PERSPECTIVES

CLIMATOLOGY

Genetic insight on ice sheet history

Octopus DNA reveals timing of the most recent collapse of the West Antarctic Ice Sheet

By **A. Dutton**[1] and **R. M. DeConto**[2]

At the South Pole of Earth sits a landmass that has been home to a continent-sized ice sheet for the past 34 million years. Scientists have long been drawn to this icy expanse, initially to explore and discover, and later to study the evolution of the Antarctic continent, climate, and ice sheet. Despite decades of probing the region from the surface and from space, some important aspects of Antarctic history remain elusive. On page 1384 of this issue, Lau *et al.* (*1*) make headway to fill one such knowledge gap by reporting genetic evidence that two distinct populations of octopus were connected by a waterway across an area now completely covered by the ice sheet. This suggests that the West Antarctic Ice Sheet (WAIS) collapsed during a past warm period ~129,000 to 116,000 years ago, known as the Last Interglacial.

More than 50 years ago, glaciologist John Mercer was the first to deduce from sedimentary evidence that the WAIS melted away at some point during the Pleistocene (2.58 million to 11,700 years ago) (*2*). By leveraging independent evidence for sea levels that were several meters higher than present day during the Last Interglacial, Mercer hypothesized that the WAIS disintegrated during that warm period. Presciently, Mercer proposed that if that had indeed happened, then within 50 years, the disintegration of the WAIS would be imminent, leading to a globally averaged sea-level rise of about 5 m (*3*).

Although global mean sea surface temperature during the Last Interglacial was roughly the same as today (*4*), the Antarctic warmed to temperatures that were several degrees higher than present day (*5*). Future warming scenarios suggest that WAIS collapse could be triggered within several decades (*6*), if it has not already begun (*7*). This would bring about an estimated average 4 to 5 m of global sea-level rise (*8*), although the seas would rise higher in some places (such as the US east coast) relative to others because of changes in the gravity field associated with ice loss (*9*). Knowing the conditions under which the WAIS collapsed during the Last Interglacial should help pinpoint how and when such an event will unfold again under anthropogenically driven future warming, with enormous policy implications for global mitigation and adaptation efforts.

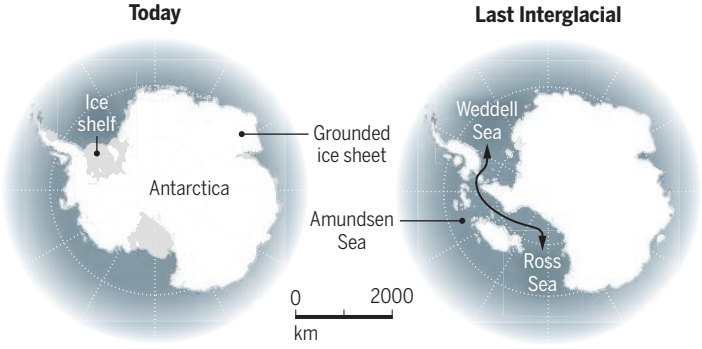
In the decades that followed Mercer's work, scientists set out to test his hypothesis in various ways. Some focused on looking for evidence within the Antarctic ice sheet itself (*10*) or within sediments off shore (*11*). Others searched further afield to combine estimates of total sea-level rise with existing estimates of Greenland melt volume to calculate the Antarctic contribution (by subtraction) (*12*). Modelers tried to discern how the Antarctic ice sheet would have responded to the Last Interglacial climate conditions (*6*). Using this multipronged approach, firmly centered on the geologic history, evidence has been mounting that the WAIS may have collapsed during the Last Interglacial. However, each study's findings have come with caveats. The general conclusion from much of this work is that the findings are largely circumstantial, with multiple possible interpretations.

In a pioneering study, Lau *et al.* bring an entirely different dataset to bear on the increasingly urgent question of whether or not the WAIS collapsed during the Last Interglacial. The study brings molecular biologists and geologists together to discern whether the genetic history of Turquet's octopus (*Pareledone turqueti*) could reveal the timing of when a waterway may have formed if the WAIS fully retreated. Although a disappearance of the WAIS would result in a massive inundation of coastal regions, it would simultaneously open up areas on the seafloor that are currently covered by ice, allowing Turquet's octopus to colonize new habitats and mix genes with populations that were formerly geographically isolated from each other.

Lau *et al.* focused on the modern populations of *P. turqueti* in the Amundsen, Ross, and Weddell Seas that are situated in the Southern Ocean off the coast of the WAIS. The authors determined that these populations are genetically distinct but have some admixture, indicating a potential historical trans–West Antarctic seaway (see the figure). Given the current ice sheet configuration, historical gene flow could only occur if connected by an interior waterway across regions of the WAIS that are currently grounded below sea level. Their genomic data analysis detected a historical gene flow from the Ross Sea to the Weddell Sea and vice versa. Specifically, the timing of this connection in their demographic model agrees with the timing of the Last

Ice sheet and octopus geography

Octopuses in the Amundsen, Ross, and Weddell Seas are isolated by today's ice sheet (left). If the vulnerable, marine-based sectors of the ice sheet retreated during the Last Interglacial (right), the resulting seaways would have allowed ancient connections between octopus populations compatible with genetic data.



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Interglacial, implying WAIS retreat of the marine-based portions of the ice sheet. Whether or not this analysis withstands further scrutiny and the test of time, the implications of this result pose some intriguing questions, including whether this history will be repeated, given Earth's current temperature trajectory.

Answering this question requires resolving additional questions about the timing, nature, and conditions of past deterioration of the WAIS. What were the physical conditions that primed this sector of the ice sheet to retreat, and precisely when did it happen? If the WAIS retreated early in the Last Interglacial as some data suggest (*10*, *12*), was this event the consequence of changes in ocean currents, temperatures, and/or solid earth response that preceded the interglacial? If the trigger occurred just before the warm period, then perhaps the simplistic emphasis on how warm it got during the interglacial should not be a focus.

There are also questions about how quickly sea level rises as the WAIS disintegrates. Would it rise relatively slowly and gradually, drawn out over millennia, or would it rise in one or more rapid jumps as vulnerable sectors of the ice sheet retreat? Understanding the past nature of ice loss informs future sea-level rise projections, which are of fundamental importance for coastal planners.

The problem, perhaps, runs even deeper than these specific, scientific questions. The challenge in identifying a precise tipping point—and all the conditions thereof—is that the tipping point will likely not be apparent until it has been passed. Policy-makers will always have to make decisions in the face of uncertainty about the future, and this latest piece of evidence from octopus DNA stacks one more card on an already unstable house of cards. ■

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SIGNALING

Deciphering downstream receptor signaling

Advancing drug discovery requires increasingly integrative structural biology approaches

By **Marta Filizola**[1] *and* **Jonathan A. Javitch**[2,3,4]

G protein–coupled receptors (GPCRs) are important cell-surface signaling proteins that are responsive to diverse extracellular stimuli and are key drug targets (*1*). Understanding how compounds activate GPCRs and modulate their interactions with intracellular proteins such as G proteins and β-arrestins is crucial for drug discovery because these proteins transduce signals to downstream effectors, triggering biological responses. This includes elucidating the molecular details behind the ability of the drug–GPCR complex to generate a functional response (efficacy) and the concentration of the drug required to produce half-maximal response (potency) (*2*). Although agonist binding to a GPCR triggers conformational rearrangements throughout the receptor and its transducer (*3*), the molecular mechanisms that govern ligand efficacy and potency are difficult to ascertain. On page 1378 of this issue, Heydenreich *et al.* (*4*) explored how individual amino acids in the prototypical G_s-coupled β_2-adrenergic receptor "interpret" information encoded in the atoms of its endogenous agonist, adrenaline, to drive its efficacy and potency.

"...the molecular mechanisms that govern ligand efficacy and potency are difficult to ascertain."

Traditionally, the quest to decipher GPCR signaling has focused on recording agonist-specific functional responses, but the molecular determinants and steps involved in these responses have largely remained obscure. Most pharmacological, structural, and mutational studies of GPCRs have focused on the ligand-binding pocket, the GPCR–transducer interface, or both. In a painstaking study spanning multiple domains of investigation, including alanine mutagenesis, a bioluminescence resonance energy transfer (BRET) functional assay, analysis of inactive and active crystallographic structures, computational data analysis, and evolutionary analysis, Heydenreich *et al.* have undertaken what they call an integrative approach to understand the GPCR communication network (that is, the allosteric pathway through which agonist binding is communicated from its binding site on the receptor to the GPCR–G protein interface). Changes on the receptor's surface or at distant allosteric sites can be just as impactful as those at the ligand-binding site or the receptor–transducer interface. Notably, the allosteric network of noncovalent contacts that they identify in the β_2-adrenergic receptor, a major drug target for the treatment of respiratory diseases and heart failure, involves pharmacologically important residues that contribute as drivers, modulators, passengers, and bystanders to the molecular and structural foundations of adrenaline's potency and efficacy.

Although distinct from key concepts of probability and information theory analyses that provide insights into the rules that govern information and uncertainty (*5*, *6*) in physics-based evaluations of the molecular dynamics of a system, the important residues identified by Heydenreich *et al.* can in principle be used to guide ligand design. This could enable the identification of chemical groups that can be modified to achieve desired signaling responses and eventually be tested iteratively and also explored in the context of other agonists. Notably, the observation that surface-exposed driver, modulator, and passenger residues identified with an endogenous ligand are also targeted by drugs acting as negative and positive allosteric modulators suggests that these sites should be prioritized in high-throughput virtual screening efforts for the discovery of new allosteric modulators.

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