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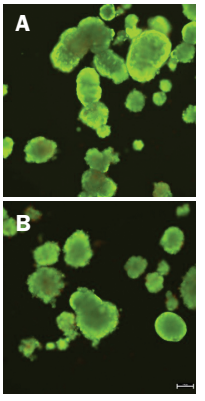
In This Issue of *Diabetes*

By Max Bingham, PhD

Burn Wound Material Appears to Support Islet Transplantation in Preclinical Studies

A biodegradable polymer material may hold the key to successful islet transplantation via skin, according to Rojas-Canales et al. (**p. 758**). The authors show in preclinical models that the material known as biodegradable temporizing matrix (BTM) does not harm islets and, once transplanted, remains differentiated as insulin-producing cells. According to the authors, the material results in the generation of highly vascularized tissue that crucially contains spaces where other cell types can be implanted, thus addressing the relatively hypoxic nature of the dermis and its suitability for islet transplantation. In presently used methods, islets are transplanted into the liver, but the procedure is often unsuccessful because of a host of issues. "Generation of this preclinical data has paved the way for a first-in-human proof-of-concept trial investigating intracutaneous in-the-skin islet transplantation," said author P. Toby Coates. "Further, we envisage this novel transplant site as one that will facilitate new islet cell therapies, including stem cell–derived, porcine, and gene-modified islets." In a series of experiments, the authors found that in mice, BTM material did not impede the function or viability of syngeneic islets when transplanted under the kidney capsule. Indeed, the transplantation resulted in the cure of induced diabetes for over 150 days. In a porcine model, they were able to track the development of a highly vascularized network in the material, and when syngeneic neonatal islets were injected into the material, they remained differentiated and survived for >100 days with normal islet architecture and C-peptide secretion. The authors note that the BTM appears to support vascular development and islet engraftment early on but is then degraded and excreted from the body. The BTM material is already approved for use in the U.S. as a treatment for severe burns. "This preclinical research is exciting, as a successful intracutaneous skin transplant site for islet transplantation may open the doorway for safe advancement of new islet replacement therapies," Coates added.

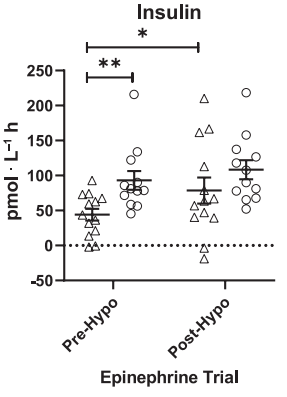


No differences between islets cultured alone (*A*) and islets cultured with the BTM (*B*).

Rojas-Canales et al. Intracutaneous transplantation of islets within a biodegradable temporizing matrix (BTM) as an alternative site for islet transplantation. Diabetes 2023;72:758–768

Metabolic Response to Epinephrine Depends on β_2-Receptor Genotype and Hypoglycemia Episodes

A polymorphism called Gly16Arg in the β_2-receptor gene appears to modulate metabolic responses to epinephrine (adrenaline), according to Rokamp et al. (**p. 728**). At least in healthy individuals, those with the Gly16 genotype had greater metabolic response to epinephrine than individuals with the Arg16 genotype. Notably, however, responses did not differ between the groups following three episodes of induced hypoglycemia. The findings might help explain why some individuals with type 1 diabetes have more severe episodes of hypoglycemia than others. The modulating role of polymorphisms in the β_2-receptor gene in response to epinephrine and the effects of hypoglycemia had not previously been investigated, according to the authors. They identified 12 healthy male individuals with the Gly16 genotype and 13 with the Arg16 genotype. These individuals then participated in four trial days, receiving epinephrine on days 1 and 4 and exposure to three episodes of hypoglycemia over days 2 and 3. They found that prior to hypoglycemia, responses of insulin, glycerol, and free fatty acid to epinephrine all were lower in the Arg16 group than in the Gly16 group. Glucose response was not different between the groups, however. Following episodes of hypoglycemia, no major differences were seen in responses between the groups. As such, they conclude that those with the Gly16 genotype had a greater metabolic response to epinephrine but that repeated hypoglycemia effectively blocks the response. "This finding may contribute to the understanding of glucose counterregulation beyond the magnitude of the epinephrine response," they write. The authors note that while they used controlled conditions and male-only participants, the single dose of epinephrine precluded any assessment of a dose-response relationship, which would have strengthened the findings. Commenting further, author Kim Z. Rokamp said, "This study may contribute to understanding of glucose counterregulation and the varying risk of hypoglycemia among people with type 1 diabetes. We also show an apparent dissociation between metabolic and circulatory β_2-receptor sensitivity that may have broad physiologic and pathophysiologic implications."



Insulin responses to epinephrine according to Arg16 (triangles) or Gly16 (circles) genotype and the effect of repeated hypoglycemia episodes. Post-Hypo, posthypoglycemia; Pre-Hypo, prehypoglycemia.

Rokamp et al. Impact of polymorphism in the β_2-receptor gene on the metabolic response to epinephrine after repeated hypoglycemia. Diabetes 2023;72:728–734

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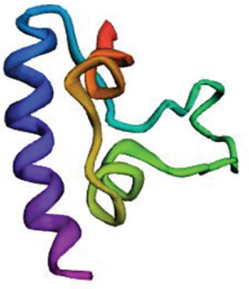
Glucose Switch System Regulates Insulin Secretion and Enables Glucose Control in Mice

A glucose-activated insulin switch, or GAIS, system appears to control blood glucose in mice with streptozotocin-induced diabetes, according to Xie et al. (**p. 703**). Using a series of in vitro and mouse model–based experiments, they show how the system can affect (variously) long-term insulin secretion, blood glucose control and tolerance, and HbA_{1c} levels. The approach involves temporarily keeping a single-strand insulin analog in the endoplasmic reticulum, which is then automatically released into the bloodstream under conditions of hyperglycemia. Specifically, they describe an approach that uses a "conditional aggregation domain–furin cleavage sequence–SIA [single-strand insulin analog] fusion protein" that is encoded by a plasmid delivered intramuscularly. The protein is then temporarily kept in endoplasmic reticulum via binding to another protein, called GRP78, with the insulin part released into the blood under conditions of hyperglycemia. Previous efforts in this domain have shown therapeutic potential but often resulted in either delivery of protein levels that are too low or, in the case of insulin, its uncontrolled release and hypoglycemia. Therefore, a key step in the experiments was an adjustment to the insulin analog structure to improve efficiency of delivery, specifically with the introduction of a series of flexible peptides to replace proinsulin C-peptide. Based on the findings, the authors propose that their system offers a treatment for type 1 diabetes and, with further studies, potentially a permanent treatment for diabetes. Specifically, they suggest that these studies should look at combining the GAIS system with transcriptional switches and then use CRISPR-Cas9 to integrate the combination into safe genomic sites. More widely, they suggest the system has the potential to deliver a variety of other therapeutics. "In addition to being used for diabetes, the GAIS system–mediated smart production factory platform can be used to express and secrete a variety of therapeutic proteins/peptides for the treatment of different diseases, such as treatments for muscular dystrophy and severe osteoporosis and immunotherapy of tumors," they write.



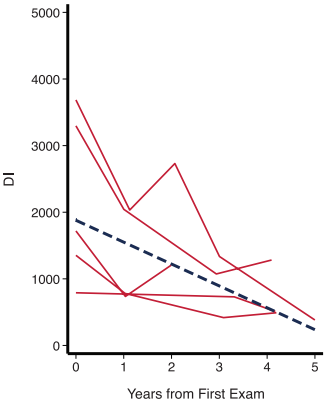
SIA-B2

Predicted structure of single-stranded insulin analog B2 used in the overall study.

Xie et al. Glucose-activated switch regulating insulin analog secretion enables long-term precise glucose control in mice with type 1 diabetes. Diabetes 2023;72:703–714

Rapid Decline in β-Cell Function and Increases in Adiposity Precede Type 2 Diabetes in Latino Youth

The development of type 2 diabetes in Latino youth with obesity appears to be preceded by a rapid decline in β-cell function and increases in various measures of adiposity, according to Vidmar et al. (**p. 735**). Specifically, they found that development of diabetes was associated with a rapid decline in a measure of β-cell function called the disposition index, or DI, and that it directly correlated with increases in fasting glucose, HbA_{1c}, and adiposity. Using a longitudinal cohort study, the authors looked at how 262 Latino children with overweight/obesity and at risk for type 2 diabetes developed over a period of 5 years. Specifically, they were looking for predictive factors in those who developed type 2 diabetes compared with those who did not, including matched control participants. They found that six individuals (i.e., 2%) developed type 2 diabetes in the study period, which is a low rate compared with those of equivalent studies. Using the DI measure, they found that case participants had a rate of decline in β-cell function that was 3 times higher than that for the overall cohort and 20 times that of matched control participants. The authors note that the findings might have clinical implications in that prevention strategies for preserving β-cell function could have benefits in at-risk individuals. Conversely, they also note that the DI measure was obtained with an intravenous glucose tolerance test, which would be impractical in clinical settings, and that oral glucose tolerance test measures did not have any relationship with any diabetes outcomes. "Even though this was a 20-year effort that required significant funding, the fact that only six cases of type 2 diabetes development were observed justifies the need for larger studies," said author Michael I. Goran. "This should include other at-risk groups beyond Latinos." He added, "These studies are needed to fully understand the factors that are contributing to the very rapid rate of β-cell deterioration during pubertal development, so that we can identify ways to prevent it for future generations."



DI (i.e., β-cell function) in six Latino youth who developed type 2 diabetes within 5 years. Red, observed values; black, predicted values.

Vidmar et al. Rapid decline in β-cell function and increasing adiposity are associated with conversion to type 2 diabetes in at-risk Latino youth. Diabetes 2023;72:735–745

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