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Cellular feast or famine

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Not all cholesterol is bad. Every cell requires it for growth – they either have to get cholesterol somewhere or they die. In a new study published April 6 in the journal *Cell Metabolism*, researchers from Sanford-Burnham Medical Research Institute (Sanford-Burnham) and their collaborators found that a protein sensor known to balance cholesterol sources can also access a previously underappreciated cellular fat storage depot.

The sensor, called sterol regulatory element-binding protein 2 (SREBP-2), monitors cellular cholesterol levels and responds to low levels by switching on genes that allow the cell to either 1) take up more from the bloodstream or 2) manufacture more from cholesterol building blocks inside the cell. Now, Sanford-Burnham's Timothy Osborne, Ph.D., and his team have uncovered a third cholesterol source also controlled by SREBP-2: fat droplets stored inside the cell itself.

"We were searching the mouse liver cell genome to find DNA sequences specifically bound by SREBP-2," said Dr. Osborne, director of the Metabolic Signaling and Disease Program in Sanford-Burnham's Diabetes and Obesity Research Center. "First we were surprised that SREBP-2 binds very close to the genes it regulates – that's not typical. Second, we were surprised to find that in addition to genes related to fat metabolism and cholesterol balance, SREBP-2 also binds and activates genes responsible for autophagy."

When times get tough, autophagy is the cell's way of recycling its own old or damaged parts. Dr. Osborne and his team found that SREBP-2

uses autophagy as a way to liberate cholesterol stored by some cells in fat droplets. (Here they looked at liver cells, which have large fat droplets. In contrast, other cell types – neurons, for example – aren't known to store fat.) When cholesterol was limited, autophagy genes were switched on and fat droplets were joined by autophagosomes (bags of enzymes the cell deploys for self-destruction). As a result, more cholesterol was available for cells to repair membranes, burn as energy or drive other life-sustaining processes.

The role of SREBP-2 in autophagy and cholesterol generation was confirmed using cells engineered to lack the protein. Facing cholesterol shortage, SREBP-2-deficient cells were unable to switch on autophagy genes and autophagosomes did not form as readily as they did in normal cells.

"This study identified a key regulatory step that determines how cells decide whether they have sufficient stored fat, or whether new fat needs to be produced internal cellular sources or obtained from the environment," Dr. Osborne said. "Genetic or environmental conditions that interfere with this regulatory step could lead to diseases such as obesity or cardiovascular disease."

More information: Seo Y-K, Jeon T-I, Chong HK, Biesinger J, Xie X, Osborne TF. Genome-wide localization of SREBP-2 in hepatic chromatin predicts a role in autophagy. Cell Metabolism. April 6, 2011.

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