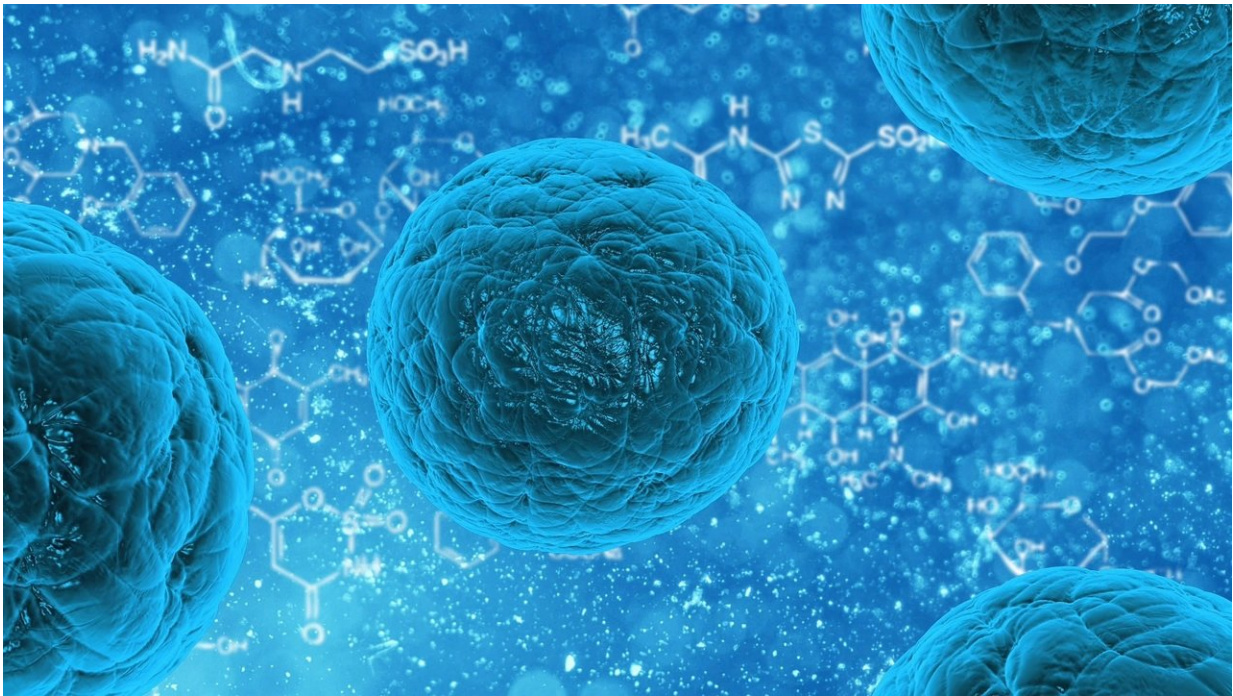


# Brown fat can burn energy in an unexpected way

April 6 2020

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When we are exposed to sufficient cold or exercise, small clusters of brown fat cells in our bodies begin to burn up energy. Since 2009, when researchers at Joslin Diabetes Center and other institutions discovered that this helpful form of fat can be active in adults, scientists have sought to turn up the heat from these cells to treat obesity, diabetes and other metabolic conditions.

Researchers in the lab of Joslin's Yu-Hua Tseng, Ph.D., a Senior Investigator in the Section on Integrative Physiology and Metabolism, now have discovered an unexpected biological [pathway](#) by which brown [fat cells](#) can translate energy into heat.

Studies in mice showed that activating this pathway in precursors of brown or white fat cells boosts the heat-generating capacity of these cells without pushing the cells to accumulate fat, says Farnaz Shamsi, a postdoctoral associate in the Tseng lab and lead author on a paper describing the findings in *Nature Communications*.

Previously, researchers have found that certain biological signals that boost the production of brown fat cells are also likely to create unhelpful white fat cells, thus posing one of research challenges in enhancing brown fat activity. The finding, however, suggests that the pathway the Joslin team uncovered might offer a solution to that challenge.

The research began with a protein called UCP1 that is located on mitochondria, the cell's powerhouses. UCP1 is known to be a crucial component in activating brown fat cells, explains Tseng, who is also an Associate Professor of Medicine at Harvard Medical School.

Her team screened more than 5,000 mammalian proteins to identify factors that heightened UCP1 production in brown fat precursor cells. The screen identified two proteins called FGF6 and FGF9, members of the "fibroblast growth factor" family of proteins that can help to regulate diverse biological processes including cell development and growth.

Next, the investigators tried increasing the levels of the two proteins, and thus increasing UCP1 production, in immature mouse brown fat cells. The scientists expected that these cells would start to accumulate fats and other lipids, and to develop into mature brown fat cells—but surprisingly, that didn't happen.

Painstakingly uncovering the reasons for this unexpected outcome, "we found step-by-step the molecular events that happened downstream that eventually lead to UCP1 production in fat cells," says Shamsi. "This novel downstream pathway was completely different from what researchers in our field have understood as the mechanism to induce UCP1 in these [cells](#)."

Shamsi, Tseng and their colleagues saw that the two FGF proteins provide similar effects on production of UCP1 but are driven by different exposures in mice. FGF9 is stimulated by cold, while FGF6 is stimulated by exercise.

When the Joslin scientists went on to analyze samples of human fat tissues, they also recognized this pathway at work. Among their results, levels of FGF9 and FGFR3 (the receptor protein that FGF9 and FGF6 both activate) were associated with higher levels of UCP1 in human brown and white fat. More strikingly, expression of FGFR3 in human white fat negatively correlated with the person's body mass index (a measure of obesity) and insulin resistance (a condition that can drive type 2 diabetes).

"This suggests that if we can activate this pathway, we potentially can benefit people with obesity, diabetes and related metabolic diseases," Tseng says.

Her team is working with collaborators to synthesize a version of the FGF [protein](#) that is optimized for greater efficacy and easier delivery, she says. Since her group has traced the mechanisms at work in this pathway, it also may eventually be possible to develop drugs that build up UCP1 production by targeting specific molecular steps in the pathway.

"As obesity becomes epidemic, we hope that our research in brown fat

can help," Tseng says. "With a collective effort from many labs around the globe, we are getting closer to that goal."

**More information:** Farnaz Shamsi et al, FGF6 and FGF9 regulate UCP1 expression independent of brown adipogenesis, *Nature Communications* (2020). [DOI: 10.1038/s41467-020-15055-9](https://doi.org/10.1038/s41467-020-15055-9)

Provided by Joslin Diabetes Center

Citation: Brown fat can burn energy in an unexpected way (2020, April 6) retrieved 20 March 2024 from <https://medicalxpress.com/news/2020-04-brown-fat-energy-unexpected.html>

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