UNIVERSITÉ DE GENÈVE

PRESS RELEASE

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How depleting the gut microbiota protects from obesity

In the past few years, research on gut microbiota (that is, all microorganisms, mainly bacteria, inhabiting our gut) has started to unravel its tremendous role in our body, and how it symbiotically affects the functioning of our organs. In particular, microbiota has also an impact on the way calories are absorbed and how fat cells develop. By studying mice without microbiota, scientists from the University of Geneva (UNIGE) Faculty of Medicine, Switzerland, were able to demonstrate how the absence of microbiota has a remarkable effect against obesity. Indeed, it triggers a surprising metabolic mechanism: white fat cells – which in excess cause obesity and insulin resistance – are transformed into cells similar to brown fat (they are called "beige fat"), that protects the body against excess weight and its damaging consequences. This discovery, published in *Nature Medicine*, could open the door to completely new anti-obesity treatments.

Mammals have two types of fat: brown fat, whose primary function is to burn calories to produce heat; and white fat, which is used as energy storage. In healthy humans, white adipose tissue constitutes about 25% of the body mass. However, when in excess, white fat contributes to insulin resistance and diabetes. Conversely, brown fat improves insulin sensitivity and is reversely correlated to obesity.
In response to cold or exercise, cells similar to brown fat – the beige fat – can appear within the white fat, a phenomenon known as "browning". Although the origin of these beige cells seems alike to that of the white fat, their function differs: the more beige fat appear within the white adipose tissue, the more calories are burned. This suggests that stimulating beige fat growth could be a way to reduce obesity and limit insulin resistance.

The unexpected role of gut microbiota

Only recently, scientists have started to grasp the extent of the relationships between the gut microbiota and its human host. An increasing number of studies are now highlighting its impact on the regulation of multiple metabolic pathways, thus interconnecting the gastrointestinal tract, skin, liver, brain and many other organs.
Today, researchers from UNIGE Faculty of Medicine demonstrate that it also has a direct impact on obesity: the microbiota of obese people has a specific composition, different from the microbiota of lean people. Indeed, germ-free mice (born and kept in sterile conditions, i.e. without microbiota), which receive gut microbiota transplant from obese people, tend to develop obesity and insulin resistance. "Having observed that microbiota can affect the obesity onset, we suspected that microbiota depletion can change the insulin sensitivity by modifying the amount and balance of these various types of fat", explains Mirko Trajkovski, lead author of the study and Professor at the Faculty of Medicine Department of Cell Physiology and Metabolism. To confirm their hypothesis, the researchers fed three groups of mice with a high-calorie diet: germ-free mice, standard mice and mice previously treated with high doses of antibiotics that have the effect of totally depleting their microbiota. While normal mice exposed to a high-calorie diet did develop obesity and insulin resistance, the two other groups remained lean,

had an improved sensitivity to insulin and tolerated glucose better. Importantly, their amount of white fat decreased, and this was accompanied with increased levels of brown fat markers.

Reducing obesity by creating additional beige fat

The scientists observed that depleting microbiota - either through antibiotics or in germ-free mice – stimulated the development of functional beige fat within the white fat, in the same way as when exposed to cold or exercise. But how does this work? It all has to do with a specific cell type, called macrophages. Macrophages are an essential component of the immune system and fulfil various metabolic functions, including tissue remodelling. They express different functional programmes in response to micro-environmental signals, a process called "polarization". Polarized macrophages can be broadly classified in two main groups: M1 and M2, the latter being able to act on the adipose and increase the production of beige fat. When the microbiota is depleted, the number of specific cells, called eosinophils, increases in white fat, which secretes small signalling proteins ("type 2 cytokines") that act on macrophages polarization. Thanks to these proteins, M1 macrophages turn into M2 macrophages, which activate the browning of white fat and reduce obesity.

"In mice, the effect of the antibiotics lasts for a couple of weeks after the treatment", stress Nicolas Suarez-Zamorano and Salvatore Fabbiano, the first co-authors of this study. "Although treating obesity with high doses of antibiotics is unrealistic – mainly due to the risk of antibiotic resistance – we want to explore alternative ways of supressing or modifying the microbiota, and to identify the exact bacterial genes responsible for this phenomenon. We would then target only those, without having to deplete the entire microbiota", explains Mirko Trajkovski. To search for effective clinical treatments of obesity, the scientists will use particular antibiotics, as well as bacterial phages, a kind of virus that kills only specific bacterial strains. The possibility of microbiota transplant from a lean to an obese person whose microbiota would have been previously depleted will also be studied.

contact

Mirko Trajkovski
+41 22 379 5256
Mirko.Trajkovski@unige.ch

UNIVERSITÉ DE GENÈVE
Service de communication
24 rue du Général-Dufour
CH-1211 Genève 4

Tél. 022 379 77 17

media@unige.ch
www.unige.ch