

Shifting the balance between good fat and bad fat

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Sanford-Burnham professors Jorge Moscat, Ph.D., and Maria Diaz-Meco, Ph.D., co-authored a study on p62's role in fat metabolism. Credit: Sanford-Burnham Medical Research Institute

In many cases, obesity is caused by more than just overeating and a lack of exercise. Something in the body goes haywire, causing it to store more fat and burn less energy. But what is it? Researchers at Sanford-Burnham Medical Research Institute have a new theory—a protein called p62. According to a study the team published in the *Journal of Clinical Investigation*, when p62 is missing in fat tissue, the body's metabolic balance shifts—inhibiting "good" brown fat, while favoring "bad" white fat. These findings indicate that p62 might make a promising target for new therapies aimed at curbing obesity.

"Without p62 you're making lots of fat but not burning energy, and the

body thinks it needs to store energy," said Jorge Moscat, Ph.D., Sanford-Burnham professor. "It's a [double whammy](#)." Moscat led the study with collaborators at Helmholtz Zentrum München in Germany and the University of Cincinnati.

p62 and obesity

Moscat's team had previously produced mice that completely lack the p62 protein everywhere in their bodies. As a result, the animals were obese. They also had [metabolic syndrome](#). In other words, as compared to mice with p62, mice lacking p62 weighed more, expended less energy, had diabetes and had a hyper-[inflammatory response](#) that's characteristic of [obesity](#).

While those results showed that the lack of p62 leads to obesity, "we didn't know which tissue was responsible for these effects, because p62 was missing in all of them," Moscat said.

Some researchers believe that [muscle tissue](#), where energy is expended, controls obesity. Others suspect the liver is a key player, or that the brain's [appetite control](#) center is most responsible for obesity.

But then there's fat itself—both white fat and brown fat. White fat is the type we think of as unwanted body fat. Brown fat, on the other hand, is beneficial because it burns calories. Many researchers now believe that brown fat somehow malfunctions in obesity, but the details are unclear.

p62 shifts the balance between white fat and brown fat

In their latest study, Moscat and colleagues set out to pinpoint the specific tissue responsible for obesity when p62 is missing. They made

several different mouse models, each missing p62 in just one specific organ system, such as the central nervous system, the liver, or muscle. In every case, the mice were normal. They weren't obese like the mice lacking p62 everywhere.

Then they made a mouse model lacking p62 only in their fat tissue. These mice were obese, just like the mice missing p62 in all tissues. Upon further study, the researchers found that p62 blocks the action of an enzyme called ERK while activating another enzyme called p38. When p62 is missing, the enzyme p38 is less active in brown fat, while ERK is more active in white fat. As a result, Moscat said, p62 is "a master regulator" in normal fat metabolism.

According to Moscat, the discovery of p62's role in [brown fat](#) tissue is encouraging, because fat tissue is much more accessible than other parts of the body—the brain, for example—for potential drug therapies. "This makes it easier to think about new strategies to control obesity," he said.

New methods for preventing or treating obesity, a major epidemic in the United States, are urgently needed. Drug therapies designed to minimize the intake of food have had limited success and also produce considerable side effects.

Provided by Sanford-Burnham Medical Research Institute

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