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## **TEACHING FAT TO BURN FAT**

**Researchers from the University of Padua and the Veneto Institute of Molecular Medicine discover a fundamental mechanism that opens new ways to combat obesity**

The obesity epidemic in the Western world represents one of the challenges of modern medicine. In the United States almost 43% of the population is obese, in the WHO European Region 20%, in Italy almost 10%. Obesity is a serious risk factor for cardiovascular disease, type 2 diabetes and certain types of cancer, but drugs to combat obesity are lacking.

One appealing possibility is to "change" the type of fat. Our body harbours two types of fat: white fat, responsible for the storage of lipids, and brown fat, responsible instead for the dissolution of fat, which in this tissue is converted into heat. In short, brown fat "burns fat". However, how to instruct white fat cells to become brown or brown-like (beige, as scientists call them) is largely unclear. Scientists know that cell identity can be changed by modifying gene expression, but how can they specifically teach white fat cells to become beige? Clues to answer this question can come from the analysis of differences between fat in lean individuals and in persons with obesity.

**The study *The mitochondrial protein Opa1 promotes adipocyte browning that is dependent on urea cycle metabolites* published in «Nature Metabolism», led by Dr. Camilla Bean of the Veneto Institute of Molecular Medicine (VIMM) and coordinated by Prof. Luca Scorrano, Professor at the Department of Biology of the University of Padua, Principal Investigator of VIMM of which he was Scientific Director, contributes to closing this gap and offers an appealing therapeutic strategy.**

**In their study, Scorrano and colleagues discover a link between mitochondria, the powerhouses of the cell, the "urea cycle", a metabolic pathway involved in aminoacid metabolism, fumarate, a key metabolite known for its ability to change gene expression, and the identity of white and beige fat cells.**



*Roberto Vettor*

By analyzing the differences between white fat of obesity patients and that of normal weight individuals, the teams of Prof. Scorrano, Prof. Roberto Vettor, Director of the Department of Medicine of the University of Padua and Prof. Kirsi Pietilainen, Director of the Clinical and Molecular Metabolism Program of the University of Helsinki (Finland) found high levels of a protein called Opa1 in the fat of normal weight individuals. This protein resides in mitochondria, the cell's powerhouses, and is essential for controlling their metabolism as well as their role as "switch" in the process of cellular suicide. Dr Bean confirmed these clinical data in several experimental models of obesity: high levels of Opa1 protected from weight gain and from the deleterious consequences of high fat diet on metabolism. Opa1 protected through an unsuspected mechanism: it stimulated the conversion of white fat into beige fat.

In collaboration with Prof. Nico Mitro of the University of Milan, scientists discovered that Opa1 in fat stimulated the synthesis of urea, a by-product of aminoacid metabolism normally produced in the liver and eliminated in the urine. An intermediate product, called fumarate, accumulates during the synthesis of urea in the adipocytes. Fumarate teaches to the white adipocytes to turn beige, by changing the profile of gene expression. In fact, feeding fumarate to

white adipocytes in the lab pushes them to become beige, transforming them from "fat stores" to cells capable of "burning fat".

«Our study identifies three unsuspected actors: Opa1, the "urea cycle" and fumarate - **explains Prof. Scorrano** -. We trust that this discovery might open the door to innovative therapies that instruct our white fat cells to become beige and burn fat, with the aim of countering the obesity epidemic that afflicts the Western world».



*Luca Scorrano*

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### ***Abstract***

White to brown/beige adipocytes conversion is a possible therapeutic strategy to tackle the current obesity epidemics. While mitochondria are key for energy dissipation in brown fat, it is unknown if they can drive adipocyte browning. Here, we show that the mitochondrial cristae biogenesis protein Opa1 facilitates cell autonomous adipocyte browning. In two cohorts of patients with obesity, including weight discordant monozygotic twin pairs, adipose tissue OPA1 levels are reduced. In the mouse, Opa1 overexpression favors white adipose tissue expandability as well as browning, ultimately improving glucose tolerance and insulin sensitivity. Transcriptomics and metabolomics analyses identify the Jumanji family chromatin remodeling protein Kdm3a and urea cycle metabolites, including fumarate, as effectors of Opa1-dependent browning. Mechanistically, the higher cyclic AMP levels in Opa1 preadipocytes activate CREB, which transcribes urea cycle enzymes. Flux analyses in preadipocytes indicate that Opa1-dependent fumarate accumulation depends on the urea cycle. Conversely, adipocyte-specific Opa1 deletion curtails urea cycle and beige differentiation of preadipocytes, and is rescued by fumarate supplementation. Thus, urea cycle links the mitochondrial dynamics protein Opa1 to white adipocyte browning.

Link to the study: <https://www.nature.com/articles/s42255-021-00497-2>

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