'Protective shield' for beta-cells suggests new option to treat diabetes

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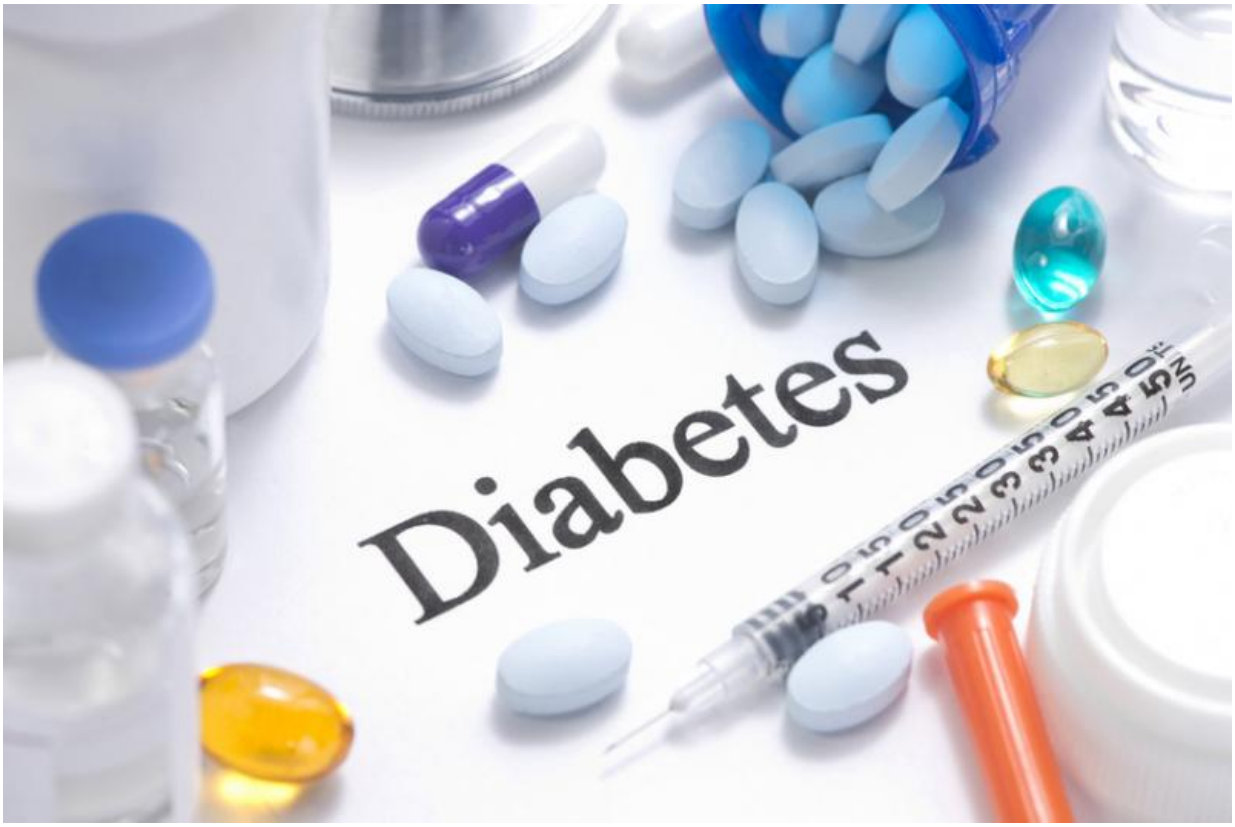

Credit: Medical University of Vienna

The islets of Langerhans in the human pancreas produce and release insulin to regulate blood glucose levels. Insulin, which is specifically produced in b-cells, serves to prompt cells to take up glucose circulating

in blood. Thus, insulin release lowers the level of glucose in blood. In diabetes, this cycle is disrupted by the premature death of b-cells. Working with an international team of researchers, Katarzyna Malenczyk from the Department of Molecular Neurosciences at MedUni Vienna's Center for Brain Research showed in the study published in the *EMBO Journal* today that the loss of a key protein, secretagogin, triggers the death of b-cells and, conversely, that these cells can be protected by increasing the amount of this protein in those suffering from diabetes.

"Although researchers have been trying for decades to find effective means of protecting b-cells in diabetes, we still haven't found curative therapies. Understanding the mechanism that could lead to the development of a medication is therefore of enormous value," says Dr. Malenczyk, lead author of a new study. "We were able to show in animal models and also in b-cells from diabetic donors that, in disease conditions the level of secretagogin is significantly reduced, suggesting a direct correlation between this protein and the severity of the disease," explains Tibor Harkany, Head of the Department of Molecular Neurosciences of MedUni Vienna's Center for Brain Research. "If we find molecular tools to keep b-cells active, we could also ensure their survival."

So far, research on the protein secretagogin has been limited. Yet, Dr. Malencyzk and an international team led by the Department of Molecular Neurosciences at the Center for Brain Research have now discovered that the presence of this protein is critical for b—cells to remain healthy, and therefore represents a target for the development of an effective treatment for diabetes – whether prevention or therapy at clinical onset is considered.

Mechanism explained

The most important outcome of this study is to show that secretagogin

regulates whether and how b-cells shed all those proteins that are no longer required or useful to maintain their physiological integrity and functions. Professor Harkany remarks: "If secretagogin is turned off, toxic proteins as waste products can rapidly accumulate in b—cells – and this inevitably leads to their death." And so, if levels of secretagogin in b-cells could be boosted in diabetes to remain near-physiological, this would offer an attractive avenue of their self-protection.

Secretagogin – a Viennese discovery

The protein secretagogin was first identified by Ludwig Wagner (Department of Medicine III), who is also co-author of the current paper, in Vienna in 2000. Seventeen years later, the present study demonstrates the exact role of this protein. Professor Wagner says: "It is nail-biting to see that our continued study of this single protein has reached a stage where the molecular understanding of its function can realize the development of new treatment options."

Fuelling secretagogin levels

But how can cellular levels of this protein be boosted in diabetes? Dr. Malenczyk and the international research team around her showed that the protein can be retained in diabetes and its activity increased by stimulating TRPV ion channels. TRPV1 is a transmembrane protein that besides the nervous system is also expressed in pancreatic beta-cells. If this receptor is stimulated, more secretagogin is being produces in b-cells. TRPV1 is easiest stimulated by capsaicin, an alkaloid that occurs in various types of bell and chilli pepper. Capsaicin binds directly to TRPV1 ion channels and by stimulating them has a profound effect on b-cell biology. Dr. Malenczyk notes: "In a first step, our discovery could be an efficient treatment for diabetes but, of course, this requires follow-up studies in human sufferers. We are cautious to suggest that that diabetics

could improve their diets by consuming more peppers or chillies. TRPV1 is a promising target for potential drugs, because, in diabetes, it continues to be found with its levels largely unaltered in b-cells.

More information: A TRPV1-to-secretagogin regulatory axis controls pancreatic beta-cell survival by modulating protein turnover. Katarzyna Malenczyk, Fatima Girach, Edit Szodorai, Petter Storm, Åsa Segerstolpe, Giuseppe Tortoriello, Robert Schnell, Jan Mulder, Roman A. Romanov, Erzsébet Borók, Fabiana Piscitelli, Vincenzo Di Marzo, Gábor Szabó, Rickard Sandberg, Stefan Kubicek, Gert Lubec, Tomas Hökfelt, Ludwig Wagner, Leif Groop and Tibor Harkany, *EMBO Journal*, 2017. DOI: 10.15252/emboj.201695347

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