Website address: https://www.gesundheitsindustrie-bw.de/en/article/press-release/cancercachexia-liver-identified-driver-body-wasting

Cancer Cachexia: Liver Identified as Driver of Body Wasting

Many people with cancer experience dramatic loss of muscle and fat tissue. In many cases, even the heart muscle is affected, which further weakens the body. This wasting syndrome, known as cachexia, affects around half of all cancer patients. It is a major cause of therapy resistance, complications, and increased mortality. Researchers from Helmholtz Munich, in collaboration with Heidelberg University Hospital, the Technical University of Munich, and the German Center for Diabetes Research, have now identified a previously overlooked driver of cachexia: the liver. It responds systemically to tumors in other organs – such as the intestine or pancreas – and contributes to tissue wasting by releasing specific signaling molecules.

The Silenced Clock Gene

In cachexia, liver metabolism is fundamentally reprogrammed. One gene, which normally regulates the liver's activity throughout the day, ceases to function properly. Using a mouse model, the researchers discovered that this "internal clock" was almost completely shut down. "After reactivating the gene, known as REV-ERB α , specifically in the liver of affected mice, the loss of body mass was significantly reduced," says Dr. Doris Kaltenecker, co-first author of the study alongside Dr. Søren Fisker Schmidt, and researcher at the Institute for Diabetes and Cancer at Helmholtz Munich.

Liver-Derived Signaling Molecules Drive Cachexia

The team showed that REV-ERB α regulates several genes involved in the production of liver-derived signaling molecules. When this clock gene is inactive, the liver releases increased levels of factors that promote disease progression. Three of these so-called hepatokines (LBP, ITIH3, and IGFBP1) are central to the newly discovered mechanism. In cell culture experiments, they triggered catabolic, that is tissue-degrading, processes in muscle and fat cells, which are precisely the processes responsible for the physical wasting seen in cachexia. In addition, the levels of these proteins were markedly elevated in the blood of cachectic patients with various types of cancer. In preclinical models, targeted inhibition of these factors successfully mitigated their harmful effects.

Perspectives for Diagnosis and Therapy

"For the first time, we were able to show that the liver is not merely a passive responder to cachexia, but actively contributes to the progression of the disease," says Dr. Mauricio Berriel Diaz, who led the study at Helmholtz Munich. "Our findings open up new possibilities to better diagnose the syndrome and explore therapeutic interventions." The study also provides a comprehensive data resource on the role of the liver in cachexia – ranging from molecular networks to cell type-specific changes and functional outcomes in preclinical models. This dataset is now available to the scientific community and can be used well beyond the model system studied.

In the long term, the identified factors could serve as biomarkers for cachexia risk or as targets for new therapies.

"Given that there is currently no approved treatment for cachexia, we urgently need new approaches," emphasizes Prof. Stephan Herzig, Director of the Helmholtz Diabetes Center and the Institute for Diabetes and Cancer at Helmholtz Munich, and Professor at the Technical University of Munich. "These results clearly demonstrate the importance of systemic organ interactions in the progression of cancer."

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Further information

• Deutsches Zentrum für Diabetesforschung e.V.