Need oxygen? Cells know how to spend and save

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Researchers at Johns Hopkins have discovered how cells fine-tune their oxygen use to make do with whatever amount is available at the moment.

Too little oxygen threatens life by compromising mitochondria that power it, so when oxygen is scarce, cells appear to adjust by replacing one protein with an energy-efficient substitute that "is specialized to keep the motor running smoothly even as it begins to run out of gas," says Gregg Semenza, M.D., Ph.D., a professor of pediatrics and director of the vascular biology program in the Institute for Cell Engineering at Hopkins. "This is one way that cells maintain energy production under less than ideal conditions." A report on the work is in the April 6 issue of *Cell*.

"Cells require a constant supply of oxygen," Semenza says, "so it's vital for them to quickly react to slight changes in oxygen levels." The protein-swap is how they do it.

In the mitochondria, the tiny powerhouses found in every cell, energy is produced by passing electrons through a series of relay stations called cytochromes until they eventually join with oxygen to form water. This final step is directed by the protein cytochrome coxidase, or COX for short. If electrons react with oxygen before reaching COX, they generate "free radicals" that can damage or destroy cells. The mitochondria are designed to produce energy without excess free radical production at normal oxygen levels.

Semenza's team noticed that one particular component of the COX protein complex, COX4, comes in two different forms, COX4-1 and COX4-2. Under normal oxygen conditions, the cells' mitochondria contain mostly COX4-1. The researchers suspected that COX 4-2 might be the active protein under stressful, low-oxygen conditions, which the researchers refer to as hypoxia.

To test the idea, the team compared the growth of human cells in normal oxygen conditions (what's generally present in normal room air) compared to cells grown in hypoxia. In low oxygen, liver, uterus, lung and colon cells all made COX4-2. The researchers then exposed mice to hypoxia for a few weeks and found that they too showed increased levels of COX4-2.

In 1992, Semenza's team had discovered a protein which they called HIF-1 (for hypoxia-inducible factor 1) that cells make in response to hypoxia. HIF-1 turns on genes that help cells survive when oxygen is low, such as during a heart attack or stroke. The researchers set out to figure out if the sensor protein HIF-1 triggers the COX-swapping.

By examining the gene control regions of COX4, they found that the HIF-1 sensor switched on COX4-2 activity when oxygen is low. And they learned that because COX4-1 already is in the mitochondria, the swap for COX4-2 occurs when the sensor turns on yet another gene that produces an enzyme to specifically chew up COX4-1. Engineering human cells to lack this enzyme and subjecting them to low oxygen, the scientists found the cells unable to rid themselves of COX4-1.

"It's remarkable that the one-celled yeast also swap COX subunits in response to hypoxia, but because they lack HIF-1, they accomplish the swap in a completely different way," says Semenza. "This suggests that adapting mitochondria to changes in oxygen levels may be a major challenge for most organisms on Earth."

Source: Johns Hopkins Medical Institutions