

Fatty Liver – How a Serious Problem Arises

If there is an oversupply of energy-rich fat molecules, liver cells reduce the production of an important regulatory protein. This is a key molecular step in the development of fatty liver, as has now been reported by scientists of the Division of Molecular Metabolic Control, a joint research group of the German Cancer Research Center (DKFZ), the Center for Molecular Biology of Heidelberg University (ZMBH) and Heidelberg University Hospitals.

Excess fat around the hips and belly may not really be compatible with current beauty ideals, but, to a certain degree, it is a normal, even vital energy store of our body. However, it is a different matter if the organism stores fat in organs such as the liver, pancreas or muscles. This is a clear sign of a metabolic disorder.

Up to 80 percent of obese people develop fatty liver disease, which is regarded a typical characteristic of the dangerous metabolic syndrome. Deposition of fat in the liver may lead to chronic liver inflammation and even to liver cancer. In addition, fatty liver is considered to be an independent risk factor for coronary heart disease and atherosclerosis.

The great medical relevance of fatty liver as a severe condition accompanying insulin resistance and type II diabetes caused the research group headed by Dr. Stephan Herzig of the Division of Molecular Metabolic Control to investigate how this syndrome arises. Which molecular switches are turned on or off in a cell when food delivers too much energy-rich fat molecules, or triglycerides?

To this end, the investigators determined the level of particular proteins involved in specific gene activation in the liver tissue of mice. These proteins, which are known as transcriptional co-activators, regulate which proteins are read and transcribed into messenger RNA molecules in a cell. In overweight mice, the researchers observed that a high triglyceride level in the liver was always associated with reduced production of a co-activator called TBL1. This was found both in animals that developed fatty liver for hereditary reasons and in those animals that received calorie-rich food.

TBL1 was originally discovered in connection with a rare hereditary hearing disorder. In the liver, but not in other tissues, an oversupply of fat reduces the production of TBL1. As a result, fat burning in the liver is reduced so that more fat molecules are deposited in liver cells. "This, in turn, may lead to a further reduction of TBL1," says Stephan Herzig.

Not only in mice is TBL1 linked to the liver fat (lipid) metabolism. The group found the same pattern in human liver tissue samples: the higher their triglyceride levels, the lower their TBL1 levels.

Stephan Herzig expects a practical use of these results. "We might be able in the future to use TBL1 levels for identifying those obese persons who have a special risk of developing fatty liver. We could then give specific dietary recommendations to counteract this."

Philipp Kulozik, Allan Jones, Frits Mattijssen, Adam J. Rose, Anja Reimann, Daniela Strzoda, Stefan Kleinsorg, Christina Raupp, Jürgen Kleinschmidt, Karin Müller-Decker, Walter Wahli, Carsten Sticht, Norbert Gretz, Christian von Loeffelholz, Martin Stockmann, Andreas Pfeiffer, Sigrid Stöhr, Geesje M. Dallinga-Thie, Peter P. Nawroth, Mauricio Berriel Diaz and Stephan Herzig: Hepatic deficiency in

transcriptional co-factor TBL1 promotes liver steatosis and hypertriglyceridemia. Cell Metabolism, 2011, DOI: [10.1016/j.cmet.2011.02.011](https://doi.org/10.1016/j.cmet.2011.02.011)

A picture is available on the Internet:

<http://www.dkfz.de/de/presse/pressemitteilungen/2011/images/Liver.jpg>

Picture caption: 3D-illustration of a human liver with blood vessels (red and blue) and bile duct (green)

Source: Prof. Dr. Hans-Peter Meinzer, Deutsches Krebsforschungszentrum

The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ), employing over 2,500 staff members, is the largest biomedical research institute in Germany. More than 1,000 scientists are working to investigate the mechanisms of cancer development, identify cancer risk factors and develop new strategies for better cancer prevention, more precise diagnosis and effective treatment of cancer patients. In addition, the staff of the Cancer Information Service (KID) provides information about this widespread disease for patients, their families, and the general public. DKFZ is funded by the German Federal Ministry of Education and Research (90%) and the State of Baden-Wuerttemberg (10%) and is a member of the Helmholtz Association of National Research Centers.

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