



# Relieving Stress on Beta Cells May Aid in Type 2 Diabetes

**Joslin Diabetes Center scientists find that high blood glucose levels damage a key enzyme that guards insulin-producing cells**

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Cells in your body are constantly churning out poisonous forms of oxygen (oxidants) and mopping them up with a countervailing force of proteins and chemicals (anti-oxidants). This balancing act of oxidative stress is particularly likely to go haywire in beta cells, the insulin-producing cells that malfunction and then start to die off in type 2 diabetes. Scientists at Joslin Diabetes Center now have found that a relatively little-studied enzyme plays a central role in defending beta cells against oxidants, but is damaged by the high levels of blood glucose produced in diabetes.

Joslin Principal Investigator Robert Stanton, M.D., who led the research, says the discovery raises hopes of finding drugs that protect the enzyme, and thus the beta cells and their insulin production. Such drugs could help to stem the tide against type 2 diabetes, which now afflicts more than a quarter of a billion people worldwide.

Scientists in the Stanton lab previously had found that lowered activity of the enzyme G6PD, the main producer of an antioxidant called NADPH, can inflict damage on several cell types.

In fact, Zhaoyun Zhang, a postdoctoral fellow and first author of the paper published in *The FASEB Journal* online, was investigating G6PD activity's effect on other cell types when she made the initial discovery about beta cells.

In her earlier project, whose results were published in *The FASEB Journal* in October, she was examining the diabetes-like complications that appeared in a line of mice modified to produce less G6PD.

Zhang hadn't planned to look at the pancreas, which is where the insulin-producing beta cells are packaged together with other hormone-producing cells in structures called islets.

But she and Chong Wee Liew, a postdoctoral fellow in the neighboring lab of Principal Investigator Rohit Kulkarni, M.D., Ph.D., decided to take a look at islets in a pancreas from one of the experimental mice.

The islets were tiny compared to those in normal animals, suggesting extensive damage to the beta cells. "It was very, very surprising," she recalls.

Zhang and her co-workers followed up with investigations of G6PD in beta cells and islets, as well as studies of mice with variations in G6PD activity (and thus in production of the NADPH antioxidant).

"The research showed that NADPH, an essential antioxidant upon which all cellular antioxidants ultimately depend, can regulate the growth and death of beta cells," says Stanton, who also is Chief of the Nephrology Section at Joslin Clinic and Associate Professor of Medicine at Harvard Medical School.

The Joslin team went on to demonstrate that increases in the level of blood glucose cause a decrease in NADPH that ends up killing beta cells—and that increasing the level of this antioxidant guards against this effect, at least in mouse beta cells.

"Preventing the death of beta cells or stimulating beta cells to grow is a kind of Holy Grail in diabetes prevention," Stanton notes. "Treatments aimed at increasing this essential antioxidant hold great promise for treating or preventing diabetes in people."

If this approach is successful, it could prove important for other illnesses as well. Abnormally high level of oxidants are thought to be a major cause of kidney disease, heart disease, hypertension, Alzheimer's disease and many other conditions. "I hope that a new era of highly specific, targeted treatments will emerge that very effectively treat or possibly prevent many of these diseases," Stanton says.

Other contributors to the research include Chong Wee Liew, Ph.D., Ji Hu, Ph.D., Lili Guo, Ph.D., and Rohit N. Kulkarni, M.D., of Joslin; and Diane E. Handy, Ph.D., Yingyi Zhang, Ph.D., Jane A. Leopold, M.D., and Joseph Loscalzo, M.D., Ph.D., of Brigham and Women's Hospital in Boston. The research was funded by the National Institutes of Health.

Joslin Diabetes Center is the world's leading diabetes research and clinical care organization. At Joslin, the world's best researchers and clinicians prevent, treat and strive to cure diabetes and its complications. Our discoveries improve the lives of people with diabetes worldwide and offer the greatest hope for a cure.

Among the Harvard Medical School Affiliated institutions, Joslin is one of the most research-intensive academic medical centers and is unique in its sole focus on diabetes.

