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Why the Blood Sugar Level Gets Out of Balance in Diabetes

Molecular controller CARM1 regulates the pacers of glucose synthesis

Scientists of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have found out why specific genes are read as a response to hunger signals such as glucagon or glucocorticoids and, thus, mediate glucose release from the liver. A team of researchers headed by **Dr. Anja Krones-Herzig** identified the CARM1 molecule as a transcription factor that activates key enzymes of glucose synthesis under certain conditions, thus causing the blood sugar level to rise. The research results were presented recently in the *Journal of Biological Chemistry**.

A typical feature of metabolic disorders such as type 2 (adult onset) diabetes is that important organs such as liver, muscles, and fatty tissue cease to respond to the pancreatic hormone insulin (insulin resistance), while other, opposing hormones such as glucagon or glucocorticoids continue to unfold their effects. The result is that sugar from the blood is no longer transported to and stored in muscle tissue or the liver. On the contrary: the hunger signal glucagon or its intracellular "mediator" cAMP, respectively, triggers a signaling cascade in liver cells. One of the consequences is that the genes for special enzymes of the sugar household are read. The enzymes PEPCK and G6Pase are biocatalysts which are in charge of synthesis of new glucose in the liver and its release into the blood (gluconeogenesis).

The secret of how PEPCK and G6Pase, the pacers of glucose synthesis, are regulated, has now been disclosed by **Dr. Anja Krones-Herzig** from the working group "Molecular Metabolic Control". Jointly with team colleagues and researchers from the Institute of Genetics and Center for Molecular Medicine at Cologne University, Krones-Herzig found out that the CARM1 transcription factor plays an important role in the activation of key enzymes of gluconeogenesis. Depending on the messenger substance cAMP, CARM1 attaches itself to the starting sequence of the blueprints for PEPCK and G6Pase, thus giving the signal for the genes to be read.

Another case of disrupted insulin-dependent metabolism is cachexia, a frequent and severe condition associated with advanced cancer. The consequences are weight loss, weakness and increasing failure of organ functions. Group leader Dr. Stephan Herzig plans to investigate with his team whether the same or related genes or gene products – transcription factors, to be more precise – that influence the insulin-dependent metabolism in diabetes, might also play a role in tumor-asociated cachexia. While in diabetes the liver is in the center of attention, in the wasting syndrome (cachexia) researchers are focusing on the metabolism of the muscle tissue.

The medium-term goal of the cancer researchers is to find out whether dysregulated components of the insulin signaling cascade might be used as targets for drugs. "Once we have sufficient evidence suggesting that a transcription factor is causally involved in one of the metabolic disorders, we will start looking for suitable substances to counteract or reinforce the effect."

** Anja Krones-Herzig et al.: "Signal-dependent control of gluconeogenic key enzyme genes through coactivator- associated arginine methyltransferase 1", Journal of Biological Chemistry, Dec 2005; doi:10.1074/jbc.M509770200*

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.).

This press release is available at www.dkfz.de/pressemitteilungen

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