

# YEAST FINDING LINKS PROCESSES IN HEART DISEASE AND CANCER

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By studying a little-known yeast too primitive to get diseases, Johns Hopkins researchers have uncovered a surprising link between two processes at play in heart disease and cancer in people.

In experiments with yeast known as *S. pombe*, the researchers discovered that a gene that helps the organism make cholesterol also helps it survive when oxygen is scarce. The finding, described in the March 25 issue of [Cell](#), offers a new strategy for killing infectious yeast, but it also suggests that cells' efforts to make cholesterol and detect oxygen levels might be connected in people, too.

"We were simply trying to establish that this yeast could be a model for studying cholesterol-related activities in human cells," says the study's leader, [Peter Espenshade](#), Ph.D., assistant professor of [cell biology](#) in Johns Hopkins' [Institute for Basic Biomedical Sciences](#). "We certainly didn't expect to find a completely new role for this gene."

It's already well established that human cells can both make cholesterol and sense oxygen. In people, high levels of cholesterol in the blood are a major risk factor for heart disease, and many human cancer cells are able to survive despite being in tumors' oxygen-starved centers.

"We don't know yet whether cholesterol production and oxygen sensing are connected in human cells, but now we're trying to find out," says Espenshade.

In people, the gene in question, known as SREBP, controls other genes whose products help make or import cholesterol. Cholesterol-lowering drugs called statins mimic this gene's natural role by triggering cells to import more cholesterol, clearing the artery-clogging stuff from the blood.

Despite the obvious medical relevance of SREBP, no one had ever looked at the equivalent system -- or even determined whether there was one -- in yeast, the simple, single-celled relatives with which we share many genes. Because yeast can be easily manipulated and studied, Espenshade figured they might be a good model for figuring out exactly how SREBP is turned on, what it does and how it's shut off -- if the organism has an equivalent process.

Turning first to databases of the entire genetic sequences of various yeast, Espenshade sought yeast genes that looked like SREBP and its binding partner SCAP. Nothing turned up in the

well-studied *S. cerevisiae*, or brewer's yeast, but *S. pombe* seemed to have the right stuff.

Graduate student Adam Hughes then examined the role of these similar genes to prove that they in fact duplicate the human process. Indeed, the yeast gene they called *sre1* triggered activation of cholesterol-producing genes, aided by a gene called *scp1* that behaves like SCAP.

As in humans, *sre1* somehow gets turned on when cholesterol levels are low, increasing the cell's production of cholesterol. As cholesterol builds up in the cell, *sre1* is gradually turned off.

"Essentially, SREBP and *sre1* both try to maintain an optimal level of cholesterol in the cells," says Espenshade.

But, based on what he now knows, Espenshade suspects that the yeast use cholesterol levels to figure out whether there's enough oxygen around for biology as usual. Single-celled yeast can alter their biology to live without oxygen, and human cells can do so to a certain extent. Johns Hopkins researcher [Gregg Semenza](#), M.D., Ph.D., discovered a number of years ago how human cells react to low oxygen levels, but that process has never been connected to cholesterol production.

"Our cells can adjust to lowered oxygen by turning on a specific set of genes when oxygen levels drop [using a gene called HIF1-alpha]," says Espenshade. "While there's no known connection between this process and cholesterol production, our results in the yeast suggest that perhaps SREBP itself, or something in the cholesterol pathway, might also serve as an oxygen sensor for mammalian cells."

It makes sense, he says, that the yeast could use its cholesterol levels as an indirect measure of oxygen levels. The cell uses a few oxygen molecules each time it makes cholesterol, so lowered cholesterol levels could signal that there's not enough oxygen around to make it. And because low cholesterol levels automatically turn on the yeast's version of SREBP, it's an easy solution to have the same gene sound the alarm that the cell needs to adapt to low levels of oxygen.

Espenshade says *sre1*'s role in the yeast's production of cholesterol (actually a similar molecule called ergosterol) and sensing of oxygen might offer a new opportunity to kill infectious yeast and fungi that share the gene with *S. pombe*.

"Without the *sre1* gene, the yeast in our experiments died in low oxygen conditions," says Espenshade. "Because low oxygen levels are common in infected tissues, if we can block infectious yeasts' SREBP pathway without affecting human cells' cholesterol pathways, we might be able to treat certain infections."

Espenshade and his team have found that infection-causing yeast *Aspergillus*, *Neurospora*, *Cryptococcus* and *Ustilago* share *S. pombe*'s cholesterol-related genes, while *S. cerevisiae* and the yeast *Candida* do not.

The researchers were funded by the National Institute of General Medical Sciences, the National Heart, Lung and Blood Institute and the Burroughs Wellcome Fund. Authors on the paper are

Hughes, Bridget Todd and Espenshade, all of Hopkins. Hughes and Todd are both graduate students in the Biochemistry, Molecular and Cell Biology program.

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