

A Common Denominator of Inflammations and Fatty Liver: Cancer Researchers Find Key Molecule for Tumor Cachexia

Many cancer patients lose a lot of weight during their disease: Fat and muscle mass are reduced, free fatty acids accumulate in the liver, and this eventually leads to fatty liver in affected patients. What is called tumor cachexia appears to be caused by signals emitted by the tumor itself. Despite vigorous searching, scientists have not yet been able to identify these “degradation signals” of tumors. Therefore, a research team at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in Heidelberg, Germany, decided to take the opposite approach: Instead of searching for “hunger signals” in the tumor, they investigated the other end of the signaling chain: liver cells of mice affected by cancer. In the process, they discovered a molecular marker which controls both metabolic processes and inflammatory responses.

In advanced stages of cancer, particularly in pancreatic and lung cancers, patients frequently suffer from a wasting syndrome known as cancer cachexia. Affected patients grow very thin and weak, often there is a danger of organ failure. Body fat, in particular, is reduced and its accumulation in the liver leads to fatty liver. This process seems to be caused by signals from the tumor itself, which radically direct metabolic processes in the body towards degradation and cause a state of chronic inflammation in the body. Despite intensive efforts to identify these signals, they remain unknown.

Stephan Herzig, head of the Emmy Noether and Marie Curie Junior Research Group “Molecular Metabolic Control” at DKFZ, and his co-workers have focused on the other end of the signaling chain: They studied liver cells of tumor-bearing mice showing signs of severe cancer cachexia. In particular, they searched for a molecule called RIP140, previously identified by Herzig as a regulator suppressing fat breakdown in the livers of healthy mice. Indeed, the investigators found a high activity of RIP140 in the cancerous mice and, accordingly, signs of fatty liver in these animals. When Herzig specifically switched off this molecule in the liver cells of tumor-bearing mice, the lipid balance of the liver normalized within a few days. The researchers have now published their results in *Hepatology*.

Apart from fatty liver, highly active immune cells are another characteristic of wasting in tumor patients: Increased levels of macrophages invade fatty or liver tissue and release messaging substances such as interleukin-6 and tumor necrosis factor-alpha. The result is an inflammatory response in these organs, which eventually contributes to a disruption of metabolism and loss of energy in affected patients. Collaboration partners of Stephan Herzig in London have bred mice that completely lack the RIP140 molecule. These animals are lean and stay lean, even on a rich diet. When the researchers in Herzig’s group compared these animals to normal mice, they also found that their macrophages release only small amounts of proinflammatory messaging substances. The RIP140 molecule in these inflammatory cells exercises its effect through another “master regulator”: the NFkB transcription factor. These results have just been published in *Blood*.

“Thus we have put another small link into the long unknown signaling chain from tumor to tumor cachexia,” says Stephan Herzig, characterizing the relevance of his two papers. “Now, of course, we will search for the activator of RIP140,” Herzig explains. “Thus, we will proceed from one link to the next until we arrive at the tumor.” And, hopefully, find the “hunger signal” of tumors one day.

Mauricio Berriel Diaz, Anja Krones-Herzig, Dagmar Metzger, Anja Ziegler, Alexandros Vegiopoulos, Martin Klingenspor, Karin Müller-Decker, Stephan Herzig. Nuclear receptor co-factor RIP140 controls hepatic triglyceride metabolism during wasting in mice. *Hepatology* 2008, DOI: 10.1002/hep.22383

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The task of the Deutsches Krebsforschungszentrum in Heidelberg (German Cancer Research Center, DKFZ) is to systematically investigate the mechanisms of cancer development and to identify cancer risk factors. The results of this basic research are expected to lead to new approaches in the prevention, diagnosis and treatment of cancer. The Center is financed to 90 percent by the Federal Ministry of Education and Research and to 10 percent by the State of Baden-Wuerttemberg. It is a member of the Helmholtz Association of National Research Centers (Helmholtz-Gemeinschaft Deutscher Forschungszentren e.V.).