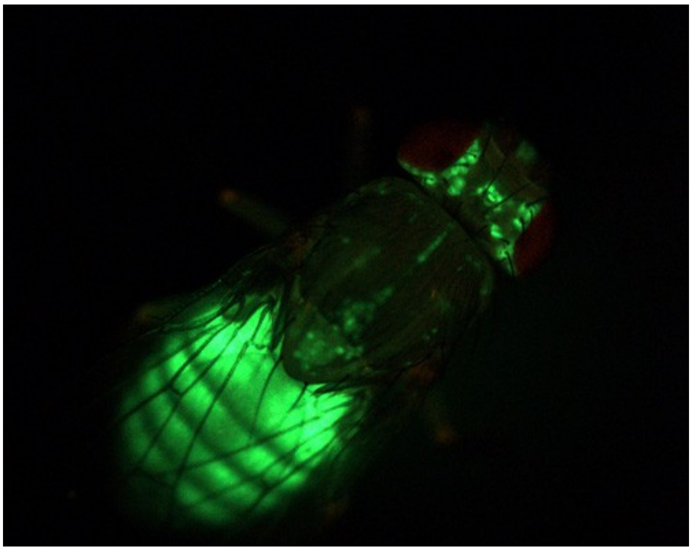
A gene that regulates body heat and fat storage

Researchers from Heidelberg have shown that the organismal balance between heat production and energy storage is regulated by a gene called THADA. In animal experiments, knocking out the THADA gene leads to excessive food intake, obesity and sensitivity to cold. As humans spread throughout the world and settled in different climate zones, THADA was exposed to high selection pressure due to evolutionary adaptation. This explains why human susceptibility to obesity is more prevalent in warm climates.



The fruit fly Drosophila serves as an obesity model. Fat tissue can be distinguished from other tissue with GFP (green fluorescent protein) expression.
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Obesity is a complex chronic disease in which food intake and energy consumption are out of balance. According to the World Health Organisation (2015), over 700 million people worldwide suffer from obesity. The health and economic costs are immense, mainly due to obesity-related complications such as type 2 diabetes and cardiovascular disease. There is no doubt that food and lifestyle are hugely implicated in the spread of obesity across the globe. Paul Zimmet, a well-known Australian diabetologist, has coined the ironic term "coca colonisation" to describe the observation that lifestyle changes, the increase in obesity and obesity-related diseases are associated with the consumption of fast food and sugary soft drinks, popular in equal measure across the globe.

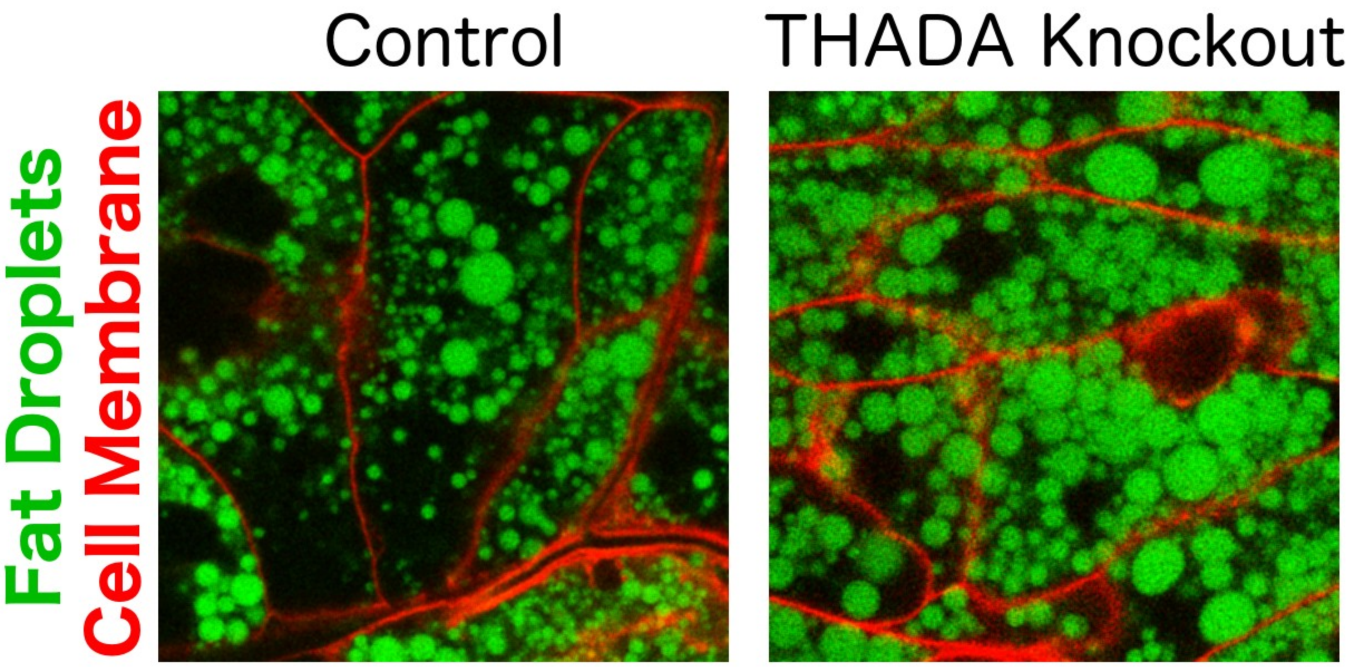
However, twin and epidemiological studies involving many different populations also show that susceptibility to obesity is genetic as well. For example, the population of the Pacific Islands, Australian Aboriginals and American Indians are more prone to obesity than people of European and East Asian descent. Obesity is very rare in populations in Siberia and Greenland.

Fruit flies as obesity models

The resistance to obesity in human populations living in cold climates in contrast to the increased susceptibility to obesity of people living in warm areas is generally put down to evolutionary adaptation to climate. The theory holds that high energy consumption is advantageous for people in cold climates as the energy can be used for producing body heat (see article entitled "Differences between white, brown and brite fat tissue"), and people are more resistant to obesity. In contrast, lower metabolic rates and hence reduced heat production is seen as an adaptation to warmer climates. Surplus energy is stored as fat. “If this is true,” says Prof. Dr. Aurelio Teleman from the German Cancer Research Center (DKFZ) in Heidelberg, “then there must be genes that regulate the balance between heat production and fat storage. People living at different degrees of latitude are therefore thought to have different genes.”

Teleman and his colleagues from the University of Heidelberg have now discovered that a gene called THADA regulates the balance between body heat and fat storage. The researchers used the fruit fly Drosophila as a model organism for their investigations. THADA knockout flies put on weight, ate more and were more sensitive to cold than the flies with THADA. “Their fat does not insulate them, and we were able to show that they in fact produced less heat,” says Alexandra Moraru, the first author of a paper published in the journal “Developmental Cell”. The researchers were able to show that the protein encoded by THADA regulates the insects’ energy metabolism via the cellular calcium signalling pathway by targeting the membrane enzyme SERCA (sarco/ER Ca^{2+} ATPase) which transports calcium ions from the cytosol into the cisterns of the endoplasmic reticulum. THADA knockout flies have a dramatically increased calcium pump activity. The experimental decrease of calcium pumping compensates THADA deficiency, and makes the flies resistant to obesity.

The human THADA gene



Adipose tissue in Drosophila fruit flies; control animals (left), THADA knockout mutants (right). The fat droplets (stained green) of THADA mutants are much bigger than those in control animals. The membranes of the fat droplets are stained red.

Teleman and his team have also shown that the human THADA gene appears to have the same functions as that of the fruit fly. In THADA knockout flies, THADA gene deficiency-related obesity was compensated with the expression of the human THADA gene. THADA knockdown HeLa cells (human tumour cells in cell culture) had elevated ER calcium levels, just like THADA knockout fruit flies.

The human THADA ("thyroid adenoma associated") gene was first discovered in 2003 in benign enlargements of the thyroid gland (which plays a key role in regulating the energy metabolism and calcium level in the body). In genetic studies, the gene was found to be associated with an increased risk of developing type 2 diabetes, which was substantiated by the new findings on the gene's function. Analyses of DNA sequences of human individuals of different origins have shown that the THADA gene locus on chromosome 2 is one of the genome regions with the largest number of SNPs ("single nucleotide polymorphisms"). Comparison of the Neanderthal genome, which has since also been sequenced, with the genome of current-day humans reveals that THADA is one of the genes that have accumulated the largest number of modifications during the evolution of modern humans. It can be inferred from this that after the separation of Homo sapiens and Neanderthals, which are our closest relatives, THADA continued to be exposed to a strong selection pressure, including as modern humans spread across the globe. This gene differs greatly in people from different climates. The susceptibility to obesity is highest in populations that have adapted to warmer climates, and the changes in the THADA gene provide a convincing explanation for a molecular and genetic link between climate adaptation and obesity. People in warm climates evolved reduced metabolic rates in order to prevent overheating. However, in combination with our modern diet, this reduced metabolic rate leads to obesity.

THADA and cancer

Prof. Dr. Aurelio Teleman, head of the Division of Signal Transduction in Cancer and Metabolism at the DKFZ.
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Obesity not only increases the risk of type 2 diabetes and cardiovascular disease, but also represents a major risk factor for many cancers. For this reason, THADA potentially also plays a role in cancer. Scientists from the Pittsburgh Medical School, USA, recently reported on specific changes in the

THADA gene in patients with thyroid cancer (which is not so surprising given the fact that the THADA was identified for the first time in thyroid adenoma). Defects in the THADA gene have also been implicated in acute leukaemia, prostate and colorectal cancer. However, according to Teleman, it is still too early to say "whether this association is down to the influence of THADA on the energy metabolism, or whether it is associated with a still unknown function of the gene." Potentially, THADA is not only the molecular link between calcium transport, fat metabolism and body heat, but also a target for future medical interventions in cancer treatment.

Original publication:
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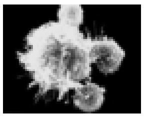

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