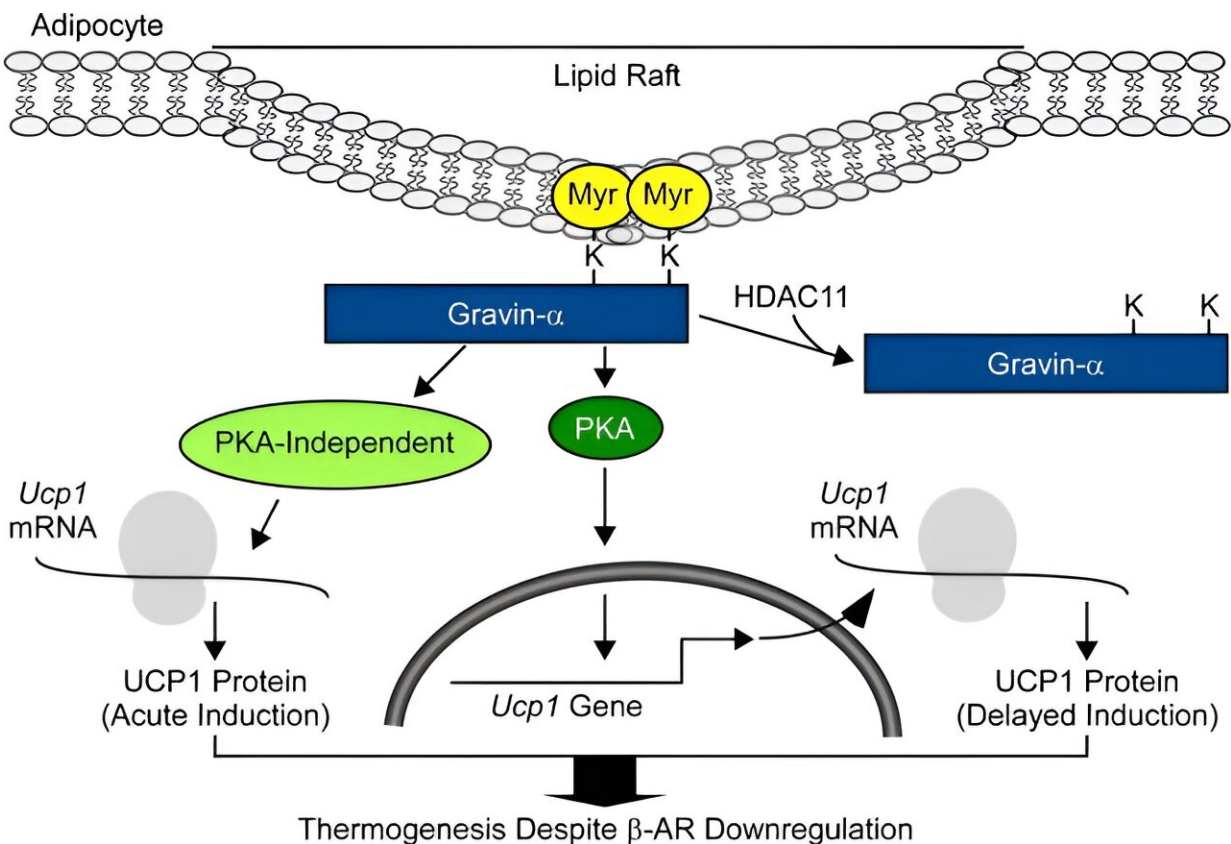


# Researchers find potential target for prompting fat cells to expend energy

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Credit: *Journal of Clinical Investigation* (2023). DOI: 10.1172/JCI168192

A research team led by Emma Robinson, Ph.D., and Timothy McKinsey, Ph.D., at the University of Colorado School of Medicine has identified a potential target for treating obesity and metabolic disease that could

enhance the effectiveness of existing anti-obesity drugs.

In an [article](#) published today by *The Journal of Clinical Investigation*, the CU-led team of researchers report on their study of an enzyme known as histone deacetylase 11 (HDAC11), which serves important roles in controlling [adipose tissue](#) function. Adipose tissue is commonly known as fat. McKinsey is the senior author and Robinson, a senior postdoctoral fellow in McKinsey's lab, is the first author on the article.

McKinsey, professor of medicine and co-director of the Consortium for Fibrosis Research & Translation, explains that the study is the first to show that inhibiting HDAC11 can have the beneficial impact of causing fat cells to expend energy by inducing a protein called UCP1, or uncoupling protein 1.

There are different types of adipose tissue. The primary role of white adipose tissue is to store energy in the form of triglycerides, while brown adipose tissue has an abundance of mitochondria, which dissipate [chemical energy](#) as heat through a process known as non-shivering thermogenesis, in part through the action of UCP1.

"There's a third type of fat called beige," says McKinsey. "It's when you take white fat, which normally isn't all that good, and turn it into something that looks more like brown fat. By inhibiting HDAC11, we are stimulating the beiging of white fat. HDAC11 inhibition is changing the phenotype of fat tissue in a favorable way."

The discovery opens the possibility that [fat cells](#) could be prompted to expend energy by targeting distinct molecular mechanisms in adipose tissue. Prior attempts to do this in humans have focused on stimulating the b3-adrenergic receptor (b3-AR) with drugs such as mirabegron. These attempts have been unsuccessful in most cases, possibly due to a decrease in the number of the receptors on the surface of target cells.

That process results in a state called adipose tissue catecholamine resistance.

Through their experiments, Robinson and colleagues were able to show that HDAC11 inhibition stimulates UCP1 expression even in the context of catecholamine resistance. The results suggest potential for HDAC11 inhibitors to enhance [brown adipose tissue](#) activity and the beiging of white adipose tissue in cases where b3-AR stimulating drugs have previously failed.

This discovery shows that HDAC11 inhibition could help counter harmful effects of excess body fat, such as insulin resistance, inflammation, and fibrosis.

The CU-led team studied the effects of inhibiting HDAC11 in mice and in human fat tissue that had been removed from obese patients undergoing bariatric surgery. Seeing the same study results in the separate models indicates the potential of eventually translating the findings from the bench to the bedside to treat obesity and metabolic disease in humans, McKinsey says.

McKinsey and his colleagues plan to continue their study of HDAC11 inhibition, with the ultimate goal of developing innovative approaches to treat human diseases. McKinsey says an improved understanding of HDAC11's functions in [adipose tissue](#) could enhance or offer alternatives to existing weight loss drugs, such as GLP-1 agonists, which are reporting outstanding results, although there are cases where the drugs can lead to muscle loss. Another adverse factor is that many patients regain weight when they discontinue the drugs.

Co-authors with Robinson and McKinsey are Rushita A. Bagchi, Ph.D., from the University of Arkansas for Medical Sciences; Jennifer L. Major, Ph.D., from Memorial University of Newfoundland, CA; Bryan

C. Berman, Ph.D., professor of medicine at CU School of Medicine, and Jennifer L. Matsuda, Ph.D., associate professor of immunology and genomic medicine at National Jewish Health.

**More information:** Emma L. Robinson et al, HDAC11 inhibition triggers bimodal thermogenic pathways to circumvent adipocyte catecholamine resistance, *Journal of Clinical Investigation* (2023). [DOI: 10.1172/JCI168192](https://doi.org/10.1172/JCI168192)

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