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REVIEW

Interorgan crosstalk in pancreatic islet function and pathology

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Pancreatic β cells secrete insulin in response to glucose, a process that is regulated at multiple levels, including a network of input signals from other organ systems. Impaired islet function contributes to the pathogenesis of type 2 diabetes mellitus (T2DM), and targeting inter-organ communications, such as GLP-1 signalling, to enhance β-cell function has been proven to be a successful therapeutic strategy in the last decade. In this review, we will discuss recent advances in inter-organ communication from the metabolic, immune and neural system to pancreatic islets, their biological implication in normal pancreas endocrine function and their role in the (mal)adaptive responses of islet to nutrition-induced stress.

Keywords: GLP-1; inter-organ crosstalk; pancreatic β cells; type 2 diabetes mellitus

Already a global epidemic, the incidence of T2DM is expected to rapidly escalate in the coming decades. In 2018, 34.2 million people (or 10.5% of the population) within the United States were diabetic; by the year 2030, the diabetic population in the United States is expected to increase by 35% [1]. Accordingly, diabetes has been classified as a pandemic disease. Diabetes underpins a multitude of severely debilitating pathologies in patients, including blindness, kidney failure, stroke, cancer, heart disease, depression, neuropathy, loss of limbs, infertility and death. Because of these complications, millions of people rely daily upon medications to regulate their fundamental metabolic processes.

β-cell dysfunction and failure are the driving force of diabetes pathogenesis, and are characterized by defective insulin secretion, ER stress, eventual β-cell loss and disease progression [2–5]. A number of stress factors, including excessive nutrients (glucose and/or lipids), systemic inflammation and insulin resistance, contribute to β-cell dysfunction [6,7]. Inside β cells, stress induces proinflammatory responses [8], ER stress [9], oxidative stress [10,11], mitochondrial dysfunction [12] and dedifferentiation [13,14], causing reduced insulin synthesis and secretion, eventually resulting in β-cell failure [15,16]. Though many therapeutic approaches are deployed to combat hyperglycaemia, few (if any) treatments directly target β-cell pathogenesis. Thus, long-term control of disease progression remains a persistent challenge.

The islet functional loss in the T2DM is a combinatory result of genetics and complex whole-body

Abbreviations
BPD, biliopancreatic diversion; GIP, glucose-dependent insulinotropic peptide; GLP-1, glucagon-like peptide-1; GLP-1R, GLP-1 receptor; HFD, high-fat diet; IGFBPs, insulin-like growth factor proteins; NMU, neuromedin U; RYGB, Roux-en-Y gastric bypass; SCFAs, short-chain fatty acids; VIP, vasoactive intestinal polypeptide; VSG, vertical sleeve gastrectomy.

metabolic dysregulation. Compared with the well-characterized intra-islet signalling and cell-autonomous regulation of the pancreatic endocrine cells, the inter-organ communication that regulates islet function, and how it is disrupted in obesity and T2DM, has just started to be elucidated in the past decades. There is accumulating evidence suggesting that secreted factors deriving from distant organs are crucial regulators of islet homeostasis, dysfunction and regeneration. In this review, we focus on the metabolic tissues that communicate with islets through direct contact or circulating factors (Fig. 1), and discuss the implication of tissue crosstalk in diabetes pathogenesis and the potential for therapeutic development.

Communication from the gastrointestinal system to pancreatic islets

Incretins and decretins

The concept of gut-secreting hormones can be traced back to the early 20th century, when it was recognized that simple nutrients trigger the release of secretory

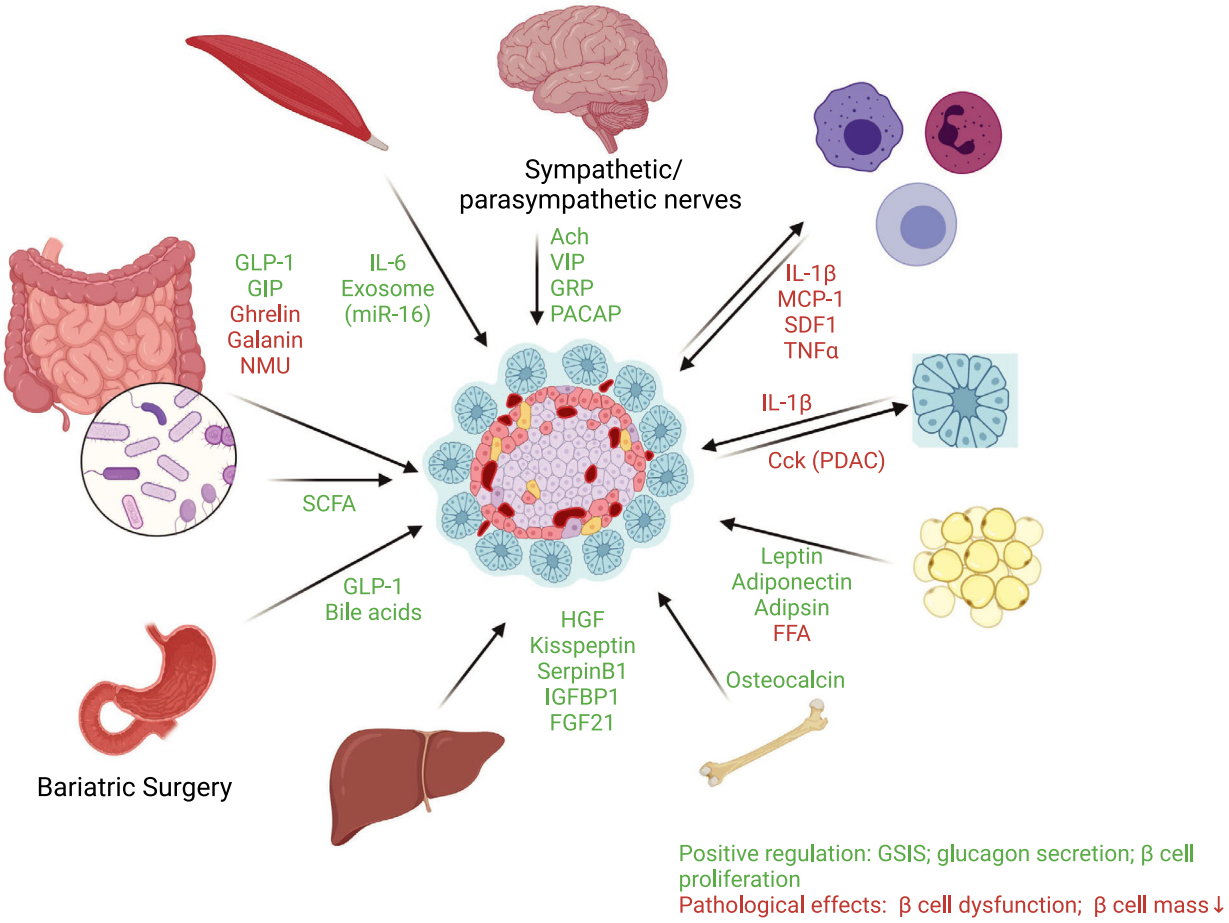

Fig. 1. Inter-organ crosstalk regulating pancreatic islet function. Multiple distal metabolic organs, such as liver, adipose, intestine, bone and skeletal muscle, modulate pancreatic islet function through a variety of circulating factors. The specific mediators of this inter-organ crosstalk include intestine-released incretin/decretin (GLP-1, GIP, ghrelin, galanin and NMU) and metabolites from microbiome such as SCFA; adipose secreted leptin, adiponectin, adipsin and free fatty acids (FFA); liver secreted HGF, kisspeptin, SerpinB1, IGFBP1 and FGF21; skeletal muscle secreted IL-6 and miR-16; and bone secreted osteocalcin. Multiple components in the pancreatic microenvironment, such as sympathetic/parasympathetic nerves, infiltrating immune cells and exocrine compartment, also crosstalk with islet in both normal physiological and pathological settings, such as proinflammatory cytokines (IL-1β, etc.) from immune cells and neuropeptides (VIP, etc.) from sympathetic/parasympathetic nerves. The inter-organ signalling converges on islets to promote or impair glucose-stimulated insulin response in both homeostatic and dysfunctional settings. Red: signalling molecules causing islet dysfunction. Green: signalling molecules enhancing islet function. Created with Biorender.com.

factors from gut mucosa to regulate blood glucose [17]. The incretin concept was later confirmed by administrating the same dose of oral or intravenous glucose. Oral glucose leads to a higher level of circulating insulin [18]. The best-characterized incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). GLP-1 is a cleaved product from pre-proglucagon, secreted from intestinal L cells (and from alpha cells) and released into circulation [19]. It binds to GLP-1 receptor (GLP-1R) and, directly and indirectly, suppresses alpha-cell glucagon secretion while increasing insulin secretion in a glucose-dependent manner [20]. Re-expression of pancreatic GLP-1R in the background of whole-body GLP-1R knockout mice restored the glucose tolerance, suggesting a direct role for GLP-1 signalling in pancreatic islets [21]. Interestingly, mice with β-cell-specific deletion of GLP-1R remain glucose-tolerant with oral glucose, but become glucose-intolerant with intraperitoneal glucose injection [22]. These results suggest that the mechanisms of GLP-1 on β-cell insulin secretion likely include paracrine signalling by GLP-1 from alpha cells, or inputs from neural systems. Besides acute insulin secretion, GLP-1 also induces β-cell proliferation and up-regulates insulin biosynthesis while reducing ER stress [23]. Therefore, it is likely that the chronic benefit of GLP-1 activation in improving islet function is a combinatory result of enhancing insulin secretion and preserving the β-cell mass. Alongside β cells, GLP-1 also suppresses glucagon secretion from alpha cells [24] while concurrently promoting somatostatin secretion from delta cells [25]. Whether these actions are mediated directly by GLP-1R on alpha/delta cells, or through indirect crosstalk between β cells and alpha/delta cells, remains to be determined.

The clinical success of GLP-1R agonists (reviewed in [19]) also suggests the therapeutic potential in other incretins such as GIP. While the administration of synthetic GIP failed to enhance the GSIS in human T2DM patients [26], recent progress in the development of GLP-1;GIP dual agonist has resulted in encouraging clinical data [27]. Future mechanistic studies will be needed to address whether the superior glycaemia benefits are mediated directly by islet endocrine cells.

Contrary to incretins, decretins are secreted by intestine to dampen insulin secretion from β cells [20]. Typically induced by fasting, decretins suppress insulin secretion to protect against hypoglycaemia. The decretin peptide family includes ghrelin [28], galanin [29] and NMU [30], all of which suppress insulin secretion in *ex vivo* and *in vivo* conditions. Ghrelin is produced in stomach epithelium and islet epsilon cells. Pharmacological inhibition of the ghrelin O-acyltransferase (GOAT), the enzyme required for ghrelin activation, improved GSIS in animal models [31]. Galanin is expressed in neurons and intestine acting to inhibit insulin secretion through G02 proteins in the β cells [29]. NMU is additionally found in Drosophila, the human stomach and duodenum, and can inhibit GSIS in human islets [30]. Given their significance in physiological regulation of insulin secretion, decretins could be valuable targets in future T2DM therapeutic development.

Bariatric surgery

Initially developed to treat morbid obesity, bariatric surgery procedures quickly attracted the attention of diabetes researchers, as clinical studies consistently revealed that the procedure strongly improves glucose metabolism (see a review from Douros et al. [32]). Although the beneficial effects of bariatric surgery come from a complex combination of weight loss, insulin sensitivity and insulin secretion, there is substantial evidence that the islet function is significantly improved directly and indirectly by bariatric surgery. Here, we summarize the clinical and preclinical evidence of signalling changes that contribute to islet function improvement after bariatric surgery.

Bariatric surgeries, such as Roux-en-Y gastric bypass (RYGB), vertical sleeve gastrectomy (VSG), adjustable gastric band (AGC) and biliopancreatic diversion (BPD), change the anatomy of gastrointestinal tract, achieve long-term weight loss and, importantly, significantly improve glucose control [33–36]. The effects of bariatric surgeries on T2DM are striking, as half of the patients with diabetes can achieve a nondiabetic HbA1C without diabetic medication [37]. Remarkably, RYGB, VSG and BPD dramatically improve glucose control immediately after surgery [38,39], suggesting mechanisms independent of weight loss. Distinct mechanisms, such as caloric restriction, improvement in insulin resistance, changed postprandial glycaemia and increased insulin secretion, may all contribute to the superior glucose control after bariatric surgery [32].

The improvement in islet function in T2DM patient after bariatric surgery is supported by consistent findings that first-phase insulin release is quickly restored in T2DM patients underwent RYGB or BPD [40–43]. This is consistent with the observation that patients after RYGB or VSG have a significant increase in GLP-1 release after meals [44], which is likely caused by the rapid passage of nutrient into intestine [45–47]. As GLP-1 signalling is critical for enhancing insulin

secretion, it is natural to speculate that the increased L-cell secretion of GLP-1 accounts for the improvement in glucose metabolism. However, a series of studies consistently showed that although GLP-1R blockade by exendin-(9-39) impairs the insulin secretion after meal, the changes are no different from that before surgery, arguing against the hypothesis that increased GLP-1 is responsible for the enhanced insulin secretion after surgery [48–52]. Consistent with the clinical observation, mice with whole-body deletion of GLP-1R demonstrate similar benefits in glucose tolerances after VSG or RYGB surgeries [53–55].

Besides GLP-1, other incretins, circulating hormones and metabolites are also altered and could potentially contribute to the beneficial effects of bariatric surgeries [32]. For example, mice with whole-body deletion of bile acid receptor FXR failed to show weight reduction or glucose improvement after VSG, strongly suggesting that circulating bile acids are signalling mediators [56]. However, it should be noted that mice with total knockout of FXR are leaner and have better glucose tolerance before surgery [56]. Importantly, it is shown recently that the intestinal bile acids and lipid absorption are reduced in VSG and contribute to the metabolic benefits [57]. However, the exact molecular modulators for the improvement in insulin secretion on islets after bariatric surgeries remain to be identified.

Intestinal microbiota

The roles of intestinal microbiota in health and disease have become an emerging area of interest. It is clear that in both T1DM and T2DM, the intestinal microbiota is significantly altered [58,59]. Mechanistically, the alteration in bacterial composition leads to changes in metabolites and vitamin levels, many of which have profound influence on islet function. An example is short-chain fatty acids (SCFAs). Produced by distal gut from fermentation of nondigestive carbohydrates [60], circulating SCFAs are anti-inflammatory mediators in both immune components and β cells [61–64]. SCFAs, such as sodium acetate and sodium propionate, act through the receptor FFAR2 to potentiate GSIS and prevent cytokine-induced apoptosis in both mouse and human islets [65]. Besides altering β-cell function, SCFAs also induce production of CRAMP, an anti-microbial peptide in β cells, which induces an increase in regulatory macrophages, regulatory dendritic cells and Treg cells in the pancreatic microenvironment [63]. The complex inter-organ communication among islets, immune environment and intestinal microbiota, and the underlying signalling and mechanisms, is still largely a black box and remains to be explored.

Communication from the adipose tissue to pancreatic islets

Adipose tissue actively produces adipokines, in response to nutrient and other systemic signals, to influence whole-body metabolism. As the most extensively characterized adipokine, leptin is secreted from adipose and regulates both food intake and energy expenditure. Global mutations in both the leptin and the leptin receptor result in mild-to-severe impairment to islet insulin secretion [66]. At least part of the effect of leptin action on islet is direct through activation of the K_{ATP} and NMDA channels [67–70]. The indirect actions of leptin, possibly through neural innervation, remain to be characterized.

Another key adipokine, adiponectin, is thought to act on the regeneration of β cells. In the β-cell ablation model, adiponectin stimulates islet regeneration through HNF4α and PPARα mediated antilipotoxic effects [71,72]. In gestational diabetes mellitus, adiponectin also promotes β-cell proliferation through lactogen expression [73]. Therefore, it is likely the downstream mediators of adiponectin in β cells are context-dependent.

Recently, a novel adipokine, adipsin, was identified an essential factor for islet insulin secretion and glucose tolerance [74]. Genetic deletion of adipsin results in insulinopenia [74]. Conversely, administration of adipsin in diabetic mice increases insulin secretion and reverses hyperglycaemia [74,75]. Adipsin generates C3a and increases ATP, OxPhos and $Ca2^{+}$ levels in β cells [75]. Mechanistically, this acts through phosphatase Dusp26 to increase insulin secretion and promote β-cell survival in murine and human islets [75]. These data suggest that adipsin and its downstream pathways are possible targets for T2DM therapeutics.

Communication from skeletal muscle to pancreatic islets

It is widely known that exercise can prevent or mitigate metabolic diseases such as obesity, T2DM and cardiovascular diseases [76]. Similarly, PPARδ agonists (aka: exercise mimetics) also powerful mitigators of metabolic disease, by promoting oxidative metabolism, lowering blood glucose, enhancing muscle performance and stimulating weight loss [76,77]. Besides its role in consuming carbohydrates and lipids, skeletal muscle produces multiple endocrine signals, known as myokines, which regulate distal metabolic organs including

pancreatic islets. As one of the best-characterized myokines, IL-6 is secreted from contracting muscle and release into circulation [78]. As a pleiotropic factor, IL-6 can trigger nutrient availability and improve insulin sensitivity [79,80]. Besides its direct effect on β cells, IL-6 also act on enteroendocrine cells (L cells) and islet alpha cells to increase prohormone convertase 1/3, proglucagon and GLP-1 expression, enhancing the GSIS function of islet [81]. Importantly, exercise increases the IL-6 expression in skeletal muscle [81], providing a molecular explanation for the exercise benefit.

Besides myokines, skeletal muscle also secretes exosome-like vesicles, which contains key microRNAs that may target islet function. In insulin-resistant muscle, excess palmitate induces release of exosome-like vesicles containing overexpressed miR-16 [82]. miR-16 regulates the expression of Ptch1 and other developmental genes, which may also enable the expansion of islet mass [82]. The molecular underpinnings of skeletal muscle-derived exosomes and miRNAs in human islets and its therapeutic values remain an important emerging field.

Communication from liver to pancreatic islets

As a major organ for energy storage, liver oversees glucose and lipid homeostasis and can therefore contribute to islet health or dysfunction by changing the circulating metabolite composition and levels. In addition, other liver-derived hormones and growth factors, such as IGF-1, can influence islet function and mass.

Kisspeptin (encoded by *KISS1*) is widely expressed in many tissues and initially characterized as a tumour suppressor [83]. However, recent studies revealed novel roles of kisspeptin and its receptor, KISS1R, in endocrine regulation, from puberty and fertility to islet function [83]. Importantly, the liver production of kisspeptin is regulated by glucagon [84]. Kisspeptin can suppress GSIS from β cells [84]. Importantly, this crosstalk is defective in T2DM models, as hyperglucagonaemia enhances kisspeptin production to ultimately reduce insulin secretion [84].

FGF21 is a critical metabolic regulator, which is secreted from liver upon fasting or ketogenic diet [85]. An early study demonstrated that FGF21 can improve β-cell function and survival by activating Akt signalling [86]. However, the benefit of FGF21 on islet function may be a result of multiple parallel mechanisms, such as activation of insulin-like growth factor proteins (IGFBPs) [87]. When activated by FGF21 [88], IGFBPs improve insulin sensitivity, protect against atherosclerosis and promote β-cell regeneration in multiple animal models [89,90].

Another regenerative factor from liver is hepatic growth factor (HGF). HGF acts on its receptor c-Met, to promote regeneration in multiple tissues including islets [91]. While c-Met deletion does not disrupt β-cell development or normal physiology, it does impair the regenerative potential of β cells in low-dose streptozotocin or partial pancreatectomy-induced β-cell loss [92].

In addition to injury-induced β-cell regeneration, it is well documented that obesity and/or insulin resistance induce β-cell proliferation [93]. Insulin resistance induces widespread changes in the liver secretome, which acts on islets to promote β-cell proliferation in an attempt to restore glucose homeostasis [94]. More recently, a search for potential β-cell expansion factors in liver insulin receptor knockout mice discovered serpinB1, a circulating factor that inhibits elastase to facilitate β-cell regeneration [95]. Small molecule compound sivelestat, which targets elastase, also resulted in similar regenerating capacity in cultured and transplanted islets [95]. Together, these studies revealed the potential therapeutic value of targeting serpinB1 and elastase. SerpinB1 as a hepatocyte-secretory protease inhibitor regulates b-cell proliferation in humans, mice and zebrafish. SerpinB1 acts by modulating canonical growth and survival signalling pathways.

Communication from nervous system to pancreatic islets

Rodent pancreatic islets are innervated by both parasympathetic nervous system and sympathetic nervous system [96]. In humans, 3D imaging of the pancreatic tissue also showed dense innervation similar to rodents [97]. In hyperglycaemia, parasympathetic nerves release acetylcholine, which activate muscarinic receptor signalling (m3AchR) in β cells to potentiate insulin secretion [98]. Other parasympathetic nerves also release peptides, including pituitary adenylate cycle-activating peptide (PACAP), vasoactive intestinal polypeptide (VIP) and gastrin-related peptide (GRP), which also influence insulin secretion from β cells [96]. It is known that the insulin secretion in response to feeding can happen before the increase in blood glucose, which is termed as the cephalic-phase insulin release [99]. The cephalic phase of insulin secretion is mediated by vagal cholinergic signals and contributes to glucose tolerance [99]. Besides the regulation of cephalic insulin release, neural control is also likely to contribute to postprandial insulin secretion, though the specific regulator remains to be defined [100].

The signals from central nervous system also involve in glucagon secretion [101]. In contrast to the hyperglycaemia-induced activation of parasympathetic nervous system, hypoglycaemia-induced activation of sympathetic nervous system induces glucagon secretion from islet alpha cells [97]. The glucagon response to hypoglycaemia is impaired when islets are denervated, supporting the causality between sympathetic activity and alpha cell function [97]. The postprandial glucagon secretion, which influences the nutrient-induced insulin secretion, is also partly regulated by the parasympathetic input [102].

Though the neural input is considered as a significant contributor to islet function in both rodents and humans, the innervation patterns are strikingly different between species [103]. In mouse, islets display a dense innervation of parasympathetic nerves in the islet core, while sympathetic nerves are enriched in the periphery [103]. In contrast, in human islets parasympathetic nerves typically avoid the islet core, and sympathetic nerves projected to the intra-islet blood vessels [104]. Thus, for humans, the alpha cells (rather than the cholinergic nerves) are the main source of acetylcholine that regulate β-cell function [104]. This type of structural divergence suggests that despite a dominance of similarities, variation in the regulation of islet function by neural inputs between rodents and humans is to be expected and that therapeutic outcomes in one species may not always extend to the other.

Communication from innate immune system to pancreatic islets

Chronic stress and inflammation within the islet has an indispensable role in T2DM pathogenesis [7]. Typically mediated by the innate immune system, the resulting elevated circulation of paracrine proinflammatory signals has long been considered as a principal cause for islet dysfunction and loss of β-cell mass. In T2DM, obesity and overnutrition create an increased demand on insulin production. This chronic provocation in turn induces conjoined inflammatory responses in multiple tissues, including adipose, liver and pancreatic islets [105]. This pathological cascade results in an increased level of lipids, gut-derived antigens (such as lipopolysaccharide) and damage-associated molecular proteins (DAMPs) [106]. As expected, an increase in macrophage population is observed in adipose and islets [105,107]. Due to proximity, these local macrophages tend to be more inflammatory, demonstrated by an increased level of TNF-α and chemokines, and align with traditional 'M1 macrophages' [107–109]. Enlargement of the adipose depot, linked to HFDs, results in insulin resistance, which triggers proinflammatory macrophages to increase cytokine production [105,110]. The islet macrophages are considered as a 'sensor' of the inflammatory signals, which effectively become the paracrine cytokines that drive β-cell stress and eventually β-cell failure [108,109,111]. In this pathological state, proinflammatory cytokines such as IL-1β and chemokines such as MCP1 are produced by β cells under stress from high free fatty acids and hyperglycaemia [112]. The chemokines are known to increase infiltration of monocyte-derived macrophages into the islets [4]. Conversely, inhibition of M1 macrophage accumulation protects β cells from palmitate acid-induced β-cell loss [4]. Insulin resistance and the stress induced by high glucose activate NLRP3-dependent inflammasome activation in islet residential macrophages, leading to IL-1β cleavage by the proinflammatory caspase-1 [113]. The resulting high level of IL-1β represses β-cell lineage gene expression, induces β-cell dysfunction and ultimately β-cell death [114–116]. Therefore, the IL-1β signalling is a key pathway responsible for the vicious cycle of the crosstalk between β cells and macrophages in the obesity settings.

It should also be noted that the action of IL-1β on islets partly depends on its concentration. While the high level of IL-1β clearly is detrimental for islet function, low level of IL-1β is known to, paradoxically, increase the insulin secretion [117]. It has been shown that nutrient uptake induced release by low level IL-1β will actually enhance GSIS [117]. Therefore, the differential mechanisms of IL-1β in regulating both normal physiological responses and pathological inflammatory response will be an interesting topic for future study and a potential area to exploit. In addition, other chemotaxis signals, such as fractalkine/CX3CR1 and SDF1/CXCR4, are also known to increase GSIS and β-cell proliferation/regeneration [118–120]. Therefore, the inflammatory pathways mediated by islet macrophages may also promote islet function in the context of obesity and nutrient stress.

Another outstanding question remains the origin of islet macrophages. In recent years, the lineage tracing studies suggest that the residential islet macrophages are mainly from yolk sac, whereas the recruited macrophages in obesity are from bone marrow ($Ly6c^{+}CD11b^{+}$) [121]. The classic view of the origin of islet macrophages is that the increased number of islet residential macrophages is mainly recruited from circulating monocytes [121]. This was challenged by a recent study, which characterized two distinct populations, the peri-islet macrophages ($F4/80^{hi}Cd11c^{-}$) and the intra-islet macrophage ($F4/80^{lo}Cd11c^{hi}$) [109]. In obese mice, the increase in residential macrophages

appears to be of intra-islet origin [109]. Further studies using genetic tracing models will be needed to solve this discrepancy.

In brief, obesity induces a complex pathological cascade principally comprised of islet residential and infiltrating immune populations, especially macrophages. These changes clearly correlate and contribute to islet dysfunction, and diabetes progression.

Communication from bone to pancreatic islet

Bone is now considered as an endocrine organ that can crosstalk with other metabolic organs. In mice lacking the protein tyrosine phosphatase OST-PTP in osteoblasts treated with HFD, β-cell proliferation and insulin secretion are enhanced, and glucose metabolism is improved, compared with wild-type HFD-treated mice [122]. Mechanistically, OST-PTP negatively regulates osteocalcin [122]. Mice with osteocalcin deletion, on the contrary, have defects in β-cell proliferation and are glucose-intolerant [122]. The β-cell protective effect of osteocalcin is mediated by β-cell-specific expression of its receptor Gprc6a [123]. Other than osteocalcin, neuropeptide Y (NPY) from osteoblast is also shown to promote insulin gene expression in β cells [124]. Together, these data support the model that distant crosstalk between osteoblasts and β cells modulate the function of β cells.

Exocrine–endocrine crosstalk

While the crosstalk between distant organs and islets are essential for islet function and pathology, it should not be ignored that islets are embedded in the exocrine pancreas (and ducts), and the interactions between endocrine and exocrine pancreas are critical not only for islet function but for exocrine pathology as well. This is best demonstrated in the case of pancreatogenic diabetes, or type 3c diabetes (T3cDM), a distinct class of diabetes secondary to pancreatic exocrine disease [125]. It is well known that chronic pancreatitis [126,127] and cystic fibrosis [128] are associated with islet dysfunction and diabetes, possibly due to injury, inflammation and fibrosis in the acini. Elevated proinflammatory cytokines, such as IL-1β, and inflammatory infiltration are likely the causes of β-cell dysfunction in both pancreatitis [129] and cystic fibrosis [130].

The exocrine–endocrine crosstalk in the pancreatic ductal adenocarcinoma (PDAC) is complex and intriguing. Diabetes frequency is elevated in PDAC patients [131]. 74% of the PDAC patients with diabetes are diagnosed within 24 months before PDAC diagnosis [132], suggesting a potential link between new-onset diabetes and PDAC. Most importantly, a large portion of PDAC patients with new-onset diabetes have resolved their diabetes after surgery, strongly suggesting a casual relation between PDAC and T3cDM [131]. A number of studies have revealed potential diabetogenic mediators of T3cDM in PDAC include connexin 26 [133], S-100A8 N-terminal peptide [134], vanin-1 [135], MMP9 [135], adrenomedullin [136] and exosomes [137]. Inside the islets, it has been shown that β cells are dedifferentiated in PDAC patients [138]. The direct signalling cues that mediate this crosstalk, however, remain undetermined.

Besides the mounting evidence of exocrine–endocrine crosstalk in causing islet dysfunction, it should also be noted that the dysfunctional islets could also drive the carcinogenesis. Recently, Chuang et al. [139] elegantly showed that obesity leads to aberrant expression of cholecystokinin expression in islets and subsequently drives the PDAC development in leptin knockout, Kras-driven mouse pancreatic cancer model. Whether a similar mechanism exists in human PDAC remains to be determined.

Conclusions and perspectives

In the past decades, significant advances have been made in our understanding of how signals from other organs regulate islet function in homeostasis and dysfunction. It is now clear that the islet is an integrative hub for circulating signals from a variety of metabolically related tissues (Fig. 1). Besides sensing glucose and nutrients, circulating factors from other distal organs influence the baseline of islet function. The dysregulation of these inter-organ communications is key to pancreatic islet pathogenesis. However, a number of outstanding questions remain: How does the regulation of islet physiology differ in humans *vs.* rodents? What are the roles of exosomes and microbiome-derived metabolites in regulating β-cell function? What are the chronic transcriptional and epigenetic responses of β cells to individual signalling? Further investigations in these areas may provide insights into developing next-generation diabetes therapies.

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