began. Constraining this timing could help to confirm whether the southerly shift of the Southern Hemisphere westerly wind belt led to the intensification of CDW inflow. Furthermore, the bottom-water temperature data are of lower resolution than the other data used, and do not extend back beyond about 8,000 years. Additional analyses from new sediment cores would help to confirm the authors' findings. Nevertheless, their study represents a major advance in our understanding of the drivers of ice-shelf collapse. ■

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IMMUNOLOGY

The patterns of T-cell target recognition

The binding of T-cell receptors to peptide molecules not normally present in the body can trigger an immune response. Predicting which peptide a T-cell receptor will bind to — a difficult feat — has now been achieved. SEE LETTERS P.89 & P.94

SAI T. REDDY

The T cells of the immune system are covered in protein complexes called T-cell receptors (TCRs). If a TCR binds a peptide fragment of a protein known as an antigen that is not usually present in the body, such as an antigen from a pathogen, this can trigger an immune response. Target recognition by TCRs is often essential in providing immunological protection against infectious diseases and cancer. However, trying to determine or predict the antigen specificity of a TCR on the basis of TCR amino-acid sequence alone is extremely challenging. On pages 89 and 94, respectively, Dash *et al.*[1] and Glanville *et al.*[2] report studies that investigated the relationship between TCR sequence and TCR antigen specificity.

A large collection of gene segments encodes the variable regions of TCR sequences. These genetic fragments undergo a rearrangement process during T-cell development that results in each T cell in the body possessing a unique TCR. The entire assembly of TCRs in an individual is referred to as the TCR repertoire, the scale of which is enormous — estimated[3] to be in the range of about 10^{18} different TCRs (a number similar to the predicted number of grains of sand on Earth). This immense