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EXTRACELLULAR MATRIX BIOMIMETICS FOR PANCREATIC TISSUE ENGINEERING

A.S. Ponomareva[1], N.V. Baranova[1], Yu.B. Basok[1], V.I. Sevastianov[1, 2]

[1] Shumakov National Medical Research Center of Transplantology and Artificial Organs, Moscow, Russian Federation

[2] Institute of Biomedical Research and Technology, Moscow, Russian Federation

Isolated islet transplantation offers a safer and less invasive alternative to whole pancreas transplantation for patients with complicated type 1 diabetes mellitus. However, the procedure faces significant challenges, including the loss of vascularization, innervation, and extracellular matrix (ECM) support. Additionally, factors such as hypoxia, oxidative stress, inflammatory responses, and the cytotoxic effects of immunosuppressive therapy compromise islet viability significantly and limit long-term graft function. Tissue engineering and regenerative medicine strategies aim to address these challenges. A central objective is the development of biocompatible, biomimetic ECM scaffolds (frameworks, carriers, or matrices) that can provide both mechanical support and a suitable microenvironment for islet cells *in vitro* and *in vivo*. This review aims to systematize current data on the use of biomimetic ECMs in the creation of stable, tissue-engineered pancreatic constructs.

Keywords: diabetes mellitus, pancreas, islets of Langerhans, extracellular matrix, biomimetics, scaffold, biomaterials.

INTRODUCTION

Type I diabetes mellitus (T1D) is characterized by autoimmune destruction of insulin-producing pancreatic beta cells, resulting in absolute insulin deficiency and development of diabetic complications such as angiopathy, retinopathy, nephropathy, and neuropathy [1, 2]. In patients with high susceptibility to severe hypoglycemia and poor glycemic control, transplantation of functionally active pancreatic islets using the Edmonton protocol has emerged as a modern therapeutic option. This approach typically requires a substantial islet mass, often obtained from multiple donors [3]. Pancreatic islet transplantation represents a safer and less invasive alternative to whole-organ transplantation [4, 5], enabling the achievement of stable euglycemia, lowering the risk of secondary diabetic complications, and improving quality of life compared with conventional insulin therapy [6–8].

Despite advances in clinical islet transplantation, its widespread application remains limited by the shortage of donor organs and decline in islet viability at all stages of graft isolation, preparation, and engraftment. The reduction in functional activity is primarily associated with impaired blood supply, loss of innervation and contact with the extracellular matrix (ECM), oxidative stress, hypoxia, inflammatory responses, and the toxic effects of immunosuppressants [9]. At the same time, there is currently no alternative source of insulin-producing cells suitable for clinical use other than islets. Although induced pluripotent stem cells are under intensive research, their clinical translation is hindered by risks such as teratoma formation and other unpredictable consequences related mainly to genetic modifications. Another major challenge is preserving the feedback mechanisms that regulate glucose homeostasis, which are mediated by the coordinated activity of islet cell types: alpha cells (secreting glucagon), beta cells (secreting insulin), delta cells (secreting somatostatin), and minor populations producing pancreatic polypeptide and ghrelin [10, 11]. The main advantage of islet transplantation over insulin-producing cells of other origins is the retention of intra-islet paracrine interactions between beta cells and other endocrine cell types [12].

Recent studies provide encouraging evidence for the potential of tissue engineering and regenerative medicine technologies to ensure long-term preservation of the viability and functional activity of human pancreatic islets after transplantation [13]. Of particular interest is the development of tissue-engineered pancreatic constructs (TEPCs), which are based on insulin-producing cells immobilized within a biocompatible scaffold. Such scaffolds not only provide mechanical support but also prolongs cell viability and function. The creation and application of these constructs may offer an alternative therapeutic strategy for diabetes mellitus and serve as a valuable platform for the development and preclinical testing of new drugs.

Biocompatible scaffolds are also used for encapsulation of islet cells, an effective strategy to protect transplants from immune rejection [14]. This encapsulation technology involves placing insulin-producing cells

Corresponding author: Anna Ponomareva. Address: 1, Shchukinskaya str., Moscow, 123182, Russian Federation. Phone: (499) 196-26-61; (926) 585-23-73. E-mail: a.s.ponomareva@gmail.com

within semi-permeable biomaterials, where the defined pore size of the capsule membrane allows diffusion of nutrients and secreted insulin while blocking immune cells and large molecules such as immunoglobulins. Successful encapsulation is expected to eliminate the need for lifelong immunosuppression. The use of biocompatible materials for encapsulation has resulted in increased survival and functional activity of islet grafts [15, 16].

To further improve the secretory function of transplanted islets, co-encapsulation approaches have been explored, incorporating ECM molecules or supportive cells such as mesenchymal stromal cells. These cells exert beneficial paracrine and immunoregulatory effects [12, 17]. Some of the developed immunosuppressive devices, such as PEC-Encap (ViaCyte, Inc., USA), βAir (BetaO2 Technologies Ltd., Israel), and the Cell Housing Device (Vertex Pharmaceuticals, USA), have already undergone clinical trials [14].

Despite these advances, translation of encapsulation technology into routine clinical practice faces several critical challenges. Among them are insufficient biocompatibility of capsules that may trigger inflammatory responses and foreign-body reactions; fibrotic overgrowth around implanted capsules; and incomplete vascularization of surrounding tissues, leading to cell hypoxia [16].

The key tasks in the development of TEPCs are to establish optimal conditions for obtaining and culturing enough insulin-producing cells and to identify suitable scaffolds (frames, matrices, carriers) capable of mimicking the structure and composition of the native ECM. Such scaffolds should provide the most favorable microenvironment for sustaining the functional activity of the transplanted cells [18].

DEVELOPMENT OF SCAFFOLDS FOR TISSUE-ENGINEERED CONSTRUCTS

Scaffolds used in tissue engineering must have physical, mechanical, and biological properties that support the survival and functionality of specific cell types both *in vitro* and *in vivo*. Investigations into the composition and organization of native tissue ECM are critical, as they reveal the specific structural and biochemical characteristics that should guide the selection of scaffold materials.

ECM is a complex and dynamic network of macromolecules synthesized by cells, essential for maintaining tissue integrity and providing rigidity, elasticity, and resilience [15]. The ECM supports tissue-specific cell homeostasis, phenotype, and function. Its components interact with growth factors and cell surface receptors to regulate key cellular processes, including proliferation, differentiation, morphology, gene expression, intracellular signaling, adhesion, migration, secretory activity, and survival [19].

Recent studies in mice and pigs have identified 12 distinct ECM proteins in the pancreas, including collagens I, III, IV, V, and VI, laminin, elastin, fibronectin, fibrillin, glycosaminoglycans (GAGs), among others [18, 20–23]. The three-dimensional (3D) architecture of the pancreatic ECM determines the topographical location of endocrine cells, which influences the viability and secretory function of the islets [12].

When selecting a scaffold, it is essential to account for the multicomponent, biochemically complex composition of the ECM, its structural specificity, and tissue-specific functions. For the creation of TEPCs, bioresorbable scaffolds designed to mimic the properties of native ECM, the so-called ECM mimetics, are used. These scaffolds are developed from natural and synthetic materials, as well as their composites [12, 15, 18]. Critically, scaffold materials must provide controlled 3D structural parameters, including porosity, pore size, and surface roughness, in order to mimic the native cellular niche [15, 24–26].

Examples of biomaterials applied in liver tissue engineering are presented in Table 1.

Various types of scaffolds are used in tissue engineering, including films, membranes, sponges, gels, cryogels, fibrous materials produced by electrospinning, as well as decellularized tissues and organs [26].

Simpler two-dimensional scaffolds can reproduce certain aspects of cell–matrix interactions and help modulate cell behavior and signaling. However, they may also alter the normal cell phenotype compared to more complex 3D structures. In contrast, porous 3D scaffolds more closely simulate the native tissue microenvironment, enabling higher cell density, improved nutrient and oxygen diffusion, thereby prolonging cell survival and enhancing secretory capacity [18, 25, 83].

In a study by Buitinga et al., three methods for fabricating scaffolds with microcavities and pore diameters not exceeding 40 μm were compared: leaching, casting, and laser drilling. The evaluation focused on pore size and geometry, reproducibility of the method, and the shape and stability of the resulting scaffold. In a T1D

Table 1

Biomaterials used for pancreatic tissue engineering

Natural	
Alginate	[27–32]
Collagen	[33–42]
Chitosan	[35, 38, 43]
Fibrin	[44–48]
Gelatin	[43, 49, 50]
Silk	[51–53]
Decellularized tissues	[13, 54–64]
Synthetic	
Polyethylene glycol	[65–73]
Polycaprolactone	[74–76]
Polyglycolic acid	[77–79]
Poly(lactic-co-glycolic acid)	[51, 80–82]

mouse model, scaffolds produced by laser drilling proved most effective, ensuring the retention and engraftment of islets when implanted into the white adipose tissue of the epididymis. Transplantation of 300 islets using the scaffold restored normoglycemia in 75% of diabetic mice, whereas transplantation of the same number of islets without a scaffold achieved stable glucose control in only 28.5% of animals [84].

A promising strategy for creating macroporous scaffolds with interconnected pore networks – meeting the structural requirements for cell-based technologies and tissue engineering – is cryogenic structuring of polymer systems [85–87]. For example, cryogenically structured biopolymer substrates based on spongy agarose cryogels modified with gelatin have shown high biocompatibility and supported the long-term viability and insulin-secreting activity of mouse islet cell lines *in vitro* [88, 89].

It is worth noting that scaffold modification with ECM components not only provides structural and mechanical support for islets, thereby preserving their viability and insulin-secreting function, but also serves as a reservoir of growth factors, cytokines, and antioxidants [19]. Furthermore, incorporating biochemical cues that promote rapid vascularization, such as vascular endothelial growth factor (VEGF), into the scaffold prolongs the functional lifespan of the islet transplant [90].

SCAFFOLDS MADE OF SYNTHETIC MATERIALS

Synthetic materials such as polyethylene glycol, polycaprolactone, polylactic acid, polyglycolic acid, and their copolymers are widely applied in tissue engineering owing to their adjustable physicochemical properties. These materials allow precise control and reproducibility of scaffold characteristics, including elasticity, stiffness, porosity, biodegradability, and ease of chemical modification [14, 15, 91]. Both single-polymer systems and multi-component composites can be processed into scaffolds with predetermined architectures, for example, using 3D printing and electrospinning.

In an experimental study, Chun et al. demonstrated that islets immobilized on a fibrous scaffold made of polyglycolic acid exhibited a four-fold increase in insulin secretion index and a two-fold increase in cell survival compared with islets cultured without a scaffold over 15 days [77].

In a comparative study, Daoud et al. cultured equal numbers of human islets for 10 days under different conditions: on microscaffolds composed of a polylactic–polyglycolic acid copolymer modified with ECM proteins (type I collagen, type IV collagen, and fibronectin); in a gel containing the same ECM proteins; in a gel containing only type I collagen; and in suspension culture without additives as a control. The highest glucose stimulation index, comparable to that of freshly isolated islets, was observed when islets were immobilized on microscaffolds. This effect was attributed to the combined influence of mechanical support, presence of ECM components, and enhanced diffusion and cell–cell interactions afforded by the interconnected pore system of the scaffold [81].

Knobeloch et al. further explored the potential of a polyethylene glycol–based injectable hydrogel as an encapsulation material. Human islets cultured in this hydrogel for 6 days maintained their shape and structural integrity, both of which are crucial for functional performance. Importantly, basal and glucose-stimulated insulin secretion were significantly higher in hydrogel-encapsulated islets compared to those cultured in suspension [73].

Despite examples of successful use of synthetic scaffolds in tissue engineering, their inherent limitations, such as hydrophobicity, absence of cell adhesion sites, and lack of cell recognition signals, often necessitate pre-modification with angiogenic factors or ECM components.

SCAFFOLDS FROM NATURAL MATERIALS

Natural materials such as polysaccharides (chitosan, alginate, hyaluronic acid) and proteins (collagen, fibrin, silk), are also widely employed in the creation of TEPCs. These materials offer several advantages, such as low toxicity, biocompatibility, and biodegradability. Moreover, scaffolds derived from natural sources contain bioactive components that facilitate stronger interactions with insulin-producing cells, thereby enhancing the functionality of the formed TEPC. However, their use is not without limitations, which include temperature sensitivity, potential immunogenicity, and heterogeneity that may vary depending on the source material.

Alginate, a natural and biocompatible polysaccharide with mild gel-forming properties, is widely used as a functional biomaterial for the production of injectable hydrogels designed for encapsulating islets [32].

Collagen, the most abundant protein in mammals, plays a central role in providing structural support to tissues, mediating intercellular contacts, and regulating cell behavior, including the function of islet cells [15, 19]. Studies have shown that isolated islets incubated with collagen-containing scaffolds retain their integrity, viability, and secretory function for longer periods compared to islets cultured in suspension.

In particular, Pinkse et al. reported that rat pancreatic islets cultured in standard Petri dishes rapidly underwent structural degradation, with fewer than 10% remaining viable after 48 hours of incubation. Coating the culture surface with type I collagen improved islet viability to 60%, while modification with type IV collagen – the principal protein of the basement membrane – further enhanced survival to 89% [92].

Llacua et al. demonstrated that the addition of type VI collagen to alginate capsules positively influences

both the viability and functional activity of encapsulated human pancreatic islets *in vitro* [23].

Among biomimetic materials that replicate the composition of native ECM, particular attention has been given to collagen-containing hydrogels such as Sphero®GEL (AO BIOMIR, Russia), derived from natural compounds. This material has been successfully applied to the development of liver and cartilage tissue-engineered constructs [13, 93]. In a related study, Baranova et al. reported that rat islets cultured within a collagen-containing hydrogel remained structurally intact and free from degradation for 10 days compared to islets cultured in suspension [42].

Taken together, these findings confirm that collagen-containing scaffolds play a critical role in preserving the native architecture and functional integrity of islets, both *in vitro* and *in vivo* [13, 18, 23].

Gelatin, a water-soluble substrate derived from collagen hydrolysis, retains peptide sequences that promote cell adhesion and migration. Muthyala et al. demonstrated that incorporating gelatin into polymer scaffolds preserved the structural integrity and viability of mouse islets of Langerhans *in vitro* for up to 30 days, compared to scaffolds without gelatin [49].

Laminin, a structural non-collagenous glycoprotein of the basement membrane, interacts with all ECM components and plays a crucial role in modulating cell behavior. It influences cell morphology, proliferation, motility, and differentiation, thereby enhancing the survival and insulin-producing function of islet cells *in vitro* [19]. Sojoodi et al. reported upregulation of specific genes and increased insulin secretion in rat islets of Langerhans cultured for 7 days on laminin-coated scaffolds [20]. Similarly, Sigmundsson et al. reported sustained functional activity of both mouse and human islets incubated on α5-laminin–coated membranes for 1–2 weeks. Notably, implantation of 110–150 islets on laminin-coated membranes under the renal capsule of T1D mice restored normoglycemia in 27% of animals within 3 days, in 68% by 7 days, and in 100% by 14 days [21].

Fibronectin is a non-collagenous ECM glycoprotein predominantly expressed in blood vessels, ductal cells of the developing mammary gland, and in the basement membrane. It plays a central role in cell adhesion, migration, proliferation, differentiation, and apoptosis by directly mediating cell interactions. In tissue engineering, fibronectin is used as a component of the culture medium or as a substrate in cell culture, including islet cells, in order to preserve their viability and functionality. Incubation of human and rat islets with soluble fibronectin has been shown to enhance insulin secretion in response to glucose stimulation and to increase the expression of the t-SNARE proteins syntaxin 1 and SNAP-25 *in vitro* [22]. Similarly, Hamamoto et al. reported improved secretory function of islets after 48 hours of culture with fibronectin compared to standard culture conditions. Notably, transplantation of islets preconditioned with fibronectin into rats resulted in decreased blood glucose levels and elevated plasma insulin concentrations within 2 weeks [94].

Thus, the use of fibronectin in pancreatic tissue engineering improves the preservation and function of islets *in vitro* and extends the viability of islet transplants *in vivo*.

Elastin is the principal fibrillar protein of elastic fibers in native tissue, providing mechanical strength, elasticity, resilience, and extensibility. Scaffolds composed of elastin and collagen have been shown to stimulate vascularization at extrahepatic transplantation sites in mice, thereby enhancing islet engraftment, survival, and function sufficient to restore euglycemia in diabetic recipients [90]. Modern strategies in pancreatic tissue engineering increasingly employ decellularized tissues enriched with elastin, elastin-containing synthetic biomaterials, and methods that stimulate *de novo* elastin synthesis [95].

In summary, scaffolds derived from natural materials, owing to their intrinsic bioactive components, are promising for use in pancreatic tissue engineering.

TISSUE-SPECIFIC SCAFFOLDS

Current research in tissue engineering is increasingly directed toward the development of scaffolds derived from decellularized tissues and organs [13, 19]. Decellularization is a multi-step process in which the cellular components of native tissue are removed while preserving the ECM architecture and composition [96]. This strategy enables the production of biomimetic ECM scaffolds with high biocompatibility, reduced immunogenicity, and structural and biochemical characteristics resembling native tissue, thereby providing a microenvironment close to the native one for recellularized cells.

Effective decellularization typically requires the use of combined approaches – integrating physical, chemical, and enzymatic methods of tissue processing (Table 2).

Among the physical methods of decellularization, the most widely used are freezing–thawing, perfusion, mechanical agitation, grinding, and ultrasonic exposure [13]. Freezing causes the formation of ice crystals within cells, leading to membrane rupture and subsequent cell lysis. However, this process can also damage ECM proteins; therefore, careful control of the cooling and thawing rates is required to regulate crystal size [97].

Cell lysis can also be achieved by applying direct pressure to the tissue, though this approach is effective primarily for organs with a less dense ECM organization, such as the liver or lungs. In addition, mechanical mixing methods – including rotation, rocking, or shaking – help to dislodge and remove cellular debris [62].

Physical methods alone are insufficient to ensure complete removal of cellular components from the tissue. Combining them with chemical and enzymatic techniques significantly improves decellularization ef-

Table 2

Tissue decellularization methods

Physical methods
Freezing/thawing Mechanical grinding Micronization Mixing, rotation, shaking Perfusion Mechanical pressure Ultrasonic exposure
Chemical methods
Ionic surfactants (SDS) Nonionic surfactants (Triton X-100) Zwitterionic (amphoteric) surfactants (CHAPS) Acids (EDTA) Alkalis (NaOH) Hypotonic/hypertonic solutions
Enzymatic methods
Proteases (trypsin, pepsin) Nucleases (DNase, RNase)

ficiency. For example, surfactants are commonly applied to dissociate and dissolve cell membranes and residual debris.

Among the chemical methods of decellularization, the most commonly used surfactants are Triton X-100 (nonionic) and sodium dodecyl sulfate (SDS) (ionic). Triton X-100 disrupts lipid–protein and lipid–lipid interactions while largely preserving protein–protein bonds, leading to cell separation and membrane lysis. Because of its relatively mild effect, it is often applied to tissues with high protein content, though caution is required when decellularizing tissues rich in glycosaminoglycans (GAGs) [64].

SDS dissolves both cytoplasmic and nuclear cell membranes well and can denature proteins by disrupting protein-protein interactions. However, prolonged SDS exposure may damage the overall structure of ECM [13]. Another chemical approach is osmotic shock, achieved by sequential exposure of tissue to hypotonic and hypertonic solutions. While this effectively induces cell lysis, it does not fully remove cellular debris [98].

The zwitterionic surfactant CHAPS (a bile acid derivative) acts by disrupting lipid–lipid and lipid–protein interactions, thereby lysing cell membranes. Due to its limited penetration capacity, CHAPS is primarily used for thin-layer tissues [96].

Because residual nuclear material can strongly bind to ECM proteins, enzymatic processing is often combined with chemical methods. DNases are widely used to degrade and remove nuclear remnants [62, 96]. Proteolytic enzymes are also employed, including trypsin (hydrolyzes proteins), elastase (degrades elastin), and dispase (cleaves type I/IV collagen and fibronectin). However, excessive enzymatic exposure may result in loss of ECM components such as collagen, elastin, fibronectin, and laminin [96].

Trypsin is frequently used in combination with ethylenediaminetetraacetic acid (EDTA) to detach cells from the ECM. Yet, prolonged trypsin–EDTA treatment can significantly alter ECM integrity by degrading laminin, removing GAGs, and ultimately reducing the mechanical strength of the tissue [13].

When developing decellularization protocols, it is essential to account for all processing conditions, since physical methods may disrupt ECM ultrastructure, while chemical and enzymatic treatments can degrade ECM components or trigger reactions that alter its biochemical composition [96]. To obtain an optimal scaffold, it is also important to consider the structural characteristics of the native tissue, such as thickness, density, and the presence of fibrosis or lipomatosis, which depend on the individual characteristics of the donor [99]. Therefore, for each individual case of obtaining a tissue-specific scaffold, it is necessary to determine a special original protocol for effective decellularization.

Several studies have reported the generation of scaffolds through whole-pancreas decellularization (Table 3). However, major challenges remain, particularly in achieving uniform recellularization and restoring functional vascularization within these large scaffolds. As an alternative, researchers have proposed the development of injectable TEPCs derived from finely dispersed pancreatic ECM fragments that are recellularized with insulin-producing cells [63, 64, 99]. The availability of TEPCs with specific functional properties and the minimally invasive administration of such a construct make this approach promising for tissue engineering technologies [19, 100]. Moreover, by preserving the natural ECM composition, such scaffolds provide a biomimetic microenvironment for the recellularized islet cells, while complete removal of cellular material from the scaffold ensures low immunogenicity [15, 62, 96, 97].

The liver and pancreas share similar embryonic origins and possess comparable ECM components, including collagens (types I, III, and IV), elastin, laminin, fibronectin, and GAGs [105, 106]. Consequently, decellularized liver scaffolds have emerged as promising alternatives for developing TEPCs, providing a favorable microenvironment for insulin-producing cells. For example, Xu et al. demonstrated that scaffolds derived from decellularized whole mouse liver lobes supported long-term survival and functional maintenance of isolated mouse islets *in vitro* [54]. Similarly, Goh et al. reported successful colonization of decellularized mouse liver scaffolds with insulin-producing cell aggregates differentiated from human pluripotent stem cells [104].

The potential of scaffolds derived from other decellularized organs to prolong the function of insulin-producing cells has also been reported. Khorsandi et al. showed that a rat spleen-derived scaffold increased insulin secretion of MIN6 cells compared with conventional monolayer culture, identifying it as a suitable carrier for

Table 3

Examples of protocols for decellularization of pancreatic tissue

Human	Whole organ	Cold perfusion was performed sequentially using the following solutions: phosphate-buffered saline (PBS) with heparin; Triton X-100 combined with ammonium hydroxide; DNase IV with magnesium chloride; PBS (for removal of remaining surfactants) [101]
	Fragments	Homogenization of pancreatic tissue, followed by centrifugation to remove insoluble fat. The tissue was then incubated in PBS and sodium deoxycholate, followed by treatment with PBS and an antibiotic/antimycotic solution to remove residual surfactants. The material was subsequently lyophilized and subjected to gelation [62]
		Mechanical grinding of pancreatic tissue with sequential treatment using hypotonic and hypertonic solutions containing SDS. This was followed by SDS treatment in the presence of PBS, and surfactant removal with PBS and an antibiotic/antimycotic solution [102]
		For pancreases with lipomatosis: Three cycles of freezing at –80 °C and thawing at +37 °C were performed. The tissue was then ground and treated with surfactant solutions (SDS and Triton X-100). Final rinsing was done using PBS and an antibiotic/antimycotic solution to remove residual surfactants [98, 99]
		For pancreases with fibrosis: The tissue was mechanically ground and subjected to sequential treatment with hypertonic and hypotonic solutions containing SDS. This was followed by treatment with SDS in PBS, and final surfactant removal using PBS with antibiotic/antimycotic agents [98]
Pig	Whole organ	Perfusion with sequential solutions: distilled H_2O, EDTA, and sodium azide; sodium deoxycholate, Triton X-100, and DNase. Cold perfusion using sodium deoxycholate, Triton X-100, and phenylmethylsulfonyl fluoride; distilled H_2O; DNase I in Dulbecco's PBS supplemented with calcium and magnesium chloride. Final surfactant removal was achieved using distilled H_2O containing sodium azide [103]
	Fragments	A total of 8 decellularization protocols were tested, varying by temperature (+4 °C *vs* +24 °C), washing agent (PBS *vs* $NH_3 \cdot H_2O$), and native tissue disintegration method (grinding *vs* cutting). Sequential treatment involving Triton X-100, $NH_3 \cdot H_2O$, and PBS; followed by $NH_3 \cdot H_2O$ washing; DNase incubation in PBS with calcium and magnesium ions; and repeated PBS washes [64]
		Tissue grinding; sequential treatment with hypotonic and hypertonic solutions containing SDS; subsequent treatment with SDS in PBS; and surfactant removal using PBS with antibiotic/antimycotic agents [13]
Rat	Whole organ	Perfusion via the pancreatic duct, gastric artery, portal vein, or splenic vein using the following sequence of solutions: Triton X-100 → SDS → Triton X-100 → DNase → PBS with antibiotic/antimycotic (for surfactant removal) [63]
		Sequential perfusion using: Triton X-100 → SDS → Triton X-100 → PBS (for surfactant removal) [61]
	Fragments	Grinding of fresh pancreatic tissue; sequential treatment with hypotonic and hypertonic solutions containing SDS; SDS treatment in FSB; surfactant removal with PBS containing antibiotic/antimycotic agents [42]
Mouse	Whole organ	Sequential perfusion using: SDS in deionized water; deionized water rinse; Triton X-100 in deionized water; benzonase solution; final wash with PBS containing 10% fetal bovine serum (FBS) and antibiotic/antimycotic agents for surfactant removal [104]
		Perfusion with double-distilled water, followed by freezing of the lipid bilayer at –80 °C and thawing at room temperature. Subsequent perfusion was performed using PBS, Triton X-100, and ammonium hydroxide, with final washing in PBS to remove residual surfactants [55]

beta-cell transplantation [107]. A bioartificial pancreas generated from decellularized pig lung tissue seeded with human islets exhibited prolonged viability and insulin secretion *in vitro*, comparable to freshly isolated islets. This construct was recommended as a reliable platform for real-time drug screening [108].

The introduction of a hydrogel phase into the composition of TEPC can prevent sticking and rapid sedimentation of scaffold microparticles derived from decellularized pancreatic tissue [15, 62]. Recent approaches have focused on the development of hydrogels based on decellularized pancreatic tissue that are capable of polymerizing *in situ* under physiological conditions [109]. Hydrogels not only facilitate the delivery of ECM components and growth factors to insulin-producing cells within TEPC, but can also be applied for encapsulating islet cells or serve as bio-inks for bioprinting.

In addition, methods have been established for fabricating 3D macroporous spongy scaffolds from hydrolysates of decellularized tissues, with cryogenic structuring emerging as a particularly promising technique. In this process, the macroporous architecture is generated at subzero temperatures, where frozen solvent crystals function as porogens [110]. For example, Kim et al. produced a macroporous sponge material from decellularized pig kidney tissue by creating a chemically cross-linked cryogel followed by lyophilization [111]. This material was successfully applied both as a hemostatic sponge and as a cell carrier in tissue-engineered constructs using fibroblasts isolated from rat kidneys. Borg et al. showed that the interconnected macroporous structure of cryogels of varying sizes enabled uniform colonization by mesenchymal stem cells and immobilization of islets. The survival and functional activity of

islets seeded into cryogels were confirmed *in vitro* and *in vivo* following implantation in mice [112].

As shown by the data reviewed, the development of biocompatible and functional scaffolds based on natural ECM, possessing properties characteristic of the native pancreatic microenvironment, remains a pressing challenge.

CONCLUSION

The design of ECM biomimetic scaffolds that closely mimic the native microenvironment of insulin-producing cells holds great potential for improving the clinical outcomes of islet transplantation by prolonging cell viability and maintaining insulin secretory function both *in vitro* and *in vivo*. Various scaffold materials, derived from different sources, offer distinct advantages and limitations, underscoring the need for ongoing research to determine the optimal composition and architecture of scaffolds for TEPC formation and clinical translation.

Among the most promising approaches in regenerative medicine is the use of scaffolds generated from decellularized tissues, whose multicomponent composition closely resembles that of native ECM. Particularly noteworthy is the emerging technology of cryogenic structuring of decellularized tissue hydrolysates, which enables fabrication of highly biocompatible scaffolds with predefined shapes, optimal mechanical properties, and interconnected porous networks.

At the same time, the search for renewable and functionally active insulin-producing cells, capable of responding to fluctuations in the recipient's blood glucose levels, remains a priority. The synergistic integration of innovations in materials science and cell technologies will advance the effectiveness and accessibility of cell replacement therapies for type 1 diabetes, making them available to a broader patient population.

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