

World Journal of *Gastroenterology*

World J Gastroenterol 2020 June 14; 26(22): 2889-3117



OPINION REVIEW

- 2889 Circulating exosomal miRNAs as potential biomarkers for Barrett's esophagus and esophageal adenocarcinoma
Lu J, Zhao HP, Dai K, Cheng Y, Zhang J, Guo L

REVIEW

- 2902 Ever-increasing diversity of drug-induced pancreatitis
Weissman S, Aziz M, Perumpail RB, Mehta TI, Patel R, Tabibian JH
- 2916 Nutrition in alcohol-related liver disease: Physiopathology and management
Kamran U, Towey J, Khanna A, Chauhan A, Rajoriya N, Holt A
- 2931 Liver-related effects of chronic hepatitis C antiviral treatment
Laursen TL, Sandahl TD, Kazankov K, George J, Grønbaek H
- 2948 Regenerative medicine of pancreatic islets
Arutyunyan IV, Fatkhudinov TK, Makarov AV, Elchaninov AV, Sukhikh GT
- 2967 Benign gallbladder diseases: Imaging techniques and tips for differentiating with malignant gallbladder diseases
Yu MH, Kim YJ, Park HS, Jung SI

MINIREVIEWS

- 2987 COVID-19 pandemic: Its impact on liver disease and liver transplantation
Sahin TT, Akbulut S, Yilmaz S
- 3000 Diagnostic challenges in non-cirrhotic portal hypertension - porto sinusoidal vascular disease
Nicoară-Farcău O, Rusu I, Stefănescu H, Tanțău M, Badea RI, Procopeț B
- 3012 Extralevator abdominoperineal excision for advanced low rectal cancer: Where to go
Tao Y, Han JG, Wang ZJ

ORIGINAL ARTICLE**Basic Study**

- 3024 High plasma levels of COL10A1 are associated with advanced tumor stage in gastric cancer patients
Necula L, Matei L, Dragu D, Pitica I, Neagu AI, Bleotu C, Dima S, Popescu I, Diaconu CC, Chivu-Economescu M

3034 Hsa_circRNA_102610 upregulation in Crohn's disease promotes transforming growth factor- β 1-induced epithelial-mesenchymal transition *via* sponging of hsa-miR-130a-3p
Yin J, Ye YL, Hu T, Xu LJ, Zhang LP, Ji RN, Li P, Chen Q, Zhu JY, Pang Z

3056 Optimal dosing time of Dachengqi decoction for protection of extrapancreatic organs in rats with experimental acute pancreatitis
Yao JQ, Zhu L, Miao YF, Zhu L, Chen H, Yuan L, Hu J, Yi XL, Wu QT, Yang XJ, Wan MH, Tang WF

Case Control Study

3076 Single-nucleotide polymorphisms based genetic risk score in the prediction of pancreatic cancer risk
Wang XY, Chen HT, Na R, Jiang DK, Lin XL, Yang F, Jin C, Fu DL, Xu JF

Retrospective Study

3087 Infection recurrence following minimally invasive treatment in patients with infectious pancreatic necrosis
Gao CC, Li J, Cao F, Wang XH, Li A, Wang Z, Li F

Observational Study

3098 Intestinal dysbiosis in pediatric Crohn's disease patients with *IL10RA* mutations
Xue AJ, Miao SJ, Sun H, Qiu XX, Wang SN, Wang L, Ye ZQ, Zheng CF, Huang ZH, Wang YH, Huang Y

CASE REPORT

3110 Giant splenic artery aneurysm presenting with massive upper gastrointestinal bleeding: A case report and review of literature
Panzer F, Inchingolo R, Rizzi M, Biscaglia A, Schievenin MG, Tallarico E, Pacifico G, Di Venere B

ABOUT COVER

Editorial Board Member of *World Journal of Gastroenterology*, Michele Barone, MD, PhD, Adjunct Professor, Research Associate, Section of Gastroenterology, Department of Emergency and Organ Transplantation, University of Bari, Bari 70124, Italy

AIMS AND SCOPE

The primary aim of *World Journal of Gastroenterology (WJG, World J Gastroenterol)* is to provide scholars and readers from various fields of gastroenterology and hepatology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

INDEXING/ABSTRACTING

The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2019 edition of Journal Citation Report® cites the 2018 impact factor for WJG as 3.411 (5-year impact factor: 3.579), ranking WJG as 35th among 84 journals in gastroenterology and hepatology (quartile in category Q2). CiteScore (2018): 3.43.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Yan-Liang Zhang*
 Proofing Production Department Director: *Yun-Xiaojuan Wu*
 Responsible Editorial Office Director: *Ze-Mao Gong*

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Subrata Ghosh, Andrzej S Tarnawski

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

June 14, 2020

COPYRIGHT

© 2020 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Regenerative medicine of pancreatic islets

Irina V Arutyunyan, Timur Kh Fatkhudinov, Andrey V Makarov, Andrey V Elchaninov, Gennady T Sukhikh

ORCID number: Irina V Arutyunyan (0000-0002-4344-8943); Timur Kh Fatkhudinov (0000-0002-6498-5764); Andrey V Makarov (0000-0003-2133-2293); Andrey V Elchaninov (0000-0002-2392-4439); Gennady T Sukhikh (0000-0003-0214-1213).

Author contributions: Arutyunyan IV, Fatkhudinov TK, Makarov AV, Elchaninov AV, Sukhikh GT performed the literature review and wrote and edited portions of the final manuscript; all authors approved the submitted version of the manuscript.

Supported by the President Grant for Government Support of Young Russian Scientists, No. 075-15-2019-1120.

Conflict-of-interest statement: The authors do not have any commercial or other association that might pose a conflict of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: December 30, 2019

Irina V Arutyunyan, Andrey V Makarov, Andrey V Elchaninov, Gennady T Sukhikh, National Medical Research Center for Obstetrics, Gynecology and Perinatology named after Academician V. I. Kulakov of Ministry of Healthcare of Russian Federation, Moscow 117997, Russia

Timur Kh Fatkhudinov, Research Institute of Human Morphology, Moscow 117418, Russia

Timur Kh Fatkhudinov, Peoples Friendship University of Russia, Moscow 117198, Russia

Andrey V Makarov, Pirogov Russian National Research Medical University, Ministry of Healthcare of the Russian Federation, Moscow 117997, Russia

Corresponding author: Timur Kh Fatkhudinov, MD, PhD, Deputy Director for Scientific Development, Laboratory of Growth and Development, Scientific Research Institute of Human Morphology, 3 Tsurupa Street, Moscow 117418, Russia. tfat@yandex.ru

Abstract

The pancreas became one of the first objects of regenerative medicine, since other possibilities of dealing with the pancreatic endocrine insufficiency were clearly exhausted. The number of people living with diabetes mellitus is currently approaching half a billion, hence the crucial relevance of new methods to stimulate regeneration of the insulin-secreting β -cells of the islets of Langerhans. Natural restrictions on the islet regeneration are very tight; nevertheless, the islets are capable of physiological regeneration *via* β -cell self-replication, direct differentiation of multipotent progenitor cells and spontaneous α - to β - or δ - to β -cell conversion (trans-differentiation). The existing preclinical models of β -cell dysfunction or ablation (induced surgically, chemically or genetically) have significantly expanded our understanding of reparative regeneration of the islets and possible ways of its stimulation. The ultimate goal, sufficient level of functional activity of β -cells or their substitutes can be achieved by two prospective broad strategies: β -cell replacement and β -cell regeneration. The "regeneration" strategy aims to maintain a preserved population of β -cells through *in situ* exposure to biologically active substances that improve β -cell survival, replication and insulin secretion, or to evoke the intrinsic adaptive mechanisms triggering the spontaneous non- β - to β -cell conversion. The "replacement" strategy implies transplantation of β -cells (as non-disintegrated pancreatic material or isolated donor islets) or β -like cells obtained *ex vivo* from progenitors or mature somatic cells (for example, hepatocytes or α -cells) under the action of small-molecule inducers or by genetic modification. We believe that the huge volume of experimental and clinical studies will finally allow a safe and effective solution to a seemingly simple goal-restoration of the functionally active β -cells, the innermost hope of millions of people globally.

Peer-review started: December 30, 2019

First decision: January 19, 2020

Revised: May 13, 2020

Accepted: May 26, 2020

Article in press: May 26, 2020

Published online: June 14, 2020

P-Reviewer: Kita K, Labusca L

S-Editor: Zhang H

L-Editor: A

E-Editor: Zhang YL



Key words: Pancreas; Islets of langerhans; β -cells; Regeneration; Replacement; Transplantation; Reprogramming

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The review discusses the most promising strategies for regenerative medicine to stimulate the regeneration or replacement of the islet of the pancreas. The “regeneration” strategy aims to maintain a preserved population of β -cells through replication, or evoke the intrinsic adaptive mechanisms. The “replacement” strategy implies transplantation of β -cells or β -like cells obtained *ex vivo* from progenitors or mature somatic cells (hepatocytes or α -cells). We believe that the huge volume of experimental and clinical studies currently under way will finally allow a safe and effective solution to simple goal-restoration of the active β -cells.

Citation: Arutyunyan IV, Fatkhudinov TK, Makarov AV, Elchaninov AV, Sukhikh GT. Regenerative medicine of pancreatic islets. *World J Gastroenterol* 2020; 26(22): 2948-2966
URL: <https://www.wjgnet.com/1007-9327/full/v26/i22/2948.htm>
DOI: <https://dx.doi.org/10.3748/wjg.v26.i22.2948>

INTRODUCTION

Development of methods and tools to stimulate regeneration of damaged tissues and organs has always been a prominent theme in medical science. However, only recently, in connection with the unprecedented development of biotech, regenerative medicine has acquired independent significance. Our ideas about reparative regeneration (restoration of the structure and function of tissues and organs damaged by pathology or trauma) are constantly expanding and replenishing the existing clinical strategies.

The pancreas historically became one of the first objects of regenerative medicine, apparently in connection with notable inconsistency of other approaches in relation to this organ. The first transplantation of pancreatic material to a patient took place at the University of Minnesota in 1966. Since then, > 50000 diabetic patients received the transplants in > 200 of medical centers; the global lead is held by the United States^[1]. Despite the continuous technological upgrade, cadaveric donations are obviously a “dead end”. The general shortage of donor organs, as well as the complexity and high costs of the procedure, will never meet the demand for such operations.

The pancreas consists of exocrine and endocrine portions. The exocrine function of the organ is to produce and excrete digestive enzymes in the form of inactive precursors into the duodenum, thus ensuring the luminal digestion of basic nutrients (proteins, fats and carbohydrates). The exocrine pancreatic deficiencies (up to complete dysfunction) can be effectively treated with advanced enzyme formulations to provide acceptable life quality for the patients^[2]. Extremely serious problems arise with the endocrine failure caused by abnormal functioning of the hormone-producing cells of the Langerhans islets. Each islet comprises at least five types of endocrine cells, including insulin-producing β -cells (65%-80%), glucagon-producing α -cells (15%-20%), somatostatin-producing δ -cells (3%-10%), pancreatic polypeptide-producing PP-cells (1%) and ghrelin-producing ϵ -cells^[3]. Some of the related hormonal deficiencies can be partially counteracted by enhanced function of the amine-precursor-uptake-and-decarboxylation endocrine cells distributed in the lamina propria mucosae of the gut. The amine-precursor-uptake-and-decarboxylation cells are capable of producing all pancreatic hormones except insulin^[4]. Insufficient production of insulin by pancreatic β -cells, which cannot be relieved endogenously, results in the development of the insulin-dependent diabetes mellitus (DM). At the same time, it is obvious that not only insulin but the entire hormonal complex released by sum total of the functionally united Langerhans islet cell types are involved in regulation of the nutrient and glucose homeostasis^[5]. Nevertheless, it is functional assessment of β -cells (by evaluation of the insulin and C-peptide levels) that serves an integral diagnostic indicator of DM development. The insulin-dependent DM commonly develops without any surgical, infectious or traumatic damage to the pancreas, but as a hereditary autoimmune damage to the islet cells (DM type 1). However, many insulin-independent forms of diabetes (DM type 2)

proceed with progressive depletion of β -cells, which in some cases leads to insulin dependence. In the new-onset DM type 2, β -cell population of the pancreas has been estimated to decrease by 24%-65%, whereas in DM type 1 it is decreased by over 80% (Table 1)^[6]. A number of studies indicate that hormonal dysfunctions are typical for both types of diabetes and are not limited to insulin deficiency^[7].

According to the International Diabetes Federation^[8], about 425 million adults (20- to 79-year-olds) globally were living with diabetes in 2017; by 2045 the number will increase to 629 million. This dramatic prognosis is predominantly associated with DM type 2, which partly belittles the problem of insulin-dependent diabetes. Meanwhile, the delayed diagnosis and poor control of glucose levels in DM type 1 cause severe complications including nephro-, retino- and neuropathies, cardiac and vascular diseases. Administration of short- and long-acting exogenous insulins, smart selection of administration regimens, and even the use of insulin pumps are insufficient for the proper control of glucose levels in some patients; effective means for stimulating regeneration of the pancreas are therefore extremely relevant.

DEVELOPMENT OF THE PANCREAS

Mature pancreas is comprised of acinar cells, connected to the intestine *via* the highly branched ductal tree; the islets, which constitute about 1%-2% of the organ mass, are scattered throughout its central regions. Both portions of the pancreas (exocrine and endocrine) arise as thickenings (buds) at the dorsal and ventral surfaces of the posterior foregut, in the close vicinity of prospective hepatic endoderm. Specification of the hepatic and pancreatic domains in the endodermal epithelium proceeds under the influence of inducing stimuli from the adjacent mesoderm: Extensive suppression of the mesodermal Wnt and Fgf4 signaling in the foregut allows the hepatic and pancreatic induction. The newly defined pancreatic endoderm specifically expresses transcription factor-encoding genes *px1* and *ptf1a*; the *px1⁺ptf1a⁺* cells are progenitors of all parenchymal cell types in the mature pancreas, including the duct, islet and acinar cells. The proper balance of endocrine and exocrine cells, descending from pancreatic progenitor cells within the pancreatic buds, is dependent on Notch signaling. The arrest of Notch signaling disinhibits *ngn3*, a transcription factor-encoding gene, master regulator of the endocrine-type development in the pancreatic endoderm. The *ngn3⁺* endocrine precursors rapidly develop a specific expression signature of transcription factor-encoding genes, including *neuroD*, *ia1*, *isl1* and *pax6*, and differentiate into the five cell types of the islets (α , β , δ , ϵ and PP cells)^[9-11].

After birth, the total volume of the islets of Langerhans increases 20-fold. The islets are capable of compensatory growth in response to physiological demands (*e.g.*, in pregnancy, obesity or after partial pancreatectomy)^[11]. The decreased demand for exogenous insulin, observed during the period of partial clinical remission in DM patients, is explained by partial functional recovery of β -cells^[12,13]. These observations indicate the considerable physiological regeneration capacity of the endocrine pancreas and suggest the principal feasibility of its substantive repair. In medical literature, the term "islets" most frequently refers to β -cells as the major subpopulation of the islets that prevails in number and clinical significance; "regeneration of the islets", therefore, specifically means "the insulin-producing cell recovery" (unless otherwise stated) and designates the most clinically desirable process in the endocrine portion of the pancreas.

Physiological regeneration of the islets by means of proliferation of the pre-existing β -cells occurs in response to certain factors, *e.g.*, insulin-like growth factor-1 (IGF1), hepatocyte growth factor (HGF), incretins and prolactin^[5,14,15]. In the perinatal period, β -cells actively proliferate; a multiple increase in the mass of β -cells after birth occurs due to an increase in their number inside the islets, rather than an increase in the number of islets^[16]. In humans, similarly with rodents, proliferative activity of β -cells in pancreatic islets declines with age. The most rapid reduction occurs in juveniles; by the age of 6 mo, the proportion of dividing β -cells drops from 3% in fetuses to less than 0.5% and continues to decrease thereafter^[17]. As has been demonstrated in animal models, the residual proliferative activity of β -cells is insufficient to compensate for massive losses in adulthood. For instance, by 4 wk after 90% partial pancreatectomy in adult rats (leaving a 10% remnant pancreas), the weight of the pancreatic remnant reaches only 27% of the initial weight of the organ^[18]. The proliferative activity of β -cells is controlled epigenetically; in particular, it depends on histone modifications regulated by trithorax group (TrxG) and polycomb group (PcG) complexes. TrxG and PcG proteins are the evolutionarily conserved transcription factors that act as heteromeric complexes and modulate gene expression by modifying the structure of chromatin. TrxG and PcG complexes repress a set of cell cycle-inhibiting genes in β -

Table 1 Comparison of type 1, type 2 and surgically induced diabetes mellitus

	Type 1 DM	Type 2 DM	Type 3 DM
Pathogenesis	Chronic autoimmune disorder; the immune system attacks endogenous pancreatic β -cells	Progressive metabolic disorder characterized by insulin resistance	Chronic disorder induced by partial or total pancreatectomy
Prevalence	5% to 10% of diagnosed diabetics	90% to 95% percent of diagnosed diabetics	1% of diagnosed diabetics
Onset	Abrupt	Gradual	Shortly after surgery
Age of onset	Varies (commonly in childhood or puberty)	Commonly over 35 yr	Commonly over 50 yr
Genetic predisposition	Moderate	Very strong	Moderate
Body habitus	Thin or normal	Often obese	Normal, overweight or obese
Ketoacidosis	Common	Rare	Rare
β -cell depletion	Severe (over 80%)	Mild (24% to 65%)	Mild to total (up to 100%)
Plasma insulin	Low to absent	Normal or increased	Low to absent

DM: Diabetes mellitus.

cells, thereby facilitating physiological and adaptive β -cell expansion^[19,20].

MODELING THE ENDOCRINE PANCREAS REGENERATION

Several experimental models for studying the endocrine pancreas regeneration are available. The first of them, wirsung duct ligation, was introduced as early as in 1920 by F. Banting as a possible treatment for DM. The procedure, indeed, led to an increase in the mass and number of the islets^[21,22]; it used to be applied widely for DM treatment in children, but provided only short-term results^[23]. Nowadays, the pancreatic duct ligation model is still employed in animal studies; it is considered an acceptable representation of the adult pancreatic tissue remodeling. The pancreatic duct ligation predominantly affects the tail region of the pancreas, resulting in acute pancreatitis followed by regeneration of ductal complexes from the surviving metaplastic acinar cells^[24].

Two other surgical models, cellophane wrapping and partial pancreatectomy, similarly result in the partial obstruction of the pancreatic products drainage. In the partial pancreatectomy, the extent of tissue removal is variable; in rodents, 60%–70% pancreatic resections are non-diabetogenic, while 90% resections are diabetogenic. Both types of intervention induce a transient wave of β -cell proliferation^[24]; however, the usability of these approaches is limited, as they are critically non-selective and exert major influence on the exocrine portion of the pancreas.

Experimental models of selective ablation of β -cells with cytotoxic agents have emerged later on. Streptozotocin, originally developed as antimicrobial, is one of the most harsh diabetogenic drugs; it is notably toxic to β -cells and used routinely for the induction of DM in animals. Depending on the animal strain, dose and route of delivery, streptozotocin causes severe or mild diabetes (blood glucose levels above 200/300 mg/dL and 120–200/300 mg/dL, respectively)^[3]. Alloxan, a pyrimidine derivative, is comparable to streptozotocin in its ability to induce diabetes in pregnant animals; the mechanism involves formation of reactive oxygen species in cytosol, which leads to β -cell necrosis and consequent failure of the normal glucose homeostasis; the effective dosage depends on the rodent species, term of pregnancy, age and diet^[25]. *In vitro* study on the isolated pancreatic islets of C57BL/6 mice revealed differential influence of streptozotocin and alloxan on the transport and metabolism of glucose in β -cells: Glucose transporter 2 protein is the main target of streptozotocin, whereas alloxan targets glucose transporter 2 and glucokinase mRNA molecules^[26].

In addition to surgical and pharmacological interventions, dysfunction or ablation of β -cells can be achieved by genetic manipulations. In this case, main strategies are switching of particular gene(s) or selective genetic labeling of β -cells. The first strategy implies creation of genetically engineered mice, in which the studied gene (*e.g.*, *Ins1*) is knocked out, *e.g.*, with the use of tetracycline- or doxycycline-dependent system or Cre-Lox recombinase technology^[24,27–29]. The second strategy implies creation of transgenic mice with specific expression of cognate receptors for toxins in β -cells. For example, in mice, transgenic expression of the diphtheria toxin receptor followed by

systemic administration of diphtheria toxin permits an exquisite, specific β -cell ablation by apoptosis^[30]. The third strategy is the inducible ablation of pancreatic β -cells by conditional targeted activation of genes. For example, regulated expression and activation of *c-myc* in transgenic mice after administration of synthetic reagent tamoxifen promotes controlled temporal loss of β -cells without the general cellular toxicity caused by chemicals such as alloxan or streptozotocin^[31]. In another transgenic model, the pancreatic islet β -cell apoptosis through targeted activation of caspase 8) mouse, β -cell death is induced in a specific and well-defined manner through the treatment with a commercially available dimerizer^[32].

THE SOURCES OF ISLET REGENERATION

Thus, intrinsic potential of the pancreas for the replication of β -cells is limited. Studies of pancreatic regeneration in experimental models indicate low proliferative capacity of the functionally mature β -cells. An alternative regeneration pathway, neogenesis of islets, apparently involves non-endocrine components of the pancreas (acinar and ductal cells, vascular and neuronal structures) in complex microenvironments, which surround and penetrate the islets^[24]. The islet neogenesis, aimed at the in situ expansion of the insulin-producing cells, may proceed by two main routes—mobilization of putative precursors present in the adult pancreas (direct differentiation) and reprogramming of other mature cell types into insulin-producing cells (trans-differentiation)^[17,33].

Pancreatic stem cells apparently reside in the ductal epithelium and provide the renewal of both exocrine and endocrine parts of the organ^[34,35]. The phenotype of multipotent pancreatic progenitor cells (MPCs) is defined as *pdx1+ptfla+sox9+foxa2+nkx6.1+hnf6+*; these cells form a highly proliferative pool which differentiates into distinct cell types including exocrine, ductal and islet cells^[36,37]. The total mass of the adult pancreas is thought to correspond to proliferative capacity of the embryonic MPC pool^[38]; however, any traceable presence of embryonic MPCs in the adult mammalian pancreas is highly doubtful^[39].

In adult mammals, the trans-differentiation scenario is more plausible. Interestingly, the chief candidate cell source resides in the islets themselves, as β -cells share developmental characteristics and implement similar gene expression programs with the neighboring α -cells. Knockout of *pax4* in mice leads to the loss of β -cells and concomitant increase in the number of α -cells^[17]. Subtotal ablation of β -cells may trigger reprogramming in α -cells; for instance, under the selective induction of β -cell apoptosis with diphtheria anatoxin, α -cells start to produce insulin and co-express the adult β -cell markers *pdx1* and *nkx6.1*^[30]. Similar results were obtained in the RIP-B7.1 transgenic mouse model of autoimmune diabetes; the observed increases in the size of α -cells and the levels of α -cell proliferation and ductal neogenesis were accompanied by an increase in the content of the glucagon-producing cells positive for insulin or β -cell-specific transcription factor *pdx1*^[40]. As indicated by ChIP sequencing and RNA sequencing analysis of differentiated α -cells, thousands of genes are bivalently marked with activating and repressing histone modifications (respectively, H3K4me3 and H3K27me3) in α -cells, while exhibiting the monovalent state in β cells (*i.e.* showing the signs of either activation or repression). These epigenomic findings suggest that the α -to- β cell reprogramming may result from alterations in the histone methylation signature of the islet cells^[41]. It has been suggested that in mature individuals, from puberty to old age, α -cells can be reprogrammed to produce insulin, even after the complete loss of β -cells, whereas before puberty, β -cells are replenished by spontaneous *en masse* reprogramming of the somatostatin-producing δ -cells while the α -cell conversion is negligible^[42].

Trans-differentiation of the non-islet cell types into functional β -cells is also possible. In certain settings, exocrine cells of the pancreas spontaneously (in the absence of specific inductive stimuli) differentiate towards β -cell phenotype, although it is hard to exclude replication or fusion of β -cells *per se* in this case^[11].

Participation of other, non-endodermal, stem cell niches in regeneration of the pancreas is another disputable issue. According to modern concepts, multipotent stromal/stem cells (MSCs) are mobilized from the red bone marrow (and probably from other stromal sources) in response to organ damage, migrate to the damaged area and contribute to its regeneration^[43,44]. The vast majority of the studies on participation of MSCs in regeneration of the pancreatic islets have been using donor MSCs. For instance, in mice, upon transplantation of bone marrow cells from male donors into lethally irradiated female recipients, a small percentage of donor cells that expressed insulin and *pdx1* was found among the Langerhans islet cells; notably, the design of the experiment excluded the possibility of fusion of the donor bone marrow

cells with β -cells of the host^[45]. However, other studies failed to reproduce this phenomenon in models of pancreatic damage: The transplanted labeled cells either were not detected in the pancreas at all, or only solitary labeled cells expressed insulin, while most of the cells participated in angiogenesis and restoration of the pancreatic stroma^[46-48]. In the experiments with transplantation of the GFP-labeled bone marrow-derived MSCs to newborn mice, solitary cells that co-expressed GFP and insulin were found within the islets, whereas up to 40% of the ducts (median 4.6%) contained the epithelial cells derived from the transplanted bone marrow MSCs of the donor. The authors conclude that a lineage of stem cells (or epithelial precursors) can migrate from bone marrow to the pancreas and differentiate into complex organ-specific structures, at least in neonatal period^[49].

Thus, the hypothetical sources of β -cells during physiological or reparative regeneration of the endocrine pancreas include mitotic expansion of mature functional β -cells, direct differentiation of the multipotent pancreatic progenitors (or developmentally related progenitor cells of the intestine and the liver) and trans-differentiation of mature cell types inside the islets (α -cells) or outside of them (in the exocrine pancreas or elsewhere). Despite the diverse possibilities, reparative potential of the endocrine pancreas is extremely limited, and its damage still invariably leads to insulin deficiency.

THE METHODS FOR STIMULATING REPARATIVE REGENERATION OF THE PANCREAS

The main goal of any attempt to stimulate pancreatic repair is to restore the number of functionally active β -cells to ensure the maintenance of sufficient insulin production. This goal can be achieved in two ways: The reduction in the death rates of β -cells or the production of new β -cells. The methods of regenerative medicine relevant to these tasks can be listed as follows: (1) The use of biologically active substances, especially peptide or protein growth and differentiation factors, that regulate cell cycle, apoptosis, inflammation and repair; (2) Transplantation of donor β -cells or progenitor cells to replace the damaged islets; (3) Transplantation of the tissue-engineered bioartificial pancreatic constructs; and (4) Reprogramming of cells into insulin-producing phenotypes (in situ or prior to transplantation).

APPLICATION OF BIOLOGICALLY ACTIVE SUBSTANCES FOR THE REGULATION OF CELL CYCLE IN β -CELLS

Many experimental studies have been aimed at the regulation of β -cell growth and regeneration^[14,50]. It is well known that IGF1, HGF, growth hormone, prolactin, incretin hormones [glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1)], insulin, and even certain metabolites including glucose, are mitogens for β -cells^[5,15]. Complex effects of biologically active molecules on β -cells include stimulation of cell growth and protection against apoptotic death. For instance, IGF1 protects β -cells against the cytokine-induced apoptosis^[51]. The incretin hormone GLP-1 exerts similar action by amplifying the efficiency of the autocrine loop of IGF-2/IGF-1 receptor^[52] and regulating cholecystokinin production in β -cells in a paracrine manner^[53].

The Reg (“regenerating”) protein family was reported independently by research groups studying pancreatitis and pancreatic islet regeneration. The family includes several small protein molecules named “pancreatic stone protein”, “pancreatic thread protein”, “islet neogenesis-associated protein” and C-type lectin-like protein, which exhibit anti-inflammatory, anti-apoptotic and mitogen properties^[54]. The action of Reg proteins (as acute phase reactants, lectins, antiapoptotic factors, growth factors) has wider specificity than has been supposed initially, as their targets include not only β -cells, but also neural and epithelial cells in the intestine^[55]. The islet neogenesis-associated protein peptide molecule successfully stimulated recovery of β -cell mass in animal models and showed some promising results in clinical trials^[56].

The list of chemicals that stimulate β -cell proliferation and reduce β -cell apoptosis, thus protecting the insulin-producing cell reserve, includes small molecules (glucokinase activators, inducers of calcium and adenosine signaling, diarylamide WS6), growth factors and hormones [platelet-derived growth factor, insulin-like growth factors, epidermal growth factor (EGF), HGF, parathyroid hormone-related protein, insulin, placental lactogen, estrogen, incretins, betatrophin, triiodothyronine] and phytochemicals (resveratrol, phenylpropenoic acid glucoside, flavonoids,

glutathione peroxidase mimetics)^[57] and is likely to be expanded further. Applied significance of these studies is in utilization of modern synthetic approaches for the production of regulatory molecules that stimulate proliferation of β -cells. A number of pharmaceuticals that exert their action by stimulating β -cell mitosis have already been developed. These include incretin mimetics exenatide [the Food and Drug Administration (FDA) approved 2005], liraglutide, semaglutide and other GLP-1 receptor agonists, incretin enhancers sitagliptin (FDA approved 2006), vildagliptin, saxagliptin and other selective inhibitors of dipeptidyl peptidase-4 (DPP-4, the enzyme responsible for the rapid degradation of the incretin hormones GLP-1 and GIP)^[58,59]. These drugs are considered suitable for the treatment of DM type 2, because the level of functional preservation of β -cells in DM type 2 is much higher than in DM type 1^[60,61]. According to patient-reported outcomes from eight clinical trials, the DM type 2 patients are more satisfied with the modern incretin-based therapies in comparison with the traditional therapies due to the higher glucose-lowering efficacy of the former and also their ability to facilitate weight loss^[62]. The drugs of this group were initially used with caution due to their suspected side effects on the exocrine pancreas associated with the risks of adenocarcinoma development^[63]. However, clinical data accumulated over the years of its use indicate that the incretin-based therapy is not associated with increased risks of pancreatic cancer^[64,65], pancreatitis^[66,67] or all-cause mortality^[68] in DM type 2 patients.

The effectiveness of other classes of biologically active substances requires verification. Clinical trials of phytochemicals, *e.g.*, green tea, herbal tisanes rooibos and honeybush and their polyphenols, resveratrol (phytoalexin from *Vitis vinifera*), yielded contraverted results, which prevents considering these substances as effective stimulators of islet regeneration^[69-71]. Another example is glucokinase activators (GKAs). In animal models, GKAs promote insulin release from β -cells and stimulate β -cell proliferation. However, the results of recent phase II trials indicate that GKA efficacy drops within few months of use for as yet unclear reasons^[72].

It should be noted that a considerable reduction of DM symptoms observed upon transplantation of MSCs (one of the most widespread therapeutic tools of regenerative medicine) cannot be attributed to the alleged capacity of MSCs to trans-differentiate into β -cells^[73,74]. The data from preclinical experimental studies and clinical trials indicate that MSCs promote β -cell regeneration by protecting the endogenous β -cells from apoptosis, as well as attenuating the autoimmune processes that destroy β -cells. In addition, the transplanted MSCs ameliorate the insulin resistance of peripheral tissues by providing supportive niche microenvironments *via* the paracrine factors secretion and the extracellular matrix deposition^[75,76]. In this aspect, MSCs may be considered as short-lived "mobile factories", or "pharmacies", which, during their survival in the recipient's body, manage to synthesize a wholesome pool of biologically active substances that stimulate regeneration. The recent studies indicate that the anti-diabetic effect of transplantation of the MSC-derived exosomes is similar to the effects of MSC transplantation^[77,78].

ALLOGENEIC ISLET TRANSPLANTATION

The idea of pancreatic islets transplantation has a long history; the first experimental study in rodents was published in 1970s. The first experimental reversal of diabetes by a pancreas transplant in rats was achieved in 1972. Delivery of the transplant by infusion to the liver *via* portal vein was found more effective than intraperitoneal infusion; to date, the site still remains a primary choice for the clinical islet infusion^[79]. In 1979, allogeneic pancreatic fragments were successfully transplanted for the first time, in conjunction with a kidney transplant in a patient with DM type 1^[80].

In 1980–1990s, the priorities of most experts were in favor of pancreatic transplants from cadaveric donors, because the ways of isolation of the endocrine portion from the bulk of pancreatic tissue were not effective enough and the amount of donor tissue was critical. A total of 267 allogeneic pancreas transplants accomplished in 1990–1999 had very moderate success: Only 12.4% of the patients had a remission without insulin therapy lasting longer than a wk, and only in 8.2% of the patients the effect lasted for more than a year^[81]. This apparently negative result is explained by ineffective techniques of islet isolation in combination with aggressive and inadequate immunosuppression regimens.

In 2000, a principal breakthrough in the field of allogeneic transplantation of the islets was done by Shapiro *et al*^[82] at the University of Alberta (Edmonton, Canada). The surgeons succeeded in developing a protocol surpassing all the previous attempts in its effectiveness. The protocol was tested in seven DM type 1 patients with critically reduced responses to exogenous insulin. The brain-dead donors were selected by

multifactorial analysis of the donor choice for the optimal pancreatic islets isolation, the criteria for which were developed back in 1996 by Lackey *et al*^[83]. The donor pancreas was perfused *via* the excretory ducts with a cold mixture of enzymes, after which the islets of Langerhans were isolated by passing the tissue through ficoll-diatrizoic acid gradients as described elsewhere^[84], with the difference that 25% human albumin was used instead of the xenogeneic serum. Over 4000 islet-equivalents per kg of body weight of a recipient were infused *via* the portal vein; the required quantity of transplant was normally obtained from 2-3 donors. The resulting therapeutic effects exceeded all previous achievements; the positive indicators included the increased C-peptide levels, improved glucose tolerance, decreased glycosylated hemoglobin levels and cessation of the acute hypoglycemia episodes. In 2006, the team published the outcome of a clinical trial (FDA NCT00014911) with participation of 36 DM type 1 patients. In particular, in 21 patients (58%), independence from exogenous insulin lasted for a year; of this number, 16 patients maintained this effect through the second year, and 5 of the patients maintained it for more than 2 years^[85].

In opinion of the authors of the protocol, the success was largely due to the correct immunosuppression scheme, which included sirolimus, low-dose tacrolimus and the anti-interleukin-2 receptor monoclonal antibody under the complete exclusion of glucocorticoids. The authors also concluded that, to ensure getting off exogenous insulin, the minimum amount of islet-equivalents per kg of body weight should be 10000. The developed protocol, known as “the Edmonton protocol”, became the gold standard for allogeneic transplantation of the pancreatic islets. As of 12/2019, FDA has registered about a hundred clinical trials using the Edmonton protocol or its modifications (mainly in the United States and Canada).

The achievements contributed to the spread of the pancreas transplants technology with the establishment of specialized medical centers worldwide. Back in 2001, the National Institute of Diabetes and Digestive and Kidney Diseases created the Collaborative Islet Transplant Registry (CITR) which collects and summarizes information on this technology^[86].

According to CITR, during the period from 1999 to 2015, 1086 diabetic patients underwent the donor islet transplantation, with 81% of the patients receiving the islet transplant alone (ITA) and 19% of the patients receiving the islet-after-kidney, simultaneous-islet-kidney or kidney-after-islet transplants. The largest number of operations occurred between 2002 and 2005^[87]; the activity reflected the enthusiasm raised by implementation of the Edmonton protocol and the prolonged (up to 3 years) islet transplantation effect.

The islet isolation and transplantation procedures in different settings were similar, but the immunosuppression scheme evolved significantly, which explains the observed increase in the transplantation efficiency. The Edmonton protocol was considered the gold standard until the middle of 2000s, when the anti-interleukin-2 receptor-specific antibodies-based immunosuppression was replaced with a scheme involving the induction with T-cell depletion and/or TNF-alpha inhibitor and maintenance with mTOR and calcineurin inhibitors. Immunosuppression regimens of this type have minimal diabetogenic side effects and low toxicity against the transplanted islet cells. In 2008, the Edmonton protocol was succeeded by clinical islet transplantation (CIT)-protocol developed by the CIT consortium^[88]. Based on the Edmonton protocol, CIT-protocol accumulates modifications and technical tips directed primarily towards the increase in survival and secretory activity of the transplanted allogeneic β -cells. Recent amendments to CIT-protocol (besides minor corrections to the immunosuppression scheme) were as follows: The islets for a transplant were obtained from a single donor; the islets were cultured for 36–72 h prior to transplantation to get rid of the dead and non-viable cells in order to attenuate the inflammatory response to the procedure; large doses of heparin were added to the transplant, and additionally pentoxifylline and anticoagulants were administered for one wk after the procedure, in order to decrease the risks of portal vein thrombosis and to enhance the graft vascularization; the intense insulin therapy was carried on for two mo after the procedure^[89].

The effectiveness of allogeneic islet transplantation is continuously increasing. In 2017, according to CITR, the proportions of patients who maintained insulin independence for 1 year and 5 years after ITA were, respectively, 76.9% and 47.0%. A recent comparison of the outcomes of ITA and solitary pancreas transplantation alone for DM type 1 shows similar safety, graft function and cost indicators for these procedures^[90]. Thus, allogeneic transplantation of the pancreatic islets holds its position as a safe and effective way to treat insulin-dependent DM, especially in cases when administration of exogenous insulin is useless and transplantation of the whole pancreas is inadvisable due to the severity of the patient’s condition.

Moreover, the use of donor islets for the replacement therapy in DM has certain

potential for further development. The efficiency of β -cell isolation, cultivation and survival is subject to upgrades, *e.g.*, by promoting the interactions of β -cells with MSCs. Co-culturing with MSCs is likely to protect the islets from injury in cell culture prior to infusion^[91]. Multiple experimental studies show that co-transplantation of MSCs with the islets improves the graft survival and the overall outcome; apparently, the MSC secretome enhances survival of the donor islet cell against immune response, hypoxia, oxidative stress and the host niche inconsistency^[75,92,93].

A number of currently registered clinical trials employ new strategies aimed at increasing the efficacy of allogeneic transplantation for the restoration of the islets of Langerhans in the following aspects: (1) Modification of the immunosuppression scheme by various formulations including Infliximab (chimeric monoclonal antibody to TNF alpha; NCT00021788), Reparixin (non-competitive allosteric inhibitor of CXCL8; NCT01220856, NCT01817959), Basiliximab (chimeric mouse-human monoclonal antibody to CD25 which acts as alpha subunit of the IL-2 receptor on the surface of T cells; NCT01049633), immunosuppressant chemical Deoxyspergualin (NCT00434850), *ex vivo* selected and *ex vivo* expanded autologous regulatory T cells (NCT03444064); (2) The search for alternative transplant site(s) instead of the intraportal infusion prescribed by the Edmonton protocol, for instance, transplantation of the islets into the gastric submucosa (NCT02402439, NCT01571817), the omentum (NCT02213003, NCT02821026), the bone marrow (NCT01722682, NCT01345227), the arm muscles (NCT01967186), the anterior chamber of a severely impaired diabetic eye (NCT02916680); (3) Visual monitoring of the β -cell engraftment by introducing radiolabeled tracer (NCT03785236) or MRI contrast agent (NCT00453817, NCT01050166); and (4) Increasing the transplant survival by co-transplantation of the islets with other cells, *e.g.*, allogeneic CD34+ bone marrow cells (NCT00315614, NCT00021801), autologous MSCs (NC 00646724, NCT02384018), allogeneic parathyroid glands (NCT 03977662).

AUTOLOGOUS ISLET TRANSPLANTATION

Autologous transplantations of the islets are only used for chronic pancreatitis of various etiologies, specifically in the cases of total pancreatectomy and the concomitant surgically induced DM (Table 1). The first transplantation of autologous islets after pancreatectomy was implemented back in 1979^[94]. Since 1995, an increasing number of centers have reported total pancreatectomy with islet autotransplantation. The procedure involves isolation of the patient's own islets and their infusion to the liver *via* the portal vein; the material effectively engrafts within hepatic parenchyma without the need for immunosuppression, which is one of the huge advantages of autologous transplantation^[95].

The yields of viable islets from the resected pancreases are poor because of the advanced damage to the pancreatic parenchyma caused by chronic inflammation and fibrosis^[95]. However, the efficiency of transplantation for autologous cells is significantly higher than for allogeneic. In a large clinical trial, which included 173 pancreatectomized participants with autologous transplants and 262 DM patients with allogeneic transplants, 85% of the recipients with autologous transplants were maintained without exogenous insulin for two years after surgery, as compared with only 66% of the recipients with allogeneic transplants, whereas five-year therapeutic effects were achieved in 69% and 47% of the patients, respectively^[96]. The protocol for isolation of the islets for autologous transplantations^[97] and the method of their infusion *via* the portal system^[98] are principally the same as for allogeneic transplantations. However, autologous transplantations of the islets are less common because of the difficulty or sheer impossibility of isolating the required amount of the robust islet material from the patient's tissues.

TISSUE ENGINEERING OF THE PANCREAS

The idea of tissue-engineered (bioartificial) pancreas arose as one of the possible strategies for enhancing the allogeneic β -cell grafting. Major challenges associated with bioartificial pancreas transplantations are the efficient delivery of β -cells and the efficient promotion of conditions for the long (preferably lifetime) functioning of the transplanted β -cells without the use of massive immunosuppression. The ultimate goal is creation of an artificial immune-privileged site effectively separated from the host immune system^[99].

The technical requirements for bioartificial pancreas are exacting and very hard to solve. The critical issues are: (1) Avoiding the foreign-body response; (2) Enabling

oxygen permeability of the device; (3) Assembling the device without damaging the islets; and (4) Positioning the device in close proximity to microcirculatory blood vessels to ensure the delivery of oxygen and nutrients to the islets and the delivery of secreted insulin to the rest of the body^[99,100]. Development of new protocols for the production of microencapsulated (“individually wrapped”) or macroencapsulated (“packaged”) islets with the use of advanced biological and synthetic materials (alginate, poly-L-lysine, poly-L-ornithine, chitosan-polyvinylpyrrolidone), which would provide survival of cells within the construct while contributing to its immunoisolation properties^[101].

The first transplantation of the alginate-encapsulated neonatal porcine islets dates back to 1996. The transplant was infused intraperitoneally to a 41-year-old DM type 1 Caucasian male patient at a dose of 15000 islet-equivalents per kg of body weight. The detectable and distinctly glucose-responsive blood levels of porcine insulin and C-peptide were observed for 11 mo after the procedure. However, the overall effect was rather weak, especially against the success of the Edmonton protocol; the patient failed to get off the exogenous insulin^[102]. Nevertheless, the research in this direction was continued. An Open-label Investigation of the Safety and Efficacy of DIABECCELL in Patients With Type 1 Diabetes Mellitus (NCT01736228, Phase 2) started in 2012; DIABECCELL stands for the alginate-encapsulated porcine islets for xenotransplantation by Diatrans Otsuka Ltd. The study exposed multiple pitfalls of the alginate-encapsulated islets including immunogenic alginate impurities triggering the immune-mediated destruction, unfavorable surface properties of the transplant, the release of membrane-permeating antigens and the lack of proper standards for encapsulation, cell grafting and alginate composition modifications^[103].

A different type of bioartificial pancreas, the β Air device (Beta-O2 Technologies Ltd) comprises a composite membrane (includes two hydrophilized 25 μ m PTFE membranes comprising 0.45 μ m pores, with the highly viscous high-mannuronic-acid alginate impregnated into the pores). The membrane is impermeable to macromolecules (*e.g.*, antibodies and the complement) and prevents cell-cell contacts, while allowing the free passage of glucose, low molecular weight nutrients, glucagon and insulin^[101]. At the end of 2014, four patients were recruited to An Open Label, Pilot Investigation, to Assess the Safety and Efficacy of Transplantation of Macroencapsulated Human Islets Within the Bioartificial Pancreas Beta-Air in Patients With Type 1 Diabetes Mellitus (NCT02064309, Phase 1/2) with the results as yet unpublished.

Another clinical study, A Safety, Tolerability, and Efficacy Study of VC-01™ Combination Product in Subjects With Type I Diabetes Mellitus (NCT02239354, Phase 1/2), started in 2014. By contrast with related products, VC-01™ (also known as PEC-Encap™, ViaCyte Inc.) is based on PEC-01 cells, a proprietary pancreatic endoderm cell product derived through directed differentiation of an inexhaustible human embryonic stem cell line, delivered in the immune-protecting and retrievable encapsulation medical device. Cohort 1 of the study, designed to test sub-therapeutic doses of PEC-01 cells, enrolled 19 patients with the established but stable DM type 1. The patients were implanted subcutaneously with two different PEC-Encap unit sizes: The larger VC-01-250 units were used primarily to evaluate the safety and tolerability, and eventually the efficacy, while the smaller VC-01-20 units were used as “sentinels” removed for analysis (histology, *etc.*) at different time-points; the efficacy will be evaluated in Cohort 2.

A Safety, Tolerability and Efficacy Study of Sernova's Cell Pouch™ (Sernova Corp) for Clinical Islet Transplantation (NCT03513939, Phase 1/2) has been launched quite recently. The Cell Pouch™ device has been designed as a scaffold made of non-degradable polymers, molded into small cylindrical parts. Placed subcutaneously, the device is overgrown by connective tissue and microvessels to form the living tissue chambers around the removable non-degradable plugs. The process takes about 2 wk; the plugs are eventually removed, leaving the fully formed empty tissue chambers for the transplant. The Cell Pouch™ forms a natural environment rich in microvessels, which provides the islets with core microcirculatory bed thus facilitating the engraftment.

Conceptually, bioartificial pancreases are superior to the conventional suspension transplants of insulin-releasing cells in a number of ways and certainly have the potential. For instance, they enable protection of the islet grafts under minimized immunosuppression and provide a choice of the implantation site. Besides, the retrievable encapsulated devices allow straightaway removal of the transplant in cases when transplanted cells (*e.g.*, the iPSC/ESC-derived β -like cells) proceed to uncontrolled proliferation and tumorigenesis.

The mentioned clinical trials are aimed at preventing glucose variability and hypo/hyper glycemia as assessed by using a continuous glucose monitoring system. In 2018, FDA approved the first implantable continuous glucose monitoring device

(the Eversense Continuous Glucose Monitoring (CGM) System, Senseonics) for adults (18 years and older) with type 1 and type 2 DM. It is the first fully implantable device that can be used for 90 d without changing the sensor. The Eversense CGM System uses a fluorescent chemical that produces a flash of light when exposed to blood sugar. The light intensity is measured, and every 5 min the measurements are sent *via* Bluetooth to a mobile app that displays readings while identifying trends and alerts.

It should be noticed that the term “artificial pancreas” is sometimes used to refer to the implantable insulin pumps. Medtronic’s MiniMed 670G, a hybrid closed loop system, became the first implantable insulin pump approved by FDA in 2016 for the patients over 14 years old. The system includes a sensor attached to the body to measure glucose levels every 5 min, an insulin pump, and an infusion patch connected with the pump by a catheter that delivers insulin. The implantable insulin pumps still lack in perfection, as the patients need to calibrate the device by themselves, to reload it with insulin, to make manual adjustments for the physical activity, *etc.* Besides, under extreme conditions or with a slightest manufacturing defect, the device may deliver a critically inaccurate dose of insulin, the possibility totally excluded when using “artificial pancreas” with insulin-producing β -cells. Nevertheless, we hope that continuous upgrade of insulin pumps will significantly improve the life quality of DM patients in the future.

STEM/PROGENITOR CELL REPROGRAMMING

The transplantation of the islets of Langerhans has proven to be an effective interim solution for the treatment of insulin-dependent DM. Further improvements in this therapy face two major unresolved issues: The shortage of donor β -cells and the gradual rejection of allogeneic β -cells despite immunosuppression. Both problems can be possibly solved by using alternative cell sources, particularly the autologous stem/progenitor cells that can be effectively expanded and reprogrammed into insulin-producing phenotypes.

Three types of stem/progenitor cells can be effectively reprogrammed into functional β -cells: Adult/somatic stem cells, embryonic stem cells and the induced pluripotent cells. Two major strategies of stem cells reprogramming are the use of specific cell differentiation media and the use of genetic modification.

Adult stem cells are undifferentiated cells located at various sites in the adult body (hemopoietic organs, epithelial tissues, periosteum, perichondrium, *etc.*). The adult mammalian pancreas is believed to contain a small population of the pancreas-derived multipotent precursors (PMPs). PMPs were derived from human pancreas with an efficiency of about 2.6 generated spheres/10000 isolated cells; they distinctly expressed the neural and endocrine progenitor markers. After the Matrigel-induced differentiation, the PMP colonies contained 11.6% of the insulin+/*pdx1*+ β -like cells and 3.3 ng of insulin, whereas a human islet contains -55% β cells and 45.5 ng of insulin on the average^[104]. Another study suggests that β -cell metabolic stress and hyperglycemia enhance proliferation capacity of PMPs and bias differentiation of their progeny toward β -cells in mice and humans^[105]. The possibility of PMP expansion would have major implications for regenerative therapy; a weak spot in this concept is the very low cell turnover in the islets^[33].

Multipotent stromal cells (mesenchymal stem cells, MSCs) are often considered as the most promising type of adult stem cells for regenerative medicine. MSCs can be effectively obtained from bone marrow, adipose tissue, dental pulp, mobilized peripheral blood and birth tissues. According to the International Society for Cellular Therapy, MSCs must meet three criteria: Adherent growth on raw plastic in conventional culture flasks; surface expression of CD105, CD73 and CD90 and the lack of surface expression of CD45, CD34, CD14/CD11b, CD79 α /CD19 and human leukocyte antigen (HLA) class II by $\geq 95\%$ and $\leq 2\%$ of the cells, respectively; the ability to differentiate into osteoblasts, chondroblasts or adipocytes. In addition, under specific culture conditions, MSCs can differentiate into multiple mesenchymal derivatives (endothelial cells, fibroblasts, tenocytes, vascular smooth muscle cells, sarcomere muscular cells) and non-mesodermal lineages (hepatocytes, neurons, cardiac muscle cells, astrocytes, pancreatic cells)^[106,107].

The ability of bone marrow-derived MSCs to differentiate into β -cells in selective culture media was reported over 10 years ago^[108]. Convincing results on differentiation of β -cells from MSCs derived from other sources (umbilical cord, umbilical cord blood, placenta, adipose tissue, urine, dental pulp) were published later on. The possible formulations of inducers included EGF, betacellulin (a member of the EGF family), HGF, retinoic acid, GLP-1, exendin-4 (a long-acting GLP-1 receptor agonist), activin A (a member of transforming growth factor- β family),

nicotinamide, L-Taurin, β -mercaptoethanol, plant-derived alkaloid conophylline, high glucose concentrations, *etc.*^[108-112]. However, the use of differentiation media frequently resulted in non-homogeneous or unstable cell cultures^[113]. Despite the large number of available protocols, very few of them succeeded in producing glucose-responsive insulin-secreting cells from MSCs. Moreover, the multistage exposure to complex mixtures (cocktails) of inducers occasionally results in destabilized or mixed expression of pancreatic markers (*e.g.*, β and δ genes co-expressed in one cell)^[112].

The first experiments on differentiation of MSCs into insulin-producing cells by genetic modification were published around the same time. By using a retroviral vector, the cells were compelled to express the *pdx1*, which activated the expression of all four hormones of the islets; however, the cells lacked expression of Neurod1, a key transcription factor in differentiated β -cells. Transplantation of the cells to immunodeficient mice with experimental streptozotocin-induced DM resulted in further differentiation of the transplant to the point of the induction of Neurod1 and consequent reduction of hyperglycemia^[114]. Trans-differentiation of MSCs into insulin-producing cells can be triggered by induction of several genes, the key of which are *pdx1*, *neurog3*, *pax4* and *mafa*^[115]. The nucleic acid transfer-mediated switching of these major regulatory genes is a powerful albeit unsafe tool of reprogramming; the use of genetically modified MSCs is still limited to experimental studies^[116].

We have already mentioned that, according to the latest findings, the observed therapeutic effect of MSC transplantation in DM can hardly be considered a consequence of grafting of the *in vitro* pre-differentiated β -like cells; instead, it is almost entirely due to the production of various immunomodulatory and tissue repair molecules by transplanted MSCs. The term “medicinal signaling cells” has been proposed to reconcile the new concept of the “pharmacy for injured tissues” with the established knowledge about MSCs and their clinical classification^[117].

An alternative source of stem cells for the reprogramming are embryonic stem cells (ESCs) derived from the inner cell mass of the blastocyst. These cells are pluripotent, that is, capable of differentiation into any cell type. The first attempt of obtaining β -cells from ESCs dates back to 2001: The cells self-assembled to form three-dimensional clusters similar to normal pancreatic islets in topology and showing glucose-responsiveness (glucose triggered the release of insulin from these clusters)^[118]. ESCs can be readily differentiated into insulin-producing cells; the protocols are similar to the protocols used for MSCs^[119,120]. However, by contrast with MSCs which can be expanded from the recipient’s own material, the differentiated cells derived from ESCs are invariably allogeneic to recipients, and one of the critical problems facing the *in vivo* maturation of ESC-derived β -cells is their low survival in host environments. A possible route for obtaining autologous β -cells from ESCs is to use the “therapeutic cloning” strategy, which involves the transfer of the patient’s somatic cell nucleus to the donor ESC cytoplasm. The “therapeutic cloning” technologies have not been recognized primarily due to the ethical and religious restrictions; in most countries, research in this area is prohibited^[121]. The clinical use of ESCs is a long-term prospect also because the transplantation of ESCs and their derivatives, including those pre-differentiated into β -cells, carries a possible risk of teratomas and embryocarcinomas^[122].

In 2006, the prospective Nobel laureate Shinya Yamanaka published the procedure for reprogramming of somatic cells (exemplified by murine dermal fibroblasts) into pluripotent cells by transferring only four genes, *oct3/4*, *sox2*, *c-myc* and *klf4*. The reprogrammed cells, designated as induced pluripotent stem cells (iPSCs), exhibited morphological and growth properties of ESCs and expressed the ESC marker genes^[123]. The iPSCs can be differentiated into cells of all three germinal layers, *e.g.*, into β -cells^[124]. However, these studies are not yet out of the fundamental stage, and many problems continuously emerge, *e.g.*, the means for eventual substitution of the defective resident β -cells, standardization of the treatment protocol, quality control and safety issues. Nevertheless, a number of experts believe that eventual standardization of iPSCs will bring the autologous cell therapy of DM to the fore^[125].

MATURE SOMATIC CELL REPROGRAMMING

Mature somatic cells of the body are increasingly being considered as a source for β -cell population renewal: The insulin-producing cells have been successfully obtained from keratinocytes^[126], pancreatic exocrine cells^[127], hepatocytes^[128], gastrointestinal epithelium^[129], thyroid neuroendocrine cells^[130] and non- β -cells of the islets, particularly the glucagon-producing α -cells and the pancreatic polypeptide (PPY)-producing γ -cells^[131]. In the majority of cases, the reprogramming was accomplished

by viral delivery of coding sequences for transcription factors *pdx1*, *ngn3*, *mafA* or *hnf6*, less commonly – by using small molecules (5-aza-2'-deoxycytidine, trichostatin A, retinoic acid, insulin-transferrin-selenium, nicotinamide). The reprogrammed cells successfully produce and secrete insulin in glucose-responsive manner *in vitro* and successfully reverse diabetes by sustained production of insulin *in vivo*, upon transplantation in a streptozotocin-induced murine DM model.

More specifically, the viral delivery of *ngn3*, *pdx1* and *mafA* constructs to adult immunodeficient Rag1-/- mice allowed *in vivo* reprogramming of the differentiated pancreatic exocrine cells into insulin-secreting β -cells; replacement of *ngn3* with *neuroD* reduced the induction efficiency^[132]. Specific combination of transcription factors *ngn3*, *pdx1* and *mafA* is apparently essential for the β -cell development and maturation^[115]. Introducing adenoviral *pdx1*, *ngn3* and *mafA* constructs to AR42j-B13 rat exocrine pancreatic cells *in vitro* caused a dramatic alteration of the cell identity, manifested by inhibited expression of the exocrine markers and up-regulated expression of both insulin genes. The cells secreted insulin and were capable of relieving diabetes in streptozotocin-treated NOD-SCID mice. At the same time, the lack of glucose responsiveness indicated incompleteness of the reprogramming^[133], which might be due to the poorly defined culture conditions for the maintenance of β -cell function and identity *in vitro*^[17].

Hepatic cells reportedly acquire the capability of insulin synthesis upon transduction with *pdx1* alone^[134] or *pdx1* in combination with *neuroD*^[135] or *ngn3*^[136]. Some of the authors consider trans-differentiation of hepatic cells into β -cells possible (given that the pancreas, intestinal epithelium and the liver originate from a single source – the foregut endoderm), although comprehensive evidence is missing^[137]. On the other hand, the residual presence of extra-organ endodermal stem cells in peribiliary glands, hepato-pancreatic common duct, cystic duct, hilum is conceivable as well; these multipotent progenitors may participate in pancreatic and hepatic regeneration by differentiating into hepatocytes or pancreatic cells (exocrine or endocrine)^[138]. This view is supported by the fact that overexpression of *pdx1* (possibly in combination with *mafA* and *ngn3*) affords the insulin-secreting β -like cells not only from hepatic cells, but also from intestinal epithelia^[139,140].

The reprogramming efficiency may vary depending on the cell type. For instance, although all gastrointestinal insulin-positive cells can respond to high glucose, responsiveness of the antral insulin-positive cells is about 2-fold higher than that of duodenal and colonic insulin-positive cells^[129], while secretion of insulin by the γ -cell-derived pseudo-islets upon glucose stimulation is 4.5-fold stronger than that of the converted α -cells^[131].

However, some experts consider α -cells as optimal trans-differentiation targets for β -cell regeneration; the reasons are as follows: (1) α -cells are the closest to β -cells in origin; (2) The pancreatic islets are their native niche; (3) Sufficient numbers of α -cells are preserved in the islets in DM type 1 and 2, which makes their *in situ* reprogramming conceivable; (4) α -cells are apparently committed to β -cell differentiation, as under certain conditions they produce insulin and co-express the adult β -cell markers *pdx1* and *nkx6.1*; (5) The life-long capability of α -to- β conversion in mammals; and (6) Loss of even a significant portion of α -cells has no major physiological effect^[131,141]. As has been mentioned above, α -cells and β -cells descend from common *ngn3*+ endocrine precursors; their destiny as α -cells or β -cells is specified by activation of certain transcription factors. Thus, the α -to- β conversion may proceed *via* either up-regulation of β -cell-specific factors (*pdx1*, *mafA*, *nkx6.1* or *pax4*) or down-regulation of α -cell-specific factor (*arx*). Both of these options have been successfully implemented: Ectopic expression of *pdx1*, *mafA*, *nkx6.1* or *pax4* in α -cells induces β -cell features in fetal or adult α -cells^[115,131,142], whereas selective inhibition of the *arx* gene in α -cells promotes conversion of the adult α -cells into β -like cells through an intermediate bihormonal state^[143,144]. However, the sufficiency of the *arx* inactivation in α -cells for the direct α -to- β conversion is questionable^[145]. Epigenetic mechanisms (DNA methylation, histone modifications, non-coding RNA expression) have been reported to contribute to the control of islet cell development including differentiation and maturation of α - and β -cells^[41,146]; therefore, to increase the efficiency of reprogramming, it was proposed to modulate the *arx* axis in combination with epigenetic factors. Simultaneous inactivation of *arx* and *dnmt1* (DNA methyltransferase 1) in murine α -cells promoted efficient conversion of α -cells into β -like progeny; the functional hallmarks included characteristic gene expression signatures, electrophysiological responses and notably the glucose-dependent production and secretion of insulin^[145]. Although the reprogramming of mature somatic cells into β -cells is still in its infancy, the pioneering studies support the feasibility of the directed trans-differentiation for repair purposes.

CONCLUSION

According to ClinicalTrials.gov, a database of privately and publicly funded clinical studies, more than 10000 interventional studies of diabetes mellitus treatment have been registered since 2000, which indicates the complexity, global significance and enormous scale of the problem. The ultimate goal, which is to provide an acceptable level of functional activity of the insulin-secreting β -cells, is pursued by two prospective broad strategies of regenerative medicine: β -cell replacement and β -cell regeneration.

The “regeneration” strategy is aimed at either maintenance of a preserved population of β -cells (through in situ exposure to a wide range of biologically active substances that improve β -cell survival, replication and insulin secretion), or stimulation of the intrinsic adaptive mechanisms triggering the spontaneous non- β - to β -cell conversion. In our opinion, transplantations of undifferentiated stem/progenitor cells should be also included in this group, as the therapeutic activity of the transplant in this case is determined not by cell replacement, but by the paracrine and immunomodulatory mechanisms.

The “replacement” strategy implies the transplantation of β -cells or β -like cells after certain *ex vivo* pretreatments. Most straightforwardly, it can be implemented as a transplantation of the natural mature β -cells in the form of donor pancreas or cadaveric/xenogeneic islets, necessarily accompanied by a heavy immunosuppression regimen. An advanced alternative, artificial pancreas transplants, is essentially the same donor islets placed in a medical device ensuring their isolation from the immune system of the recipient. A much more complicated approach is the obtaining of β -like cells *ex vivo* from progenitors (MSCs, ESCs, iPSCs) or differentiated somatic cells (*e.g.*, hepatocytes or α -cells) by exposure to small-molecule inducers or genetic modifications. Such reprogrammed cells are similar to β -cells in many respects, including expression of specific genes and insulin secretion in response to glucose stimulation, but still partially retain their original properties (genetic and epigenetic determinants, secretome, plasticity), which requires additional studies on their safety.

In summary, great progress in expanding our knowledge of the origin, growth, and physiological or stimulated regeneration of the pancreatic islets, their isolation and transplantation, and the production of reprogrammed β -like cells is evident. We believe that the huge volume of experimental and clinical studies currently under way will finally allow a safe and effective solution to a seemingly simple goal-restoration of the functionally active β -cells, the innermost hope of millions of people globally.

REFERENCES

- 1 **Casanova D**; en nombre de Grupo Español de Trasplante de Páncreas. Pancreas transplantation: 50 years of experience. *Cir Esp* 2017; **95**: 254-260 [PMID: 28595751 DOI: 10.1016/j.ciresp.2017.02.005]
 - 2 **Capurso G**, Traini M, Piciucchi M, Signoretti M, Arcidiacono PG. Exocrine pancreatic insufficiency: prevalence, diagnosis, and management. *Clin Exp Gastroenterol* 2019; **12**: 129-139 [PMID: 30962702 DOI: 10.2147/CEG.S168266]
 - 3 **Damasceno DC**, Netto AO, Jessi IL, Gallego FQ, Corvino SB, Dallaqua B, Sinzato YK, Bueno A, Calderon IM, Rudge MV. Streptozotocin-induced diabetes models: pathophysiological mechanisms and fetal outcomes. *Biomed Res Int* 2014; **2014**: 819065 [PMID: 24977161 DOI: 10.1155/2014/819065]
 - 4 **Kasacka I**. Review article--involvement of gastric APUD cells in chronic renal failure. *Acta Histochem* 2003; **105**: 319-327 [PMID: 14656005 DOI: 10.1078/0065-1281-00730]
 - 5 **Assmann A**, Hinault C, Kulkarni RN. Growth factor control of pancreatic islet regeneration and function. *Pediatr Diabetes* 2009; **10**: 14-32 [PMID: 18828795 DOI: 10.1111/j.1399-5448.2008.00468.x]
 - 6 **Chen C**, Cohrs CM, Stertman J, Bozsak R, Speier S. Human beta cell mass and function in diabetes: Recent advances in knowledge and technologies to understand disease pathogenesis. *Mol Metab* 2017; **6**: 943-957 [PMID: 28951820 DOI: 10.1016/j.molmet.2017.06.019]
 - 7 **Levetan C**. Distinctions between islet neogenesis and β -cell replication: implications for reversal of Type 1 and 2 diabetes. *J Diabetes* 2010; **2**: 76-84 [PMID: 20923488 DOI: 10.1111/j.1753-0407.2010.00074.x]
 - 8 The International Diabetes Federation (IDF) [Internet]. [cited 2019 December 25]. Available from: <https://www.idf.org/>
 - 9 **Murtaugh LC**. Pancreas and beta-cell development: from the actual to the possible. *Development* 2007; **134**: 427-438 [PMID: 17185316 DOI: 10.1242/dev.02770]
 - 10 **Zaret KS**, Grompe M. Generation and regeneration of cells of the liver and pancreas. *Science* 2008; **322**: 1490-1494 [PMID: 19056973 DOI: 10.1126/science.1161431]
 - 11 **Jiang FX**, Morahan G. Pancreatic stem cells: from possible to probable. *Stem Cell Rev Rep* 2012; **8**: 647-657 [PMID: 22090024 DOI: 10.1007/s12015-011-9333-8]
 - 12 **Karges B**, Durinovic-Belló I, Heinze E, Debatin KM, Boehm B, Karges W. Immunological mechanisms associated with long-term remission of human type 1 diabetes. *Diabetes Metab Res Rev* 2006; **22**: 184-189 [PMID: 16222648 DOI: 10.1002/dmrr.600]
 - 13 **Dost A**, Herbst A, Kintzel K, Haberland H, Roth CL, Gortner L, Holl RW. Shorter remission period in young versus older children with diabetes mellitus type 1. *Exp Clin Endocrinol Diabetes* 2007; **115**: 33-37 [PMID: 17286232 DOI: 10.1055/s-2007-948214]
- Brennan K**, Melton D. Slow and steady is the key to beta-cell replication. *J Cell Mol Med* 2009; **13**: 472-

- 14 487 [PMID: 19379145 DOI: 10.1111/j.1582-4934.2008.00635.x]
- 15 **Huang Y**, Chang Y. Regulation of pancreatic islet beta-cell mass by growth factor and hormone signaling. *Prog Mol Biol Transl Sci* 2014; **121**: 321-349 [PMID: 24373242 DOI: 10.1016/B978-0-12-800101-1.00010-7]
- 16 **Meier JJ**, Butler AE, Saisho Y, Monchamp T, Galasso R, Bhushan A, Rizza RA, Butler PC. Beta-cell repletion is the primary mechanism subserving the postnatal expansion of beta-cell mass in humans. *Diabetes* 2008; **57**: 1584-1594 [PMID: 18334605 DOI: 10.2337/db07-1369]
- 17 **Pagliuca FW**, Melton DA. How to make a functional β -cell. *Development* 2013; **140**: 2472-2483 [PMID: 23715541 DOI: 10.1242/dev.093187]
- 18 **Li WC**, Chen CY, Chien HY, Bonner-Weir S. (2016) Pancreatic Regeneration After Partial Pancreatectomy in Rodents. In: A. Hardikar A. (eds) *Pancreatic Islet Biology*. Stem Cell Biology and Regenerative Medicine. Springer, Cham [DOI: 10.1007/978-3-319-45307-1_5]
- 19 **Chen H**, Gu X, Su IH, Bottino R, Contreras JL, Tarakhovskiy A, Kim SK. Polycomb protein Ezh2 regulates pancreatic beta-cell Ink4a/Arf expression and regeneration in diabetes mellitus. *Genes Dev* 2009; **23**: 975-985 [PMID: 19390090 DOI: 10.1101/gad.1742509]
- 20 **Krishnamurthy J**, Ramsey MR, Ligon KL, Torrice C, Koh A, Bonner-Weir S, Sharpless NE. p16INK4a induces an age-dependent decline in islet regenerative potential. *Nature* 2006; **443**: 453-457 [PMID: 16957737 DOI: 10.1038/nature05092]
- 21 **Vecchio I**, Tornali C, Bragazzi NL, Martini M. The Discovery of Insulin: An Important Milestone in the History of Medicine. *Front Endocrinol (Lausanne)* 2018; **9**: 613 [PMID: 30405529 DOI: 10.3389/fendo.2018.00613]
- 22 **Karamitsos DT**. The story of insulin discovery. *Diabetes Res Clin Pract* 2011; **93** Suppl 1: S2-S8 [PMID: 21864746 DOI: 10.1016/S0168-8227(11)70007-9]
- 23 **Rosenberg L**, Lipsett M, Yoon JW, Prentki M, Wang R, Jun HS, Pittenger GL, Taylor-Fishwick D, Vinik AI. A pentadecapeptide fragment of islet neogenesis-associated protein increases beta-cell mass and reverses diabetes in C57BL/6J mice. *Ann Surg* 2004; **240**: 875-884 [PMID: 15492571 DOI: 10.1097/01.sla.0000143270.99191.10]
- 24 **Herrera PL**. Transgenic and other experimental models of pancreas and islet damage. *Diabetes Obes Metab* 2009; **11** Suppl 4: 91-96 [PMID: 19817792 DOI: 10.1111/j.1463-1326.2009.01104.x]
- 25 **Pasek RC**, Gannon M. Advancements and challenges in generating accurate animal models of gestational diabetes mellitus. *Am J Physiol Endocrinol Metab* 2013; **305**: E1327-E1338 [PMID: 24085033 DOI: 10.1152/ajpendo.00425.2013]
- 26 **Gai W**, Schott-Ohly P, Schulte im Walde S, Gleichmann H. Differential target molecules for toxicity induced by streptozotocin and alloxan in pancreatic islets of mice *in vitro*. *Exp Clin Endocrinol Diabetes* 2004; **112**: 29-37 [PMID: 14758569 DOI: 10.1055/s-2004-815724]
- 27 **Holland AM**, Hale MA, Kagami H, Hammer RE, MacDonald RJ. Experimental control of pancreatic development and maintenance. *Proc Natl Acad Sci USA* 2002; **99**: 12236-12241 [PMID: 12221286 DOI: 10.1073/pnas.192255099]
- 28 **Blondeau B**, Sahly I, Massouridès E, Singh-Estivalet A, Valtat B, Dorchene D, Jaisser F, Bréant B, Tronche F. Novel transgenic mice for inducible gene overexpression in pancreatic cells define glucocorticoid receptor-mediated regulations of beta cells. *PLoS One* 2012; **7**: e30210 [PMID: 22363422 DOI: 10.1371/journal.pone.0030210]
- 29 **Johnson JD**. A practical guide to genetic engineering of pancreatic β -cells *in vivo*: getting a grip on RIP and MIP. *Islets* 2014; **6**: e944439 [PMID: 25322827 DOI: 10.4161/19382014.2014.944439]
- 30 **Thorel F**, Népote V, Avril I, Kohno K, Desgraz R, Chera S, Herrera PL. Conversion of adult pancreatic alpha-cells to beta-cells after extreme beta-cell loss. *Nature* 2010; **464**: 1149-1154 [PMID: 20364121 DOI: 10.1038/nature08894]
- 31 **Cano DA**, Rulifson IC, Heiser PW, Swigart LB, Pelengaris S, German M, Evan GI, Bluestone JA, Hebrok M. Regulated beta-cell regeneration in the adult mouse pancreas. *Diabetes* 2008; **57**: 958-966 [PMID: 18083786 DOI: 10.2337/db07-0913]
- 32 **Wang ZV**, Mu J, Schraw TD, Gautron L, Elmquist JK, Zhang BB, Brownlee M, Scherer PE. PANIC-ATTAC: a mouse model for inducible and reversible beta-cell ablation. *Diabetes* 2008; **57**: 2137-2148 [PMID: 18469203 DOI: 10.2337/db07-1631]
- 33 **Tritschler S**, Theis FJ, Lickert H, Böttcher A. Systematic single-cell analysis provides new insights into heterogeneity and plasticity of the pancreas. *Mol Metab* 2017; **6**: 974-990 [PMID: 28951822 DOI: 10.1016/j.molmet.2017.06.021]
- 34 **Xu X**, D'Hoker J, Stangé G, Bonnè S, De Leu N, Xiao X, Van de Castele M, Mellitzer G, Ling Z, Pipeleers D, Bouwens L, Scharfmann R, Gradwohl G, Heimberg H. Beta cells can be generated from endogenous progenitors in injured adult mouse pancreas. *Cell* 2008; **132**: 197-207 [PMID: 18243096 DOI: 10.1016/j.cell.2007.12.015]
- 35 **Bonner-Weir S**, Inada A, Yatoh S, Li WC, Aye T, Toschi E, Sharma A. Transdifferentiation of pancreatic ductal cells to endocrine beta-cells. *Biochem Soc Trans* 2008; **36**: 353-356 [PMID: 18481956 DOI: 10.1042/BST0360353]
- 36 **Aigha II**, Memon B, Elsayed AK, Abdelalim EM. Differentiation of human pluripotent stem cells into two distinct NKX6.1 populations of pancreatic progenitors. *Stem Cell Res Ther* 2018; **9**: 83 [PMID: 29615106 DOI: 10.1186/s13287-018-0834-0]
- 37 **Spaeth JM**, Liu JH, Peters D, Guo M, Osipovich AB, Mohammadi F, Roy N, Bhushan A, Magnuson MA, Hebrok M, Wright CVE, Stein R. The Pdx1-Bound Swi/Snf Chromatin Remodeling Complex Regulates Pancreatic Progenitor Cell Proliferation and Mature Islet β -Cell Function. *Diabetes* 2019; **68**: 1806-1818 [PMID: 31201281 DOI: 10.2337/db19-0349]
- 38 **Stanger BZ**, Tanaka AJ, Melton DA. Organ size is limited by the number of embryonic progenitor cells in the pancreas but not the liver. *Nature* 2007; **445**: 886-891 [PMID: 17259975 DOI: 10.1038/nature05537]
- 39 **Solar M**, Cardalda C, Houbracken I, Martín M, Maestro MA, De Medts N, Xu X, Grau V, Heimberg H, Bouwens L, Ferrer J. Pancreatic exocrine duct cells give rise to insulin-producing beta cells during embryogenesis but not after birth. *Dev Cell* 2009; **17**: 849-860 [PMID: 20059954 DOI: 10.1016/j.devcel.2009.11.003]
- 40 **Bru-Tari E**, Cobo-Vuilleumier N, Alonso-Magdalena P, Dos Santos RS, Marroqui L, Nadal A, Gauthier BR, Quesada I. Pancreatic alpha-cell mass in the early-onset and advanced stage of a mouse model of experimental autoimmune diabetes. *Sci Rep* 2019; **9**: 9515 [PMID: 31266981 DOI: 10.1038/s41598-019-45853-1]
- 41 **Bramswig NC**, Everett LJ, Schug J, Dorrell C, Liu C, Luo Y, Streeter PR, Naji A, Grompe M, Kaestner

- KH. Epigenomic plasticity enables human pancreatic α to β cell reprogramming. *J Clin Invest* 2013; **123**: 1275-1284 [PMID: 23434589 DOI: 10.1172/JCI66514]
- 42 **Chera S**, Baronnier D, Ghila L, Cigliola V, Jensen JN, Gu G, Furuyama K, Thorel F, Gribble FM, Reimann F, Herrera PL. Diabetes recovery by age-dependent conversion of pancreatic δ -cells into insulin producers. *Nature* 2014; **514**: 503-507 [PMID: 25141178 DOI: 10.1038/nature13633]
- 43 **Theise ND**, Nimmakayalu M, Gardner R, Illei PB, Morgan G, Teperman L, Henegariu O, Krause DS. Liver from bone marrow in humans. *Hepatology* 2000; **32**: 11-16 [PMID: 10869283 DOI: 10.1053/jhep.2000.9124]
- 44 **Körbling M**, Katz RL, Khanna A, Ruifrok AC, Rondon G, Albitar M, Champlin RE, Estrov Z. Hepatocytes and epithelial cells of donor origin in recipients of peripheral-blood stem cells. *N Engl J Med* 2002; **346**: 738-746 [PMID: 11882729 DOI: 10.1056/NEJMoa3461002]
- 45 **Ianus A**, Holz GG, Theise ND, Hussain MA. *In vivo* derivation of glucose-competent pancreatic endocrine cells from bone marrow without evidence of cell fusion. *J Clin Invest* 2003; **111**: 843-850 [PMID: 12639990 DOI: 10.1172/JCI16502]
- 46 **Choi JB**, Uchino H, Azuma K, Iwashita N, Tanaka Y, Mochizuki H, Migita M, Shimada T, Kawamori R, Watada H. Little evidence of transdifferentiation of bone marrow-derived cells into pancreatic beta cells. *Diabetologia* 2003; **46**: 1366-1374 [PMID: 12898006 DOI: 10.1007/s00125-003-1182-9]
- 47 **Lechner A**, Yang YG, Blacken RA, Wang L, Nolan AL, Habener JF. No evidence for significant transdifferentiation of bone marrow into pancreatic beta-cells *in vivo*. *Diabetes* 2004; **53**: 616-623 [PMID: 14988245 DOI: 10.2337/diabetes.53.3.616]
- 48 **Mathews V**, Hanson PT, Ford E, Fujita J, Polonsky KS, Graubert TA. Recruitment of bone marrow-derived endothelial cells to sites of pancreatic beta-cell injury. *Diabetes* 2004; **53**: 91-98 [PMID: 14693702 DOI: 10.2337/diabetes.53.1.91]
- 49 **Wang X**, Ge S, Gonzalez I, McNamara G, Rountree CB, Xi KK, Huang G, Bhushan A, Crooks GM. Formation of pancreatic duct epithelium from bone marrow during neonatal development. *Stem Cells* 2006; **24**: 307-314 [PMID: 16510429 DOI: 10.1634/stemcells.2005-0052]
- 50 **Bonner-Weir S**, Li WC, Ouziel-Yahalom L, Guo L, Weir GC, Sharma A. Beta-cell growth and regeneration: replication is only part of the story. *Diabetes* 2010; **59**: 2340-2348 [PMID: 20876724 DOI: 10.2337/db10-0084]
- 51 **Hughes A**, Mohanasundaram D, Kireta S, Jessup CF, Drogemuller CJ, Coates PT. Insulin-Like growth factor-II (IGF-II) prevents proinflammatory cytokine-induced apoptosis and significantly improves islet survival after transplantation. *Transplantation* 2013; **95**: 671-678 [PMID: 23364485 DOI: 10.1097/TP.0b013e31827fa453]
- 52 **Cornu M**, Yang JY, Jaccard E, Poussin C, Widmann C, Thorens B. Glucagon-like peptide-1 protects beta-cells against apoptosis by increasing the activity of an IGF-2/IGF-1 receptor autocrine loop. *Diabetes* 2009; **58**: 1816-1825 [PMID: 19401425 DOI: 10.2337/db09-0063]
- 53 **Linnemann AK**, Neuman JC, Battiola TJ, Wisinski JA, Kimple ME, Davis DB. Glucagon-Like Peptide-1 Regulates Cholecystokinin Production in β -Cells to Protect From Apoptosis. *Mol Endocrinol* 2015; **29**: 978-987 [PMID: 25984632 DOI: 10.1210/me.2015-1030]
- 54 **Parikh A**, Stephan AF, Tzanakakis ES. Regenerating proteins and their expression, regulation and signaling. *Biomol Concepts* 2012; **3**: 57-70 [PMID: 22582090 DOI: 10.1515/bmc.2011.055]
- 55 **Okamoto H**. The Reg gene family and Reg proteins: with special attention to the regeneration of pancreatic beta-cells. *J Hepatobiliary Pancreat Surg* 1999; **6**: 254-262 [PMID: 10526060 DOI: 10.1007/s005340050115]
- 56 **Pittenger GL**, Taylor-Fishwick D, Vinik AI. The role of islet neogenesis-associated protein (INGAP) in pancreatic islet neogenesis. *Curr Protein Pept Sci* 2009; **10**: 37-45 [PMID: 19275671 DOI: 10.2174/138920309787315211]
- 57 **Sabir S**, Saleem A, Akhtar MF, Saleem M, Raza M. Increasing beta cell mass to treat diabetes mellitus. *Adv Clin Exp Med* 2018; **27**: 1309-1315 [PMID: 29912482 DOI: 10.17219/acem/74452]
- 58 **Neumiller JJ**. Incretin-based therapies. *Med Clin North Am* 2015; **99**: 107-129 [PMID: 25456646 DOI: 10.1016/j.mena.2014.08.013]
- 59 **Cahn A**, Cernea S, Raz I. An update on DPP-4 inhibitors in the management of type 2 diabetes. *Expert Opin Emerg Drugs* 2016; **21**: 409-419 [PMID: 27809608 DOI: 10.1080/14728214.2016.1257608]
- 60 **Garber AJ**. The importance of incretin therapies for managing type 2 diabetes. *Lancet Diabetes Endocrinol* 2014; **2**: 95-97 [PMID: 24622701 DOI: 10.1016/S2213-8587(13)70157-8]
- 61 **Samson SL**, Garber AJ. A Plethora of GLP-1 Agonists: Decisions About What to Use and When. *Curr Diab Rep* 2016; **16**: 120 [PMID: 27766579 DOI: 10.1007/s11892-016-0823-6]
- 62 **Davies M**, Speight J. Patient-reported outcomes in trials of incretin-based therapies in patients with type 2 diabetes mellitus. *Diabetes Obes Metab* 2012; **14**: 882-892 [PMID: 22420869 DOI: 10.1111/j.1463-1326.2012.01595.x]
- 63 **Schneider G**, Siveke JT, Eckel F, Schmid RM. Pancreatic cancer: basic and clinical aspects. *Gastroenterology* 2005; **128**: 1606-1625 [PMID: 15887154 DOI: 10.1053/j.gastro.2005.04.001]
- 64 **Chen H**, Zhou X, Chen T, Liu B, Jin W, Gu H, Hong T, Zhang G. Incretin-Based Therapy and Risk of Pancreatic Cancer in Patients with Type 2 Diabetes Mellitus: A Meta-analysis of Randomized Controlled Trials. *Diabetes Ther* 2016; **7**: 725-742 [PMID: 27655330 DOI: 10.1007/s13300-016-0198-3]
- 65 **Giorda CB**, Picariello R, Tartaglino B, Nada E, Costa G, Gnani R. Incretin-based therapy and risk of cholangiocarcinoma: a nested case-control study in a population of subjects with type 2 diabetes. *Acta Diabetol* 2020; **57**: 401-408 [PMID: 31691043 DOI: 10.1007/s00592-019-01444-0]
- 66 **Li L**, Shen J, Bala MM, Busse JW, Ebrahim S, Vandvik PO, Rios LP, Malaga G, Wong E, Sohani Z, Guyatt GH, Sun X. Incretin treatment and risk of pancreatitis in patients with type 2 diabetes mellitus: systematic review and meta-analysis of randomised and non-randomised studies. *BMJ* 2014; **348**: g2366 [PMID: 24736555 DOI: 10.1136/bmj.g2366]
- 67 **Wang T**, Wang F, Gou Z, Tang H, Li C, Shi L, Zhai S. Using real-world data to evaluate the association of incretin-based therapies with risk of acute pancreatitis: a meta-analysis of 1,324,515 patients from observational studies. *Diabetes Obes Metab* 2015; **17**: 32-41 [PMID: 25200423 DOI: 10.1111/dom.12386]
- 68 **Liu J**, Li L, Deng K, Xu C, Busse JW, Vandvik PO, Li S, Guyatt GH, Sun X. Incretin based treatments and mortality in patients with type 2 diabetes: systematic review and meta-analysis. *BMJ* 2017; **357**: j2499 [PMID: 28596247 DOI: 10.1136/bmj.j2499]
- 69 **Hunt RH**. Prostaglandins for peptic ulcer disease. *Lancet* 1987; **1**: 1262 [PMID: 2884391 DOI: 10.1016/j.biopha.2017.08.070]
- 70 **Ajuwon OR**, Ayeleso AO, Adefolaju GA. The Potential of South African Herbal Tisanes, Rooibos and

- Honeybush in the Management of Type 2 Diabetes Mellitus. *Molecules* 2018; **23**: 3207 [PMID: 30563087 DOI: 10.3390/molecules23123207]
- 71 **Park JH**, Bae JH, Im SS, Song DK. Green tea and type 2 diabetes. *Integr Med Res* 2014; **3**: 4-10 [PMID: 28664072 DOI: 10.1016/j.imr.2013.12.002]
- 72 **Nakamura A**, Terauchi Y. Present status of clinical deployment of glucokinase activators. *J Diabetes Investig* 2015; **6**: 124-132 [PMID: 25802718 DOI: 10.1111/jdi.12294]
- 73 **Banerjee M**, Kumar A, Bhonde RR. Reversal of experimental diabetes by multiple bone marrow transplantation. *Biochem Biophys Res Commun* 2005; **328**: 318-325 [PMID: 15670786 DOI: 10.1016/j.bbrc.2004.12.176]
- 74 **Uccelli A**, Prockop DJ. Why should mesenchymal stem cells (MSCs) cure autoimmune diseases? *Curr Opin Immunol* 2010; **22**: 768-774 [PMID: 21093239 DOI: 10.1016/j.coi.2010.10.012]
- 75 **Zang L**, Hao H, Liu J, Li Y, Han W, Mu Y. Mesenchymal stem cell therapy in type 2 diabetes mellitus. *Diabetol Metab Syndr* 2017; **9**: 36 [PMID: 28515792 DOI: 10.1186/s13098-017-0233-1]
- 76 **Zhang Y**, Chen W, Feng B, Cao H. The Clinical Efficacy and Safety of Stem Cell Therapy for Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Aging Dis* 2020; **11**: 141-153 [PMID: 32010488 DOI: 10.14336/AD.2019.0421]
- 77 **Newton WC**, Kim JW, Luo JZQ, Luo L. Stem cell-derived exosomes: a novel vector for tissue repair and diabetic therapy. *J Mol Endocrinol* 2017; **59**: R155-R165 [PMID: 28835418 DOI: 10.1530/JME-17-0080]
- 78 **Sun Y**, Shi H, Yin S, Ji C, Zhang X, Zhang B, Wu P, Shi Y, Mao F, Yan Y, Xu W, Qian H. Human Mesenchymal Stem Cell Derived Exosomes Alleviate Type 2 Diabetes Mellitus by Reversing Peripheral Insulin Resistance and Relieving β -Cell Destruction. *ACS Nano* 2018; **12**: 7613-7628 [PMID: 30052036 DOI: 10.1021/acsnano.7b07643]
- 79 **Bottino R**, Knoll MF, Knoll CA, Bertera S, Trucco MM. The Future of Islet Transplantation Is Now. *Front Med (Lausanne)* 2018; **5**: 202 [PMID: 30057900 DOI: 10.3389/fmed.2018.00202]
- 80 **Largiadèr F**, Kolb E, Binswanger U. A long-term functioning human pancreatic islet allotransplant. *Transplantation* 1980; **29**: 76-77 [PMID: 6768175 DOI: 10.1097/00007890-198001000-00017]
- 81 **Brendel M**, Hering B, Schulz A, Bretzel R. International Islet Transplant Registry report. Giessen, Germany: University of Giessen, 1999: 1-20
- 82 **Shapiro AM**, Lakey JR, Ryan EA, Korbitt GS, Toth E, Warnock GL, Kneteman NM, Rajotte RV. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med* 2000; **343**: 230-238 [PMID: 10911004 DOI: 10.1056/NEJM200007273430401]
- 83 **Lakey JR**, Warnock GL, Rajotte RV, Suarez-Alamazor ME, Ao Z, Shapiro AM, Kneteman NM. Variables in organ donors that affect the recovery of human islets of Langerhans. *Transplantation* 1996; **61**: 1047-1053 [PMID: 8623183 DOI: 10.1097/00007890-199604150-00010]
- 84 **Brandhorst H**, Brandhorst D, Brendel MD, Hering BJ, Bretzel RG. Assessment of intracellular insulin content during all steps of human islet isolation procedure. *Cell Transplant* 1998; **7**: 489-495 [PMID: 9786069 DOI: 10.1016/s0963-6897(98)0028-1]
- 85 **Shapiro AM**, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson RP, Secchi A, Brendel MD, Berney T, Brennan DC, Cagliero E, Alejandro R, Ryan EA, DiMercurio B, Morel P, Polonsky KS, Reems JA, Bretzel RG, Bertuzzi F, Froud T, Kandaswamy R, Sutherland DE, Eisenbarth G, Segal M, Preiksaitis J, Korbitt GS, Barton FB, Viviano L, Seyfert-Margolis V, Bluestone J, Lakey JR. International trial of the Edmonton protocol for islet transplantation. *N Engl J Med* 2006; **355**: 1318-1330 [PMID: 17005949 DOI: 10.1056/NEJMoa061267]
- 86 The Collaborative Islet Transplant Registry (CITR) [Internet]. [cited 2019 December 25]. Available from: <http://www.citrregistry.org/>
- 87 **Barton FB**, Rickels MR, Alejandro R, Hering BJ, Wease S, Naziruddin B, Oberholzer J, Odorico JS, Garfinkel MR, Levy M, Pattou F, Berney T, Secchi A, Messinger S, Senior PA, Maffi P, Posselt A, Stock PG, Kaufman DB, Luo X, Kandeel F, Cagliero E, Turgeon NA, Witkowski P, Naji A, O'Connell PJ, Greenbaum C, Kudva YC, Brayman KL, Aull MJ, Larsen C, Kay TW, Fernandez LA, Vantyghe MC, Bellin M, Shapiro AM. Improvement in outcomes of clinical islet transplantation: 1999-2010. *Diabetes Care* 2012; **35**: 1436-1445 [PMID: 22723582 DOI: 10.2337/dc12-0063]
- 88 The Clinical Islet Transplantation (CIT) Consortium [Internet]. [cited 2019 December 25]. Available from: <http://www.citisletstudy.org/>
- 89 **Rickels MR**, Liu C, Shlansky-Goldberg RD, Soleimanpour SA, Vivek K, Kamoun M, Min Z, Markmann E, Palangian M, Dalton-Bakes C, Fuller C, Chiou AJ, Barker CF, Luning Prak ET, Naji A. Improvement in β -cell secretory capacity after human islet transplantation according to the CIT07 protocol. *Diabetes* 2013; **62**: 2890-2897 [PMID: 23630300 DOI: 10.2337/db12-1802]
- 90 **Moassesfar S**, Masharani U, Frassetto LA, Szot GL, Tavakol M, Stock PG, Posselt AM. A Comparative Analysis of the Safety, Efficacy, and Cost of Islet Versus Pancreas Transplantation in Nonuremic Patients With Type 1 Diabetes. *Am J Transplant* 2016; **16**: 518-526 [PMID: 26595767 DOI: 10.1111/ajt.13536]
- 91 **de Souza BM**, Bouças AP, Oliveira FD, Reis KP, Ziegelmann P, Bauer AC, Crispim D. Effect of co-culture of mesenchymal stem/stromal cells with pancreatic islets on viability and function outcomes: a systematic review and meta-analysis. *Islets* 2017; **9**: 30-42 [PMID: 28151049 DOI: 10.1080/19382014.2017.1286434]
- 92 **Arzouni AA**, Vargas-Seymour A, Nardi N, J F King A, Jones PM. Using Mesenchymal Stromal Cells in Islet Transplantation. *Stem Cells Transl Med* 2018; **7**: 559-563 [PMID: 29749717 DOI: 10.1002/sctm.18-0033]
- 93 **Rackham CL**, Jones PM. Potential of mesenchymal stromal cells for improving islet transplantation outcomes. *Curr Opin Pharmacol* 2018; **43**: 34-39 [PMID: 30103073 DOI: 10.1016/j.coph.2018.07.011]
- 94 **Najarian JS**, Sutherland DE, Matas AJ, Goetz FC. Human islet autotransplantation following pancreatotomy. *Transplant Proc* 1979; **11**: 336-340 [PMID: 109963]
- 95 **Witkowski P**, Savari O, Matthews JB. Islet autotransplantation and total pancreatectomy. *Adv Surg* 2014; **48**: 223-233 [PMID: 25293618 DOI: 10.1016/j.yasu.2014.05.006]
- 96 **Sutherland DE**, Gruessner AC, Carlson AM, Blondet JJ, Balamurugan AN, Reigstad KF, Beilman GJ, Bellin MD, Hering BJ. Islet autotransplant outcomes after total pancreatectomy: a contrast to islet allograft outcomes. *Transplantation* 2008; **86**: 1799-1802 [PMID: 19104425 DOI: 10.1097/TP.0b013e31819143ec]
- 97 **Ricordi C**, Lacy PE, Scharp DW. Automated islet isolation from human pancreas. *Diabetes* 1989; **38** Suppl 1: 140-142 [PMID: 2642838 DOI: 10.2337/diab.38.1.s140]
- 98 **Casey JJ**, Lakey JR, Ryan EA, Paty BW, Owen R, O'Kelly K, Nanji S, Rajotte RV, Korbitt GS, Bigam D, Kneteman NN, Shapiro AM. Portal venous pressure changes after sequential clinical islet transplantation.

- Transplantation* 2002; **74**: 913-915 [PMID: 12394830 DOI: 10.1097/00007890-200210150-00002]
- 99 **Sumi S.** Regenerative medicine for insulin deficiency: creation of pancreatic islets and bioartificial pancreas. *J Hepatobiliary Pancreat Sci* 2011; **18**: 6-12 [PMID: 20589399 DOI: 10.1007/s00534-010-0303-3]
- 100 **Iwata H,** Arima Y, Tsutsui Y. Design of Bioartificial Pancreases From the Standpoint of Oxygen Supply. *Artif Organs* 2018; **42**: E168-E185 [PMID: 29611212 DOI: 10.1111/aor.13106]
- 101 **Barkai U,** Rotem A, de Vos P. Survival of encapsulated islets: More than a membrane story. *World J Transplant* 2016; **6**: 69-90 [PMID: 27011906 DOI: 10.5500/wjt.v6.i1.69]
- 102 **Elliott RB,** Escobar L, Tan PL, Muzina M, Zwain S, Buchanan C. Live encapsulated porcine islets from a type 1 diabetic patient 9.5 yr after xenotransplantation. *Xenotransplantation* 2007; **14**: 157-161 [PMID: 17381690 DOI: 10.1111/j.1399-3089.2007.00384.x]
- 103 **Krishnan R,** Ko D, Foster CE, Liu W, Smink AM, de Haan B, De Vos P, Lakey JR. Immunological Challenges Facing Translation of Alginate Encapsulated Porcine Islet Xenotransplantation to Human Clinical Trials. *Methods Mol Biol* 2017; **1479**: 305-333 [PMID: 27738946 DOI: 10.1007/978-1-4939-6364-5_24]
- 104 **Smukler SR,** Arntfield ME, Razavi R, Bikopoulos G, Karpowicz P, Seaberg R, Dai F, Lee S, Ahrens R, Fraser PE, Wheeler MB, van der Kooy D. The adult mouse and human pancreas contain rare multipotent stem cells that express insulin. *Cell Stem Cell* 2011; **8**: 281-293 [PMID: 21362568 DOI: 10.1016/j.stem.2011.01.015]
- 105 **Razavi R,** Najafabadi HS, Abdullah S, Smukler S, Arntfield M, van der Kooy D. Diabetes enhances the proliferation of adult pancreatic multipotent progenitor cells and biases their differentiation to more β -cell production. *Diabetes* 2015; **64**: 1311-1323 [PMID: 25392245 DOI: 10.2337/db14-0070]
- 106 **Berebichez-Fridman R,** Gómez-García R, Granados-Montiel J, Berebichez-Fastlicht E, Olivios-Meza A, Granados J, Velasquillo C, Ibarra C. The Holy Grail of Orthopedic Surgery: Mesenchymal Stem Cells- Their Current Uses and Potential Applications. *Stem Cells Int* 2017; **2017**: 2638305 [PMID: 28698718 DOI: 10.1155/2017/2638305]
- 107 **Berebichez-Fridman R,** Montero-Olvera PR. Sources and Clinical Applications of Mesenchymal Stem Cells: State-of-the-art review. *Sultan Qaboos Univ Med J* 2018; **18**: e264-e277 [PMID: 30607265 DOI: 10.18295/squmj.2018.18.03.002]
- 108 **Wu XH,** Liu CP, Xu KF, Mao XD, Zhu J, Jiang JJ, Cui D, Zhang M, Xu Y, Liu C. Reversal of hyperglycemia in diabetic rats by portal vein transplantation of islet-like cells generated from bone marrow mesenchymal stem cells. *World J Gastroenterol* 2007; **13**: 3342-3349 [PMID: 17659673 DOI: 10.3748/wjg.v13.i24.3342]
- 109 **Hisanaga E,** Park KY, Yamada S, Hashimoto H, Takeuchi T, Mori M, Seno M, Umezawa K, Takei I, Kojima I. A simple method to induce differentiation of murine bone marrow mesenchymal cells to insulin-producing cells using conophylline and betacellulin-delta4. *Endocr J* 2008; **55**: 535-543 [PMID: 18480554 DOI: 10.1507/endocrj.k07e-173]
- 110 **Chandra V,** G S, Phadnis S, Nair PD, Bhone RR. Generation of pancreatic hormone-expressing islet-like cell aggregates from murine adipose tissue-derived stem cells. *Stem Cells* 2009; **27**: 1941-1953 [PMID: 19544426 DOI: 10.1002/stem.117]
- 111 **Wartchow KM,** Rodrigues L, Suardi LZ, Federhen BC, Selistre NG, Gonçalves CA, Sesterheim P. Short-Term Protocols to Obtain Insulin-Producing Cells from Rat Adipose Tissue: Signaling Pathways and *In Vivo* Effect. *Int J Mol Sci* 2019; **20**: 2458 [PMID: 31109026 DOI: 10.3390/ijms20102458]
- 112 **Pavathuparambil Abdul Manaph N,** Sivanathan KN, Nitschke J, Zhou XF, Coates PT, Drogemuller CJ. An overview on small molecule-induced differentiation of mesenchymal stem cells into beta cells for diabetic therapy. *Stem Cell Res Ther* 2019; **10**: 293 [PMID: 31547868 DOI: 10.1186/s13287-019-1396-5]
- 113 **Efrat S,** Russ HA. Making β cells from adult tissues. *Trends Endocrinol Metab* 2012; **23**: 278-285 [PMID: 22537825 DOI: 10.1016/j.tem.2012.03.005]
- 114 **Karnieli O,** Izhar-Prato Y, Bulvik S, Efrat S. Generation of insulin-producing cells from human bone marrow mesenchymal stem cells by genetic manipulation. *Stem Cells* 2007; **25**: 2837-2844 [PMID: 17615265 DOI: 10.1634/stemcells.2007-0164]
- 115 **Zhu Y,** Liu Q, Zhou Z, Ikeda Y, PDX1, Neurogenin-3, and MAFA: critical transcription regulators for beta cell development and regeneration. *Stem Cell Res Ther* 2017; **8**: 240 [PMID: 29096722 DOI: 10.1186/s13287-017-0694-z]
- 116 **Wei W,** Huang Y, Li D, Gou HF, Wang W. Improved therapeutic potential of MSCs by genetic modification. *Gene Ther* 2018; **25**: 538-547 [PMID: 30254305 DOI: 10.1038/s41434-018-0041-8]
- 117 **Päth G,** Perakakis N, Mantzoros CS, Seufert J. Stem cells in the treatment of diabetes mellitus - Focus on mesenchymal stem cells. *Metabolism* 2019; **90**: 1-15 [PMID: 30342065 DOI: 10.1016/j.metabol.2018.10.005]
- 118 **Lumelsky N,** Blondel O, Laeng P, Velasco I, Ravin R, McKay R. Differentiation of embryonic stem cells to insulin-secreting structures similar to pancreatic islets. *Science* 2001; **292**: 1389-1394 [PMID: 11326082 DOI: 10.1126/science.1058866]
- 119 **Zulewski H.** Differentiation of embryonic and adult stem cells into insulin producing cells. *Panminerva Med* 2008; **50**: 73-79 [PMID: 18427390]
- 120 **Shahjalal HM,** Abdal Dayem A, Lim KM, Jeon TI, Cho SG. Generation of pancreatic β cells for treatment of diabetes: advances and challenges. *Stem Cell Res Ther* 2018; **9**: 355 [PMID: 30594258 DOI: 10.1186/s13287-018-1099-3]
- 121 **Kfoury C.** Therapeutic cloning: promises and issues. *McGill J Med* 2007; **10**: 112-120 [PMID: 18523539]
- 122 **Fujikawa T,** Oh SH, Pi L, Hatch HM, Shupe T, Petersen BE. Teratoma formation leads to failure of treatment for type 1 diabetes using embryonic stem cell-derived insulin-producing cells. *Am J Pathol* 2005; **166**: 1781-1791 [PMID: 15920163 DOI: 10.1016/S0002-9440(10)62488-1]
- 123 **Takahashi K,** Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 2006; **126**: 663-676 [PMID: 16904174 DOI: 10.1016/j.cell.2006.07.024]
- 124 **Hosoya M,** Kunisada Y, Kurisaki A, Asashima M. Induction of differentiation of undifferentiated cells into pancreatic beta cells in vertebrates. *Int J Dev Biol* 2012; **56**: 313-323 [PMID: 22689376 DOI: 10.1387/ijdb.123522mh]
- 125 **Hosoya M.** Preparation of pancreatic β -cells from human iPSCs with small molecules. *Islets* 2012; **4**: 249-252 [PMID: 22722666 DOI: 10.4161/isl.20856]
- 126 **Mauda-Havakuk M,** Litichever N, Chernichovski E, Nakar O, Winkler E, Mazkereth R, Orenstein A, Bar-Meir E, Ravassard P, Meivar-Levy I, Ferber S. Ectopic PDX-1 expression directly reprograms human

- keratinocytes along pancreatic insulin-producing cells fate. *PLoS One* 2011; **6**: e26298 [PMID: 22028850 DOI: 10.1371/journal.pone.0026298]
- 127 **Cavelti-Weder C**, Li W, Zumsteg A, Stemann-Andersen M, Zhang Y, Yamada T, Wang M, Lu J, Jermendy A, Bee YM, Bonner-Weir S, Weir GC, Zhou Q. Hyperglycaemia attenuates *in vivo* reprogramming of pancreatic exocrine cells to beta cells in mice. *Diabetologia* 2016; **59**: 522-532 [PMID: 26693711 DOI: 10.1007/s00125-015-3838-7]
- 128 **Pan G**, Hao H, Liu J. Induction of hepatocytes-derived insulin-producing cells using small molecules and identification of microRNA profiles during this procedure. *Biochem Biophys Res Commun* 2018; **498**: 646-653 [PMID: 29524422 DOI: 10.1016/j.bbrc.2018.03.036]
- 129 **Ariyachet C**, Tovaglieri A, Xiang G, Lu J, Shah MS, Richmond CA, Verbeke C, Melton DA, Stanger BZ, Mooney D, Shivdasani RA, Mahony S, Xia Q, Breault DT, Zhou Q. Reprogrammed Stomach Tissue as a Renewable Source of Functional β Cells for Blood Glucose Regulation. *Cell Stem Cell* 2016; **18**: 410-421 [PMID: 26908146 DOI: 10.1016/j.stem.2016.01.003]
- 130 **Thulé PM**, Jia D, Safley S, Gordon K, Barber G, Yi H, Nalli S, Onderci M, Sharma J, Shires J, Weber CJ. Engineered insulin secretion from neuroendocrine cells isolated from human thyroid. *World J Surg* 2014; **38**: 1251-1261 [PMID: 24549997 DOI: 10.1007/s00268-014-2457-7]
- 131 **Furuyama K**, Chera S, van Gurp L, Oropeza D, Ghila L, Damond N, Vethe H, Paulo JA, Joosten AM, Berney T, Bosco D, Dorrell C, Grompe M, Ræder H, Roep BO, Thorel F, Herrera PL. Diabetes relief in mice by glucose-sensing insulin-secreting human α -cells. *Nature* 2019; **567**: 43-48 [PMID: 30760930 DOI: 10.1038/s41586-019-0942-8]
- 132 **Zhou Q**, Brown J, Kanarek A, Rajagopal J, Melton DA. *In vivo* reprogramming of adult pancreatic exocrine cells to beta-cells. *Nature* 2008; **455**: 627-632 [PMID: 18754011 DOI: 10.1038/nature07314]
- 133 **Akinci E**, Banga A, Greder LV, Dutton JR, Slack JM. Reprogramming of pancreatic exocrine cells towards a beta (β) cell character using Pdx1, Ngn3 and MafA. *Biochem J* 2012; **442**: 539-550 [PMID: 22150363 DOI: 10.1042/BJ20111678]
- 134 **Ferber S**, Halkin A, Cohen H, Ber I, Einav Y, Goldberg I, Barshack I, Seiffers R, Kopolovic J, Kaiser N, Karasik A. Pancreatic and duodenal homeobox gene 1 induces expression of insulin genes in liver and ameliorates streptozotocin-induced hyperglycemia. *Nat Med* 2000; **6**: 568-572 [PMID: 10802714 DOI: 10.1038/75050]
- 135 **Kaneto H**, Nakatani Y, Miyatsuka T, Matsuoka TA, Matsuhisa M, Hori M, Yamasaki Y. PDX-1/VP16 fusion protein, together with NeuroD or Ngn3, markedly induces insulin gene transcription and ameliorates glucose tolerance. *Diabetes* 2005; **54**: 1009-1022 [PMID: 15793239 DOI: 10.2337/diabetes.54.4.1009]
- 136 **Wang AY**, Ehrhardt A, Xu H, Kay MA. Adenovirus transduction is required for the correction of diabetes using Pdx-1 or Neurogenin-3 in the liver. *Mol Ther* 2007; **15**: 255-263 [PMID: 17235302 DOI: 10.1038/sj.mt.6300032]
- 137 **Cito M**, Pellegrini S, Piemonti L, Sordi V. The potential and challenges of alternative sources of β cells for the cure of type 1 diabetes. *Endocr Connect* 2018; **7**: R114-R125 [PMID: 29555660 DOI: 10.1530/EC-18-0012]
- 138 **Cardinale V**, Wang Y, Carpino G, Cui CB, Gatto M, Rossi M, Berloco PB, Cantafora A, Wauthier E, Furth ME, Inverardi L, Dominguez-Bendala J, Ricordi C, Gerber D, Gaudio E, Alvaro D, Reid L. Multipotent stem/progenitor cells in human biliary tree give rise to hepatocytes, cholangiocytes, and pancreatic islets. *Hepatology* 2011; **54**: 2159-2172 [PMID: 21809358 DOI: 10.1002/hep.24590]
- 139 **Koizumi M**, Nagai K, Kida A, Kami K, Ito D, Fujimoto K, Kawaguchi Y, Doi R. Forced expression of PDX-1 induces insulin production in intestinal epithelia. *Surgery* 2006; **140**: 273-280 [PMID: 16904980 DOI: 10.1016/j.surg.2006.06.014]
- 140 **Chen YJ**, Finkbeiner SR, Weinblatt D, Emmett MJ, Tameire F, Yousefi M, Yang C, Maehr R, Zhou Q, Shemer R, Dor Y, Li C, Spence JR, Stanger BZ. De novo formation of insulin-producing "neo- β cell islets" from intestinal crypts. *Cell Rep* 2014; **6**: 1046-1058 [PMID: 24613355 DOI: 10.1016/j.celrep.2014.02.013]
- 141 **Chera S**, Herrera PL. Regeneration of pancreatic insulin-producing cells by *in situ* adaptive cell conversion. *Curr Opin Genet Dev* 2016; **40**: 1-10 [PMID: 27266969 DOI: 10.1016/j.gde.2016.05.010]
- 142 **Yang YP**, Thorel F, Boyer DF, Herrera PL, Wright CV. Context-specific α -to- β -cell reprogramming by forced Pdx1 expression. *Genes Dev* 2011; **25**: 1680-1685 [PMID: 21852533 DOI: 10.1101/gad.16875711]
- 143 **Courtney M**, Gjernes E, Druelle N, Ravaud C, Vieira A, Ben-Othman N, Pfeifer A, Avolio F, Leuckx G, Lacas-Gervais S, Burel-Vandenbos F, Ambrosetti D, Hecksher-Sorensen J, Ravassard P, Heimberg H, Mansouri A, Collombat P. The inactivation of Arx in pancreatic α -cells triggers their neogenesis and conversion into functional β -like cells. *PLoS Genet* 2013; **9**: e1003934 [PMID: 24204325 DOI: 10.1371/journal.pgen.1003934]
- 144 **Wilcox CL**, Terry NA, Walp ER, Lee RA, May CL. Pancreatic α -cell specific deletion of mouse Arx leads to α -cell identity loss. *PLoS One* 2013; **8**: e66214 [PMID: 23785486 DOI: 10.1371/journal.pone.0066214]
- 145 **Chakravarthy H**, Gu X, Enge M, Dai X, Wang Y, Damond N, Downie C, Liu K, Wang J, Xing Y, Chera S, Thorel F, Quake S, Oberholzer J, MacDonald PE, Herrera PL, Kim SK. Converting Adult Pancreatic Islet α Cells into β Cells by Targeting Both Dnm1 and Arx. *Cell Metab* 2017; **25**: 622-634 [PMID: 28215845 DOI: 10.1016/j.cmet.2017.01.009]
- 146 **Haumaitre C**. Epigenetic regulation of pancreatic islets. *Curr Diab Rep* 2013; **13**: 624-632 [PMID: 23907485 DOI: 10.1007/s11892-013-0403-y]



Published by Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>

