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IMPACT OF PANCREATIC CELL-ENGINEERED CONSTRUCTS ON THE ISLET APPARATUS IN RECIPIENT RATS WITH TYPE I DIABETES MELLITUS

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Current research focuses on exploring strategies to stimulate the regenerative capacity of pancreatic beta cells as a potential therapeutic approach for diabetes mellitus (DM). **Objective:** this study aims to perform a comparative histological analysis of the islet apparatus in rats with streptozotocin (STZ)-induced DM following the implantation of a pancreatic cell-engineered construct (PCEC). The PCEC consists of isolated allogeneic islets of Langerhans embedded within a scaffold derived from decellularized human pancreatic fragments. **Materials and methods.** The pancreases of rats from the control group (n = 4; untreated type 1 DM – T1DM), experimental group 1 (n = 4; intraperitoneal injection of pancreatic islets), and experimental group 2 (n = 4; intraperitoneal injection of PCEC) underwent histological analysis. Immunohistochemical staining for insulin and glucagon was performed using specific antibodies and an imaging system. **Results.** In the pancreatic islets of the control group, insulin-immunopositive beta cells were either absent or detected as isolated cells, with alpha cells predominating. In the pancreases of experimental group 1 rats, beta cells were observed in most islets and within the surrounding exocrine parenchyma, albeit in low numbers (1–2 per field of view), while alpha cells remained the dominant population. A significant increase in insulin-positive cells was observed in the pancreas of rats in experimental group 2, along with a reduction in glucagon-positive cell numbers. **Conclusion.** Morphological examination of the pancreatic islet apparatus in the experimental animals revealed that implantation of the PCEC had a beneficial effect on restoration of the recipient's pool of functionally active beta cells, serving as a trigger for the regenerative process.

Keywords: diabetes mellitus, pancreas, pancreatic islets, regeneration.

INTRODUCTION

Restoring insulin-producing β-cells lost in type 1 diabetes mellitus (T1DM) is a major challenge. The regenerative capacity of pancreatic islet is inherently limited [1]. Consequently, current research efforts are increasingly focused on strategies aimed at stimulating β-cell formation from alternative pancreatic cell populations [2], as well as generating β-cells from stem cells of various origins [3].

Presently, considerable attention is being directed toward understanding the mechanisms of β-cell regeneration within the pancreas and elucidating the molecular pathways involved in this process. The insights gained from such studies may facilitate the development of novel, effective, and safe therapeutic approaches for the treatment of diabetes mellitus (DM) [4, 5].

Restoration of the β-cell pool involves several mechanisms, including limited β-cell proliferation, hypertrophy, and transdifferentiation of other pancreatic cell types such as ductal epithelial cells, acinar cells, and other insulocytes [5–8]. Recent research shows that various pancreatic cells possess significant plasticity, meaning they can change their identity and adopt characteristics of other cell types within the pancreas [5]. In murine models, when β-cells are injured or destroyed, a small percentage of glucagon-producing α-cells and somatostatin-producing δ-cells can begin to express insulin [9].

Remedi et al. further revealed that multiple pancreatic cell types, including ductal cells, centroacinar cells, α-cells [10], and δ-cells [11], can transdifferentiate into functional β-cells, thereby compensating for impaired insulin secretion, a key factor in maintaining normoglycemia. The regeneration process involving ductal cells appears to mimic key aspects of embryonic β-cell differentiation, underscoring the plasticity of pancreatic tissue [12, 13]. Supporting this, W.-C. Li et al. demonstrated that β-cell regeneration can dedifferentiate to a precursor-like state, and then redifferentiate through specific signaling pathways that parallel those active during embryonic development [14].

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Given that acinar cells constitute the most abundant cell population in the pancreas, they have emerged as a promising source for generating new β-cells [15–19]. In a landmark study, Q. Zhou et al. demonstrated that differentiated acinar cells in adult mice possess the capacity to transdifferentiate into β-cells phenotypically similar to endogenous islet insulin-producing cells, capable of expressing insulin and alleviating hyperglycemia [20].

The concept of restoring lost cell populations by stimulating intrinsic adaptive plasticity *in situ* presents a compelling therapeutic avenue for the treatment of degenerative diseases [21]. However, it remains unclear whether human pancreatic cells exhibit a comparable degree of plasticity, particularly under diabetic conditions. This uncertainty stems from potential differences in the signaling pathways and molecular mediators – such as glucose levels, hormones, and growth factors – that govern β-cell regeneration in humans compared to animal models [9].

One of the strategies for cell replacement therapy in patients with T1DM is pancreatic islet transplantation. This approach not only ensures physiological insulin delivery but may also exert a stimulatory effect on endogenous β-cell regeneration. Jörns et al. support the concept that long-term normoglycemia maintained by insulin-producing grafts provides an optimal environment for β-cell regeneration and replication within the pancreas [22]. This regenerative stimulation is likely mediated by the paracrine effects of transplanted endocrine cells, which secrete bioactive polypeptides such as C-peptide and amylin, each with distinct physiological roles [23]. Supporting this concept, studies have shown that islet transplantation following partial pancreatectomy in mice enhances the regeneration and preservation of endogenous β-cells, resulting in increased β-cell mass and improved glycemic stability [24].

Previously, we showed a more pronounced reduction in glycemia levels in T1DM rats following intraperitoneal administration of a pancreatic cell-engineered construct (PCEC). This construct was based on isolated allogeneic islets of Langerhans and a scaffold derived from decellularized human pancreatic tissue fragments [25]. Morphological changes in the pancreas indicative of β-cell regeneration were also observed.

The objective of the present study was to conduct a comparative histological analysis of the islet apparatus between control and experimental animal groups.

MATERIALS AND METHODS

Composition of pancreatic cell-engineered construct (PCEC)

The PCEC was composed of two main components: viable insulin-producing rat pancreatic islets (PIs), cultured for 24 hours under standard conditions (37 °C, 5% CO_2), and a tissue-specific, fine-dispersed scaffold derived from decellularized human pancreatic fragments (dHPF scaffold) [26–28].

Each PCEC sample contained 2000 islets immobilized within 10.0 ± 0.1 mg of sterile dHPF scaffold, suspended in 100 μL of Hanks' balanced salt solution.

Islet viability within the PCEC was assessed using vital fluorescent dyes – acridine orange and propidium iodide (AO/PI) (PanEco, Russia).

The prepared PCEC samples were administered intraperitoneally to rats with streptozotocin (STZ)-induced T1DM using a 23G syringe needle.

In vivo experiment design

A T1DM model was induced in male Wistar rats (300–380 g) by fractional intraperitoneal administration of STZ (Biorbyt, India) at a dose of 15 mg/kg/day every 5 days. To confirm the stability of the T1DM model and exclude spontaneous reversion, glycemia levels were assessed 14 days after the final STZ dose. Only animals with fasting blood glucose levels exceeding 20.0 mmol/L were included in subsequent experiments.

The selected diabetic rats (n = 12) were randomly allocated into three groups: control group (n = 4; no treatment), experimental group 1 (n = 4; received intraperitoneal injection of 2000 isolated PIs) and experimental group 2 (n = 4; intraperitoneal injection of PCEC).

Fasting capillary blood glucose levels were measured weekly for 10 weeks. At the end of the experimental period, animals were euthanized, and pancreatic tissue was harvested for morphological and histological analysis.

Histologic study

A histologic examination of the pancreas was performed in control and experimental groups to identify morphological features of the islet apparatus. The excised pancreas samples were fixed in 10% buffered formalin for 24 hours. Dehydration was carried out using a graded ethanol series (50%, 60%, 70%, 80%, 95%), followed by sequential incubation in a mixture of ethanol and chloroform, pure chloroform, and a chloroform-paraffin mixture at +37 °C. Tissues were embedded in paraffin (Paraplast® X-tra™, Leica, Germany), and 4–5 μm sections were prepared using a rotary microtome (RM2245, Leica, Germany).

The paraffin sections were stained with hematoxylin and eosin. To identify the main islet cell types, immunohistochemical (IHC) staining for insulin and glucagon was performed using specific primary anti-insulin antibody (Abcam, UK) and anti-glucagon antibody (Merck, Germany). Visualization of immunoreactivity was carried out using the Rabbit Specific HRP/DAB (ABC) Detection IHC kit (Abcam, UK) according to the manufacturer's protocol.

RESULTS

Pancreatic cell-engineered construct (PCEC)

PCEC was formed immediately prior to intraperitoneal administration in rats with experimentally induced T1DM. PIs, pre-cultured for 24 hours, exhibited adhesive properties, attaching effectively to the surface of the decellularized pancreatic scaffold (Fig. 1, a). Only a few isolated islets remained free-floating in the culture medium.

Viability of the islets within PCEC was assessed using acridine orange and propidium iodide (AO/PI) vital staining. The staining results confirmed high islet viability within the construct, which was found to be 95 ± 2% (Fig. 1, b).

Comparative evaluation of functional efficiency of PCEC and PIs in rats with streptozotocin-induced diabetes mellitus

The study showed that intraperitoneal administration of PCEC in rats of experimental group 2 led to a significant reduction in blood glucose levels – by an average of 19.5 ± 3.9 mmol/L (from 25.8 ± 5.1 mmol/L to 6.3 ± 2.7 mmol/L). By week 10 of observation, glycemia levels were reduced to less than half of their baseline values.

In contrast, administration of a suspension of PIs in rats from experimental group 1 resulted in a mean glucose reduction of 14.8 ± 3.4 mmol/L (from 28.2 ± 4.2 mmol/L to 13.4 ± 2.6 mmol/L). However, this glycemic control was transient, lasting approximately 7 weeks, after which glucose levels began to rise and, in some cases, approached baseline values.

Thus, the administration of PCEC in T1DM rats demonstrated a more pronounced and sustained hypoglycemic effect compared to administration of a suspension of PIs alone [25, 29].

Morphologic changes in the islet apparatus of diabetic rats after intraperitoneal injection of pancreatic islets or PCEC

In **healthy rats**, the pancreas is characterized by diffuse structure with well-defined lobularity of the exocrine parenchyma interspersed with discrete PIs. These islets typically appear as spherical or oval clusters with sharply defined borders. Within the islets, insulocyte cells are arranged uniformly and display pale, fine-granular cytoplasm and rounded nuclei containing one to two prominent nucleoli (Fig. 2, a). The main endocrine cell types in rat islets exhibit a distinct spatial distribution: insulin-positive β-cells are primarily located in the central zone of the islet (Fig. 2, b), while glucagon-positive α-cells are arranged along the periphery, forming the characteristic “mantle” structure (Fig. 2, c).

The administration of STZ, which selectively targets insulin-producing β-cells in pancreatic islets, led to notable morphological alterations in the islet architecture. In pancreatic tissue samples from **control group rats** (10 weeks post-induction without treatment), islets appeared irregular in shape, with uneven contours and small protrusions extending into the surrounding exocrine parenchyma (Fig. 3, a). The cytotoxic effect of STZ culminated in β-cell death, predominantly affecting the central zone of the islets. This was evidenced by the presence of hypertrophied cells, necrotic cells exhibiting karyolysis, vacuolated cells, and areas of cellular debris. Additionally, islet cytoarchitecture was disrupted, with regions of hypercellularity emerging – these areas displayed a strong immunopositive signal for glucagon (Fig. 3, c). The observed hypercellularity likely reflected compensatory α-cell proliferation triggered by chronic

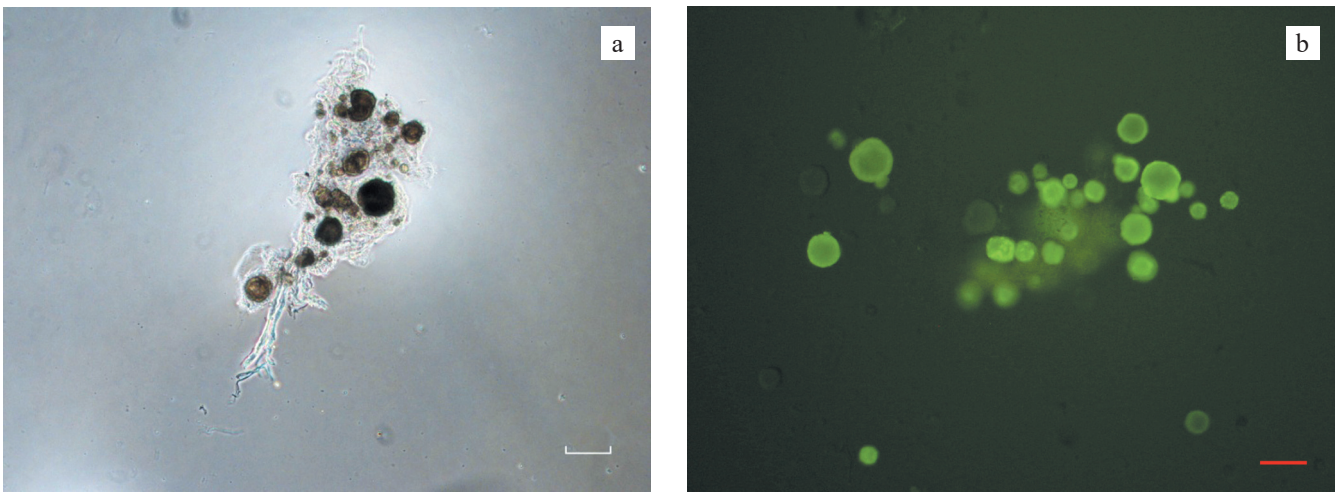

Fig. 1. Pancreatic cell-engineered construct (PCEC) composed of rat Pancreatic islets and a tissue-specific scaffold derived from decellularized human pancreas (DHP scaffold). (a) Inverted phase-contrast microscopy; (b) Acridine Orange/Propidium Iodide (AO/PI) fluorescence staining. Scale bar: 100 μm

hyperglycemia and altered paracrine signaling due to β-cell loss. Consequently, α-cells became the dominant islet population. In contrast, insulin-positive cells were absent in most islets or detected only as isolated cells (Fig. 3, b).

By the end of the 10-week experiment, histological examination of the pancreatic tissue in rats from experimental group 1 (injected with PIs) revealed no substantial morphological improvement compared to the control group. The islets retained an irregular shape and contours, with evident vacuolized and necrotic cells, as well as zones of hypercellularity (Fig. 4, a). IHC staining demonstrated the presence of β-cells, albeit in very small numbers (typically 1–2 cells per field of view), both within the islets and occasionally in the surrounding exocrine parenchyma (Fig. 4, b). However, the limited number of these cells likely rendered them insufficient to significantly impact glycemic regulation. Notably, α-cells continued to represent the predominant islet population (Fig. 4, c). These findings suggest that the observed reduction in blood glucose levels in this group was primarily mediated by the exogenous insulin secreted by the transplanted islets rather than endogenous β-cell regeneration.

Intraperitoneal injection of PCEC induced certain morphological changes in the islet apparatus of **rats in experimental group 2**. In addition to islets exhibiting hypercellularity and necrotic alterations, distinctive is-

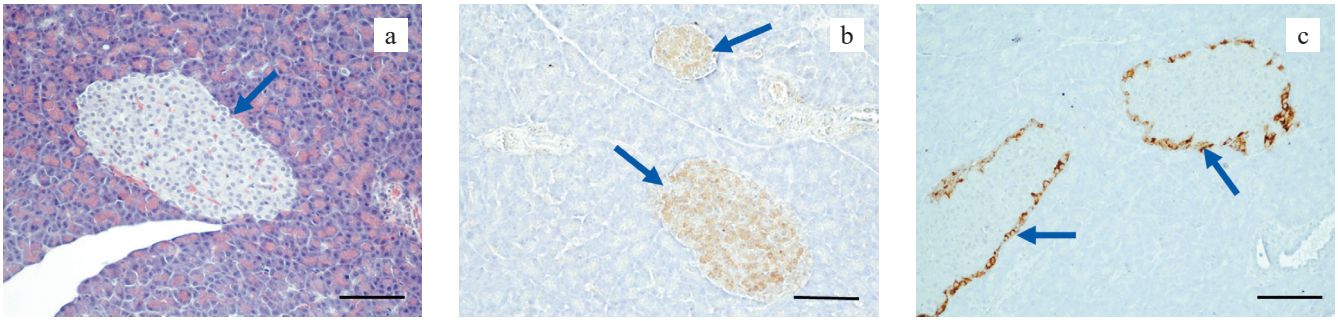

Fig. 2. Histological appearance of the pancreas in a healthy rat. (a) Hematoxylin and eosin (H&E) staining; (b) Immunohistochemical (IHC) staining for insulin; (c) IHC staining for glucagon. Blue arrows indicate pancreatic islets. Scale bar: 100 μm

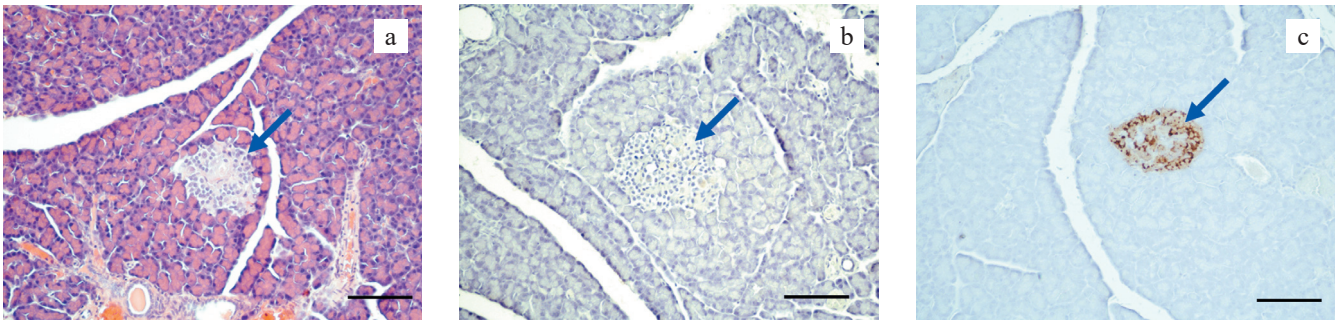

Fig. 3. Histological appearance of the pancreas in a control group rat with experimental T1DM (10 weeks without treatment). (a) Hematoxylin and eosin (H&E) staining; (b) Immunohistochemical (IHC) staining for insulin; (c) IHC staining for glucagon. Blue arrows indicate pancreatic islets. Scale bar: 100 μm

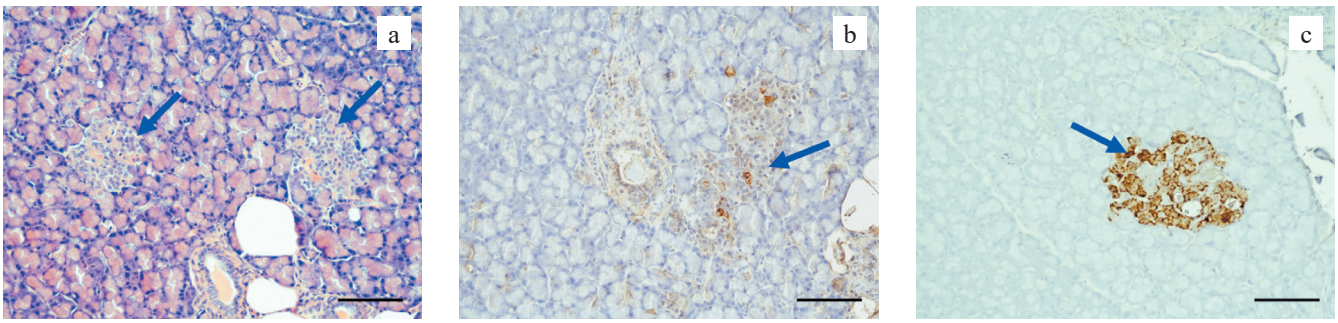

Fig. 4. Histological appearance of the pancreas in a rat from experimental group 1 with experimental T1DM after intraperitoneal injection of pancreatic islets (10 weeks post-treatment). (a) Hematoxylin and eosin (H&E) staining; (b) Immunohistochemical (IHC) staining for insulin; (c) IHC staining for glucagon. Blue arrows indicate pancreatic islets. Scale bar: 100 μm

lets with irregular morphology and branching structures extending into the adjacent exocrine parenchyma were observed in half of the animals (n = 2) (Fig. 5, a). These atypical islets lacked zones of hypercellularity and displayed a relatively uniform distribution of insulocytes (Fig. 5, b). A marked increase in the number of insulin-

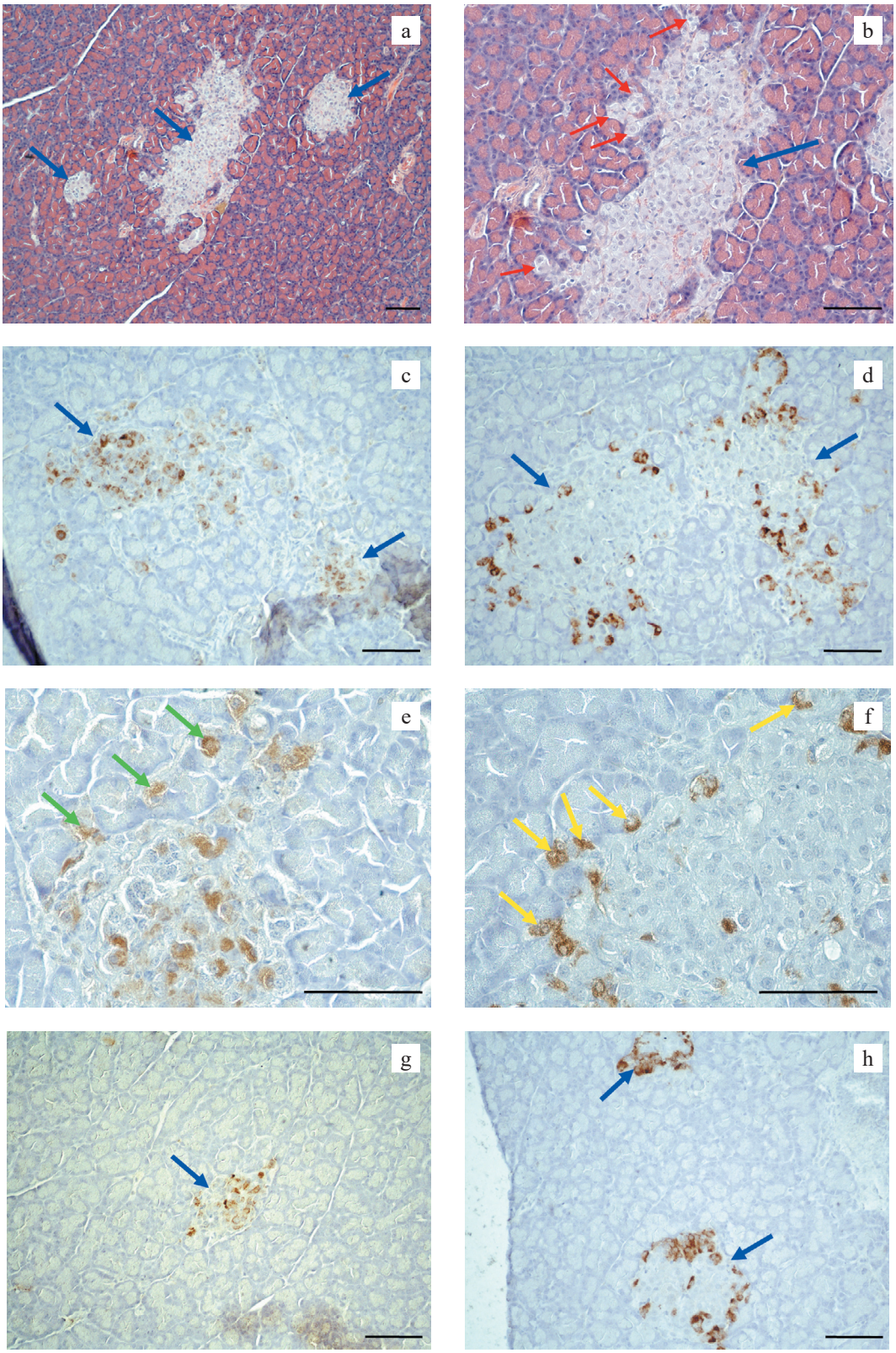

Fig. 5. Histological appearance of the pancreas in rats from experimental group 2 with T1DM after intraperitoneal injection of pancreatic cell-engineered construct (10 weeks post-treatment). (a, b) Hematoxylin and eosin (H&E) staining; (c, e, g) Immunohistochemical (IHC) staining for insulin; (d, f, h) IHC staining for glucagon. Blue arrows indicate pancreatic islets; green arrows indicate insulin-positive cells in the acinus; yellow arrows indicate glucagon-positive cells in the acinus; red arrows indicate acino-insular complexes. Scale bar: 100 μm

immunopositive β-cells was detected in these islets, reaching several dozen per islet – substantially exceeding the levels observed in control specimens (Fig. 5, c). Glucagon-positive α-cells no longer constituted the dominant islet cell population (Fig. 5, d).

At the same time, light-colored cells with no apical-basal polarity, fine-grained cytoplasm and large, well-structured nucleus were detected in the neighboring acinus, directly in the lining. Their number ranged from one to several per acinus. IHC staining revealed that a subset of these cells expressed either insulin (Fig. 5, e) or glucagon (Fig. 5, f), hormones characteristic of β- and α-cells, respectively.

It is noteworthy that the described structures, known as acino-insular complexes (Fig. 5, b), are typically observed in the developing pancreas of certain animal species during intrauterine life and are considered to play a significant role in the ontogeny of the islet apparatus [30–32]. Standard-shaped islets in other animals (n = 2) from experimental group 2 also showed a more prominent replenishment of insulin-positive β-cells compared to those receiving only PIs suspensions (Fig. 5, f). Concurrently, a reduction in the number of glucagon-positive α-cells was observed relative to the control group (Fig. 5, g). Such islets were observed in other rats (n = 2) of experimental group 2.

These findings suggest that the observed replenishment of the β-cell population likely resulted from induced reprogramming and transdifferentiation processes involving both acinar epithelial cells and certain islet-resident insulocytes. This regenerative activity may represent a compensatory mechanism. We believe that the most significant reduction in glycemia observed in the experiment was due not only to the sustained insulin secretion from the implanted PCECs, but also to endogenous insulin production by the regenerated population of the recipient's own β-cells.

Thus, our findings support the current understanding of pancreatic cell plasticity, suggesting that β-cell regeneration can occur not only from other insulocyte types but also from the exocrine components of the pancreas [7, 21, 33]. These results highlight the relevance of further research to explore and elucidate this regenerative potential.

Partial restoration of the endogenous β-cell pool was observed following the intraperitoneal implantation of a pancreatic tissue-engineered construct composed of floating islet-like cultures derived from the PIs of newborn rabbits and a collagen-containing hydrogel [34].

Identifying and harnessing factors that induce β-cell regenerative capacity could provide novel therapeutic avenues for diabetes treatment. However, further investigation is needed to elucidate the mechanisms, regulatory pathways, and specific cell types involved in β-cell regeneration under both physiological and pathological conditions [21].

CONCLUSION

Based on the presented data, it can be concluded that PCEC implantation in rats with STZ-induced T1DM not only compensates for lost β-cell function and exerts a direct antidiabetic effect, but also serves as a catalyst for regenerative processes, potentially restoring the recipient's insulinocyte pool.

Therefore, the use of PCEC for stimulating β-cell regeneration represents a promising therapeutic strategy in the treatment of diabetes characterized by β-cell deficiency.

The authors declare no conflict of interest.

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