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Review

From architecture to function: mechanisms shaping pancreatic islet morphogenesis

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Islets of Langerhans are highly structured mini-organs containing hormone-producing cells of the pancreas that regulate glucose metabolism. Studies of endocrine cell differentiation and clustering into immature proto-islets, as well as remodeling into mature islets, are beginning to clarify the critical timepoints and mechanisms governing islet formation across species. In this review, we compare the mechanistic features of the current models of islet morphogenesis, linking them to established intrinsic and extrinsic signals. These signals coordinate endocrine cell differentiation, migration, and clustering to form a distinct 3D islet architecture, while their disruption leads to islet dysfunction. Understanding 3D islet morphogenesis will enable the generation of mature stem cell-derived islets for regenerative therapies and help identify druggable pathways to restore islet function in diabetes.

Highlights

Models of islet morphogenesis differ in the extent of endocrine cell migration and self-segregation.

Pancreatic niche signals guide endocrine cell differentiation and morphogenesis.

Extrinsic signaling cues play critical roles in shaping 3D islet architecture and morphogenesis.

Distinct congenital disorders impairing islet morphogenesis provide insight into the mechanisms governing islet development and function.

Understanding 3D islet morphogenesis can lead to improved stem cell-derived islet products for regenerative therapy.

Islets of Langerhans as structural units

Islets of Langerhans (islets) (see Glossary) are endocrine, highly vascularized mini-organs embedded in the pancreatic parenchyma. They contain specialized cells secreting the five main pancreatic hormones: glucagon (α-cells), insulin (β-cells), pancreatic polypeptide (γ-cells), somatostatin (δ-cells), and ghrelin (ε-cells). Pancreatic islet hormones are the main systemic regulators in an intricate metabolic network that secures glucose homeostasis. Disruption of islet paracrine signaling is central to diabetes development, in which β-cells have been heavily implicated.

Islets, as mini-organs, have a stereotypical 3D architecture across mammals. There is long-standing evidence that the 3D architecture and morphology of islets are important for the paracrine regulation of hormone secretion [1,2]. However, recent studies have challenged the notion that islet paracrine signaling is important for their secretory function. A study in mice suggested that β-cells respond normally to glucose stimulation in the absence of all other non-β islet cells [3]. In conjunction, recent evidence in humans has revealed abundant extra-islet objects containing β-cells but not α-cells, adding to the complex discourse about islet architecture and its link to function [4]. Recently, it has been proposed that these small extra-islet objects are the first to be targeted by autoimmune destruction in type 1 diabetes (T1D) patients [5]. However, others have shown them to be preferentially conserved in late-onset T1D [6], potentially representing different states of disease progression. New mechanisms of paracrine hormone regulation are constantly being discovered, as exemplified by the decreased glycemic setpoint of β-cells following δ-cell ablation in mice [7], painting an intricate picture of the relationship between islet architecture, composition, functional output, and resilience to metabolic stress. Moreover, we now understand that the pancreas contains heterogeneous islet cell populations that vary in size, composition, and functionality, with these features collectively influencing their paracrine functions and susceptibility to disease [8,9]. Reconstructing islet morphogenesis, accounting for these variations, and clarifying

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how dysregulation of the canonical islet architecture can lead to disease is therefore of great importance. To address these topics, in this review, we discuss the leading hypotheses of islet morphogenesis from embryogenesis into the early postnatal period. Our goal is to present a framework of the models proposed in the field and to outline a consensus on the current state of the art, with a focus on intrinsic and extrinsic signals as key determinants of islet formation.

Models of islet morphogenesis

The morphogenetic processes involved in **endocrinogenesis** consist of two main phenomena: first, endocrine progenitors detach from the ductal epithelium, commit to their endocrine lineage, and assemble into an immature form of proto-islets. Second, proto-islets expand and self-organize into the highly specialized architecture that characterizes mature islets [10]. The duration of these transient phases of islet organization across species remains a topic of debate (Box 1).

Different morphogenetic models have been proposed to explain islet formation, for example, delamination, **epithelial-to-mesenchymal transition (EMT)**, or egression. The prevailing hypothesis in the field has been the delamination and aggregation theory, which argues that islet formation begins at late embryonic stages when endocrine progenitors delaminate or egress from the ductal epithelium, potentially through an EMT-like process, although the exact mechanism remains to be determined [18]. In delamination-and-aggregation-based models, an unresolved question is whether **endocrine precursors (EPs)** acquire migratory capacity. EPs could become motile and disperse through the pancreatic parenchyma until they (randomly) coalesce to form islet-like clusters of variable size and composition (Figure 1A, 'migratory model') [18]. An alternative interpretation within this model is that EPs do not migrate individually but rather accumulate locally, followed by endocrine cell fate specification. Independent islet-like clusters are later generated through a process of fission, which is proposed to occur postnatally (Figure 1B, 'fusion–fission model') [13]. This fission process is thought to account for the heterogeneity in islet size observed in the adult pancreas; however, the exact cellular mechanism remains unknown. According to these models (Figure 1A,B), islet morphogenesis begins with the

Box 1. Islet morphogenesis across species

Organisms differ in their complexity and, consequently, in their developmental timing, which leads to species-specific morphological outcomes. In recent years, pigs have been the focus of attention as a potential source for islet xenotransplantation and have proven to be valuable large animal models to understand human pancreas development [11]. A single-cell multiome atlas of the pig pancreas across its 114-day gestation showed that, like in mice, most β-cells appear during the secondary transition (E40), but a few early insulin-positive cells can also be found during the primary transition (E20) [11]. In humans, a study revealed that the first insulin-positive cells appeared as early as postconception week 5 (PCW5) [12]. Interestingly, these first cells emerge exclusively in the dorsal pancreatic bud and are absent from the ventral bud, highlighting regional differences during development. The process of islet morphogenesis begins at E18.5 in mice, E85 in pigs, and PCW11–12 in humans [11–13]. Proliferation analysis of these early insulin-positive cells showed a low rate of cell division during late gestation time in pigs (2%) [14] and humans (1%), suggesting that the formation of these primary proto-islets occurs through aggregation of endocrine cells [12].

Fetal islet formation is a much longer process in humans (82% of gestation) and pigs (65%) than in mice (42%), where the process is highly compressed [11]. Although an in-depth islet morphogenetic analysis comparing postnatal islet development in mice, pigs, and humans is missing, it is expected that proportional developmental times will apply. Unlike mice, pigs do not present a core–mantle islet organization but rather resemble a more human-like structure, where different endocrine cells are intermingled in a salt-and-pepper architecture [15]. Interestingly, a recent study reports that developing human islets transiently display a core–mantle organization before transitioning to an intermingled architecture [16]. This shift occurs from infancy to childhood and coincides with a period of rapid growth and increased nutritional demand. A similar core–mantle arrangement has also been observed during human fetal islet development [17], suggesting it represents a conserved intermediate stage that is lost in organisms with longer developmental times. Much remains to be discovered about islet development during the human postnatal period. Fortunately, large-scale consortia such as the Network for Pancreatic Organ Donors with Diabetes and the Human Islet Research Network are overcoming long-standing limitations in human pancreas research by making donor pancreata accessible to researchers as never before.

Glossary

Apical–basal polarity: the orientation of a cell in space that determines cytoskeleton organization and membrane protein expression, characterized by the asymmetrical separation of proteins within the cell. It is most prominent in epithelial cells.
Cell egression: the active process by which a cell exits a specific tissue compartment, normally a structured epithelium.
Cytoskeletal remodeling: the active or passive reconstruction of intracellular actin and/or microtubule networks through polymerization, depolymerization, and crosslinking.
Endocrine clustering: aggregation of endocrine lineage-committed cells with other endocrine cells.
Endocrine precursors (EPs): transiently existing progenitors that ultimately give rise to the endocrine cells of the pancreas, characterized by the expression of the NEUROG3 transcription factor.
Endocrinogenesis: the process of *de novo* endocrine cell formation from endocrine progenitors in the pancreas during embryonic or postnatal development.
Epidermal growth factor receptor (EGFR) signaling: a signaling pathway mediated by epidermal growth factor ligands binding to their respective receptors and regulating processes including growth, survival, differentiation, and morphogenesis.
Epithelial-to-mesenchymal transition (EMT): a process whereby cells lose their polarity and adhesive properties in an epithelium while acquiring migratory capacity and mesenchymal cell characteristics.
Extracellular matrix (ECM): structural components surrounding cells, including collagens, proteoglycans, and glycoproteins, supporting tissue organization, integrity, and cohesiveness.
Islets of Langerhans (islets): vascularized micro-organs of the pancreas that contain hormone-producing cells and are the main regulators of blood glucose homeostasis.
Notch signaling: a signaling pathway mediated by lateral inhibition based on direct contact between neighboring cells.
Planar cell polarity (PCP): coordinated organization of a cell's

formation of mixed endocrine proto-islets, and cell self-segregation and allocation are established at later developmental stages during islet maturation.

More recently, another mode of islet morphogenesis has been proposed in mice that challenges the above models. Termed the budding-peninsula model, endocrine cells accumulate along the ductal epithelium, forming budding peninsulas in which the temporal order of appearance of each endocrine cell type determines the final islet cytoarchitecture (Figure 1C, 'budding-peninsula model') [19]. In this model, the sequential emergence of α-cells followed by a wave of β-cells is what gives rise to the core–mantle islet architecture in mice. This implies that islet architecture is established early during development and, therefore, is independent of islet maturation, at least in mice. This time-dependent hypothesis also supports the idea that the final spherical islet-like clusters arise through a fission process [19]. Finally, individual islet units migrate away from the ductal epithelium and toward the pancreas periphery [17], a process that could be facilitated by passive exocrine expansion during postnatal development.

Coupling endocrine cell differentiation to islet morphogenesis

Several cellular and molecular mechanisms have been proposed to support the models of islet morphogenesis [10,20], ranging from differences in cell identity and polarization to extracellular cues that guide the process. Although these mechanisms have been studied mostly in isolation, we propose that they are interconnected and tightly coordinated.

Endocrine cell differentiation

The process of islet cell specification begins during middle to late embryogenesis and concludes postnatally with cell maturation over several weeks. Several comprehensive reviews of pancreas development have described the process in detail [10,21]. Briefly, multipotent pancreatic progenitors with tri-lineage potential give rise to the epithelial tissues of the pancreas. Morphogenetically, this occurs through epithelial stratification of the multilayered progenitor epithelium into a plexus structure, in which the bipotent duct/endocrine progenitors reside (trunk domain). For the purposes of this review, we note that all islet cells are derived from the bipotent duct/endocrine progenitors through a transient and, as recent data from human pancreatic differentiation showed, perhaps oscillatory activation of the master regulator of endocrinogenesis, Neurogenin-3 (NEUROG3 or NGN3) [22,23]. Although NEUROG3 is a critical transcription factor for endocrinogenesis in large mammals, including humans, NEUROG3-independent endocrinogenesis has been proposed [11,24]. Distinct islet cell specification is less explored, particularly outside of the α/β cell fate decision, yet our molecular understanding of endocrine cell fate decisions in human stem cell models continuously expands [25]. Currently, high-throughput spatial assessment of mammalian embryogenesis will further advance our understanding of the paracrine signaling involved in human endocrinogenesis and islet cell maturation [26].

Mechanistic links of islet cell differentiation and morphogenesis

Endocrine cell differentiation and identity acquisition are primary drivers of islet morphogenesis [10]. Polarity cues and cytoskeletal/mechanosignaling mechanisms tightly regulate the timing of fate commitment and morphogenetic processes underlying **cell egression** of EPs from the ductal epithelium. A key convergence point is the crosstalk between NEUROG3 induction and cell polarity cues [27]. **Epidermal growth factor receptor (EGFR) signaling** inhibits atypical protein kinase C (aPKC) to induce a narrowing of the apical side of the membrane, leading to reduced **Notch signaling**, upregulation of NEUROG3, and ultimately, cell egression during mouse development [28]. Ligand-specific EGFR signaling regulates the establishment of **apical–basal polarity** via Rac family small GTPase 1 (Rac1) and phosphoinositide 3-kinases

polarity along the axis of the tissue plane, perpendicular to the apical–basal axis.
Transdifferentiation: the conversion of a mature cell type to a different mature cell type without prior dedifferentiation.
Vascularization: the process where the vascular network invades an organ or structure to supply blood flow.
WNT signaling: a signaling pathway mediated by WNT ligands and divided into the canonical and noncanonical branches, which can regulate proliferation, survival, differentiation, and cytoskeletal dynamics.

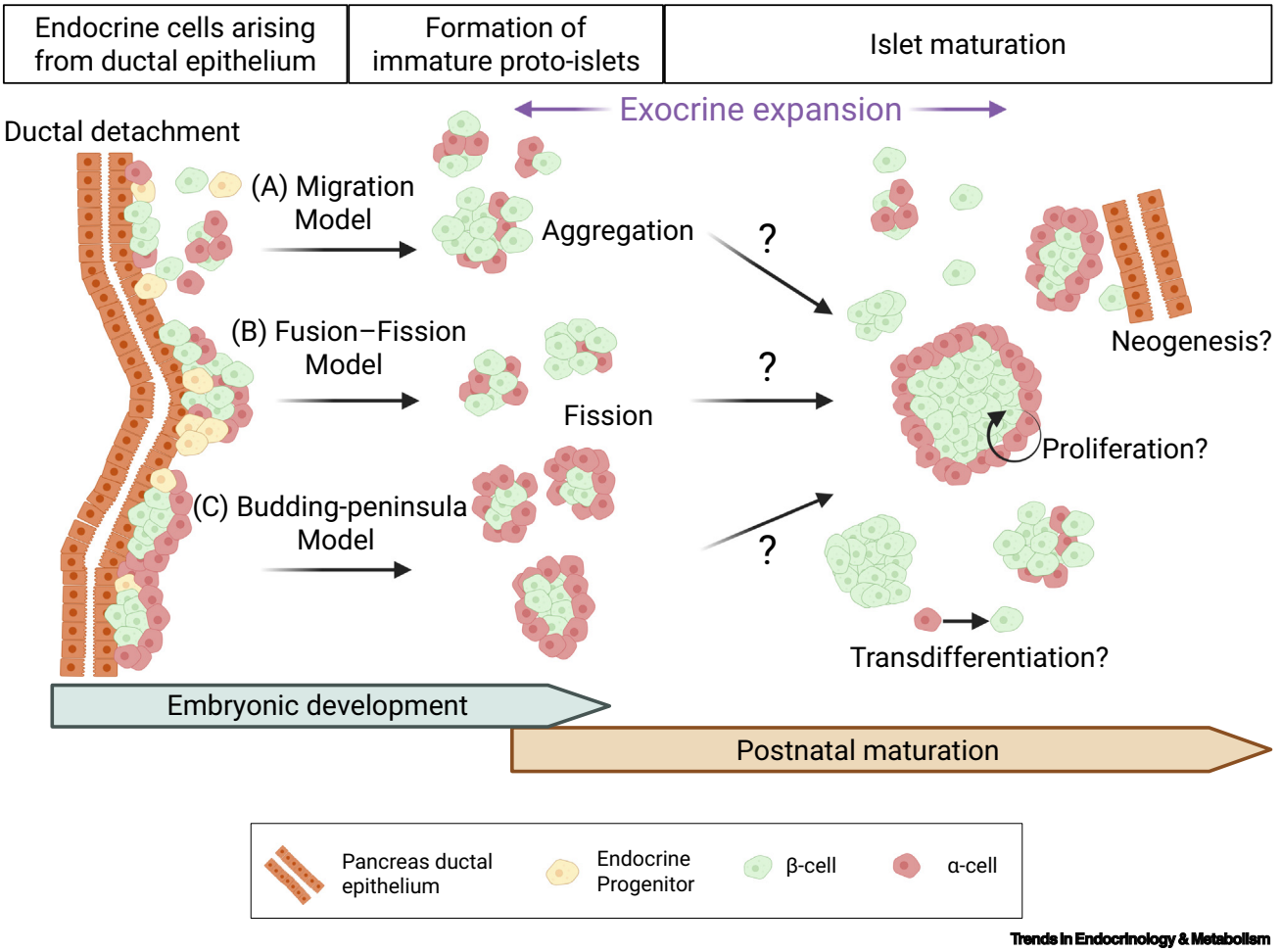


Figure 1. Models of pancreatic islet morphogenesis. Islet morphogenesis begins during late embryonic pancreas development and lasts until the late postnatal stage. Different morphological models have been proposed to explain islet formation. The (A) migration model (top) suggests that endocrine progenitors delaminate from the ductal epithelium and differentiate toward endocrine lineages while acquiring identity, polarity cues, and migratory capacity. These cells subsequently aggregate into proto-islets with other endocrine cells, a process that may be modulated by extrinsic signaling cues from the surrounding microenvironment. By contrast, the (B) fusion–fission model (middle) proposes that endocrine cells fuse into large ductal-attached endocrine cell clusters upon egression. In a subsequent fission process, individual proto-islets are formed. In both of these models, proto-islets subsequently undergo a remodeling step to acquire the mature islet cytoarchitecture. In the (C) budding-peninsula model (bottom), endocrine cells arise sequentially from the ductal epithelium, forming peninsulas that remain attached to the ducts, giving rise to the final islet cytoarchitecture—a hypothesis particularly relevant in mice and the formation of the core–mantle structure. In this model, the endocrine peninsula undergoes a process of fission, generating a wide range of islet sizes. Although all models offer plausible explanations for islet formation, none fully account for the broad spectrum of endocrine organizations observed in the adult pancreas, including large islets, scattered single endocrine cells, small duct-associated clusters, and homotypic islet structures. Whether these nonclassical endocrine assemblies arise from postnatal neogenesis, transdifferentiation, or proliferative expansion remains incompletely understood. This figure was created using BioRender (https://biorender.com/).

(PI3Ks), and subsequently murine β-cell differentiation, a process conserved in human stem cell endocrine differentiation [28]. Additionally, the Rho-associated kinase (ROCK)/Nonmuscle myosin II (nmMyoII)-pathway facilitates cell egression via apical narrowing and, at the same time, regulates NEUROG3 expression levels during murine EP emergence [29]. Repolarization and remodeling of the endocrine cell–**extracellular matrix (ECM)** interaction, as shown by internalization of integrins by Synaptotagmin-13 (Syt13) in murine EP development, are crucial processes for their egression from the ductal epithelium [30], highlighting the link between fate specification and cell polarity. Overexpression of NEUROG3 in human ductal organoids *in vitro* can promote EP cell differentiation and delamination [31], suggesting a reciprocal relationship

between NEUROG3 and cell polarity. The crucial role of apical–basal polarity cues as regulators of specific human endocrine cell fate differentiation, especially α- versus β-cell fate, has been further supported by recent studies [32]. Following this line, the acquisition of apical–basal polarity in emerging EPs agrees with the idea of a prenatally established islet cytoarchitecture. Linking the developmental timing of hormone cell differentiation to the dynamic ECM microenvironment will likely resolve the hypothesis brought forward by the peninsula model of islet morphogenesis. The exact mechanisms of early endocrine lineage specification and how they ultimately affect islet architecture are a matter of ongoing investigation.

ECM/cell–cell interaction

Next to cell polarity cues, it is known that cytoskeletal/mechanosignaling pathways regulate endocrine fate differentiation, delamination, and morphogenetic remodeling. Mesenchyme-derived cues, such as Wnt family member 5A (WNT5A) and ECM interactions, drive human and mouse endocrine cell specification via the modulation of pathways that orchestrate cytoskeletal dynamics and are essential for morphogenetic processes, such as the noncanonical Wingless-Type MMTV Integration Site Family (WNT)/**planar cell polarity (PCP)** signaling pathway [33–35]. In general, mechanosensitive pathways are mediated by cadherin and integrin signaling, linking the extracellular space to the actin cytoskeleton. Cell–cell adhesion is mediated by cadherins, a family of calcium-dependent transmembrane proteins that form junctions to strengthen intercellular connections. Integrins mediate cell–ECM interactions through interaction with focal adhesion complexes, transducing signals from the environment [36]. These ECM/cell–cell adhesion interactions regulate islet cell specification and **endocrine clustering** through mechanosignaling pathways. The levels of p120-catenin expression, a master regulator of E-cadherin stability, influence cell delamination and niche positioning, thereby determining pancreatic or endocrine progenitors' fate in mice [37]. Mechanical cues arising from ECM–integrin α5 interactions can also negatively regulate endocrinogenesis via activation of the F-actin–Yes1 associated transcriptional regulator (YAP1)–Notch axis, as confirmed in a human stem cell model [38]. Critically, conditional ablation of integrin β1 (Itgb1) and/or α-catenin (Ctnna1) in NEUROG3-positive progenitors impairs normal islet formation in mice and alters vascular organization, but through opposing mechanisms. Loss of Itgb1 resulted in excessive cell–cell adhesion, large islet structures attached to ducts, and poor **vascularization**, whereas loss of Ctnna1 caused weakened cell–cell adhesion, resulting in very small clusters and excessive vascularization [39]. These findings highlight that a finely tuned balance between integrin-mediated cell–matrix and cadherin-mediated cell–cell adhesion is essential for proper islet differentiation and morphogenesis. Similarly, the neural cell adhesion molecule 1 (NCAM1) stands out as an important player in endocrine cell segregation and structure maintenance, as when knocked out in mouse islets, they lose the core–mantle organization [40].

Overall, these findings imply a reciprocal relationship between morphogenetic processes and islet cell differentiation pathways, enabling temporally and spatially coordinated endocrine cell differentiation and egression from the epithelium. This suggests that endocrine progenitors acquire the capacity to migrate away from the ductal epithelium before they become mature endocrine cells, although the extent to which they become motile is still unclear. This observation stands in contrast to the budding-peninsula model, which proposes that endocrine cells differentiate *in situ* along the ductal epithelium without prior migration.

Extrinsic cues in islet morphogenesis

Pancreatic niches

In parallel to islet cell differentiation, the broader pancreatic microenvironment—including the exocrine compartment, an intricate vascular network, epithelial–mesenchymal interactions via ECM-dependent and independent signaling mechanisms, and autonomic innervation—is

established during embryogenesis. Here, we briefly highlight established pathways of these compartments in creating specialized signaling niches that promote the acquisition of endocrine cell identity and islet morphogenesis. For instance, mice with a knockout of *Ptf1a*, a key transcription factor for acinar cell development, die shortly after birth and lack acinar cells. Although hormone-producing cells are still present, they fail to assemble into organized islet structures and instead remain dispersed throughout the pancreatic parenchyma [41]. However, the exact mechanisms by which acinar cells influence islet morphogenesis remain to be elucidated. Endothelial cells can influence endocrine cell growth and differentiation through angiocrine signaling [42]. Members of the vascular endothelial growth factor family, particularly vascular endothelial growth factor A, and the connective tissue growth factor play critical roles in this process, since dysregulation of their signaling impairs islet formation in embryonic and postnatal mice [43,44]. Pericytes, integral cells covering the microvascular network, also regulate β-cell expansion, maturation, and function [45]. They further produce ECM that forms the islet basement membrane, thereby regulating β-cell identity [46]. Consistent with this, a study covering all mouse development, from embryo to adult, showed that the ECM undergoes extensive remodeling during early developmental stages and becomes more stable in adults [47]. These transient, developmentally regulated ECM niches promote a pro-endocrine environment that supports and shapes islet formation [35,48]. The evolving niches might also support the progressive and dynamic construction of islet architecture during development, as conceptualized by the migratory and fusion–fission models, rather than a finalized architecture after endocrine cell egression, as proposed by the peninsula model (Figure 1). Similarly, autonomic innervation is not only essential for islet function but also plays a role during islet development, as a mouse model with perturbed sympathetic innervation presented severe islet disorganization [49]. Additionally, 3D imaging shows that innervated adult mice and human islets are larger, implying that neuronal signals might influence islet growth during development [50]. Finally, numerous studies have explored the role of mesenchyme in islet cell differentiation and morphogenesis [51] culminating in the establishment of advanced *in vitro* models to study these processes [52,53]. According to the islet morphogenesis models discussed earlier, passive expansion of the extracellular space likely facilitates the physical separation of ductal-attached endocrine clusters (fusion–fission model). However, based on the current literature, the developing pancreatic microenvironment might play a more active role as a navigational scaffold that guides EPs toward one another (migratory model).

Molecular switches guiding islet morphogenesis

During islet morphogenesis, endocrine cells selectively display a set of membrane-bound or secreted protein mediators that regulate signal transduction. Some of these mediators are constitutively expressed and allow constant homeostatic communication with the environment, while others are highly dynamic and exhibit stage-specific expression patterns. Capturing the latter during islet morphogenesis has been one of the major challenges in the field. Nevertheless, several players have been proposed as potential guides of islet morphogenesis within the transforming milieu (Figure 2).

Chemoattractant and chemorepulsive signals

Axon-guidance molecules represent an important class of chemoattractant and chemorepulsive cues involved in islet morphogenesis [54]. Among them, the Slit glycoproteins and Roundabout (Robo) receptors have a particularly prominent role [55]. Slits are a family of large, secreted glycoproteins that bind to Robo, a single-pass transmembrane receptor. Upon Slit–Robo interaction, adaptor proteins induce **cytoskeletal remodeling**, cell polarization, and the expression of cell adhesion molecules, thereby regulating cell proliferation, motility, and migration [56]. In the mouse pancreas, Slit-2 and Slit-3 are primarily expressed outside the islets, in the pancreatic mesenchyme and acinar or ductal cells, whereas Slit-1 is expressed in β-cells [55].

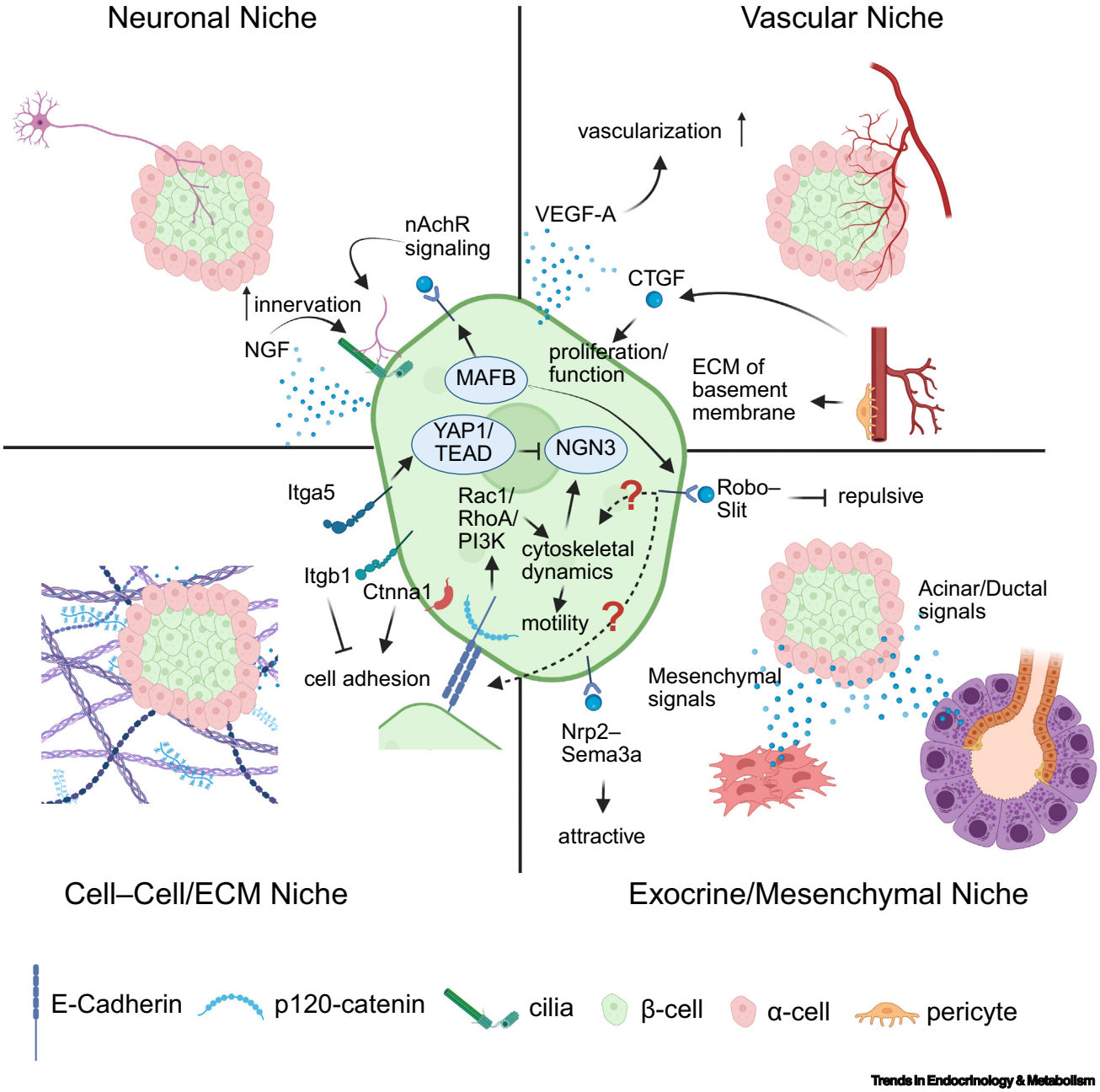


Figure 2. Extracellular cues modulating endocrine cell clustering. Islet morphogenesis and endocrine cell migration are modulated by various stimuli from endocrine cells, as well as external nonendocrine sources in the developing pancreas. Broadly, the latter can be divided into neuronal, vascular, cell–cell/cell–extracellular matrix (ECM), and exocrine/mesenchymal niches. Top left: Neuronal innervation of islets, including the formation of axo-ciliary synapses with β-cells, is promoted by β-cell-secreted nerve growth factor (NGF) and is crucial for islet formation. Furthermore, several neurotransmitter signaling pathways, mediated, for example, by nicotinic receptors, are involved in the regulation of islet morphogenesis. Top right: Vascularization is crucial for nutrient exchange, but also during initial islet formation. Secreted factors, such as vascular endothelial growth factor A (VEGF-A) and connective tissue growth factor (CTGF), modulate islet vascularization and are essential for proper islet architecture. Furthermore, pericytes enhance β-cell proliferation and maturation and secrete essential ECM components of the islets' basement membrane that enhance the expression of β-cell-specific genes. Bottom left: ECM molecules and cell–cell contacts guide morphogenetic processes during islet formation. Cell adhesion and cytoskeletal dynamics are tightly regulated to enable fate acquisition, initial egression from the ductal epithelium, migration, and final islet architecture via integrin-, cadherin-, and catenin-mediated signaling. Bottom right: The exocrine pancreas, composed of ductal and acinar cells, might provide

(Figure legend continued at the bottom of the next page.)

Loss of extra-islet Slits (Slit-2/Slit-3 double knockout or Slit-1/Slit-2/Slit-3 triple knockout mice) leads to severely disorganized and fragmented islets at late embryonic stages or at birth, while Slit-1 deficiency alone does not cause islet malformation. These findings suggest that the clustering of endocrine cells and the formation of the core–mantle mouse islet architecture are shaped in part by repulsive Slit-2/Slit-3 signals originating from the pancreatic mesenchyme. It remains to be elucidated whether conditional knockout of Slit proteins also plays a role during postnatal islet development, when islet fission is postulated to occur. By contrast, β-cell-specific loss of Robo1/2 preserves endocrine clustering but disrupts islet organization, producing intermingling of α- and δ-cells in adult mouse islets [57]. Together, these findings suggest that Slit ligands guide endocrine cell clustering, whereas Robo receptors are required for proper islet architecture and maintenance.

Another important ligand–receptor pair is semaphorin–neuropilin. Similar to Slits–Robo, semaphorins are secreted or membrane-bound guidance cues originally identified for their roles in axon guidance during neural development, with neuropilins acting as the corresponding receptors. Semaphorin 3A (Sema3a) is expressed in the pancreatic mesenchyme and Neuropilin 2 (Nrp2) in nascent endocrine cells [58]. Whole-body Nrp2 knockout mice exhibit impaired endocrine cell migration and severe defects in islet morphogenesis. Specifically, knockout islets aggregate centrally, form elongated ribbons along ducts, and fail to disperse radially throughout the pancreas in all developmental stages. Together, these findings define a radial signaling axis in which mesenchyme-derived Sema3a acts as a chemoattractive cue, directing Nrp2-expressing endocrine cells away from the ductal epithelium during islet morphogenesis [58].

Neuromodulators

Linking to the role of the autonomic nervous system in islet morphogenesis, endocrine cells respond to a variety of neuromodulators, which help direct cells toward their functional targets. Multipotent neural crest (NC) cells are believed to be the first to innervate the embryonic pancreas [59]. Interestingly, the loss of NC in mouse embryos led to an increase in β-cell number and proliferation but reduced β-cell maturation [60,61]. An important guiding cue during sympathetic innervation is the neurotrophin nerve growth factor (NGF), as mice deficient in NGF exhibit reduced islet innervation at embryonic and early neonatal stages [62]. Interestingly, β-cells are also able to produce and secrete NGF, stimulating the innervation and vascularization of the islets [63]. Other neuropeptides have also been shown to be important for islet morphogenesis and function, including catestatin, neuropeptide Y, and catecholamines [64–66]. Coculture experiments of neurons and islets demonstrated that sympathetic neurons release norepinephrine, which acts through β-adrenoceptors to guide islet migration. On that note, the loss of nicotinic acetylcholine receptor (nAchR) function in mouse and human β-cells impaired β-cell migration and clustering [67]. Importantly, these studies highlight the migratory capacity of differentiated β-cells, a process normally observed in EPs and mostly studied during embryonic islet development.

Cellular signaling hubs: cilia

The cilium serves as the cell's primary antenna and, therefore, can incorporate diverse signals from the extracellular environment. Several studies have demonstrated that cilia play an important role in mediating a broad range of external signaling cues, such as Sonic Hedgehog (SHH), G protein-coupled receptors, and **WNT signaling** [68], many of which are relevant for islet

signaling cues to guide pancreas and islet architecture, as well as the surrounding mesenchymal cells that, through chemoattractant and repulsive mechanisms, mediate islet cell migration and clustering. Ctnna1: α-catenin; Itga1: integrin α1; Itgb1: integrin β1; nAchR: nicotinic acetylcholine receptor; NGN3: neurogenin-3; PI3K: phosphoinositide 3-kinase; Rac1: Rac family small GTPase 1; YAP1: Yes1 associated transcriptional regulator; TEAD: TEA domain transcription factor; Nrp2: neuropilin 2; Sema3a: semaphorin 3A; Robo: Roundabout; RhoA: Ras homolog family member A. This figure was created using BioRender (https://biorender.com/).

development [10]. Due to the high density and spatial restriction of receptors in this organelle, the cilium can generate local concentration gradients that dynamically potentiate the signaling response [68]. During mouse development, depletion of the key PCP and ciliogenic components Celsr2 and Celsr3 impairs the formation of endocrine cells and the delamination of endocrine progenitors from the ductal epithelium [69,70]. Furthermore, repression of SHH signaling, a pathway regulated by the cilium, is essential for endocrine cell formation in the murine pancreatic endoderm, and mutations in cilia components are associated with pancreatic cyst formation [71]. Another example of a cilia-modulated pathway is the WNT signaling pathway, which has long been implicated in pancreas development. Recent studies have highlighted the importance of WNT signaling regulation during mouse β-cell formation and maturation [72]. However, the exact role of cilia during endocrine cell differentiation and islet morphogenesis is still unknown. In mature human and mouse islets, cilia are crucial for glucose sensing and insulin secretion by modulating Ephrin-type A receptors (EphA) processing, cilia-resident G-protein-coupled receptors (GPCRs), and enabling paracrine islet cell crosstalk [73–75] as well as neuronal innervation points forming axo-ciliary synapses [76]. Other reviews have thoroughly addressed this topic, and we refer readers to this source for an in-depth discussion [77]. Considering the importance of ECM, vasculature, mesenchymal, and neuronal-derived input for islet morphogenesis, the cilium might act as an element for cellular responsiveness to these signals. However, more research is required to investigate how cilia-mediated signaling and cell polarization guide islet formation, architecture, and function.

Integration into islet morphogenesis models

The intrinsic and extrinsic molecular cues defined earlier can be conceptually integrated into the models of islet morphogenesis through distinct modes of action. Within the migratory model, intracellular cues driving cytoskeletal rearrangement and polarization could enhance migratory capacity and determine cell directionality for newly egressed EPs. Repulsive and attractive extracellular signals, together with vascular and neuronal input, may help prevent excessive dispersion by guiding endocrine cells toward one another and enabling their aggregation. The final islet structure then consolidates through a switch in the expression of specific ECM/cell–cell adhesion molecules. However, the extent to which ductal-detached endocrine cells possess sufficient intrinsic migratory capacity remains unclear and warrants further investigation.

By contrast, within the fusion–fission model and the budding-peninsula model, the surrounding mesenchyme could actively destabilize the elongated ribbon-like or cord-like endocrine structures emerging from the ductal epithelium, promoting their fission into spherical proto-islets. Similarly, the expansion of the acinar compartment, together with an increasing vasculature and neuronal network invasion, might also contribute to the physical separation of the immature endocrine clusters. Although mesenchyme-derived repulsive/attractive forces are likely active players in this remodeling, a loosening of intra-proto-islet cell–cell adhesion, combined with a progressive reduction in their anchorage to the ductal basement membrane, might also be required. Yet a direct mechanistic link between these processes has not yet been described in the pancreas.

Islet reconstruction for regenerative diabetes therapies

Pancreatic β-cell regeneration has been explored as a potential therapeutic approach to treat T1D [78]. In terms of islet morphogenesis, it is important to understand how the regenerating β-cells couple to the pre-existing islet unit. We have learned that, in instances where regeneration is induced by β-cell proliferation or **transdifferentiation** of other endocrine cells to β-cells, the newly generated cells are already embedded in the islet structure, but how this occurs remains an open question (see Outstanding questions). Functional studies have shown that newly formed β-cells, through proliferation or transdifferentiation, can normalize glucose levels in diabetic mice

[78]. Neogenesis has been proposed as a β-cell regenerative mechanism through the induction of dormant pancreatic progenitors in adult animals following injury. However, the experimental evidence for adult pancreatic progenitors varies depending on the model organism used, the age at which the pancreatic injury was induced, and the lineage-tracing strategy employed [79–82]. The ductal tree of the pancreas is proposed as the anatomical location for the facultative progenitors in zebrafish, mice, and humans. In terms of islet morphogenesis, studies point to isolated insulin-expressing β-cells within the ductal trees or fully formed islets adjacent to them as the ones originating from these facultative endocrine progenitors, but without lineage-tracing evidence [83,84]. Using the zebrafish as a model of β-cell neogenesis, we can conclude that peri-islet ductal cells are more competent to form new β-cells, suggesting perhaps islet-derived factors that can aid the delamination and incorporation of newly formed β-cells into islets [85]. Of note, peri-islet ductal cells have also been proposed in mice as a source for new β-cells [86]. In the human pancreas, evidence for new scattered islet cell formation exists within ductal cells but not for fully formed islet cell clusters [87]. Regardless of the β-cell regeneration mechanism, it is currently unknown how the new β-cells functionally couple to the pre-existing islets and how the ECM around the islet or ductal cells can affect β-cell regeneration and functionality. It will be important to understand the connection between the developmentally relevant morphogenesis models and how they can be applied to regenerative settings. Whether the peninsula or migration model could be applicable in adult endocrine regeneration could help us prioritize the targeted pathways for inducing functional hormone coupling of regenerating cells.

Outstanding questions

Could the different islet morphogenesis models coexist?

Is endocrine cell maturation a prerequisite for islet formation, or do endocrine cells mature within the islet architecture?

What is the functional significance of the islet structure from an evolutionary perspective?

How are regenerated islet cells coupled to pre-existing islets in the absence of developmental cues?

Can we decipher the local and temporally dynamic signals and niches guiding islet morphogenesis?

Can we learn from islet morphogenesis to induce or preserve endocrine cell clustering *in vivo*?

New technologies to study islet morphogenesis

New technologies advance our understanding of human islet morphogenesis with the goal of improving regenerative therapies. Heterogeneous islet composition and distribution have already been appreciated through the use of whole pancreas clearing and imaging [4,12]. Human pancreatic tissue slices, adapted from mouse [88] to human pancreas [89], provide the opportunity to study human islet morphogenesis following β-cell death live *in vitro*. Tissue slices can be prepared from the stage of proto-islet formation to study this process *in vitro*. Studies have already utilized this technology to investigate β-cell neogenesis *in vivo*, identifying a crucial role for bone morphogenetic protein signaling in the regenerative response [87,89]. Organoid technologies can complement tissue slice studies to better understand epithelium-to-endocrine cell formation processes [90]. Three-dimensional organoid cystic models of ductal epithelium have been established across species to study endocrine induction, budding, and egression [91–93]. These models can be further exploited for advanced live-cell imaging applications to deepen our understanding of islet morphogenesis across species. The study of pancreatic niches guiding islet morphogenesis is rapidly advancing with the latest spatial transcriptomics and multiplex proteomics technologies [47,94]. By using these tools, we can enhance our understanding of ductal-derived islets in the human adult pancreas and clarify the gene regulatory networks and models governing embryonic proto-islet morphogenesis.

Concluding remarks and future perspectives

The morphological transition of endocrine cells arising from the ductal epithelium to mature islets reflects an underlying molecular program driven by changes in the pancreatic microenvironment. As endocrinogenesis progresses, pancreatic niches emerge in parallel, enabling the exchange of molecular and mechanosignaling cues that shape endocrine cell fate, migration, and intra-islet organization. Here, we review the predominant models of islet morphogenesis and how transcription factors, signaling mediators, and ECM/cell adhesion molecules guide this complex process. It is important to note that most available studies assessing islet morphogenesis rely on embryonic or early postnatal mouse models (Table 1). From an evolutionary perspective, islet architecture is adjusted to metabolic needs and differs between species, making a cross-

Table 1. Examples of mouse models causing islet dysmorphogenesis

		Developmental stage analyzed				Islet dysmorphogenesis phenotype						
Gene	Mice model	Embryo	Neonatal	Juvenile	Adult	Endocrine lineage failure	Scattered cells or small clusters	Ductal-attached clusters or limited migration	Core–mantle disruption	Shifts cell type composition	Impaired endocrine cell maturation	Islet functional defects
Mafa/Mafb	Pancreas-specific Pdx1+ MafA null;MafB heterozygote [95]	X		X		X				X	X	X
Mnx1	Endocrine progenitors Ngn3+ Mnx1 knockout (KO) [96]	X	X			X				X		X
Neurod1	Neuronal differentiation 1 (Neurod1) self-terminating/Neurod1 conditional knockout (CKO) [97]	X	X			X	X	X	X	X	X	X
Rfx6	Rfx6 null mice [98]		X	X		X				X	X	X
Ptf1a	*Ptf1a* null mutant mice [41]	X	X				X					X
Ctnna1	Ngn3+ Ctnna1 KO [39]	X	X	X	X		X					
Itgb1/Ctnna1	Ngn3+ Itgb1/Ctnna1 double knockout (DKO) [39]	X	X	X	X		X				X	
Slit2/Slit3	Whole-body DKO [99]	X	X				X		X	X		
Trka	Sympathetic neurons tyrosine hydroxylase+ tropomyosin receptor kinase A CKO [49]		X		X		X	X	X			X
Nrp2	Nrp2 null mutant mice [58]	X	X					X				
Itgb1	Endocrine progenitors Ngn3+ Itgb1 KO [39]	X	X	X	X			X	X			
Robo1/2	Endocrine progenitors Ngn3+ Robo1/2 KO [57]				X			X	X			
Mafa	Pancreas-specific Pdx1+ MafA KO [95]			X					X	X	X	X

(continued on next page)

Table 1. (continued)

		Developmental stage analyzed				Islet dysmorphogenesis phenotype						
Gene	Mice model	Embryo	Neonatal	Juvenile	Adult	Endocrine lineage failure	Scattered cells or small clusters	Ductal-attached clusters or limited migration	Core–mantle disruption	Shifts cell type composition	Impaired endocrine cell maturation	Islet functional defects
Robo2	Beta-cells Ins1+ Robo2 KO [100]				X				X			
Ncam1	NCAM1 null mice [40]	X		X	X				X			
Abcc8	ATP binding cassette subfamily C member 8 (Abcc8) null mice [101]			X	X					X		X
Ift88	Beta-cells insulin 1+ Intraflagellar transport 88 (Ift88) CKO [102]			X	X					X		X
Mafb	MafB$^{-/-}$ whole-body KO mice [67]	X						X		X	X	
Rfx3	Regulatory factor X3 (RFX3) null mutant mice [103]	X			X		X		X			X
Hnf1a	Hepatocyte nuclear factor 1 (HNF1a) (P291fsinsC mutant)/maturity-onset diabetes of the young (MODY)-3 [[104]		X	X	X		X		X			X
Bbs5	Bardet-Biedl syndrome 5 (Bbs5) null mutant mice [105]				X					X (islet hypertrophy)		X
Alms1	Alstrom syndrome protein 1 (Alms1) foz/foz [106]			X	X					X (islet hypertrophy)		X
Invs	Inversin (Invs) null mutant mice [107]		X							X (islet hypertrophy)		

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Box 2. Cell replacement approaches for diabetes treatment

Cadaveric human islets have been employed as a curative approach for T1D for over 25 years [109]. Clinical advances in stem cell-derived islets as an unlimited islet source for regenerative cell replacement give hope for widespread use in clinical research [110]. Depending on the application and the purpose of the study, islet products can be generated *in vitro* or isolated, purified and cultured in a variety of ways. Given the importance of the microenvironment in islet formation, survival, and maturation, researchers are now trying to reproduce these mechanisms *in vitro* through pre-coating of dishes, coculturing strategies, microfluidic devices, bioprinting, or 3D scaffolds of biocompatible materials to improve the viability of these products prior to transplantation.

The need for the ECM and endothelial cell signaling has been recognized by researchers trying to generate functional *in vitro* β-cells and islet-like organoid cultures [111,112]. Engineered models of microfluidic platforms that integrate oxygen sensors, ECM hydrogels, and coculturing of islets and other cell types [113,114] successfully reproduce endocrine function and metabolism. A strategy that synergistically utilizes bioprinting technology and specially formulated bioink to create bioprinted human islet-like cellular aggregates-vasculatures is able to mimic the peri-niche of islets *in vivo* [115]. Other innovative avenues of bioartificial nonpancreas, such as decellularization and re-endothelialization of rat liver or pig lung scaffolds for islet infusion, also demonstrated increased insulin secretion *ex vivo* [116], and proposed an interesting alternative to improve islet engraftment. In fact, current efforts focus on the optimization of sites for transplantation suitable for the islet microenvironment, as well as testing of novel cotransplantation candidates that could boost islet survival and angiogenesis [117]. Furthermore, novel bioengineering strategies for transplantation increasingly employ biomaterials that support vascular infiltration while limiting immune cell penetration, which are considered the next generation of encapsulated cell therapies [118,119].

species lens necessary to understand islet morphogenesis and function. This highlights the need for research focused on the later postnatal period, a developmental window during which the pancreas remains highly plastic and may be particularly relevant for permanent neonatal diabetes or T1D.

During early postnatal life, endocrine cells undergo progressive maturation, characterized by the stabilization of cell type identity and the gradual acquisition of key functional markers. Several studies suggest that the dietary shift associated with weaning may act as a critical trigger for the final stages of endocrine cell maturation and proper islet morphogenesis [108]. Whether endocrine cell maturation is a prerequisite for endocrine cell clustering, or whether islet structural organization itself drives endocrine cell maturation, remains an open question (see Outstanding questions) and brings opposing islet morphogenesis models into conflict (Figure 1). Furthermore, different species might reach full islet maturity at different developmental speeds, adding complexity to islet maturation assessment (Box 1).

In the future, incorporating new technologies into the current pipelines can shed light on the morphological details of islet formation. Learning from the basic mechanisms of islet morphogenesis will greatly advance efforts for the next generation of functional regenerative and cell replacement therapies (Box 2) for treating diabetes.

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Declaration of interests

The authors declare no competing interests.

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