late an earlier event in organ morphogenesis. Interestingly, the replacement in mammals of insulin-producing pancreatic cells in the adult requires preexisting cells (*7*), but it could also involve the reappearance of embryonic-like endocrine progenitor cells (*4*).

To become progenitor cells, class I and class II cells appear to escape the differentiation programs characteristic of more prosaic tracheal cells. This behavior could be determined by innate genetic instructions, by their cellular environment (much like the activity of a stem cell niche), or both. Mechanisms that maintain certain stem cell characteristics could be acting on specific cells to make them refractory to differentiation, as is the case in the murine embryonic stem cells (*8*). Regardless of the mechanism, "arrest" in the larval differentiation program to keep a cell as a potential progenitor cell appears to be a stepwise process. Thus, class II cells, capable of forming branches that transport air, can still behave as progenitor cells.

It is still unclear what establishes the "point of no return" after which a committed cell cannot revert into a progenitor cell. In the case of the *Drosophila* tracheal system, evidence points toward the triggering of endoreplication as a determining event (*1*–*3*), but many features of progenitor cell specification and activation in other systems remain to be elucidated. The study by Weaver and Krasnow is another excellent example of how the use of simpler, genetically tractable models such as the *Drosophila* tracheal system can aid in the interpretation of the genetic factors underlying progenitor cell biology in normal development or in stress conditions, an essential step for regenerative therapies.


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EVOLUTION

# Dynamics of Body Size Evolution

Is bigger better? Does climate affect size? The processes controlling body size evolution remain unclear.

**Kaustuv Roy**

Body size is one of the simplest organismic traits one can measure, yet it correlates with almost every aspect of the biology of a species, from physiology and life history to ecology. So, not surprisingly, biologists have long been interested in understanding how body size evolves. Two things are obvious when one looks at the distribution of body sizes of species within large groups: The sizes span multiple orders of magnitude, and species are not distributed uniformly within this range. Instead, most species tend to be small to intermediate in size, with few in the smallest and largest size classes. Thus, in most groups, size frequency distributions are skewed, even on a logarithmic scale, with the mode shifted toward smaller sizes. For example, living mammalian species range from about 2 g to $10^8$ g with a modal size of about 100 g (*1*). Surprisingly, this bias toward smaller sizes persists despite a tendency for average size to increase over evolutionary time, a trend generally known as Cope's rule (*2*, *3*).

Models of body size evolution need to reconcile these two seemingly contradictory observations—a general tendency of size to increase over evolutionary time, yet the overall size frequency distribution staying biased toward small-bodied species. Two different types of evolutionary dynamics can lead to an increase in the average size of species over time. The first, Cope's rule in a strict sense, is a channeled increase in size where large species get larger and small ones go extinct (*3*). Alternatively, if groups arise near the small end of their size range—and paleontological data suggest that many do—then even random diffusion with a lower size limit increases the variance in size over time, leading to an increase in mean size (*2*). Reconciling such models with the shapes of empirical size frequency distributions is more difficult. Channeled increases in size obviously cannot produce a distribution that is biased toward smaller sizes. Similarly, even though stochastic models with a lower size bound can produce an increase in mean size over time, the resulting size distributions tend to be log-normal rather than the log-skewed distributions common in nature (*2*, *4*).

A recent model (*5*) provides one solution to this by making simple but elegant modifications to the multiplicative diffusion process. By incorporating a size-biased extinction rate and a strengthening of Cope's rule for the smallest species into a stochastic model, it successfully reproduced the size frequency distributions of mammal species. The model does make some key assumptions about size dependence of extinction and size change, but those seem well supported in mammals. More important, this model provides a general framework for modeling body size evolution that preserves insights from previous work (*2*, *4*) but also incorporates group-specific dynamics. It is too early to know whether the model is generally applicable; that would depend on whether it can predict size frequency distributions of groups such as marine mollusks, where neither extinction (*6*, *7*) nor Cope's rule (*3*) relate to size in the same way as in mammals.

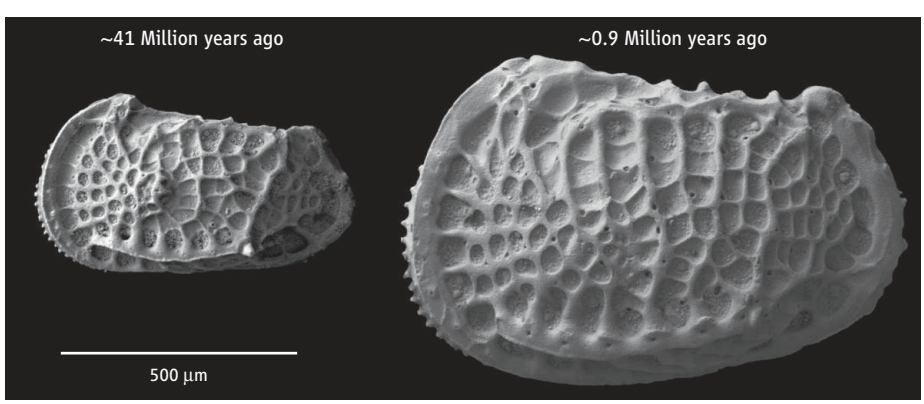


PHOTO CREDIT: GENE HUNT/NATIONAL MUSEUM OF NATURAL HISTORY, WASHINGTON, DC

**Body size evolution in deep-sea ostracodes in response to temperature.** *Poseidonamicus rudis*, at left, lived earlier and under much warmer conditions than did *Poseidonamicus major* at right (*12*).

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Although phenomenological models are important for identifying key elements of body size evolution, they provide limited insights regarding the underlying processes. For example, if Cope's rule is indeed stronger for small mammals, then one has to ask why. Unfortunately, we are still far from such a process-based understanding of body size evolution, largely because of the complexity of the problem. Consider two generalizations about the connections among size, environment, and fitness that were suggested recently: "bigger is better" and "hotter is smaller" (*8*). The first is based on data from natural populations showing that larger individuals tend to have higher fitness. The second stems from observations that in laboratory-rearing experiments, higher temperatures generally result in smaller body sizes and also that species and individuals in cold climates are often larger than those in hotter areas, a trend known as Bergmann's rule.

Translating these "rules" into predictions about trajectories of size evolution is not straightforward. If bigger really is better, then we should have a world full of giants, yet most species are small. Clearly there are costs to getting bigger, which prevent a runaway Cope's rule. Such costs involve complex interactions among a multitude of factors including development time, population size, and patterns of resource use (*8*, *9*). In addition, the temperature-size rule suggests that the external environment, which changes in a complex and nonlinear manner over geologic time, is also important in driving size evolution. So, not surprisingly, simple process-based models of size evolution (such as one based on energetics) have not been widely accepted (*10*).

There is also the problem of scaling up from observations at the population level to macroevolutionary trends in size. The "bigger is better" rule is based on data from a few generations, and it is unclear whether it holds across geographically separated populations and macroevolutionary time. On the other hand, the temperature-size rule may indeed be relevant for macroevolution. Past climatic changes led to body size evolution consistent with the temperature-size rule in groups as disparate as woodrats (*11*) and deep-sea crustaceans (*12*) (see the figure). Furthermore, in some groups the temperature-size rule may have a relatively simple genetic basis; in the nematode *Caenorhabditis elegans*, it can be disrupted by a single nucleotide polymorphism (*13*).

Even though the processes governing body size evolution remain obscure, our collective actions are negatively affecting body sizes of many living species. Human exploitation of biological resources, from fisheries to forestry, is inherently size-selective where larger species and individuals are preferentially taken. As a result, body sizes of many species are much smaller now than, say, a century ago (*14*). Furthermore, abundances of large terrestrial and marine species are declining because of anthropogenic impacts, and many are threatened with extinction (*15*, *16*). Global warming may reinforce this trend toward smaller sizes through the temperature-size rule. In effect, then, our actions have set up a grand selection experiment where bigger is no longer better. Rapid microevolutionary responses to such selection have already been documented in laboratory experiments and in wild populations (*14*). Cope's rule is unlikely to be common in the future.

In a world where temperatures are rising and human exploitation of species is rampant, better understanding of ecological and evolutionary processes affecting body size is not simply an academic exercise; it is essential for effective management and conservation of species and ecosystems (*14*). The question now is not just why the world has so few giants, but how to keep the existing ones around for future generations.


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CHEMISTRY

# Bringing Stability to Highly Reduced Iron-Sulfur Clusters

A synthetic mimic of the most reduced iron-sulfur cluster in electron-transfer proteins shows a remarkable resemblance to protein-bound clusters.

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Many biochemical reactions are driven by electrons that are transferred to the reaction site from afar. Iron–sulfur clusters in proteins (*1*), including those with cuboidal $Fe_4S_4$ cores, can access different oxidation states and act as way stations for electrons; the oxidation state is designated by $[Fe_4S_4]^z$, where $z = 0, 1+, 2+, 3+$ is the formal core charge. In general, proteins use the (3+, 2+) or, most frequently, the (2+, 1+) redox couple. Evidence for the participation of the fully reduced $[Fe_4S_4]^0$ cluster in protein electron transfer has been scant, and a synthetic model in support of this oxidation state, as available for the higher oxidation states (*2*–*4*), has been lacking. Deng and Holm (*5*) have now provided such support in an innovative approach that replaces thiolates, used to simulate cysteinate binding in proteins, by electron-donating carbene ligands.

Some evidence supporting a role for the neutral (referred to as all-ferrous) cluster has come from one of the most intensely studied systems, namely nitrogenase from the bacterium *Azotobacter vinelandii*. Nitrogenase consists of two proteins: the molybdenum-iron protein (Av1), the locus of nitrogen reduction, and the Fe-protein (Av2), an electron transfer and effector protein. Av2 is a dimer of identical subunits that symmetrically coordinate a single $Fe_4S_4$ cluster through cysteine sulfurs (see the figure, left panel) (*6*). The Av2 dimer binds two molecules of MgATP (adenosine triphosphate), which are hydrolyzed in a coupled reaction that transfers electrons to Av1.

The accepted model for this electron transfer has been that Av2 uses the $[Fe_4S_4]^{2+,1+}$ redox couple. The electron transfer to Av1

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