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How obesity also affects the next generation

Children born to obese mothers are at higher risk of developing metabolic disorders, even if they follow a healthy diet themselves. A new study from the University of Bonn offers an explanation for this phenomenon. In obese mice, certain cells in the embryo's liver are reprogrammed during pregnancy. This leads to long-term changes in the offspring's metabolism. The researchers believe that these findings could also be relevant for humans. The study has now been published in the journal Nature. STRICTLY EMBARGOED: Do not publish before Wednesday, June 18, 5 p.m. CEST!

The team focused on the so-called Kupffer cells. These are macrophages – so-called 'big eaters' – that help protect the body as part of the innate immune system. During embryonic development, they migrate into the liver, where they take up permanent residence. There, they fight off pathogens and break down aging or damaged cells.

"But these Kupffer cells also act as conductors," explains Prof. Dr. Elvira Mass from the LIMES Institute at the University of Bonn. "They instruct the surrounding liver cells on what to do. In this way, they help ensure that the liver, as a central metabolic organ, performs its many tasks correctly."

Changing the tune: From Beethoven to Vivaldi

It appears, however, that it is this conducting function that is changed by obesity. This is what mouse experiments carried out by Mass in cooperation with other research groups at the University of Bonn suggest. "We were able to show that the offspring of obese mothers frequently developed a fatty liver shortly after birth," says Dr. Hao Huang from Mass's lab. "And this happened even when the young animals were fed a completely normal diet."

The cause of this disorder seems to be a kind of "reprogramming" of the Kupffer cells in the offspring. As a result, they send out molecular signals that instruct the liver cells to take up more fat. Figuratively speaking, they no longer conduct one of Beethoven's symphonies but rather a piece by Vivaldi.

This shift already seems to occur during embryonic development and is triggered by metabolic products from the mother. These activate a kind of metabolic switch in the Kupffer cells and change the way these cells direct liver cells in the long term. "This switch is a so-called transcription factor," says Mass. "It controls which genes are active in Kupffer cells."

No fatty liver without the molecular switch

When the researchers genetically removed this switch in the Kupffer cells during pregnancy, the offspring did not develop a fatty liver. Whether this mechanism could also be targeted with medication is still unclear. The teams now plan to investigate this in follow-up studies.

If new treatment approaches emerge from this, it would be good news. The altered behavior of the Kupffer cells likely has many negative consequences. Fat accumulation in the liver, for example, is accompanied by strong inflammatory responses. These can cause increasing numbers of liver cells to die and be replaced with scar tissue. The result is fibrosis, which gradually impairs liver function. At the same time, the risk that liver cells degenerate and become cancerous increases.

“It is becoming ever more evident that many diseases in humans already begin at a very early developmental stage,” says Mass, who is also spokesperson for the transdisciplinary research area “Life & Health” and a board member of the “ImmunoSensation2” Cluster of Excellence at the University of Bonn. “Our study is one of the few to explain in detail how this early programming can happen.”

Participating institutes and funding:

In addition to the University of Bonn, the German Center for Neurodegenerative Diseases (DZNE), the University of Vienna (Austria), Ghent University (Belgium), and Shanghai University (China) were involved in the study. The research was supported by the German Research Foundation (DFG, in particular SFB 1454 Metaflammation), the European Research Council (ERC), the Jürgen Manchot Foundation, the Boehringer Ingelheim Fonds and the European Molecular Biology Organization (EMBO).

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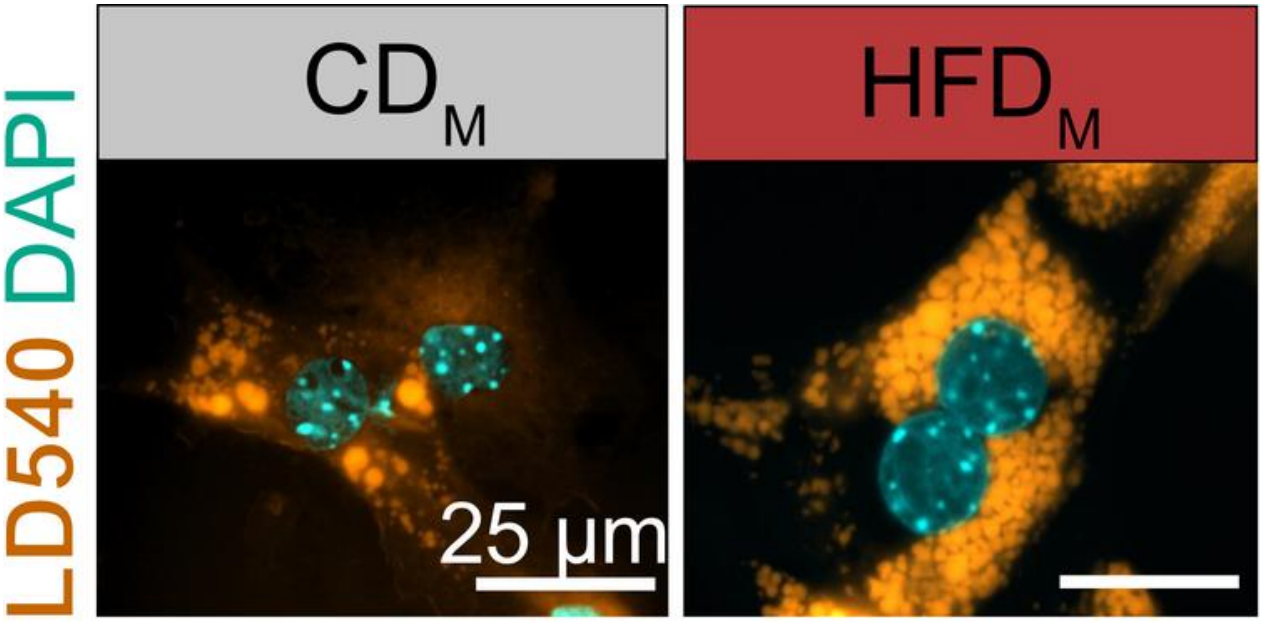
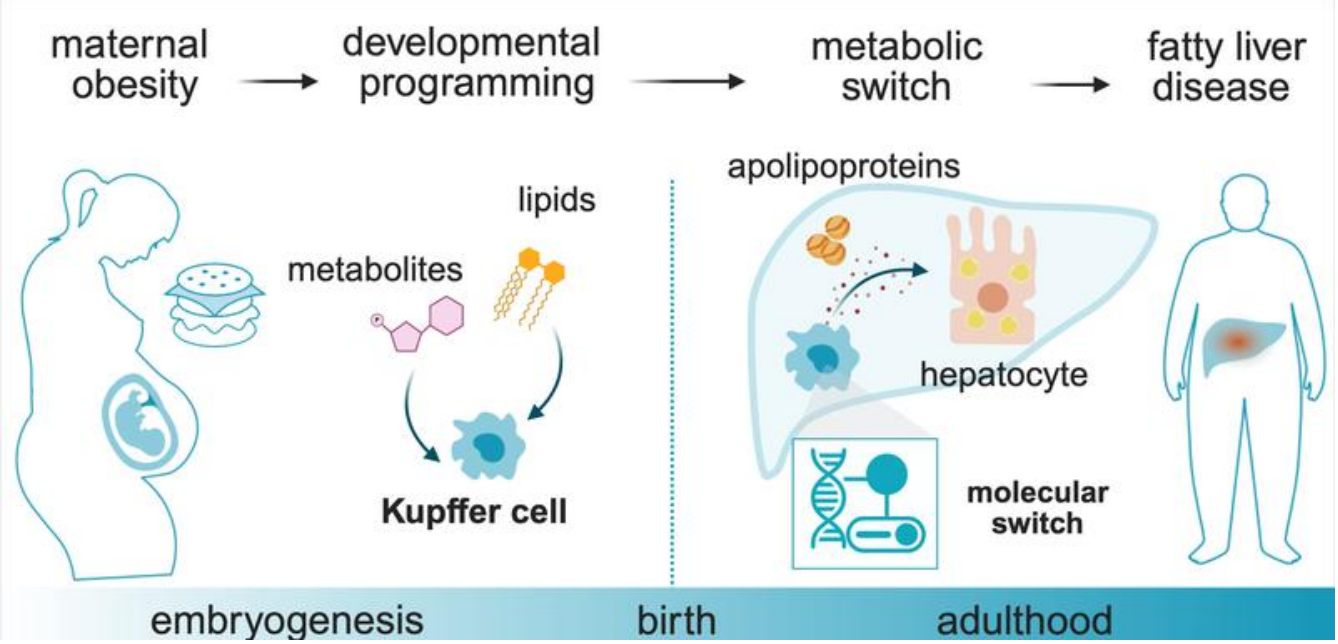
URL zur Pressemitteilung: https://www.sfb1454-metaflammation.de/outreach/was-ist-metaflammation



Liver cells store more lipids (yellow, LD540) when exposed to molecules from Kupffer cells taken from the offspring of obese mice (right, HFDM). Left: Liver cells exposed to factors from offspring of normal-weight mothers (CDM).
Image: AG Mass/University of Bonn



Metabolites from the mother permanently reprogram Kupffer cells. This changes their function, causes liver cells (hepatocytes) to accumulate fat and leads to fatty liver. The graphic was created with BioRender.com.
Image: AG Mass/University of Bonn