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Innate immune priming of insulin secretion

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Increasing evidence suggests a role for the immune system to finely tune metabolic homeostasis. The possibility that the immune system can likewise regulate islet endocrine function has only commenced drawing attention. Islet beta cells are the main producers of insulin and have to dynamically respond to fluctuating insulin demands of the body. While inflammation has long been considered as an important pathogenic feature of diabetes development, pioneer studies have shown that immune cells reside inside pancreatic islets under steady state and that components of the immune system can promote beta cell insulin production. The present review will thus highlight the recent research on specific immune pathways regulating beta cell function discussing the beneficial influence of innate immune cells.

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Introduction

Distributed within the exocrine pancreas, the islets of Langherans are micro-organs that are essential for glucose homeostasis. Among various cell types, β cells are the major cellular component of islets. In response to glucose, they produce, within seconds, the amount of insulin required for optimal energy supply to the insulin-sensitive tissues. Throughout lifespan, β cells have to dynamically respond to fluctuating insulin demands of the body, from daily needs after food intake to complex physiological processes. For instance, conditions including weaning, obesity and pregnancy all require an increase in insulin production, whether it is temporary or chronic. In those cases, islet adaptation to meet insulin needs is mediated by enhanced β cell secretory function and/or expansion of the β cell mass by proliferation of existing β cells or neogenesis [1]. These β cell abilities to adapt are crucial. Failure to do so is associated with a high risk of developing type 2 diabetes (T2D), the disease of insufficient insulin secretion.

It has now been acknowledged for decades that the immune system is involved in the regulation of metabolism, a function not related to classical immune responses of defense. Extensive studies showed that the nature of immune cells residing within the adipose tissue and the liver greatly influences their functions [2,3]. The possibility that the immune system can likewise regulate islet endocrine function and β cell adaptation has only commenced drawing attention. Immune cells reside inside mouse islets ranging from two to ten per islet under steady state [4,5,6••,7••]. Interestingly, mouse strains that strongly differ in their immune cell repertoires also show differences in β cell function, implying a connection between the immune and endocrine systems [7••]. In the context of T2D, the number of intra-islet macrophages is increased and associated with local inflammation and β cell dysfunction in obese rodents and patients compared to controls [4,5,8,9]. Accordingly, anti-inflammatory drugs are currently under development for the treatment of T2D [10]. However, components of the immune system, localized within islets or not, may also play a physiological role and support islet homeostasis. This concept illustrates a novel and growing field of research. The present review will thus explore the immune pathways regulating β cell insulin production focusing on the beneficial influence of innate immune cells.

Macrophages and β cells, a close relationship

Macrophages populate healthy mouse islets since the perinatal stages and represent more than 80% of total intra-islet immune cells, depending of the mouse strains [6••,7••,11]. Most importantly, macrophage deficiency clearly impairs the establishment of a functional β cell mass during early life development [11,12]. Islet-resident macrophages originate from definitive hematopoiesis, strongly depend on Colony Stimulatory Factor (CSF)-1 and are self-maintained by in situ local proliferation [6••,13]. More than thirty years after their discovery, the phenotype of these cells remains unclear, as they do not recapitulate the classical M1/M2 macrophage pattern well established in other tissues [14]. Macrophages of healthy islets constitutively express M1-like markers including Cluster of differentiation (CD)11c and Class II histocompatibility molecules (MHCII) while expressing high levels of Interleukin(Il)-1β, Tumor necrosis factor(Tnf)-α and the transcription factor Interferon Regulatory Factor (Irf)5 [6••,7••,15]. Plus, islet macrophages do not express M2-like markers such as

the mannose receptor CD206, in comparison to the neighboring stromal macrophages of the exocrine pancreas [6••]. Islet-resident macrophages thus adopt a M1-like activated phenotype at steady state, in opposition to adipose tissue wherein the M1 polarization is triggered by metabolic stress such as obesity [3,16]. In that way, the phenotype of islet macrophages resembles barrier macrophages as characterized in the lung and the gastro-intestinal tract [17•], questioning their physiological role in β cell function. in situ imaging of mouse islets showed that macrophages are in close contact with both β cells and blood vessels. Thanks to their long filopodia, resident macrophages can dynamically probe whole islet area, including the vessel lumen [18•]. Considering that islets are highly vascularized micro-organs [19], resident macrophages may get activated by sensing blood-borne products [17•], for instance during the postprandial period [20••]. In parallel, macrophages monitor β cell secretory activity by detecting endogenous levels of ATP via their purinergic receptors [21•]. ATP is co-released with insulin in response to glucose and may trigger important physiological processes in islet macrophages. The ways that islet macrophages then feed back to the β cell are still under investigation but local production of cytokines may be involved.

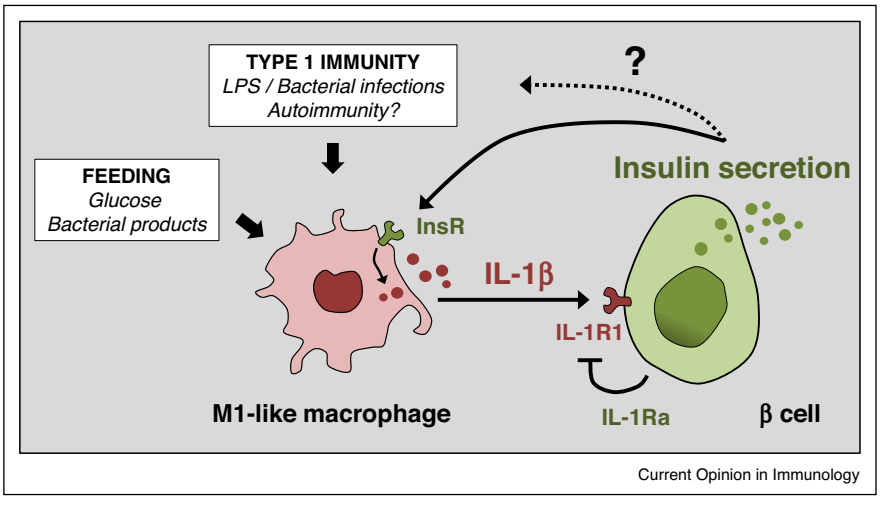
IL-1β potentiates insulin secretion

It has long been recognized that acute but not chronic exposure of islets to IL-1β promotes insulin secretion in mouse and human islets [22,23]. The underlying mechanisms are still unclear but may involve increased exocytosis subsequent to enhanced insulin granule docking at the plasma membrane [23]. Interestingly, this effect is lost in islets isolated from T2D donor, suggesting that IL-1β does not act as an insulinotropic agent in a pathological context [23]. β cells have the highest expression of the signaling IL-1 receptor 1 (IL-1R1) of any other tissues, pointing to a physiological role of IL-1β in islet function [24,25]. Using transgenic mouse models, two recent studies confirmed this hypothesis. Specific deletion of IL-1R1 on β cells impaired whole-body glucose tolerance via the reduction of glucose-stimulated insulin secretion in male mice [26••]. Furthermore, Dror *et al.* found that feeding induces a physiological rise in circulating IL-1β that potentiates postprandial insulin secretion in mice [20••]. In this context, macrophages from the peritoneal cavity produce IL-1β in response to bacterial products and glucose metabolism, acting back on the β cells [20••]. As macrophages are likely to be the main source of IL-1β inside islets, it is not ruled out that islet-resident macrophages may also produce local IL-1β during this postprandial window. In healthy humans, the IL-1β-dependent chemokine IL-8 (also known as chemokine C-X-C motif ligand 1) is positively correlated with insulin secretion during an oral glucose tolerance tests [27]. Thus, IL-1β appears to play a critical role in potentiating insulin secretion at physiological doses as illustrated in Figure 1. Of note, islets express all members of the IL-1 regulatory system, highlighting the needs for subtle control of IL-1β signaling. As such, deletion of the IL-1R antagonist IL-1Ra in β cells disrupts β cell function and proliferation [28].

Macrophages at the rescue of β cells

Beyond their ability to control the secretory function of β cells, macrophages may also contribute to the

Figure 1



IL-1β-driven priming of immune secretion.
Upon feeding, glucose and bacterial products trigger IL-1β release from macrophages. IL-1β then signals to the β cells via the IL-1R1 to potentiate insulin secretion. This process may also occur during type 1 immune responses such as bacterial infections and autoimmune diseases, characterized by high levels of IL-1β production. IL-1β signaling is tightly controlled by endogenous β cell IL-1Ra production. In turn, insulin may feed back to the macrophages via the Insulin receptor (InsR) to boost M1-like macrophage activation and IL-1β release.

maintenance of the β cell mass. This property was first demonstrated in different models of acute β cell injury, eliciting a robust proliferative response in surviving β cells. Intriguingly, β cell replication was concomitant with macrophage accumulation around or inside islets [29–33]. Using a conditional β cell ablation model, Nir *et al.* were the first to show that β cell regeneration was prevented by immunosuppressant treatment [29]. In models of pancreatic duct ligation and diphtheria toxin receptor–mediated β cell ablation, loss-of-function experiments showed that M2-like macrophages licensed β cell proliferation [30,31,33]. In this context, recruited macrophages produced Transforming Growth Factor (TGF)-β and Epidermal Growth Factor (EGF) that together promoted β cell proliferation [30]. In a model of inducible Vascular Endothelial Growth Factor (VEGF)-A overexpression in β-cells, massive endothelial cell expansion leads to β cell loss, which was reversed upon VEGF-A withdrawal and β cell replication. Therein, M2-like macrophages accumulated from the bone marrow inside islets and blocking their recruitment by partial bone marrow ablation significantly reduced β cell response [32]. Thus, β cell regeneration following cell injury and death may be dependent on myeloid recruitment and polarization into M2-like macrophages. Questions remain regarding the distinct role of islet-resident, interacinar stromal and recruited monocyte-derived macrophages in these acute conditions and whether it would hold true in physiological stress conditions. Interestingly, in the case of mouse high fat diet feeding, a peak of β cell proliferation is observed and associated with intra-islet macrophage accumulation during the first week of regimen compared to controls [34,35•]. Although the macrophage phenotype remains unknown, macrophage depletion alters the rapid adaptive response of β cell to dietary cues [35•]. These pioneer studies overall suggest that islet-associated macrophages may license β cell recovery and adaptation to stress conditions, ensuring an adequate insulin production as shown in Figure 1. The mechanisms by which macrophages promote β cell replication are still unclear, but may involved TGF-β and EGF [30]. The mitogenic Insulin-like growth factor (IGF)-2 may also be a candidate as it was found produced by macrophages during the perinatal development of the pancreas [12].

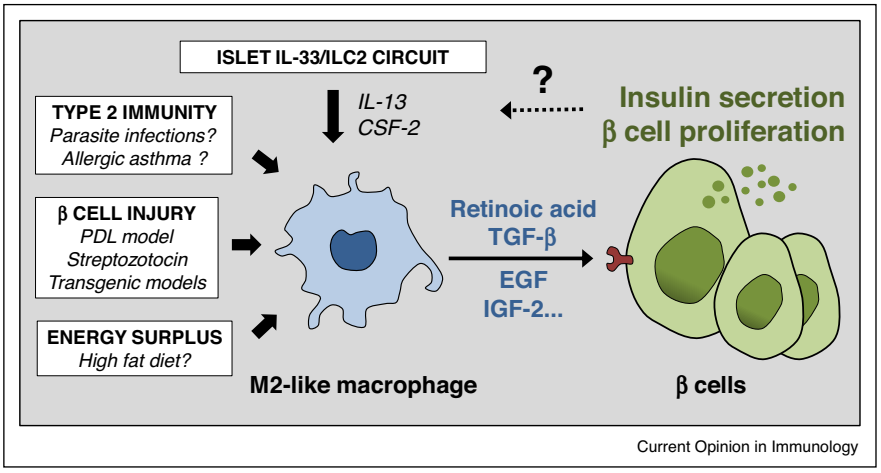
IL-33 orchestrates an insulinotropic immune crosstalk

Beside macrophages, pancreatic islets contain other cells from specific branches of innate immunity. Discrepancies concerning the nature and the quantification of these cells exist in the literature due to variability in mouse strains and methods used to isolate islets, from one or pooled mice. It may affect immune-cell purity, frequency and surface marker expression. Although low in numbers, dendritic cells, natural killer cells and group 2 innate lymphoid cells (ILC2) were detected in islets isolated from C57BL/6 and BALB/c mice, with a higher frequency in the type 2 immunity-skewed BALB/c background [7••]. Balb/c islets also showed increased expression of the IL-1 family member IL-33, a potent activator of ILC2, in islet mesenchymal cells [36]. Importantly, both the presence of intra-islet ILC2 and IL-33 expression correlated with an optimal β cell function in different mouse models. Besides, IL-33 expression was increased in response to acute metabolic cues and streptozotocin-induced β cell injury, proposing IL-33 as a new islet stress signal. Conversely, IL-33-deficient mice showed impaired glucose-induced insulin secretion. When activated by IL-33, islet-resident ILC2 engaged in a complex immunometabolic crosstalk with neighboring M2-like macrophages and dendritic cells via their secretion of IL-13 and CSF-2. In turn, islet myeloid cells acquire retinoic acid-producing capacities and the retinoic acid signals to the β cells to promote insulin secretion [7••]. Thus, the IL-33/ILC2 axis may be a physiological pathway to preserve or restore islet secretory function in the context of metabolic stress. Considering macrophage-induced β cell proliferation, activation of the IL-33/ILC2 pathway may also lead to increased β cell mass over a longer timeframe. Indeed, ILC2 are recognized to be rare yet potent resident cells that mediate tissue protection and repair processes [37]. Further studies are required to fully explore their properties inside the islet microenvironment. Interestingly, this IL-33/ILC2 immune loop is lost in islets during chronic obesity, which may set the stage for T2D development [7••]. Thus, β cells and resident immune cells have jointly developed protective and regenerative mechanisms to face recurring metabolic stress as illustrated in Figure 2. The IL-33/ILC2 circuit is part of them, but many more are to be discovered.

Complement, a surprising guest in insulin regulation

As part of innate immunity, the complement system has multiple roles in homeostasis, including in the physiology of pancreatic islets. Mouse and human islets express high levels of C3a receptor [38,39]. The molecule C3a, from the alternative complement pathway, was shown to promote insulin secretion in mouse and human β cells via increased levels of ATP and calcium [38,39]. Conversely, mice deficient for adipsin, the complement factor D responsible for the generation of C3a, had impaired glucose tolerance and decreased insulin secretion when fed a high fat diet [38]. In healthy subjects, plasma complement C3a concentrations were positively associated with insulin secretion during an oral glucose tolerance test, independently of adiposity measures [40]. In contrast, T2D patients with β cell failure have decreased adipsin levels in their adipose tissues and in the circulation [38]. Interestingly, macrophages have been reported to synthesize a wide variety of complement components [41]. The possibility that islet macrophages influence β cell insulin production via the local secretion of

Figure 2



Type 2 immune priming of immune secretion.
The IL-33/ILC2 circuit polarizes islet-resident myeloid cells to produce retinoic acid in an IL-13 and CSF-2 dependent manner. In turn, retinoic acid signals to the β cells and stimulates insulin secretion. This activation pathway may occur during type 2 immune responses such as parasitoses and allergic asthma. In parallel, β cell injury and nutritional stress are associated with accumulation of M2-like macrophages inside islets. These macrophages may produce TGF-β, EGF, IGF-2 and yet unknown factors to promote proliferation of surviving β cells, overall increasing insulin production. The impact of elevated insulin production on these type 2 immune responses is currently unknown.

complements factors, including C3a, is to be examined. Endocrine cells also express complement proteins such as CD59, a membrane bound complement inhibitor. As well as protecting cells from complement activation, CD59 has specific intracellular functions in β cells. Namely, CD59 is required for glucose-dependent, depolarization-evoked, insulin secretion [42]. Further mechanistic studies are required to decipher the role of the complement system, as an immune compartment *per se* or endogenously expressed by β cells, in the regulation of insulin production.

Insulin secretion in the immunological context

While the frontier between metabolism and immunity starts to blur, one can wonder about the actual impact of increased insulin secretion in the context of a specific immune response. Should these metabolic outcomes only be considered as side effects during immune activation? During type 1 immune responses, elevated insulin production may contribute to the activation of immune effector cells. For instance, lipopolysaccharide (LPS) injection, an experimental surrogate for sepsis, increases insulin secretion in an IL-1β-dependent manner [20••,23]. Glucose is the primary fuel for the immune system and most of immune cells express the insulin receptor. Dror *et al.* showed that insulin upregulated glucose uptake, the inflammasome NLRP3 activation and IL-1β secretion in M1-like macrophages [20••]. IL-1β-induced insulin secretion may thus mediate the required metabolic adaptations in immune cells for a proper immune defense. This ability may be favorable during bacterial infections but deleterious in an autoimmune context. Conversely, IL-33/ILC2-induced insulin production may directly modulate type 2 immune diseases, such as parasitic infections and allergic asthma. For blood-stage parasites, increased insulin levels may signal to the parasite and directly impact its growth and survival. In contrast, insulin-mediated glucose lowering effects may help starving blood-stage parasites, such as malaria parasite that relies on host nutrient availability for its replication and virulence [43]. In bronchial disorders, it is acknowledged that insulin has adverse effects on lung structure and airway smooth muscle cell hyper-responsiveness, promoting asthma attacks [44]. Long ago, hyperinsulinemia and nocturnal hypoglycemic episodes have been described in asthmatic patients [45]. These observations overall suggest that innate immune priming of insulin secretion may alleviate or worsen the pathological conditions at stake. Further studies should determine whether parasitic infections and allergic sensitivity are associated with increased insulin secretion in an IL-33/ILC2-dependent manner.

Conclusions

Mounting evidence indicates that components of the innate immune system contribute to the regulation of islet β cell function and mass, that is the level of insulin production. Notably, the IL-1 family appears to be the most important chaperone of β cell activities. On one hand, IL-1β-driven type 1 immunity potentiates insulin secretion. On the other hand, IL-33/ILC2-mediated type 2 immune responses promote β cell adaptation to metabolic stress and cell injury. These immunometabolic properties represent a growing field of interest with

innovative therapeutic potential. Indeed, while inflammation has long been considered as a pathogenic trait of diabetes, it is relevant to wonder whether a fine-tuning of the immune responsiveness, rather than shutting it off with anti-inflammatory treatments, may be an interesting approach to preserve insulin production. However, further studies are warranted to fully understand the role of islet-resident versus peripheral innate immune cells in insulin secretion priming. A lot is still to be learnt about intra-islet macrophages that may have essential monitoring functions. Other immune compartment may also be involved including the pancreatic lymph nodes as recently reported in the context of autoimmune diabetes [46]. Finally, the physiological aim of modulating insulin secretion during specific immune responses needs to be investigated.

Conflict of interest statement

Nothing declared.

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