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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Evolutionary analyses indicate possible overlaps in closely related systems (*7*). The study of Heydenreich *et al.* concludes that the functional role of a residue cannot be predicted solely on the basis of evolutionary conservation. It is plausible that the residues and networks involved in the efficacy or potency resulting from ligand binding are distinct and nonoverlapping, varying with the specific ligand, GPCR, and/or intracellular partner subtypes.

Notably, a data analysis based on efficacy and potency measurements for a single ligand derived from a highly amplified assay, point mutations limited to substitution with alanine in a single receptor, and allosteric networks derived from the analysis of two static receptor conformations inevitably overlooks two critical aspects of GPCR signaling that have emerged in the past decade. These are pluridimensional efficacy, the ability of the GPCR to engage multiple G protein and non–G protein effectors; and biased agonism, which is the ability of the GPCR to preferentially engage one effector over another (*8*). Contrary to the traditional view of GPCR-mediated signal transduction as a linear pathway mediated by single GPCR–G protein complexes, it is now evident that the inherent conformational plasticity of the receptors is exploited by ligands inducing maximal stimulation (full agonism) or lower efficacy (partial agonism). These ligands stabilize receptor conformations that preferentially couple to and/or activate different G protein subtypes or non–G protein effectors, enabling different downstream signaling cascades that can result in either beneficial or adverse physiological effects.

"...changes in amino acids far from the ligand-binding site can substantially alter drug response and receptor signaling..."

The resulting functional selectivity can originate not only from ligand-specific conformational changes in the receptors but also in the G protein or non–G protein partners, as well as from the varying kinetics of the transducer's conformational dynamics and its association with and dissociation from the receptor (*9*). These aspects of GPCR signaling necessitate high-resolution spatiotemporal measurements of the stability, dynamics, and activation kinetics of the GPCR–transducer complex, which can be conflated in amplified assays such as the BRET functional assays used by Heydenreich *et al.* Readouts from these assays are time-averaged and represent an ensemble average of the receptor–G protein complex, interpreted through the lens of a steady-state impact on BRET between the G_s α and γ subunits. The conclusion of Heydenreich *et al.* that the pharmacological importance of a residue cannot be inferred merely from the extent of its conformational change during receptor activation, as determined from the analysis of only two high-resolution receptor–G protein complex structures, underscores that the system's dynamics cannot be ignored. These dynamics can be crucial for characterizing agonist-induced allosteric pathways that extend beyond the receptor and receptor-transducer interface into the transducer protein. This consideration should also account for the impact of different lipid environments on signaling, given the growing evidence that not only cholesterol, but also other cell membrane lipids such as anionic lipids, can influence both receptor activation and G protein coupling (*10, 11*).

The realization that changes in amino acids far from the ligand-binding site can substantially alter drug response and receptor signaling challenges both the pharmaceutical industry and academic researchers to rethink drug design strategies—to not just focus on hypotheses of chemical optimization derived from analyses of direct ligand–receptor interactions in the orthosteric binding site. Instead, it is necessary to explore the rich landscape of a receptor's molecular surface and its internal communication network, as indicated by the analyses of Heydenreich *et al.* In the future, such studies can be further enhanced by integrating computational and experimental measurements of ligand-specific conformational dynamics and activation kinetics in GPCR–transducer complexes to fully decipher the molecular basis of ligand efficacy and potency at GPCRs for the development of improved therapeutics. ■

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MATERIALS SCIENCE

Mimicking polar bear hairs in aerogel fibers

Encapsulated aerogel fibers offer thermal insulation, breathability, and strength

By **Zhizhi Sheng**[1] *and* **Xuetong Zhang**[1,2]

Aerogels have been considered as super thermal insulators since their invention in 1931. The successful adoption of aerogels, which are made by replacing the liquid in a gel with gas while maintaining a stable network, in NASA vehicles such as the Mars rover has inspired the use of aerogels in personal warming. But applications of aerogels in textiles have been limited by their insufficient moisture permeability. Aerogel fibers are being developed to address the trade-off between thermal insulation and moisture permeability. However, aerogel fibers presently lack the strength and flexibility necessary to allow weaving or knitting into a wearable fabric. On page 1379 of this issue, Wu *et al.* (*1*) report a feasible strategy to construct bioinspired knittable aerogel fibers with superb thermal insulation and mechanical robustness, which allows weaving into fabric with air permeability. This could instigate the development of advanced thermal textiles for personal warming.

Aerogel fibers can be obtained by spinning nanoscale building blocks (e.g., aramid nanofibers, silica nanoparticles, graphene nanosheets, and so on) in a spinning dope with sol-gel transition and subsequent special drying (*2*–*7*). By modulating the interactions between these building blocks, various aerogel fibers with desired mechanical properties can be achieved, making bending, knotting, twisting, and weaving possible (*8*). However, at the present time, aerogel fibers cannot be woven into large textiles because of their insufficient strength; they also cannot withstand

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