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Glowing Insight into the Liver: New Reporter System Detects Connection between Inflammation and Blood Sugar Level

Inflammations disrupt the balance of the tightly regulated blood sugar level. During acute sepsis, for example, glucose in the blood drops to a dangerously low level. One of the reasons for this is that production of new glucose in the liver is blocked. Using a new detection system, scientists of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have unraveled the molecular mechanisms by which inflammations influence the glucose concentration in the blood. They have published their results in *Hepatology*.

Normally, the blood glucose level is very tightly regulated. If it drops only slightly, the liver produces new glucose in a process called gluconeogenesis to ensure that the brain and the muscles can continue functioning. In the opposite case, an elevated blood sugar level is immediately lowered by the secretion of insulin from the pancreas to prevent long-term damage to the blood vessels. “However, when there is an inflammation, these regulation mechanisms are disrupted,” says Dr. Stephan Herzig, head of the Junior Research Group “Molecular Metabolic Control” at the German Cancer Research Center (DKFZ). “With our new reporter system we were able to find out why this is so.”

The key enzyme for gluconeogenesis in the liver is called phosphoenolpyruvate carboxykinase, or PEPCK for short. The more active it is, the more glucose is produced. Its activity is regulated by various hormones: Stress hormones glucagon and cortisol boost its activity, while insulin slows it down.

In their new reporter system, the researchers have connected several segments of the PEPCK gene to the luciferase gene, the gene that makes fireflies glow. This construct was introduced into living mice. Then the scientists artificially caused an inflammation in the animals and studied, which PEPCK gene segments were active in response to inflammation, i.e., made the liver glow, and which were not, i.e., everything remained dark. They found out that an inflammation of the kind that occurs in sepsis prevents the molecular cooperation of the two hormones glucagon and cortisol and, thus, blocks PEPCK and, consequently, gluconeogenesis. This could be a target for drugs which eliminate the block and boost gluconeogenesis in the liver. Stephan Herzig stresses:”The results could also be interesting for cancer patients, who often suffer from a condition called cachexia. This extreme wasting of the whole body is also characterized by a strong inflammatory response and disrupted regulation of gluconeogenesis. Here, too, medical intervention might be possible.”

***In vivo* PEPCK promoter mapping identifies disrupted hormonal synergism as a target of inflammation during sepsis in mice (p NA)**
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