Researchers discover pathway with implications for obesity

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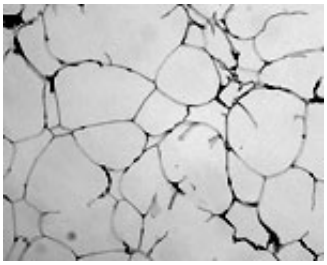

Mature fat cells, known as adipocytes. Image: Ling Qi

(PhysOrg.com) -- Cornell scientists have discovered how two related proteins and their roles in a key molecular pathway are critical to creating obesity-causing fat cells.

Targeting the proteins, known as IRE1alpha and XBP1, could hopefully lead to drug therapies to fight obesity, which affects one in three adults and contributes to heart disease, diabetes, some cancers and high blood pressure.

"We're trying to understand the mechanisms underlying the development of fat cells," said Ling Qi, Cornell assistant professor of nutritional sciences and senior author of the paper, published in the June 3 issue of the journal Cell Metabolism (Vol. 9, No. 6). "The overall goal of my group is to find therapeutic strategies for treatment of obesity and obesity-associated complications."

The creation of fat cells involves a two-step process: Stem cells first develop into precursors of fat cells called pre-adipocytes, and then these cells develop into mature fat cells, called adipocytes.

The new study focuses on this second phase in which the pre-adipocytes experience a low level of stress in the endoplasmic reticulum, the organelle where new proteins are made and folded and then transported out for use by the cell. The stress caused by an accumulation of mis- or un-folded proteins is critical for the transition from pre-adipocytes to mature fat cells, the researchers found.

To counter the stress, cells activate IRE1alpha, a protein that resides in the endoplasmic reticulum and that senses unfolded proteins as a part of a cellular defense mechanism called the unfolded protein response. Qi and his colleagues created cells lacking IRE1alpha and demonstrated that these cells were unable to develop from pre-adipocytes into adipocytes. This evidence suggests that IRE1alpha is a key component of the pathway that leads to fat cell development, Qi said.

Activated IRE1alpha then converts the protein XBP1 into a new form. In its new configuration, XBP1 moves into the cell's nucleus, where it turns on genes that work to resume normal protein folding and balance to the endoplasmic reticulum. The researchers also found that loss of XBP1 interferes with the conversion of pre-adipocytes into mature fat cells.

The research is the first to show that the endoplasmic reticulum and the IRE1alpha-XBP1 pathway are involved in the genesis of fat cells, Qi said.

"The unfolded protein response keeps the balance of endoplasmic reticulum homeostasis," said Haibo Sha, the paper's lead author and a postdoctoral associate in Qi's lab. "If there are defects in the endoplasmic reticulum, then pre-adipocytes will not be able to

differentiate into the adipocytes."

While lack of physical activity and overeating can lead to obesity, genetic mutations also can cause the condition. The researchers hope that drugs that target XPB1 or IRE1alpha may lead to treatment for obesity in the future, Qi said.

Provided by Cornell University (news : web)