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Advances in Vascularization of Islet Organoids: Engineering Strategies, Functional Evaluation, and Transplantation Applications

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Abstract: *The growth and evolution of diabetes, especially Type 1 and Type 2, are highly correlated to the failure of islet β cells and consequently replacing of β cells is an area of interest in research. In recent years, stem cell-based islet organoids have offered a novel therapeutic approach to diabetes treatment; nevertheless, additional functional development and clinical use remain restricted due to the absence of vascular microenvironment. The present paper discusses main engineering strategies, evaluation parameters, revascularization after transplantation and clinical translation issues concerning vascularization of islet organoids. Recent vascularization methods have largely involved co-culturing with vascular-associated cells, building vascular organoids and multi-lineage co-differentiation. Such strategies have been shown to have some success at promoting beta-cell maturation, increasing glucose sensitivity, and boosting post-transplantation survival rates. However, at this stage of development, research has faced the challenge of insufficient vascular maturity, poor long-term perfusion performance, low efficiency of integration in vivo, and the challenge of achieving both immune protection and fast vascularization. Further studies should be conducted to create working vascular systems and reach synergistic optimization in immune regulation, anti-fibrosis design and standardized preparation to promote the clinical use of islet organoids in cellular replacement therapy in diabetes.*

Keywords: *Diabetes;Islet Organoids; Vascularization; Stem Cells; β Cell Replacement Therapy; Transplantation*

INTRODUCTION

Diabetes has become one of the leading concerns of the global public health system as its prevalence has also increased during the last several years. Diabetes contributed to about 1.5 million deaths in the year 2019; and 48 out of every hundred people who died were aged less than 70 years old[1]. To provide uniformity in the study of the causes of diabetes in different parts of the world, the World Health Organization (WHO) has developed an official classification of the etiology of diabetes that includes four general groups: Type 1 Diabetes Mellitus (T1DM), Type 2 Diabetes Mellitus (T2DM), gestational diabetes mellitus (GDM) and other specified types of diabetes[2]. Of these, T1DM and T2DM are the most frequent. T1DM is described as a T-cell driven autoimmune condition, mainly defined by islet -cell destruction, resulting in absolute insulin deficiency and chronic hyperglycemia, which is commonly thought to be highly associated with genetic, environmental and immune influences. T2DM, which comprises about 80 percent of all the cases of diabetes, is viewed as a polygenic disorder, which is mostly defined by insulin resistance and islet -cell dysfunction[3,4].

To address the problem of β cell dysfunction as an underlying pathological cause, the International Pancreas and Islet Transplant Association (IPITA) and the European Pancreas and Islet Transplant Association (EPITA) have come to a consensus that beta cell replacement therapies like islet transplantation or pancreas transplantation are viable ways of treating beta cell failure[5]. Nevertheless, serious donor shortages and adverse effects on long-term immunosuppressant use post-transplantation due to complications and infections are still the significant bottlenecks to its wide usage[6]. Therefore, searching other sources of cells has taken center stage in recent studies. During the last ten years, great advances have been achieved in the in vitro expansion and functional induction of islet beta cells[7]. At present, the most common stem cell sources used in the research of islet regeneration and replacement therapy are Embryonic Stem Cells (ESCs) and Induced Pluripotent Stem Cells (iPSCs)[8]. Although there has been some advancement in the functional development of stem cell-derived islet organoids, the major bottleneck in the process of growing them in larger quantities, their maturation process and transplantation remains not only the effectiveness of endocrine cell differentiation but also the absence of vascular microenvironment resembling natural islets. Existing in vitro culture models of islet organoids usually produce avascular dense spheroid structures[9]. Because the effective diffusion distance of oxygen is usually about 100-200 μm, cell survival rates will significantly drop as cell location exceeds this area[10]. It has been demonstrated[11] that natural islets are strongly reliant on high-density capillary networks to supply them with oxygen where they are around 5-10-fold denser than surrounding acinar tissue and the volume of blood flow per unit is approximately tenfold that of the exocrine portion. Due to the fact that natural islets require to sense the changes in blood glucose levels and secrete hormones such as insulin promptly, the blood supply in natural islets is much greater than that of exocrine tissues. The special vascular network is involved in the development of the pancreas and the formation of endocrine functions since the embryonic period. On the other hand, organoids grown in vitro that exceed the diffusion limit in terms of diameters are very susceptible to core necrosis because the core regions tend to be starved of oxygen and nutrients, which restricts the scale of organoid growth and survival rates early after transplantation[12]. Thus, building successful vascular networks in vitro and speeding up the vascularization process after transplantation have become the key problems of this field moving towards the clinical use. Accordingly, the paper discusses the main engineering approaches to islet organoid vascularization, the complications of post-transplant revascularization, and clinical translation with the purpose of offering references on how to build working replacement tissues of islets that are more similar to physiological conditions.

1. Vascular-Associated Co-Culture

Over the past few years, there have been numerous reports that show that co-culture of endothelial cells and stem cell-derived islets of beta cells represent an important approach towards the promotion of β-cell maturation and formation of vascularized islet-like structures. At the initial stages of three dimensional vascularization, Weizman et al used very porous PLGA/PLLA polymer scaffolds to create a three dimensional multicellular construct using pancreatic progenitor cell clusters which were derived using human embryonic stem cells (hESCs), human endothelial cells, and fibroblasts, and hence, modeled the vascular niche during the process of developing pancreas in vitro. The present study indicated that the vascular microenvironment produced by the combination of the three-dimensional porous scaffold and endothelial cells supports the maturation of the pancreatic progenitors into β-like cells[13]. Based on this ground, later studies have sought to recreate the vascularized microenvironment under less complex and organoid-like culture circumstances with natural matrix systems. One research established a

three-dimensional co-culture model involving undiluted Matrigel hydrogel and was able to efficiently assemble stem cell derived insulin positive cell (SC-β cells) with human umbilical vein endothelial cells (HUVECS) in vitro. It was an efficient solution to the problems of cell integration in conventional suspensions and two dimensional culture conditions, which promoted the formation of endothelial cell networks and the ability to aggregate SC-β cells, resulting in more morphologically and functional islet organoids. The functionality test revealed that, along with the high level of cell viability, this three-dimensional assembly had a significantly increased glucose stimulated insulin secretion, with 3.9 times more insulin production and the significant expression of important β cell indicators including INS, PDX1 and NKX6-1[14]. Additional progress made by Jun et al. involved integrating engineered microvascular networks into a microfluidic organ-on-a-chip system, which takes the study of vascularization of stem-cell derived islet organoids (SC-islets) to a new level that involves the combination of an architectural reconstruction with fluid dynamic stimulation. The cells of the study co-assembled hPSC-derived SC-islet cells and human primary endothelial cells and fibroblasts in a threedimensional matrix, forming vascularized islet organoids in both non perfused three dimensional models and chip systems with perfusable microvasculature. Compared with SC-islets without vascular elements, SC-β cells in vascularized organoids showed greater and more regular Ca 2 + dynamics in reaction to glucose and GLP-1 stimulation and greater insulin secretion capacity. Also in a diabetic mouse model, the same subtherapeutic dose of vascularized organoids was able to restore glucose homeostasis faster and longer, indicating that the designed microvasculature can be highly effective in improving the efficiency of graft functionality [15]. On the whole, these approaches have their benefits in the rather simple technical directions that would be easy to implement in the current organoid culture systems. The addition of endothelial cells and supporting cells leads to significant enhancement of organoid cell viability, β cell maturation, and glucose responsiveness. Nonetheless, there are some disadvantages of using this method that should be mentioned: the vascular networks created mostly rely on the exogenous endothelial cells, and they have only a small level of intrinsic formation capability and long-term stability. Furthermore, most vascular networks in current studies remain at the structural construction level, with their potential for long-term perfusion capacity and mature vascular wall structure still requiring further validation.

2. Assembly of Organoids with Vascular Organoids

In addition to introducing scattered endothelial cells directly into organoids, another important strategy is to first construct structurally complete blood vessel organoids (BVOs) and then assemble them with islet organoids to form assembloids. Compared to simply mixing scattered endothelial cells into islet organoids, BVOs already possess an initial endothelial cell-pericyte-basement membrane structure, making BVO-islet assembloids more likely to simulate true microvascular beds rather than forming discrete endothelial-like networks. This model is particularly suited for studying the impact of vascular microenvironments on long-term islet maintenance, revascularization processes, and changes in the microenvironment under diseased conditions. Wimmer et al. developed a vascular organoid system which is based on human pluripotent stem cells and showed that hPSCs could be prompted to differentiate via the mesoderm and self-assemble into a matrix to produce three-dimensional vascular organoids comprising endothelial cells and pericytes, with lumen and basement membrane structures, that have been applied to model different microvascular disease processes including diabetic vascular lesions[16].

This foundation was built upon by Tubbs et al., who described the asembloid model of co-culturing human BVOs with human donor islets. The researchers found that preformed hPSC-derived BVOs were co-cultured with primary human islets where the BVOs were slowly covering the islets and self-organizing into three-dimensional assembloids in less than a week. Light sheet microscopy showed infiltration of CD31^{+} endothelial cells into the islet indicating a process resembling the post transplantation revascularisation[17]. Functionally, BVO-islet assembloids demonstrated more stable glucose-stimulated insulin secretion abilities across islets from different donors. Compared to separately cultured islets, which experienced a significant decrease in stimulation index during up to 14 days of in vitro culture, islets in assembloids maintained a relatively stable stimulation index, indicating that the microvascular beds provided by the vascular organoids and their secretion of various angiogenesis-related factors contribute to sustaining long-term islet function and viability[18]. This research not only validated the feasibility of achieving prevascularization and functional maintenance of islet–vascular organoid assembloids in vitro but also offered a promising research platform for future applications combining BVOs with stem cell-derived islet organoids for systemic studies on pre-transplantation conditioning, donor-recipient differences, and the effects of diabetic vascular complications on islet function. Nevertheless, the construction of these systems is quite complex due to the great heterogeneity of islets of various donors and BVOs of various batches. At present, this technique is still mostly on the in vitro model validation level and there are huge gaps in terms of scaling and standardization needed to apply it clinically.

3. Multilineage Co-Differentiation in Islet-Vessel-Stroma Multicellular Organoids

The use of multilineage co-differentiation strategies is more systematic way to integrate islet, vascular, and stromal cells based on current studies on islet organoids and vascular organoids. The post-assembly of islets and vessels discussed previously do not involve the simultaneous co-induction of various lineage cells of the same cell batch of hPSCs, but rather the emphasis is on the synchronous development of both. Investigators want to induce the differentiation of endoderm and mesoderm simultaneously under a single set of induction conditions, and promote the synchronized development of pancreatic epithelium, endothelium and stromal cells on relatively similar developmental pathways. This method is very similar to the relationship of endodermal buds with neighboring mesoderm/stroma during the embryonic pancreas development. As an example, Sang et al. obtained about 70 percent endoderm and 30 percent mesoderm cells in one culture system by fine-tuning combinations of WNT/CHIR99021 and mTeSR1. The following induction in VEGF-A and other factors led to the formation of vascular pancreatic progenitors (vPP) which consisted of both PDX1^{+}/NKX6.1^{+} pancreatic progenitor cells and CD31^{+}/CD34^{+} endothelial cells. These vPPs may also be differentiated to beta cell populations that have the ability to secrete insulin providing a new paradigm in the construction of islet-vascular dual component tissues using developmental origins[19]. The organ bud model introduced by Takebe et al. is another example of how the idea of multicellular cooperative construction can be applied. This model involves a mixture of organ progenitor cells, endothelial cells and mesenchymal stem cells (MSCs) that are turned into transplantable organ buds through MSC-mediated cell aggregation under soft matrix conditions, and it also contains organ buds with the properties of pancreatic lineages. After transplantation, these pancreatic organ buds quickly vascularize and organize themselves into pancreatic-like tissue structures with the capability of three-dimensional spatial co-assembly of islet-vascular-stroma multicellular elements[20]. Furthermore, decellularized lung scaffolds were used by Campo et al. as three-dimensional perfusion matrices to reconstitute vascularized endocrinological precursors made of human iPSC-

derived endocrine precursors, endothelial cells, and stromal cells, forming iVEP (integrated Vascularized Endocrine Pancreas). In addition to enhancing the functionality and survivability of β cells in vitro, this system also facilitated a more rapid reconstruction of blood flow and improved implantation performance in vivo[21]. To sum up, the most important benefit of multilineage co-differentiation strategies is that they are consistent with the underlying principles of tissue formation during embryogenesis that may create synchronous spatial and signal regulative networks between islets, vessels and stroma right off the bat. Nevertheless, the implementation of this strategy is highly problematic. The cells of various lineages require different amounts of time to be induced, different types and concentrations of growth factors, and slight changes in conditions of induction can result in unbalanced cell compositions or lack of maturity. Hence, the precise regulation of the different cell types in synchronous multilineage induction constitutes a major challenge in the optimization and development of this strategy.

4. Evaluation Criteria for Vascularized Islet Organoids

Although the current developments of approaches to vascularize islet organoids are endothelial cell co-culture, vascular organoid assembly, and multilineage co-differentiation, the high variability in cell sources, culture systems, and engineering platforms makes it difficult to evaluate them uniformly by only considering their ability to form vessels or improve functionality. Therefore, a systematic evaluation framework is needed because it needs to evaluate vascularized islet organoids in multiple dimensions including structural integrity, functional efficacy, and capacity to integrate into vivo[22]. It is important to define what should be considered really effective vascularization to be able to compare the strengths and weaknesses of various strategies with accuracy and create the foundation of future transplantation studies and clinical applications. To begin with, the effect of vascularization ought to be assessed structurally with respect to the systematic approach. The mere fact that endothelial-like cells are present in organoids does not necessarily mean the existence of a steady microvascular network. An integrated review of vascular-related markers and morphological parameters is also required. The common endothelial markers CD31, VE-cadherin, endomucin, and CD34 can be utilized to measure the distribution of endothelial cells and tubules, whereas the vascular support structures, pericytes, and vascular support cells are usually analyzed with NG2, PDGFRβ, and alpha-SMA to determine the development of vascular wall support structures. At the same time, the deposition of basement membrane proteins including laminin, collagen IV and nidogen is a significant marker of vascular maturity. Quantitative measures must equally be concerned with the total length of the vascular network, the number of branches, complexity of branching, average diameter of the vessels, coverage by pericytes and the surface area between vessels and islet cells. Three-dimensional organoid systems can be better evaluated spatially by using confocal microscopy, light sheet imaging and tissue clearing methods to reconstruct vascular networks. To sum up, structural assessment is focused not only on the verification of the presence of vascular elements but also on the identification of whether they create continuous networks with initial maturation properties and are closely linked with islet cells[23,24]. Second, considering the functional point of view, it is important to determine if vascularization really does enhance the condition of the organoids. Experiments to perfuse the channels of the vascular network offer an important way of assessing the channel functionality of the vascular network. Researchers can observe the movement and distribution of fluorescent tracers, microspheres, or dextran molecules infused into the vascular lumen of organoids to determine the continuity of the lumen and its ability to transport material. The ability of vascularization to relieve hypoxic conditions in the center of the organoids can be assessed by hypoxia staining or hypoxic probe detection, including

pimonidazole staining and HIF-1alpha expression analysis. However, more importantly, the endocrine function must be confirmed. The glucose-stimulated insulin secretion (GSIS) test is still a fundamental assessment tool that allows comparing the amount of insulin or C-peptide released at low- and high-glucose levels to define whether vascularization increases the glucose sensitivity and secretion capabilities of the β cells. Also, the dynamics of Ca^{2+} imaging may indicate the excitation-secretion coupling functionality of β cells, and metabolic parameters like oxygen consumption rate (OCR) help to determine the energy metabolism state [15,25]. Therefore, functional assessment is not restricted to the observation of the presence of vasculature, but also the determination of whether it actually improves the oxygen and nutrient delivery conditions, thus enhancing the functional maturity of the β cells. In vivo assessment is an important consideration when testing the translational value of vascularized islet organoids intended to be used in the context of transplantation. It should first be considered how quickly the anastomosis occurs with the host circulatory system, i.e., whether the host vasculature can rapidly invade the graft or whether the pre-built vascular network may form connections with the host vessels in a short period. They are usually assessed by in vivo fluorescence perfusion, host-specific endothelial marker staining, or blood flow tracing[26,27]. Also, it is important to evaluate whether prevascularization methods can minimize necrosis and hypoxia during the early post-transplantation stage. Subsequent functional measurements ought to be focused on changes in the rate of glucose metabolism such as the time to recover host blood glucose, the duration of this recovery period, better glucose tolerance and human C-peptide levels where human C-peptide particularly acts as a vital indicator of the long-term viability of human ß cells in the graft[28]. Long term follow-ups are also needed to determine whether the graft has been able to preserve stable tissue patterns and vascular networks, and to ascertain any instances of vascular degradation, fibrotic encapsulation, or functional deterioration.[29] On the whole, in vivo evaluation should encompass not only the short-term survival of the graft and its ability to lower glucose but also its capacity to create a viable and lasting vascular support system in the host microenvironment. Combining the structural, functional and in vivo integration criteria would allow making a thorough assessment of the practical efficiency of vascularized islet organoids.

5. Post-Transplant Revascularization and Optimization of Transplantation Strategies

It is necessary to mention that the given evaluation model can be used to fully characterize the construction quality of vascularized islet organoids both in vitro and in animals but the vascularization effect per se may not always be associated with success after transplantation[30]. Particularly in organoid products to be translated into clinical use, it is of utmost importance that the blood vessel networks established in vitro are able to quickly form anastomosis with the host circulation upon transplantation, can tolerate the complex immune and inflammatory milieu, and that various transplantation sites can offer sufficient space and blood flow, which are critical determinants of the end efficacy[31]. So, following the assessment of the effects of vascularization themselves, it is recommended to focus on post-transplant revascularization and optimizing transplantation strategies[32]. The decision to transplant islet organoids is a crucial consideration that affects the survival, revascularization and long term functional preservation of the transplanted islet organoids. Despite portal vein/liver transplantation being the protocol of choice in clinical islet transplantation because of its developed procedural methods and portal vein reflux approaching physiological conditions, it has problems including instant blood-mediated inflammatory reaction (IBMIR), thrombosis, early post-transplant hypoxia, and local liver metabolism abnormalities, thus rendering it undesirable as the transplantation site of vascularized organoids. Relatively, the omentum, having a high blood flow, significant volume, and good

potential of tissue repair that would support scaffold-based implants, is seen as one of the most promising extra-hepatic transplant locations. Subcutaneous sites, because of their least invasive character, simplicity of monitoring, and retrievability, have also become significant candidate sites in engineered organoids but usually require addressing their natural poor blood supply constraints through prevascularization and biomaterial support[33,35]. The intramuscular sites are more accessible and provide some benefits in terms of oxygen supply, yet they are prone to local inflammatory reactions and mechanical stress[36]. The subcapsular renal site, although widely used in small animal experiments, is more limited in capacity and less clinically operable, thus mainly used for preliminary functional validation[37]. Overall, an ideal transplantation site should simultaneously possess the following characteristics: ample blood supply to support rapid revascularization, capacity to accommodate three-dimensional constructs, ease of real-time monitoring, and the ability to retrieve the grafts when necessary. Based on existing research evidence, the omentum and subcutaneous sites, pre-engineered for transplantation, better fulfill the needs for next-generation islet organoid transplantation. In contrast, intrahepatic sites still have some clinical validity but are more suited for traditional free islet infusion, not necessarily suitable for structurally complex vascularized organoid products.

6. Balancing Vascularization and Immune Protection

Vascularization is a critical factor in improving survival rates and functional reconstruction efficiency post-transplantation of islet organoids[38]. However, increased vascularization does not necessarily lead to better long-term graft outcomes due to the evident trade-off between vascular reconstruction and immune protection. On one hand, rapid revascularization can shorten the avascular period following graft implantation, improve oxygenation and nutrient supply, reduce early hypoxic necrosis and apoptosis, and help maintain β cell function[39]. However, when the vascular interface opens, the graft is more directly exposed to the blood flow and inflammatory agents of the host, and to its immune cells. With islet transplantation, such early exposure may induce the immediate blood-induced inflam matory response (IBMIR) with coagulation, complement activation, and leukocyte recruitment contributing to early graft injury and failure[40]. An open vascular interface may also help with the exposure of antigens and penetration of immune cells into allogeneic or stem cell-derived islet organoids and promote the likelihood of later rejection responses[41]. However, encapsulation approaches that are intended to achieve immune isolation can be effective in reducing immune recognition to a certain degree, but they tend to suffer due to insufficient oxygen delivery, limited revascularization, foreign body rejection, and fibrotic encapsulation[42]. Recent studies have therefore slowly moved away towards not just promoting vascularization but simultaneously engineering vascularization and immune regulation[43]. An illustration of this would be incorporating local immunosuppression, immune-modulatory helper cells, low-immunogenic engineered cells and anti-fibrotic materials into the transplantation microenvironment so as to provide the necessary material transfer and fast perfusion without stimulating attacks to the host immune system and sustaining the long-term stability of the graft[44]. To sum up, the future optimization of vascularized islet organoids should not only aim at speeding up vascular ingress but should reach an equilibrium in which oxygen supply, formation of immune barriers, local immune tolerance, and anti-fibrotic responses will be balanced to really increase the clinical translation potential ofvascularized islet organoids.

7. Conclusion and Future Directions

To summarize, vascularization has become one of the key factors in improving the structural maturity, functional stability and transplantability of islet organoids. The natural islets are not just clusters of endocrine cells but rather, rely on an extremely specialized microenvironment made

up of endothelial cells, pericytes, basement membrane, and extracellular matrix to rapidly exchange substances and regulate signals with great accuracy. It is not enough to increase the efficiency of beta cell differentiation to mimic the natural islets in vitro; the development of a supportive vascular network should be reconstructed at the same time. The latest developments in endothelial cell co-culture, vascular organoid assembly, multilineage co-differentiation, and microfluidics-based engineering systems indicate that vascularization may also enhance oxygenation and nutrient delivery to organoids, facilitate the maturation of beta cells, and their glucose responsiveness, and lead to better survival rates after early transplantation and glycemic control. However, the existing studies on vascularization of islet organoids are still in the shift towards the formation of vessels like structures to the creation of functional vascular networks. Although numerous systems have shown a certain degree of network morphology and short-term functionality improvement in vitro, there has been no consistent and complete data on vascular maturity, perfusion stability, and in vivo integration efficiency and long-term transplant results. Also, the fact that the balance between fast vascularization and immune protection shows that such future approaches should not only aim to increase the speed at which the blood supply is restored but also incorporate immune regulation, anti-fibrotic design, and long-term stability aspects. To sum up, vascularized islet organoids optimization is not just about enhancing the structure of individual units, but it is about the concerted reconstruction of the endocrine function vascular support immune microenvironment system as a whole. The future of this domain must change to the emphasis on the improvement of vascular quality rather than increasing the number of vascular connections. The studies must not only seek to observe endothelial cell organization or the development of a vessel-like network structure, but should extend further to determine if these have uninterrupted lumens, pericyte coverage, full basement membrane deposition, and steady perfusion properties. The creation of mature microcirculatory systems similar to the natural islets is necessary if the vascularization plans are to be truly beneficial to long-term β cell survival and function preservation. Also, the development of vascularized islet organoids will put more and more focus on the cooperation of multiple cells and developmental compatibility. Multilineage co-differentiation systems with constant origins and synchronized timings may be more favorable to the reconstruction of tissue architecture and cell interaction networks similar to those found in natural islets than simple heterologous cell assembly systems. Furthermore, the process of closing the gap between in vitro prevascularization and in vivo transplant integration will play a key role when it comes to establishing clinical translation value. Follow up studies must not only address the question of whether organoids are capable of building vascular networks in vitro but whether such networks can quickly develop anastomosis with the host vasculature after transplantation, withstand the inflammatory and immune stresses and promote prolonged graft function output. It suggests that it is necessary to create more holistic assessment mechanisms that would smoothly combine in vitro structural assessment, functional assessment, and long term in vivo results to determine vascularization solutions that have actual translational capabilities. At the same time, immune protection stays as a problem that cannot be avoided. Although quick creation of blood supply reduces the effects of hypoxic injury, it might also increase the chances of the graft becoming exposed to the host immune system. Therefore, the most promising methods are going to include the promotion of perfusion reconstruction coupled with the incorporation of local immune modulation, cells that are of low immunogenicity, immune isolation materials, and anti-fibrotic design to strike a balance between oxygen provision and immune protection.

Lastly, the requirements of standardization and scale-up preparations will be required before vascularized islet organoids can proceed to clinical use. At present, there is still a great heterogeneity in terms of cell sources, induction protocols, scaffold materials, culture conditions, and evaluation criteria used in studies, which makes cross-study comparisons and technology scaling difficult. The future work needs to aim at creating uniform quality control guidelines and functional assessment systems and encouraging clinical-grade preparation procedures that do not contain xenogenic substances, are scaleable and have a track record. On the whole, due to the current interdisciplinarity of stem cell biology, tissue engineering, microfluidics, immune regulation, and transplant medicine, making islet organoids with mature vasculature networks, steady endocrine activity, and positive transplantation compatibility is likely to emerge as one of the directions of cell replacement therapy of diabetes.

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