



**The Costs of Breathing**  
Nick Lane  
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the dynamics of self-assembly (8) suitably complemented with theoretical models of the dynamics (9, 10) may clarify this issue. The ability to extend the size of crystals and even realize single crystals would dramatically enhance the already huge value of these materials. Other studies will be necessary to characterize, control, or adjust the rheological properties of these materials.

With such an impressive inventory of nanoparticles available (1), one direction is to classify the self-assembled structures resulting from the different properties of these nanoparticles. Some preliminary work focusing on nanoparticle geometry has already appeared (11), but many more possibilities remain to be explored.

So far, nanoparticles with only a single species of DNA linker have been considered. With the current sophistication in experimental methods, nanoparticles consisting of patches with different linkers can be synthesized, thus endowing them with an anisotropic interaction or discrete valence (12). This possibility is briefly explored in the work of Macfarlane *et al.*, where a given nanoparticle is endowed with two different linker types resulting in NaCl and simple cubic lattices. DNA-programmed self-assembly has also been extended to particles with diameters on the micrometer scale (13). However, the resulting structures do not show the same degree of order as in the nanometer-scale experiments. The largest nanoparticles considered by Macfarlane *et al.* are only about one order of magnitude smaller, so it seems likely that smooth interpolation between these diverse size scales is in sight. There has been amazing progress in building structures with DNA, ranging from DNA origami to three-dimensional periodic structures where nanoparticles can be attached (14)—providing even more exciting opportunities.

The implications of the work extend to less obvious situations. A major unresolved problem, with very far-reaching applications in materials science, has been how to design materials consisting of polymers and nanoparticles such that the nanoparticles are homogeneously dispersed (do not cluster) and display long-range order. There are very few experimental examples, if any, where this has been successfully accomplished (15). It has been predicted theoretically (10, 16) that generalizations of the work of Macfarlane *et al.* polymers with attached single-stranded DNA complementary to nanoparticle linkers would lead to polymer nanocomposites with homogeneous nanoparticle dispersion and displaying long-range order with a wide range of lattice symmetries, thus resulting in

an elegant solution to this crucial problem in materials science.

Being able to assemble nanoparticles with such control represents a major accomplishment in our quest to manipulate matter. There are immediate important applications related to catalysis, medical sensing, new optical materials or metamaterials, and others that will follow from these studies. Most likely, however, many other applications will arise as we dig deeper, understand better, expand further, and tinker with the opportunities provided by these materials.

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## EVOLUTION

# The Costs of Breathing

Nick Lane

Selection for respiratory function has implications for organism fitness, fertility, and life span.

**E**ukaryotic cell respiration depends on the interactions of proteins encoded by two genomes, mitochondrial and nuclear, which evolve in radically different ways. Mitochondrial genes evolve asexually (mitochondrial DNA is generally passed from mother to offspring without recombination), unlike nuclear genes, and their mutation rate can be orders of magnitude faster than the nuclear average (1). Despite these differences, the two genomes coadapt to each other over evolutionary time (2): Mutations in one genome are offset by changes in the other, preserving respiratory function and possibly adapting it to changes in diet and climate (3). The details of selection may hold surprising implications for fitness, fertility, and aging.

Outcrossing between different species or genetically distinct populations can lead to hybrid breakdown—that is, poorly viable or inviable offspring—through the loss of mitochondrial coadaptation (2, 4). The problem is that cellular respiration (which takes place in mitochondria) depends on the flow of electrons to oxygen or other acceptors through

respiratory chains composed of numerous interacting protein subunits encoded in both genomes. Electrons normally pass swiftly down the full length of the respiratory chain, and ultimately reduce oxygen safely to water, the energy released driving adenosine 5'-triphosphate (ATP) synthesis. But if the progress of electrons down the full length of this chain is blocked for any reason, they are more likely to escape and react directly with oxygen to form reactive, partially reduced intermediates known as reactive oxygen species (ROS). In the same way, a partially dammed stream is more likely to burst its banks. Any impedance to electron flux increases ROS leak, and—because fewer electrons make it down the whole respiratory chain in a given time—reduces the amount of ATP produced. This combination of high ROS leak and low ATP synthesis is the classic trigger for the release of cytochrome c (a component of the respiratory chain) from the mitochondria, an event that initiates programmed cell death (apoptosis) in most eukaryotic cells.

This is exactly the problem that occurs if the mitochondrial and nuclear genes are mismatched through outcrossing between species or genetically distant populations. The two sets of genes encode proteins that

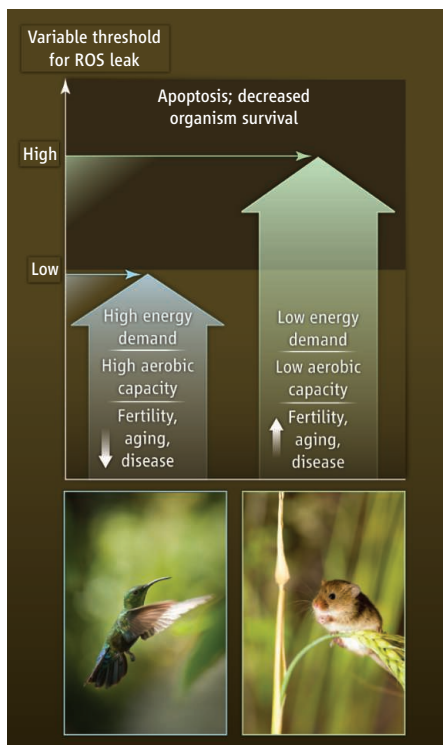
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must operate together with nanoscopic precision to convey electrons down the respiratory chain, and given the major disparities in their tempo and mode of evolution, only selection for coadaptation can ensure that they do indeed cooperate properly together. Outcrossing can undermine this exquisite coadaptation. Proteins encoded by maternal mitochondrial genes do not interact properly with proteins encoded by genetically distant paternal nuclear genes. This physical mismatch impedes electron flow, compromising respiration. ROS leak rises, ATP synthesis falls, and cytochrome c is released, triggering apoptosis. This in turn undermines development, leading to low fitness, sterility, inviability, or developmental abnormalities (4), outcomes that potentially are a step en route to speciation (5).

Thus, the involvement of respiratory proteins like cytochrome c in apoptosis makes good sense as a form of selection for cells and organisms with functional respiration (6). Mitonuclear mismatch leads to high ROS leak and loss of cytochrome c, so cells with compromised respiration are eliminated by apoptosis. Because mitochondrial genes operate against a new nuclear background every generation, selection for mitonuclear coadaptation must normally take place every generation. And because the new nuclear background is only resolved after zygote formation, this selection must take place during embryonic development or after birth.

But how good does mitonuclear match need to be? To attain optimal respiration, electrons must flow freely down the full respiratory chain to oxygen, and any impedance must be eliminated. That could mean eliminating even slight mitonuclear mismatches via apoptosis, which in turn would mean sacrificing even mildly substandard embryos. Such sacrifice could only make sense if respiratory demand is high. High energy demand, as in flight in bats and birds, certainly requires fast electron flux, and so stricter selection for mitonuclear match could be beneficial despite the high cost. From this point of view, even a small increase in ROS leak would betray mitonuclear mismatch, and might therefore be penalized by apoptosis during embryonic development. On the other hand, such a stringent penalty could hardly benefit animals with less exacting energetic requirements. Presumably, animals with lower aerobic demands, like rats, should tolerate more ROS leak during embryonic development. If so, that would imply a variable “apoptotic threshold” across species.

A variable apoptotic threshold model allows testable predictions about fitness, fer-



**The apoptotic threshold.** In this model, if the threshold for ROS leak from the respiratory chain in mitochondria is low, even a small increase in ROS leak during cellular respiration triggers apoptosis. A low tolerance for ROS leak selects for good mitonuclear match; high tolerance raises the threshold for apoptosis and relaxes selection for mitonuclear match. See SOM text for suggested resources related to mitonuclear coadaptation.

tility, life span, and age-related diseases (see the figure). For example, if there is a requirement for good mitonuclear match (fast electron flux, hence low ROS leakage during respiration), then organisms with poor matches should be eliminated during development as a result of high sensitivity to ROS leak. If all embryos with even modest ROS leak are eliminated during embryonic development, then the few individuals that do survive development should have low mitochondrial ROS leak. The prediction is that fertility and ROS leak should covary across species. Flighted birds and bats are predicted to have low ROS leak (which they do), corresponding to low fertility, and small litter sizes, whereas rats should have higher ROS leak, higher fertility, and larger litter sizes. ROS leak is therefore, according to the model, critical to selection: Tolerance of high ROS leak can be beneficial and positively selected; it is not simply an unwelcome side-effect of respiration.

That has an important corollary. The rate of ROS leak corresponds closely to life span across species (7). Pigeons and rats have similar body size and resting metabolic rate, but

ROS leak in pigeons is a fraction of that in rats, and pigeons live up to 10 times longer. The apoptotic threshold view is a possible explanation for why birds and bats should have low ROS leak: They require a high aerobic capacity and good mitonuclear match, so only individuals with low ROS leak make it through embryonic development. Thus, the link between low ROS leak and life span may not necessarily be the result of direct selection, but a side-effect of selection for mitonuclear match, optimizing fitness and fertility over generations.

The apoptotic threshold could also operate within each generation, affecting aging and disease. The problem is that mutations in mitochondrial DNA arise over time as a result of simple usage; and mitochondrial heteroplasmy (a mixture of mutant and normal DNA in the mitochondria of the same cell) is indeed common in aging tissues and many tumors (8). Heteroplasmy potentiates mitonuclear mismatch, increasing ROS leak and the likelihood of apoptosis, which can lead to tissue loss. As the most metabolically active tissues—notably brain and muscle—approach the apoptotic threshold faster, they are preferentially lost, which can lead to degenerative diseases. Some cells escape that fate. Senescent cells survive by glycolysis, often with high mitochondrial ROS leak, which gives rise to oxidative stress. This drives epigenetic changes and the expression of proinflammatory factors (3) associated with chronic inflammatory conditions such as diabetes, and cancer (9).

Mitonuclear coadaptation can explain the relationship between fitness, fertility, and life span across species through a simple biophysical mechanism, ROS leak. If true, this view has implications for how we might tackle aging and age-related disease. Empirical investigation will reveal if genome matching has played, and continues to play, a role in eukaryotic evolution.

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