Gene network helps to turn white fat into beneficial calorie-burning fat

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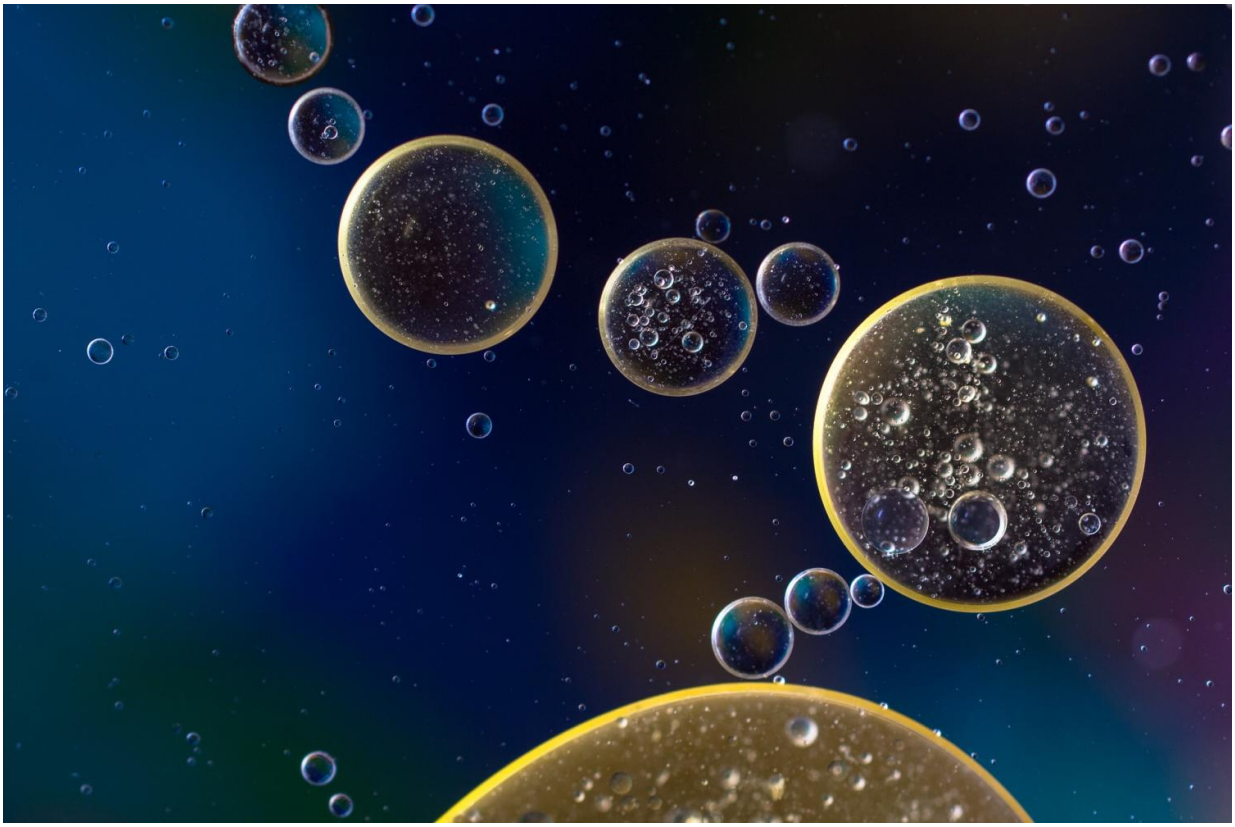

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1.9 billion people around the world are overweight. Of these, 650 million people are obese, which increases the risk of secondary diseases such as cancer. Professor Martin Klingenspor and his team at the Technical

University of Munich (TUM) have examined how fat metabolism affects health. In cooperation with the École Polytechnique Fédérale de Lausanne (EPFL), the team has uncovered a network of genes that could turn energy-storing fat into beneficial calorie-burning fat.

Our fat cells, technically referred to as adipocytes, play an essential role in regulating energy balance in our body. "Adipocytes are not merely an energy storage for times of deprivation, but they also release hormones into the blood, regulating our metabolism as well as feelings of hunger and satiety through the brain and other organs. Nevertheless, too much of a good thing causes harm," said Professor Klingenspor, chair of molecular nutritional science at the TUM Else Kröner-Fresenius Center.

Humans have different types of fat tissue that can be categorized according to color. White fat cells are primarily responsible for energy storage. Brown and beige fat cells can convert nutritional energy into heat. This process is referred to as non-shivering thermogenesis—a principle that small mammals and human newborns use to maintain a stable body temperature.

The occurrence and activity of brown and beige fat cells vary among individuals. There is some evidence suggesting that people with a high number of thermogenic fat cells possess a lower risk to develop obesity and associated metabolic disorders. The growth of beige fat cells within white fat tissue may have particular health benefits.

Browning ability of white fat is genetically determined

"We want to understand how thermogenic fat cells develop, and thus, how beige fat cells grow inside white fat tissue," said Klingenspor. By "browning" the white fat tissue, an energy-storing organ could be

partially transformed into an energy-dissipating organ, thereby improving metabolic health.

The development of beige fat cells is controlled by a still largely unknown genetic program. Mouse strains with divergent genetic backgrounds largely differ in their ability to brown the white fat tissue. "By systematically comparing fat cells among these different strains of mice, we were able to discover which genes or regulators might explain the variation in beige cell differentiation—in other words, the growth of beige fat cells," said Klingenspor.

New possibilities due to transcriptomics and network analyses

By sequencing all transcripts of a cell using next-generation sequencing technology, all gene activities across the entire genome can be registered in a snap-shot. For the current study, the joint TUM/EPFL team performed a comparative analysis of the transcriptomics of fat cells from genetically divergent mouse strains. The study goes beyond other work in this field in that it not only identifies important individual factors, but also relates them to each other in a molecular network.

With this approach, the team has provided a systematic overview of the network of cell-intrinsic regulatory mechanisms that represent the underlying principle for the development of beige fat cells, making them the first team of scientists to achieve this.

"Now, we have gained a unique insight into the genetic architecture driving the molecular mechanisms of beige fat cell development. What we managed to confirm in a cell culture can be examined in vivo as our next step," said Klingenspor.

More information: Yongguo Li et al, Systems-Genetics-Based Inference of a Core Regulatory Network Underlying White Fat Browning, *Cell Reports* (2019). DOI: 10.1016/j.celrep.2019.11.053