Metabolism Research

How Obesity Promotes Breast Cancer

Obesity leads to the release of cytokines into the bloodstream which impact the metabolism of breast cancer cells, making them more aggressive as a result. Scientists from Helmholtz Zentrum München, Technische Universität München (TUM), and Heidelberg University Hospital report on this in 'Cell Metabolism'. The team has already been able to halt this mechanism with an antibody treatment.

The number of people with obesity is increasing rapidly worldwide. The German Cancer Research Center (DKFZ) recently reported that according to the WHO the number of children and adolescents with obesity increased tenfold between 1975 and 2016. Severe overweight can lead to various health impairments. Besides inducing cardiovascular diseases, obesity for example also promotes the development of cancer and metastases.

The current study elucidates an as yet unknown mechanism making breast cancer more aggressive. The enzyme ACC1* plays a central role in this process," said Dr. Mauricio Berriel Diaz, deputy director of the Institute for Diabetes and Cancer (IDC) at Helmholtz Zentrum München. He led the study together with Stephan Herzig, director of the IDC and professor for Molecular Metabolic Control at TUM and Heidelberg University Hospital. "ACC1 is a key component of fatty acid synthesis," said Berriel Diaz. "However, its function is impaired by the cytokines leptin and TGF-β." The levels of these cytokines are increased particularly in the blood of severely overweight subjects.

Fatty acid precursors promote metastases

The scientists demonstrated that the described inhibition of ACC1 leads to the accumulation of the fatty acid precursor acetyl-CoA. This precursor is transferred to certain gene "switches" that in turn increase the metastatic capacity of cancer cells by activating a specific gene program.

"Using human tissue from breast cancer metastases, we were able to show that ACC1 was significantly less active there," said Marcos Rios Garcia, first author of the study. When the scientists blocked the as yet unknown signaling pathway with an antibody (directed against the leptin receptor), this led to a significantly reduced metastatic spread of breast cancer tumors in an experimental model.

In the future, the researchers want to substantiate the data on the newly discovered mechanism in further studies. In addition, they are also considering related intervention points that could possibly be exploited therapeutically. "Blocking the signaling pathways and switching off the metastasis-related genes could be a therapeutic target," Herzig said. "As part of the so-called neoadjuvant therapy, the risk of metastases or the recurrence of tumors could be reduced prior to the surgical removal of the tumor."

Further Information

***** ACC1 stands for acetyl-CoA-carboxylase 1, a central component of fatty acid synthesis. ACC1 mediates the chemical addition of carbon dioxide to acetyl-CoA, which results in malonyl-CoA. This reaction is the first and speed determining step in the fatty acid synthesis of all living organisms.

Background:

Metastasis of breast cancer or recurrence after surgical removal of the primary tumor is the main cause of cancer-related deaths in women. In addition, epidemiological studies show that obesity is associated with aggressive forms of breast cancer and that postmenopausal women in particular are at a higher risk of developing metastatic breast cancer.

The role of fatty acid synthesis for the altered energy metabolism of cancer cells is only incompletely understood. Various studies suggest that activation of fatty acid synthesis makes cancer cells independent from the supply with extracellular lipids. The present study reveals a new mechanism that is independent of fatty acid synthesis, in which the inactivation of ACC1 leads to the accumulation of acetyl-CoA, since it is no longer used for fatty acid synthesis but rather for the modification (acetylation) of regulatory proteins (transcription factors, e.g. SMAD2). The regulatory proteins modified in this way in turn switch on genes that contribute to increased aggressiveness of cancer cells.

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The Helmholtz Zentrum München, the German Research Center for Environmental Health, pursues the goal of developing personalized medical approaches for the prevention and therapy of major common diseases such as diabetes and lung diseases. To achieve this, it investigates the interaction of genetics, environmental factors and lifestyle. The Helmholtz Zentrum München is headquartered in Neuherberg in the north of Munich and has about 2,300 staff members. It is a member of the Helmholtz Association, a community of 18 scientific-technical and medical-biological research centers with a total of about 37,000 staff members. www.helmholtz-muenchen.de/en

The Institute for Diabetes and Cancer (IDC) is a member of the Helmholtz Diabetes Center (HDC) at the Helmholtz Zentrum München and a partner in the joint Heidelberg-IDC Translational Diabetes Program. The Institute for Diabetes and Cancer is tightly integrated into the German Center for Diabetes Research (DZD) and into the special research area "Reactive Metabolites and Diabetic Complications" at the Heidelberg University Medical School. The IDC conducts research on the molecular basis of severe metabolic disorders, including metabolic syndrome and type 2 diabetes, as well as their roles in tumor initiation and progression. www.helmholtz-muenchen.de/idc

Technical University of Munich (TUM) is one of Europe's leading research universities, with more than 500 professors, around 10,000 academic and non-academic staff, and 40,000 students. Its focus areas are the engineering sciences, natural sciences, life sciences and medicine, reinforced by schools of management and education. TUM acts as an entrepreneurial university that promotes talents and creates value for society. In that it profits from having strong partners in science and industry. It is represented worldwide with a campus in Singapore as well as offices in Beijing, Brussels, Cairo, Mumbai, San Francisco, and São Paulo. Nobel Prize winners and inventors such as Rudolf Diesel, Carl von Linde, and Rudolf Mößbauer have done research at TUM. In 2006 and 2012 it won recognition as a German "Excellence University." In international rankings, TUM regularly places among the best universities in Germany. www.tum.de/en/homepage

Heidelberg University Hospital is one of the largest and most prestigious medical centers in Germany. The Medical Faculty of Heidelberg University belongs to the internationally most renowned biomedical research institutions in Europe. Both institutions have the common goal of developing new therapies and implementing them rapidly for patients. With about 13,000 employees, training and qualification is an important issue. Every year, around 65,000 patients are treated on an inpatient basis, 56,000 cases on a day patient basis and more than 1,000,000 cases on an outpatient basis in more than 50 clinics and departments with almost 2,000 beds. Jointly with the German Cancer Research Center (DKFZ) and German Cancer Aid, Heidelberg University Hospital has established the National Center for Tumor Diseases (NCT) Heidelberg, where promising approaches from cancer research are translated into the clinic. Currently, about 3,700 future physicians are studying in Heidelberg; the reform Heidelberg Curriculum Medicinale (HeiCuMed) is one of the top medical training programs in Germany. www.klinikum.uni-heidelberg.de

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