

## TOO MUCH OXYGEN ON THE CELL BIOLOGY BENCH? NEW STUDY SUGGESTS SO

COLUMBUS, Ohio -- Research conducted at Ohio State University suggests that cell biologists may be exposing the cell cultures they study to too much oxygen.

This finding could have broad implications for cellular biology research, which receives billions of dollars of funding nationally, said Ohio State scientist [Chandan Sen](#). He is the lead author of a study which suggests that cells act differently depending on how much oxygen they are exposed to, especially when it is too much.

The air we breathe contains about 21 percent oxygen. But cells in our body are used to much less than that usually in the range of 10 to 0.5 percent. And most cellular biology research is done in an open-air environment that contains atmospheric oxygen levels. The result: experiments are often done in an environment so unnaturally rich in oxygen that it triggers cellular stress, said Sen, who directs the [Laboratory of Molecular Medicine](#) at [Ohio States Davis Heart and Lung Research Institute](#).



Chandan Sen

When Sen and his colleagues exposed mouse heart cells to normal open-air oxygen levels, cell growth slowed and the cells underwent some significant physiological changes, such as producing arrays of free radicals and specific oxygen-sensitive genes. These are two fundamental differences between what happens to cells in the laboratory and what really happens to them inside the body, Sen said. To get meaningful results from cell biology, it is important to mimic biological conditions in the body. It is clear that cells aren't blind to oxygen.

The research appears online in the current issue of the journal [Circulation Research](#).

The study of cancer tumors is one example of the effect open-air oxygen can have on cellular research. Tumors thrive on about 1 to 3 percent oxygen, Sen said. Radiation used to kill cancerous tumors interacts with the available oxygen and creates free radicals. Current research suggests that adding oxygen to tumors will increase the concentration of free radicals made in the tumor and therefore promote the effectiveness of radiation therapy.

But almost all of us working on cell biology do our research in laboratories that have 21 percent oxygen levels and relate those findings to a tumor that is inside the body, Sen said. The significance of conducting tumor cell research under lower oxygen conditions should be considered.

To test the theory that ambient oxygen really does matter to a cell, Sen and his colleagues extracted heart cells from mice and

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put groups of these cells into three separate incubators. (A typical incubator is about half the height of a refrigerator, and about the same width and depth.) Each incubator had a controller, which let the researchers control the amount of oxygen entering the chamber. Oxygen levels were set at 3 percent, 10 percent and 21 percent. Such oxygen controls are not present in a typical incubator.

Most healthy organs are used to a roughly 5 percent oxygen level, Sen said. Arterial blood, which carries oxygen to the organs, contains roughly 14 percent oxygen. The heart contains about 5 percent, while the skin and liver both contain around 3 percent oxygen.

While 10 percent represents a slightly hyperoxic higher-than-normal oxygen environment for the heart cells used in this study, studies by other researchers have shown that oxygen concentrations in heart cells can vary based on where the cells are located and how oxygen levels are measured. Oxygen levels can fluctuate within an organ depending on how far cells are located from the closest blood vessel that distributes oxygen, Sen said. The body maintains cellular oxygen concentrations within a narrow range due to the risk of damage from too much oxygen and death due to too little oxygen. The normal amount of oxygen for a cell depends on where that cell is in the body and what it does.

At the highest level of oxygen used in this study 21 percent cell growth slowed. But cell size increased three- to six-fold.

The cells got flat and stuck firmly to the culture dish, Sen said. They also nearly stopped moving. They didn't look or act like they would inside the body. The cells incubated at a 3 percent oxygen level remained mobile and continued to grow. The growth of cells incubated at 10 percent oxygen showed behavior similar to the cells grown at the highest level of oxygen, but to a lesser extent.

The researchers think that cells contain oxygen-sensitive genes that are activated when oxygen levels are higher than what the cells are used to in the body. High levels of oxygen also induced the formation of free radicals, compounds that can alter gene expression patterns.

The researchers tested the effects of varying the oxygen levels of some of the cell cultures. Some of the cultures were kept in 21 percent oxygen during the day and in 3 percent at night. Growth in these cells dropped during the day, but sped up when oxygen levels dropped at night.

This suggests that growth halted by hyperoxia can be reversed, at least when the hyperoxic insult is short, Sen said. He also noted that it takes about 15 to 20 minutes before a change in oxygen level begins to affect a cell.

With funding for cellular biology in the billions, Sen said it might be time for he and his cell biology colleagues to rethink whether room air is the right environment in which to grow cells that are isolated from organs in the body. Although oxygen levels in a cell culture dish are slightly lower than the levels in normal room air, these levels are still much higher than what most cells would see in the body, Sen said. While all cellular responses may not be sensitive to a changing oxygen environment, it is fair to assume that several key cellular processes are affected by oxygen levels in the culture environment.

High oxygen levels in a laboratory may halt cell growth, and even change a cell's physical characteristics, he said. There is a clear risk of seeing cellular

responses that normally don't happen inside the body. Regulating oxygen levels for cell cultures should take us a step closer to what goes on in real life. Sen conducted the study with Sashwati Roy, Savita Khanna, Alice Bickerstaff, Sukanya Subramanian, Mustafa Atalay, Srikanth Pendyala, Dana Levy, Nidhi Sharma, Mika Venojarvi, Arthur Strauch and Charles Orosz, all with [Ohio States College of Medicine and Public Health](#); and Michael Bierl, with the [College of Biological Sciences at Ohio State](#).

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