CNIC research identifies a key protein for ‘burning’ fat

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This work reveals a new mechanism by which brown fat is converted into heat, and which protects from pathologies associated with obesity.

Obesity, which affects 650 million people worldwide, influences the development of cardiometabolic diseases and increases the risk of cancer. A new study conducted at the Centro Nacional de Investigaciones Cardiovasculares (CNIC) and Centro Nacional de Investigaciones Oncológicas (CNIO), led by Guadalupe Sabio and Cintia Folgueira, has uncovered a mechanism through which the body burns brown fat and converts it into heat. This process plays a protective role against obesity and related metabolic diseases.

The mechanism now identified is controlled by the protein called MCJ, present in mitochondria (the organelles of the cell where energy is produced). Sabio and Folgueira have discovered that, when the MCJ protein is removed from obese mice, these animals produce more heat and lose weight. The researchers have also managed to reduce the weight of obese mice just by having them transplanted with fat without that protein.

Obesity is the result of either excessive food intake or inadequate total energy expenditure. We now know that adipose tissue –body fat–, in addition to storing energy, plays a crucial role in the management of that energy by the body. Adipose tissue is a complex organ that acts as a regulator of the whole body's metabolism, and therefore modulating its function could well be a way to combat obesity", the authors write in *Nature Communications*.

There are two types of fatty or adipose tissue: white and brown. White adipose tissue mostly stores energy, while brown fat (its cells have more mitochondria and that gives them a brown hue) is responsible for heat generation or thermogenesis, the process that maintains body temperature and which is triggered by cold or other stimuli.

Several studies in the last decade have shown that activating brown fat protects against obesity and metabolic disease. "For some time," explains Sabio, "it has been thought that obesity could be prevented by getting this fat to spend more energy by generating heat. So the first thing is to understand how it works."

"Discovering new mechanisms of heat production in brown fat is one of the most interesting targets in the study of obesity," says Sabio.

How to burn brown fat

For a long time it was thought that brown fat used a single mechanism to generate heat, but today we know that this is not the case. There are several mechanisms involved. The research led by Sabio and Folgueira has discovered one of them, controlled by a mitochondrial protein called MCJ.

The research conducted at CNIO has discovered that when the MCJ protein is removed from obese mice, these animals produce more heat and lose weight. Moreover, it was enough to transplant into the animals brown fat without the MCJ protein to reduce their weight

The researchers also observed that "animals without MCJ in brown fat are protected against health problems caused by obesity, such as diabetes or increased blood lipids," explain the two scientists. Therefore, they believe that the MCJ protein could be a new therapeutic target to correct diseases associated with obesity**.**

"This protection," explains CNIO researcher Beatriz Cicuéndez, lead author of the article, "is due to the activation of an essential signalling pathway to adapt to the stress caused by obesity. Known as the catabolic pathway, it causes an increase in the consumption of fats, sugars and proteins to produce heat in brown fat. It is a mechanism that also happens in people with very active brown fat.

The research is now seeking to develop a therapy to block this protein in obese patients, but to do so they must first investigate whether the MCJ protein has vital functions in other tissues. At the same

time, Guadalupe Sabio says, “we are trying to see if these changes in fat affect tumour growth or cachexia – loss of muscle and fat – which is also sometimes linked to cancer.”

- Cicuéndez B, Mora A, López JA, Curtabbi A, Pérez-García J, Porteiro B, Jimenez-Blasco D, Latorre-Muro P, Vo P, Jerome M, Gómez-Santos B, Romero-Becerra R, Leiva M, Rodríguez E, León M, Leiva-Vega L, Gómez-Lado N, Torres JL, Hernández-Cosido L, Aguiar P, Marcos M, Jastroch M, Daiber A, Aspichueta P, Bolaños JP, Spinelli JB, Puigserver P, Enriquez JA, Vázquez J, Folgueira C, Sabio G. Absence of MCJ/DnaJC15 promotes brown adipose tissue thermogenesis. **Nat Commun.** 2025 Jan 13;16(1):229. doi: 10.1038/s41467-024-54353-4. PMID: 39805849.

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