

## New mouse model mimics hyperglycemia, aids in diabetes research

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UT Southwestern Medical Center researchers have genetically engineered a laboratory mouse in which pancreatic beta cells can regenerate after being induced to die. The new animal model's regenerative ability may provide future insights into improved treatments of diabetes, which affects millions of Americans.

The model, named the PANIC-ATTAC mouse, mimics what occurs in humans with type 1 diabetes, a condition that develops when the body's immune system destroys pancreatic beta cells, as well as in type 2 diabetes, where beta cells die from working overtime.

After inducing death in the beta cells – which make and release the hormone insulin – the researchers found that the engineered mice's betacell populations can regenerate, which makes the animal useful for studying conditions such as type 1 diabetes, hyperglycemia (high blood sugar) and gestational diabetes.

The animal model is described online and in a future print issue of the journal *Diabetes*.

"The ability to induce cell death is not novel. The fact that the beta cells regenerate after we kill them is really the new aspect of the model," said Dr. Philipp Scherer, professor of internal medicine, director of the Touchstone Center for Diabetes Research at UT Southwestern and senior author of the study. "It enables us to see what kind of event or pharmacological intervention might stimulate or enhance the



regeneration."

In the study, the researchers genetically manipulated mature, insulinpositive pancreatic beta cells in the PANIC-ATTAC mice so that these cells would die when they came in contact with a drug. When the researchers stopped administering the drug and allowed the animals to recover, they found that the animals' beta cells had regenerated and their blood glucose levels returned to normal after two months.

Dr. Scherer said it's unclear what caused the pancreatic beta cells to regenerate, but uncovering the mechanisms that allow beta cells to rebound in this environment could provide major insights in type 1 diabetes research. He and his colleagues are now developing a way to isolate the cell population that gives rise to the newly emerging beta cells.

About 1 million people, between 5 percent and 10 percent of all diagnosed cases of diabetes, in the U.S. are affected by type 1 diabetes, for which there is no cure or preventive measure.

"This model allows us to get a transcriptional signature, a fingerprint, of how beta cells fend off the pharmaceutical stimulus we provide to prompt cell death," Dr. Scherer said. "In other words, it provides a way to identify the most critical factors that protect against beta cell death and to potentially find ways to increase these factors in people with type 1 diabetes."

The key, Dr. Scherer said, is that the process researchers use to kill beta cells is very targeted.

"It creates very little inflammation, so we can eliminate specific cells with minimal collateral damage," he said. "The other nice aspect is that we can do it in a very dose-dependent way, so we can ablate, or kill, just



a few cells, or we can ablate almost all of them."

Dr. Scherer said this model lends itself to studying conditions of temporary hyperglycemia such as gestational diabetes, a condition in which pregnant women who have never had diabetes develop hyperglycemia. Gestational diabetes usually disappears after pregnancy, but it is not clear whether these transient bouts of elevated glucose can cause permanent damage in the vasculature that persists even after normal glucose levels have been restored.

Dr. Zhao Wang, a postdoctoral researcher at UT Southwestern and lead author of the study, said the strength of the PANIC-ATTAC mouse as a research tool lies partly in the ability to test how specific pharmaceuticals impact beta-cell regeneration.

"We can test which drugs can more rapidly repair the damage," Dr. Wang said. "We can also test which drugs are protective. That's probably more important physiologically because it allows us to screen for interventions that could protect beta cells during the early stages of diabetes to slow down and prevent the onset of hyperglycemia."

Source: UT Southwestern Medical Center

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