Clues about controlling cholesterol rise from yeast studies

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Having discovered how a lowly, single-celled fungus regulates its version of cholesterol, Johns Hopkins researchers are gaining new insight about the target and action of cholesterol-lowering drugs taken daily by millions of people to stave off heart attacks and strokes. Their work appears in the December issue of *Cell Metabolism*.

In humans, statin drugs inhibit an enzyme, HMG-CoA reductase, to lower blood cholesterol. What's not as well understood are the multiple layers of control for the enzyme, especially the regulatory protein Insig.

Because components of the cholesterol-regulatory system have been conserved across 400 million years of evolution, a yeast called fission yeast is a good model for delving fast and deep into molecular details of how mammalian cells regulate HMG-CoA reductase.

The Hopkins team found that in these yeast, so named because they divide in the middle, Insig also regulates HMG-CoA reductase but does it differently. In mammals, Insig degrades this enzyme — essentially destroying it — while in fission yeast, Insig inactivates the enzyme simply by promoting the attachment of a phosphate.

"This is a surprising fundamental difference," says Peter J. Espenshade, a physiologist in the Department of Cell Biology and member of the Center for Metabolism and Obesity Research at the Johns Hopkins University School of Medicine.

Despite a decidedly bad rep, cholesterol has good purpose — in the right amounts and in the right places — as the raw material for the production of steroid hormones and bile acids. Cholesterol also sits in the membranes of cells, maintaining the barrier between them and their environment. But the thing that makes it most useful in cell function — its absolute inability to dissolve in water — also makes it lethal. When cholesterol accumulates in the wrong place — say, within the wall of an artery — it leads to plaque formation and atherosclerosis.

The Johns Hopkins team's seek-and-find mission for new parts of the molecular machine that regulates the manufacture of cholesterol builds on Nobel-prize winning research by Michael S. Brown and Joseph L. Goldstein of the Department of Molecular Genetics, University of Texas - Southwestern Medical School, who discovered that cells of the human body have receptors on their surfaces that trap and absorb bloodstream particles containing cholesterol.

Using fission yeast, the Johns Hopkins scientists identified the protein Insig as an integral part of the sensor system in cells that measures cholesterol levels. When all is well with cells, they happily go about their business of manufacturing cholesterol in just the right amounts, as determined by their Insig-regulated sensors, Espenshade says.

As in humans, Insig in yeast limits cholesterol production by inactivating the enzyme HMG-CoA reductase. How the yeast stopped synthesizing cholesterol was what surprised the scientists, however.

Stressed fission yeast activated a protein called MAPK which, partnering with the protein Insig, attaches a phosphate onto the enzyme HMG-CoA reductase by a process known as phosphorylation and shuts down cholesterol manufacture. These findings explain how a cell can change cholesterol production in response to a stressful environment.

"In this study, we not only learned something new about how Insig works and cholesterol biology, but we also found a rare example of a MAPK controlling a biosynthetic enzyme," Espenshade says.

By studying Insig control of HMG-CoA reductase in yeast, the researchers hope to inform improvements to the efficacy of statin and other cholesterol-lowering therapies.

Source: Johns Hopkins Medical Institutions