

grafting of antigen binding loops from rodent into human antibody scaffolds (7). Grafting enzyme loops is far more tricky an exercise. As demonstrated by Park *et al.* (1), the combination of rational design (or “rationalized design,” i.e., deciding which loops to replace and the simultaneous insertion of several loops containing randomized sequences) and directed evolution has proven useful. However, the engineering of artificial enzymes with catalytic efficiencies that rival those of natural enzymes remains a challenge. The engineered enzyme (evMBL8) is inferior to its natural counterparts by a factor of 1000—and so are other designed enzymes (8). Future work may provide additional examples, improved design rules, and computational algorithms that direct the grafting of active-site loops or even replace the scaffold (9).

From an evolutionary point of view, the key to success seems to be the preservation of scaffold and chemistry. Notably, the latter is mediated by the key catalytic residues that are often associated with the scaffold, whereas the active-site loops vary from one family member to another. This hierarchy of enzyme structure is seen in many

enzymes and is probably one of the keys to enzyme evolvability (10). Two important questions remain, however. First, can loop swapping be exercised in nature? Homologous recombination of genes encoding different family members seems a most feasible mechanism (see the figure). Second, an essence of Darwinian processes is that they occur gradually while maintaining organism fitness throughout. But the first steps toward evMBL8 led to a complete loss of function. Can a switch in enzyme function that involves multiple and drastic changes in sequence evolve gradually? Well, nature’s starting point might have been an enzyme that promiscuously exhibits low levels of the desired function. Indeed, promiscuous activities, or cross-reactivities, are often observed between members of the same superfamily (11, 12). The next step may involve mutations that increase this promiscuous function while maintaining the original function, thereby providing a bifunctional evolutionary intermediate (10). Gene duplication could then lead to the divergence of the new gene through recombination with homologous family members and further

mutation and selection. Individual steps along these routes have been demonstrated in the laboratory, but reproducing this process in its entirety remains a challenge.

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ATMOSPHERE

Climate Change and Human Evolution

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Climate and biological evolution have interacted throughout Earth’s history, together creating many small and a few major transformations in the planet’s atmosphere and biota. The role of climate in the origin and adaptations of humans relates not only to our past but also, potentially, to our future (1). A number of hypotheses propose that climate-driven environmental changes during the past 7 million years were responsible for hominin speciation, the morphological shift to bipedality, enlarged cranial capacity, behavioral adaptability, cultural innovations, and intercontinental immigration events (2–9). These hypotheses are based on correlations between global-scale climate shifts documented in oceanic deposits and events in hominin evolution recorded in continental fossil-bearing strata. Establishing cause-effect relationships between climate and human evolution is tantalizing but presents many challenges for paleoanthropology and the geological sciences.

The biggest challenge involves how to relate different types and scales of paleoclimatic evidence between the marine and terrestrial realms. Marine-core records show that a cooler, drier,

and more variable global climate regime began about 3.0 million years ago (Ma), gradually intensifying into northern continental glacial cycles by 1.0 Ma (10–12). The climate shift between ~3.0 and 2.5 Ma thus marks the onset of Northern Hemisphere glaciation (10–13), and this coincides generally with the timing of the origin of the genus *Homo* [reviewed in (8, 14)] (see the figure). Fluctuations in continent-derived dust and biomarkers in the marine record indicate that climate shifts recorded in the oceans affected the land as well (12, 15). However, in the continental basins that preserve hominin fossils, the record of climate change is much harder to decipher. Paleoclimatic proxy evidence includes stable isotope (8, 16, 17), pollen (18), mammal faunas (7), and lake versus land deposits (9, 19, 20). Although these signals are documented in many vertebrate fossil-bearing localities (17, 21–23), each stratigraphic sequence represents only limited portions of the time-space framework of hominin evolution. In addition, the proxy records are subject to local tectonic and climatic processes that often obscure or completely overprint global-scale climate signals. Thus, we must confront the problem of relating a fossil record preserved in strata dominated by local- to regional-scale paleoenvironmental signals to a marine record dominated

What can we learn about cause and effect relationships between climate and human evolution from the late Cenozoic?

by continental- to global-scale signals. Long cores from deep African lakes could provide more continuous data and a stronger bridge between oceanic and continental climate records, but these are only beginning to be tapped (24).

Another challenge is deciding what constitutes a strong case for a causal link between a climate change and an evolutionary event. We can’t step into a laboratory to test the impact of climate change on the human genome, but we do have the results of natural experiments—the proxy evidence for environmental changes in continental rock sequences, as well as many fossils of hominins and other organisms that were evolving on different continents during that same time period. There is a rich body of data to draw upon, but hypotheses are often structured around an assumption that “synchronous” events in the geological and paleontological record constitute evidence for cause and effect. These hypotheses, while seductive in their simple explanation of how our species came to be, do not do justice to the complexity of the climate-evolution problem (see the figure) or to the full range of evidence and scientific methodologies that now can be brought to bear on this problem.

Research into human origins, as well as other fields of science, uses probability-based evidence to test cause-effect hypotheses. Establishing a

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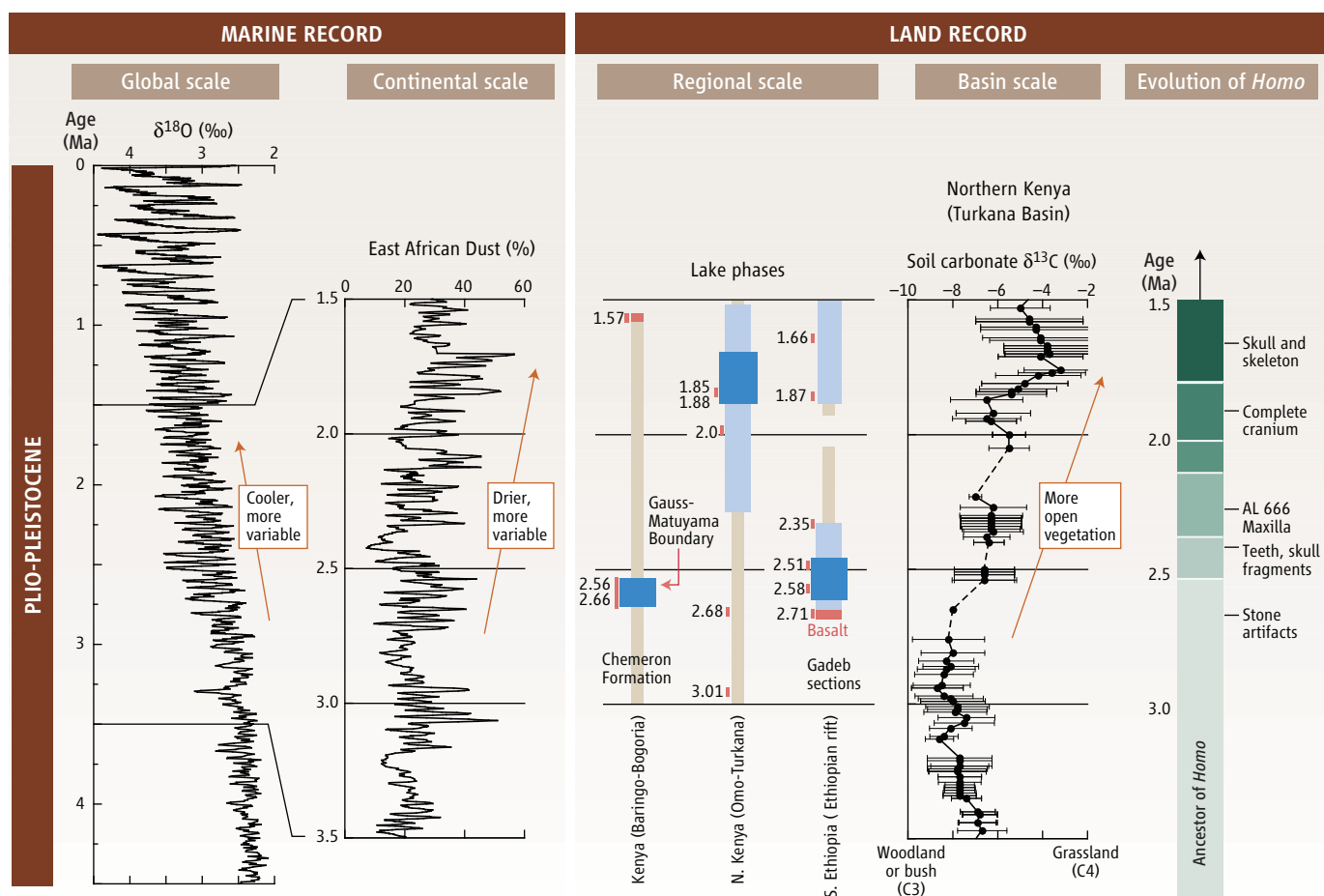
credible cause-effect relationship between events or trends in the geological record requires (i) a clear definition of what “synchronous” means, (ii) consideration of the mechanism for transmitting climatic cause to evolutionary effect, and (iii) multiple lines of proxy evidence supporting interpretations of the climatic trends or events. A recently proposed link between climate and human evolution provides an example of how these criteria can be used to assess hypotheses.

A new compilation of paleolimnological evidence concludes that lake levels were high in the East African Rift between 2.7 and 2.5 Ma (9) based on two generally synchronous lacustrine deposits in Kenya and southern Ethiopia [see the figure, land record (left)]. Radiometric dating shows that the two phases of lacustrine deposition occurred within a period of about 200,000 years (9). It is tempting to speculate [as in (9)] that there may be a cause and effect between this wet climate phase and the origin of *Homo*, but let us consider this in light of the

three criteria above. There is debate about the precise time and place of the origin of the genus *Homo* (8, 14), with time estimates ranging from 2.6 to 1.7 Ma. Synchrony of the climatic signal and the evolutionary event thus remains in question. The related notion that fluctuating lake levels provided environmental stress that drove speciation does not provide a mechanism for how this could have exerted selective pressure on the immediate ancestor of *Homo* and resulted in the emergence of a new genus and species. Other proposals instead have linked human evolution with increasing aridity and climate variability (4, 6, 25). Finally, other paleoclimatic evidence indicates drier rather than wetter climatic conditions between 2.7 and 2.5 Ma (8, 17, 26) [see the figure, land record (center)], bringing into question the extent of a prolonged high lake phase throughout East Africa. Although the multibasin approach to establishing regional paleoclimate trends is commendable, the proposed causal link between a wet climate phase

and the origin of *Homo* is not yet supported by sufficient evidence to establish its credibility.

The way forward is to carefully match the quality and scale of the data with the scale of the question. We cannot expect to link global- or continental-scale climate processes to major events and trends in human evolution without first disentangling basin- and regional-scale environmental signals in strata that contain the hominin fossil record (17, 27, 28). This complexity can work in our favor, however. A multibasin, multiproxy approach is now possible because paleoclimate data and chronostratigraphic correlations are becoming available for a large number of rock sequences (9, 29, 30). If many stratigraphic sequences and independent climate proxies show similar, synchronous environmental shifts, this would be strong evidence for climate change affecting large regions of a continent, particularly when such trends can be matched to the marine core data. On the other hand, if basins show independent patterns of environmental change, this



Marine and land records showing paleoclimatic trends during human evolution. Marine record: (Left) Global ice volume trend based on composite oxygen stable isotope ($\delta^{18}\text{O}$) data from seven different marine cores (31). (Right) Cycles of aridity in the Sahara Desert, based on percent terrigenous dust in the ODP (Ocean Drilling Program) Site 721/722 core from the Arabian Sea (32). Land records: (Left) Multibasin records of lake phases. Darkest vertical bars indicate deep lakes, lighter bars indicate shallow lakes, and lightest bars indicate land; red bars mark radiometric dating levels (9). (Center) Carbon stable isotope

($\delta^{13}\text{C}$) record of closed (woodland or bush) versus open (grassland) vegetation in the Turkana Basin of northern Kenya (8) (same basin as central lake phase record); (right) milestones in the fossil and archaeological record that are used as evidence for the timing of the appearance of *Homo* (14). There is no simple translation of the marine Plio-Pleistocene global climate shifts into the continental records, but future integration of marine and land-based evidence will allow rigorous testing of the impact of global change on the environments and evolutionary trajectories of our ancestors.

implies that they were locally buffered against larger-scale climate forcing, or that the available evidence is not sufficient to resolve small- versus large-scale environmental processes. The hominin fossil and cultural record could be reconsidered in light of such paleoclimatic meta-data sets. The strength of this approach depends on the number of sample points (that is, different basins and regions), accurate interpretations of climatic proxies, well-resolved correlations between basins, and a healthy dose of devil's advocacy before making a leap to global-scale interpretations. It is also worth remembering that climate was only one of many factors affecting human evolution; biological processes including genetic innovation, interspecies competition, and dispersal ability also could have played defining roles (14).

Rather than a simple story of global climate drumbeat and evolutionary response, more informative and exciting revelations about the 7-million-year development of hominin morphology, behavior, and culture will likely come from detailing the prolonged tension between local ecosystems and global climate change. This is also a strikingly relevant theme for the future of our species.

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GEOCHEMISTRY

Rising Mountain Ranges

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Stable isotope measurements of ancient soil minerals reveal the elevation history of a mountainous region in the Bolivian Andes.

Mountain ranges and plateaus are among the largest and most alluring physiographic features on Earth's surface. Their elevational histories are important in understanding tectonic processes as well as ancient climate change. Determining the timing and magnitude of surface uplift—paleoaltimetry—has been notoriously difficult because of a lack of direct elevation proxies in the geologic record. Consequently, estimates for the timing of mountain range formation often differ by millions of years, even for geologically young regions.

Geoscientists have developed several methods to constrain estimates of paleoelevation (1–3). Each has limitations, and the applicability of any method to a specific region depends in part on the availability of appropriate samples and the ability to account for confounding factors. On page 511 of this issue, Ghosh *et al.* (4) report their reconstruction of the elevation history of the Altiplano of the Bolivian Andes. They achieve this by combining data from a new geochemical technique, the “clumped isotope thermometer” (5), with conventional stable isotopic data (6) from ancient soil minerals. Their novel approach addresses several long-standing problems facing the field of paleoaltimetry.

Fundamental to many paleoaltimetry studies is an understanding of changes in the stable isotopic composition of precipitation through time (7–10). As air masses rise across a high region, continual rainout creates an oxygen isotope

composition gradient in the precipitation ($\delta^{18}\text{O}_p$), quantitatively related to the elevation of the land surface (see the figure). In the case of a rising mountain range or plateau, changes in elevation at a given location will influence $\delta^{18}\text{O}_p$ accordingly. The isotopic composition of ancient precipitation can be preserved in the geologic record by oxygen-containing minerals formed in equilibrium with precipitation-derived waters (e.g., soil water or shallow groundwater). For example, the $\delta^{18}\text{O}$ of soil-formed (pedogenic) calcite (CaCO_3) is related to the $\delta^{18}\text{O}$ of precipitation-derived soil water by a temperature-dependent isotopic fractionation factor. Isotopic analysis of an established chronosequence of proxy minerals such as calcite allows for a first-order reconstruction of changes in $\delta^{18}\text{O}_p$ through time. Using the modern incremental change in $\delta^{18}\text{O}_p$ with elevation, researchers can then place constraints on a region's elevational history (3).

Natural systems are complex, however, with uncertainties and confounding factors often muddling the reconstruction of paleoelevation. Ghosh *et al.* (4) specifically address several aspects of this complexity in their analysis of a pedogenic calcite chronosequence from the Bolivian Altiplano. They use the clumped isotope thermometer, which involves measuring the abundance of ^{13}C - ^{18}O bonds in carbonate minerals, to determine a sample-specific calcite growth temperature (5). When combined with the $\delta^{18}\text{O}$ from the same calcite sample, this paleotemperature permits precise evaluation of the $\delta^{18}\text{O}$ of the soil water present during sample growth.

Isotope paleoaltimetry studies have typically relied on less direct temperature estimates to relate the $\delta^{18}\text{O}$ of a proxy mineral to the $\delta^{18}\text{O}$ of the water from which it formed. The resultant iso-

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