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Role of macrophages in obesity-associated islet inflammation and beta cell abnormalities

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Abstract

Chronic, unresolved tissue inflammation is a well described feature of obesity, type 2 diabetes mellitus (T2DM), and other insulin resistant states and adipose tissue and liver inflammation have been particularly well studied. However, this proinflammatory state is not restricted to liver and adipose tissue, and abundant evidence demonstrates that inflammatory processes are also activated in islets from obese animals, humans, and subjects with T2DM. The nature of the inflammatory response in each of these tissues is quite different, and in this review we focus on the characteristics of immune cell-mediated inflammation in islets and the consequences of this with respect to beta cell function. In contrast to type 1 diabetes mellitus (T1DM), the dominant immune cell type causing inflammation in obese and T2DM islets is the macrophage. This emphasizes the importance of the innate immune system, as opposed to adaptive immunity, in this pathophysiologic process. The increased macrophage accumulation in these islets primarily arises through local proliferation of resident macrophages. These macrophages then provide signals, such as PDGF, which drive beta cell hyperplasia which is a classic feature of obesity. In addition, through a number of mechanisms, islet macrophages also impair beta cell insulin secretory capacity. Through these mechanisms, resident islet macrophages underly the inflammatory response in obesity and mechanistically participate in the beta-cell hyperplasia and dysfunction which characterizes this insulin resistant state. These findings point to the possibility that methods to interrupt islet inflammation could have beneficial effects on beta cell function and glycemia.

Introduction

The global prevalence of type 2 diabetes mellitus (T2DM) continues to increase at an alarming rate, with a corresponding rise in morbidity and mortality, representing an

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enormous burden on healthcare costs[1]. Insulin resistance is a key antecedent pathophysiologic feature in T2DM. The majority of patients with T2DM are obese, and obesity is far and away the major cause of insulin resistance in humans. Thus, obesity and T2DM are closely linked, and the parallel worldwide increase in rates of obesity is the driver of the T2DM epidemic. However, not all obese patients advance to T2DM. In those subjects that do progress, a second metabolic defect occurs involving beta cell dysfunction [2,3]. Thus, when beta cells can no longer secrete excessive amounts of insulin to compensate for the insulin resistance, hyperglycemia ensues. There is an enormous literature on beta cell dysfunction in T2DM. Glucotoxicity, lipotoxicity, genetic defects, oxidative responses, ER stress, inflammation, and other mechanisms have all been implicated as causally related to decreased insulin secretion. With respect to the insulin resistance side of this metabolic disease, it is well known that obesity confers a state of chronic low-grade inflammation, particularly in adipose tissue and liver [4–6]. Many studies point to this inflammatory state as an underlying mechanism for the development of insulin resistance in obesity and T2DM. A number of papers have now demonstrated that this chronic tissue inflammatory state also includes pancreatic islets [7–9]. Islet inflammation has been described in a variety of mouse models of obesity and T2DM as well as in human islets from obese and/or type 2 diabetic patients. The mechanisms leading to islet inflammation are incompletely understood, but it is likely that islet inflammation contributes to the beta cell dysfunction which characterizes Type 2 diabetes. In this review, we will focus on the concept of islet inflammation with particular attention on the innate immune system, i.e. macrophages. We will discuss the distribution and accumulation of macrophages in pancreatic islets in normal and obese conditions and how macrophages influence beta cell abnormalities.

Macrophages in pancreatic islets.

1. Pancreas-resident macrophages during embryonic development and at steady state.

Studies in mice show that during embryonic development, macrophages in the pancreas are derived from yolk sac-derived primitive hematopoiesis[10]. These pancreatic macrophages are found in close proximity to insulin$^+$ beta cells [10] and additional studies suggested that these macrophages are involved in islet morphogenesis [11]. Consistent with this idea, the deficit of macrophage development in osteopetrotic *op/op* mice, lacking colony stimulating factor 1 (CSF-1), dampened pancreatic islet development and beta cell expansion [11,12].

Pancreatic macrophages display heterogenous phenotypes, depending on developmental stage [11,13], anatomical location [9,13], or metabolic setting [9]. With respect to the latter, using immunostaining and flow cytometry analyses, Ying and colleagues found that pancreatic islets harbored two phenotypically distinct macrophage subsets at steady state. The F4/80^{lo} CD11c$^+$ population was enriched within the islets, whereas F4/80^{hi} CD11c$^-$ macrophages largely resided in the peripheral islet area [9]. Knowledge about the role of these pancreas- or islet- resident cells at steady state remains incomplete. In addition to promoting islet organogenesis [12,13], how these macrophages participate in tissue homeostasis and function of beta cells remains to be fully defined.

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2. Inflammation in T2DM Islets

Numerous studies have revealed that macrophage infiltration is increased in T2DM islets, and islet macrophage content generally correlates with the degree of beta cell dysfunction [14–19]. While it is now clear that insulitis is a common feature of T1DM and T2DM islets, there is a clear distinction between these two conditions. For example, in T2DM islet inflammation, macrophages dominate, whereas T lymphocytes dominates in T1DM islets [8]. Thus, Ehses et al. reported that the number of $CD68^+$ macrophages were increased in T2DM islets without changes in $CD3^+$ T lymphocytes [14]. They reported that the majority of $CD68^+$ macrophages were positive for resident macrophage makers such as CD163 and HLA-2. In another study, Kamata et al. showed that, the number of CD68 and iNOS double-positive macrophages increased in amyloid-positive T2DM islets, without changes in CD163 and CD204-positive macrophages [15], suggesting that T2DM increases M1-like macrophage accumulation in the islets.

3. Accumulation of macrophages in obesity-associated islet inflammation.

Tissue inflammation is characterized by the accumulation and differentiation of various types of immune cells in local pathological lesions[20–23]. Macrophages are key cell types that orchestrate the initiation, specification and resolution of tissue-specific inflammation [6,24,25]. During the course of obesity, islet inflammation has been reported, characterized by the accumulation of immune cells [7–9,19] along with elevated production of inflammatory cytokines and chemokines [19,26,27]. Studies have reported increased numbers of myeloid-lineage cells (primarily monocytes and macrophages) in the islets of obese animal models [7,14,17,28]. The first comprehensive analysis of obesity-associated islet macrophages was performed by Ehses and colleagues [14]. Using CD68 and CD11b as markers, they found an increased number of macrophages in the pancreas of HFD-fed C57BL/6J mice and GK rats. Another key observation from this study was that the islets from T2D subjects released substantial amounts of inflammatory cytokines and chemokines such as IL-6, IL-8, CXCL1, G-CSF and MIP1a. While these data showed a correlation between the abundance of macrophages and increased inflammatory cytokines, the cellular origins of these cytokines and their roles in beta cell function remained undetermined. Using leptin receptor deficient *db/db* mice, Cucak and colleagues found significantly increased accumulation of pancreatic macrophages in diabetic mice. Their further characterization showed that both $CD68^+$ $F4/80^-$ and $CD68^+$ $F4/80^+$ subsets exhibited a proinflammatory M1-like phenotype [28]. Eguchi et al reported that saturated fatty acids induced beta cells to produce chemokines that attracted $CD11b^+$ $Ly\text{-}6C^+$ M1-type proinflammatory monocytes/macrophages to the islets [7]. Using both diet- and genetically- induced rodent models of obesity, Ying et al provided an in-depth assessment of obesity-associated islet metaflammation in mice [9]. They found that obesity-associated islet inflammation is dominated by macrophages, with negligible involvement of adaptive immune cells [9] (Figure 1).

Thus, macrophages in islets and in the exocrine stroma are distinct in origin and phenotypic properties. While it is not certain whether this is due to location or different lineages, the reconstitution after irradiation experiments performed by Calderon et al and Ying et al suggest that location plays a key role in programming macrophages to gain specific phenotypes and functions [9].

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4. What causes the accumulation of islet macrophages?

4.1. Obesity induces local proliferation of islet macrophages.—

Ying et al revealed a new mechanism of intra-islet macrophage accumulation in obese mice [9]. They found that in lean mice, both intra-islet and peri-islet macrophages were maintained at a very low turnover rate. This is consistent with a previous report showing that, at steady state, islet macrophages are only minimally derived from blood cells and replicate locally at a low rate [13]. However, under obese conditions, local proliferation of islet resident macrophages was significantly enhanced [9]. Local proliferation has also been demonstrated for adipose tissue macrophages (ATMs) under obese condition [29–32]. Reports have shown that IL-6 [29], CCL2 [31], CSF-1 [33] or osteopontin [32] might promote ATM replication.

Macrophages can adapt to local environmental cues [34,35] and it is possible that intra-islet resident macrophage proliferation is an adaptive response to pathophysiological stimuli. However, the factors that mediate this adaptation remain to be defined. An interesting question is whether elevated glucose and/or fatty acids (FAs) in obesity can trigger the release of stimulating factors that promote the local proliferation of islet macrophages.

4.2. Circulating monocytes and islet macrophages.—

During chronic inflammation, circulating monocytes infiltrate and accumulate in inflamed tissue sites. Whether this also explains obesity-associated islet inflammation is an important question. In a saturated FA treatment model, Eguchi et al found that ethyl palmitate infusion significantly increased the number of $CD11b^+$ $Ly6C^+$ cells in pancreatic islets [7]. However, the exact distribution of these monocytes (intra- or peri- islet) was not determined. Using adoptive transfer, Ying et al found that transferred fluorescently labeled $Ly6C^+$ monocytes reached the boundary between the exocrine and endocrine pancreas but did not penetrate into the islets in obese mice. Furthermore, these transferred cells retained their monocyte phenotype and did not differentiate into macrophages in the pancreas. Interestingly, time-course analysis showed that these peri-islet monocytes eventually migrate to pancreas-draining lymph nodes [9] (Figure 1). However, it remains possible that the lack of penetration of transferred monocytes into the HFD islets was due to the lack of an available tissue niche. Indeed, a previous study reported that monocytes can replace islet macrophages in mice after lethal irradiation [13].

4.3. The initiating factors for islet inflammation.—

An important and unanswered question is what triggers islet inflammation in obese animals. Since obesity is associated with systemic low-grade inflammation, it is possible that systemic metabolic or inflammatory factors could impinge on the islet microenvironment. For example, in vitro high glucose stimulation can induce IL-1β secretion from islets through activation of the NLRP3 inflammasome [36,37]. Circulating SFAs could also promote islet inflammation, particularly in the presence of hyperglycemia [7,38,39]. While circulating cytokine levels are often increased in obesity/diabetes, these serve primarily as biomarkers of systemic inflammation, since the concentration of circulating cytokines is much lower than the biologically active levels within the local tissue microenvironment. Thus, the blood concentration of cytokines such as TNFα or IL-1β, are 10–100 fold lower than the levels required to induce pro-inflammatory biologic effects and, thus, are unlikely to trigger

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obesity-induced islet inflammation. Alternatively, islet-derived local signals could also play an important role in initiating the inflammatory cascade[40]. Islet-resident macrophages could act as first-line responders to sense systemic metabolic changes. As a consequence, these macrophages could alter their function and/or expand locally. On the other hand, as mentioned above, Eguchi et al suggested that beta cells were early responders, as these cells can sense excessive fatty acids and produce chemokines to recruit Ly6C^{+} monocytes/macrophages to the islets [7]. Weitz et al reported that ATP released from stressed beta cells led to macrophage activation [41]. In T2DM patients, aggregated islet amyloid polypeptide (IAPP), the major component forming amyloid deposits, can induce proinflammatory responses in islet macrophages. Using synthetic human IAPP (hIAPP) treatment or the hIAPP transgenic mouse model, Westwell-Roper et al demonstrated that hIAPP can enhance the synthesis of IL-1β in islet resident macrophages[42]. While it remains unclear whether islet macrophages, beta cells, or both are the first responders to metabolic insults, local interactions between these two cell types seem to accelerate the inflammatory process.

5. Transcriptional profile of islet macrophages.

Obesity affects islet macrophage transcriptomes, resulting in altered functions. Earlier studies have reported that macrophages within the islets of obese mice exhibited a pro-inflammatory M1-like phenotype [7,28]. However, Calderon et al found that in lean mice, islet-resident macrophages constitutively expressed M1 cytokines, including IL-1β and TNF-α [13]. In a recent study [9], RNA-seq analysis of isolated macrophages from lean and obese mice showed no clear shift between M1 and M2 profiles in either intra- or peri- islet macrophage subsets. Interestingly, Cucak et al proposed that islet macrophages in mice exhibited a shift from an early stage pro-inflammatory phenotype toward late stage profibrotic characteristics [28]. Thus, during the development of obesity and T2D, the nature of the inflammation in the islets is not simply polarization from an M2 to M1 state, but, rather, a mixed continuum. Consistent with this notion, in adipose tissue of obese mice, adipose tissue macrophages exhibit diverse phenotypes across a broad spectrum of M1/M2 polarization states [43–45].

6. Other immune and non-immune cells

A few studies reported the presence of T and B lymphocytes [19,46] in pancreatic islets. In contrast, Ying et al did not detect the presence of T cells or B cells in the islets of HFD mice, arguing against the involvement of the adaptive immune system in obesity-associated islet pathology [9]. Instead, T cells can be detected in the exocrine pancreas at very low abundancy and HFD did not alter their number [9]. Another study reported that type 2 innate lymphoid cells (ILC2) were present in the islets and promoted insulin secretion through retinoic acid produced by myeloid cells in the islets [47]. They also found that an IL-33-ILC2 axis was activated after acute beta cell stress but was defective during chronic obesity. Thus, it is possible that other types of immune cells may be involved in obesity-associated islet inflammation in a model, or stage-dependent manner. In addition, islet endothelial cells and neurons also play important roles in modulating the islet microenvironment, influencing beta cell function [41,48].

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Effects of islet macrophages on beta cell function.

The deficit of beta cell function in T2DM is characterized by decreased mass and impaired GSIS [49]. Incubation of primary islets or beta cell lines with pro-inflammatory cytokines such as IL-1β or TNF-α increases beta cell apoptosis and decreases glucose-stimulated insulin secretion (GSIS) [50]. On the other hand, clodronate liposome-mediated depletion of macrophages in the islets of HFD mice improves GSIS [9]. Consistent with this, depletion of tissue macrophages by clodronate liposomes improves glucose tolerance in obese mice [7]. While the full mechanisms by which islet macrophages impair GSIS are not clearly understood, it likely involves both macrophage-derived soluble factors, and direct cell-cell contact between islet macrophages and beta cells (Figure 2).

1. Soluble factors.

Several cytokines such as TNF-α and IL-1β are increased in obese and T2DM islets and suppress beta cell GSIS [50,51]. The most well-studied cytokine produced by islet macrophages is IL-1β. Beta cells express the IL-1 receptor, and obesity increases IL-1β expression in islet macrophages [7,52]. In vitro incubation of macrophages in media containing high concentrations of glucose or free fatty acids (FAA) induce increased IL-1β production, suggesting that metabolic stress in obesity and/or T2DM can stimulate islet macrophages to produce more IL-1β. Indeed, while both beta cells and macrophages can produce IL-1β, macrophages appear to be the major source of islet IL-1β production in obesity [7,52]. Incubation of primary human or mouse islets, or beta cell lines, with IL-1β decreases GSIS and increases beta cell apoptosis. Moreover, secretion of inflammatory cytokines from islet macrophages amplifies lipotoxic effects of chronic palmitate treatment, including decreased GSIS and decreased expression of the genes involved in beta cell differentiation and function [7]. Thus, the enhanced lipotoxic effects of FFAs by co-culture with macrophages is ameliorated by addition of neutralizing antibodies against the pro-inflammatory cytokines TNF-α and IL-1β to the culture media.

The intracellular events through which inflammation impairs beta cell function involve the JNK and NF-κB signaling pathways. For example, TNF-α-induced NF-κB activation in beta cells decreases expression of genes involved in beta cell differentiation and insulin secretion. Beta cell NF-κB activation can reduce expression of an ER calcium ion (Ca^{2+}) pump (sarcoplasmic reticulum Ca^{2+} ATPase type 2b), leading to decreased GSIS by promoting ER stress [53]. Unlike TNF-α and IFN-γ, IL-1β also stimulates JNK in beta cells [54–57]. IL-1β-induced JNK activation decreases GSIS by suppressing the IRS/PI3K/Akt signaling pathway. This results in reduced FoxO1 phosphorylation with increased nuclear localization of active FoxO1 and decreased DNA binding to PDX-1 [58–60]. It has also been suggested that normal FoxO1 function is necessary for maintenance of the full beta cell differentiation state [61]. Additionally, Grunnet et al have shown that combination IL-1β/TNF-α/IFN-γ treatment can result in beta cell apoptosis by inducing mitochondrial stress and activation of proapoptotic Bcl-2 family proteins [62].

However, IL-1β treatment does not fully recapitulate the glucolipotoxicity-induced gene expression changes in islets, suggesting some divergence of mechanisms may also exist [63,64]. Welsh et al reported data that questioned the importance of IL-1β in human islets

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showing high glucose in vitro, or the diabetic milieu in vivo, did not induce IL-1β production or NF-κB activation [65]. Together, these results indicate the existence of other factors and mechanisms involved in high glucose or FFA-induced beta cell dysfunction.

2. Cell-cell contact and macrophage-mediated impaired beta cell insulin secretion.

Another mechanism by which macrophages can decrease beta cell insulin secretion is through direct cell-cell contact. Ying et al found that co-incubation of the Min6 beta cell line with intra-islet macrophages isolated from HFD mice decreases GSIS. Interestingly, this effect was seen only when the macrophages were directly added to the Min6 cells. Preventing cell-cell direct contact by culturing the two cell types in Transwell plate chambers, which allows interactions through soluble factors, blocks the effect to impair GSIS [9]. These results suggest that the inhibitory effect of intra-islet macrophages on beta cell GSIS includes a cell-cell contact process. The concept of beta cell-macrophage interaction through direct cell-cell contact is not new, and was previously suggested by Vomund et al [66].They found that, in the context of mouse T1D, islet macrophages can engulf insulin secretory vesicles [66]. Similar to their findings, Ying et al observed that intra-islet macrophages contain intact insulin vesicles, and this was greatly increased in obesity [9]. While it remains unclear how islet macrophages incorporate insulin secretory vesicles from beta cells and how obesity promotes this process, it has been demonstrated that macrophages can generate open-ended channels called tunneling nanotubes (TNT) to transport cytoplasmic materials between connected cells [67]. Therefore, it is theoretically possible that tunneling nanotubes mediate macrophage uptake of beta cell secretory granules, and that obesity and islet inflammation promote this process (Figure 2). It is also possible that transport of macrophage-derived factors to beta cells through these nanotubes impacts beta cell insulin secretion.

Effect of macrophages on beta cell proliferation.

In adult humans, the turnover rate of beta cells is extremely low. However, beta cells are not permanently quiescent. Under certain conditions, such as pregnancy and obesity, these cells are able to reenter the cell cycle. In addition, adaptive expansion of beta cell mass has been observed in the pre-diabetic stage in rodent models of obesity [68–72]. Multiple factors, including glucose [73–75], insulin [76], and hepatocyte growth factor [77–79] can stimulate beta cell replication under obese conditions. Recently, a number of studies suggest that macrophages can play an important role in beta cell replication.

1. Macrophages are involved in recovery of beta cell mass after injury or acute beta cell depletion.

An increasing body of evidence has supported a role for macrophages in beta cell expansion. Using a pancreatic injury model induced by partial duct ligation, Xiao et al observed that islet macrophages can promote beta cell proliferation through TGF and downstream SMAD7 signaling [80]. Conversely, depletion of islet macrophages using in vivo or ex vivo clodronate liposome treatment results in a decreased number of the BrdU+ beta cells [80]. Using a mouse model with 50% beta cell depletion, followed by beta cell specific overexpression of connective tissue growth factor (CTGF), Riley et al found that beta cells

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released CTGF as a chemoattractant to recruit macrophages which then promote the recovery of beta cell mass [81]. In another study, transiently increased expression of VEGF-A in beta cells led to beta cell loss and withdrawal of VEGF-A stimulated a robust, but transient, burst in proliferation of pre-existing beta cells [48]. They also found that bone marrow-derived macrophages were recruited to the site of beta cell injury and are important for beta cell proliferation. Taken together, these studies indicate that macrophages play a critical role in maintaining steady state beta cell mass and promote increased beta cell proliferation and mass in pathophysiologic insulin resistant states.

2. Islet Macrophages from obese mice promote beta cell proliferation.

Obesity-induced insulin resistance provokes a compensatory expansion of pancreatic beta cells. Ying et al showed that islet macrophages from obese mice, regardless of their anatomical location, exhibited an enhanced capacity to promote beta cell proliferation and both intra-islet and peri-islet macrophages showed similar effects. This effect was mediated by PDGF-PDGFR signaling [9]. Thus, the PDGF/PDGFR pathway plays an important role in mouse and human beta-cell proliferation and Chen et al have suggested that the reduction of PDGFR signaling in beta cells accounts for the decline of beta cell replication in aged mice and humans [82]. Macrophages are a major source of PDGF [83–86] and the expression of *Pdgfa* was increased in both $CD11c^+$ intra-islet macrophages and $CD11c^-$ peri-islet macrophages [9]. Furthermore, inhibition of PDGFR signaling blocked the effect of islet macrophages to promote beta cell replication [9]. Therefore, in addition to the expression of PDGFR on beta cells, the production of PDGF by islet macrophages forms a signaling system promoting beta cell proliferation (Figure 2).

3. Proinflammatory cytokines and macrophage-mediated beta cell proliferation.

Proinflammatory cytokines, such as TNF-α and IL-1β, are key components of the islet inflammatory microenvironment [27], and the role of IL-1b has been extensively studied [87]. Knockout of beta cell IL1R causes beta cell dedifferentiation [88]. In addition, low concentrations of IL-1β can promote beta cell proliferation by activating the FAS-FLIP pathway [89]. Lean mice lacking IL-1β production exhibited down-regulation of FAS-FLIP activation, as well as decreased beta cell proliferation. IL-1β can also suppress the expression of genes associated with a fully differentiated beta cell phenotype. This can facilitate beta cell apoptosis and can also induce beta cell dedifferentiation into islet endocrine cells which express both insulin and glucagon. These latter dual positive endocrine cells generally demonstrate impaired GSIS, providing another mechanism whereby IL-1β adversely effects beta cell GSIS. Given all of these findings, the IL-1β “tone” within the islet provides an important control point for regulation of beta cell mass. IL-1 receptor antagonist (IL-1Ra) expression is increased in the blood during obesity and T2DM but decreased in islets from T2DM patients [90,91]. Beta-cell specific IL-1Ra ablation resulted in a reduction in beta cell proliferation and impaired insulin secretion. Decreased levels of IL-1Ra promote IL-1β action and studies have shown that treatment of GK rats with IL-1Ra led to a reduction in islet inflammation and improved beta cell GSIS. Taken together, these results provide compelling evidence for the role of this inflammatory cytokine in islet inflammation and beta cell dysfunction.

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Beneficial effects of macrophages on beta cells.

Although depletion of islet macrophages improves GSIS in HFD/obese mice, macrophage depletion dampens beta cell GSIS in lean/normal islets [9]. This suggests that in the normal lean state, islet macrophages may have a beneficial role on beta cell insulin secretion. It remains unclear why islet macrophages from lean and obese mice apparently play opposite roles in beta cell function. It is possible that in obesity, islet macrophages are reprogrammed to impair beta cell GSIS. This could be due to effects of FFAs, glucose, or cytokines, such as IL-1β. One possible explanation is the level of IL-1β. As reported by Calderon et al, islet macrophages in non-obese mice exhibit a proinflammatory activation state and produce IL-1β [13]. Dror et al demonstrated that acute post-prandial rise in IL-1β production by myeloid cells contributes to meal-induced insulin secretion in a fasting-refeeding setting and is necessary for normal glycemic control [92]. In line with this, IL-1 receptor 1 (IL-1R1) deficient mice exhibited an impaired adaptive increase of plasma insulin after HFD feeding [93]. However, chronic accumulation or elevated production of IL-1β (mainly by islet macrophages) is detrimental to beta cell GSIS [87].

In addition to IL-1β, other factors and mechanisms could also play a role in shifting the effect of islet macrophages on beta cells. For instance, Ying et al found that pathways related to synapse-formation were more activated in islet macrophages in obese mice compared to lean mice [9], suggesting that obesity alters cell-cell interaction between macrophages and beta cells.

The above discussion raises several questions: what induces islet macrophages to change their effects on beta cell GSIS going from the lean to obese state? At which stage of obesity does this functional switch of islet macrophages happen? What modifications can reverse the macrophage-mediated "detrimental" effects on beta cells? To answer these questions, it will be necessary to perform longitudinal studies that can parse out the functional properties of islet macrophages and assess the effects of these cells on beta cell function in a stage-dependent manner.

Lipids as mediators of crosstalk between islet macrophages and beta cells.

Several studies have indicated that saturated fatty acids (SFAs), and perhaps lipoproteins, are circulating factors that might contribute to islet inflammation, beta cell dysfunction, and beta cell hyperplasia [7,38,39]. Thus, experimental elevation of palmitate levels in mice promotes islet inflammation [7]. In vivo treatment with SFAs increased the accumulation of islet macrophages and other markers of islet inflammation, as well as decreased GSIS. SFAs activate intracellular proinflammatory pathways by binding to TLR4 and studies show that TLR4 is required for the SFA-induced effect on islet inflammation and further show that islet macrophage TLR4 was essential for this process. TLR4 is also expressed on beta cells, and SFAs induce beta cells to secrete chemokines and other factors which promote islet macrophage accumulation. The SFAs act on macrophage TLR4 to stimulate the NF-κB pathway, resulting in cytokine secretion, particularly IL1β and TNFα, which can negatively influence beta cell GSIS. In addition to these effects of SFAs on beta cell secretory function, elevated SFA levels can also affect beta cell proliferation. This is particularly true when

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elevated SFA levels are combined with hyperglycemia, since this combination appears to cause additive effects on beta cell proliferation. Apoptosis is the other side of the equation regulating overall beta cell mass and, within the islet, SFAs can be converted to ceramides which promote apoptosis [94,95]. Cunha et al reported that exposure to palmitate can trigger human beta cell apoptosis by promoting death protein 5-mediated ER stress [96]. Thus, by enhancing apoptosis and promoting proliferation, SFAs may have important effects on increasing overall beta cell mass in the context of obesity and T2DM.

Another interesting connection between dyslipidemia and beta cell function has been reported. LDL receptor related protein 1 (LRP1) can interact with extracellular lipoproteins. Ye et al generated beta cell specific LRP1 KO mice and showed that these animals were partially protected from the adverse effects of HFD on beta cell insulin secretion, as well as HFD-induced beta cell hyperplasia [39]. They also found that this could be related to the effect of LRP1 deletion to upregulate beta cell PPARγ2 in HFD mice since transgenic overexpression of PPARγ2 in beta cells partially recapitulated the LRP1 phenotype.

Senescence.

Cellular senescence is characterized by stable cell-cycle arrest and a pro-inflammatory secretory phenotype [97]. The current theory is that the senescent signal can spread from one senescent cell to other surrounding cells. How this occurs remain to be resolved, but some indications suggest that T1D humans and the non-obese diabetic (NOD) mouse express a set of senescent beta cells with increased levels of the pro-survival mediator Bcl-2 [98]. Interestingly, treatment with Bcl-2 inhibitor can efficiently deplete senescent beta cells and prevent T1D occurrence in the NOD mouse model [98]. It is possible that obesity might promote a beta cell senescence response which drives the pathogenesis of type 2 diabetes. In an early study, Sone and Kagawa observed that the number of acidic beta-galactosidase-positive senescent beta cells was increased in HFD-induced mice [99]. Recently, Aguayo-Mazzucato et al. found that insulin resistance can promote senescence state of beta cells, leading to decreased insulin secretion [100]. Consistent with this idea, the number of senescent beta cells is increased in T2DM human islets [100]. However, it remains unknown whether islet macrophages also develop senescent phenotypes in the context of obesity or if senescent beta cells can regulate islet macrophage activation.

Clinical studies.

A number of clinical trials targeting inflammatory pathways have been tested in patients with T2DM, including the salicylic acid derivative, salsalate and anti-inflammatory TNFα inhibitors [101,102]. In some clinical trials, the effects on beta cells have been assessed. In one study, the administration of the recombinant a IL-1 receptor antagonist, Anakinra (recombinant IL-1Ra) confers a moderate but significant decrease in fasting blood glucose and glycated hemoglobin (−0.3–0.4%) levels [103]. In this study, the authors reported that Anakinra treatment increases insulin secretion without affecting insulin sensitivity. Moreover, the larger scale CANTOS trial using the anti-IL-1β antibody Canakinumab demonstrated that IL-1β neutralization lowers glycated hemoglobin levels in the plasma and delays new onset of T2DM by 2–3 years [104]. Since Canakinumab treatment significantly

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reduces recurrence of cardiovascular events, these results suggest that anti-inflammatory therapy can provide beneficial effects for T2DM. A recent meta-analysis of 2921 individuals from eight studies found a significant overall HbA1c-lowering effect of IL-1 antagonism, through either anti-IL-1 antibodies or IL-1R antagonists[105]. In this meta-analysis, a significant correlation between baseline C-reactive protein and C-peptide, and HbA1c outcomes was also revealed. However, the authors also cautioned that identification of further biomarkers are needed to define the potential of anti-IL-1 therapies in T2DM.

Concluding remarks and future perspectives.

Islet inflammation has emerged as a key feature of obesity and T2DM, and islet macrophages are the defining immune cell-type in these conditions. While much has been learned about macrophage-beta cell interactions, many important questions remain unresolved. What are the triggering events with respect to islet macrophage proliferation and expansion? Are initiating signals derived from the beta-cell or are they extrinsic to the islet? Islet macrophage proliferation is not significantly increased until 12–16 weeks HFD. If beta-cell insulin secretory function is affected prior to this time, then what is the cause? Have macrophages already started to reprogram before proliferation ensues, or is there a macrophage-independent mechanism causing the initial defect in GSIS? Why do circulating monocytes migrate to the peri-islet area but do not enter the islets? Finally, more information is needed on the role of islet inflammation and macrophages in the insulin secretory defects which characterize human T2DM?

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Box 1:

main points of this review

Obesity is associated with low-grade tissue inflammation, which is characterized by the accumulation of immune cells, metabolic and inflammatory mediators at multiple tissue sites, including pancreatic islets. In both animal models and human subjects, it is evident that increased number of immune cells (predominantly macrophages) is seen in pancreatic islets. The origin, phenotype and function of these macrophages are subjects of active investigations. Different mechanisms (local proliferation versus replenishment by blood monocytes) have been proposed to explain the increase of islet macrophages in obesity. The interactions between macrophages and beta cells are multifaceted. In rodent models of obesity, islet macrophages can dampen beta cell insulin secretion and beta cell proliferation through distinct mechanisms, suggesting that macrophages may exert both beneficial and detrimental roles in beta cells. Metabolic factors (glucose and free fatty acids), inflammatory cytokines or cell-cell contact may each play a critical role in the crosstalk between macrophages and beta cells. In addition to macrophages, other types of immune and non-immune cells are also found to participate in composing obesity-associated islet inflammation and influencing beta cell activities.

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Box 2:

Protective and harmful inflammation.

Inflammation is an adaptive response exploited by the host to deal with harmful conditions [24]. Acute inflammation is best exemplified as a result of infection whereas, whereas chronic inflammation is widely associated with more complex disorders, such as diabetes and cardiovascular diseases[20,21,23]. Evolutionarily, inflammation is a beneficial protective mechanism to eliminate infectious pathogens, elicit tissue repair and restore tissue homeostasis[24]. In contrast, it is generally appreciated that chronic, low-grade inflammation results in pathological consequences in the targeted tissue or cell, such as functional impairment, cell death and tissue damage [6].

Macrophages are key players in orchestrating the initiation, specification and resolution of tissue inflammation[6,24,25]. Macrophages are heterogenous in terms of their origin, tissue phenotype and function[106]. By adapting to tissue environmental cues, macrophages can acquire different functionalities and are programmed into pro-inflammatory, anti-inflammatory, or reparative states.

Dissecting the phenotypic and functional heterogeneity of islet macrophages and the interactions between macrophages and beta cells will improve our understanding of obesity and diabetes. This could lead to the development of new immunomodulatory regimens to prevent or reverse these disorders.

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Key points

1. Macrophages are the primary immune-type cells involved in obesity-associated islet inflammation in both mice and humans.

2. Obesity reconstructs the islet immune microenvironment by promoting local replication of islet-resident macrophages or recruiting circulating monocytes.

3. Islet macrophages in obese mice display multiple functions, including dampening beta cell insulin secretion and promoting beta cell proliferation.

4. Islet macrophages are potential therapeutic targets to modulate beta cell function.

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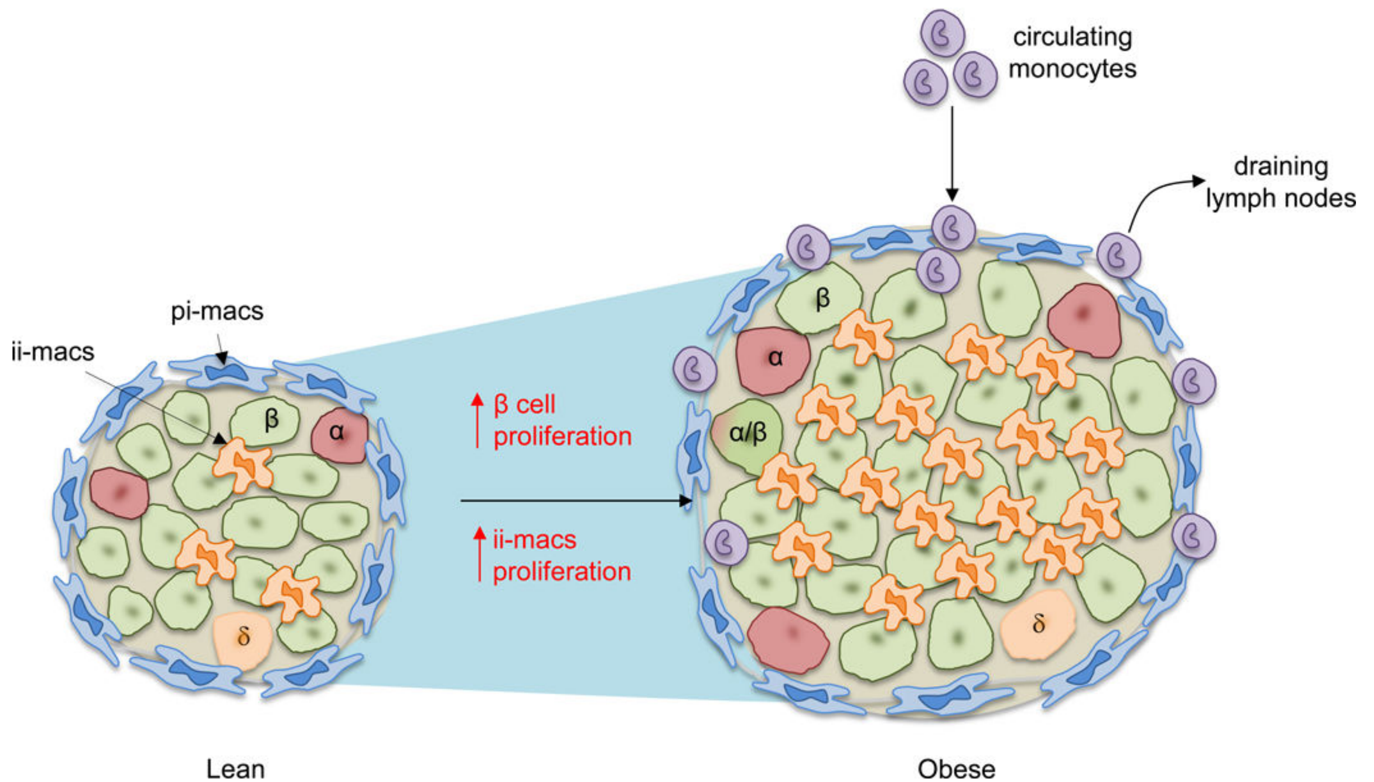

Figure 1. Macrophages dominate obesity-associated islet inflammation.

Illustrated here is a comparison of mouse islets between lean and obese conditions. In lean mice, two major populations of macrophages can be detected based on their anatomical distributions: peri-islet macrophages (pi-macs) ($F4/80^{hi}$ $CD11c^{-}$) and intra-islet macrophages (ii-macs) ($F4/80^{lo}$ $CD11c^{hi}$). Both are islet-resident cells. In contrast, in obesity, the size of islet is increased due to increased beta cell replication and cell size. Multiple studies have demonstrated the increase of islet macrophages. However, different mechanisms have been proposed to explain obesity-associated macrophage accumulation in the islet. In one model, stressed beta cells recruit circulating monocytes which differentiate into pro-inflammatory macrophages after infiltrating into the islets. This model has been challenged by other studies showing that even though monocytes can be detected in the pancreas, they do not infiltrate into the islets. Instead, the accumulation of intra-islet macrophages is caused by local proliferation of resident macrophages.

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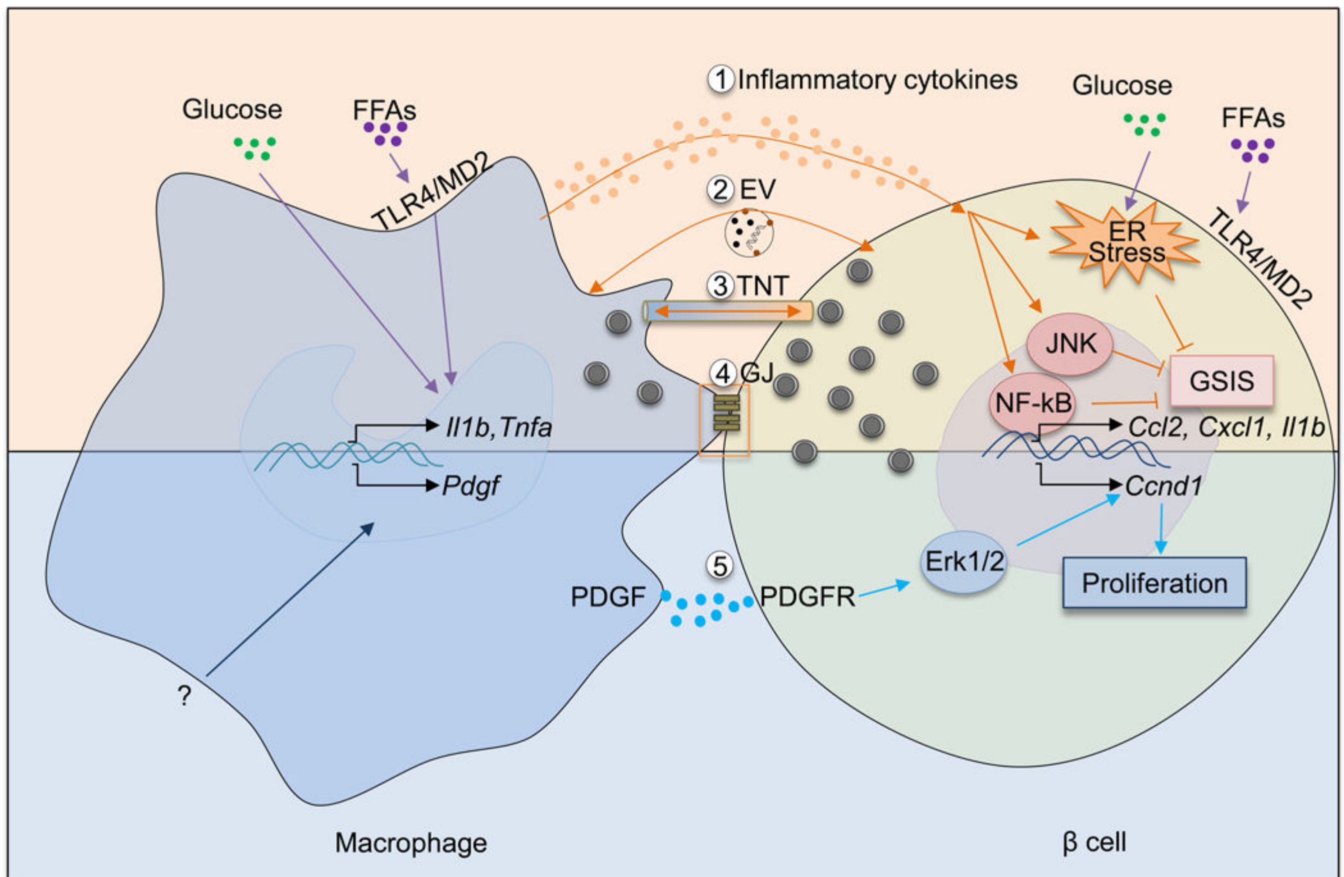

Figure 2. Interactions of islet macrophages and beta cells in obesity.

An increasing body of evidence supports the idea that islet macrophages influence beta cells in multiple ways. In obesity, elevated levels of glucose and free fatty acids can induce a pro-inflammatory phenotype of islet macrophages. As a result, macrophages produce increased amounts of proinflammatory cytokines such as IL-1β and TNF-α. These cytokines activate NF-κB and JNK pathways in beta cells and also exacerbate ER stress. Synergistically, these responses dampen beta cell GSIS. In addition to inflammatory cytokines, other mechanisms involving macrophage-mediated beta cell dysfunction exist. There mechanisms include: extracellular vesicles (EV) containing insulin released by beta cells and phagocytosed by islet macrophages; the formation of tunneling nanotubes (TNT) or gap junctions (GJ) between macrophages and beta cells allowing for bidirectional exchange of cellular contents. Obesity increases PDGF expression in islet macrophages via unclear mechanisms. Through PDGFR expressed in beta cells, PDGF promotes beta cell proliferation by activating downstream Erk signaling and inducing cell cycle gene (e.g., *Ccnd1*) expression.

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Table 1.

The roles of islet macrophages in non-inflammatory state versus obese/T2DM conditions

Non-Inflammatory State	Obesity/T2DM
Intra-islet macrophages and peri-islet macrophages[9,13]	Increased number of intra-islet macrophages[7,9,14,17,28]
Supports islet (β cell) development and regeneration[11–13]	Promotes compensatory β cell proliferation[9]
Promotes GSIS[9]	Suppresses GSIS with decreased expression of β cell-specific genes[7,9,49,50]
Low concentration of IL-1β [7,13,88,91]	Elevated production of IL-1β[7,40,49]