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Cell's Power Plants Also Sense Low Oxygen

Researchers have produced the strongest evidence yet that mitochondria—the organelles that generate energy to power the cell—also monitor oxygen concentration in the cell. If oxygen slips below a critical threshold, the mitochondrial “sensor” triggers protective responses to promote survival.

Understanding how the cell senses and protects itself against hypoxia (low oxygen) has both important basic and clinical implications for biology and medicine, said one of the study's senior authors, M. Celeste Simon, a Howard Hughes Medical Institute investigator at the University of Pennsylvania.

“Oxygen is absolutely essential for life, so the biological mechanisms underlying response to low oxygen are central to the cell,” she said. “For example, during early development, the embryo exists in a naturally hypoxic environment until it is connected to the maternal cardiovascular system.

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“In the adult, changes in oxygen levels occur during inflammation and atherosclerosis; and even transient oxygen starvation can have a profound impact on the brain,” said Simon. “For example, the well-known case of the late Terry Schiavo, in which a cardiac episode reduced her to a vegetative state, was the result of only brief oxygen starvation.”

The new studies may suggest ways to enhance the body's natural protective response to low oxygen environments. These strategies might be employed to help the brain fend off the effects of transient oxygen starvation that can quickly cause irreversible brain damage.

The research team that included Simon and senior author Paul T. Schumacker of the University of Chicago, as well Ulrich Hammerling and colleagues

from Memorial Sloan-Kettering Cancer Center, reported their findings in two articles published in the June 2005 issue of the journal *Cell Metabolism*. A third article in the same issue by Navdeep Chandel and his colleagues at Northwestern University presented additional evidence that mitochondria function as oxygen sensors.

According to Simon, the idea that mitochondria sense cellular oxygen concentrations has been controversial. “It has been a reasonable idea around for many decades, because mitochondria are the primary consumers of oxygen in the cell,” she said. “However, the idea was discarded, because it appears that the mitochondrion still functions perfectly well in a range of oxygen concentrations where it is known that limiting oxygen results in an accumulation of HIF.” HIF, or hypoxia inducible factor, is the protein that triggers the cell's broad protective response to low oxygen conditions.

In previous studies, Simon and her colleagues had found evidence implicating mitochondria as oxygen sensors. They found that in response to low oxygen, mitochondria produce chemicals called reactive oxygen species (ROS)—such as hydrogen peroxide—that trigger the activity of HIF. However, other researchers had performed experiments that argued against a mitochondrial role in oxygen sensing. They showed that enzymes called prolyl hydroxylases (PHDs), which normally inhibit HIF activity, depend on oxygen. Thus, low oxygen would reduce PHD activity, triggering HIF. “As a result of these findings, in many people's minds, PHDs, became the long-sought-after oxygen sensor,” said Simon.

In their latest experiments, which sought to demonstrate more conclusively that mitochondria were oxygen sensors, the researchers used new techniques to produce cells with defective mitochondrial machinery, or in which they could transiently switch off that machinery. They also used a new technique to precisely measure ROS levels in hypoxic cells.

“Our studies of cells with mitochondrial deficiencies showed that they do not accumulate HIF in response to moderate hypoxia,” said Simon. “Also, our highly sensitive probe for ROS showed that the cells do not produce these species, either. Further, we found that in these cells, we can supply the missing signal that triggers HIF accumulation by adding back ROS.”

One of the group's most important observations, according to Simon, was finding that reducing oxygen levels to near zero, called anoxia, triggers an entirely different protective response that is independent of the mitochondria. This response involves the enzyme PHD as the oxygen sensor.

“So, now we think we have something for everybody,” said Simon. “In oxygen ranges that are moderately low, the mitochondria control the protective response by releasing ROS. But when you get to a really low level of anoxia, the PHD becomes the oxygen sensor.” Such a dual-mode mechanism makes evolutionary sense, said Simon, because it enables the cell

to adjust to a wide range of low oxygen levels, even the “emergency” created by total oxygen starvation.

The group's findings might also have implications for cancer therapy since tumors use this protective response to thrive in a low-oxygen environment. If one could develop drugs to block that response, it could potentially take away one of the survival strategies exploited by tumors, said the researchers.

Simon said that tumor growth seems to depend on the tumor's ability, via the HIF-triggered machinery, to adapt to low oxygen levels until it can develop its own blood supply. Thus, she said, results from her laboratory are being used as a guide to develop drugs that inhibit HIF in tumors, to render them vulnerable to hypoxia and thwart their ability to grow blood vessels.