GERMAN CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

No. 03 14 January, 2013 (Koh)

Liver Controls Cachexia in Cancer

Activated gene in the liver brings blood fat levels down

Many cancer patients suffer from a dramatic loss of fat and muscle tissue. This extreme wasting, or cachexia, is often the actual cause of death in cancer patients. Heidelberg scientists have now discovered in mice that tumors stimulate the production of a key gene switch in the liver. Activity of this switch lowers blood fat levels so that the animals lose weight. The researchers have been the first to demonstrate that the liver controls cancer-induced cachexia. This finding may lead to approaches to slow down this fatal loss of body mass.

Cachexia or wasting affects up to 70 percent of all cancer patients depending on the type of cancer. It is characterized by a dramatic loss of body weight independent of food intake. Cachexia is seen particularly often and most pronounced in patients suffering from cancers of the digestive tract and the lungs. They may lose up to 80 percent of body fat and skeletal muscle. Muscle loss leads to weakness and immobility of patients and poorer response to treatment. An estimated 20 percent of cancer deaths are considered to be a direct consequence of cachexia, with failure of the respiratory muscles as a frequent cause of death.

“Doctors used to believe that cancer re-programs metabolism focusing all energy into tumor growth,” says Prof. Dr. Stephan Herzig, who heads a joint research department of the German Cancer Research Center (DKFZ), Heidelberg University and Heidelberg University Hospital. However, by now researchers presume that cachexia is the body’s response to various harmful stimuli originating directly from the growing tumor. To explore the causes of cachexia, Stephan Herzig, an expert in metabolism, took a closer look at the liver as the key controlling point of metabolism. “Cachexia patients frequently show an inflamed fatty liver – this was a major clue for this organ being involved.”

The researchers found extremely low lipid (blood fat) levels in cancerous mice, therefore they lack the most important energy source. However, they accumulate fat in the liver. The low lipid levels in the diseased animals are due to their liver releasing only very little VLDL (very low density lipoprotein). VLDL facilitates the transport of fat in the bloodstream. Moreover, the genes for all major steps of lipogenesis are blocked in the livers of cancerous mice.

“This is a clear indication of a central gene switch in the liver driving cachexia”, says Stephan Herzig. He therefore searched for differences in protein switches regulating gene activity and hence hepatic energy metabolism in cancerous and healthy mice. Herzig’s team found significant differences in a poorly studied gene switch called TSC22D4, which is found in larger amounts in cancerous mice than in healthy control mice.

Herzig’s team was able to clearly demonstrate the key role of TSC22D4 in the onset of cachexia. When the researchers silenced the switch specifically in the animals’ livers the organ subsequently went back to producing enough VLDL to make lipid levels in the cancerous animals rise. In addition, the genes involved in lipogenesis got boosted again.

“Our results prove, for the first time, that dramatic loss of body mass may be controlled by the liver,” says Stephan Herzig. “We also learned recently that TSC22D4 shows exactly the same effect in human hepatic cells. There is evidence that certain metabolites control this

gene switch and might offer the possibility to slow down the fatal wasting process. However, we don´t have proven this approach by now. This is what we will do next."

Allan Jones, Kilian Friedrich, Maria Rohm, Michaela Schäfer, Carolyn Algire, Philipp Kulozik, Oksana Seibert, Karin Müller-Decker, Tjeerd Sijmonsma, Daniela Strzoda, Carsten Sticht, Norbert Gretz, Geesje M. Dallinga-Thie, Barbara Leuchs, Manfred Kögl, Wolfgang Stremmel, Mauricio Berriel Diaz and Stephan Herzig: Transforming growth factor-beta1 Stimulated Clone-22 D4 is a molecular output of hepatic wasting metabolism, EMBO Molecular Medicine 2012

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