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Beta cell dysfunction in diabetes: the islet microenvironment as an unusual suspect

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Abstract

Cells in different tissues, including endocrine cells in the pancreas, live in complex microenvironments that are rich in cellular and acellular components. Intricate interactions with their microenvironment dictate most cellular properties, such as their function, structure and size, and maintain tissue homeostasis. Pancreatic islets are populated by endocrine, vascular and immune cells that are immersed in the extracellular matrix. While the intrinsic properties of beta cells have been vastly investigated, our understanding of their interactions with their surroundings has only recently begun to unveil. Here, we review current research on the interplay between the islet cellular and acellular components, and the role these components play in beta cell physiology and pathophysiology. Although beta cell failure is a key pathomechanism in diabetes, its causes are far from being fully elucidated. We, thus, propose deleterious alterations of the islet niche as potential underlying mechanisms contributing to beta cell failure. In sum, this review emphasises that the function of the pancreatic islet depends on all of its components.

Keywords

Extracellular matrix; Homeostasis; Microenvironment; Pancreatic islet; Pericytes; Review

Introduction

The main cellular compartment in charge of the specific tissue function of an organ is the parenchyma, which in the pancreatic islet consists of the endocrine cell mass. Endocrine cells of the pancreas, however, do not exist in a vacuum. The endocrine parenchyma is infiltrated by vascular cells that form capillary tubes, thus connecting the organ to the systemic circulation. The parenchymal and vascular elements are immersed in a web of macromolecules, the extracellular matrix (ECM). Within this matrix, stretched between

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blood vessels and the parenchyma, live other cells, such as fibroblasts and macrophages. The microenvironment is not only a scaffold holding beta cells together or a conduit for nutrients and gases; it is clear now that the microenvironment plays a more active and complex role in regulating the function of cells immersed in it. Most research in islet biology, however, focuses on the insulin-secreting beta cell. This narrow view is oblivious to the fact that pathologies in nearly every organ system are caused by, or reflect, dysfunction or destruction of the microenvironment's integrity. The goal of this review is to present the biology of the islet from the point of view of the islet microenvironment and, using recent findings on the interactions between pericytes and beta cells, illustrate how the microenvironment and beta cells depend on each other. The take-home message is that the function of the pancreatic islet is only as good as the sum of all of its parts.

Acellular components of the islet microenvironment

The ECM and basement membrane

The ECM is a three-dimensional network composed of fibrous-forming proteins, such as collagens, elastin, laminins, glycoproteins, proteoglycans and glycosaminoglycans [1, 2]. The reader can consult several excellent reviews for a catalogue raisonné of the components of the islet ECM [3–5]. Yet the authors of these reviews also point out that there is no consensus about the production and distribution of ECM components in islets. If results vary from study to study, it is mainly because the ECM differs between species and changes during development [6–11]. To date, most studies aimed to demonstrate how beta cell interactions with the ECM increase insulin secretion and beta cell proliferation. Although these outcomes may be desirable from a clinical perspective, this strategy does not reveal how the ECM contributes to long-term tissue homeostasis (e.g. constancy of islet structure and size). In vivo studies, pointing to the ECM as a guide of pancreas development and beta cell function, are limited to rodent islets, which may not accurately model the human islet microenvironment. Cell-to-ECM signalling in human islets is generally studied after isolation, under in vitro conditions and with a partially digested ECM, which may not reflect the local interactions in the native environment. Under in vivo conditions, beta cells in mouse and human islets are polarised towards islet blood vessels, and insulin-granule fusion occurs mostly in regions that contact the vascular basement membrane and are enriched in synaptic scaffold proteins [12, 13]. Clearly, we still have much to learn about the mechanisms producing the distinctive, fine-tuned composition of the islet ECM that empowers endocrine cells to adequately secrete their hormones during an organism's lifespan.

The basement membrane is a specialised and denser form of ECM that is associated with cells that gives structural support, stores growth factors, determines cell polarity and influences cell metabolism [1]. The individual basement membrane consists of two distinct layers: the basal lamina that is immediately contiguous to the vascular cells and contains various ECM glycoproteins, including collagen IV, laminin, fibronectin and proteoglycans [14]; and the reticular lamina, which is generally produced by fibroblasts of the underlying connective tissue and contains fibrillar collagens. The basement membrane exemplifies how islet matrix architecture differs between species; the interior of the human islet is lined by

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two layers of basement membrane, a vascular and an endocrine layer, whereas the interior of the mouse islet lacks the endocrine basement membrane [11]. These differences are likely to have an impact on how leucocytes infiltrate the islet in type 1 diabetes [15] or how fibrosis develops inside the islet (see below).

Anatomical and functional disruption of the microenvironment leads to organ dysfunction

ECM composition and dynamics are tightly regulated and ensure tissue homeostasis. This involves multilayered, redundant mechanisms that affect the cellular expression and secretion of ECM molecules and their degradation by ECM-modifying enzymes. If left unchecked, the potent ECM degrading and remodelling enzymes can destroy tissues. The vast majority of known diseases can be traced back to hardening, manipulating or dysregulating the composition of the ECM [16–19].

Already in 1884, Frerichs reported gross changes in the pancreas of individuals with diabetes [20], with 70% showing demonstrable histopathology in islets. Most of the alterations associated with diabetes involve the ECM (fibrosis, amyloidosis) and insulitis, which in turn potentiates fibrosis [21]. Fibrosis is a damaging process that results from excessive production of connective tissue. It is very common in the islets of people with diabetes (present in 60% of early-onset cases, as well as in maturity-onset cases [22, 23]). Perivascular accumulation of ECM is seen in chronic type 1 diabetes and in type 2 diabetes and is associated with diffuse pancreatic fibrosis. The causes of islet fibrosis are not known in detail and may not be singular. While an inflammatory aetiology has been proposed [24, 25], a vascular aetiology may play a predominant role [26].

Amyloidosis results from deposition of a hyalin substance between the capillaries and islet cells. This substance, islet amyloid polypeptide (IAPP or amylin), is produced and secreted by beta cells [27, 28]. Islet amyloidosis is more common in individuals with type 2 diabetes, than in those with type 1 diabetes [22], with studies showing that it is present in every person with type 2 diabetes [29]. Amyloid deposition in perivascular regions in human islets is associated with decreased beta cell mass [30]. Indeed, amyloid leads to apoptosis of beta cells, as assembly of IAPP into small oligomers exerts toxic effects on beta cells by interfering with plasma membrane integrity [31].

By limiting the capacity for beta cell proliferation, inducing apoptosis, disrupting the islet cytoarchitecture or by compromising nutrient and gas exchanges, vascular fibrosis and amyloidosis may contribute to diabetes pathogenesis or aggravate diabetes [22, 32–34]. Why these mechanisms are not universally included in models of diabetes pathogenesis is probably because the evidence is not conclusive [35]. It is difficult to study the functional consequences of a disrupted microenvironment and establish causal relationships given that long-term interventional studies are not possible in human beings. Common mouse strains do not model human islet vascular fibrosis and amyloidosis [36]. Nevertheless, studies using transgenic mice producing human islet amyloid or rodent models showing increased islet fibrosis [37–41] may help elucidate the pathophysiological mechanisms related to these vascular aberrations. For instance, a transgenic mouse model of beta cell expansion shows significant vascular alterations in islets, such as perivascular fibrosis and altered pericyte phenotype and coverage of islet capillaries [41].

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Cellular components of the islet microenvironment

Beta cells interact with other cells that populate the islet niche, including neurons, immune cells, Schwann cells and vascular cells, all of which are known to support proper insulin secretion [42]. The other endocrine cell populations in the islet work together with beta cells, establishing complex paracrine communication networks that ensure proper control of blood glucose levels [43]. By secreting hormones (e.g. somatostatin, glucagon), delta and alpha cells regulate the function of beta cells [44, 45]. In addition, islets are scattered throughout the exocrine pancreas and, thus, maintain intimate anatomical and functional interactions with acinar tissues. Indeed, diabetes is often associated with reduced pancreas size and abnormal pancreatic exocrine function [46, 47], and individuals with pancreatic ductal adenocarcinomas also have an increased risk of developing diabetes [48]. Below, we review the role of vascular cells, and cells residing between the islet vasculature and parenchyma.

Cells residing between the vascular and parenchymal compartments

By synthesising several components of the ECM, fibroblasts produce the structural framework of the islet and determine the tissue's physical properties. Fibroblasts are thought to reside in the islet's periphery, where they produce the capsule's collagens. However, it is likely that there is an additional population of fibroblasts that produce the relatively higher levels of collagen and laminin that surround the microvasculature inside the human islet, as compared with the mouse islet (Fig. 1). Research on islet fibroblasts is fixated on how islet-derived fibroblasts or fibroblast factors promote beta cell glucose sensing, insulin processing, clustering, postnatal expansion and survival in tissue culture or after transplantation [49–58]. Studies aimed at demonstrating the beneficial effects of ECM components added in vitro are, thus, plentiful, but little is known about the production of ECM molecules by endogenous fibroblasts and their interactions with other cells inside the islet.

While fibroblasts synthesise ECM molecules, resident tissue macrophages have been shown to remodel the ECM by producing enzymes involved in ECM breakdown. The main role of the resident macrophage is to regulate tissue homeostasis [59], but most research has focused on their immune functions. Only recently have bona fide resident macrophages been demonstrated in the mouse islet [60]. Recent findings support a positive role for macrophages in promoting beta cell mass and function through the secretion of different signalling molecules [61–64]. While supporting beta cells in the steady state, obesity-associated changes in the number and phenotype of islet macrophages have been suggested to contribute to beta cell failure during type 2 diabetes [65, 66]. In human islets, perivascular macrophages are the main local source of the anti-inflammatory cytokine IL-10 and, also, matrix metalloproteinase (MMP)-9. Expression of the receptors for these two homeostatic factors is reduced in obese and diabetic states [67].

Vascular cells of the islet microcirculation

Blood vessels not only deliver nutrients and oxygen but are also an important source of developmental signals during pancreatic organogenesis. Islets form next to blood vessels and

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require signals from endothelial cells for their differentiation [68]. Endocrine and endothelial cells depend on each other to establish and maintain normal islet vascularisation, innervation and function, in vascular endothelial growth factor-A (VEGF-A)-dependent manners [62, 69–71]. Islet endothelial cells contribute key components of the ECM, such as different laminins (α_4 and α_5) and collagen IV α_1 and α_2 chains. Recent findings show that the islet microvasculature also contains pericytes, which are mural cells that extend contractile cytoplasmic processes along the endothelial tube [72]. Of note, pericytes have enormous plasticity and can adopt various phenotypes [73, 74]. In particular, pericytes can be a source of myofibroblasts and produce ECM proteins in fibrotic diseases in different tissues [41, 75–77].

Communication between pericytes and beta cells

Although endothelial cells have been shown to support beta cell function and mass [78], research on the role of islet pericytes has lagged behind. Until very recently, pericytes had mainly been studied in tissues that suffer from complications of diabetes (e.g. the retina). Work by us and others point to pericytes as key players in pancreatic islet function [72, 79–82]. Pericytes are present in mouse and human islets (Fig. 2). They regulate islet blood flow and serve as a source of cues that regulate beta cell function and replication (Fig. 3). Furthermore, abnormal pericyte phenotype, gene expression and coverage of islet capillaries have been associated with impaired beta cell function during diabetes [72, 80, 83–85]. Pericyte loss leads to endothelial cell hyperplasia, vessel dilation and vascular leakage [86–89]. Thus, pericyte abnormalities may directly contribute to diabetes by affecting beta cells and islet blood flow, or indirectly through influencing other cell types (e.g. endothelial cells) or the islet ECM.

Adequate insulin secretion from beta cells depends on them having a mature phenotype. Mature beta cells are equipped with sophisticated machinery, allowing accurate glucose-stimulated insulin secretion [90]. A series of studies by us and others showed that pancreatic pericytes support the mature beta cell phenotype and regulate glucose-stimulated insulin secretion [79–81]. Ablation of pancreatic pericytes resulted in glucose intolerance due to impaired glucose-stimulated insulin secretion and loss of the mature beta cell phenotype [81]. Ex vivo depletion of pericytes in isolated islets also resulted in beta cell dedifferentiation [81], indicating that pericytes act within the islets to support beta cell function independent of their role in blood flow regulation, through either the secretion of critical signals or a direct cell–cell interaction.

Nerve growth factor (NGF) was recently shown by Houtz et al to be involved in pericyte-dependent beta cell function, by acutely regulating glucose-stimulated insulin exocytosis [79]. Beta cells express the NGF receptor tropomyosin receptor kinase A (TrkA) and the activation of this receptor promotes the release of insulin from its granules. NGF is expressed by pancreatic pericytes and vascular smooth muscle cells when its secretion from these cells is stimulated by high glucose levels [79]. Thus, pericytes promote acute insulin secretion directly through the secretion of NGF.

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The primary route of new beta cells after birth is via replication [91–93]. Beta cell replication rate declines with age, reaching its peak in the neonatal period [94–96]. Recently, we showed that pancreatic pericytes promote physiological neonatal beta cell proliferation [82]. Furthermore, neonatal pericytes stimulate adult beta cell replication in an integrin-dependent manner, suggesting that pericytes promote beta cell proliferation through the production of basement membrane components.

Type 2 diabetes is influenced by several lifestyle factors, including age, pregnancy and obesity, and has a strong genetic component [97, 98]. Polymorphism in *TCF7L2*, which encodes a member of the T cell factor/lymphoid enhancer factor (TCF/LEF) transcription factors family, transcription factor 7-like 2 (TCF7L2), has a strong positive correlation with beta cell dysfunction and type 2 diabetes in humans [99]. TCF7L2 functions downstream of the canonical Wnt signalling pathway by recruiting β-catenin to target genes [100]. Recently, we showed that pancreatic pericytes express *Tcf7l2* at higher levels than other pancreatic cell types [80]. Selective inactivation of *Tcf7l2* in pancreatic pericytes resulted in glucose intolerance due to impaired beta cell function and diminished glucose-stimulated insulin secretion [80]. TCF7L2 regulates the pericytic transcription of several secreted factors with the ability to regulate beta cell function [80], among which is bone morphogenic protein 4 (BMP4; [101]). Thus, abnormal TCF7L2 activity may lead to beta cell dysfunction and type 2 diabetes progression by interfering with pericytic function.

We further showed that type 2 diabetes is associated with the progressive loss of islet pericytes [72]; however, it is not known what happens to islet pericytes during the progression of type 2 diabetes. Changes in the phenotype of islet pericytes have been reported in different mouse models of insulin resistance and are among the microvascular alterations that occur in the islet in response to a higher demand for insulin. In particular, concomitantly with dilation of islet blood vessels and increased thickness of the vascular basement membrane, pericytes undergo hypertrophy and adopt a myofibroblast-like appearance [84, 102–104]. Our findings and the findings of others published in the literature, thus, point to a contribution of abnormalities in islet pericyte function/phenotype to the beta cell dysfunction associated with diabetes.

Effects of beta cells on the islet microenvironment

It is now important to consider the impact that beta cell secretory activity can have on the microenvironment. Beta cells secrete insulin and other signalling molecules, such as ATP and serotonin [105–107], all of which can exert effects on vascular and stromal cells. Insulin, to start with, is a potent mitogenic peptide that controls cellular growth, proliferation, differentiation and migration. Insulin has been shown to stimulate the proliferation of endothelial cells and pericytes in the retina [108, 109]. Insulin further stimulates the proliferation of islet myofibroblasts (pancreatic stellate cells and α-smooth muscle actin [αSMA]-expressing cells) and the production of ECM proteins through robust and sustained activation of the Akt/mammalian target of rapamycin (mTOR) signalling pathway [110]. This helps explain the potent antifibrotic properties of the mTOR inhibitor rapamycin in different tissues [111–114]. VEGF-A, also produced by beta cells, leads to

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endothelial cell proliferation, thickening of the basement membrane of islet blood vessels, progressive macrophage infiltration and proinflammatory cytokine production [115].

And then there is ATP and its breakdown products ADP and adenosine. These purinergic signals are potent autacoids that regulate local tissue function. Being co-released with insulin by beta cells [105, 106], ATP is poised to be a regulator of islet homeostasis: ATP extracellular levels fluctuate with the rate of insulin-granule exocytosis and, thus, serve to gauge beta cell secretory activity [116]. The responses ATP evokes in the surrounding microenvironment consequently commensurate with the pressure beta cells are under from systemic deviations in blood glucose levels, hence connecting systemic glucose homeostasis to islet tissue homeostasis. In recent years, we have explored how purinergic signals affect cells in the islet microenvironment by using living pancreas slices [72, 117], our preferred tool for the study of islets in an environment with a preserved ECM that allows experimental intervention. We have so far found that beta cell-derived ATP activates purinergic receptors on resident macrophages in mouse and human islets, thus making them aware of beta cell secretory activity [67, 117] and that endogenous adenosine, broken down from beta cell-derived ATP, inhibits pericytes, dilates islet capillaries and increases local blood flow in mouse islets [72].

Therapies in type 2 diabetes include approaches aimed at stimulating insulin secretion. This strategy, however, may be counterproductive. For instance, over-production of insulin, often seen as a response to insulin resistance, is associated with increased release of IAPP [118]. Exacerbated insulin levels may also promote differentiation of pericytes into profibrotic myofibroblasts and, ultimately, hasten their demise. There may be further unknown detrimental effects of chronic potentiation of beta cell function through incretin mimetic therapy [119]. The continued attempts to push beta cells to produce more and more insulin to treat diabetes ignores that this may disturb the delicate, balanced interactions taking place in the microenvironment that maintains islet function.

Concluding remarks

Cells do not live immersed in culture media in two-dimensional environments, but in intricate cellular and non-cellular arrangements called tissues. This is a reality often overlooked by investigators focusing passionately and narrowly on the beta cell, a cell deemed crucial for survival and too important to fail. This focus in the field of diabetes research, though deserved, often disregards the multiple local interactions happening in the pancreatic islet that actually enable beta cell function. Searching in beta cell databases for genetic programs linked to cell identity, proliferation and survival will likely miss important actors in the survival saga. Beta cells are not controlled solely by their genome, but also by their environment, the history of their interactions and the way they respond to local stimuli. It is difficult to conduct experiments without reducing complexity, but every time a cell is dislodged and isolated it changes its phenotype. Beta cells should thus be studied while immersed in their tissue, with an emphasis on their interactions with the microenvironment. This can be done using living pancreas slices, for instance. By systemically adding its cellular and acellular components, reverse engineering of the islet could further show how islet function emerges. Alexandre Dumas' musketeers famously used to proclaim, '*all for*

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one and one for all, united we stand divided we fall' [120]—nothing more appropriate could be said for the biology of the pancreatic islet.

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Abbreviations

ECM	Extracellular matrix
IAPP	Islet amyloid polypeptide
mTOR	Mammalian target of rapamycin
NGF	Nerve growth factor
TCF7L2	Transcription factor 7-like 2
VEGF-A	Vascular endothelial growth factor-A

Glossary

Amyloidosis
Results from deposition of IAPP, which is produced and secreted by beta cells, between capillaries and islet cells. IAPP deposition in human islets is associated with decreased beta cell mass. Islet amyloidosis is more common in type 2 than type 1 diabetes

Basement membrane
A specialised form of ECM that gives structural support, stores growth factors, determines cell polarity and influences cell metabolism. Consists of two layers: the basal lamina, which is adjacent to vascular cells and contains ECM glycoproteins (e.g. collagen IV, laminin, fibronectin, proteoglycans), and the reticular lamina, which is produced by fibroblasts and contains fibrillar collagens

Endothelial cells
Islets require signals from endothelial cells in the vasculature for differentiation. VEGF-A-dependent endocrine–endothelial cell interactions maintain normal islet vascularisation, innervation and function. Islet endothelial cells also produce key ECM components (e.g. laminins, collagen IV)

ECM
A three-dimensional network composed of fibrous-forming proteins, such as collagens, elastin, laminins, glycoproteins, proteoglycans and glycosaminoglycans

Fibroblasts

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Synthesise several ECM components (including collagen) to produce the structural framework of the islet and determine its physical properties. Thought to reside in the islet's periphery and (in humans) to surround the microvasculature

Fibrosis
Results from excessive production of connective tissue. Very common in the islets in diabetes; perivascular accumulation of ECM in type 1 and type 2 diabetes is associated with diffuse pancreatic fibrosis

Insulin
Potent mitogenic peptide produced by beta cells that controls cellular growth, proliferation, differentiation and migration. Stimulates the proliferation of endothelial cells, pericytes and islet myofibroblasts. It also promotes production of ECM proteins

Parenchyma
The main cellular compartment in charge of the specific tissue function of an organ. In the pancreatic islet, the parenchyma consists of the endocrine cell mass

Pericytes
Found in the islet microvasculature, these mural cells extend contractile cytoplasmic processes along the endothelial tube. Pericytes are highly plastic cells that can adopt various phenotypes (e.g. myofibroblasts) and produce ECM proteins. They regulate islet blood flow and beta cell function and replication. Pericyte abnormalities are associated with impaired beta cell function in diabetes

Purinergic signals
ATP is co-released with insulin by beta cells. ATP and its breakdown products ADP and adenosine are purinergic signals that regulate local tissue function. ATP is thought to be a regulator of islet homeostasis and connects systemic glucose homeostasis to islet tissue homeostasis. For example, it activates purinergic receptors on resident islet macrophages to make them aware of beta cell secretory activity. Endogenous adenosine inhibits pericytes, dilates islet capillaries and increases local blood flow

Resident tissue macrophages
Produce enzymes involved in ECM breakdown/ECM remodelling. Regulate tissue homeostasis, but also promote beta cell mass and function by secreting signalling molecules. Obesity-associated changes in islet macrophages may contribute to beta cell failure in type 2 diabetes

VEGF-A
Produced by beta cells. Promotes endothelial cell proliferation, thickening of the basement membrane of islet blood vessels, macrophage infiltration and proinflammatory cytokine production

References

1. Kalluri R (2003) Basement membranes: structure, assembly and role in tumour angiogenesis. Nat Rev Cancer 3(6):422–433. 10.1038/nrc1094 [PubMed: 12778132]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

2. Paulsson M (1992) Basement membrane proteins: structure, assembly, and cellular interactions. Crit Rev Biochem Mol Biol 27(1–2):93–127. 10.3109/10409239209082560 [PubMed: 1309319]
3. Aamodt KI, Powers AC (2017) Signals in the pancreatic islet microenvironment influence β-cell proliferation. Diabetes Obes Metab 19(Suppl 1):124–136. 10.1111/dom.13031 [PubMed: 28880471]
4. Stendahl JC, Kaufman DB, Stupp SI (2009) Extracellular matrix in pancreatic islets: relevance to scaffold design and transplantation. Cell Transplant 18(1):1–12. 10.3727/096368909788237195 [PubMed: 19476204]
5. Townsend SE, Gannon M (2019) Extracellular matrix-associated factors play critical roles in regulating pancreatic β-Cell proliferation and survival. Endocrinology 160(8):1885–1894. 10.1210/en.2019-00206 [PubMed: 31271410]
6. Bosco D, Meda P, Halban PA, Rouiller DG (2000) Importance of cell-matrix interactions in rat islet β-cell secretion in vitro: role of α6 β1 integrin. Diabetes 49(2):233–243. 10.2337/diabetes.49.2.233 [PubMed: 10868940]
7. Cirulli V, Beattie GM, Klier G et al. (2000) Expression and function of α_v β_3 and α_v β_5 integrins in the developing pancreas: roles in the adhesion and migration of putative endocrine progenitor cells. J Cell Biol 150(6):1445–1460. 10.1083/jcb.150.6.1445 [PubMed: 10995448]
8. Kaido T, Yebra M, Cirulli V, Montgomery AM(2004)Regulation of human β-cell adhesion, motility, and insulin secretion by collagen IV and its receptor α_1 β_1. J Biol Chem 279(51):53762–53769. 10.1074/jbc.M411202200 [PubMed: 15485856]
9. Nikolova G, Jabs N, Konstantinova I et al. (2006) The vascular basement membrane: a niche for insulin gene expression and Beta cell proliferation. Dev Cell 10(3):397–405. 10.1016/j.devcel.2006.01.015 [PubMed: 16516842]
10. Parnaud G, Hammar E, Rouiller DG, Armanet M, Halban PA, Bosco D (2006) Blockade of β1 integrin-laminin-5 interaction affects spreading and insulin secretion of rat β-cells attached on extracellular matrix. Diabetes 55(5):1413–1420. 10.2337/db05-1388 [PubMed: 16644699]
11. Virtanen I, Banerjee M, Palgi J et al. (2008) Blood vessels of human islets of Langerhans are surrounded by a double basement membrane. Diabetologia 51(7):1181–1191. 10.1007/s00125-008-0997-9 [PubMed: 18438639]
12. Gan WJ, Do OH, Cottle L et al. (2018) Local integrin activation in pancreatic β cells targets insulin secretion to the vasculature. Cell Rep 24(11):2819–2826.e2813. 10.1016/j.celrep.2018.08.035 [PubMed: 30208309]
13. Gan WJ, Zavortink M, Ludick C et al. (2017) Cell polarity defines three distinct domains in pancreatic β-cells. J Cell Sci 130(1):143–151. 10.1242/jcs.185116 [PubMed: 26919978]
14. Mosher DF, Sottile J, Wu C, McDonald JA (1992) Assembly of extracellular matrix. Curr Opin Cell Biol 4(5):810–818. 10.1016/0955-0674(92)90104-k [PubMed: 1419058]
15. Korpos E, Kadri N, Kappelhoff R et al. (2013) The peri-islet basement membrane, a barrier to infiltrating leukocytes in type 1 diabetes in mouse and human. Diabetes 62(2):531–542. 10.2337/db12-0432 [PubMed: 23139348]
16. Iozzo RV, Gubbiotti MA (2018) Extracellular matrix: the driving force of mammalian diseases. Matrix Biol 71–72:1–9. 10.1016/j.matbio.2018.03.023
17. Sonbol HS (2018) Extracellular matrix remodeling in human disease. J Microsc Ultrastruct 6(3):123–128. 10.4103/jmau.Jmau_4_18 [PubMed: 30221137]
18. Olsen BR (1995) New insights into the function of collagens from genetic analysis. Curr Opin Cell Biol 7(5):720–727. 10.1016/0955-0674(95)80115-4 [PubMed: 8573348]
19. Kalluri R, Gattone VH 2nd, Noelken ME, Hudson BG(1994) The alpha 3 chain of type IV collagen induces autoimmune Goodpasture syndrome. Proc Natl Acad Sci U S A 91(13):6201–6205. 10.1073/pnas.91.13.6201 [PubMed: 8016138]
20. Frerichs FT (1884) Uber den Diabetes. August Hirschwald, Berlin [book in German]
21. Wynn TA (2008) Cellular and molecular mechanisms of fibrosis. J Pathol 214(2):199–210. 10.1002/path.2277 [PubMed: 18161745]
22. Gepts W, Lecompte PM (1981) The pancreatic islets in diabetes. Am J Med 70(1):105–115 [PubMed: 7006384]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

23. Gepts W (1957) Contribution to the morphological study of the islands of Langerhans in diabetes; study of the quantitative variations of the different insular constituents. Ann Soc R Sci Med Nat Brux 10(1):5–108 [article in French] [PubMed: 13425197]
24. LeCompte PM, Steinke J, Soeldner JS, Renold AE (1966) Changes in the islets of Langerhans in cows injected with heterologous and homologous insulin. Diabetes 15(8):586–596. 10.2337/diab.15.8.586 [PubMed: 5330244]
25. Toreson WE, Lee JC, Grodsky GM (1968) The histopathology of immune diabetes in the rabbit. Am J Pathol 52(5):1099–1115 [PubMed: 4869188]
26. Heydinger DK, Lacy PE(1974) Islet cell changes in the rat following injection of homogenized islets. Diabetes 23(7):579–582. 10.2337/diab.23.7.579 [PubMed: 4601450]
27. Westermark P, Wernstedt C, Wilander E, Sletten K (1986) A novel peptide in the calcitonin gene related peptide family as an amyloid fibril protein in the endocrine pancreas. Biochem Biophys Res Commun 140(3):827–831. 10.1016/0006-291x(86)90708-4 [PubMed: 3535798]
28. Westermark P (1973) Fine structure of islets of Langerhans in insular amyloidosis. Virchows Arch A Pathol Pathol Anat 359(1):1–18. 10.1007/bf00549079 [PubMed: 4632997]
29. Westermark P, Wilander E (1978) The influence of amyloid deposits on the islet volume in maturity onset diabetes mellitus. Diabetologia 15(5):417–421. 10.1007/bf01219652 [PubMed: 367856]
30. Clark A, Nilsson MR (2004) Islet amyloid: a complication of islet dysfunction or an aetiological factor in type 2 diabetes? Diabetologia 47(2):157–169. 10.1007/s00125-003-1304-4 [PubMed: 14722650]
31. Janson J, Ashley RH, Harrison D, McIntyre S, Butler PC (1999) The mechanism of islet amyloid polypeptide toxicity is membrane disruption by intermediate-sized toxic amyloid particles. Diabetes 48(3):491–498. 10.2337/diabetes.48.3.491 [PubMed: 10078548]
32. Leahy JL (2005) Pathogenesis of type 2 diabetes mellitus. Arch Med Res 36(3):197–209. 10.1016/j.arcmed.2005.01.003 [PubMed: 15925010]
33. Halban PA, Polonsky KS, Bowden DW et al. (2014) β-Cell failure in type 2 diabetes: postulated mechanisms and prospects for prevention and treatment. Diabetes Care 37(6):1751–1758. 10.2337/dc14-0396 [PubMed: 24812433]
34. Kim JW, Ko SH, Cho JH et al. (2008) Loss of beta-cells with fibrotic islet destruction in type 2 diabetes mellitus. Front Biosci 13:6022–6033. 10.2741/3133 [PubMed: 18508639]
35. Stumvoll M, Goldstein BJ, van Haeften TW (2005) Type 2 diabetes: principles of pathogenesis and therapy. Lancet 365(9467):1333–1346. 10.1016/s0140-6736(05)61032-x [PubMed: 15823385]
36. Westermark P, Engstrom U, Johnson KH, Westermark GT, Betsholtz C (1990) Islet amyloid polypeptide: pinpointing amino acid residues linked to amyloid fibril formation. Proc Natl Acad Sci U S A 87(13):5036–5040. 10.1073/pnas.87.13.5036 [PubMed: 2195544]
37. Movassat J, Saulnier C, Serradas P, Portha B (1997) Impaired development of pancreatic beta-cell mass is a primary event during the progression to diabetes in the GK rat. Diabetologia 40(8):916–925. 10.1007/s001250050768 [PubMed: 9267986]
38. Shima K, Shi K, Sano T, Iwami T, Mizuno A, Noma Y (1993) Is exercise training effective in preventing diabetes mellitus in the Otsuka-Long-Evans-Tokushima fatty rat, a model of spontaneous non-insulin-dependent diabetes mellitus? Metab Clin Exp 42(8):971–977. 10.1016/0026-0495(93)90009-d [PubMed: 8345821]
39. Reaven EP, Reaven GM (1981) Structure and function changes in the endocrine pancreas of aging rats with reference to the modulating effects of exercise and caloric restriction. J Clin Invest 68(1):75–84. 10.1172/jci110256 [PubMed: 7019247]
40. Shino A, Matsuo T, Iwatsuka H, Suzuoki Z (1973) Structural changes of pancreatic islets in genetically obese rats. Diabetologia 9(5):413–421. 10.1007/bf01239438 [PubMed: 4589719]
41. Mateus Gonçalves L, Pereira E, Werneck de Castro JP, Bernal-Mizrachi E, Almaça J (2020) Islet pericytes convert into profibrotic myofibroblasts in a mouse model of islet vascular fibrosis. Diabetologia 10.1007/s00125-020-05168-7
42. Tang SC, Jessup CF, Campbell-Thompson M (2018) The role of accessory cells in islet homeostasis. Curr Diab Rep 18(11):117 10.1007/s11892-018-1096-z [PubMed: 30267158]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

43. Rodriguez-Diaz R, Molano RD, Weitz JR et al. (2018) Paracrine interactions within the pancreatic islet determine the glycemic set point. Cell Metab 27(3):549–558.e544. 10.1016/j.cmet.2018.01.015 [PubMed: 29514065]
44. Huising MO, van der Meulen T, Huang JL, Pourhosseinzadeh MS, Noguchi GM (2018) The difference δ-cells make in glucose control. Physiology (Bethesda) 33(6):403–411. 10.1152/physiol.00029.2018 [PubMed: 30303773]
45. Rodriguez-Diaz R, Tamayo A, Hara M, Caicedo A (2020) The local paracrine actions of the pancreatic α-cell. Diabetes 69(4):550–558. 10.2337/dbi19-0002 [PubMed: 31882565]
46. Campbell-Thompson ML, Kaddis JS, Wasserfall C et al. (2016) The influence of type 1 diabetes on pancreatic weight. Diabetologia 59(1):217–221. 10.1007/s00125-015-3752-z [PubMed: 26358584]
47. Augustine P, Gent R, Louise J et al. (2019) Pancreas size and exocrine function is decreased in young children with recent-onset type 1 diabetes. Diabet Med 10.1111/dme.13987
48. Andersen DK, Korc M, Petersen GM et al. (2017) Diabetes, pancreatogenic diabetes, and pancreatic cancer. Diabetes 66(5):1103–1110. 10.2337/db16-1477 [PubMed: 28507210]
49. Zhu S, Russ HA, Wang X et al. (2016) Human pancreatic β-like cells converted from fibroblasts. Nat Commun 7:10080 10.1038/ncomms10080 [PubMed: 26733021]
50. Miki A, Narushima M, Okitsu T et al. (2006) Maintenance of mouse, rat, and pig pancreatic islet functions by coculture with human islet-derived fibroblasts. Cell Transplant 15(4):325–334
51. Rabinovitch A, Russell T, Mintz DH (1979) Factors from fibroblasts promote pancreatic islet B cell survival in tissue culture. Diabetes 28(12):1108–1113. 10.2337/diab.28.12.1108 [PubMed: 389715]
52. Perez-Basterrechea M, Esteban MM, Alvarez-Viejo M et al. (2017) Fibroblasts accelerate islet revascularization and improve long-term graft survival in a mouse model of subcutaneous islet transplantation. PLoS One 12(7):e0180695 10.1371/journal.pone.0180695 [PubMed: 28672010]
53. Otonkoski T, Beattie GM, Rubin JS, Lopez AD, Baird A, Hayek A (1994) Hepatocyte growth factor/scatter factor has insulinotropic activity in human fetal pancreatic cells. Diabetes 43(7):947–953. 10.2337/diab.43.7.947 [PubMed: 8013761]
54. Otonkoski T, Cirulli V, Beattie M et al. (1996) A role for hepatocyte growth factor/scatter factor in fetal mesenchyme-induced pancreatic β-cell growth. Endocrinology 137(7):3131–3139. 10.1210/endo.137.7.8770939 [PubMed: 8770939]
55. Alvarez-Perez JC, Ernst S, Demirci C et al. (2014) Hepatocyte growth factor/c-Met signaling is required for β-cell regeneration. Diabetes 63(1):216–223. 10.2337/db13-0333 [PubMed: 24089510]
56. Mellado-Gil J, Rosa TC, Demirci C et al. (2011) Disruption of hepatocyte growth factor/c-Met signaling enhances pancreatic β-cell death and accelerates the onset of diabetes. Diabetes 60(2):525–536. 10.2337/db09-1305 [PubMed: 20980460]
57. Norgaard GA, Jensen JN, Jensen J (2003) FGF10 signaling maintains the pancreatic progenitor cell state revealing a novel role of Notch in organ development. Dev Biol 264(2):323–338. 10.1016/j.ydbio.2003.08.013 [PubMed: 14651921]
58. Hart A, Papadopoulou S, Edlund H (2003) Fgf10 maintains notch activation, stimulates proliferation, and blocks differentiation of pancreatic epithelial cells. Dev Dyn 228(2):185–193. 10.1002/dvdy.10368 [PubMed: 14517990]
59. Okabe Y, Medzhitov R (2016) Tissue biology perspective on macrophages. Nat Immunol 17(1):9–17. 10.1038/ni.3320 [PubMed: 26681457]
60. Calderon B, Carrero JA, Ferris ST et al. (2015) The pancreas anatomy conditions the origin and properties of resident macrophages. J Exp Med 212(10):1497–1512. 10.1084/jem.20150496 [PubMed: 26347472]
61. Xiao X, Gaffar I, Guo P et al. (2014) M2 macrophages promote beta-cell proliferation by up-regulation of SMAD7. Proc Natl Acad Sci U S A 111(13):E1211–E1220. 10.1073/pnas.1321347111 [PubMed: 24639504]
62. Brissova M, Aamodt K, Brahmachary P et al. (2014) Islet microenvironment, modulated by vascular endothelial growth factor-A signaling, promotes beta cell regeneration. Cell Metab 19(3):498–511. 10.1016/j.cmet.2014.02.001 [PubMed: 24561261]

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63. Riley KG, Pasek RC, Maulis MF et al. (2015) Macrophages are essential for CTGF-mediated adult β-cell proliferation after injury. Mol Metab 4(8):584–591. 10.1016/j.molmet.2015.05.002 [PubMed: 26266091]
64. Mussar K, Pardike S, Hohl TM, Hardiman G, Cirulli V, Crisa L (2017) A CCR2+ myeloid cell niche required for pancreatic β cell growth. JCI Insight 2(15):e93834 10.1172/jci.insight.93834
65. Ying W, Lee YS, Dong Y et al. (2019) Expansion of islet-resident macrophages leads to inflammation affecting β cell proliferation and function in obesity. Cell Metab 29(2):457–474.e455. 10.1016/j.cmet.2018.12.003 [PubMed: 30595478]
66. Chan JY, Lee K, Maxwell EL, Liang C, Laybutt DR (2019) Macrophage alterations in islets of obese mice linked to beta cell disruption in diabetes. Diabetologia 62(6):993–999. 10.1007/s00125-019-4844-y [PubMed: 30830262]
67. Weitz JR, Jacques-Silva C, Fahd Qadir MM et al. (2020) Secretory functions of macrophages in the human pancreatic islet are regulated by endogenous purinergic signaling. Diabetes 10.2337/db19-0687
68. Lammert E, Cleaver O, Melton D (2001) Induction of pancreatic differentiation by signals from blood vessels. Science 294(5542):564–567. 10.1126/science.1064344 [PubMed: 11577200]
69. Brissova M, Shostak A, Shiota M et al. (2006) Pancreatic islet production of vascular endothelial growth factor-A is essential for islet vascularization, revascularization, and function. Diabetes 55(11):2974–2985. 10.2337/db06-0690 [PubMed: 17065333]
70. Lammert E, Gu G, McLaughlin M et al. (2003) Role of VEGF-A in vascularization of pancreatic islets. Curr Biol 13(12):1070–1074. 10.1016/s0960-9822(03)00378-6 [PubMed: 12814555]
71. Reinert RB, Cai Q, Hong JY et al. (2014) Vascular endothelial growth factor coordinates islet innervation via vascular scaffolding. Development 141(7):1480–1491. 10.1242/dev.098657 [PubMed: 24574008]
72. Almaca J, Weitz J, Rodriguez-Diaz R, Pereira E, Caicedo A (2018) The pericyte of the pancreatic islet regulates capillary diameter and local blood flow. Cell Metab 27(3):630–644 e634. 10.1016/j.cmet.2018.02.016 [PubMed: 29514070]
73. da Silva Meirelles L, Bellagamba BC, Camassola M, Nardi NB (2016) Mesenchymal stem cells and their relationship to pericytes. Front Biosci (Landmark Ed) 21:130–156 [PubMed: 26709765]
74. Hayden MR, Yang Y, Habibi J, Bagree SV, Sowers JR (2010) Pericytopathy: oxidative stress and impaired cellular longevity in the pancreas and skeletal muscle in metabolic syndrome and type 2 diabetes. Oxidative Med Cell Longev 3(5):290–303
75. Dulauroy S, Di Carlo SE, Langa F, Eberl G, Peduto L (2012) Lineage tracing and genetic ablation of ADAM12^{+} perivascular cells identify a major source of profibrotic cells during acute tissue injury. Nat Med 18(8):1262–1270. 10.1038/nm.2848 [PubMed: 22842476]
76. Goritz C, Dias DO, Tomilin N, Barbacid M, Shupliakov O, Frisen J (2011) A pericyte origin of spinal cord scar tissue. Science 333(6039):238–242. 10.1126/science.1203165 [PubMed: 21737741]
77. Humphreys BD, Lin SL, Kobayashi A et al. (2010) Fate tracing reveals the pericyte and not epithelial origin of myofibroblasts in kidney fibrosis. Am J Pathol 176(1):85–97. 10.2353/ajpath.2010.090517 [PubMed: 20008127]
78. Hogan MF, Hull RL (2017) The islet endothelial cell: a novel contributor to beta cell secretory dysfunction in diabetes. Diabetologia 60(6):952–959. 10.1007/s00125-017-4272-9 [PubMed: 28396983]
79. Houtz J, Borden P, Ceasrine A, Minichiello L, Kuruvilla R (2016) Neurotrophin signaling is required for glucose-induced insulin secretion. Dev Cell 39(3):329–345. 10.1016/j.devcel.2016.10.003 [PubMed: 27825441]
80. Sakhneny L, Rachi E, Epshtein A et al. (2018) Pancreatic pericytes support β-cell function in a Tcf7l2-dependent manner. Diabetes 67(3):437–447. 10.2337/db17-0697 [PubMed: 29246974]
81. Sasson A, Rachi E, Sakhneny L et al. (2016) Islet pericytes are required for β-cell maturity. Diabetes 65(10):3008–3014. 10.2337/db16-0365 [PubMed: 27388217]
82. Epshtein A, Rachi E, Sakhneny L, Mizrachi S, Baer D, Landsman L (2017) Neonatal pancreatic pericytes support beta-cell proliferation. Mol Metab 6(10):1330–1338. 10.1016/j.molmet.2017.07.010 [PubMed: 29031732]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

83. Tang SC, Chiu YC, Hsu CT, Peng SJ, Fu YY (2013) Plasticity of Schwann cells and pericytes in response to islet injury in mice. Diabetologia 56(11):2424–2434. 10.1007/s00125-013-2977-y [PubMed: 23801221]
84. Hayden MR, Karuparthi PR, Habibi J et al. (2008) Ultrastructure of islet microcirculation, pericytes and the islet exocrine interface in the HIP rat model of diabetes. Exp Biol Med 233(9):1109–1123. 10.3181/0709-rm-251
85. Hayden MR, Karuparthi PR, Habibi J et al. (2007) Ultrastructural islet study of early fibrosis in the Ren2 rat model of hypertension. Emerging role of the islet pancreatic pericyte-stellate cell. JOP 8(6):725–738 [PubMed: 17993725]
86. Hellstrom M, Gerhardt H, Kalen M et al. (2001) Lack of pericytes leads to endothelial hyperplasia and abnormal vascular morphogenesis. J Cell Biol 153(3):543–553 [PubMed: 11331305]
87. Hellstrom M, Kalen M, Lindahl P, Abramsson A, Betsholtz C (1999) Role of PDGF-B and PDGFR-beta in recruitment of vascular smooth muscle cells and pericytes during embryonic blood vessel formation in the mouse. Development 126(14):3047–3055 [PubMed: 10375497]
88. Lindblom P, Gerhardt H, Liebner S et al. (2003) Endothelial PDGF-B retention is required for proper investment of pericytes in the microvessel wall. Genes Dev 17(15):1835–1840. 10.1101/gad.266803 [PubMed: 12897053]
89. Raines SM, Richards OC, Schneider LR et al. (2011) Loss of PDGF-B activity increases hepatic vascular permeability and enhances insulin sensitivity. Am J Phys Endocrinol Metab 301(3):E517–E526. 10.1152/ajpendo.00241.2011
90. Bonner-Weir S, Aguayo-Mazzucato C (2016) Physiology: pancreatic β-cell heterogeneity revisited. Nature 535(7612):365–366. 10.1038/nature18907 [PubMed: 27398615]
91. Georgia S, Bhushan A (2004) β Cell replication is the primary mechanism for maintaining postnatal beta cell mass. J Clin Invest 114(7):963–968. 10.1172/jci22098 [PubMed: 15467835]
92. Dor Y, Brown J, Martinez OI, Melton DA (2004) Adult pancreatic β-cells are formed by self-duplication rather than stem-cell differentiation. Nature 429(6987):41–46. 10.1038/nature02520 [PubMed: 15129273]
93. Meier JJ, Butler AE, Saisho Y et al. (2008) β-Cell replication is the primary mechanism subserving the postnatal expansion of β-cell mass in humans. Diabetes 57(6):1584–1594. 10.2337/db07-1369 [PubMed: 18334605]
94. Gregg BE, Moore PC, Demozay D et al. (2012) Formation of a human β-cell population within pancreatic islets is set early in life. J Clin Endocrinol Metab 97(9):3197–3206. 10.1210/jc.2012-1206 [PubMed: 22745242]
95. Finegood DT, Scaglia L, Bonner-Weir S (1995) Dynamics of β-cell mass in the growing rat pancreas. Estimation with a simple mathematical model. Diabetes 44(3):249–256. 10.2337/diab.44.3.249 [PubMed: 7883109]
96. Wang P, Fiaschi-Taesch NM, Vasavada RC, Scott DK, Garcia-Ocana A, Stewart AF (2015) Diabetes mellitus - advances and challenges in human β-cell proliferation. Nat Rev Endocrinol 11(4):201–212. 10.1038/nrendo.2015.9 [PubMed: 25687999]
97. DeFronzo RA, Ferrannini E, Groop L et al. (2015) Type 2 diabetes mellitus. Nat Rev Dis Primers 1:15019 10.1038/nrdp.2015.19 [PubMed: 27189025]
98. Fuchsberger C, Flannick J, Teslovich TM et al. (2016) The genetic architecture of type 2 diabetes. Nature 536(7614):41–47. 10.1038/nature18642 [PubMed: 27398621]
99. Grant SF, Thorleifsson G, Reynisdottir I et al. (2006) Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet 38(3):320–323. 10.1038/ng1732 [PubMed: 16415884]
100. Clevers H, Nusse R (2012) Wnt/beta-catenin signaling and disease. Cell 149(6):1192–1205. 10.1016/j.cell.2012.05.012 [PubMed: 22682243]
101. Goulley J, Dahl U, Baeza N, Mishina Y, Edlund H (2007) BMP4-BMPR1A signaling in β cells is required for and augments glucose-stimulated insulin secretion. Cell Metab 5(3):207–219. 10.1016/j.cmet.2007.01.009 [PubMed: 17339028]
102. Chien HJ, Peng SJ, Hua TE, Kuo CH, Juang JH, Tang SC (2016) 3-D imaging of islets in obesity: formation of the islet-duct complex and neurovascular remodeling in young hyperphagic mice. Int J Obes 40(4):685–697. 10.1038/ijo.2015.224

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

103. Dai C, Brissova M, Reinert RB et al. (2013) Pancreatic islet vasculature adapts to insulin resistance through dilation and not angiogenesis. Diabetes 62(12):4144–4153. 10.2337/db12-1657 [PubMed: 23630302]

104. Nakamura M, Kitamura H, Konishi S et al. (1995) The endocrine pancreas of spontaneously diabetic db/db mice: microangiopathy as revealed by transmission electron microscopy. Diabetes Res Clin Pract 30(2):89–100 [PubMed: 8833629]

105. Jacques-Silva MC, Correa-Medina M, Cabrera O et al. (2010) ATP-gated P2X3 receptors constitute a positive autocrine signal for insulin release in the human pancreatic β cell. Proc Natl Acad Sci U S A 107(14):6465–6470. 10.1073/pnas.0908935107 [PubMed: 20308565]

106. Khan S, Yan-Do R, Duong E et al. (2014) Autocrine activation of P2Y1 receptors couples Ca^{2+} influx to Ca^{2+} release in human pancreatic β cells. Diabetologia 57(12):2535–2545. 10.1007/s00125-014-3368-8 [PubMed: 25208758]

107. Almaca J, Molina J, Menegaz D et al. (2016) Human beta cells produce and release serotonin to inhibit glucagon secretion from alpha cells. Cell Rep 17(12):3281–3291. 10.1016/j.celrep.2016.11.072 [PubMed: 28009296]

108. King GL, Buzney SM, Kahn CR et al. (1983) Differential responsiveness to insulin of endothelial and support cells from micro- and macrovessels. J Clin Invest 71(4):974–979. 10.1172/jci110852 [PubMed: 6339562]

109. King GL, Goodman AD, Buzney S, Moses A, Kahn CR (1985) Receptors and growth-promoting effects of insulin and insulinlike growth factors on cells from bovine retinal capillaries and aorta. J Clin Invest 75(3):1028–1036. 10.1172/jci111764 [PubMed: 2984251]

110. Yang J, Waldron RT, Su HY et al. (2016) Insulin promotes proliferation and fibrosing responses in activated pancreatic stellate cells. Am J Physiol Gastrointest Liver Physiol 311(4):G675–G687. 10.1152/ajpgi.00251.2016 [PubMed: 27609771]

111. Chen G, Chen H, Wang C et al. (2012) Rapamycin ameliorates kidney fibrosis by inhibiting the activation of mTOR signaling in interstitial macrophages and myofibroblasts. PLoS One 7(3):e33626 10.1371/journal.pone.0033626 [PubMed: 22470459]

112. Korfhagen TR, Le Cras TD, Davidson CR et al. (2009) Rapamycin prevents transforming growth factor-α-induced pulmonary fibrosis. Am J Respir Cell Mol Biol 41(5):562–572. 10.1165/rcmb.2008-0377OC [PubMed: 19244201]

113. Lieberthal W, Levine JS (2009) The role of the mammalian target of rapamycin (mTOR) in renal disease. J Am Soc Nephrol 20(12):2493–2502. 10.1681/asn.2008111186 [PubMed: 19875810]

114. Zhu J, Wu J, Frizell E et al. (1999) Rapamycin inhibits hepatic stellate cell proliferation in vitro and limits fibrogenesis in an in vivo model of liver fibrosis. Gastroenterology 117(5):1198–1204 [PubMed: 10535884]

115. Agudo J, Ayuso E, Jimenez V et al. (2012) Vascular endothelial growth factor-mediated islet hypervascularization and inflammation contribute to progressive reduction of β-cell mass. Diabetes 61(11):2851–2861. 10.2337/db12-0134 [PubMed: 22961079]

116. Karanauskaite J, Hoppa MB, Braun M, Galvanovskis J, Rorsman P (2009) Quantal ATP release in rat β-cells by exocytosis of insulin-containing LDCVs. Pflugers Arch 458(2):389–401. 10.1007/s00424-008-0610-6 [PubMed: 19018564]

117. Weitz JR, Makhmutova M, Almaca J et al. (2018) Mouse pancreatic islet macrophages use locally released ATP to monitor beta cell activity. Diabetologia 61(1):182–192. 10.1007/s00125-017-4416-y [PubMed: 28884198]

118. Mulder H, Ahren B, Sundler F (1996) Islet amyloid polypeptide and insulin gene expression are regulated in parallel by glucose in vivo in rats. Am J Phys 271(6 Pt 1):E1008–E1014. 10.1152/ajpendo.1996.271.6.E1008

119. Abdulreda MH, Rodriguez-Diaz R, Caicedo A, Berggren PO (2016) Liraglutide compromises pancreatic β cell function in a humanized mouse model. Cell Metab 23(3):541–546. 10.1016/j.cmet.2016.01.009 [PubMed: 26876561]

120. Duman A (1893) The three musketeers Little, Brown, Boston

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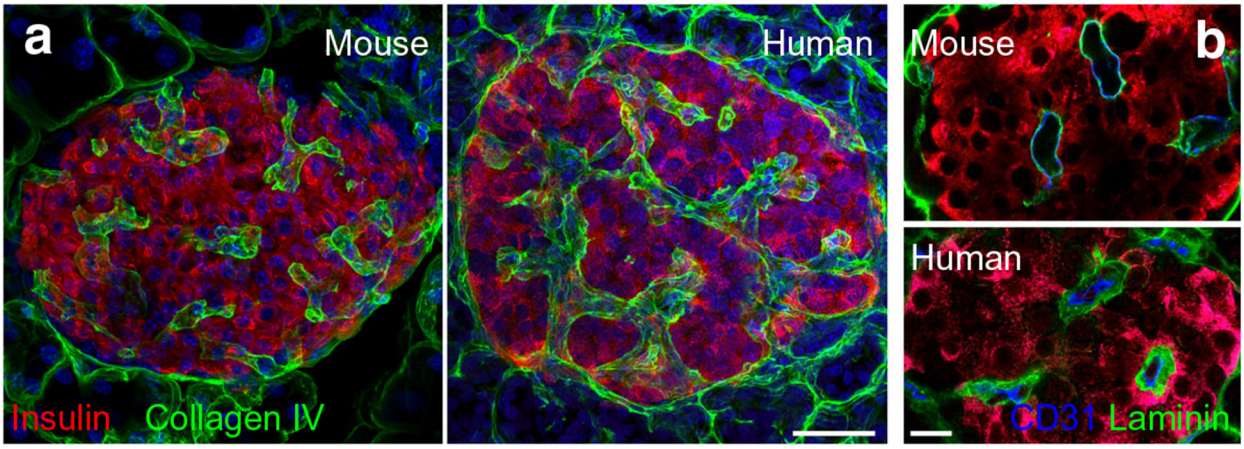

Fig. 1.

Higher collagen IV and laminin densities in human islets than in mouse islets. (**a**) Maximal projections of confocal images of a mouse and human islet in the pancreas, immunostained for insulin (red) and the basement membrane protein collagen IV (green). (**b**) Confocal images of regions in a mouse and human islet immunostained for insulin (red), laminin (green) and CD31 (blue). Scale bars: (**a**), 40 μm; (**b**), 10 μm.

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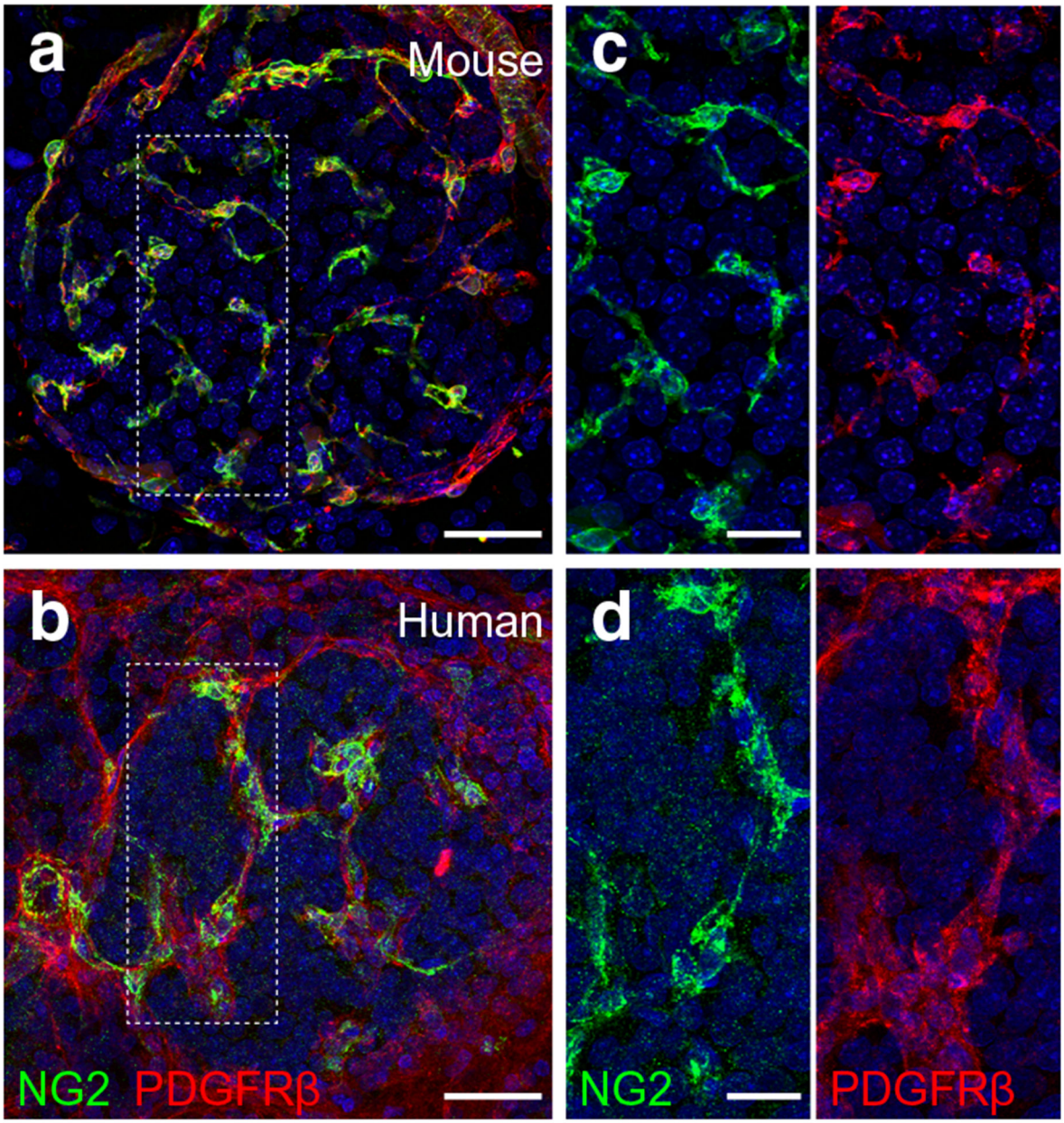

Fig. 2.

Pericytes in mouse and human islets. (**a, b**) Maximal projections of confocal images of a mouse (**a**) and human (**b**) islet, immunostained for the pericyte markers neural-glial antigen 2 (NG2; green) and platelet-derived growth factor receptor β (PDGFRβ; red). (**c, d**) Enlarged images of the regions within the dashed boxes in (**a**) and (**b**), respectively. Pericytes in mouse islets express NG2 and PDGFRβ but not all PDGFRβ-positive cells in human islets express the proteoglycan NG2. Scale bars: (**a**) and (**b**), 20 μm; (**c**) and (**d**), 10 μm.

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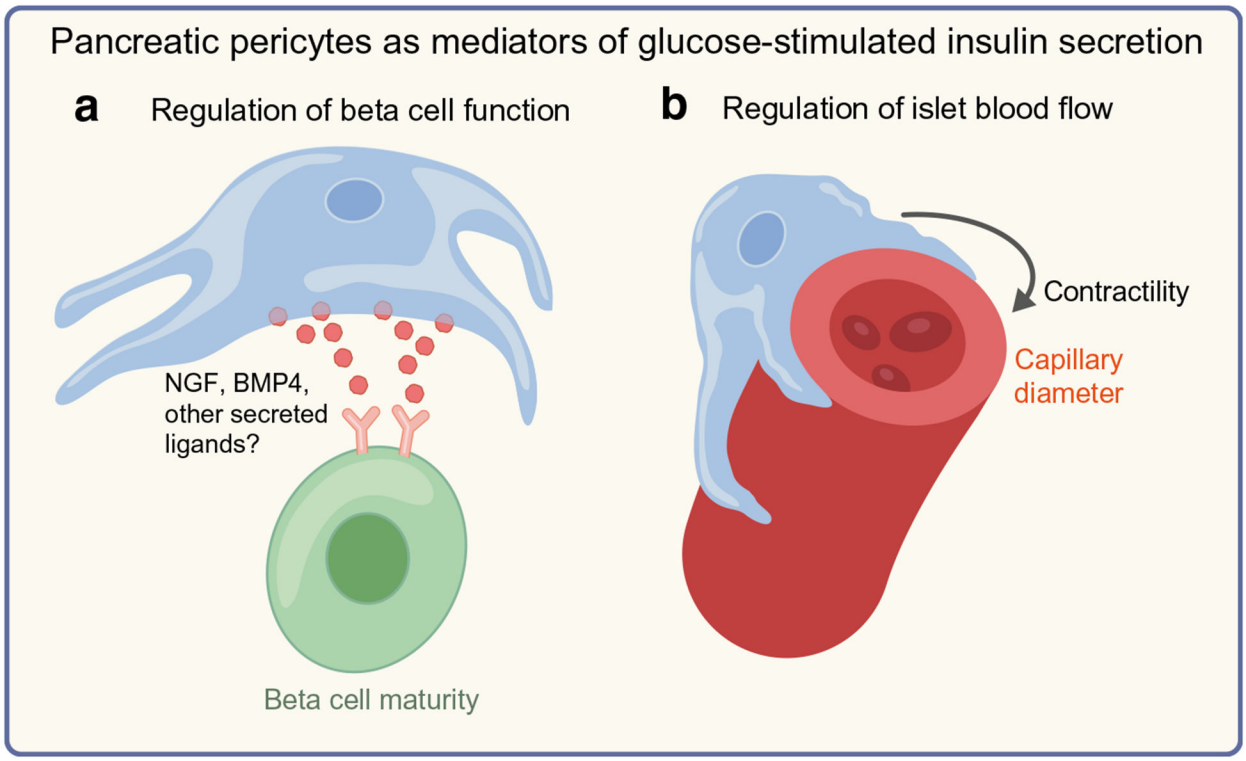

Fig. 3.

Model of the function of islet pericytes. In pancreatic islets, pericytes are the source of trophic factors that support beta cell differentiation, maturation and proliferation and stimulate insulin secretion (**a**). However, they are also responsible for the local control of islet capillary diameter and blood flow (**b**). BMP4, bone morphogenic protein 4.