nature REVIEWS
DRUG DISCOVERY

Strategies to increase pancreatic β-cell mass and function

Amedeo Vetere, Amit Choudhary and Bridget K. Wagner

Since the discovery of insulin in 1922, the pancreatic β-cell has been a major focus in the study of diabetes. More recently, genetic and clinical studies have highlighted the role of β-cell failure in diabetes pathogenesis. Despite the loss of β-cell number in type 1 diabetes and deficient β-cell function in type 2 diabetes, few existing drugs are effective at protecting or restoring this cell type in humans. Advances in primary cell culture, cellular reprogramming and high-throughput screening have enabled a modern focus on identifying novel small molecules that are capable of inducing β-cell proliferation and insulin secretion, reprogramming from other cell types or protection from apoptosis. The β-cell is a key cell type in advancing the promise of regenerative medicine.

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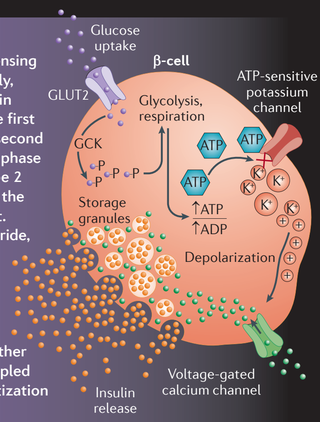
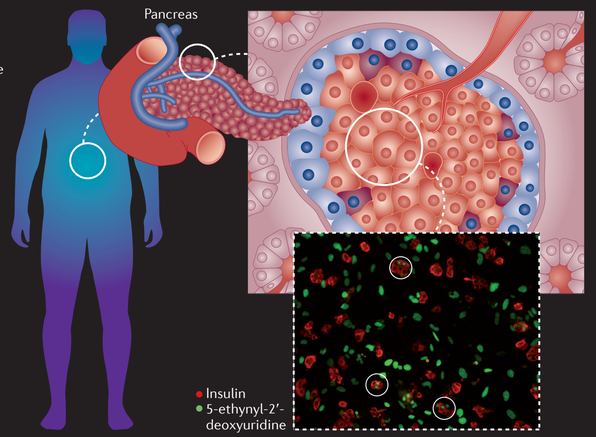
Insulin secretion

Insulin secretion by β-cells is triggered by sensing changes in ambient glucose levels. Normally, glucose induces a biphasic pattern of insulin release, with the first phase occurring in the first few minutes, followed by a more enduring second phase. The important observation that first-phase insulin secretion is lost in patients with type 2 diabetes led to this phenomenon becoming the main pharmacological target for treatment. The sulphonylurea drugs (for example, glyburide, glimepiride and glipizide) bind to an ATP-dependent potassium channel in the β-cell membrane, causing a steady secretion of insulin. The 'glinide' drug family (for example, nateglinide and repaglinide) also binds this channel, but at a different site. Other emerging targets include the G protein-coupled receptors GPR40 and GPR119. Insulin sensitization may occur by targeting PPARγ or GPR120.





Incretin-based therapies

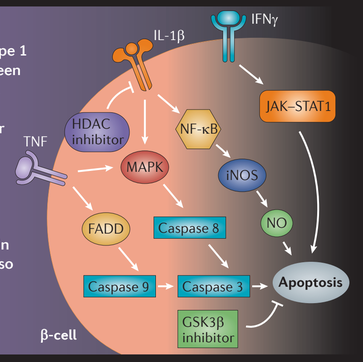
Incretins such as GLP1 are humoral factors that are responsible for the gut-associated potentiation of insulin secretion. GLP1 is synthesized by gut endocrine L cells and stimulates glucose-dependent insulin secretion by activating specific G protein-coupled receptors localized on β-cells. Incretin-based therapy for the treatment of type 2 diabetes has emerged as an attractive approach since the observation that continuous administration of GLP1 lowers blood glucose levels in patients with type 2 diabetes. The therapeutic use of GLP1 was hindered by its short half-life until the discovery of exendin 4, which is a naturally occurring peptide that is resistant to DPP4 cleavage and was originally isolated from the venom of the Gila Monster (*Heloderma suspectum*) in 1992. Complementary approaches to improve the use of GLP1 or GLP1 agonists are based on the generation of long-acting DPP4-resistant forms of these drugs, such as liraglutide and GSK716155, or inhibitors of DPP4 itself, such as the gliptin class of drugs. Despite 20 years of research since the molecular identification and cloning of the GLP1 receptor, no orally available small-molecule GLP1 receptor activator has yet been developed for therapeutic use.

β-cell proliferation

β-cell mass is maintained at optimal levels through a very slow turnover rate. In humans, it has been shown that β-cell mass expands several-fold from birth and during the first few years of childhood. After this initial growth burst, the replication potential of β-cells gradually declines until adulthood. Opposing actions of CDKs and cell-cycle inhibitors, such as p16 and p27, reduce β-cell replication to negligible levels. Efforts to identify small molecules that induce β-cell proliferation are complicated by the need for cell specificity. For example, inhibitors of GSK3β can induce proliferation, but not in a cell type-selective manner. Other emerging targets include menin and GCK. The recent discovery of betatrophin, a protein that is secreted by the liver and increases β-cell proliferation, may be leveraged in the future to develop novel therapeutics for diabetes.

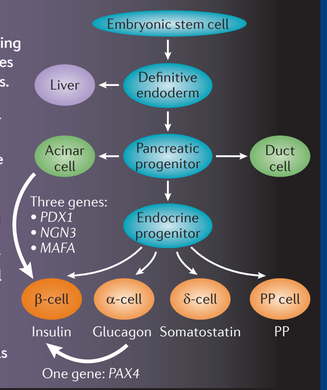
Protection from apoptosis

The factors contributing to β-cell death are different in type 1 versus type 2 diabetes. Cytokine-induced apoptosis has been targeted by both genetic and small-molecule approaches. The NF-κB pathway has been targeted genetically by expressing a degradation-resistant NF-κB protein inhibitor (known as ΔNIκBα) in β-cells, and siRNA-mediated knockdown of STAT1 in rodent β-cell lines protected them from apoptosis. Small-molecule-based approaches have targeted JAK–STAT signalling with a polyphenolic flavonoid (silymarin), or they have targeted HDACs with isoform-selective inhibitors to prevent β-cell dysfunction in human islets. High levels of glucose and free fatty acids also induce ER stress and reduce β-cell function and viability. These effects have been suppressed by antioxidants, GSK3β inhibitors and chemical chaperones, as well as isoform-selective HDAC inhibitors.



β-cell reprogramming

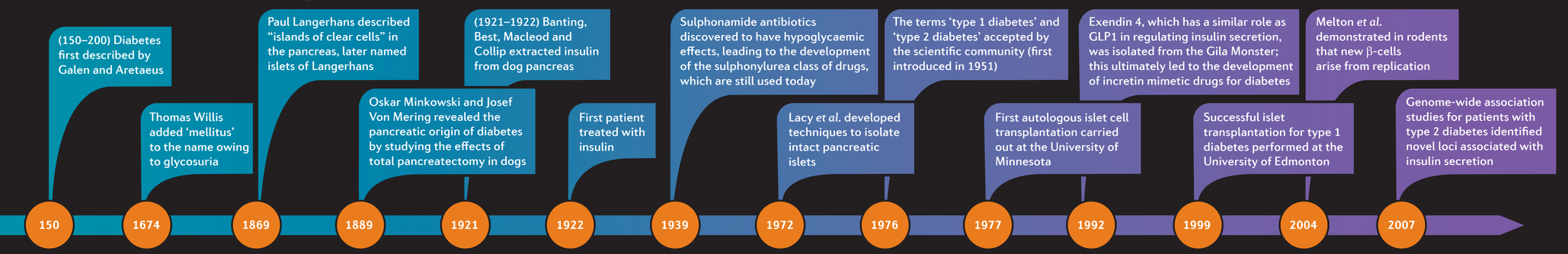
To replenish β-cell mass in patients with diabetes, attempts are being made to reprogramme or transdifferentiate closely related cell types to β-cells by overexpressing master regulatory transcription factors. Early studies focused on the conversion of hepatocytes to β-like cells through the overexpression of PDX1, the transcription factor MAFA and NeuroD. *In vivo* transdifferentiation of acinar cells to β-cells has been achieved by transient viral overexpression of three transcription factors (PDX1, NGN3 and MAFA), whereas over-expression of a single transcription factor — PAX4 — has successfully converted α-cells to β-cells through NGN3-expressing duct cells. The development of β-cells from acinar tissue is especially promising. Innovations in small-molecule drug discovery are making the identification of transdifferentiation-inducing small molecules more feasible. For example, (-)-indolactam V, a protein kinase C activator, directs the differentiation of embryonic stem cells to PDX1-positive progenitor cells. Two small molecules, BRD 7389 and GW8510, which induce insulin expression in α-cells by targeting several kinases, have recently been reported.



Therapeutic targets

Target	Biological role	Agents; companies	Current development phase	Refs
ABCC8	Insulin secretion	Sulphonylureas; Pfizer, Roche, Sanofi-Aventis, Boehringer Ingelheim	Approved	-
GCK	Insulin secretion, proliferation	AMG-151, PF-04937319; Array BioPharma, Pfizer	Phase II	-
GPR40	Insulin secretion	TAK-875; Takeda	Phase III	-
KCNJ11	Insulin secretion	Sulphonylureas	Approved	-
PPARγ	Insulin secretion	Thiazolidine-diones; GlaxoSmithKline, Takeda, Daiichi Sankyo	Approved	-
DPP4	Incretin effects	Gliptins; Merck, Novartis, Boehringer Ingelheim, LG Life Sciences, Takeda	Approved/ Phase III	-
GLP1	Incretin effects, proliferation	GLP1 analogues; Amylin Pharmaceuticals, Novo Nordisk	Approved	-
GPR119	Incretin effects, proliferation	MBX-2982; Metabolex	Phase II	-
GPR120	Incretin effects	Pamlico Pharmaceutical	Discovery	1
CCND1	Proliferation	-	Therapeutic target	2
CDK6	Proliferation	-	Therapeutic target	2
GSK3β	Proliferation, protection from apoptosis	CP-70949; Pfizer, Kyorin Pharmaceutical	Preclinical	3
Menin	Proliferation	Menin–MLL interaction inhibitors; Novapeutics	Lead compound	-
HDAC1	Protection from apoptosis	Non-selective inhibitors (for example, vorinostat); Merck	Approved for other indications	-
HDAC3	Protection from apoptosis	Non-selective inhibitors (for example, vorinostat); Merck	Approved for other indications	-
IL-1β	Protection from apoptosis	Anakinra; Amgen	Approved for other indications	-
JNK	Protection from apoptosis	Tool compounds available	Therapeutic target	4
NF-κB	Protection from apoptosis	HDAC inhibitors may act through this pathway	In development	5
MAFA	Reprogramming of acinar cells	-	Therapeutic target	6
NGN3	Reprogramming of acinar cells	-	Therapeutic target	6
PDX1	Reprogramming of acinar cells	-	Therapeutic target	6
PAX4	Reprogramming of α-cells	-	Therapeutic target	7

Important dates in the history of β-cell study and diabetes



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Abbreviations
ABCC8, ATP-binding cassette subfamily C member 8 (sulphonylurea receptor); CCND1, cyclin D1; CDK, cyclin-dependent kinase; DPP4, dipeptidyl peptidase 4; ER, endoplasmic reticulum; FADD, FAS-associated death domain protein; GCK, glucokinase, GLP1, glucagon-like peptide 1; GLUT2, glucose transporter type 2; GPR, G protein-coupled receptor; GPR40, free fatty acid receptor 1 (FFAR1); GPR120, free fatty acid receptor 4 (FFAR4); GSK3β, glycogen synthase kinase 3β; HDAC, histone deacetylase; IFNγ, interferon-γ; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; JAK, Janus kinase; JNK, JUN N-terminal kinase; KCNJ11, potassium inwardly rectifying channel subfamily J member 11; MAPK, mitogen-activated protein kinase; MLL, mixed lineage leukaemia; NGN3, neurogenin 3; NeuroD, neurogenic differentiation factor; NF-κB, nuclear factor-κB; NO, nitric oxide; PAX4, paired box protein 4; PDX1, pancreas/duodenum homeobox protein 1; PP, pancreatic polypeptide; PPARγ, peroxisome proliferator-activated receptor-γ; siRNA, small interfering RNA; STAT, signal transducer and activator of transcription; TNF, tumour necrosis factor.

Affiliations
Amedeo Vetere, Amit Choudhary and Bridget K. Wagner are at the Broad Institute of MIT and Harvard, 7 Cambridge Center, Cambridge, Massachussetts 02142, USA.

Competing interests statement
The authors declare no competing financial interests.

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