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Long-term diabetes complication: Liver inflammation raises cholesterol levels

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Inflammatory processes in the liver lead to elevated cholesterol levels in people with diabetes, thus promoting subsequent vascular diseases. This is the conclusion of a study by scientists at Helmholtz Zentrum München, Technische Universität München (TUM) and the Collaborative Research Center SFB 1118 at Heidelberg University Hospital. The paper has now been published in the journal *Cell Reports*.

Vascular diseases play a key role among the long-term complications in people with diabetes. Cardiovascular diseases account for 75 percent of hospitalizations, and these diseases are responsible for 50 percent of all deaths. Elevated cholesterol is an important risk factor for atherosclerosis, circulatory disorders and vascular complications.

"Even if blood glucose levels are well controlled, some people with diabetes have a higher risk of long-term complications. We wanted to understand the underlying cause for this," said metabolism researcher Dr. Mauricio Berriel Diaz, deputy director of the Institute for Diabetes and Cancer (IDC) at Helmholtz Zentrum München.

In their study, the researchers focused on inflammatory processes that are known to occur in many metabolic disorders such as type 2 diabetes and obesity and contribute significantly to long-term complications. Specifically, they concentrated on the inflammatory cytokine tumor necrosis factor α (TNF-α), which is known to induce the production of reactive oxygen species (ROSs) in the liver. The scientists demonstrated that these ROSs inactivate the transcription factor complex GAbp (GA-

binding protein). In experimental models, this loss inhibited the protein AMPK, an energy sensor of the cell. As a result, excess cholesterol was produced, and typical atherosclerosis symptoms developed.

Key Role in the Maintenance of Hepatic and Systemic Lipid Homeostasis

"Our data suggest that the liver plays a key role in the development of common diabetic vascular diseases," said first author Dr. Katharina Niopek, researcher at the IDC. "GAbp appears to be a molecular regulator at the interface between inflammation, cholesterol homeostasis and atherosclerosis. Without its protective effect, this leads to hypercholesterolemia and increased lipid deposition in the arteries."

"Since initial patient data supported our findings, the new signaling pathway—regardless of how well the blood glucose levels of the patient are controlled—may be a key component in the development of long-term diabetes complications that could be utilized therapeutically," said Herzig, who led the study.

More information: Katharina Niopek et al, A Hepatic GAbp-AMPK Axis Links Inflammatory Signaling to Systemic Vascular Damage, *Cell Reports* (2017). DOI: 10.1016/j.celrep.2017.07.023

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