

Review

## The Roles of Collagen in Islet Transplantation

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**Academic Editors:** Kenneth L. Brayman and Preeti Chhabra

**Special Issue:** [Islet Cell Transplantation](#)

*OBM Transplantation*

2020, volume 4, issue 4

doi:10.21926/obm.transplant.2004127

**Received:** October 02, 2020

**Accepted:** November 15, 2020

**Published:** November 27, 2020

### Abstract

Islet transplantation is a cellular replacement therapy for severe diabetes mellitus. Although the clinical outcome of islet transplant has been improving, the transplant efficacy of this treatment is not superior to that of pancreatic organ transplantation, a similar transplant therapy. Various factors have been characterized as 'islet transplantation specific', which includes lack of revascularization and ischemia, innate inflammation, or autoimmunity, affect the therapeutic outcome of this treatment. Among them, the impairment of islets by digestion of extracellular matrix (ECM) via the islet isolation and transplantation process is one of the major factors to avoid islet engraftment. The islet is composed of endocrine cells aggregated by ECMs. Particularly, collagen is a target for the digestion of the pancreas for islet isolation. Furthermore, collagen improves endocrine functions, survival, and proliferation. In this study, we review the importance of collagen in islet transplantation.

### Keywords



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$\beta$  Cells; collagen; collagenase; extracellular matrix; insulin; islet; islet isolation; islet transplantation

## 1. Introduction

Islet transplantation is a cellular replacement therapy for severe diabetes mellitus (DM), including brittle type 1 DM, that stabilizes blood glucose control with appropriate insulin supplies. The clinical outcome of this treatment is improved significantly because of innovations in pancreas procurement, islet isolation, methods of transplantation, and regimen of immunosuppressive agents [1]. Recently, two phase 3 clinical trials of islet transplantation for type 1 DM were reported. The first clinical trial purified human pancreatic islets in patients with type 1 DM after kidney transplant (CIT-06), which indicated that 62.5% of patients achieved the primary endpoint of evading severe hypoglycemic events and between 1% and 6.5% reduction of HbA1c level at 1 year after islet transplantation. The median hemoglobin A1c (HbA1c) level was ameliorated at 1 year compared with before transplant (6.0% vs. 8.1%). Furthermore, this protocol preserved the kidney allograft function for three years after islet transplantation [2]. The second clinical trial transplanted allogeneic pancreatic islet in type 1 DM patients complicated by severe hypoglycemia with normal renal function (CIT-07). This study demonstrated that 87.5% and 71% of patients achieved an HbA1c of 7.0% or less and prevented severe hypoglycemic events at 1 and 2 years, respectively, after the first transplantation [3]. To date, islet transplantation has been widely recognized as one of the standard therapies for type 1 DM worldwide.

In contrast, the transplant efficacy of islet transplantation is not superior to that of pancreas organ transplantation, a similar transplant therapy. Pancreas organ transplantation is a major surgery that is characterized by arterial/venous reconstruction into the right external iliac artery/vein with pancreatic drainage route using the bladder or ileum [4]. The pancreatic organ transplantation gives good therapeutic outcomes. Indeed, the graft survival rates (i.e., insulin independent rate) are almost 85% at one year and >60% at five years [5], while insulin independent rate at five years was 39% in islet transplantation [6]. The transplantation of the pancreas can be safely performed. However, this procedure is more invasive compared to islet transplantation, which is an outpatient procedure. An annual report by the Collaborative Islet Transplant Registry indicated that transplantation of a higher volume of islets (>10,450 islet equivalents per body weight [kg]) results in successful prevention of severe hypoglycemic events in more than 80% of the recipients and restoration of the HbA1c level in more than 60% in both islet alone and islet after kidney transplantation for 5 years after transplantation (<http://www.citregistry.org/>). This means several (generally >2) islet transplantations are often needed, whereas only one transplantation enables the achievement of good endocrine function in pancreas transplantation. There are various factors, including lack of revascularization and ischemia [7, 8], innate inflammation [9], or autoimmunity [10], that affect the transplant outcome of islet transplantation. Among these factors, the impairment of the extracellular matrix (ECM) in the islet is a major reason for the prevention of islet engraftment. ECM is an extracellular component that plays a role as a scaffold that contributes to the formation of tissues and organs. Conversely, ECM regulates cell-to-cell interactions via the activation of various growth factors and cytokines [11]. The islet is composed of endocrine cells

aggregated by ECM, like other tissues and organs. The breakdown of islet ECM by an enzyme is essential for the isolation of pancreatic islets from the donor pancreas. However, this leads to the destruction of islets and, as a consequence, may reduce islet dysfunction and survival.

ECM in islets comprises two macromolecules: glycosaminoglycans and fibrous proteins [11, 12]. Glycosaminoglycans are long, linear polysaccharides with a high molecular weight composed of repeating disaccharide units. Sulfated glycosaminoglycans are attached to a core protein at specific sites and form a compound known as proteoglycan. Proteoglycans are located in the interstitial tissues or the cellular membrane and provide hydrophilic conditions and interaction between the ligand and receptor via signaling molecules. There are several subtypes of glycosaminoglycans, including heparan sulfate, chondroitin sulfate, dermatan sulfate, and keratan sulfate [13]. Conversely, fibrous proteins, including collagen, elastin, fibronectin, and laminin, provide structural and functional benefits to cells, including islets [11]. Among them, we focus on collagen because it is not only a representative component of ECM but also its characteristics may affect the therapeutic outcome of islet transplantation. In this study, we review the importance of collagen in islet transplantation.

## **2. Importance of Collagen in Islet Transplantation**

### ***2.1 Overview***

Collagen occupies approximately 30% of proteins in the human body [11, 14]. The peptide chain of collagen comprises three repeating peptide triplets of glycine, amino acid X, and amino acid Y. Proline and hydroxyproline are often positioned in X and Y, respectively. The three peptide chains, known as  $\alpha$  chains, helically combine, and form collagen [14]. Presently, 28 different types of collagen are known and numbered from I to XXVIII [14]. Among them, collagens I, II, III, IV, and V have been identified as common in the human body [15]. Collagen I is the most abundant collagen and is a major component of the skin (>90% of the mass), tendon, muscle, and bone [16, 17]. Collagen II is a major component of cartilage [18], collagen III is a major component of reticular fiber and commonly coexists with collagen I [11, 17], and collagen V has primarily been detected in the cellular surface, hair, and placenta [11]. Although collagens I, II, III, V, and XI are classified as fibrillar collagen or fibril-forming collagen [17], collagen IV is categorized as non-fibrillar collagen. This is the most pivotal structural component of the basement membrane [11, 17]. Collagen VI is also classified as non-fibrillar collagen and comprises three different  $\alpha$  chains [17]. There are two main reasons why collagen is important in islet transplantation, namely, as a target of pancreatic digestion for islet isolation and as a supporter of the endocrine function of islets.

### ***2.2 The Role of Collagen in Islet Transplantation: Target of Pancreatic Digestion for Islet Isolation***

As previously mentioned, collagen is a major target of enzymatic digestion for islet isolation. It is critical to digest collagen of peri-islet effectively and not to damage islets by digestion of intra-islet collagen, leading to the acquisition of a large volume of islets with keeping original endocrine function from the donor pancreas [19]. Therefore, understanding the distribution of collagen in the pancreas is necessary. Some groups have previously elucidated that the regulation of collagenase blend might affect the acquired volume of islets in islet isolation [20, 21].

Table 1 shows the distribution of collagen in the pancreas and islets. The distribution varies according to the species. In pigs, collagens I, III, and IV are expressed in peri-islet, and the expression level is higher in older pigs than that in younger pigs [22]. Hughes et al. revealed that collagen VI was abundant in the interlobular and intralobular of acinar cells, compared with collagens I, IV, and V in juvenile and adult pigs. Furthermore, collagens I and VI are prominently detected in peri-islet, especially collagen VI [23]. Similar results were reported by Van Deijnen et al., who showed that collagen I was weakly expressed in peri-islet and in the lobar, lobular, and acinar septa and that collagen V also reacted weakly in the lobar and lobular septa [24]. Similar findings were also shown by Vigier et al., who found that the expression of collagen in pig pancreas was weaker in IV and V than in I, III, and VI [25]. Conversely, Goto et al. revealed the importance of collagen V digestion using collagenase G (collagenase I) for the success of porcine islet transplantation [26].

**Table 1** Distribution of collagen in the pancreas and islet.

Type of collagen	Author (year), Reference	Specimen	Detailed results
I, II, III, IV, V	Meier (2020), [27]	Human	Evaluated the correlation between the degree of collagen digestion and acquired human islets volume
I, IV, VI	Spiers (2019), [28]	Human	Evaluated the profiles of ECMs in human pancreatic tissue for developing the donor-specific collagenase
IV	Spiers (2018), [29]	Human	Assessment of collagenase for digestion of collagen IV and laminin in the human pancreas
IV	Cross (2017), [30]	Human	Collagen IV and laminin presented in peri-islet in humans
VI	Cross (2006), [19]	Human	Collagenase penetrates the islet by the current techniques and led to low islet yields
VI, I, IV, V	Hughes (2006), [31]	Human	Collagens IV, V, and VI were present throughout the human islet-exocrine interface, whereas collagen I was seen at more variable sites The mean peri-islet collagen VI proportion was significantly greater than that of collagen I or IV
XVIII	Choong (2015), [32]	Mouse	Collagen XVIII was stained in mouse islets
IV	Irving-Rodgers (2014), [33]	Mouse	Mouse islet basement membrane, comprising collagen IV and other ECMs, including laminin, was completely lost during islet isolation

V	Shima (2016), [26]	Pig	Collagen V is a target for collagenase G, whereas collagens I and III are targets for collagenase H (porcine islet isolation)
V, III, I	Miyazaki (2019), [34]	Rat	Collagens III and V were crucial for islet isolation, and the population was different from the strains of rat
I, III	Fujio (2014), [35]	Rat	Collagenase H reacted to collagens I and III
IV, V	Vigier (2017), [25]	Mouse, pig	Collagens IV and V were stained peri- and intra-islet in mouse
I, III, V	Van Deijnen (1994), [24]	Human, pig, dog, rat	Collagen I was expressed in peri-islet and in the lobar, lobular, and acinar septa weakly in pigs and dogs and moderately in rats and humans Collagen III is well developed on the lobar and acinar septa in rats and dogs. The peri-islet displays weakly in rats, dogs, and humans and very weakly in pigs Collagen V reacts moderately in rats, dogs, and humans and weakly in pigs in the lobar and lobular septa

It has been accepted that the distribution of pancreatic collagen in humans is similar to that in pigs. Hughes et al. revealed that collagens IV, V, and VI were distributed in the islet-exocrine interface and that the distribution of collagen I was widely observed. Particularly, peri-islet collagen VI was strongly expressed compared with collagens I and IV, as in pigs [28, 31]. They also certified that collagenase (Liberase HI; Roche Applied Science, Indianapolis, IN; Collagenase NB1 and neutral protease NB; Serva Electrophoresis, Heidelberg, Germany) digested collagen VI in not only exocrine tissues but also in peri- and intra-islets and caused damage to islets [19]. Furthermore, they showed that collagen IV was seen in the peri-islet basement membrane (peri-islet capsule) and was digested by collagenase [30]. It was digested more effectively using the blend of collagenase and neutral protease compared with single usage (collagenase or neutral protease) [29].

Regarding rodents, Irving-Rodgers et al. showed that collagen IV located in the peri- and intra-islets was digested by the isolation process and recovered after engraftment in mice [33]. Vigier et al. also showed that collagens IV and V were seen around mouse islets [25]. Choong et al. revealed that collagen XVIII, as rare collagen, was strongly expressed in mouse islets [32]. Goto's group revealed that collagens I and III were located in the exocrine tissues of rat, especially collagen III, and that collagenase H (collagenase II) reacted to collagens I and III compared with collagenase G (collagenase I) [35]. Later, they revealed that the distribution between collagens I and III depends on the difference in rat strains [34].

In summary, there are some varieties in the distribution of the types of collagen among species. We consider that the understanding of the distribution is important to select suitable collagenase and acquire more islets with good qualities in islet isolation.

### 2.3 The Role of Collagen in Islet Transplantation: Supporter for the Improvement of the Endocrine Function of Islets

Table 2 summarizes the important roles of collagen in islet transplantation regarding the improvement of the endocrine function of islets. Many studies have revealed that collagen, like laminin and fibronectin, contributed to the improvement of the viability of  $\beta$  cells, prevented apoptosis of  $\beta$  cells, and improved glucose-stimulated insulin secretion of  $\beta$  cells with the expression of insulin-associated genes, especially in collagens I and IV [36-53].

**Table 2** The roles of collagen in islet transplantation regarding the endocrine function.

Type of collagen	Author (year), Reference	Role in islet transplantation	Detailed results
VI	Wang (2020), [36]	Improved viability, insulin-releasing function, and reduced islet immunogenicity	Rat islets cultured with decellularized 3-D ECM improved the survival, insulin content, and glucose-stimulated insulin secretion The ECM restored basement membrane-related collagen VI associated with an attenuation in islet immunogenicity
IV	Hadavi (2019), [37]	Improved insulin-releasing function	Collagen IV and laminin scaffolds improved the endocrine function of human islets
IV	Hadavi (2018), [38]	Improved insulin-releasing function	Fibronectin and collagen IV improved insulin secretion $\beta$ cells
III	Olaniru (2018), [39]	Improved viability and insulin-releasing function	Collagen III prevented cytokine-induced apoptosis and preserved insulin secretion function in human islets
I	Stephens (2018), [40]	Improved viability and insulin-releasing function	Mouse islets encapsulated with collagen I improved the viability and insulin secretion Succeeded subcutaneous islet transplantation
I, IV	Nakashima (2018), [54]	Improved adhesive ability	The adhesive ability to fibronectin was better than other ECMs for porcine exocrine tissues
VI	Llacua (2018), [41]	Improved viability and insulin-releasing function	Collagen VI improved the viability and insulin-releasing function of encapsulated human islets
IV	Llacua (2018), [42]	Improved islet survival	Survival including reductions of necrosis and apoptosis of islets encapsulated with collagen IV and laminin

I	Forget (2017), [43]	Improved islet survival	Improved cultured islet survival in the IGF-2 coated porous collagen microwells
IV, I	Llacua (2016), [44]	Improved insulin-releasing function	Collagen IV improved the insulin-releasing function of human islets, whereas there was no effect in collagen I
IV	Liu (2015), [45]	Improved viability and insulin-releasing function	Collagen IV and fibronectin enhanced insulin secretion and expression of $\beta$ cell-associated genes via the integrin/ focal adhesion kinase/extracellular signal-regulated kinase pathway
IV	Yap (2013), [46]	Improved viability and insulin-releasing function	Collagen IV-modified scaffold promoted islet cell viability that enhanced insulin secretion
IV	Beenken-Rothkopf (2013), [47]	Improved insulin-releasing function	Encapsulated $\beta$ cell line improved the insulin-releasing function under the presence of collagen IV, fibronectin, or laminin
IV	Gibly (2013), [48]	Improved viability and insulin-releasing function	Scaffolds using collagen IV supported extrahepatic human islet transplantation with the improvement of the engraftment and function
IV, I	Sojoodi (2013), [55]	N/A	Laminin, but not collagens I, IV, or fibronectin, induced comparable expression of the <i>Ins1</i> and <i>Ins2</i> genes in rat adult $\beta$ cells
IV	Davis (2012), [56]	Improved insulin-releasing function	Collagen IV and/or laminin-encapsulated mouse islets with mesenchymal stem cells improved the insulin-releasing function and expression of insulin-associated genes
I	Jalili (2011), [50]	Improved viability and insulin-releasing function	A scaffold comprising collagen I and fibroblasts improved the survival and insulin-releasing function of mouse islets and improved the long-term of islet isograft function
IV	Salvay (2008), [51]	Improved insulin-releasing function	Mice transplanted islets onto scaffolds with collagen IV achieved euglycemia fastest
IV	Kaido (2006), [57]	N/A	Collagen IV induced a decline of insulin mRNA and a significant loss of insulin content in human fetal $\beta$ cells
IV, I	Pinkse (2006), [52]	Improved islet survival	Islets that had been cultured on collagen IV showed better islet survival than collagen I
I	Edamura (2003), [32]	N/A	The insulin-releasing function of cultured porcine islets was seen with laminin but not with collagen I

I, IV	Sakurai (2003), [58]	Promoted angiogenesis	Implantation of collagen I- or IV-coated foreign body promoted neovascularization
I, IV	Nagata (2001), [53]	Improved viability and insulin-releasing function	Insulin secretion of cultured islets with collagen I or a mixture of collagen I and IV was improved
I, IV	Jiang (1999), [59]	N/A	Collagens I and IV inhibited $\beta$ cell survival Laminin contributed to the proliferation of $\beta$ cells

N/A: not applicable

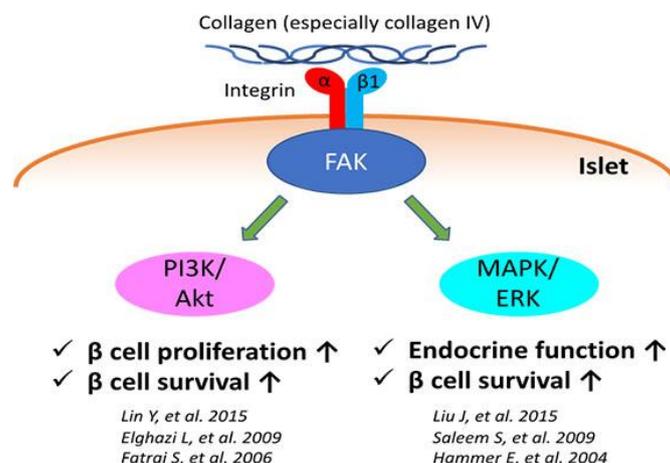
Collagen IV is a major component of the peri- and intra-islet basement membrane [33]. The collagen works as a niche for transplanted islets and supports the improvement of insulin secretion [37, 46]. For example, Yap et al. evaluated the condition of islets seeded into polymer scaffold with ECM, including collagen IV, laminin, and fibronectin, and elucidated that collagen IV improved the insulin-releasing function and viability of  $\beta$  cells compared with other ECMs and shortened the time to normoglycemia in islet transplantation [46]. Salvay et al. also revealed that islet transplantation with collagen IV-coated scaffold was superior to other ECMs such as fibronectin and laminin in controlling the blood glucose level [51]. Furthermore, Beenken-Rothkopf et al. conducted a similar study using MIN6  $\beta$  cells embedded in polymer and showed that collagen IV improved the insulin-releasing function of the cells, the same as other ECMs such as laminin and fibronectin [47]. Other previous studies also revealed the contribution of collagen IV in greater insulin release of islets [44, 48, 54, 56, 60], and the therapeutic effects were better than those of other ECMs [44]. Collagen IV also contributed to islet cell survival, prevention of apoptosis, and oxygen consumption rate of immunoisolating encapsulated islets [41, 42]. Immunoisolating encapsulation is a technology that protects the containing islets in polymers, such as alginate, by preventing the infiltration of immunocompetent cells and antibodies.

Collagen I, which is also localized within and around islets such as collagen IV [24], promoted islet cellular survival and differentiation and also improved the  $\beta$  cell function [61-63]. For example, Stephens et al. conducted the encapsulation of isolated mouse islets using collagen I oligomer and demonstrated the improvement of viability and insulin secretion of the encapsulated islets, as well as successful subcutaneous islet transplantation in both syngeneic and allogeneic models [40]. A similar trial was conducted by Jalili et al., who used a scaffold comprising collagen I and mouse fibroblasts to improve the survival and insulin-releasing function of mouse islets and improve the long-term islet isograft function [50]. Nagata et al. also reported similar results using rat islets [53]. Conversely, some groups have indicated that neither collagen I nor IV contributed to the improvement in endocrine function [32, 55, 57, 59].

These benefits of collagen in endocrine function are provided via the activation of the intracellular signaling pathway activated by ligation between collagen and integrin (Figure 1) [61]. Integrin is a transmembrane receptor that includes 24 different types and is known as an adhesion factor that combines various ECMs such as collagen, laminin, and RGD (Arg-Gly-Asp) motif [11]. Integrin is a heterodimer comprising two polypeptide chains known as  $\alpha$  and  $\beta$  subunits. There are 18  $\alpha$  and 8  $\beta$  subunits known [64]. Previous studies have revealed that integrin receptors for collagen

in islets contained  $\beta 1$  subunit ( $\alpha 1\beta 1$ ,  $\alpha 2\beta 1$ ,  $\alpha 3\beta 1$ ,  $\alpha \nu\beta 1$ ,  $\alpha 10\beta 1$ , and  $\alpha 11\beta 1$ ) [14, 57, 60, 65-69]. Integrin  $\beta 1$  plays a pivotal role in the regulation of islet cell biology, survival, and function [70-72]. In other words, collagen contributes to the improvement of endocrine function via integrin  $\beta 1$ . For example, integrin  $\alpha 3\beta 1$  improves human  $\beta$  cell survival [71] and insulin secretion of rat  $\beta$  cell [72] by attaching ECMs. Integrin  $\alpha \nu\beta 1$  promotes human  $\beta$  cell adhesion [73], and integrin  $\alpha 1\beta 1$  also contributes to the adhesion, motility, and insulin secretion of human  $\beta$  cell by binding to collagen IV [60]. Furthermore, collagen IV is localized to integrins  $\alpha 3\beta 1$ ,  $\alpha 5\beta 1$ , and  $\alpha 6\beta 1$  during the development of the human fetal pancreas [67].

After binding collagen (especially collagen IV) and integrin  $\beta 1$ , the intracellular signaling pathways associated with focal adhesion kinase (FAK), which regulates cell proliferation, differentiation, and apoptosis, are activated (Figure 1). The activation of FAK promotes the two represented downstream signaling pathways: mitogen-activated protein kinase/extracellular signal-regulated kinase (ERK) and phosphoinositide 3-kinase/Akt pathways. Liu et al. evaluated the endocrine function of rat  $\beta$  cell line encapsulated with their developed conditioned peptide containing fibronectin and collagen IV motif and the mechanism. They revealed that fibronectin- and collagen IV-encapsulated cells improved their insulin-releasing function, and the proliferation and expressions of  $\beta$  cell-associated genes (*Ins1*, *MafA*, and *Pdx-1*) were enhanced in the cells. Furthermore, phosphorylated FAK and ERK were detected, but there was no enhancement of Akt protein in the encapsulated cells. The expression of integrin  $\beta 1$  cyclin protein was also certified. They concluded that these improvements of endocrine function were caused by the activation of the FAK/ERK/cyclin signaling pathway via ligation between ECMs (including collagen) and integrin  $\beta 1$  [45]. Other groups also showed similar results regarding the mechanism of improvement of endocrine function. Hammar et al. showed that the activation of the mitogen-activated protein kinase/ERK pathway by the activation of FAK via integrin  $\beta 1$  improved the survival of rat isolated  $\beta$  cells [74]. Saleem et al. demonstrated that the activation of FAK/ERK by integrin  $\beta 1$  promoted differentiation and prolonged the survival of human fetal pancreatic islet cells [62]. Conversely, it was elucidated that the activation of the FAK/phosphoinositide 3-kinase/Akt pathway via interaction between collagen and integrin inhibited the cleavage of caspase 3 in the MIN6  $\beta$  cell line cultured with collagen IV [75] and promoted the proliferation of  $\beta$  cells [76, 77].



**Figure 1** Interaction between collagen and integrin, and the resulting therapeutic effects.

### 2.4 New strategy for Improving Islet Transplantation Using Collagen

Some research groups have attempted to show the possibility of collagen for the improvement of islet transplantation (Table 3). One strategy is to adopt a scaffold for developing new islet cells with additional values. Carvalho Oliverira et al. attempted to form swine islets with low immunogenicity by culturing single islet cells silenced by swine leucocyte antigen using collagen VI. Xenogenic T cell immune responses were significantly prevented in swine leucocyte antigen-silenced islet cells, and the clusters constructed of the silenced cells harbored similar levels in the expression of the insulin gene and insulin-releasing function compared with control islets [78]. This strategy may contribute to the resolution of limited donor supplies by using xenogenic islets with low immunogenicity. Yang et al. also attempted to form islet-like clusters from murine  $\beta$  cell line by culturing in collagen IV-treated culture dish. They form 100-150  $\mu$ m-sized pseudoislets with high survival rate and good glucose-stimulated insulin secretion and revealed the improvement of the endocrine function of diabetic animals by transplantation [79]. Recently, Kogawa, Mochizuki, and colleagues showed that the encapsulation technique using human recombinant collagen I (Celsaig) with mesenchymal stem cells contributed to the improvement of transplant efficacy of islet xenotransplantation by promoting angiogenesis [80, 81].

Another strategy is the adoption of a scaffold for differentiation into  $\beta$  cells from pluripotent or somatic stem cells. This also aims to clear the problem of limited donor supplies by forming new islets. Regarding this strategy, collagens I and IV contribute to supporting the differentiation from mesenchymal stem cells [82] and pancreatic precursor cells [83, 84].

Collagen can also be used for making bioengineered islets. For example, Gibly et al. conducted the transplantation of human islets seeded into bioscaffold using collagen IV to diabetic immunodeficient mice and succeeded in achieving normoglycemia for more than four months [48]. Hiscox et al. certified the improvement of insulin-releasing function of subcutaneously transplanted islets covered by collagen gel with prevascular treatment [85]. Furthermore, it is believed that the combination of collagen with other biomaterials that have the ability of immune isolation and growth factors can be a valuable trial for the success of islet transplantation [61].

**Table 3** Other possibilities of collagen.

Type of collagen	Author (year), Reference	Role of collagen	Detailed results
I	Kogawa, Mochizuki (2020), [80, 81]	Material for bioengineered islets	The encapsulation technique using human recombinant collagen I (Celsaig) with mesenchymal stem cells contributed to the improvement of transplant efficacy of islet xenotransplantation (rat to mouse) by promotion of angiogenesis.
VI	Carvalho Oliverira (2020), [78]	Material for the formation of newly islets	Porcine single islet cells silenced by swine leucocyte antigen were cultured with collagen VI Formed islets acquired low immunogenicity

IV	Pokrywczynska (2015), [82]	Promoted $\beta$ cell differentiation	Collagen IV contributed to the differentiation of rat mesenchymal stem cells into islet-like cells
IV	Yang (2013), [79]	Material for the formation of newly islets	Formed pseudoislets from $\beta$ cell line with improved insulin-releasing function using collagen IV-treated culture dish
I	Vernon (2012), [86]	Material for bioengineered islets	Used for bioengineered islets as a cushion aiming to prevent physical damage of the islets
I	Mason (2009), [83]	Promoted $\beta$ cell differentiation	Hydrogels containing collagen I promoted differentiation of a glucose-responsive $\beta$ cell population from dissociated precursor cells of rat
IV	Cirulli (2000), [84]	Development of endocrine progenitor cells	Integrin $\alpha\beta3$ and $\alpha\beta5$ contributed to the development of human pancreatic endocrine cells by binding to collagen IV and fibronectin

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### 3. Conclusions

We believe that the study on collagen will support the improvement of islet transplantation. For example, knowledge on the distribution of collagen in the pancreas is essential to select preferred collagenase, which digests pancreatic tissue without impairing islets, for islet isolation. This will lead not only to the increasing volume of acquired islets with good quality but also for designing suitable collagenase blends per pancreas for custom-made islet isolation. Furthermore, the benefit of collagen in improving the endocrine function of  $\beta$  cells can be adopted for the development of bioengineering islets using collagen with good reactivity to glucose change, producing a suitable volume of insulin and resistance to apoptosis in transplantation. These innovations using collagen may provide a further evolution of this treatment.

### Acknowledgments

We thank ENAGO ([www.enago.jp](http://www.enago.jp)) for English proofreading service.

### Author Contributions

Naoaki Sakata planned the theme and described the first draft of this review. Gumpei Yoshimatsu revised the manuscript. Shohta Koadama revised the final version of this review.

### Funding

This study was funded by a Grant-in-Aid for Scientific Research (C) (19K09839, NS) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

### Competing Interests

The authors declare that no competing interests exist.

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