New tool identifies novel compound targeting causes of type 2 diabetes

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Researchers have uncovered an anti-diabetic small molecule called azoramide that can improve the function and survival of insulin-producing cells in obese mice. Azoramide was discovered in a scan of the endoplasmic reticulum (ER), the cell's protein-folding center. Credit: V. Altounian/Science Translational Medicine

A new drug screening technology developed at the Harvard T.H. Chan School of Public Health has identified a new potential anti-diabetes compound—and a powerful way to quickly test whether other molecules can have a positive effect on a critical molecular pathway believed to be central to diseases ranging from diabetes to retinitis pigmentosa, cystic fibrosis, Huntington's disease, and Alzheimer's.

The study appears in the June 17, 2015 issue of *Science Translational Medicine*.

The compound, which the authors have called azoramide*, works by focusing on an organelle called the endoplasmic reticulum (ER). The ER is a tubular network within all cells where many key molecular building blocks of glucose metabolism, such as lipids and proteins, are synthesized. When someone is obese, the ER in metabolic tissues such as the liver, fat, and pancreas can no longer keep up with the demand for protein and lipid production. This results in ER stress which contributes to cellular dysfunction and the development of insulin resistance. Insulin resistance in turn makes it difficult for the body to process glucose —high blood sugar and type 2 diabetes result, as well as a cascade of other cellular malfunctions that can lead to heart and blood vessel damage.

"While we and others had previously discovered the central role that ER stress plays in diabetes and metabolic disease, efforts to translate that knowledge into clinically effective ways to improve ER function have had limited success so far," says the study's senior author, Gökhan S. Hotamisligil, chair of the Department of Genetics and Complex Diseases and the Sabri Ülker Center at Harvard T.H. Chan School of Public Health. Lead authors were current and former Hotamisligil lab members Suneng Fu, Abdullah Yalcin, and Grace Yankun Lee.

The study describes the development of two complementary assays that

allow scientists to directly monitor ER function in live cellular systems in culture in the lab. This screening system enables measurement of the amount of chaperones, molecules that patrol and promote ER function, as well as the capacity of the ER to properly fold proteins into their three-dimensional shapes. Using this technique, they showed that azoramide uniquely improved both of these aspects of ER function. In further mechanistic work, they also demonstrated that azoramide could protect cells from death and dysfunction in multiple models of ER stress.

The researchers next tested whether azoramide would be effective in mouse models of obesity and type 2 diabetes, and determined that it greatly improved blood glucose levels by improving both the function of insulin-producing beta cells and increasing the ability of peripheral tissues to sense insulin. The next phase of this research would be to test this compound, or others that work in a similar manner, in human clinical trials.

In another aspect of the paper's research the scientists determined that azoramide could potentially protect retinal cells from the genetic mutation that leads to ER stress and ultimately vision loss in one type of the disease retinitis pigmentosa.

"These results show the broad potential for azoramide or drugs with similar functions targeted at the endoplasmic reticulum," said Hotamisligil. "ER dysfunction is implicated in many other disease processes such as cystic fibrosis, Huntington's disease, and Alzheimer's—which makes this novel screening strategy an exciting new tool that can be applied by multiple labs to discover new drug candidates for diseases that are linked to ER stress."

More information: "Phenotypic assays identify azoramide, a small molecule modulator of the unfolded protein response with anti-diabetic activity," Suneng Fu, Abdullah Yalcin, Grace Y. Lee, Ping Li, Jason Fan,

Ana Paula Arruda, Benedicte M. Pers, Mustafa Yilmaz, Kosei Eguchi, Gökhan S. Hotamisligil, *Science Translational Medicine*, June 17, 2015, DOI: 10.1126/scitranslmed.aaa9134

*Azoramide is an existing compound , the complete name of which is N-{2-[2-(4-Chlorophenyl)-1,3-thiazol-4-yl]ethyl} butanamide.