MAYO CLINIC

Regenerative Medicine in Diabetes

Aleksey Matveyenko, PhD, and Adrian Vella, MD

From the Department of Physiology and Biomedical Engineering (A.M.) and Division of Endocrinology, Diabetes, Metabolism and Nutrition (A.V.), Mayo Clinic, Rochester, MN.

CME Activity

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Abstract

Diabetes is a common multisystem disease that results in hyperglycemia due to a relative or absolute insulin deficiency. Improved glycemic control decreases the risk of development and progression of microvascular and, to a lesser extent, macrovascular complications and prevents symptomatic hyperglycemia. However, complex treatment regimens aimed at improving glycemic control are associated with an increased incidence of hypoglycemia. On paper at least, cellular therapies arising from reprogramed stem cells or other somatic cell types would provide ideal therapy for diabetes and the prevention of its complications. This hypothesis has led to intensive efforts to grow β cells from various sources. In this review, we provide an overview of β-cell development as well as the efforts reported to date in terms of cellular therapy for diabetes. Engineering β-cell replacement therapy requires an understanding of how β cells respond to other metabolites such as amino acids, free fatty acids, and ketones. Indeed, efforts thus far have been characterized by an inability of cellular replacement products to adequately respond to metabolites that normally couple the metabolic state to β-cell function and insulin secretion. Efforts to date intended to capitalize on current knowledge of islet cell development and stimulus-secretion coupling of the β cell are encouraging but as yet of little clinical relevance.

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Diabetes mellitus is a common multisystem disease that results in hyperglycemia due to a relative or absolute insulin deficiency and arises from a complex interaction between genes and the environment.[1] The presence or absence of disease is defined by hyperglycemia, the degree and duration of which lead to microvascular complications such as retinopathy, nephropathy, and neuropathy. Absolute insulin deficiency is typically encountered in immune-mediated or type 1 diabetes (T1DM) in which an immune response results in destruction of β cells, the site of endogenous insulin production. In contrast, in type 2 diabetes (T2DM),

insulin deficiency, although due in part to loss of functional responsive β cells, is not absolute but relative to the impaired insulin signaling present in this disorder.[2]

Improved glycemic control decreases the risk of development and progression of the aforementioned complications and prevents symptomatic hyperglycemia. However, complex treatment regimens aimed at improving glycemic control are associated with an increased incidence of hypoglycemia. Hypoglycemia is one of the most serious complications of diabetes treatment and can lead to severe neurocognitive dysfunction and impairment of quality of life. This problem has led to a quest for alternative therapeutic strategies. On paper at least, cellular therapies arising from reprogramed stem cells or other somatic cell types would provide ideal therapy for diabetes and its complications.

CLINICAL NEED

In T1DM, and to a lesser extent long-standing T2DM, multiple daily injections of insulin are needed to achieve good glycemic control, which requires considerable commitment and resilience on the part of the patient. Indeed, achieving glycemic targets while avoiding hypoglycemia may be difficult for some. The most feared complication associated with long-standing T1DM is hypoglycemia unawareness, which occurs when a defective counterregulatory response to hypoglycemia results in frequent hypoglycemia with few prodromal symptoms. As a consequence, affected patients are at risk of cognitive dysfunction and hypoglycemic seizures and are often unable to work or drive.[3,4] To date, treatment has consisted of whole-organ pancreas transplant or islet cell transplant, which can restore endogenous insulin secretion and improve microvascular complications. However, these procedures expose patients to both surgical complications and the consequences of immunosuppression, including opportunistic infections and the toxicities of immunosuppressive agents.[5]

In addition to the problem of achieving and maintaining glycemic control, the microvascular complications of diabetes, most especially neuropathy and its consequences, may lend themselves to cell replacement therapies. Diabetic neuropathy is a common cause of foot ulceration, deformity, and amputation. Autonomic dysfunction, especially affecting the gastrointestinal tract, causes disruption of daily activities and may further complicate glycemic control and increase mortality.[6] It is in this context that better therapies for diabetes and its complications are needed.

EMBRYONIC DEVELOPMENT OF β CELLS

The pancreas arises from dorsal and ventral epithelial buds from the endoderm of the posterior foregut on approximately the 10th embryonic day (the timing is specific to rodents). The epithelial cells evaginate into surrounding mesenchyme, forming an accretion of multipotent progenitor cells (MPCs) surrounding a central lumen. All subsequent progenitor cells as well as the different cell types present in the adult pancreas (ie, acinar, ductal, and islet cells) arise from these accretions.[7] By the 13th day of embryonic development, the dorsal and ventral pancreatic buds have fused and are accompanied by expansion of the MPCs with cells exhibiting apicobasal polarity and microlumen formation. The number of MPCs allocated to the initial pancreatic buds seems to control ultimate organ size, suggesting that the MPCs giving rise to the adult pancreas are already somewhat predifferentiated and are limited in the number of cell cycles they are able to undergo while expanding tissue, developing organ architecture, and differentiating into defined cell lineages.[8] The first wave of endocrine cell differentiation is predominantly α-cell differentiation, although some cells express ghrelin (ε cells), pancreatic polypeptide, and somatostatin (δ cells). Subsequent development leads to delamination and budding of endocrine cells into architecture reminiscent of the adult pancreas. There has been a suggestion that a greater proportion of adult β cells arise from the dorsal as opposed to the ventral bud, implying that the milieu present within the dorsal bud may be more apposite to the differentiation of MPCs into functioning β cells.[9]

What drives the development of endocrine cells in the embryonic pancreas? It is apparent that a variety of factors interplay at various stages of development, including factors that are extrinsic to MPCs, and arise in the adjacent mesenchyme. There are also signals that are intrinsic to the developing epithelium acting in a paracrine fashion. The timing and combination of these signals activates a series of genetic regulatory networks through a variety of transcription

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