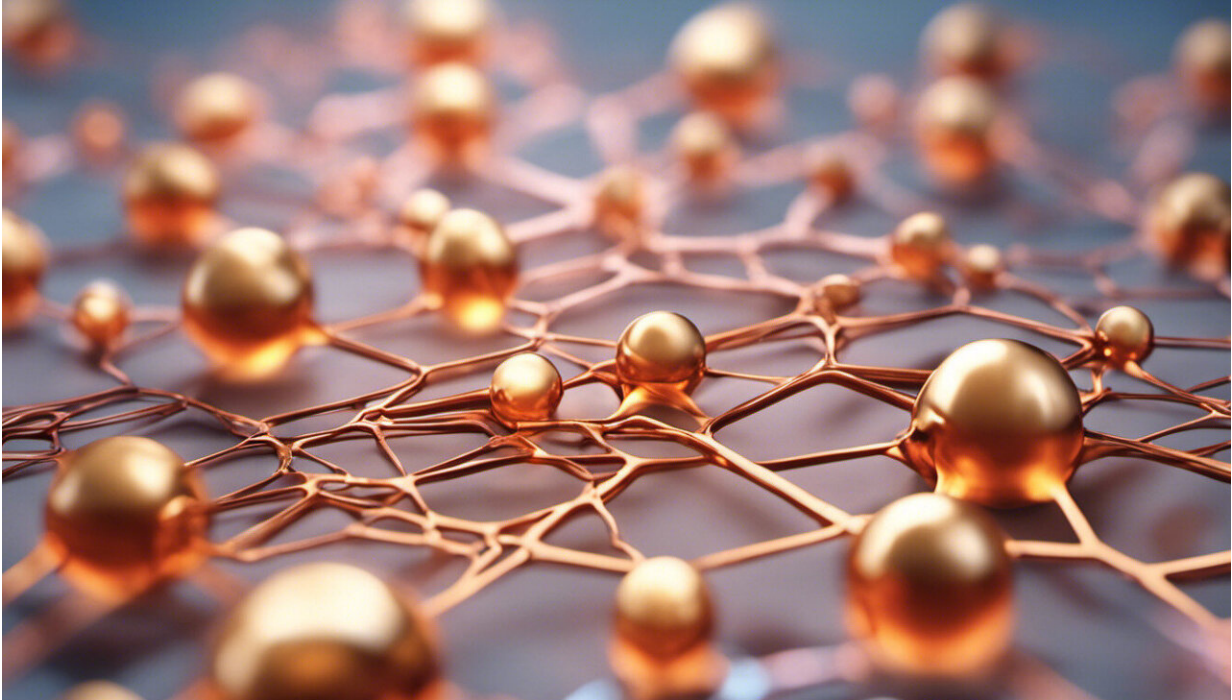


# Molecule prevents fat combustion

February 14 2012, By Peter Rüegg

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Credit: AI-generated image ([disclaimer](#))

ETH Zurich researchers have found a new role for a well-known signalling molecule, Hif1: the molecule suppresses the burning of fat, which may possibly promote obesity in humans.

Researchers in the group led by Willy Krek, Professor of [Cell Biology](#) at ETH Zurich, have bad news and good news for obese people. The scientists showed that a molecule, Hif1, is active in the [white cells](#) of the

abdominal fat in mice. It ensures that the fat does not melt away even when the diet is changed. High concentrations of this signalling molecule are also present in massively overweight people.

The good news: the process is reversible. When the researchers switched off the relevant molecule in mice, the suppressed metabolic route started working normally again, the mice burnt [fatty acids](#) and the fat deposits melted away.

## **Hif1 helps when there is too little oxygen**

Hif1 is always present when tissue becomes greatly enlarged very quickly and enters an oxygen-depleted state as a result. That is equally true for [cancerous tissue](#) and for abdominal fat. Hif1 is a signalling pathway that is conserved in [evolutionary development](#) and is present in all [vertebrate animals](#) and in all cell types.

Hif1 reprograms [cellular metabolism](#): the cells reduce the oxygen-consuming generation of energy via their power stations, the [mitochondria](#). Under the effect of Hif1 they obtain the energy to live through what is known as [glycolysis](#), which operates even without oxygen. Willi Krek says: “The Hif1 signalling pathway helps cells deal with oxygen starvation.” However, Hif1 also promotes the formation of new blood vessels that grow into new tissue to supply it with oxygen.

## **High concentration of Hif1 in white fat**

The ETH Zurich researchers first observed the connection between Hif1 and abdominal fat based on a mouse model. The animals were exclusively fed a fat-rich diet and gained weight quickly. Ultimately the scientists found high concentrations of Hif1 in the adipose tissue of these mice. This indicates that the fatty abdomen of the mice has poor

blood circulation and the white fat cells are suffering from oxygen deficiency.

However, the researchers were able to observe that Hif1 has a significant influence on the enlargement of fatty tissue when they switched off the molecule. As a result the fatty tissue in these mice stopped enlarging any further even when they continued to be fed a fat-rich diet. Their weight remained stable. These animals even lost weight when they were fed a normal diet. Krek sums it up: “From this we concluded that fat is burnt when Hif1 is absent. Even fat that had formed around the mouse hearts disappeared without being deposited in other organs.”

## **Fat burning suppressed**

Finally the researchers also discovered the mechanism by which Hif1 prevents the combustion of fat. Hif1 reduces the production of an enzyme called Sirt2, which itself in turn regulates genes that play a central role in the burning of fat. So when Hif1 is switched off in the mice, the Sirt2 enzyme becomes highly active and boosts the burning of fat.

The ETH Zurich researchers also discovered this in tissue samples from obese and lean people. They found Hif1 in high concentrations and the enzyme Sirt2 in low concentrations in the fatty tissue of overweight people. On the other hand only traces of Hif1 were present in people of normal weight.

## **Possible therapy recognized**

Possible treatments for obese people can also be inferred from the new findings. Because Hif1 does not switch the enzyme off completely, the burning of fat in overweight people could be stimulated by chemically

activating Sirt2. This could cause fat to be broken down without blocking Hif1. The researchers plan further experiments on mice to clarify what effect activating Sirt2 has on the animals' bodies. Developing a corresponding treatment for overweight people will therefore probably take some time.

**More information:** Krishnan J et al.: Dietary obesity-associated Hif1 $\alpha$  activation on adipocytes restricts fatty acid oxidation and energy expenditure via suppression of the Sirt2-NAD<sup>+</sup> system. *Genes and Development* 26. Online Publication 1st February 2012.  
[DOI:10.1101/gad.180406.111](https://doi.org/10.1101/gad.180406.111)

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