The radical life-giver

Toxic oxygen

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The introduction of oxygen into the Earth's atmosphere was a double-edged sword. It provided a fuel that would allow the evolution of complex organisms with high energy demands, but also represented a new source of toxins. Oxygen-respiring eukaryotes needed not only to develop machinery to harness the power of oxygen, which they gained through the acquisition of mitochondria, but also to build up defences against its toxic effects.

Oxygen has been a trouble-maker from the very beginning. Although by nature a sluggish reactant, it has a tendency to 'radicalize', forming incompletely reduced reactive oxygen species (ROS, such as $O^{\bullet -}$, H_2O_2 and $HO^{\bullet}$), which are highly potent oxidants. Within the cell, ROS can cause genetic degeneration and physiological dysfunction, eventually leading to cell death and progressive ageing of the organism.

Mitochondria evolved as the specialist power plants of eukaryotic cells, and mitochondrial respiration is one of the most amazing examples of the economizing principles of evolution. But a primary function of mitochondria may have been to compartmentalize respiration, to protect the cytosol from the damaging side-effects of oxygen metabolism. ROS formation — which occurred even at the low oxygen levels that prevailed a billion years ago when the earliest multicellular animals appeared — could have posed a serious problem. However, in these diffusion-limited species with only rudimentary circulatory systems, mitochondrial respiration apparently kept cellular oxygen concentrations high enough to cover tissues' oxygen demands, but low enough to minimize ROS formation. Only as oxygen levels rose, and more complex animals evolved, were more stringent antioxidant defence mechanisms required.

In air breathers, oxygen uptake is predominantly controlled by monitoring CO_2 concentrations in the blood. This makes sense, as the oxygen concentration in air is virtually constant. For water breathers, however, oxygen levels are the prime factor that controls ventilation rates, and thus the availability of oxygen to tissues and cells. As oxygen's concentration in water is typically 30 times less than in air, its tension decreases drastically when even small amounts of the gas are consumed, whereas CO_2 tension in water is stabilized by bicarbonate buffering. Many marine animals keep respiration and metabolic performance constant against fluctuating environmental oxygen levels (oxyregulation), but in phylogenetically older species the rate of oxygen uptake mirrors the ups and downs of oxygen in their environment (oxyconformity). Although the latter may sacrifice scope of activity and performance and live at a slower pace, oxyconformity is obviously advantageous when it comes to surviving environmental hypoxia.

By initiating a metabolic slowdown, oxyconforming marine invertebrates can survive extended periods of severe oxygen deficiency in a metabolically dormant state. For reasons unknown, the ocean quahog (*Arctica islandica*) vacates the oxygenated bottom water and burrows into anoxic sediments. The buried clams reduce their heart rate to as little as 10% of routine activity, and energy demand is lowered accordingly. By making use of this quiescent state, the quahog can reach the grand age of 220 years. Upon surfacing, the quahog's mitochondria increase the respiration rate, leading to an increase in ROS formation and presumably inducing antioxidant enzymes. Their voluntary anoxic mudbaths might be a trick to beef up their stress defences.

Oxyregulators liberated themselves from the energetic limitations imposed by oxyconformity and flourished in energy- and oxygen-rich environments. But this is a one-way road. In vertebrates, paradoxically, hypoxia elicits massive ROS formation as a cellular stress response. Formation of ROS under local hypoxia is known from a wide range of human pathologies, such as ischaemic brain damage in stroke patients. In higher animals (fish upwards), hypoxic mitochondrial ROS production functions as an alarm signal and induces reactions to conserve the cellular energy balance. In mammals, 'hypoxic' genes are transcribed in response to oxygen stress, expressing factors that switch on anaerobic energy production and induce vasodilation to get blood into hypoxic areas. Could this be the modern equivalent of climbing into the anoxic mud to stock up on stress defences?

When exposed to critical warming, cold-blooded marine animals experience functional hypoxia in oxygen-saturated water. Warming a cold-blooded animal increases its respiration rate and thus mitochondrial ROS production, while at the same time the increased energy demand results in oxygen deficiency. Functional hypoxia at high temperature is risky, as it overrules at least the peripheral oxygen-sensing systems and deprives hypoxia-tolerant animals of the possibility of systemic metabolic slowdown. As the animals go beyond their heat-stress limit, hypoxia impairs mitochondrial electron transport because oxygen, the final electron acceptor, is limited. Oxidative injury ensues from auto-oxidizing components of the redox chain. To make matters worse, hypoxic acidification sustains high mitochondrial proton-motive force and further stimulates leakage of electrons from the respiratory chain. Inflowing oxygen is rapidly reduced to superoxide, damaging the mitochondria themselves and eventually causing them to initiate apoptosis — cellular suicide.

In warm-blooded animals, cooling of the brain by as little as 2 °C can reduce ischaemic brain damage after stroke. Although many mechanisms may be involved in the beneficial effect of brain cooling in stroke patients, part of it is due to reduced neuronal oxygen turnover, reflecting an enforced slowdown of neuronal metabolism. This ameliorates hypoxia-induced ROS production by ischaemic brain mitochondria, preventing further oxidative injury of damaged structures.

Thus mitochondria, which began as oxygen-quenchers in early oxyconforming organisms, have become metabolic accelerators in higher-tuned oxyregulating invertebrates and fish, which risk driving their bearers into toxic oxygen injury. In higher animals, however, mitochondrial ROS formation also participates in cellular sensing and signalling during functional hypoxia, to oppose tissue damage. But when even these defences prove inadequate, mitochondria catalyse the destruction of the cells that contain them. Living with oxygen is certainly a dangerous affair. ■

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Burrowing under: the long-lived ocean quahog.

FURTHER READING

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