A spring-loaded sensor for cholesterol in cells

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Although too much cholesterol is bad for your health, some cholesterol is essential. Most of the cholesterol that the human body needs is manufactured in its own cells in a synthesis process consisting of more than 20 steps. New research from the University of New South Wales in Sydney, Australia, to be published in the *Journal of Biological Chemistry* on Dec. 8, explains how an enzyme responsible for one of these steps acts as a kind of thermostat that responds to and adjusts levels of cholesterol in the cell. This insight could lead to new strategies for combating high cholesterol.

Towards the middle of the assembly line of cholesterol production, an enzyme called squalene monooxygenase (SM) carries out a slow chemical reaction that sets the pace of cholesterol production. In 2011, Andrew Brown's laboratory at UNSW discovered that when cholesterol in the cell was high, SM was destroyed and less cholesterol was produced. The new research explains how this sensing and destruction happens.

SM is embedded in the membrane of the cell's endoplasmic reticulum (ER), which is composed of fatty molecules including cholesterol. As cholesterol in the cell increases, more and more of it is incorporated into the ER membrane.

Like all proteins, SM is composed of amino acids, and different sequences of amino acids have different properties. A particular series of twelve amino acids is a "destruction code" that tells the cell's garbage disposal machinery to degrade the SM protein.

Brown's team showed that under typical conditions, the destruction code is hidden by being tucked away inside the endoplasmic reticulum membrane as part of a spring-shaped structure. Using experiments in cell cultures and with isolated proteins and membranes, they also showed that this spring structure could only embed in membranes that contained a low percentage of cholesterol. When the amount of cholesterol making up the membrane increased, the spring popped out, exposing the destruction code.

"When cholesterol levels are low, this destruction code is hidden in the membrane like a spring-loaded trap," said Ngee Kiat Chua, the graduate student who led the new study. "However, too much cholesterol [in the membrane] springs the trap, unmasking the destruction code." When this occurs, the cell proceeds to destroy the SM.

The researchers speculate that, because the synthesis step carried out by SM is crucial to determining the amount of cholesterol a cell produces, drugs targeting SM could be used to decrease cholesterol as an alternative to the popularly used statins, which target an enzyme earlier in the cholesterol synthesis assembly line. But they also wonder whether the type of cholesterol-responsive spring they discovered might be used by other proteins involved in cholesterol metabolism to sense and adjust cholesterol levels.

"It's perhaps stretching the bow a little too far to make a connection from our little cholesterol spring mechanism to metabolic disorders," Brown said. "But we've found a fundamental cholesterol sensing mechanism, and that's where this work has advanced the field."

More information: Ngee Kiat Chua et al, A Conserved Degron Containing an Amphipathic Helix Regulates the Cholesterol-Mediated Turnover of Human Squalene Monooxygenase, a Rate-Limiting Enzyme in Cholesterol Synthesis, *Journal of Biological Chemistry* (2017). DOI:

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