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Unusual suspect: Scientists find 'second fiddle' protein's role in Type 2 diabetes

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A team of researchers at the Johns Hopkins Children's Center has found that a protein long believed to have a minor role in type 2 diabetes is, in fact, a central player in the development of the condition that affects nearly 26 million people in the United States alone and counts as one of the leading causes of heart disease, stroke and kidney, eye and nerve damage.

Working with mice, the scientists discovered that a protein called EPAC2—deemed a second-fiddle player up until now—is actually an important regulator of insulin that appears to work by nudging insulin-secreting cells of the pancreas to ramp up production of the sugar-regulating hormone when the body needs it most. Until now, EPAC2 was suspected of playing a merely supporting role as a signaling molecule, but scientists remained uncertain why and how that mattered, if at all.

The results of the federally funded research, described online April 11 in the journal *Diabetes*, also suggest EPAC2 could provide an important new target for treatment to restore pancreatic cell function, the researchers say. Current diabetes treatments halt disease progression at best and focus on controlling symptoms and averting complications, so therapies that actually reverse the disease are badly needed.

"Drugs that precision-target failing pancreatic cells and restore or boost their function have become the holy grail of diabetes research. We believe that our finding establishes a pathway to do just that," says lead investigator Mehboob Hussain, M.D., a pediatric endocrinologist at the

Johns Hopkins Children's Center and a metabolism expert at the newly formed Johns Hopkins Diabetes Institute.

The researchers say several experimental compounds known to alter EPAC2 are now lined up for testing in diabetic animals, but caution that their findings remain far from human application.

Type 2 diabetes stems from the failure of beta cells—members of a family of hormone-secreting pancreatic cells known as islets of Langerhans—to keep up with the body's demand for insulin. Insulin regulates blood sugar by transporting glucose from the blood into organs and tissues for fuel or storage. The body normally releases extra insulin when blood sugar levels surge after eating, but repeated or continued overeating and high-fat diets put added demand on the pancreas to churn out more insulin to keep up with constantly high blood sugar levels. The chronically overworked beta cells eventually slow down their insulin output until it ceases altogether. Insulin deficiency causes abnormal buildup of glucose in the blood and the body's inability to deliver it as fuel to organs and tissues. This, the researchers say, is the essence of diabetes.

Working with mice whose pancreatic cells were missing the EPAC2 signaling molecule, the researchers found that lean, healthy mice regulated their blood sugar levels even in the absence of EPAC2. Short-term surges in food consumption did not affect the mice's ability to regulate their blood sugar, but when the mice were put on a high-fat diet for a month, they developed a condition similar to human diabetes. At the same time, a group of overfed, pudgy mice with intact EPAC2 managed to control blood sugar levels without a problem. In other words, EPAC2 remained dormant and played no role in insulin production under normal conditions, but emerged as a critical factor when the fat mice needed more insulin to control their surging blood sugar levels. This finding led the scientists to believe EPAC2 is an important fail-safe

mechanism unlocked only during abnormal conditions.

"It is as if during these extreme conditions, the body calls upon EPAC2 as backup to help it balance insulin supply and demand," Hussain says.

The study further reveals that EPAC2 is critical because it acts as a link in a signaling cascade that culminates in the release of insulin by pancreatic cells. Comparing EPAC2-deficient and normal pancreatic cells under a microscope, the investigators found that the EPAC2-deficient cells were unable to regulate calcium, a well-known catalyst that triggers the release of insulin into the blood. EPAC2 functioned as calcium's gatekeeper, the researchers say. In its absence, calcium did not reach the critical mass needed to initiate the release of insulin.

The researchers say it remains unclear whether type 2 diabetes damages EPAC2 directly or whether EPAC2 can coax the cells to crank out extra insulin only for so long and eventually gives up. Either way, Hussain says, targeting EPAC2 with drugs could ratchet up the beta cells' dwindling insulin production and nip, or even reverse, diabetes at its root.

Type 2 diabetes is the predominant form of the disease, accounting for more than 90 percent of all diabetes diagnoses. It is commonly associated with diet and lifestyle. Previously seen mostly in middle-aged and older adults, type 2 diabetes is now increasingly diagnosed in younger people and children, a phenomenon fueled by growing obesity rates, experts say.

Provided by Johns Hopkins University School of Medicine

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