

Chapter 2

Comparative Analysis of Islet Development

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Introduction

Islet cells play a critical role in glucose homeostasis. The islet is a highly vascularized microorgan embedded in the exocrine pancreas, which mainly consists of endocrine hormone-secreting cells: beta cells (insulin), alpha cells (glucagon), delta cells (somatostatin), pancreatic polypeptide (PP) cells, and epsilon cells (ghrelin). Here, we review the evolutionary changes followed by a molecular hierarchy of genes involved in pancreas development and a model of islet formation that recent technological advances have made possible. Considering current concerns, species differences between humans and rodents are discussed in detail.

Fetal Endocrine Cell Development in Various Species

The development and organization of hormone-producing cells in the pancreatic islets of Langerhans is important and essential for normal islet function. Fetal pancreas and endocrine cell development is reviewed in this chapter, starting from vertebrates to large mammals.

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Zebrafish

Zebrafish is a useful model for the study of vertebrate pancreas organogenesis, with advantages of external fertilization, large progeny sizes, rapid development, and optical clarity of its embryos (Driever et al. 1996; Ober et al. 2003; Ward et al. 2007; Tehrani and Lin 2015).

The zebrafish pancreas develops from the posterior foregut endoderm (Field et al. 2003). Origin of endocrine and exocrine structures is uniquely separated in zebrafish. While dorsal bud exclusively gives rise to endocrine pancreas, ventral bud forms mostly exocrine tissue besides very little endocrine cells. The posterior-dorsal bud evaginates by 24 h post-fertilization (hpf), and the antero-ventral bud is formed by 32–40 hpf. The two buds fuse by 52 hpf to form a single primary islet consisting of beta, alpha, delta and epsilon cells (Field et al. 2003; Argenton et al. 1999; Biemar et al. 2001). However, these early endocrine cells have limited proliferation and ultimately contribute very little to the adult endocrine cell mass (Hesselson et al. 2009). Ventral bud-derived endocrine precursors migrate in a dorsal and posterior direction to envelop the principal islet. After 120 hpf, ventral bud-derived beta cells expand forming secondary islets, including PP cells (Li et al. 2009; Wang et al. 2011).

Xenopus

In *Xenopus*, the dorsal rudiment evaginates at stage 35/36 (2 days, 2 h), followed by appearance of two small ventral rudiments at stage 37/38 (2 days, 5.5 h) (Nieuwkoop and Faber 1967; Maake et al. 1998; Kelly and Melton 2000). Dorsal and ventral anlagen fuse by stage 41 (3 days, 4 h). Clusters of beta cells and singly scattered alpha cells appear at stage 41, followed by delta cells at stage 43 and PP cells at stage 46 (Maake et al. 1998). In late tadpoles at stage 54 (26 days), segregation of beta cells and alpha cells is observed where beta cells form large groups of cells distributed throughout the pancreas, whereas small clusters of alpha cells reside in the periphery (Horb and Slack 2002). This arrangement is similarly observed in the frog pancreas. During metamorphic climax, the beta cell clusters increase in size by aggregation of pre-existing beta cells following exocrine remodeling (Pearl et al. 2009).

Guinea Pig

The gestation period for guinea pig is longer than other rodents (63 days). All four endocrine cells are observed at E25, where alpha cells are the most abundant, followed by PP and beta cells (Petersson 1966; Reddy et al. 1985, 1992). Endocrine

cells are dispersed throughout primitive tubules where beta cell clusters are observed occasionally. Only a few delta cells are present. Between E35 and E40, endocrine cells are prominent in both the ductules and islet-like structures. As islets develop, beta cell mass increase and alpha cells segregate to the periphery.

Pig

The gestation period for pigs is ~114 days. Pancreas develops from ventral and dorsal buds. By embryonic day 19, all four endocrine cells are detected with no ducts or acini in the pancreatic primordial (Alumets et al. 1983; Zabel et al. 1995; Carlsson et al. 2010). Relative mass of beta cells to alpha cells increases gradually from days 25–34 (more alpha cells), ~52 (equal mass), to 60 (more beta cells). Delta cells first appear at day 31, but are rarely observed until day 89 (Carlsson et al. 2010). No islet formation, with a core of beta cells and other endocrine cells in the periphery, is observed before birth (Alumets et al. 1983).

Alligator

In *Alligator mississippiensis*, pancreas arises from dorsal and ventral pancreatic buds that develop at stages 8 and 13 (embryonic days 8–13), respectively (Jackintell and Lance 1994). Two anlagen fuse at 14th stage and become similar to adult pancreas at stage 17 (days 22–23). Number of cells in clusters increases during later stages, and pancreas become fully mature at stage 27 (days 60–63). In alligator and crocodile, alpha and beta cell development precedes by delta and PP cells, similarly in rat and mouse. Alpha cells appear as early as stage 10 (day 11.5), followed by beta cells at stage 11 (day 12.5), delta cells at stage 13 (day 15) and PP cells at stage 17 (day 22.5). Alpha cells are dominant during early stages, and then, uniquely delta cells become most abundant. This dominance of delta cells is also observed in American alligator and adult Nile crocodile and caiman (Rhoten 1987). The vertebrate endocrine pancreas shows an evolutionary trend that the dorsal pancreas contains larger islets as observed in some teleosts, crocodilians and birds (Epple and Brinn J 1987).

Cattle

In cattle, alpha cells are the first endocrine cells that appear at 26 d.p.c in dorsal pancreatic primordium and duodenum, followed by beta cells at 27 d.p.c and delta cells at 45 d.p.c (Carlsson et al. 2010). These endocrine cells are singly scattered until 50 d.p.c, and thereafter, beta and alpha cells start forming small clusters. At

this stage, alpha cells are still dominant. Between 89 and 105 d.p.c, small groups of endocrine cells assemble into larger clusters. The number of beta cells increases and exceeds alpha cells after 110 d.p.c. Islet architecture resembles rodents with a beta cell core with alpha and delta cells in periphery.

Buffalo

The gestation period of buffalo is 308–312 days. Beta, alpha and delta cells are first observed as scattered small clusters in 2nd month, followed by PP cell one month later (Lucini et al. 1998). By 8th month, islets appear to be formed with a beta cell core with alpha and delta cells in periphery. Large clusters of islets observed in early fetuses decreases in number with the 1st year after birth and become absent in 4- to 5-year-old animals.

Genes Involved in Endocrine Cell Development

The transgenic mouse technology has advanced our understanding of endocrine cell development. These mouse studies have elucidated genes that have defects, which result in a wide range of malformation in the pancreas and islet structure.

Pancreatic duodenal homeobox 1 (Pdx1) is an essential transcription factor that determines pancreas formation. The early expression of Pdx1 occurs in pancreatic progenitor cells around E8.5 in mice (Guz et al. 1995). Pdx1 null mice completely lack pancreas and die few days after birth (Jonsson et al. 1994). Pancreatic agenesis in humans caused by a homozygous point deletion of the gene (termed insulin promoter factor (IPF)-1 in humans) has also been reported (Stoffers et al. 1997). PTF1-p48 (ptf1a) basic helix–loop–helix transcription factor (bHLH) is involved in exocrine cell differentiation (Krapp et al. 1998; Kawaguchi et al. 2002). PTF1-p48 knockout mice lacked exocrine pancreas and succumbed to neonatal death. Endocrine cells were localized in intra-mesenterial ducts at E12, which then migrated to the spleen around E16–E18. These cells were singly scattered in the spleen and did not form islets. Another bHLH transcription factor neurogenin (Ngn) 3 is involved in the formation of all endocrine cell types. During development, Ngn3-expressing cells are detected as early as E 9.5, and expression level peaks at E15.5 and declines thereafter (Gradwohl et al. 2000; Schwitzgebel et al. 2000). NeuroD is a bHLH transcription factor involved in islet formation and organization. NeuroD null mice died 3–5 days after birth and showed a marked reduction in beta cells. Islet morphogenesis was arrested in mid- to late embryonic period, and endocrine cells only formed small clusters (Naya et al. 1997; Miyata et al. 1999). NKx2.2 is a homeobox transcription factor, which is expressed in beta, alpha and PP cells but not in delta cells (Sussel et al. 1998). Nkx2.2-deficient mice developed severe hyperglycemia and died shortly after birth, mainly

due to the absence of beta cells. Paired homeobox protein Pax4 is expressed in the early pancreas, but is later restricted to beta cells (Sosa-Pineda et al. 1997). Inactivation of Pax4 resulted in the absence of beta and delta cells and mice died within 3 days after birth. Arx-deficient mice developed hypoglycemia and died 2 days after birth with a loss of alpha cells concomitant with increased beta and delta cells (Collombat et al. 2003). The study further showed the opposite action of Arx and Pax4. Mice with compound deficiency of Arx and Nkx2.2 lacked alpha and beta cells with hyperplasia of epsilon cells (Kordowich et al. 2011). Mice lacking the glucagon receptor (GcgR) exhibited lower blood glucose levels, hyperglucagonemia and alpha and delta cell hyperplasia (Gelling et al. 2003; Vuguin et al. 2006). Glucagon-like peptide (GLP)-1 and GLP-1 amide content was increased in the pancreas as well as circulation (Gelling et al. 2003). GcgR null mice displayed impaired insulin secretion (Sørensen et al. 2006). However, blocking glucagon signaling led to improved insulin action as well as resistance to diet-induced obesity and streptozotocin-mediated beta cell loss and hyperglycemia (Sørensen et al. 2006; Conarello et al. 2007). Prohormone convertase 2 (PC2)-deficient mice similarly showed alpha and delta cell hyperplasia starting around 3 months of age (Furuta et al. 1997) and delayed beta cell differentiation (Vincent et al. 2003). These mice were further examined in the long term up to 18 months to see whether sustained glucagon deficiency would lead to islet tumorigenesis (Tehrani and Lin 2015). PC2-deficient mice displayed marked changes in islet morphology from alpha cell hypertrophy/hyperplasia to adenomas and carcinomas in 6–8 months (Jones et al. 2014). POU domain transcription factor Brn4 regulates the expression of proglucagon gene by its interaction with G1 promoter element (Hussain et al. 1997). However, Brn4 knockout mice showed completely normal appearances of all endocrine cells and transcription factors analyzed (Heller et al. 2004). Paired-box protein Pax6 is expressed in beta, alpha, delta and PP cells (St-Onge et al. 1997). Pax6 null mice lacked alpha cells. Double mutants lacking both Pax6 and Pax4 failed to develop any endocrine cells. In embryos homozygous for a mutant allele of the *Pax6* gene, *Small eye* (*Sey^{Neu}*), all four types of pancreatic endocrine cells were decreased, however, at the lesser degree compared to Pax6 null mice (Sander et al. 1997). Disruption of homeobox gene Nkx6.1 led to a loss of beta cell precursors, which profound defect was observed after the start of the secondary transition (Sander et al. 2000). Double-knockout mice of Nkx2.2 and Nkx6.1 had similar phenotype as Nkx2.2 mice, indicating that Nkx6.1 lies downstream of Nkx2.2 in the pathway of beta cell formation. Islet-1 (*Isl1*) is a LIM homeodomain transcription factor, which is expressed in mature pancreatic endocrine cells as well as in mesenchymal cells surrounding the dorsal bud. *Isl1* null embryos exhibited no dorsal pancreatic mesenchyme with associated failure of exocrine cell differentiation in the dorsal but not in the ventral pancreas (Ahlgren et al. 1997). There was also a complete loss of differentiated islet cells, suggesting a dual role of *Isl1* in the pancreas. MafA is a basic leucine zipper transcription factor that functions as a potent transactivator for the insulin gene (Matsuoka et al. 2003). MafA null mice showed glucose intolerance and developed diabetes with diminishing beta cell mass as they aged (Zhang et al. 2005).

Islet Formation

Pancreatic islets are formed in various sizes including single and small clusters of endocrine cells, which are unevenly distributed in the exocrine pancreas in mammals. Despite differences in the body/pancreas size and total beta cell mass, the islet size distribution falls into a similar range throughout various species, suggesting certain regulatory mechanisms of the islet size to maintain proper functional properties (Samols et al. 1986; Weir and Bonner-Weir 1990). Little is known about how pancreatic islets are formed during development in mammals. The widely accepted model of islet formation is by the local aggregation of endocrine cells that migrate from the ductal epithelium in the late embryonic stage (Pictet and Rutter 1972; Herrera et al. 1991; Bouwens and De 1996; Jensen 2004). This aggregation model is based on observations using pancreatic tissue sections from rats and mice. Two-dimensional analysis using thinly cut sections has certain limitations and could only capture part of larger structures (Hara et al. 2006), which potentially hampers deducing dynamic islet formation in the pancreas. Using transgenic mice with fluorescent-tagged beta cells combined with an automated computational analysis, we have proposed a new model for islet formation that occurs by a process of fission during neonatal development following contiguous endocrine cell proliferation (Miller et al. 2009). This model accounts for the morphological transformation from embryonic endocrine cord-like structures into distinct spherical islets of various sizes observed in the adult pancreas (Fig. 2.1). The entire distribution of beta cells in the intact pancreas at P7 shows ventral (v) and dorsal (d) pancreatic regions (Fig. 2.1A.a). Stretches of interconnected islets were identified, which are color-coded in *blue* together with spherical-shaped islets (green) and small clusters of beta cells (<10 cells, red; Fig. 2.1A.b). A closer view of the interconnected islets is shown in Fig. 2.1B. Such islet clustering is often found along large blood vessels (Fig. 2.1B.c). Immunohistochemical staining of insulin and glucagon depicts rows of alpha cells spanning each islet-like mass within a continuous elongated structure (Fig. 2.1C). Acinar cells surrounding these interconnected islet structures, which expand at a high rate during development, may also play a role in islet fission. A fission model of islet formation in the neonatal pancreas is detailed in Fig. 2.1D. Islet formation in the neonatal pancreas may occur by fission of elongated structures composed of beta cells and surrounding alpha cells, following the contiguous proliferation and branching of endocrine cells into cord-like structures in the fetal and newborn pancreas. The fission process appears to be random, which may explain the diversity of islet sizes seen in the adult pancreas. Islets including small clusters are coated with a layer of extracellular matrix (Fig. 2.1D.c) that stabilizes the structure. Beta cell mass expansion within an islet leads to an increase in islet volume and the formation of spherical-shaped islets with a reduced alpha cell ratio. This process of islet formation may also produce small isolated clusters of endocrine cells that persist throughout a lifetime.

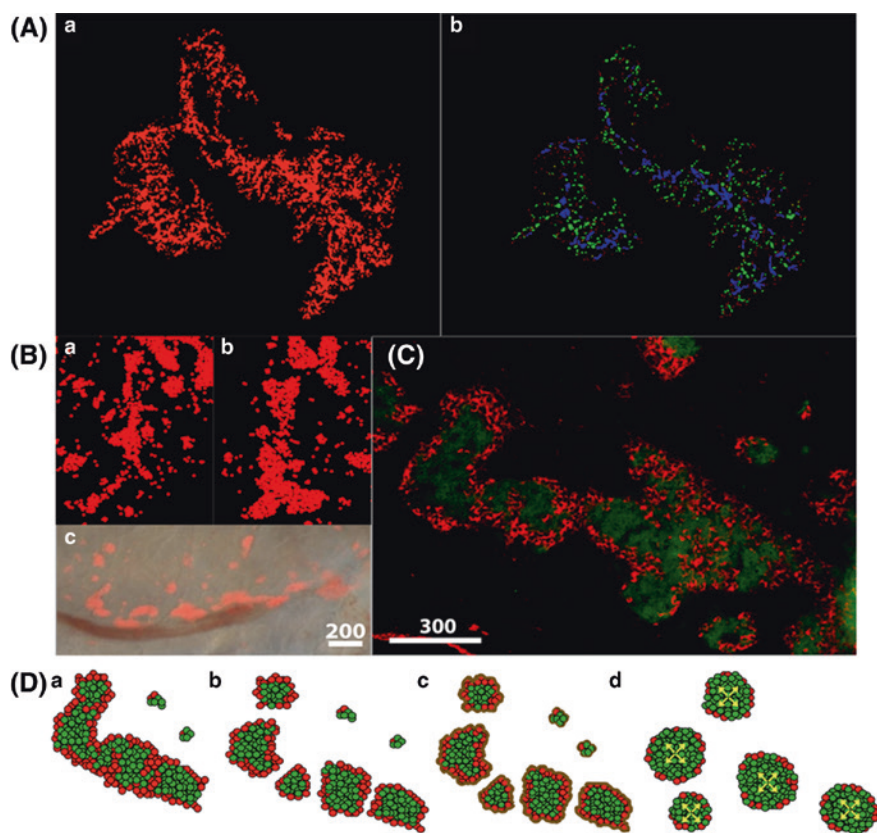


Fig. 2.1 Islet formation during neonatal development in mice. **A** **a** The entire distribution of beta cells in the intact pancreas at P7 (*d* dorsal, *v* ventral). **b** Three distinct populations of beta cell clusters are *color-coded*. *Blue* interconnected islets, *green* *spherical-shaped* islets and *red* small clusters of beta cells (<10 cells). **B** Interconnected islets. **a** P7; **b** P12; **c** a stretch of interconnected islets in the neonatal pancreas (P10). Merged image of fluorescent and bright field images of interconnected islets. Scale bar is 200 μm . **C** Immunohistochemical analysis of coalescent islets (P13). Insulin (*green*) and glucagon (*red*) staining is shown. Scale bar is 300 μm . **D** A fission model of islet formation in the neonatal pancreas. **a** Endocrine cells proliferate contiguously, forming branching cord-like structures in the fetal and newborn pancreas. **b** Islet formation in the neonatal pancreas may occur by fission of elongated structures composed of beta cells and surrounding alpha cells. The fission process appears to be random, producing islets of different size. **c** Each islet is subsequently coated with a layer of extracellular matrix that stabilizes the structure. This process of islet formation may also result in small isolated clusters of pancreatic endocrine cells that persist even in the adult pancreas. **d** Beta cell mass expansion within an islet leads to an alpha cell ratio of 5–10 %. Reproduced from (Miller et al. 2009)

Regional Differences in Islet Distribution and Composition in the Human Pancreas

The large size of the human pancreas challenges unbiased quantitative analyses that require a practical stereological approach. There is marked heterogeneity within an individual, where islet distribution/density is relatively low in the head and gradually increases through the body toward the tail region by >twofold (Wang et al. 2013). The head of human pancreas has unique characteristics in early development as well as the anatomical disposition that may lead to a preferential loss of beta cells in patients with type 2 diabetes and the development of pancreatic cancer (Savari et al. 2013). The head originates from the ventral pancreatic bud and exclusively contains the pancreatic polypeptide (PP) cell-rich area. We have shown that the PP cell-rich region is more narrowly segregated than previously reported (Adrian et al. 1982; Hazelwood 1993; Asakawa et al. 2003; Wierup et al. 2002; Andralojc et al. 2009) and largely restricted to the uncinate process (Wang et al. 2013). Regional distribution of the total endocrine cell area from a 50-year-old male is plotted from the head–body–tail region, which shows a narrowly restricted PP cell-rich area that does not cover the entire head region (Fig. 2.2A). In the inset, a deduced PP cell-rich region in the pancreas specimen (left) and in vivo (right) is illustrated. The PP cell-rich region contained a large number of irregularly shaped structures as well as islets with PP cells in the periphery (Fig. 2.2B.a), which are masked when only three major hormones are stained (adjacent section in Fig. 2.2B.b). Intra-specimen comparison of the PP cell-rich and PP cell-poor regions (Fig. 2.2C.a) revealed significantly reduced beta and alpha cell areas in the PP cell-rich region (Fig. 2.2C.b). The analysis on PP cell-rich and PP cell-poor areas in the same section (shown in Fig. 2.2C.c, d) highlights the differences in the distribution of islets/clusters and cellular composition.

Islet Plasticity in Mice and Humans

Human islets exhibit distinct islet architecture particularly in large islets that comprise of a relatively abundant fraction of alpha cells mixed with beta cells, whereas mouse islets show largely similar architecture of a beta cell core with alpha cells in the periphery. (Brissova and Fowler 2005; Cabrera et al. 2006; Kharouta et al. 2009). In human islets, islet architecture is size dependent. This size dependency of endocrine cellular composition in humans is quantitatively analyzed in comparison with mice (Fig. 2.3). Islet sizes are in a wide range from a single endocrine cell to a large islet consisting of several thousand cells. In mouse islets, the beta cell is the major component of islets throughout the size distribution (Fig. 2.3a, left). However, in human islets, while small islets show similar cellular composition with mice, in larger islets (>60 μm in diameter), the fraction of alpha and delta cells increases (Fig. 2.3a, right). These large islets typically exhibit relatively

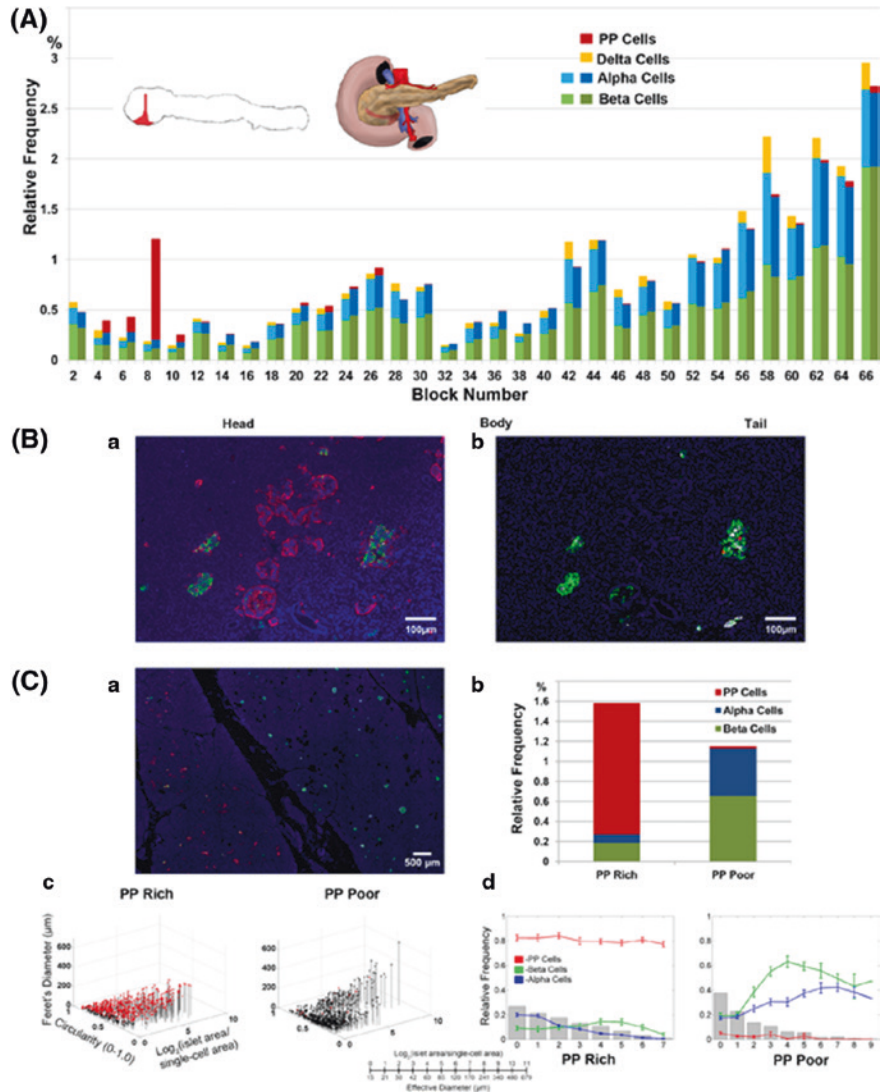


Fig. 2.2 Whole pancreas analysis of the PP cell distribution. **A** Regional distribution of PP, beta, alpha and delta cell mass. *Inset (left)* Restricted PP cell-rich area illustrated in red. *(Right)* deduced PP cell-rich region in vivo. **B a** Representative view of islets in the PP cell-rich area (PP in red, insulin in green, glucagon in white and nuclei in blue). **b** Adjacent section immunostained for insulin (green), glucagon (red), somatostatin (white) and nuclei (blue). **C** Intra-specimen comparison of the PP cell-rich and PP cell-poor regions. **a** A clear boundary between the PP cell-rich region (area in the left) and PP cell-poor region (right). **b** Total endocrine cell area in each region. **c** Three-dimensional plot of individual islet/cluster with PP cell containing clusters in red. PP cell-rich area (left) and PP cell-poor area (right). **d** Islet size distribution and cellular composition. PP cell-rich area (left) and PP cell-poor area (right). Reproduced from (Wang et al. 2013)

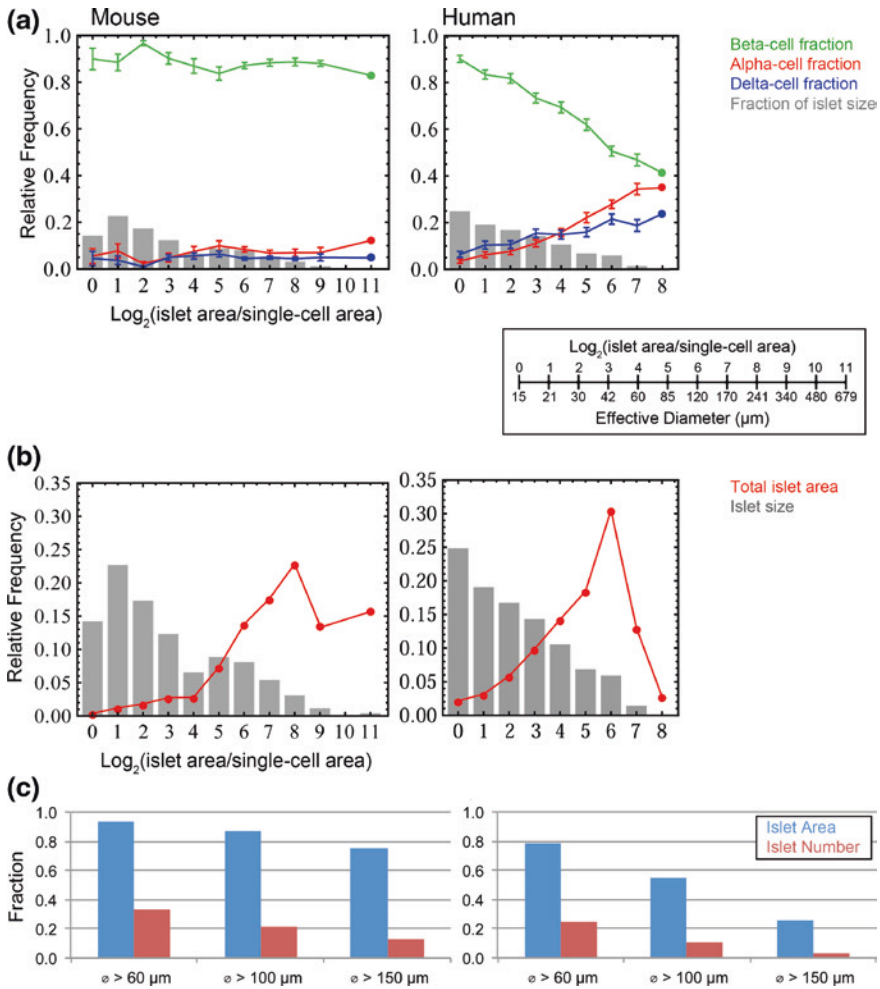


Fig. 2.3 Islet size-dependent changes in endocrine cellular composition in human islets. **a** *left*, mouse pancreas (a CD-1 female mouse at 3 month). Relative frequency of islet size (gray bar) and ratios of alpha (red), beta (green) and delta (blue) cells within islets are plotted against islet size; means $\pm$ SEM. Note that islet size is presented as a logarithmic scale considering the high number of small islets and the low number of large islets. In addition, islet area is divided by the single-cell area ($178 \mu\text{m}^2$; Hara et al. 2003) to make them as dimensionless values representing the number of cells in a given islet area. See the conversion between logarithmic islet area (logarithmic) and effective diameter (μm). *Right* human pancreas. **b** Fraction of islet size distribution (gray bar) and fraction of total islet area (red line). **c** The contribution of large islets to the total endocrine cell area is plotted with the cutoff points in islet size of >60 , 100 and $150 \mu\text{m}$ in diameter (*left* mouse; *right* human corresponding to b. Reproduced from (Kilimnik et al. 2012)

intermingled architecture of beta and non-beta cells. (Kharouta et al. 2009; Kim et al. 2009) Note that such changes in large islets are not an intrinsic characteristic of human islets, but are also observed in mice under insulin resistance such

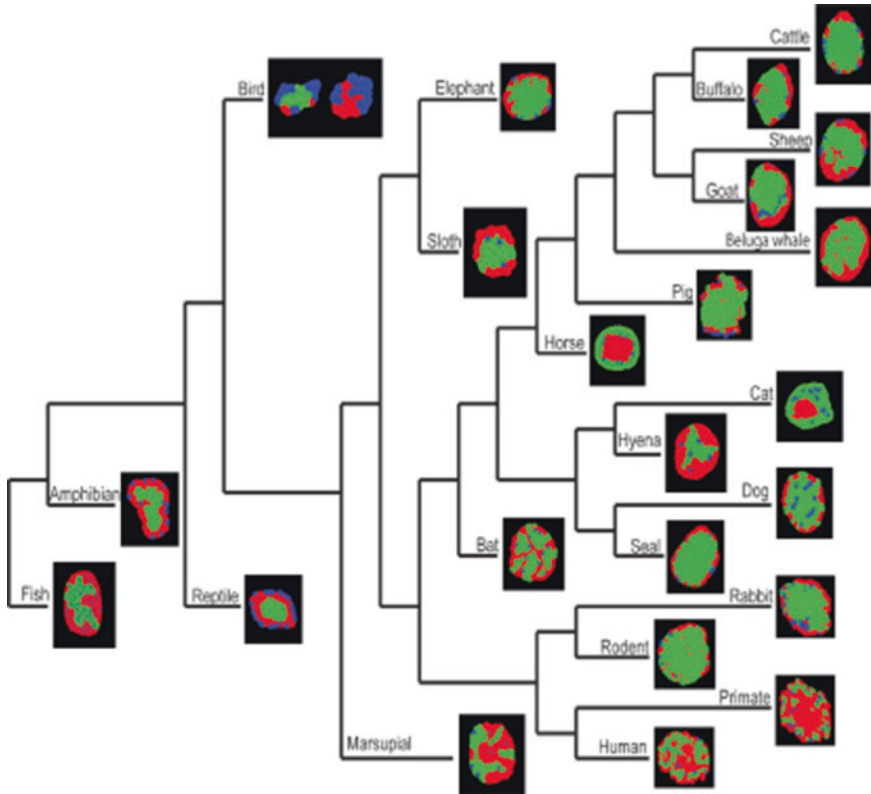


Fig. 2.4 Multi-species comparison of islet structure and composition. Islets from various species are organized into a phylogenetic tree. Representative islets are pseudo-colored models of actual islets based on immunohistochemical images composed of alpha cells (red), beta cells (green) and delta cells (blue). The following species are shown: mouse (*Mus musculus*); human (*Homo sapiens sapiens*); rhesus macaque (*Macaca mulatta*); cat (*Felis domesticus*); dog (*Canis lupus familiaris*); fur seal (*Arctocephalus pusillus*); Egyptian fruit bat (*Rousettus aegyptiacus*); horse (*Equus ferus caballus*); cattle (*Bos taurus*); domestic goat (*Capra aegagrus hircus*); domestic sheep (*Ovis aries*); domestic pig (*Sus domesticus*); European rabbit (*Oryctolagus cuniculus*); striped hyena (*Hyaena hyaena*); water buffalo (*Bubalus bubalis*); beluga whale (*Delphinapterus leucas*); African elephant (*Loxodonta africana*); three-toed sloth (*Bradypus variegatus*); common brushtail opossum (*Trichosurus vulpecula*); zebra finch (*Taeniopygia guttata*); European asp (*Vipera aspis*); northern leopard frog (*Rana pipiens*) and rainbow trout (*Salmo gairdneri*). Note that high-quality images were not available for the echidna and camel. No information on delta cells was available for the beluga whale. Reproduced from (Kim et al. 2009)

as pregnancy, obesity, diabetes and inflammation (Kim et al. 2009). Figure 2.3b shows the relative contribution of each bin of small to large islets to total endocrine cell area (left: mouse and right: human corresponding to Fig. 2.3a). The greater number of endocrine clusters and small islets (gray bars) does not markedly share the total area (plotted in a red line), but the fewer number of large islets mainly comprises the islet mass. The contribution of large islets to the total

endocrine cell area is highlighted in Fig. 2.3c with the cutoff points in islet size of >60, 100 and 150 mm in diameter (left: mouse and right: human corresponding to Fig. 2.3b).

Islet Plasticity in Various Species

Lastly, there is great diversity of islet structure among various species as shown in Fig. 2.4 (Steiner et al. 2010). Most of species generally show rodent-like islet architecture with a core of beta cells surrounded by alpha and delta cells in the periphery. However, this arrangement is not “the default,” since horses and cats conversely have islets with a core of alpha cells accompanied with a thick mantle of beta cells. In line with diverse islet plasticity, Nyman et al. have elegantly shown that blood flow is not coupled to the distinct islet cellular arrangement (Nyman et al. 2008).

Conclusion

Emerging studies have demonstrated the fundamental species differences between rodents and humans from morphology to molecular mechanisms of islet development. Challenges in studying the human pancreas are (1) inter-individual variability in endocrine cell mass; (2) intra-individual variability in endocrine cell mass (i.e., regional differences); and (3) intra-islet variability reflecting islet plasticity. It is critical to have a better understanding of human islet development, which has an important implication for the development of therapeutic surrogate beta cells for a cure for diabetes.

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