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REVIEW ARTICLE

Advancements in biomaterials and biofabrication for enhancing islet transplantation

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Abstract

Type 1 diabetes (T1D) is characterized by the degeneration of insulin-producing beta cells within pancreatic islets, resulting in impaired endogenous insulin synthesis, which necessitates exogenous insulin therapy. Although intensive insulin therapy has been effective in many patients, a subset of individuals with unstable T1D encounter challenges in maintaining optimal glycemic control through insulin injections. Pancreatic islet transplantation has emerged as a promising therapeutic alternative for such patients, offering enhanced glucose regulation, reduced risk of complications, and liberation from exogenous insulin reliance. However, impediments such as immune rejection and the need for an optimal transplantation environment limit the success of islet transplantation. Revascularization, a crucial requirement for proper islet functionality, poses a challenge in transplantation settings. Biomaterial-based biofabrication approaches have attracted considerable attention to address these challenges. Biomaterials engineered to emulate the native extracellular matrix provide a supportive environment for islet viability and functionality. This review article presents the recent advancements in biomaterials and biofabrication technologies aimed at engineering cell delivery systems to enhance the efficacy of islet transplantation. Immune protection and vascularization strategies are discussed, key biomaterials employed in islet transplantation are highlighted, and various biofabrication techniques, including electrospinning, microfabrication, and bioprinting, are explored. Furthermore, the future directions and challenges in the field of cell delivery systems for islet transplantation are discussed. The integration of appropriate biomaterials and biofabrication methods has significant potential to promote successful islet transplantation by facilitating vascularization and bolstering the immune defense mechanisms.

Keywords: Biomaterials; Biofabrication; Islet transplantation; Immunosuppression; Pre-vascularization

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1. Introduction

Pancreatic islets, composed of endocrine and insulin-producing beta cells, are diminutive cellular aggregates situated within the pancreas. In type 1 diabetes (T1D), also referred to as insulin-dependent or juvenile diabetes, the immune system specifically targets and annihilates beta cells, leading to impaired insulin production. Intensive insulin therapy presents itself as a viable solution that efficaciously ameliorates the regulation of blood glucose levels and mitigates the risk of subsequent complications, such as neuropathy, nephropathy, retinopathy, and cardiovascular ailments. Despite intensive insulin therapy, a subset of patients with unstable T1D experience challenges in sustaining glycemic control through insulin injections. Hypoglycemia is a prevalent occurrence in individuals with diabetes, irrespective of the diabetes type, particularly among those undergoing insulin therapy[1]. Unmitigated severe hypoglycemic incidents can precipitate adverse outcomes, such as unconsciousness, convulsions, and fatality.

In contrast, pancreatic islet transplantation has emerged as a viable therapeutic alternative for individuals with T1D who exhibit inadequate glucose control or insulin-induced hypoglycemia[2-4]. Islet transplantation decreases hemoglobin A1c levels, reduces the risk of diabetic complications, and eliminates the requirement for exogenous insulin, which is closely linked to an improved quality of life[5]. Although islet transplantation is a promising treatment for diabetes, it has certain challenges, such as susceptibility to the cellular microenvironment and vulnerable environments[6] and immune-hostile conditions[7]. Additionally, the transplantation site and surrounding environment often differ from those of natural islets, posing a significant obstacle to the success of insulin-producing cells. Revascularization, which involves the diffusion of oxygen, nutrients, metabolic waste, and insulin, is crucial for the proper functioning of the transplanted islets.

To address these challenges, current approaches, such as oxygenation with supplemental biomaterials, co-culturing with vascular cells, treatment with immunosuppressive drugs, and encapsulation of islets, are being actively explored. In particular, biomaterial-based biofabrication, which is considered a potential solution to overcome current problems, is under investigation.

Biomaterials are usually designed to mimic the biochemical and biophysical properties of the natural extracellular matrix (ECM), thereby providing a supportive environment for cells to thrive. Enhancing interactions between cells and biomaterials can improve cellular function, maturation, and signal transduction[8]. Consequently, suitable biomaterials and biofabrication methods can serve as novel tools for promoting vascularization and immune defense, thereby facilitating successful islet transplantation.

This review provides an overview of recent advances in biomaterials and biofabrication technologies for engineering cell delivery systems aimed at enhancing the efficacy of islet transplantation (Figure 1). First, we elucidated the pivotal components crucial for the success of islet transplantation, with a specific emphasis on the immune protection and vascularization strategies employed for optimal islet delivery. Subsequently, we offer a brief overview of the key biomaterials used in islet transplantation, underscoring their importance in implementing the full potential of islet delivery systems. In addition, we discuss recent biofabrication technologies leveraged for the development of islet delivery systems. Finally, we present an outlook on the future prospects and challenges in the field of cell delivery systems for islet transplantation.

2. Critical considerations for islet transplantation

2.1. Immunosuppression

Islet transplantation has recently garnered considerable attention due to advancements in islet isolation technology and immunosuppressive treatments[9]. The islet transplantation approach in clinical practice involves the infusion of islets into the patient's liver through the portal vein. However, the transplantation site presents a non-ideal environment characterized by high glucose concentrations, low oxygen levels, and other unfavorable factors. Furthermore, infusion of islets through the hepatic portal vein elicits an immediate blood-mediated inflammatory reaction. In addition, hypoxic islets secrete chemokines and express tissue factors that initiate thrombotic responses. Subsequently, platelets are recruited to the islet surface, attracting leukocytes and macrophages that infiltrate the islet cells and lead to their destruction. Hence, several challenges associated with islet transplantation remain, including suboptimal efficiency of cell delivery, inadequate islet functionality and viability, restricted transplant construct volume, and high dosages of immunosuppressive drugs post-transplantation[10-12]. These obstacles impede the efficacy of islet transplantation, primarily because of the host immune response against the transplanted cells and the insufficient or absent vascularization, ultimately leading to compromised survival and functionality of the islets. To circumvent these limitations, researchers are pursuing novel strategies such as immune evasion mechanisms or promoting vascularization to improve islet engraftment and functionality.

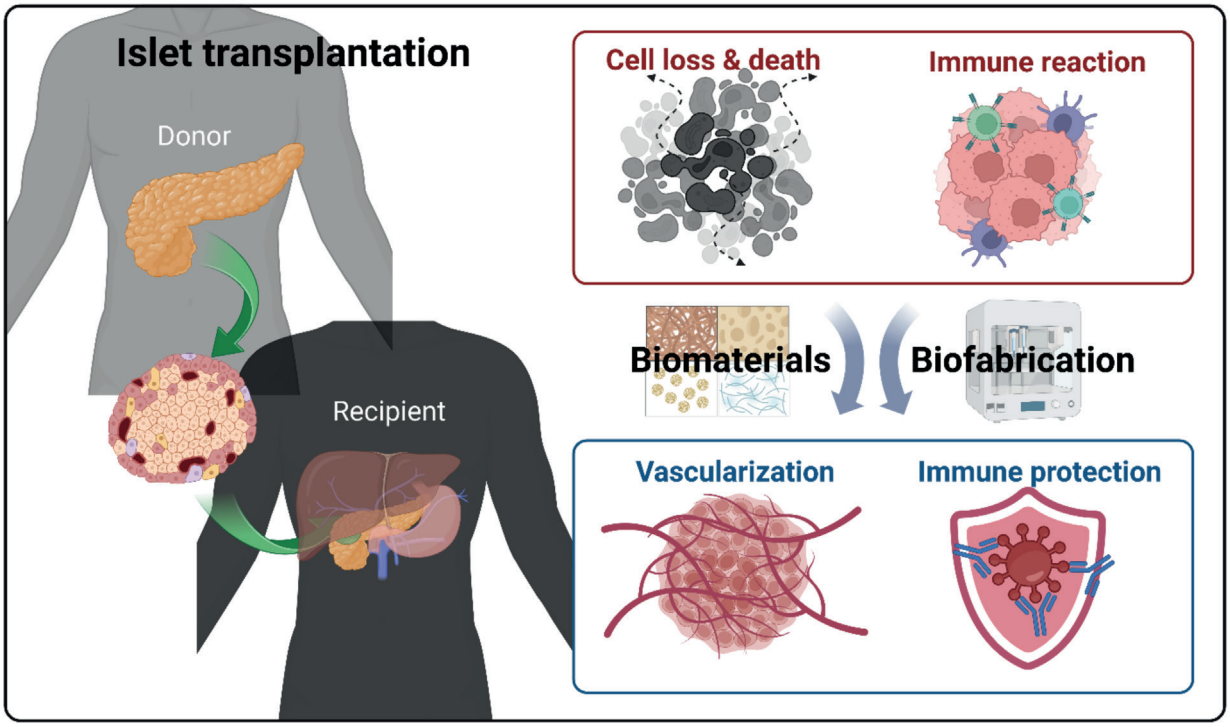

Figure 1. Overview of biomaterials and biofabrication technologies for islet delivery systems.

To mitigate the associated risk of immune-mediated destructions (e.g., autoimmune and alloimmune mechanisms), immunosuppressive tactics are commonly employed to safeguard the transplanted islets from immune-mediated harm[13]. Although these strategies effectively evade or reduce transplant rejection, they may also lead to unintended adverse effects, including hepatotoxicity, nephrotoxicity, and heightened susceptibility to infections and cancer[14]. Therefore, successful transplanted islets need to be protected from the immune system and the toxicity of immunosuppressive drugs.

However, the use of immunosuppressive drugs poses an additional challenge because of their potential toxicity to the pancreatic islets. In addition, there is some concern regarding the utilization of allogeneic and xenogeneic cell sources in islet transplantation, primarily due to their inherent immunogenic response. In light of this, induced pluripotent stem cells (iPSCs), generated through the cellular reprogramming of somatic cells, have garnered attention for their potential to differentiate into islet cells. Non-invasive collection from patients and the possibility of autografts without immunomodulation make human iPSCs (hiPSCs) a promising alternative to stem cells in the field of regenerative medicine. Notably, the use of hiPSCs potentially reduces ethical concerns associated with embryonic stem cell (ESCs) applications. Moreover, novel immune-evasive islet-like organoids have been developed that show restricted T-cell activation and graft rejection compared to non-engineered cells[14]. If it is successful, these strategies could potentially allow the transplantation of human insulin-producing cells into T1D patients without the need for long-term immunosuppression.

2.2. Vascularization

Successful transplantation of islets relies on the establishment of adequate vascularization, which is essential for the efficient exchange of oxygen, nutrients, metabolic waste products, and secreted insulin hormone. This is particularly important considering that the islets of Langerhans naturally inhabit one of the most highly vascularized tissues in the human body. Islet transplantation occurs in an environment where the surrounding capillary network is insufficient, resulting in a lack of adequate oxygen and nutrient supply to the cells during and after transplantation. This deprivation can negatively affect the survival and function of the transplanted islets. Reduced islet viability, attributed to hypoxic sensitivity, is primarily a consequence of insufficient oxygen supply[15]. Improving the survival and function of islets can be achieved by augmenting revascularization through the utilization of proangiogenic elements, including vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (FGF2), as well as by restoring the interaction

between islets and ECM using synthetic peptides and polymer scaffolds[16]. VEGF within transplants stimulates angiogenesis, improves the viability of engrafted islets, and enhances the duration of normalized glycemia in diabetic mice after transplantation[17,18]. Therefore, the local delivery of proangiogenic factors may improve the clinical outcomes of islet transplantation.

Co-culture of angiogenesis-supporting cells can also promote network growth around or within the transplanted islets. Among the endothelial cells, human umbilical vein endothelial cells (HUVECs) are widely used for demonstrating this idea because of their ability to spontaneously assemble into tubular structures in an ECM[19]. Several studies have examined the transplantation of pancreatic islets embedded in endothelialized scaffolds[20,21]. A previous study showed that islets embedded in a HUVECs module returned diabetic mice to normal glycemia. HUVECs seeded on modules maintain the structural integrity of modular implants[22]. Furthermore, facilitating the prompt sprouting of islet endothelial cells post-transplantation could enhance the engraftment process during the phase when the islets are most susceptible. This could serve as an alternative that depends solely on revascularization from the adjacent tissue, a process that typically requires several weeks[23].

3. Biomaterial-based islet encapsulation strategies

Several biomaterial-based strategies have highlighted the crucial role of the extracellular environment in governing cellular behavior, emphasizing the need for regenerative materials that provide biological cues to cells[24]. Biomaterials have emerged as promising solutions to address medical challenges, and current investigations have emphasized the significance of the extracellular milieu in modulating cellular behavior. Islet encapsulation technology is a biomaterial-based approach that involves enveloping islets within biocompatible materials and creating a supportive structure that closely mimics the micro- and macroenvironments of native islets.

3.1. Islet encapsulation strategies

Recently, islet encapsulation has been widely used to provide not only mechanical and biochemical support but also an immune barrier for encapsulated islets. During encapsulation, living cells are suspended in a biomaterial designed to act as a transport barrier, allowing nutrients, oxygen, and waste products to diffuse while providing a barrier to larger objects such as antibodies and immune cells. The three-dimensional (3D) matrix of the capsule fosters a supportive growth environment for islets, preventing merging and interference with the availability of nutrients and oxygen for islet cells located at the center of the capsules[25]. Encapsulation techniques can be broadly classified into two categories based on the size: micro- and macroencapsulation. In microencapsulation, a small number of islets are enclosed in tiny capsules, typically less than a millimeter in size. These microcapsules facilitate the rapid diffusion of nutrients and oxygen, leading to high rates of islet survival because the favorable surface area-to-volume ratio in the microcapsules is beneficial for efficient mass transport. Nevertheless, microencapsulation has limitations, such as the need for a large transplantation site to accommodate the necessary number of capsules, a suitable microvascular bed for immediate nutrient access, difficulties in capsule removal, and insufficient long-term survival rates for functional islets to meet daily insulin demands[26].

In contrast, macroencapsulation entails the entrapment of a higher quantity of islets inside larger capsules, commonly several millimeters in magnitude. These enlarged capsules allow the assembly of an elevated number of islets, leading to enhanced glycemic management and augmented insulin secretion[27]. Nevertheless, macroencapsulation faces certain obstacles, such as the challenge of ensuring proficient exchange of nutrients and oxygen, as well as the potential degradation of capsules over time[26]. Despite the hurdles faced by both microencapsulation and macroencapsulation, the encapsulation approach still holds potential for islet transplantation and offers a possible solution for sustained glycemic regulation in patients with diabetes. Current research efforts are directed toward enhancing the properties of biomaterial in order to overcome the constraints of existing technology and ultimately improve the outcomes of islet transplantation[28].

The integration of islets within the selectively permeable membrane of a macroencapsulation device has been recognized as an effective approach for circumventing the immune response, thereby enabling the transport of insulin from transplanted cellular entities[28]. Macroencapsulation devices, typically ranging in size from millimeters to centimeters, offer the advantage of accommodating multiple islets within a single construct, allowing for efficient encapsulation. The sizable dimensions of macroencapsulation devices afford remarkable adjustability because the membrane size, thickness, and pore size can be precisely tailored. Thus, a single microencapsulation device is able to accommodate the substantial number of islets required for diabetes treatment.

Thus, the utilization of macroencapsulation devices, which act as physical barriers between transplanted cells and their recipients, has emerged as a promising strategy to address specific challenges by eliminating the

need for immunosuppressive measures[29]. The primary objective of an encapsulation device is to establish an environment that fosters the normal secretion of insulin in response to dynamic fluctuations in blood glucose levels while simultaneously safeguarding cell viability through seclusion from the immune system and facilitating the efficient exchange of nutrients and waste products. However, the thickness of the encapsulation device poses challenges in the exchange of small molecules, which may lead to cell death and reduced insulin release. Moreover, the inclusion of multiple islets within a single device reduces the available surface area for small-molecule exchange[30].

3.2. Natural biomaterials

Natural biomaterials offer a cell-friendly environment and exceptional biocompatibility, which are the features incorporated into islet delivery career system. Alginate, a well-known natural biomaterial derived from brown algae and naturally occurring polysaccharide, is widely used for islet encapsulation. Upon reaction with multivalent cations, crosslinking occurs between alginate molecules, resulting in the formation of a robust three-dimensional (3D) gel network structure. The ionotropic gelation of alginate solutions using Ca, Ba, and Fe ions results in water-insoluble alginate, which is known for its biocompatibility and mechanical stability. In particular, crosslinked calcium alginate is suitable for endovascular application[31]. Numerous studies have revealed that the long-term culture viability and survival rate of islet cells improve significantly when the cells are enclosed within alginate capsules. Zhang *et al.* illustrated that a balanced charged anti-biofouling alginate/polyethylene imine (PEI) hydrogel-based encapsulation strategy for islets, which results in insulin independence and immunoisolation, could be effectively utilized in the treatment of T1D (Figure 2A)[32]. The encapsulated islets retained their glucose-responsive and insulin-producing properties. Furthermore, the alginate hydrogel efficiently evaded foreign body reactions *in vivo* following intraperitoneal implantation into an immunocompetent streptozotocin-induced diabetic mouse model (Figure 2B)[32]. Over time, alginate may undergo dissociation as a result of the exchange of divalent cation crosslinking agents with physiologically abundant monovalent cations. However, the lack of hydrolases that can break down high-molecular-weight alginate polymers makes complete degradation of alginate unfeasible, thereby posing a challenge in eliminating alginate from mammals through physiological systems[33]. The molecular weight of residual alginate polymers commonly surpasses 50 kDa, which exceeds the established renal clearance threshold. In order to prevent the accumulation of residual polymer, hydrolytically degradable alginate hydrogels have been formulated via partial oxidation of alginates[34]. Recently, the use of oxidized alginate has been explored in the development of degradable carriers for insulin delivery and islet cell replacement therapy[35]. The key advantage of this degradable carrier is its ability to prevent the accumulation of materials beyond the required insulin dose or islet cell transplantation, thereby addressing the issue of excess material buildup.

Collagen, the primary protein constituent of ECM, is known for its biocompatibility and low immunogenicity[36,37]. The physical behavior of collagen gels is temperature-dependent, where they become fluidized at 10–25°C and relatively rigid at 30–37°C[38]. This temperature responsiveness is particularly valuable for cell delivery in human body because the solution-like pre-gel collagen can be effortlessly transplanted at room temperature and subsequently solidified at body temperature. Once implanted, the gel retained its rigid state, providing mechanical stability and preventing displacement from the implantation site. This property renders collagen gels advantageous for use as scaffolds in tissue engineering and cell delivery. Moreover, collagen can serve as a useful tool for cell encapsulation given its injectable fiber pore sizes of tens of nanometers, enabling the utilization of a collagen fiber membrane that shields the transplanted tissue from the host immune system[39]. Numerous studies have explored the use of collagen-coated scaffolds or mixtures of multiple materials, including collagen, to enhance the biocompatibility of transplants and facilitate islet adhesion to surface[40,41]. Conversely, it has been demonstrated that the combination of collagen with other ECM proteins and growth factors is able to maintain glucose homeostasis after islet transplantation, thereby enabling successful long-term islet transplantation[42]. Yang *et al.* have developed an innovative 3D culture system, namely Disque Platform (DP), that effectively replicates the microenvironment and cellular interactions of pluripotent stem cell-derived beta cells (SC β cells), thereby improving their viability, differentiation, and functionality (Figure 2C)[43]. DP incorporates critical constituents of the ECM, such as laminin and type IV collagen. In the 3D condition, the SC β cells exhibited elevated levels of vital transcription factors and junctional structures compared to those observed in two-dimensional (2D) monolayer conditions (Figure 2D). This technology has the potential to mitigate the adverse effects of existing small molecules for *in vivo* beta cell expansion and provide a renewable supply of islets *in vitro* for the long-term transplantation of patients with diabetes[43].

Heparin, a well-known natural biomaterial, has garnered attention in the field of islet transplantation owing to its propensity to enhance islet angiogenesis via growth factor stabilization. Because of their capacity to

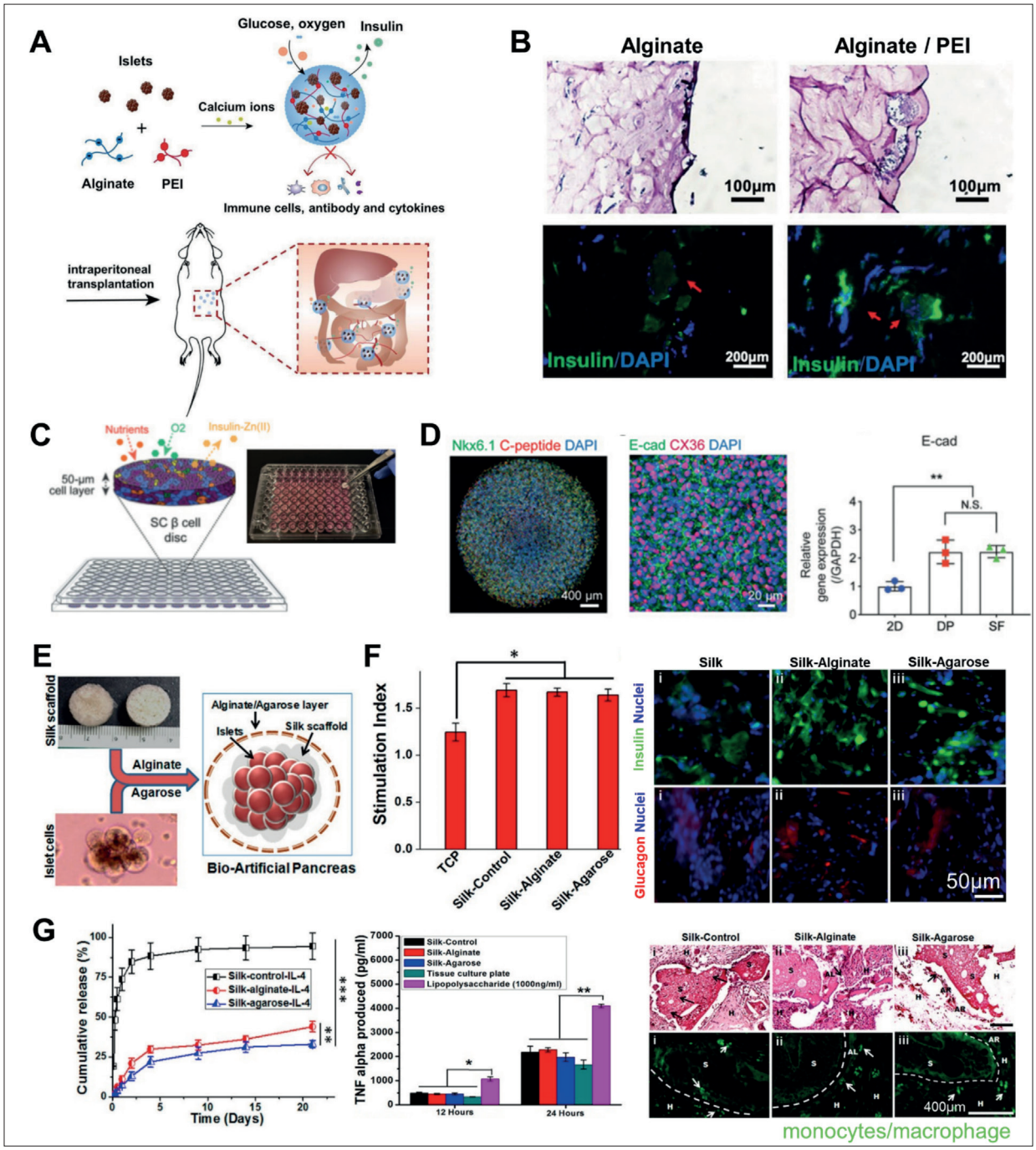

Figure 2. Application of natural hydrogels. (A) Schematic image of the encapsulation of islets using a balanced charged hydrogel that results in immunoprotection and controlled insulin secretion. (B) Representative histology and immunofluorescence images of retrieved hydrogel samples from Alginate/PEI and alginate-treated groups at 90 days post-transplantation. Adapted with permission from reference[32]. Copyright © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (C) Schematic image and gross view of the 3D reconstruction of SC β cells in the DP. (D) Immunofluorescence staining images of cell discs in DP and gene expression analysis showing higher expression of E-cadherin in SC β cells cultured in DP compared to 2D culture conditions. Adapted with permission from reference[43]. Copyright © 2020 AAAS. (E) Schematic image of the fabrication process of a silk-based bioartificial pancreas. (F) Stimulation index of primary islets encapsulated in different scaffolds and immunofluorescence images of primary islets cultured in different scaffolds after 14 days. (G) Gene expression analysis for M1 and M2 macrophage surface markers when incubated with IL-4-loaded silk-alginate scaffolds for 72 h. Comparative analysis of tumor necrosis factor-alpha produced by macrophages, suggesting lower levels of inflammatory responses in scaffolds. H&E staining and immunofluorescence staining images of retrieved acellular scaffolds after 4 weeks of subcutaneous implantation in mice. Adapted with permission from reference[51]. Copyright © 2017 American Chemical Society.

mimic the ECM, heparin-based hydrogels are promising carriers for islet delivery[44]. A previous study explored the application of macromolecular conjugates of heparin linked with VEGF to promote islet angiogenesis. Moreover, immobilized heparin on the islet surface has been shown to encourage endothelial cell adhesion to the surface of the islets[45]. In contrast, reliance on animal sources for obtaining heparin leads to supply and safety concerns, and its use is limited owing to clinical issues such as bleeding and thrombocytopenia[44]. To overcome these challenges, researchers have explored alternatives, such as heparin-mimicking polymers and hydrogels[44]. Notably, one study demonstrated the potential of heparin-mimetic peptide nanofiber gels in improving islet function and angiogenesis *in vitro* and *in vivo*[46].

Silk, a natural biomaterial, has been extensively employed in the design of islet encapsulation platforms. Multiple studies have demonstrated that encapsulation in silk can potentially replicate the native pancreatic niche and improve islet function both *in vitro* and *in vivo*[47-49]. Additionally, the use of small molecules, cytokines, chemokines, and immunomodulatory agents may offer promising strategies for extending cell survival, maintaining cell function, and minimizing immune responses[50]. Kumar *et al.* conducted a study aimed at developing 3D silk scaffolds capable of encapsulating pancreatic islets to generate bioartificial pancreatic systems that can sustain insulin release (Figure 2E)[51]. Silk-based scaffolds effectively facilitated the formation of islet-like clusters, resulting in improved cell viability, proliferation, and insulin production (Figure 2F). Moreover, the scaffolds were designed to release anti-inflammatory cytokines, which helped reduce inflammatory responses and promote an immunosuppressive environment (Figure 2G). In *in vitro* study, the scaffolds were observed to have immunomodulatory effects through the release of anti-inflammatory cytokines and the localized polarization of macrophages toward the implant site, ultimately favoring the integration of the graft with host tissues and enhancing graft function[51]. Research has been conducted to investigate the use of heparin, sodium salt, and silk fibroin solutions to produce cylindrical structures. Mao *et al.* conducted a study and evaluated the therapeutic potential of a macroporous scaffold composed of silk fibroin for islet transplantation in diabetic mice[52]. In this study, islets were co-transplanted with either a plain silk fibroin scaffold or a heparin-releasing silk fibroin scaffold into the epididymal fat pad of diabetic mice. These results demonstrate that heparin-releasing silk fibroin scaffolds facilitate islet revascularization and cell proliferation, leading to a more rapid reversal of hyperglycemia. This approach resulted in the development of a macroporous silk fibroin scaffold with the ability to enhance islet revascularization and engraftment[52].

Several natural gels including alginate, collagen, heparin, and silk fibrils have been examined in the field of islet transplantation. However, these gels exhibit limited versatility for promoting cell functions. Matrigel offers a promising solution to establish a physiologically relevant microenvironment that includes soluble growth factors, hormones, and other micro- to macromolecules that play critical roles in cellular interactions *in vivo*. Matrigel also contains the solubilized basement membrane matrix, which predominantly comprises laminin and collagen IV and is derived from Engelbreth–Holm–Swarm mouse sarcoma cells, making itself a reconstituted basement membrane. The ability of Matrigel to enhance long-term insulin secretion has been demonstrated[53]; however, the disadvantages associated with its use cannot be overlooked. These include the lot-to-lot variability that frequently occurs during the manufacturing process and the complexity and ill-defined nature of its composition, which makes it difficult to accurately determine which signals promote cell function[54]. Additionally, Matrigel originating from a tumor source is unsuitable for clinical use. Given these considerations, it is preferable to develop a standardized, non-tumor-derived ECM gel for clinical use rather than relying on Matrigel.

3.3. Synthesized biomaterials

Synthetic biomaterials are attractive platforms for protein and cell delivery in regenerative medicine. Synthetic biomaterials offer greater reproducibility and control over mechanical properties and have a biodegradable and non-immunogenic structure that can be synthesized on a large scale with consistent mechanical and physical properties[55]. Unlike natural hydrogels, synthetic polymers are generally not used as primary materials for islet encapsulation. They are predominantly employed in the production of scaffolds designed to facilitate tissue formation, as well as in auxiliary roles, such as providing structure and serving as a culture platform and encapsulation device.

Among the synthetic polymers, polylactic-co-glycolic acid (PLGA) is a highly functional biodegradable polymer synthesized from two monomers, lactic acid and glycolic acid, and offers distinct advantages. PLGA biodegradability is of particular importance, as it minimizes the potential for long-term toxicity and allows for the gradual replacement of the scaffold with new tissue as it degrades. Additionally, versatility is a major advantage of PLGA, as it can be fabricated into various forms, including fibers, films, and scaffolds, which are well suited for islet delivery applications[56,57]. Guo *et al.* fabricated microcarriers in the form of PLGA-porous microspheres using a double

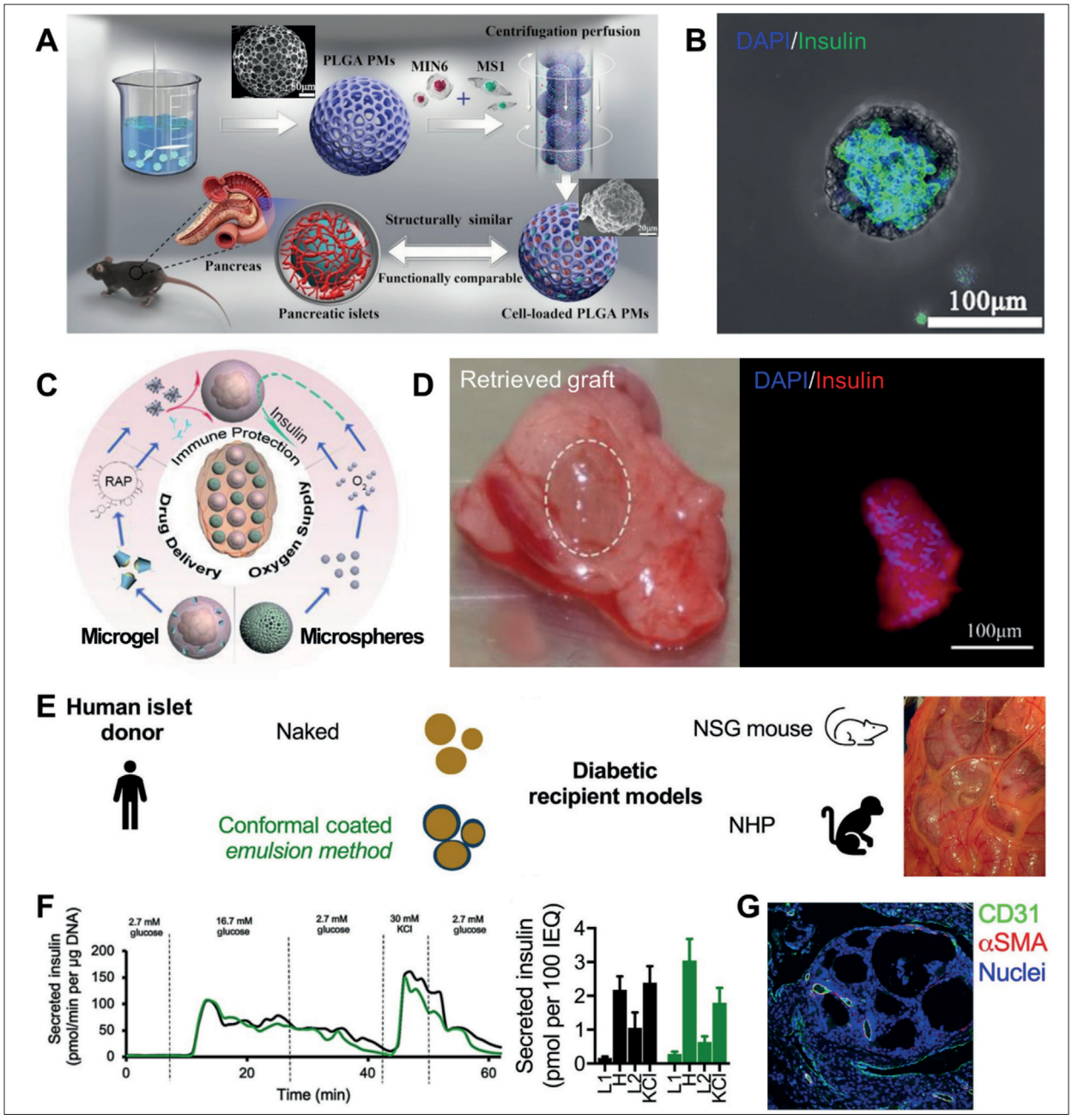

Figure 3. Application of synthesis hydrogels. (A) Schematic image of the steps involved in constructing artificial pancreatic islets by preparing MIN6 + MS1 cell-loaded PLGA microparticles. (B) Immunofluorescence staining image of MS1 and MIN6 within PLGA porous microspheres after 7 days of in vitro culture. Adapted with permission from reference[58]. Copyright © 2023 American Chemical Society. (C) Schematic image of the co-transplantation of islet-laden nanocomposite microgels and biodegradable oxygen-generating microspheres. (D) Photographic and immunofluorescence staining images of the epididymal fat pad containing the retrieved graft after 90 days of transplantation. Adapted with permission from reference[61]. Copyright © 2022 American Chemical Society. (E) Schematic image of the human islet donor and the distinction between naked islets and cell-clustered ECM islets, and the diabetic recipient model of the NSG mouse and non-human primate (NHP) with a photographic image of NHP omentum. (F) Dynamic glucose-stimulated insulin secretion of perifusion experiments conducted on naked and cell-clustered ECM human islets, representing their glucose sensitivity. (G) Immunofluorescence staining image of the explanted omental tissue containing islet grafts. Adapted with permission from reference[67]. Copyright © 2022 Stock et al.

emulsion-solvent evaporation technique (Figure 3A)[58]. The PLGA-porous microspheres were then utilized as a scaffold for artificial islet construction, where the pancreatic MIN6 cell line and the islet endothelial cell line MS1 were seeded using the developed centrifugation perfusion technique (Figure 3B). MIN6- and MS1-loaded

PLGA-porous microspheres upregulated the expression of vascular-related genes, indicating their potential to promote vascular formation during artificial organ construction using PLGA-porous microspheres[58].

Polylactic acid (PLA) is an aliphatic polyester that degrades through hydrolysis. It exhibits desirable characteristics such as biocompatibility, degradability, and printability, making it a popular choice for use as a polymeric bioink[59]. The incorporation of PLA allows for the facile production of porous scaffolds that can effectively promote the growth of neotissues. To date, a diverse array of medical products has been developed utilizing PLA, including degradable constructs and porous scaffolds for tissue engineering applications[60]. Huang *et al.* presented an innovative co-transplantation system that employed nanocomposite microgels loaded with islets and was capable of a sustained *in situ* release of immunosuppressants in conjunction with biodegradable oxygen-generating microspheres (Figure 3C)[61]. In their study, PLA was selected as the microsphere packaging material because of its biodegradability. Co-transplantation of nanocomposite microgels and biodegradable microspheres into diabetic mice restored and maintained normoglycemia (Figure 3D)[61]. Hoveizi and Tavakol successfully engineered a dependable 3D differentiation methodology for mesenchymal stem cells (MSCs) into pancreatic beta cell precursors (PBCPs) using nanofibrous PLA scaffolds[62]. The biocompatible and biodegradable nature of the nanofibrous PLA scaffold provided a suitable biophysical microenvironment for MSCs. Remarkably, transplanted PBCPs have demonstrated the ability to ameliorate hyperglycemia in a murine diabetes-induced model[62]. However, the degradation of PLA generates acidic byproducts, which negatively impact its long-term biocompatibility by triggering tissue inflammation and cellular death.

Polyethylene glycol (PEG) has emerged as a promising material for islet encapsulation owing to its tunable properties and gelation ability, which facilitate crosslinking and photopolymerization[63,64]. Several studies have demonstrated the ability of PEG to encapsulate thinner islets. For instance, a thin layer-by-layer PEG approach was utilized in one study to create an ultrathin capsule for surrounding the islets, which significantly enhanced the molecular exchange across the membrane compared with earlier methods[65]. Weaver *et al.* incorporated PEG hydrogel into a macroencapsulation device for extrahepatic islet transplantation[66]. The device comprises a hydrogel core crosslinked with non-degradable PEG dithiol and an outer layer that is vasculogenic and crosslinked with a proteolytically sensitive peptide to stimulate degradation[66]. Stock *et al.* introduced a refined strategy for encapsulating transplanted islets using a conformal coating (CC) technique with PEG hydrogels[67]. This method produces hydrogel CCs that encompass the islets at physiological pH, thereby promoting cytocompatibility and scalability. To evaluate the efficacy and efficiency of this novel method, *in vitro* and *in vivo* experiments were conducted using various small and large animal models of T1D (Figure 3E). During the evaluation of dynamic glucose-stimulated insulin secretion, both naked and emulsion-coated human islets exhibited a characteristic perifusion profile characterized by an initial phase of insulin secretion reaching its peak, followed by a subsequent phase wherein insulin secretion plateaued during the high-glucose stimulus (Figure 3F). The results revealed improved biocompatibility and abundant graft revascularization (Figure 3G)[67]. Another distinguishing feature of PEG is its potential to be modified with specific ligands to promote tissue adhesion. This property permits targeted cell attachment and proliferation, which is highly advantageous in tissue engineering applications, where successful regeneration hinges on cell adhesion. Despite their usefulness, the biocompatibility of hydrophobic materials is restricted by their inherent nature, and the breakdown of these materials can release acidic byproducts with proinflammatory effects[68]. Furthermore, several synthetic materials employed in tissue engineering, including PEG, are non-biodegradable and may remain indefinitely in the body, possibly causing unfavorable reactions or necessitating surgical removal.

3.4. Decellularized tissue-driven ECM

Tissue decellularization refers to the removal of cellular components from a tissue or solid organ, resulting in an acellular 3D structure composed of the ECM. Decellularized extracellular matrix (dECM) exhibits non-toxicity toward the proliferation and differentiation of various cell types, indicating its potential utility in regenerative medicine. Recent research on tissue-specific dECM has effectively provided a vital microenvironment for cells, allowing for the modulation of cellular processes such as migration, differentiation, and function during tissue morphogenesis[69,70]. The pancreatic dECM, comprising collagen, laminin, fibronectin, and fibrin, plays a crucial role in cytoskeletal remodeling, contractility, and cell differentiation. The dECM of the pancreas offers significant advantages, such as biocompatibility and bioactivity, which can increase islet survival and decrease cytotoxicity, thereby enhancing islet function. Research focusing on dECM derived from pancreatic tissue has validated its characteristics, especially regarding the interactions between islets and environmental cues, including viability, insulin secretion, and glucose responsiveness (Table 1)[71].

Table 1. Decellularized tissue-derived extracellular matrix for islet research

Cell sources	dECM origin	Functional evaluation	Major achievements	Ref
Human amniotic fluid-derived stem cells (hAFSC), porcine pancreatic islets	Porcine pancreas	*In vitro* islet functionality: GSIS assay	A whole organ, 3D pancreas scaffold, was successfully created using acellular porcine pancreas through the process of decellularization. The decellularized pancreas scaffold demonstrated the ability to support cellular adhesion and maintain the functions of various cell types, including stem cells and pancreatic islets.	[106]
Rat pancreatic islet	Rat pancreas	*In vitro* islet functionality: GSIS assay	A novel protocol for thorough decellularization of rat pancreas has been developed. The resulting non-immunogenic ECM retains the organ-specific protein network, including vascular and ductular structures while effectively preserving the majority of viable and intact islet cells.	[107]
Human mesenchymal stem cells (hMSC), adult human liver cells (AHLC)	Porcine pancreas	*In vivo* immunological test: Chemiluminescent array *In vivo* efficacy test: Blood glucose level monitoring, immunostaining (insulin)	Utilizing an ECM-based microcapsule system, a natural and fibrous 3D microenvironment is established, promoting cell survival and differentiation while also demonstrating immune compatibility upon *in vivo* implantation and significantly improving glycemic control in diabetic mice.	[108]
Mouse pancreatic islet	Mouse pancreas	*In vitro* islet functionality: ASIS assay	The produced ECM derived from decellularized pancreatic tissue successfully preserved the native tissue architecture, including vascular network, ductal structures, basal membranes, collagen, and glycosaminoglycan component, while being completely cell-free. The functionality of the remaining cells within the dECM was verified through GSIS assays after 48 h, and subsequent repopulation of the scaffold with green fluorescent protein-labeled INS-1 cells followed by a 120-day culture period confirmed its biocompatibility and non-toxic nature.	[72]
HUVECs, INS-1 832/13 cells	Human pancreas	*In vitro* islet functionality: GSIS assay *In vivo* immunological test: Immunostaining (HLA)	A set of effective techniques for the complete decellularization and delipidization of human pancreatic tissue were used in the comprehensive investigation of the composition and structural properties of the resulting dECM. The study further demonstrated the potential of the generated dECM as a supportive hydrogel for viable cell growth and survival, both *in vitro* and *in vivo*, with promising indications of non-immunogenic properties.	[73]
Rat pancreatic islet, HUVECs, differentiated-iPSC	Porcine pancreas	*In vitro* islet functionality: GSIS assay, immunostaining (insulin, pdx1), gene expression (insulin, pdx1)	Culturing human pluripotent stem cell-derived insulin-producing cells in a bioink composed of dECM resulted in notable improvements in insulin secretion and maturation. Additionally, incorporating human umbilical vein-derived endothelial cells in a co-culture system significantly reduced the occurrence of central necrosis in islets within a 3D culture environment.	[71]
AHLC, hMSC	Porcine pancreas	*In vitro* islet functionality: GSIS assay *In vitro* immunological study: Gene expression (TNF-α, IL-1β) *In vivo* immunological study: TNF-α, IL-6, and IL-1β in blood serum	The microcapsule system utilizing dECM establishes a favorable 3D microenvironment for cell survival and differentiation. *In vivo* implantation of dECM-based microcapsules containing cells demonstrated immune compatibility and substantially improved glycemic control in diabetic mice. The encapsulated cells within the pancreatic dECM microenvironment exhibited enhanced insulin production and secretion in response to glucose stimulation.	[109]
Mouse pancreatic islet	Porcine pancreas	*In vitro* islet functionality: Immunostaining (insulin, glucagon), GSIS assay, gene expression (insulin, pdx1)	Hybrid scaffolds made of silk fibroin and dECM derived from porcine pancreatic tissue were successfully created through electrospinning, closely resembling the native islet ECM. The hybrid dECM scaffold demonstrated improved viability of islets and enhanced insulin secretion in response to high glucose stimulation.	[110]
Rat pancreatic islet, MSCs	Rat pancreas	*In vivo* efficacy test: Magnetic resonance imaging (MRI), SEM images	Decellularized pancreas holds potential as a safer matrix for islet implantation into an omental flap. To enhance its suitability, improvements were made in terms of protein composition, decellularization quality, residual DNA content, and anatomical integrity. Utilizing pancreatic perfusion via the splenic vein resulted in smaller ECM scaffolds, facilitating transplantation into the omentum while meeting requirements such as complete removal of cellular components and preservation of pancreatic extracellular proteins.	[74]

Damodaran and Vermette developed a novel approach for perfusion decellularization of the entire pancreas, which allows for the engraftment of pancreatic cells and islets while maintaining the organ within the perfusion system (Figure 4A). Their work demonstrated the retention of islet functionality within the decellularized pancreata *in vitro*, and that the decellularized pancreas liberated pseudo-islets from the matrix (Figure 4B). Additionally, their study highlighted the favorable cytocompatibility of beta-like cells within the decellularized pancreata,

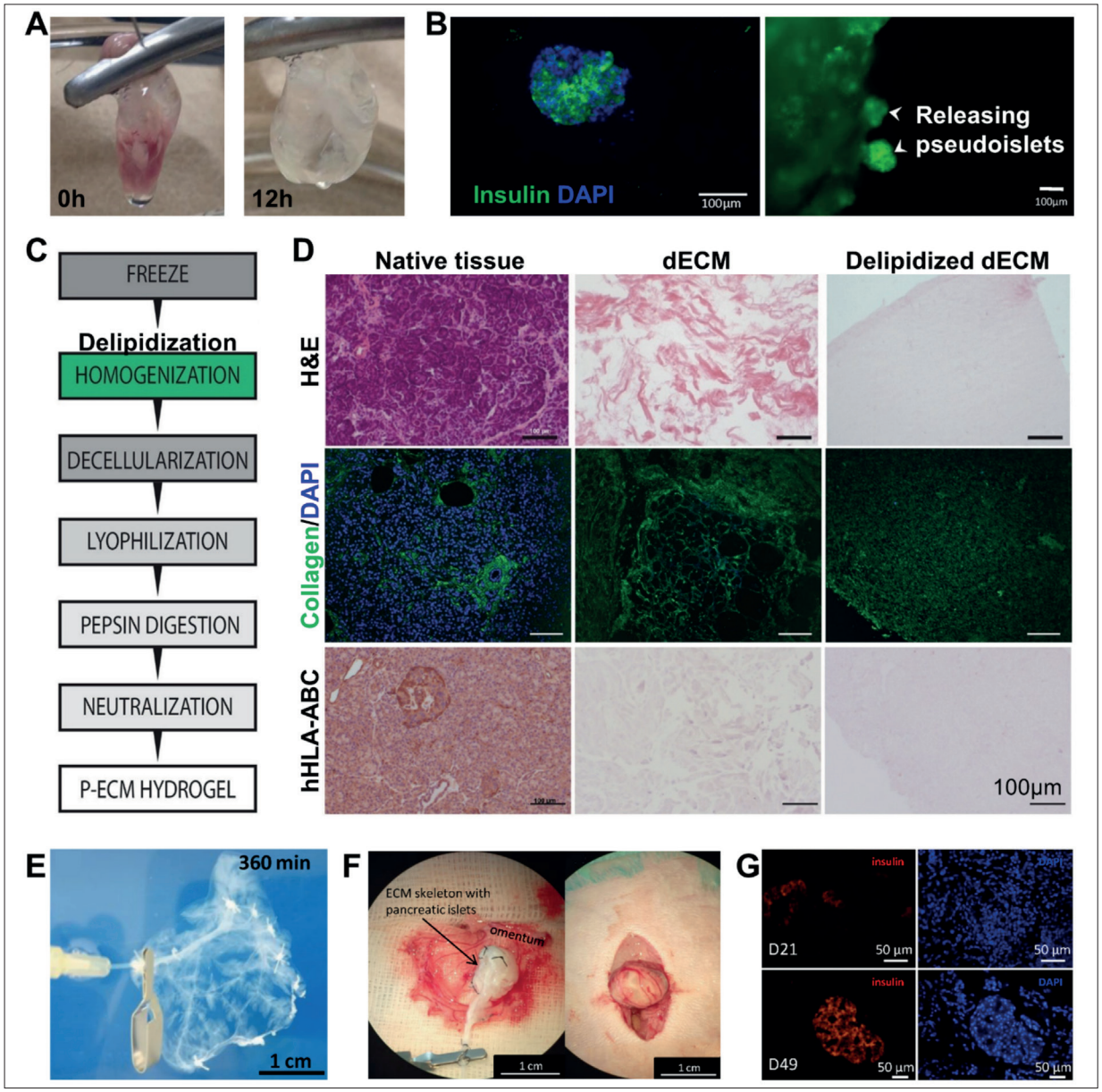

Figure 4. Application of decellularized tissue-driven ECM. (A) Photographic images illustrating the process of pancreas decellularization over a span of 12 h. (B) Immunohistochemistry staining image of GFP-transfected INS-1 cells on a decellularized pancreas, and the image of decellularized pancreas liberating pseudoislets from the matrix. Adapted with permission from reference[72]. Copyright © 2018 John Wiley and Sons. (C) Schematic image of the procedure involved in generating a dECM hydrogel from fragments of human pancreatic parenchyma. (D) H&E staining and immunohistochemistry staining image of native tissue, decellularized pancreatic hydrogels, and hydrogels for assessing the histological and morphological characteristics. Adapted with permission from reference[73]. Copyright © 2018 Sackett et al. (E) Photographic image of the process of pancreatic decellularization captured after the 360-min decellularization procedure. (F) Photographic images of the repopulated pancreatic skeleton enveloped by the omentum for transplantation. (G) Representative immunofluorescence staining images of iron-oxide-labeled islets in ECM skeletons at 21 and 49 days post-transplantation into the omentum. Adapted with permission from reference[74]. Copyright © 2022 Berkova et al.

thereby opening new possibilities for prolonged stem cell culture and differentiation[72]. Sackett *et al.* presented a pioneering approach for the efficient decellularization and elimination of lipids from the human pancreata[73]. They extensively evaluated the structure and composition of the delipidized pancreatic dECM (Figure 4C) and demonstrated the elimination of human leukocyte antigen (HLA) from decellularized materials, thereby obviating potential immune reactions (Figure 4D)[73]. Berkova *et al.* established a viable model to evaluate the potential of decellularized pancreatic skeleton (Figure 4E) as a matrix for islet graft transplantation into the omentum (Figure 4F)[74]. The transplanted islets maintained their morphology and position within the omentum and remained integrated within the skeleton (Figure 4G). They also verified islet viability and sustained insulin secretion in syngeneic recipients without diabetes[74]. Despite promising research focusing on dECM derived from pancreatic tissue, some outstanding issues remain unresolved. Although the immunomodulatory effects of dECM and the resulting breakdown products have been observed, owing to their residual physiological motifs and bioactive receptors, the precise mechanisms underlying these effects remain obscure and warrant further investigation. Furthermore, it is imperative to establish a uniform quality control standard for dECM obtained from diverse sources to ensure consistent outcomes in subsequent *in vivo* investigations. These persistent challenges are the factors driving the development of future clinical applications, as they have been thoroughly examined and resolved.

4. Biofabrication strategies for islet transplantation

Despite the use of biological materials, there are numerous obstacles to islet delivery in terms of manufacturing processes. During the encapsulation of islets into biomaterials and transplantation to the exact location, the islets are exposed to external forces. For example, severe physical forces can have fatal effects on cells encapsulated in biomaterials, resulting in cell death owing to potential damage to cell membranes. Using optimal biofabrication methods, multiple cells and biomaterials can be readily integrated into a concrete islet delivery construct. To overcome these challenges, various biofabrication methods have been adopted, including conventional scaffold fabrication methods, electrospinning, microfabrication, and 3D bioprinting technologies (Figure 5).

4.1. Electrospinning

For several decades, electrospinning has been employed to create fibrous scaffolds that mimic ECM. This technique uses electrostatic forces to generate fibrous scaffolds using biocompatible polymers. Importantly, the resulting nanofiber mats exhibited high surface areas and controllable pore sizes, which make them appropriate for the mass production of scaffolds with precisely controlled fiber diameters[75,76]. Consequently, researchers have endeavored to manipulate the electrospinning process for tissue-specific applications, leading to the development of diverse techniques for producing complex nanofibers. These techniques have also been used to fabricate islet

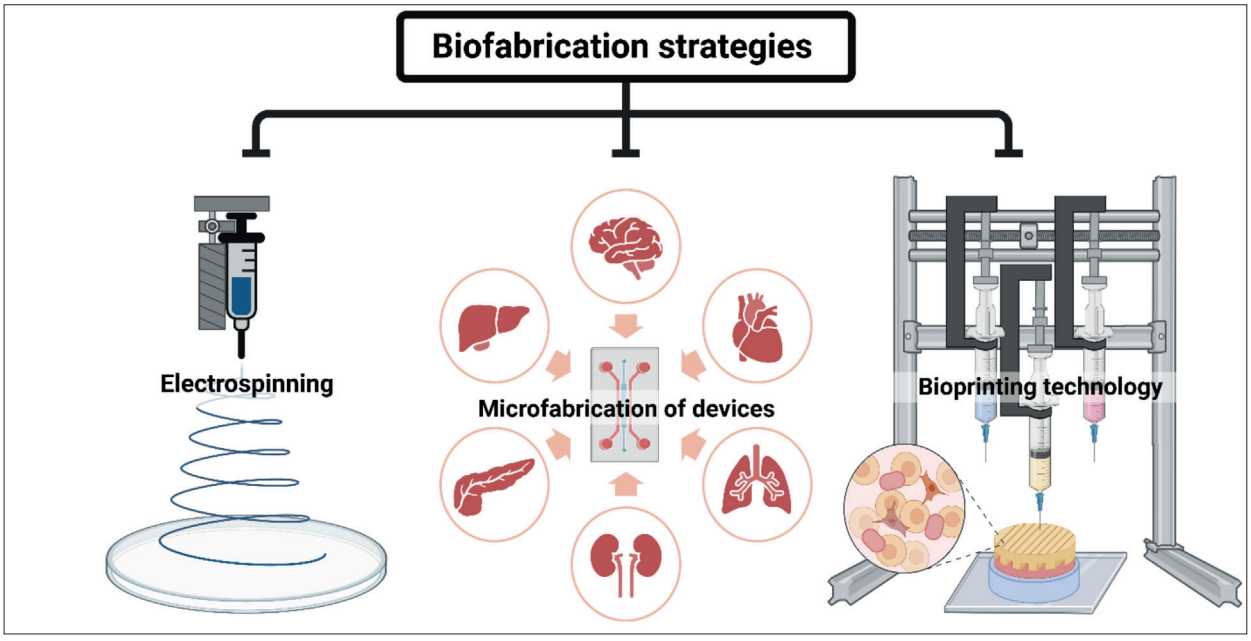

Figure 5. Biofabrication strategies for islet transplantation.

constructs. Buitinga *et al.* introduced a novel microwell scaffold as a potential transplantation device for pancreatic islets, which was prepared from non-cell-adhesive and reproducible poly (ethylene oxide terephthalate)/poly (butylene terephthalate) thin films and electrospun meshes (Figure 6A)[77]. During the 7-day culture period, the morphology of the human islets was well preserved and remained stable in the microwell scaffolds. Furthermore, the insulin release and total insulin content of the islets were comparable to that of the free-floating control islets, and the glucagon and insulin immunostaining were comparable between the two groups (Figure 6B)[77].

The research conducted by Liu *et al.* established that the use of electrospun nanoporous encapsulation devices composed of zwitterionic polyurethane (ZPU) polymers demonstrated the safety and efficacy of islet transplantation (Figure 6C)[78]. The devices possess various favorable characteristics, such as biocompatibility, robust mechanical properties, and a nanoporous structure that facilitates cell adhesion and diffusion. The upscaled ZPU device was implanted intraperitoneally into the pigs and positioned in proximity to the liver using a minimally invasive laparoscopic technique (Figure 6D). During the 3-month transplantation experiment, histological analysis

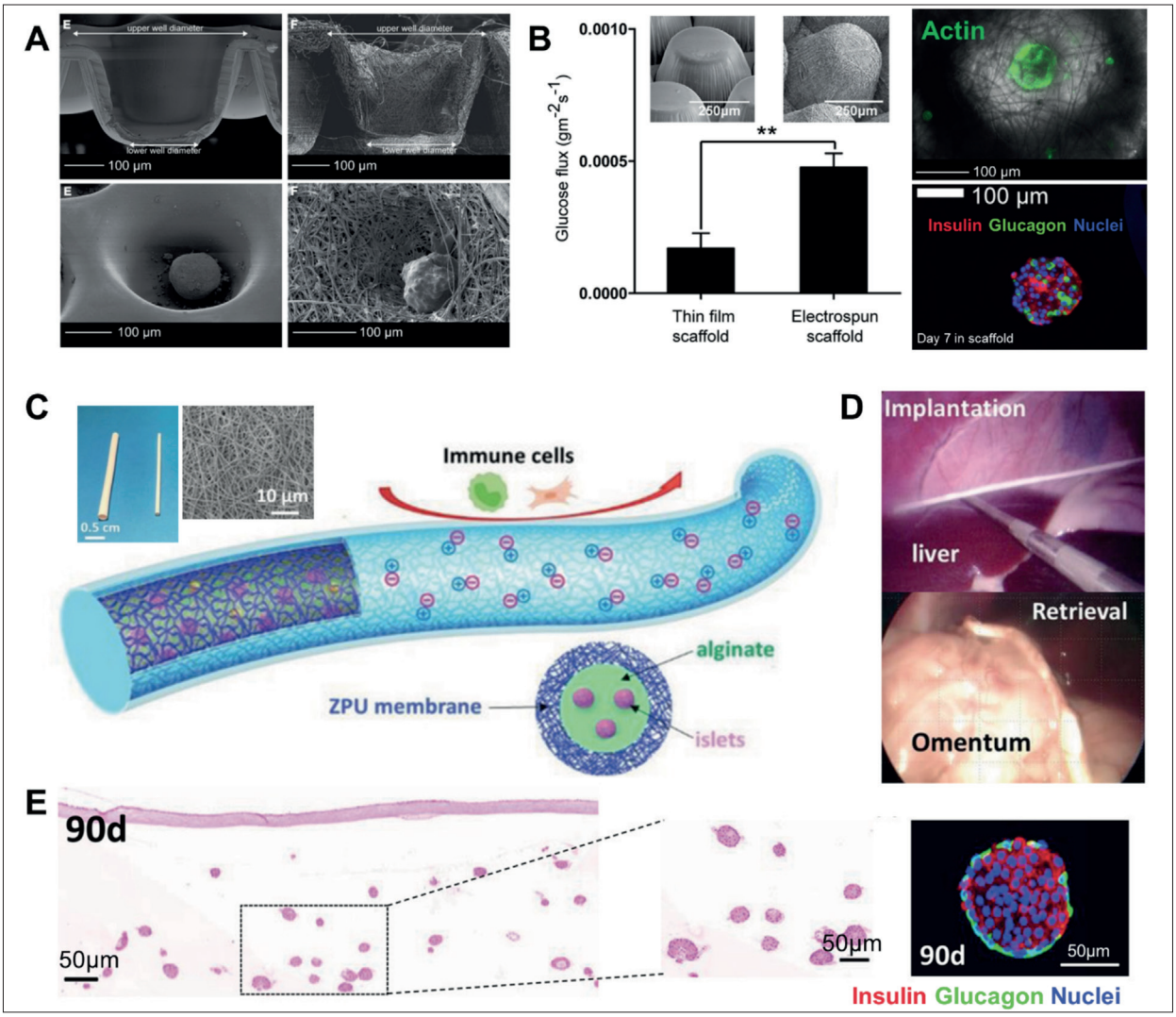

Figure 6. Electrospinning for islet transplantation. (A) Scanning electron microscopy (SEM) images of the electrospun microwell scaffold, including cross-sectional views of the fibrous network. (B) Glucose flux analysis representing glucose diffusion through the electrospun microwell scaffolds. Immunofluorescence staining images of human islets cultured in thin film microwell scaffolds. Adapted with permission from reference[77]. Copyright © 2013 Buitinga et al. (C) Schematic image of the chemical structure of the ZPU polymer and the ZPU device containing islets, which effectively prevents cell ingress or egress. (D) The process of implantation and retrieval of ZPU devices in pigs or dogs. (E) H&E staining images of retrieved ZPU devices containing islets after 90 days, and an immunohistochemistry staining image of islets in the retrieved ZPU device after 90 days. Adapted with permission from reference[78]. Copyright © 2021 Wiley-VCH GmbH.

and positive insulin staining confirmed the sustained functionality of the device over an extended period (Figure 6E). This study effectively demonstrated the potency of the device through its ability to reinstate normoglycemia in diabetic mice for a duration of 3 months post-encapsulation of proliferative cells[78]. Mridha *et al.* developed a method for providing allogeneic beta cell therapies without the need for antirejection drugs[79]. To achieve this, they propose the utilization of a bioengineered hybrid device that consists of microencapsulated beta cells enclosed within 3D polycaprolactone (PCL) scaffolds created through the melt electrospin writing technique. The researchers successfully demonstrated the construction of an implantable, consistent, and retrievable hybrid device that facilitates vascularization and enhances the viability of encapsulated islets and subcutaneously implanted the device in an allotransplantation environment while circumventing the requirement for immunosuppression[79].

4.2. Microfabrication of cell-laden devices

Extensive research and development efforts have been dedicated to the advanced microfabrication of microfluidic and lab-on-a-chip devices owing to their numerous advantages, including rapid analysis, biocompatibility, affordability, and automation. Although these devices were initially constructed from costly materials such as silicon wafer and glass, recent investigations have focused on the utilization of emerging soft polymeric materials (e.g., PDMS) that confer benefits such as automation and high-throughput screening in the realm of tools and laboratory equipment.

Compared with traditional systems, microfluidic systems offer superior control over the spatial and temporal distribution of chemical and physical stimuli at the cellular level, thereby enabling the development of diverse microsystems tailored to various tissue engineering applications. The emergence of organ-on-a-chip platforms, which synergize cell biology, engineering, and biomaterial advancements with microfluidics, has introduced innovative systems capable of mimicking the physiological or pathophysiological milieu of specific organs. These devices represent a pioneering model for pharmaceutical agent screening and the investigation of specific diseases. Numerous microfluidic devices have been developed in the field of diabetes to simulate native islet microenvironments and explore pancreatic beta cell kinetics[80]. Jun *et al.* created functional islet spheroids using a microfluidic chip that mimicked interstitial flow, reduced shear cell damage, and addressed islet size heterogeneity through precise 3D engineering of microsized islet spheroids (Figure 7A)[81]. The authors observed that flow not only enhanced the health of islets, but also promoted the maintenance of non-endocrine cells, such as islet endothelial cells (iECs), *in vitro* (Figure 7B). Furthermore, controlled-size islet spheroids exhibit higher drug sensitivity than intact islets[81]. Patel *et al.* developed a microphysiological system that enables continuous dynamic culture of pancreatic organoids in a 3D hydrogel, highlighting the importance of a dynamic *in vitro* microenvironment for primary organoid function preservation[82]. To compare traditional culture methods with the newly developed microphysiological system, rodent- and human-derived islets were embedded in alginate, and *in vitro* and *in silico* assessments were performed. Their results indicated that dynamic culture of hydrogel-embedded islets within the microphysiological system had a superior impact on islet viability[82]. Bauer *et al.* elucidated the advancement of a microfluidic two-organ-chip architecture for investigating the pancreatic islet–liver interplay in the context of drug discovery and the identification of novel therapeutic interventions (Figure 7C)[83]. The model capitalized on genetically encoded human pancreatic islet microtissues and liver spheroids subjected to glucose- and insulin-free cell culture medium. These findings suggest that insulin secretion by islet microtissues activates glucose uptake by liver spheroids, whereas the liver in isolation exhibits reduced efficiency in glucose consumption (Figure 7D)[83]. However, sample size limitations constitute a primary drawback of the majority of microfluidic systems, rendering them unsuitable for quality control of islets after isolation, as they require a considerable number of islets. One of the primary impediments to microfluidic systems is their inherent limitations in terms of sample size. Because of this limitation, it is challenging to acquire a sufficient number of islets for islet transplantation within a microfluidic system[84].

4.3. Bioprinting technology

3D bioprinting is one of the most promising technologies for the simultaneous induction of vascularization and prevention of inflammation[85,86]. It is also a state-of-the-art technology for constructing complex tissue-engineered structures. Using multiple dispensing system, various cells and materials can be placed precisely at the desired locations simultaneously. Among the various types of 3D bioprinting technologies, extrusion-based bioprinting techniques are most commonly used for the development of 3D-printed pancreatic tissue[71, 87–89]. Generally, an extrusion-based bioprinting technique driven by a pneumatic or mechanical system continuously forces the bioink through a nozzle to form predefined filaments. A bioink is a solution of a biomaterial or a mixture of several biomaterials in the form of a hydrogel. One of the common characteristics of bioinks is that the hydrogels are viscous enough to remain stable until crosslinking to create pre-designed constructs after printing[90].

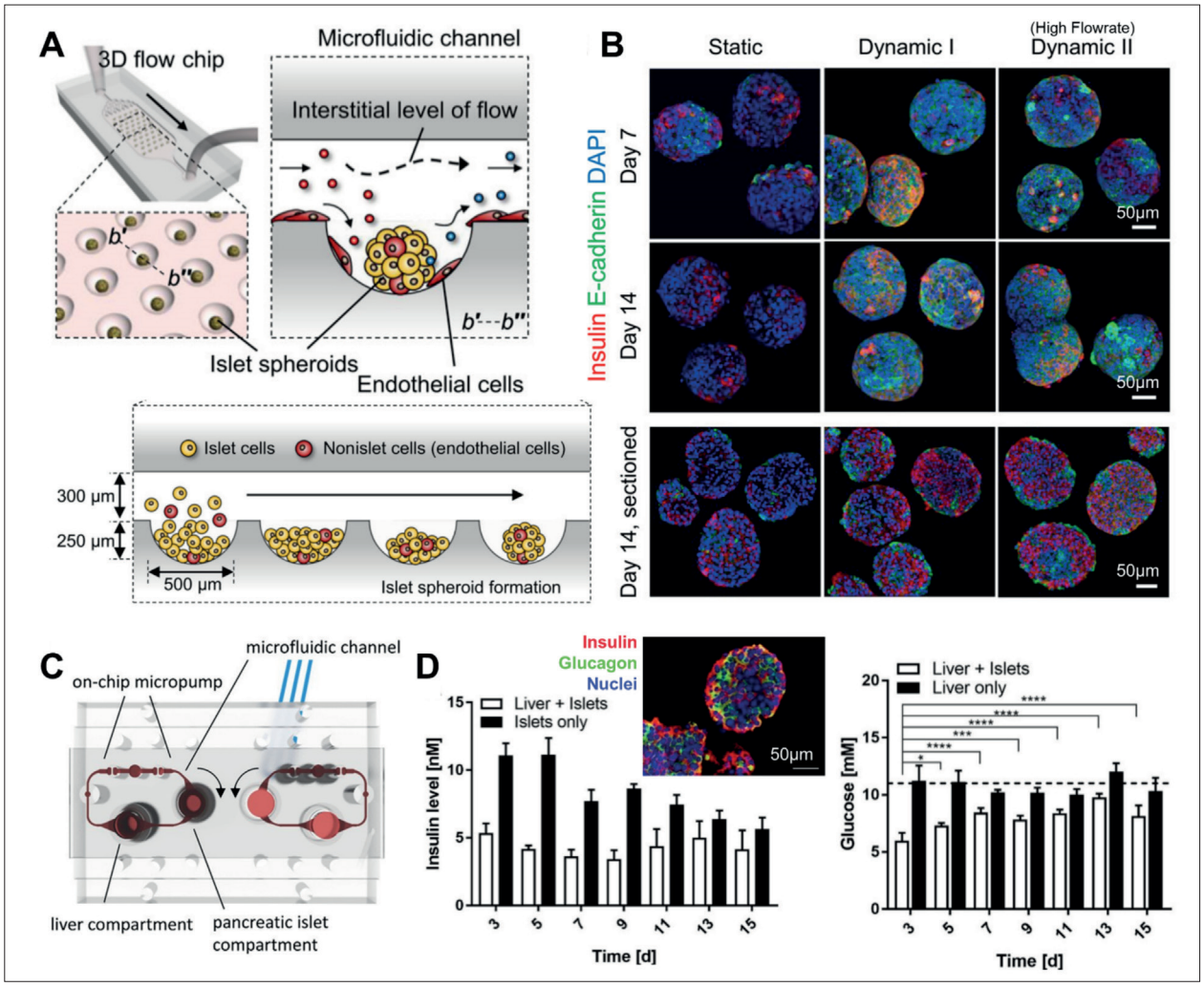

Figure 7. Microfabrication of devices for islet transplantation. (A) Schematic image of the spheroid-based microfluidic perfusion culture of pancreatic islets for mimicking the in vivo environment. (B) Immunofluorescence staining image of islet spheroids after 7 and 14 days. Confocal z-stacked and cross-sectioned images of islet spheroids exhibiting different culture conditions. Adapted with permission from reference[81]. Copyright © 2019 AAAS. (C) Bottom-view illustration image of the media circuits, respective culture compartments, and micropump valves. (D) Data of accumulation of insulin over 48-h intervals representing the pancreatic islet microtissues exhibit functional capabilities during a 15-day co-culture with liver spheroids, immunofluorescence staining image of the islet microtissues after 15 days in co-culture, and the glucose levels of liver spheroids after a medium exchange in co-culture and single culture. Adapted from reference[83]. Copyright © 2017 Bauer et al.

The first research report on the use of islets for bioprinting technology was published in 2015 using a hydrogel mixed with alginate and gelatin. The 3D scaffold had 17 layers, and the thickness of each layer was 0.1 mm[91]. Owing to the high survival rate of the functionalized 3D cultures of pancreatic islets, microvascularization is in high demand.

Thus, 3D bioprinting technology offers significant advantages in the use of multiple cells and biomaterials for blood vessel formation[92]. Subsequently, many researchers leveraged 3D bioprinting technology to investigate islet regeneration, vascularization, and transplantation (Table 2). Chen *et al.* utilized digital light processing (DLP)-3D printing technology to produce a retrievable encapsulation device for the delivery of islets to diabetic mice (Figure 8A)[93]. Encapsulated islets were found to be highly effective in ameliorating hyperglycemia in mice, even in the absence of immunosuppressive treatment. The retrievable device demonstrated sustained viability of transplanted islets and effectively prevented islet leakage over an extended period while the encapsulation capsule device was used (Figure 8B)[93]. Clua-Ferré *et al.* developed a rapid and efficient strategy for encapsulating cells in a collagen bioink crosslinked with tannic acid (TA) using a 3D bioprinter (Figure 8C)[94]. Smaller spheroid volumes and higher surface-to-volume ratios significantly improve the diffusion process, leading to a quicker response time to fluctuations

Table 2 Bioprinting technology for islet research

Bioprinting type	Cell sources	Biomaterial	Major achievements	Ref
Extrusion-based bioprinting	Mouse pancreatic islets, endothelial progenitor cells (EPC)	Alginate, gelatin methacryloyl (GelMA)	An optimized bioink formulation composed of alginate and gelatin was developed specifically for the encapsulation of islets and islet-related cells, enabling their 3D printing. Additionally, a custom-designed coaxial printer was created to facilitate the 3D printing of multicellular constructs that contain islets.	[89]
	Rat pancreatic islet, HUVEC, differentiated iPSC	dECM	Islet-laden dECM bioink was successfully bioprinted to construct 3D pancreatic tissue. The effectiveness of porcine dECM as a bioink source has demonstrated its ability to recreate tissue-specific conditions within the 3D constructs.	[71]
	Rat pancreatic islet	Alginate, methylcellulose	Macroporous 3D hydrogel constructs with precise geometry were successfully generated using a plottable hydrogel blend of ultrapure alginate and methylcellulose (Alg/MC), both of which have been approved clinically. This enabled the encapsulation of pancreatic islets while preserving their viability, morphology, and functionality. Notably, the islets within the Alg/MC hydrogel group maintained their viability and functionality, sustaining the production of insulin and glucagon.	[88]
	MIN6-m9, differentiated H1 hPSCs	dECM, PCL	A hybrid encapsulation system was developed using 3D bioprinting, combining a macroporous polymer capsule with a stagger-type membrane and assemblable structure, along with a nanoporous dECM hydrogel containing pancreatic islet-like aggregates. This hybrid system demonstrated biocompatibility both *in vitro* and *in vivo*, as evidenced by M1 macrophage polarization.	[95]
	MIN6	Alginate, PCL	In a long-term *in vivo* study, a subcutaneously implanted 3D-bioprinted construct aimed at preventing islet loss demonstrated promising results. Type 1 diabetes mice implanted with these bioprinted constructs exhibited a significant threefold increase in insulin secretion and maintained controlled glucose levels after 8 weeks of implantation.	[111]
DLP bioprinting	Mouse pancreatic islets	GelMA	Mini encapsulation devices with a groove structure, fabricated using DLP printing, were developed to prevent islet cell leakage. *In vivo* intraperitoneal glucose tolerance tests conducted at various time points showcased significant therapeutic improvement in glycemic control. Even after 15 weeks, a sufficient amount of viable islet cells were found in the retrieved implant.	[93]
	Rat pancreatic islet	dECM, hyaluronic acid methacrylate (HAMA)	The HAMA/pECM hydrogel demonstrated its ability to maintain islet cell adhesion and morphology *in vitro*. *In vivo* experiments further validated its efficacy, showing that the 3D-printed islet-encapsulated HAMA/pECM hydrogel elevated insulin levels in diabetic mice, regulated blood glucose levels within the normal range for 90 days, and exhibited rapid insulin secretion in response to blood glucose stimulation. Additionally, the HAMA/pECM hydrogel promoted the attachment and proliferation of new blood vessels, leading to an increased density of vascularization.	[98]

in blood glucose levels (Figure 8D). This approach allows the encapsulation of a significant number of cells in a short duration (less than 1 min), thereby averting hypoxic stress-induced cell dysfunction[94]. Hwang *et al.* fabricated a hybridized encapsulation scheme for pancreatic islet-like aggregates using 3D bioprinting technology (Figure 8E)[95]. The system comprises a modular macroporous polymer capsule configuration with a nanoporous pancreatic tissue-derived dECM (pdECM) hydrogel, which effectively shields the cells from the mechanical forces generated during 3D bioprinting, enabling them to maintain their viability, proliferation, and insulin-secreting functionality (Figure 8F). Biocompatibility of the amalgamated encapsulation tool was confirmed both *in vitro* and *in vivo*, demonstrating reduced immune responses. In addition, the authors successfully established a printing process to construct islet-like aggregates from human pluripotent stem cells that exhibited augmented structural maturation and functional enhancement[95]. Recently, various endothelial cells and angiogenic growth factors have been printed using islets. One research group developed microspheres containing VEGF on 3D-printed poly(dimethylsiloxane)-based constructs and loaded the islets, resulting in significant vascularization within 4 weeks[96]. Vascular cells such as endothelial progenitor cells (EPCs), human umbilical vein endothelial cells (HUVECs), and induced

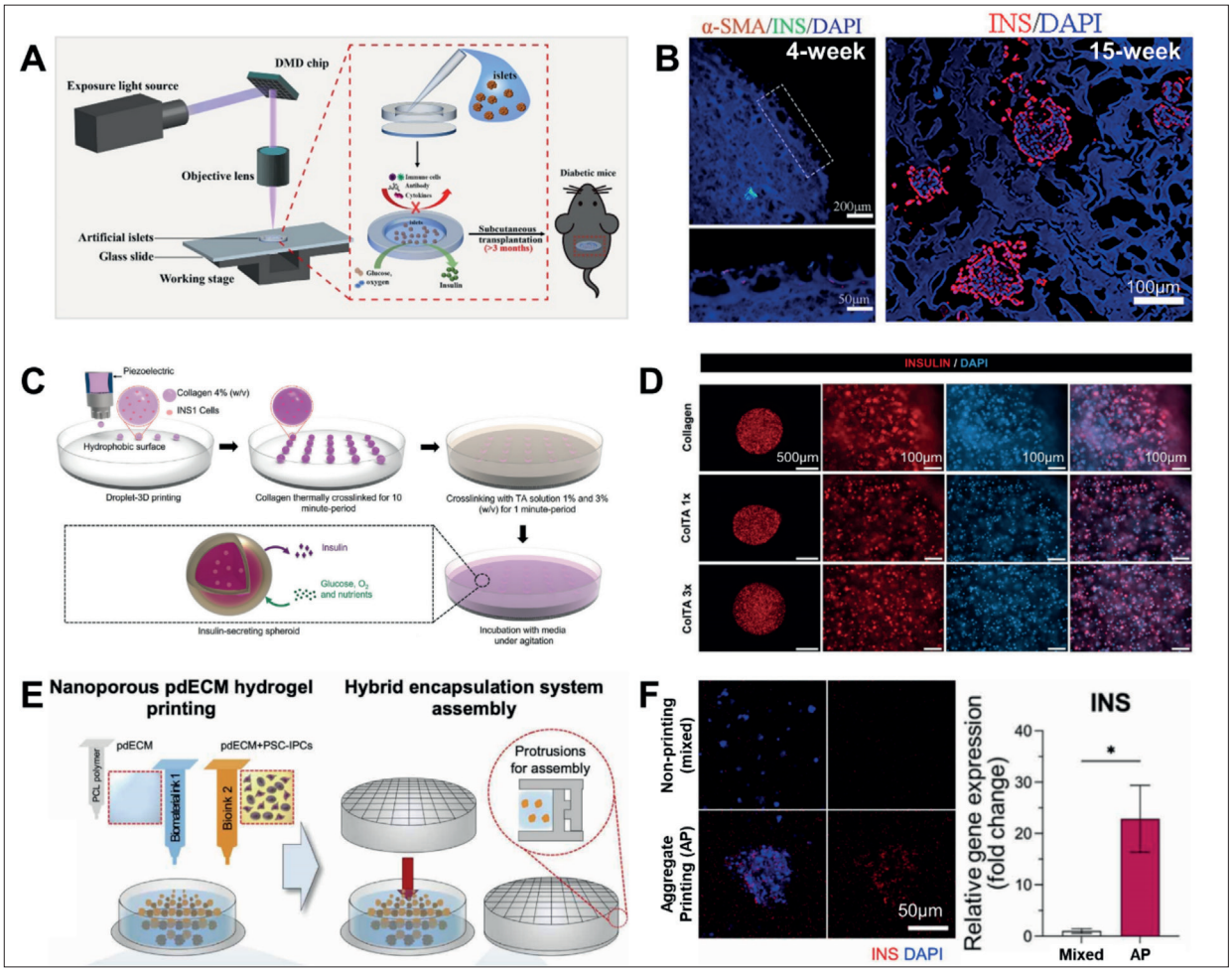

Figure 8. Bioprinting for islet transplantation. (A) Schematic image of the DLP-3D printing mini-capsule device for islet delivery to treat diabetic mice without immunosuppressant. (B) Representative immunofluorescence staining images of the retrieved grafts after transplantation for 4 weeks, and the retrieved encapsulated islet grafts after implantation for 15 weeks, which show the foreign body response after the transplantation of the encapsulated islets. Adapted with permission from reference [93]. Copyright © 2022 American Chemical Society. (C) Schematic image of cell-laden spheroids using different concentrations of TA solution, generated using a 3D bioprinter. (D) Representative immunofluorescence staining images of INS1E cells encapsulated in the spheroids after 10 days, showing that collagen crosslinked with TA enables insulin secretion. Adapted with permission from reference [94]. Copyright © 2022 John Wiley and Sons. (E) Schematic image of the fabrication process of the hybrid encapsulation system comprising a 3D-printed macroporous polymer capsule and pancreatic tissue-derived ECM hydrogel. (F) Gene expression analysis of human pluripotent stem cell-derived insulin-producing cells (hPSC-IPCs) after 7 days of encapsulation, and representative immunofluorescence staining images of hPSC-IPCs, which indicate the maturation of β-cells in aggregate printing group. Adapted with permission from reference [95]. Copyright © 2021 IOP Publishing.

pluripotent stem cell-derived endothelial cells (iPSC-ECs) are widely used with islet or insulin-producing cells[71,97]. The 3D printing technology also enables the fabrication of complex structures that can support vascularization. Wang *et al.* printed a porous structure that facilitated vascular penetration and interactions to form a vascular network on a hydrogel[98]. In addition, an idea has been introduced that a 3D-bioprinted encapsulation system could reduce immune response after the transplantation. Islet-like aggregates were microencapsulated in a tissue-specific bioink, and the printed construct was macroencapsulated in a PCL container that blocked immune cells[95]. Moreover, the utilization of genetically modified cells in bioprinting, with no immune response concerns, presents significant advantages in terms of controlling the physical and biochemical culture environment of the cells based on the specific circumstances. This, in turn, allows for the development of an efficient and precise delivery system for personalized tumor therapy, thereby amplifying the targeting effect while maintaining the structural integrity of the fabricated construct[99].

5. Future directions and conclusion

In this comprehensive review, we investigated the latest advancements in biomaterials and biofabrication technologies

and their profound implications in islet transplantation. Notably, remarkable strides toward islet transplantation have been made in recent decades, predominantly because of the remarkable progress achieved in biofabrication technology. Many biofabrication techniques have been introduced by researchers who employed diverse biomaterials as carriers for efficient islet delivery. The primary focus of these studies was to enhance islet engraftment, fortify immune protection, and, ultimately, prolong graft viability. To address the challenge of the immune response and optimize cell survival, it is imperative for researchers to prioritize the development of encapsulation technology as a viable means of islet delivery. Although ongoing clinical trials are assessing the efficacy of microencapsulated islets, sustained blood glucose control over an extended period has not yet been achieved. The fundamental objective of islet encapsulation is to mitigate the risk of immune rejection of transplanted islets while effectively emulating the pancreatic microenvironment, thereby facilitating insulin secretion and enabling the uptake of vital nutrients for sustained survival.

The careful selection of appropriate biomaterials is of paramount importance for establishing an optimal microenvironment for islets, which is crucial for the transplantation process. The microenvironment encompassing the islet graft exerts a pivotal influence, owing to a multitude of factors. A particularly promising approach for islet transplantation involves the utilization of dECM, which offers distinct advantages and specialized characteristics. Through the removal of cellular components while retaining the native ECM structure, the dECM serves as a biocompatible scaffold that facilitates the survival and functionality of islets. The integration of dECM in the context of islet transplantation enhances the biocompatibility of islet grafts, diminishes the risk of immune rejection, and fosters a favorable microenvironment conducive to sustained survival and insulin production in islets. Extensive research focused on dECM derived from pancreatic tissue has successfully validated its inherent characteristics, particularly regarding the intricate interplay between islets and their surrounding environmental cues, including viability, insulin secretion, and glucose responsiveness. Furthermore, dECM can be further functionalized to enable the targeted delivery of bioactive molecules, such as immunomodulatory factors or angiogenic agents, thereby offering additional enhancements to the therapeutic outcomes of islet transplantation.

The choice of the fabrication method is of significant importance in the development of a comprehensive islet delivery system that encompasses both biomaterials and cells. The versatile nature of the 3D bioprinting technology enables the use of multiple biomaterials and facilitates the creation of constructs with tailored properties. Furthermore, biofabrication technologies, including 3D bioprinting, have the potential to establish high-throughput manufacturing systems that allow rapid and efficient production. By incorporating biomaterials with diverse mechanical and biochemical characteristics, bioprinting technology can faithfully mimic the native pancreatic microenvironment and optimize the conditions for islet survival and functionality. Consequently, this high-throughput bioprinting technology holds promise for meeting the clinical demand for large-scale islet encapsulation constructs and for advancing the field of islet transplantation. Combining the strengths of dECM and bioprinting technology offers an opportunity to enhance the efficacy and long-term outcomes of islet transplantation, bringing us closer to curing diabetes.

Concurrently, there is an imminent need for more alternative cell sources. Multiple cell types have been used in islet delivery systems to generate insulin-producing cells. Although cell lines present advantages in terms of ease of handling and mass production, they present notable challenges in clinical trials and are inherently constrained in terms of their capabilities. The use of primary islets obtained from suitable donors poses inherent challenges, including those associated with allograft transplantation and limited availability. Consequently, a promising avenue in this domain is the utilization of insulin-producing cells differentiated from human or patient-derived iPSCs. This approach offers unrestricted access to organs and facilitates donor-independent transplantation. This approach offers unrestricted access to organs and facilitates donor-independent transplantation, while the improvement of differentiation efficiency through established protocols is still ongoing. Although several differentiation protocols have been established, the implementation of this approach is still in progress, with challenges such as difficulties in improving the efficiency of differentiation[100–103]. The iPSC differentiation technique presents technical complexities and financial challenges that require further attention[104,105]. Nevertheless, differentiation techniques to generate insulin-producing cells are expected to play a critical role in future research on islet transplantation.

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Conflict of interest

The authors declare no conflicts of interests.

Author contributions

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Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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