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The role of macrophages in obesity-associated islet inflammation and β-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. In this context, adipose tissue and liver inflammation have been particularly well studied; however, abundant evidence demonstrates that inflammatory processes are also activated in pancreatic islets from obese animals and humans with obesity and/or T2DM. In this Review, we focus on the characteristics of immune cell-mediated inflammation in islets and the consequences of this with respect to β-cell function. In contrast to type 1 diabetes mellitus, the dominant immune cell type causing inflammation in obese and T2DM islets is the macrophage. The increased macrophage accumulation in T2DM islets primarily arises through local proliferation of resident macrophages, which then provide signals (such as platelet-derived growth factor) that drive β-cell hyperplasia (a classic feature of obesity). In addition, islet macrophages also impair the insulin secretory capacity of β-cells. Through these mechanisms, islet-resident macrophages underlie the inflammatory response in obesity and mechanistically participate in the β-cell hyperplasia and dysfunction that characterizes this insulin-resistant state. These findings point to the possibility of therapeutics that target islet inflammation to elicit beneficial effects on β-cell function and glycaemia.

The global prevalence of type 2 diabetes mellitus (T2DM) continues to increase at a considerable rate, with a corresponding rise in morbidity and mortality, which places a growing burden on health-care systems[1]. Insulin resistance is a key antecedent pathophysiological feature in T2DM. The great majority of patients with T2DM are also 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 increases in obesity rates are the main driver of the T2DM epidemic. Many of these individuals with obesity are prediabetic, in that they will eventually develop T2DM. The rates of conversion can be 2–10% per year, depending on the population under study and the means of assessment[2,3]. However, not all individuals with obesity develop T2DM. In those patients who do progress, a second metabolic defect occurs in addition to insulin resistance, involving β-cell dysfunction[4,5]. In T2DM, β-cells can no longer secrete excessive amounts of insulin to compensate for the insulin resistance, and hyperglycaemia ensues. There is an enormous literature available on β-cell dysfunction in T2DM. For example, glucotoxicity, lipotoxicity, genetic defects, oxidative responses, endoplasmic reticulum (ER) stress, inflammation and other mechanisms have all been implicated as causally related to decreased insulin secretion from β-cells[6].

Obesity is well known to confer a state of chronic low-grade inflammation, particularly in adipose tissue and liver[7–9]. 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 occurs in pancreatic islets[10–12]. Islet inflammation has been described in a variety of mouse models of obesity and T2DM as well as in human islets from patients with obesity and/or T2DM[10]. The mechanisms leading to islet inflammation are incompletely understood, but it is likely that islet inflammation contributes to the β-cell dysfunction that characterizes T2DM.

In this Review, we focus on the concept of islet inflammation, with particular attention paid to the innate immune system (that is, macrophages). We discuss the distribution and accumulation of macrophages in pancreatic islets in normal and obese conditions and how macrophages influence β-cell abnormalities (BOX 1).

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Key points

- Macrophages are the primary immune cells involved in obesity-associated islet inflammation in both mice and humans.
- Obesity reprogrammes the islet immune microenvironment by inducing the local replication of islet-resident macrophages or by recruiting circulating monocytes.
- Islet macrophages in obese mice display multiple functions, including decreasing β-cell insulin secretion and stimulating β-cell proliferation.
- In the normal, lean state, islet macrophages promote islet development and maintenance of normal glucose-stimulated insulin secretion.
- Islet macrophages are potential therapeutic targets to modulate β-cell function in individuals with obesity and/or type 2 diabetes mellitus.

Macrophages in pancreatic islets

During embryonic development and at steady state. Tissue macrophages can be acquired during development or can differentiate from circulating monocytes[13]. Studies in mice show that, during embryonic development, macrophages in the pancreas are derived from yolk sac-derived primitive haematopoiesis[14]. These pancreatic macrophages are found in close proximity to insulin-positive β-cells[14], and additional studies suggested that these macrophages are involved in islet morphogenesis[15]. Consistent with this idea, a mouse model of osteopetrosis (*op/op* mice), which lacks colony-stimulating factor 1 (CSF1) and has a deficit in macrophage development, showed decreased pancreatic islet development and β-cell expansion[15,16].

Pancreatic macrophages display heterogeneous phenotypes depending on developmental stage[15,17], anatomical location[12,17] or the metabolic setting[12]. With respect to the latter, using immunostaining of macrophage-specific plasma membrane proteins (for example, the adhesion F4/80 and the integrin CD11c) and flow cytometry analyses, researchers found that pancreatic islets harboured two phenotypically distinct macrophage subsets at steady state. A F4/80^{lo}CD11c^{+} population was enriched within the islets (intra-islet macrophages), whereas F4/80^{hi}CD11c^{-} macrophages largely resided in the peripheral islet area (known as peri-islet macrophages)[12]. Knowledge about the role of these pancreas-resident or islet-resident macrophages at steady state remains incomplete. In addition to promoting islet organogenesis[16,17], how pancreatic macrophages participate in tissue homeostasis and the function of β-cells remains to be fully defined.

Inflammation in T2DM islets. Tissue inflammation is characterized by the accumulation and differentiation of various types of immune cell in local pathological lesions[18–21]. Macrophages are key cell types that orchestrate the initiation, specification and resolution of tissue-specific inflammation[9,22,23] (BOX 2). Numerous studies have revealed that macrophage infiltration is increased in T2DM islets and that the number of islet-resident macrophages generally correlates with the degree of β-cell dysfunction[24–29]. Of note, insulitis is well known as a feature common to both type 1 diabetes mellitus (T1DM) and T2DM islets derived from humans; however, a clear distinction exists between these two conditions — in T2DM islet inflammation, macrophages dominate, whereas both innate and adaptive immune cells are heavily involved in T1DM islets[11]. For example, the number of CD68^{+} (a macrophage-specific plasma membrane protein) macrophages is reportedly increased in human and mouse T2DM islets without changes in the number of CD3^{+} T cells[24]. Moreover, the same study found that the majority of CD68^{+} macrophages were positive for tissue-resident macrophage markers, such as CD163 and HLA2. In another study, the number of CD68 and inducible nitric oxide synthase double-positive macrophages increased in islet amyloid polypeptide (IAPP)-positive T2DM islets, without changes in numbers of CD163^{+} and CD204^{+} M2-like macrophages[25], suggesting that T2DM is associated with increased pro-inflammatory M1-like macrophage accumulation in pancreatic islets.

Obesity-associated islet inflammation. Islet inflammation has been reported in individuals with obesity, characterized by the accumulation of immune cells[10–12,29] along with elevated production of inflammatory cytokines and chemokines[29–31]. Furthermore, studies have reported increased numbers of myeloid-lineage cells (primarily monocytes and macrophages) in the islets of obese animal models[10,24,27,32]. The first comprehensive analysis of obesity-associated islet macrophages used CD68 and CD11b as markers and found an increased number of macrophages in the pancreas of high-fat diet (HFD)-fed C57BL/6J mice and Goto–Kakizaki rats[24]. Moreover, islets from individuals with T2DM released substantial amounts of inflammatory cytokines and chemokines such as IL-6, IL-8, CXCL1, granulocyte colony-stimulating factor (GCSF) and macrophage inflammatory protein 1α (MIP1α)[24]. Although these data showed a correlation between the abundance of macrophages and increased inflammatory cytokines, the cellular origins of these cytokines and their roles in β-cell function remained undetermined.

Further work has been carried out to characterize obesity-associated islet inflammation using various rodent models. For example, leptin receptor-deficient *db/db* mice, which are obese and used as a model of T2DM, have substantially increased accumulation of islet macrophages compared with wild-type mice. Further characterization showed that CD68^{+}F4/80^{+} macrophages found in the pancreas of *db/db* mice exhibited a pro-inflammatory M1-like phenotype[32]. In the same study, a new and less typical CD68^{+}F4/80^{+} macrophage population was also found in the islets of humans with T2DM. Another study using a palmitate acid-induced obesity model reported that saturated fatty acids (SFAs) induced β-cells to produce chemokines that attracted CD11b^{+}Ly6C^{+} M1-like pro-inflammatory monocytes and macrophages to the islets[10]. An in-depth assessment of obesity-associated metaflammation carried out using diet-induced and genetically induced mouse models of obesity found that obesity-associated islet inflammation is dominated by macrophages, with negligible involvement of adaptive immune cells[12] (FIG. 1).

Thus, macrophages in islets and in the exocrine stroma of the pancreas are distinct in origin and phenotypic properties. Whether this variation is due to location or different lineages is uncertain; however, the

Yolk sac-derived primitive haematopoiesis
The generation of blood-lineage cells, including primitive erythroid cells, platelets and macrophages, in the extra-embryonic yolk sac during early embryonic development.

Osteopetrosis
A rare inherited syndrome characterized by increased bone density due to a defect of osteoclasts, a specialized population of macrophages that can resorb bone.

Insulitis
Islet-specific inflammation characterized by the infiltration of various types of immune cell into pancreatic islets, more commonly used to describe the islet inflammation preceding or accompanying type 1 diabetes mellitus.

Islet amyloid polypeptide
(IAPP). An islet hormone that is co-secreted with insulin from β-cells and forms islet amyloids.

Metaflammation
Low-grade inflammation induced by overnutrition, which occurs in metabolic tissue (primarily adipose tissue, liver, muscle and pancreatic islets), causes dysregulation of immune cells and inflammatory responses.

Box 1 | **Physiological and pathophysiological roles of islet macrophages**

Noninflammatory state

- Intra-islet macrophages and peri-islet macrophages[12,17]
- Supports islet (β-cell) development and regeneration[15–17]
- Promotes glucose-stimulated insulin secretion[12]
- Low concentration of IL-1β[10,17,104,109]

Obesity and type 2 diabetes mellitus

- Increased number of intra-islet macrophages[10,12,24,27,32]
- Promotes compensatory β-cell proliferation[12]
- Suppresses glucose-stimulated insulin secretion with decreased expression of β-cell-specific genes[10,12,61,62]
- Elevated production of IL-1β[10,51,61]

cellular reconstitution after irradiation experiments suggests that tissue location has a key role in programming macrophages to gain specific phenotypes and functions[12].

Causes of islet macrophage accumulation

Tissue-resident macrophages are populated from several waves of precursors during the embryonic stage and are self-maintained during adulthood[13,33]. However, during inflammation and tissue injury, bone marrow-derived monocytes can infiltrate tissues and differentiate into macrophages[34].

Obesity induces local proliferation of islet macrophages. Interestingly, intra-islet and peri-islet macrophage populations are maintained in lean mice at a very low turnover rate[12]. This finding is consistent with a previous report showing that, at steady state, islet macrophages are only minimally derived from circulating blood cells and instead replicate locally at a low rate[17]. However, under obese conditions, local proliferation of islet-resident macrophages in mice was substantially increased[12]. These findings suggest a new mechanism of intra-islet macrophage accumulation in obese mice. Local proliferation has also been demonstrated for adipose tissue macrophages (ATMs) under obese conditions in mice[35–38]. In addition, reports suggest that IL-6 (REF.[35]), CCL2 (REF.[37]), CSF1 (REF.[39]) or osteopontin[38] could stimulate ATM replication in animals.

Macrophages can adapt to local environmental cues[40,41] and intra-islet-resident macrophage proliferation could possibly be an adaptive response to pathophysiological stimuli. However, the factors that mediate this adaptation remain to be defined. An interesting question is whether elevated plasma glucose and/or fatty acid levels in obesity can trigger the release of stimulating factors within the islets that activate the local proliferation of islet macrophages.

Circulating monocytes and islet macrophages. During chronic inflammation, circulating monocytes infiltrate and accumulate in inflamed tissue sites. Whether an infiltration of circulating monocytes can also explain obesity-associated islet inflammation is an important question. In a SFA treatment mouse model, ethyl palmitate infusion significantly increased the number of $CD11b^+Ly6C^+$ monocytes found in pancreatic islets[10]. However, the exact distribution of these monocytes (that is, intra-islet or peri-islet) was not determined. Importantly, adoptive transfer experiments showed that transferred fluorescently labelled $Ly6C^+$ monocytes infiltrated to the boundary between the exocrine and endocrine pancreas but did not penetrate into the islets in HFD-fed obese mice[12]. 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[12] (FIG. 1). However, the lack of penetration of transferred monocytes into the HFD islets might be 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[17].

The initiating factors for islet inflammation. An important and unanswered question is what triggers islet inflammation in obesity. As obesity is associated with systemic low-grade inflammation, systemic metabolic or inflammatory factors could potentially 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[42,43]. Circulating SFAs could also induce islet inflammation, particularly in the presence of hyperglycaemia[10,44,45]. Although circulating cytokine levels are often increased in obesity and diabetes mellitus, these cytokines serve primarily as biomarkers of systemic inflammation, as the concentration of circulating cytokines is much lower than the biologically active levels that occur within the local tissue microenvironment. The blood concentration of cytokines such as tumour necrosis factor (TNF) or IL-1β are 10-fold to 100-fold lower than the levels required to induce pro-inflammatory biological effects and are therefore unlikely to trigger obesity-induced islet inflammation[46–50].

Alternatively, islet-derived local signals could also have an important role in initiating the inflammatory cascade[51]. For example, 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. However, β-cells have been suggested to be early responders (mentioned earlier in the Review) as these cells can sense excessive fatty acids and produce chemokines to recruit $Ly6C^+$ monocytes and macrophages to pancreatic islets[10]. Moreover, ATP released from stressed β-cells has been reported to lead to macrophage activation[52].

In patients with T2DM, aggregated IAPP can induce pro-inflammatory responses in islet macrophages. For example, synthetic human IAPP (hIAPP) treatment or the use of an hIAPP transgenic mouse model showed that hIAPP can increase the synthesis of IL-1β in islet-resident macrophages[53]. Whether islet macrophages, β-cells or both are the first responders to metabolic insults remains unclear; however, local interactions between these two cell types seem to accelerate the inflammatory process.

Type 2 innate lymphoid cells (ILC2s). A subgroup of innate lymphoid cells characterized by the lack of rearranged receptors and production of type 2 cytokines such as IL-5 and IL-13.

Transcriptional profile of islet macrophages. Obesity affects islet macrophage transcriptomes, which results in altered functions. Earlier studies reported that macrophages within the islets of obese mice exhibited a pro-inflammatory, M1-like phenotype[10,32]. However, a 2015 study found that, in lean mice, islet-resident macrophages constitutively expressed M1-associated cytokines, including IL-1β and TNF[17]. Furthermore, in a 2019 study[12], RNA sequencing analysis of isolated macrophages from lean and obese mice showed no clear shift between M1-like and M2-like profiles in either intra-islet or peri-islet macrophage subsets. Interestingly, islet macrophages in leptin receptor-deficient *db/db* mice have been proposed to show a shift from an early stage (8 weeks of age) pro-inflammatory phenotype towards late-stage (28 weeks of age) profibrotic characteristics[32]. Thus, during the development of obesity and T2DM, the nature of islet inflammation is not simply polarization from an M2-like to an M1-like state (BOX 2) but instead is a mixed continuum of heterogeneous cell phenotypes. Consistent with this notion, in adipose tissue of obese mice, ATMs exhibit diverse phenotypes across a broad spectrum of M1-like and M2-like polarization states[54–56].

Other immune and nonimmune cells. A few studies reported the presence of T cells and B cells[29,57] in pancreatic islets of humans with T2DM. By contrast, another study did not detect the presence of T cells or B cells in the islets of HFD-fed mice, which is evidence against the involvement of the adaptive immune system in obesity-associated islet pathology[12]. However, T cells can be detected in the exocrine pancreas at very low abundancy, and a HFD did not alter their number[12]. Another study reported that type 2 innate lymphoid cells (ILC2s) were present in the islets of lean mice and that an HFD reduced the number of these cells in the islets. These cells stimulated insulin secretion through retinoic acid produced by islet myeloid cells[58]. Furthermore, an IL-33–ILC2 axis was activated after acute β-cell stress but was defective during chronic obesity[58]. Thus, other types of immune cell might be involved in obesity-associated islet inflammation in a model- or stage-dependent manner. In addition, islet endothelial cells and neurons also have important roles in modulating the islet microenvironment, which can influence β-cell function[52,59]. For example, central nervous system modulation of islet function has been reported, and islet endothelial cell-derived vascular endothelial growth factor (VEGF) might affect β-cell replication[60] (also see the section on Recovery of β-cell mass after injury or acute β-cell depletion).

Box 2 | **Protective and harmful inflammation**

Inflammation is an adaptive response exploited by the host to deal with harmful conditions[22]. Acute inflammation is commonly associated with infection, whereas chronic inflammation is widely associated with more complex disorders, such as diabetes mellitus and cardiovascular diseases[18,19,21]. Evolutionarily, inflammation is a beneficial protective mechanism to eliminate infectious pathogens, elicit tissue repair and restore tissue homeostasis[22]. By contrast, chronic, low-grade inflammation is generally thought to result in pathological consequences in the targeted tissue or cell, such as functional impairment, cell death and tissue damage[9].

Macrophages are key players in orchestrating the initiation, specification and resolution of tissue inflammation[9,22,23]. Macrophages are heterogenous in terms of their origin, tissue phenotype and function[124]. By adapting to tissue environmental cues, macrophages can acquire different functionalities and are programmed into pro-inflammatory (sometimes referred to as M1-like), anti-inflammatory (sometimes referred to as M2-like) or reparative states.

Dissecting the phenotypic and functional heterogeneity of islet macrophages and the interactions between macrophages and β-cells will improve our understanding of obesity and type 2 diabetes mellitus. This knowledge could lead to the development of new immunomodulatory regimens to prevent or reverse these disorders.

Effects on β-cell function

The following section discusses potential effects of islet macrophages on β-cell function. The deficit of β-cell function in T2DM is characterized by decreased β-cell mass and impaired glucose-stimulated insulin secretion (GSIS)[61]. Incubation of primary human islets or β-cell lines with pro-inflammatory cytokines, such as IL-1β or TNF, increases β-cell apoptosis and decreases GSIS[62]. By contrast, clodronate liposome-mediated depletion of macrophages in the islets of HFD-fed mice improves GSIS[12]. Consistent with this finding, systemic depletion of tissue macrophages by in vivo administration of clodronate liposomes improves glucose tolerance in obese mice[10]. The full mechanisms by which islet macrophages impair GSIS are not clearly understood; however, it probably involves both macrophage-derived soluble factors and direct cell–cell contact between islet macrophages and β-cells (FIG. 2).

Soluble factors. The levels of several cytokines, such as TNF and IL-1β, are increased in obese and T2DM islets in humans and suppress β-cell GSIS[62,63]. The best-studied cytokine produced by islet macrophages is IL-1β. Of note, β-cells express the IL-1 receptor (IL-1R) and obesity increases IL-1β expression in islet macrophages in both mice and humans[10,64]. In vitro incubation of mouse and human monocyte/macrophage cell lines in media containing high concentrations of glucose or free fatty acids (FFAs) induces increased IL-1β production. This suggests that metabolic stress in obesity and/or T2DM can stimulate islet macrophages to produce more IL-1β[10,65,66]. Indeed, while both β-cells and macrophages can produce IL-1β, macrophages are seemingly the major source of islet IL-1β production in obesity[10,64].

Incubation of primary human or mouse islets, or β-cell lines, with IL-1β decreases GSIS and increases β-cell apoptosis[62]. Moreover, the secretion of inflammatory cytokines from islet macrophages that are cocultured with Min6 cells amplifies the lipotoxic effects of chronic palmitate treatment, decreasing GSIS and expression of the genes involved in β-cell differentiation and function[10]. Furthermore, the increased lipotoxic

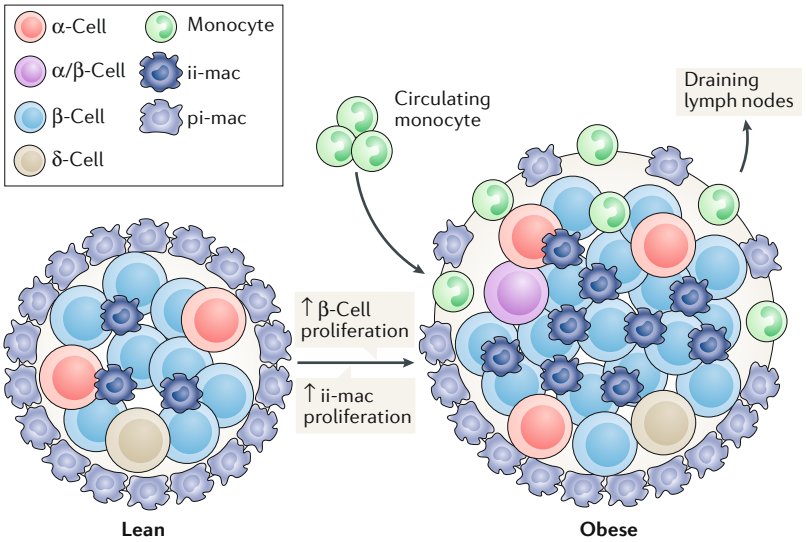

Fig. 1 | **Macrophages dominate obesity-associated islet inflammation.** A comparison of mouse islets between lean and obese conditions. In lean mice, two major populations of macrophages can be detected based on their anatomical distributions: peri-islet macrophages (pi-macs; F4/80^{hi}CD11c^{-}) and intra-islet macrophages (ii-macs; F4/80^{lo}CD11c^{hi})[12]. Both populations are islet-resident cells. By contrast, in obesity, the size of islets is increased owing to increased β-cell replication and cell size. Different mechanisms have been proposed to explain obesity-associated macrophage accumulation in the islet. In one model, stressed β-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[10]. Instead, the accumulation of ii-macs is caused by local proliferation of resident macrophages[12].

effects of FFAs on β-cells by coculture with macrophages is ameliorated by the addition of neutralizing antibodies against the pro-inflammatory cytokines TNF and IL-1β to the culture media[10].

The intracellular events through which inflammation impairs β-cell function involve the JNK and nuclear factor-κB (NF-κB) signalling pathways. For example, TNF-induced NF-κB activation in INS-1 rat insulinoma cells decreases GSIS[67]. In addition, activation of NF-κB in β-cells can reduce expression of an ER Ca^{2+} pump (sarcoplasmic reticulum Ca^{2+} ATPase type 2b), which leads to ER stress and decreased GSIS[68].

Unlike TNF and IFNγ, IL-1β also stimulates JNK in β-cell lines[69–72]. IL-1β-induced JNK activation decreases GSIS by suppressing the insulin receptor substrate (IRS)–phosphoinositide 3-kinase (PI3K)–AKT signalling pathway. This results in reduced FOXO1 phosphorylation, with increased nuclear localization of active FOXO1 and decreased DNA binding to PDX1 (REFS[73–75]). These findings are important as research suggests that normal FOXO1 function is necessary for maintenance of the full β-cell differentiation state[76]. In addition, a study showed that combination IL-1β–TNF–IFNγ treatment of human islets and INS-1 cells can result in β-cell apoptosis by inducing mitochondrial stress and activation of proapoptotic BCL-2 family proteins[77].

IL-1β treatment of primary rat β-cells does not fully recapitulate the gene expression changes induced by glucolipotoxicity, which suggests that some divergence of mechanisms might also exist[78,79]. Another study reported data that questioned the importance of IL-1β in human islets, showing that in vitro treatment with high glucose concentrations (11 and 28 mmol/l), did not induce IL-1β production or NF-κB activation[80]. Together, these results indicate the existence of other factors and mechanisms involved in high glucose or FFA-induced β-cell dysfunction.

Cell–cell contacts. Another mechanism by which macrophages can decrease β-cell insulin secretion is through direct cell–cell contact. For example, co-incubation of the Min6 β-cell line with intra-islet macrophages isolated from HFD-fed mice decreases GSIS[12]. Interestingly, this effect was seen only when the macrophages were directly added to the Min6 cells. Preventing direct cell–cell contact by culturing the two cell types in Transwell plate chambers, which still allow interactions through soluble factors, blocks the impairment in GSIS[12]. These results suggest that the inhibitory effect of intra-islet macrophages on β-cell GSIS includes a cell–cell contact process. The concept of β-cell–macrophage interactions through direct cell–cell contacts is not new. Islet macrophages can engulf insulin secretory vesicles in a mouse model of T1DM[81]. Similar to these findings, mouse intra-islet macrophages contain intact insulin secretory vesicles, and the number of engulfed vesicles was greatly increased in obesity[12].

The mechanism by which islet macrophages incorporate insulin secretory vesicles from β-cells and how obesity accelerates this process remains unclear. However, macrophages can generate open-ended channels called tunnelling nanotubes, which transport cytoplasmic materials between connected cells[82]. Therefore, tunnelling nanotubes could theoretically mediate macrophage uptake of β-cell secretory granules, and obesity and islet inflammation might increase this process (FIG. 2). The potential transport of macrophage-derived factors to β-cells through these nanotubes might also affect β-cell insulin secretion. It is also possible that extracellular vesicles or gap junctions are involved in the crosstalk between macrophages and β-cells.

Effects on β-cell proliferation

In adult humans, the turnover rate of β-cells is extremely low. However, β-cells are not permanently quiescent. Under certain conditions, such as pregnancy and obesity, these cells are able to re-enter the cell cycle[12,83]. In addition, adaptive expansion of β-cell mass has been observed in obese, insulin-resistant mice and humans[84–88]. Multiple factors, including increased plasma glucose concentrations[89–91], insulin[92] and expression of hepatocyte growth factor[93–95], can stimulate β-cell replication. Evidence now exists suggesting that macrophages can have an important role in β-cell replication.

Recovery of β-cell mass after injury or acute β-cell depletion. An increasing body of evidence has supported a role for macrophages in β-cell expansion. For example, in a pancreatic injury mouse model induced by partial duct ligation, islet macrophages were observed to increase β-cell proliferation through transforming growth factor (TGF) and downstream SMAD7 signalling[96].

Transwell plate chambers
Devices designed to study cell migration and cell–cell interaction, which are permeable to soluble factors but prevent the migration or contact of cells between the upper and lower chambers.

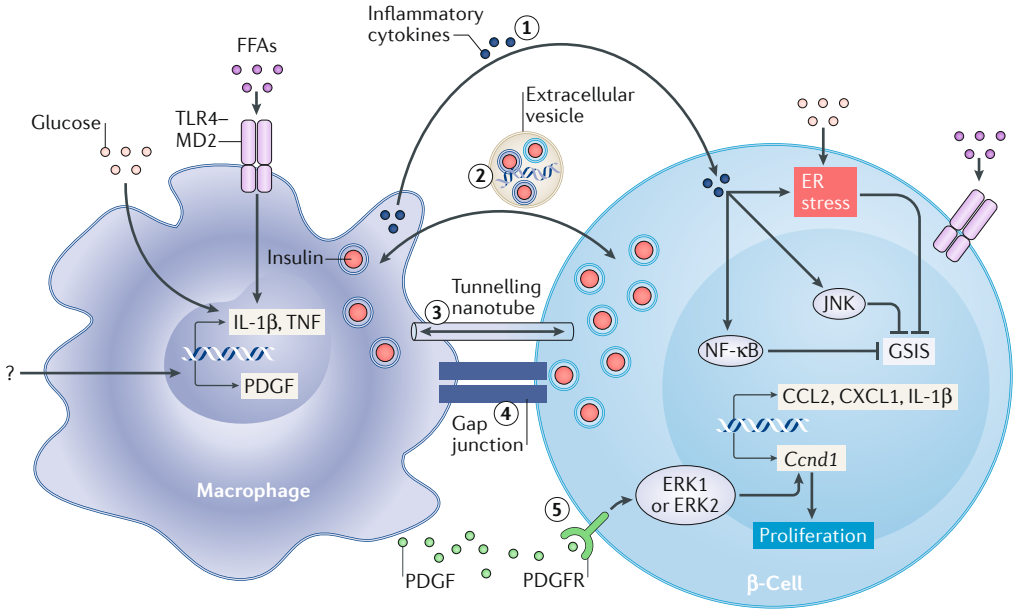

Fig. 2 | **Interactions of islet macrophages and β-cells in obesity.** An increasing body of evidence supports the idea that islet macrophages influence β-cells in multiple ways. In obesity, elevated plasma levels of glucose and free fatty acids (FFAs) can induce a pro-inflammatory phenotype of islet macrophages. As a result, macrophages produce increased amounts of pro-inflammatory cytokines such as IL-1β and tumour necrosis factor (TNF). These cytokines activate nuclear factor-κB (NF-κB) and JNK pathways in β-cells and also exacerbate endoplasmic reticulum (ER) stress (1)[67,68]. Synergistically, these responses dampen β-cell glucose-stimulated insulin secretion (GSIS). In addition to inflammatory cytokines, other mechanisms involving macrophage-mediated β-cell dysfunction exist. The mechanisms include extracellular vesicles containing insulin released by β-cells and phagocytosed by islet macrophages (2)[12]; and the formation of tunnelling nanotubes (3) or gap junctions (4) between macrophages and β-cells, allowing for bidirectional exchange of cellular contents. Obesity increases platelet-derived growth factor (PDGF) expression in islet macrophages via unclear mechanisms[12]. Through PDGF receptors (PDGFRs) expressed in β-cells, PDGF promotes β-cell proliferation by activating downstream extracellular signal-regulated kinase (ERK) signalling and inducing cell cycle gene (for example, *Ccnd1*) expression (5)[98]. MD2, myeloid differentiation factor 2; TLR4, Toll-like receptor 4.

By contrast, depletion of islet macrophages in vivo in a mouse model, or ex vivo in isolated pancreatic islets, by clodronate liposome treatment results in a decreased number of proliferating bromodeoxyuridine-positive β-cells[96].

Using a mouse model with 50% β-cell depletion, followed by β-cell-specific overexpression of connective tissue growth factor, researchers found that β-cells release connective tissue growth factor as a chemoattractant to recruit macrophages, which then facilitate the recovery of β-cell mass[97]. In another study, transiently increased expression of VEGFA in β-cells led to β-cell loss, and withdrawal of VEGFA stimulated a robust but transient increase in the proliferation of pre-existing β-cells[59]. Moreover, bone marrow-derived macrophages were recruited to the site of β-cell injury and are important for β-cell proliferation[59]. Taken together, these studies indicate that macrophages have a critical role in maintaining steady state β-cell mass and facilitate increased β-cell proliferation and mass in pathophysiological insulin-resistant states.

β-Cell proliferation in obesity. Obesity-induced insulin resistance induces an expansion of pancreatic β-cells, which compensate by secreting increased quantities of insulin. Islet macrophages from obese mice show an increased capacity to stimulate β-cell proliferation and both intra-islet and peri-islet macrophages show similar effects. This effect was mediated by platelet-derived growth factor (PDGF)–PDGF receptor (PDGFR) signalling[12]. Thus, the PDGF–PDGFR pathway has an important role in mouse and human β-cell proliferation[98]. Of note, one study suggests that the reduction of PDGFR signalling in β-cells accounts for the decline in β-cell replication in aged mice and older humans[98]. Macrophages are a major source of PDGF[99–102] and the expression of *Pdgfa* was increased in both $CD11c^+$ intra-islet macrophages and $CD11c^-$ peri-islet macrophages in obese mice[12]. Furthermore, inhibition of PDGFR signalling in vitro with a small-molecule inhibitor, CP-673451, blocked the effect of islet macrophages to stimulate β-cell replication[12]. Therefore, in addition to the expression of PDGFR on β-cells, the production of PDGF by islet macrophages forms a signalling system that induces β-cell proliferation (FIG. 2).

Proinflammatory cytokines. Proinflammatory cytokines, such as TNF and IL-1β, are key components of the islet inflammatory microenvironment[31], and the role of IL-1β has been extensively studied[103]. Knockout of β-cell IL-1R in vivo causes β-cell dedifferentiation[104]. In addition, low concentrations (0.01–0.02 ng/ml) of IL-1β can induce β-cell proliferation in vitro by activating the FAS–FLIP antiapoptotic pathway[105]. Moreover, lean

IL-1 receptor antagonist (IL-1Ra). A member of the IL-1 family of cytokines that binds to the IL-1 receptor but does not induce intracellular signalling.

mice that lack IL-1β production show downregulation of FAS–FLIP activation as well as decreased β-cell proliferation[105].

In contrast, at high concentrations (1 ng/ml), IL-1β can suppress the expression of genes associated with a fully differentiated β-cell phenotype in human and mouse islets[106]. This effect can facilitate β-cell apoptosis and can also induce β-cell dedifferentiation into islet endocrine cells, which express and secrete both insulin and glucagon[107]. These latter dual-positive endocrine cells[107] generally demonstrate impaired GSIS in vivo, which provides another potential mechanism whereby IL-1β adversely effects β-cell GSIS[106]. Given all of these findings, the IL-1β 'tone' within the islet provides an important control point for regulation of β-cell mass.

In humans, IL-1 receptor antagonist (IL-1Ra) expression is increased in the blood during obesity and T2DM but is decreased in islets from patients with T2DM[108,109]. In mice, β-cell-specific IL-1Ra ablation resulted in a reduction in β-cell proliferation and impaired insulin secretion[109]. In addition, decreased plasma levels of IL-1Ra promotes IL-1β signalling and studies have shown that treatment of Goto–Kakizaki rats with IL-1Ra led to a reduction in islet inflammation and improved β-cell GSIS. Taken together, these results provide compelling evidence for the role of the inflammatory cytokine IL-1β in islet inflammation and β-cell dysfunction.

Beneficial effects on β-cells

While depletion of islet macrophages improves GSIS in HFD-fed obese mice, macrophage depletion decreases β-cell GSIS in normal islets from lean chow-fed mice[12]. This finding suggests that, in the normal lean state, islet macrophages might have a beneficial role in β-cell insulin secretion. The mechanism (or mechanisms) by which islet macrophages from lean and obese mice have seemingly opposite roles in β-cell function remains unclear. In obesity, islet macrophages might be reprogrammed to impair β-cell GSIS, which could be due to effects of FFAs, glucose or cytokines, such as IL-1β.

One possible explanation for the metabolism-dependent effects of islet macrophages is the level of IL-1β that they produce. For example, islet macrophages in nonobese mice exhibit a pro-inflammatory activation state and produce IL-1β[17]. However, the acute postprandial rise in IL-1β production by myeloid cells has been demonstrated to contribute to meal-induced insulin secretion in a fasting–refeeding mouse model and is necessary for normal glycaemic control[110]. In line with this, IL-1R1-deficient mice exhibited an impaired adaptive increase in plasma insulin levels after HFD feeding[111]. However, chronic accumulation or elevated production of IL-1β (mainly by islet macrophages) is detrimental to β-cell GSIS[103].

In addition to IL-1β, other factors and mechanisms could also have a role in shifting the effect of islet macrophages on β-cells. For instance, pathways related to synapse formation were more activated in islet macrophages in obese mice than in lean mice[12], suggesting that obesity alters cell–cell interaction between macrophages and β-cells.

The above discussion raises several questions. First, what induces islet macrophages to change their effects on β-cell GSIS in the transition from the lean to the obese state? Second, at which stage of obesity does this functional switch of islet macrophages happen? Third, what modifications can reverse the macrophage-mediated 'detrimental' effects on β-cells? To answer these questions, it will be necessary to perform longitudinal studies that can elucidate the functional properties of islet macrophages and assess the effects of these cells on β-cell function in a stage-dependent manner.

Lipids as mediators of crosstalk

Several studies have indicated that SFAs and potentially lipoproteins are circulating factors that might contribute to islet inflammation, β-cell dysfunction and β-cell hyperplasia[10,44,45]. For example, experimental elevation of palmitate levels in mice induces islet inflammation[10]. Moreover, the same study showed that in vivo treatment with SFAs increased the accumulation of islet macrophages and other markers of islet inflammation and also decreased GSIS.

SFAs activate intracellular pro-inflammatory pathways by binding to the innate immune receptor Toll-like receptor 4 (TLR4). Studies show that TLR4 is required for the SFA-induced effect on islet inflammation and further show that TLR4 expressed on islet macrophages was essential for this process[10]. The SFAs act on macrophage TLR4 to stimulate the NF-κB pathway, resulting in cytokine secretion, particularly of IL-1β and TNF, which can negatively influence β-cell GSIS[10]. TLR4 is also expressed on β-cells, and SFAs can bind to this receptor and induce β-cells to secrete chemokines and other factors, which stimulate islet macrophage accumulation[10].

In addition to these effects of SFAs on β-cell secretory functions, elevated SFA levels can also affect β-cell proliferation[10]. This effect is particularly true when elevated SFA levels are combined with hyperglycaemia, as this combination appears to cause additive effects on β-cell proliferation. Of note, apoptosis negatively regulates overall β-cell mass and, within the islet, SFAs can be converted to ceramides, which induce apoptosis[112,113]. Furthermore, exposure to palmitate is reported to trigger human β-cell apoptosis by inducing death protein 5-mediated ER stress[114]. Thus, by inducing apoptosis and stimulating proliferation, SFAs might have important effects on increasing overall β-cell mass in the context of obesity and T2DM.

Another interesting connection between circulating lipoproteins and β-cell function has been reported. LDL receptor-related protein 1 (LRP1) can interact with extracellular lipoproteins, and one research group generated β-cell-specific LRP1-deficient mice and showed that these animals were partially protected from the adverse effects of a HFD on β-cell insulin secretion, as well as HFD-induced β-cell hyperplasia[45]. The same study also found that this could be related to the effect of LRP1 deletion to upregulate β-cell peroxisome proliferator-activated receptor-γ2 (PPARγ2) in HFD-fed mice, as transgenic overexpression of PPARγ2 in β-cells partially recapitulated the LRP1 phenotype.

Senescence

Cellular senescence is characterized by stable cell cycle arrest and a pro-inflammatory senescence-associated secretory phenotype[115]. The current theory is that the senescent signal can spread from one senescent cell to other surrounding cells; however, the mechanism remains to be resolved. Some indications suggest that individuals with T1DM and the nonobese diabetic (NOD) mouse model harbour a set of senescent β-cells that express increased levels of the prosurvival mediator BCL-2 (REF.[116]). Interestingly, treatment with a BCL-2 inhibitor can efficiently deplete senescent β-cells and prevent the occurrence of T1DM in the NOD mouse model[116].

Obesity could potentially induce a β-cell senescence response, which might drive the pathogenesis of T2DM. For example, an earlier study found that the number of acidic β-galactosidase-positive senescent β-cells was increased in HFD-fed mice[117]. More recently, a 2017 study found that insulin resistance can induce a senescent state in both mouse and human β-cells, which leads to decreased insulin secretion[118]. Consistent with this idea, the number of senescent β-cells is increased in islets from patients with T2DM[118]. However, it remains unknown whether islet macrophages also develop senescent phenotypes in the context of obesity or whether senescent β-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 TNF inhibitors[119,120]. In some clinical trials, the effects of these interventions on β-cells have been assessed. For example, in one double-blind, parallel group trial involving 70 patients with T2DM, the administration of the recombinant IL-1Ra anakinra confers a moderate but statistically significant decrease in fasting blood glucose and HbA_{1c} (−0.3 to −0.4%) levels[121]. Furthermore, anakinra treatment increases insulin secretion from β-cells without affecting insulin sensitivity. The larger scale CANTOS trial included individuals with prior myocardial infarction and high-sensitivity C-reactive protein and used an anti-IL-1β antibody (canakinumab)[122]. They demonstrated that IL-1β neutralization lowers plasma HbA_{1c} levels during the first 6–9 months of treatment but does not reduce the incidence of new-onset diabetes mellitus[122]. As canakinumab treatment substantially reduces the recurrence of cardiovascular events, these results suggest that anti-inflammatory therapy can provide beneficial effects for individuals with obesity and/or T2DM. A meta-analysis performed in 2019 of 2,921 individuals from eight phase I–IV studies found a statistically significant overall HbA_{1c}-lowering effect of IL-1 antagonism, achieved through either anti-IL-1 antibodies or IL-1R antagonists[123]. In this meta-analysis, a statistically significant correlation between baseline C-reactive protein and C-peptide, and HbA_{1c} outcomes was also revealed. However, the authors also cautioned that the identification of further biomarkers is needed to define the potential of anti-IL-1 therapies in T2DM.

Conclusions

Islet inflammation has emerged as a key feature of obesity and T2DM; in these conditions islet macrophages are the defining immune cell type. Although much has been learned about macrophage–β-cell interactions, many important questions remain unresolved. For example, the triggering events with respect to islet macrophage proliferation and expansion are unclear. Moreover, it is not clear whether the initiating signals are derived from the β-cell or whether they are extrinsic to the islet. Of note, islet macrophage proliferation is not significantly increased in mice until after 12–16 weeks of an HFD[12]. If β-cell insulin secretory function is affected prior to this time, then what is the cause? Have macrophages already started to reprogramme into a pathogenic phenotype before proliferation ensues or does a macrophage-independent mechanism cause the initial defect in GSIS? In addition, it is not currently clear why 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 that characterize human T2DM.

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