Islet Inflammation Impairs the Pancreatic β-Cell in Type 2 Diabetes

Onset of Type 2 diabetes occurs when the pancreatic β-cell fails to adapt to the increased insulin demand caused by insulin resistance. Morphological and therapeutic intervention studies have uncovered an inflammatory process in islets of patients with Type 2 diabetes characterized by the presence of cytokines, immune cells, β-cell apoptosis, amyloid deposits, and fibrosis. This insulin is due to a pathological activation of the innate immune system by metabolic stress and governed by IL-1 signaling. We propose that this insults contributes to the decrease in β-cell mass and the impaired insulin secretion observed in patients with Type 2 diabetes.

Evidence for an Islet Inflammatory Process in β-Cell Failure During Type 2 Diabetes

In 1967 it was first proposed that Type 2 diabetes is not solely due to insulin resistance but also to a failure of the insulin producing β-cell to secrete an adequate amount of insulin (5). Based on numerous investigations, it is now evident that impaired insulin secretion is not only an important etiological factor in the pathogenesis of the disease but also the driving force dictating the dynamics of the disease. Indeed, although insulin resistance is present in all stages from pre-diabetes to overt diabetes, it remains constant in a single individual as long as his or her body weight remains unchanged. In contrast, the onset of diabetes and its progression is largely determined by the progressive failure of the pancreatic islet. At a pre-diabetic stage, insulin production will increase to adapt to the enhanced demand. When this adaptation fails, diabetes occurs. This failure then continues to progress, and affected individuals will require increasing antidiabetic treatment, until eventually all Type 2 diabetes requires exogenous insulin to control their hyperglycemia. In an attempt to understand the underlying cause of this progressive failure, several mechanisms have been described. It appears that in all instances they constitute various components of an inflammatory process. The first evidence for an inflammatory process in the pancreatic islet arose from the observation that hyperglycemia induces β-cell apoptosis (14).

By unravelling the underlying mechanism, it turned out that high glucose concentrations induce the Fox receptor, which in turn upregulates via glucose-induced IL-1β production (41, 43, 44). Similarly, recent evidence shows that fatty acids also promote an inflammatory response (Refs. 1, 21; and see below). More downstream, ER stress and oxidative stress also appear linked to inflammatory events. In support of
insults in Type 2 diabetes, elevated numbers of immune cells have been detected in islets of patients with Type 2 diabetes in conjunction with increased levels of cytokines and chemokines (2, 21, 53). Of note, every animal model of Type 2 diabetes investigated to date displays islet immune cell infiltration (19, 21). Furthermore, a strong argument for the occurrence of an inflammatory process in islets is the well-described fibrosis observed in tissue sections of patients with Type 2 diabetes, characterized by amyloid deposits. Indeed, fibrosis is a hallmark of the end stage of a chronic inflammatory process. Although the concept of insulin is recent in Type 2 diabetes, it is well established in Type 1 diabetes and was considered as pathognomonic. Although the precise aetiology of the insulins in both diabetes types remains to be fully understood, differences certainly exist; for example, Type 1 diabetes is a more autoimmune-mediated process. However, a common final effector pathway seems to be activated in both types of diabetes (17). Keeping in mind that metabolic stress is a more recent threat than viruses or other possible causes of Type 1 diabetes, it is not surprising that islets respond with similar mechanisms developed over their long period of evolution. Of interest is the predominance of IL-1β, which is upregulated in islets of patients with both Type 1 and Type 2 diabetes (2, 43, 45). This master cytokine regulates numerous cytokines and also chemokines (Refs. 12, 20; and see below). Thereby, it contributes to the recruitment of immune cells implementing a broad inflammatory response. Of note is that IL-1β will also induce itself in β-cells, engendering a vicious cycle (Ref. 2, and see below). Thus insults may be considered as an integral component of the pathology observed in Type 2 diabetes, and its dependence on IL-1 supports the concept of an auto-inflammatory nature of the disease.

Regulation of IL-1β Expression by Nutrients in Human Islets

Elevation of circulating nutrients such as glucose and free fatty acids (FFAs) induce an inflammatory process within numerous tissues in the body (32, 68). The first demonstration that a high glucose concentration indeed induces IL-1β release was obtained with human islets (43), with similar observations following in rat islets (24), retinal cells (70), and human monocytes (8). Moderately elevated glucose concentrations (11 mM) were sufficient to induce transcriptional activation of IL-1β expression in human islets (2).

More recently, we also found that long-chain FFAs induce several cyto- and chemokines in human and rodent islets (1). Oleate, palmitate and stearate, which are the most abundant FFAs in human nutrition, and hence in the circulation, stimulate IL-1β expression when added individually or as mixtures. Similarly, FFAs induced the IL-1-dependent cyto- and chemokines IL-6 and IL-8 in human islets and CCL2 (also known as chemokine KC) in mouse islets. These stimulatory effects of FFAs on pro-inflammatory mediators are not restricted to islet cells but were also observed in numerous other cell types such as muscle (57), macrophage, and adipocyte cell lines (47, 58, 60), and in coronary artery endothelial cells (62). The combination of FFAs with elevated glucose concentrations further increases IL-1β expression (1) and the release of various cytokine and chemokines (21).

But how do these distinct and “nonspecific” nutrients lead to elevation? IL-1β and IL-1-regulated cyto- and chemokines in islets? Some insight was obtained when we examined specific agonists of receptors of the innate immune system, specifically the IL-1/Toll-like receptor (TLR) family (1). Their stimulation typically leads to activation of pro-inflammatory processes in response to microbial pathogens and cell stressors (49). In human islets, specific TLR2 and TLR4 agonists induce IL-1β, however, the strongest inducer of IL-1β expression is IL-1β itself, which increases its own expression by an auto-stimulatory mechanism. IL-1β auto-stimulation was particularly pronounced in purified β-cells compared with whole islets, which consist of different cell types (2). Furthermore, it was NF-κB dependent and could be interrupted by blocking the IL-1 receptor with the specific IL-1 receptor antagonist (IL-1Ra) (9), thereby neutralizing the receptor ligand or by deleting the intracellular receptor docking protein required for signal transduction (Myd88). Using these tools, we could demonstrate that both elevated glucose concentrations and FFAs increase IL-1β expression by promoting IL-1β auto-stimulation via IL-1 receptor activation. Thus IL-1β auto-stimulation via its receptor plays a pivotal role in the upregulation of intra-islet IL-1β expression provoked by nutrients. Noteworthy, we observed the highest levels of IL-1 receptor 1 expression in mouse islets and in an insulin-secreting β-cell line compared with 22 other rodent tissues (1). These data suggest that the pancreatic β-cell may be exquisitely sensitive to changes in local IL-1β concentration due to its high number of IL-1 receptors (1, 55).

Although these findings are compatible with a role for the IL-1 system as an amplifier of pro-inflammatory stimuli in islets, it leaves us with the question of how glucose or FFAs trigger and maintain this process. This is currently an open question, particularly for glucose, whereas for FFAs several mechanisms were postulated. It has been hypothesized that FFAs stimulate pro-inflammatory factors via direct activation of the lipid-sensing TLR2 and TLR4 in various cell types (39). Results with islets from TLR KO mice indeed show that both elevated glucose concentrations and FFAs induce IL-1β auto-stimulation (Myd88). Using these tools, we could demonstrate that both elevated glucose concentrations and FFAs increase IL-1β expression by promoting IL-1β auto-stimulation via IL-1 receptor activation. Thus IL-1β auto-stimulation via its receptor plays a pivotal role in the upregulation of intra-islet IL-1β expression provoked by nutrients. Noteworthy, we observed the highest levels of IL-1 receptor 1 expression in mouse islets and in an insulin-secreting β-cell line compared with 22 other rodent tissues (1). These data suggest that the pancreatic β-cell may be exquisitely sensitive to changes in local IL-1β concentration due to its high number of IL-1 receptors (1, 55).

Although these findings are compatible with a role for the IL-1 system as an amplifier of pro-inflammatory stimuli in islets, it leaves us with the question of how glucose or FFAs trigger and maintain this process. This is currently an open question, particularly for glucose, whereas for FFAs several mechanisms were postulated. It has been hypothesized that FFAs stimulate pro-inflammatory factors via direct activation of the lipid-sensing TLR2 and TLR4 in various cell types (39). Results with islets from TLR KO mice indeed show that FFA-induced pro-inflammatory factors are partly TLR dependent. Human islets express functional TLR2 and 4 (1, 64), and their activation results in increased expression of IL-1β and various cyto- and chemokines. Again, the TLR2/4 response is further amplified by IL-1β, which will itself induce IL-1β expression in human islets (2).

Intriguingly, it appears that rodent-derived endotoxin (4, 7) or elevated glucose concentrations (47, 58, 60), and in coronary artery endothelial cells (62). The combination of FFAs with elevated glucose concentrations further increases IL-1β expression (1) and the release of various cytokines and chemokines (21). But how do these distinct and “nonspecific” nutrients lead to elevation? IL-1β and IL-1-regulated cyto- and chemokines in islets? Some insight was obtained when we examined specific agonists of receptors of the innate immune system, specifically the IL-1/Toll-like receptor (TLR) family (1). Their stimulation typically leads to activation of pro-inflammatory processes in response to microbial pathogens and cell stressors (49). In human islets, specific TLR2 and TLR4 agonists induce IL-1β, however, the strongest inducer of IL-1β expression is IL-1β itself, which increases its own expression by an auto-stimulatory mechanism. IL-1β auto-stimulation was particularly pronounced in purified β-cells compared with whole islets, which consist of different cell types (2). Furthermore, it was NF-κB dependent and could be interrupted by blocking the IL-1 receptor with the specific IL-1 receptor antagonist (IL-1Ra) (9), thereby neutralizing the receptor ligand or by deleting the intracellular receptor docking protein required for signal transduction (Myd88). Using these tools, we could demonstrate that both elevated glucose concentrations and FFAs increase IL-1β expression by promoting IL-1β auto-stimulation via IL-1 receptor activation. Thus IL-1β auto-stimulation via its receptor plays a pivotal role in the upregulation of intra-islet IL-1β expression provoked by nutrients. Noteworthy, we observed the highest levels of IL-1 receptor 1 expression in mouse islets and in an insulin-secreting β-cell line compared with 22 other rodent tissues (1). These data suggest that the pancreatic β-cell may be exquisitely sensitive to changes in local IL-1β concentration due to its high number of IL-1 receptors (1, 55).

Although these findings are compatible with a role for the IL-1 system as an amplifier of pro-inflammatory stimuli in islets, it leaves us with the question of how glucose or FFAs trigger and maintain this process. This is currently an open question, particularly for glucose, whereas for FFAs several mechanisms were postulated. It has been hypothesized that FFAs stimulate pro-inflammatory factors via direct activation of the lipid-sensing TLR2 and TLR4 in various cell types (39). Results with islets from TLR KO mice indeed show that FFA-induced pro-inflammatory factors are partly TLR dependent. Human islets express functional TLR2 and 4 (1, 64), and their activation results in increased expression of IL-1β and various cyto- and chemokines. Again, the TLR2/4 response is further amplified by IL-1β, which will itself induce IL-1β expression in human islets (2)
amplified by IL-1β auto-stimulation. Thus the IL-1 system in islets not only amplifies the response to circulating nutrients but also to specific TLR agonists. Importantly, it was observed that obese subjects and rodents display elevated levels of circulating gut flora-derived endotoxins that could potentially trigger TLRs (4, 7), or alternatively, inflammatory factors derived from other organs could stimulate TLRs in islets. To this end, it was recently shown that serum amyloid A binds to TLR2 (6), which is prominently expressed on purified human and rodent β-cells (1). Elaborated, unpublished data, and Ref. 1). Alternative to TLR stimulation, FFA metabolism by neutralizing IL-1Ra (9), thus activating the potent IL-1 receptor. Overall, we conclude that elevated concentrations and position and concentrations of the ambient nutrients, depending on duration of the exposure and the composition and concentrations of the ambient nutrients, sufficient amounts of IL-1β may be triggered to overcome the protective effect of the naturally occurring IL-1Ra (9), thus activating the potent IL-1 receptor. This auto-stimulation engenders a vicious cycle precipitating a broad inflammatory process, as detailed in the next section (see also Figure 1).

**IL-1 is a Master Regulator of Tissue and Islet Inflammation in Type 2 Diabetes**

It has been known for a long time that obesity and Type 2 diabetes are associated with chronic activation of the innate immune system (50). Indeed, this activation appears to be systemic, given the increased levels of circulating cytokines and chemokines correlating with the disease and their potential in predicting Type 2 diabetes onset (30, 61). Local tissue inflammation is increasingly recognized in the pathology of both obesity-associated insulin resistance and increasing islet failure in insulin-producing cells (J. Ehses, unpublished data, 2009). Continuous or prolonged stimulation with nutrients (metabolic stress) will lead to the activation of the IL-1 system in islets by metabolic stress.

**Figure 1. Regulation of IL-1β in islets by metabolic stress**

Elevated glucose and FFA initially initiate the expression and release of low levels of IL-1β (stimulation) required for the adaptive response of islet cells. Continuous or prolonged stimulation with nutrients (metabolic stress) will lead to the activation of the IL-1β leading to a further increase of IL-1β by an autostimulatory process and to the production of IL-1β-dependent cytokine and chemokine production, attraction of macrophages, apoptosis and amyloidosis, fibrosis, and impaired insulin secretion (precipitation).

**REVIEWS**

*Volume 24 • December 2009  • www.physiologyonline.org*
expression, with concomitant decreases in islet macrophage infiltration. Supportive of this reduction in immune cell infiltration, further work has indicated that markers of endothelial cell activation, such as adhesion molecule expression (VCAM-1), were also suppressed by IL-1Ra treatment (36). Finally, reduction in islet inflammation correlated with improvements in proinsulin to insulin processing in IL-1Ra-treated animals. Since this IL-1Ra intervention study in the GK rat had minimal effects on β-cell mass, while improving β-cell insulin processing and hyperglycemia, we propose that IL-1β drives tissue inflammation, which then impacts on both insulin sensitivity and β-cell functional mass in Type 2 diabetes. However, this does not exclude some additional direct cytotoxic effects.

"Thus IL-6 regulation of the pancreatic α-cell represents a novel endocrine loop in the regulation of glucose homeostasis."

Interestingly, IL-1Ra treatment of the GK rat also reduced islet IL-1β expression itself, supporting that the auto-stimulatory role of IL-1β in the islet (as described above) plays an important role in the islet inflammatory process in vivo.

In summary, both our in vitro data on human and rodent islets and our in vivo studies on the GK rat support a central role for IL-1 in driving the expression of tissue proinflammatory cytokines and chemokines that subsequently attract immune cells to islets. This inflammatory process leads to impairment of β-cell function. These data support the function that Type 2 diabetes is an IL-1-driven auto-inflammatory disease.

**IL-6 Regulation of the Pancreatic α-Cell**

Pancreatic islet pathology in Type 2 diabetes is characterised not only by reduced β-cell function and mass but also by increased proportion of α-cells relative to β-cells, together with relative hyperglucagonemia due to α-cell dysfunction (10, 63, 71). Having recently found elevated IL-6 levels in pancreatic islets of models of Type 2 diabetes (20, 21), we re-explored its role in the regulation of α- and β-cells (22).

We confirmed the previously published detrimental effects of IL-6 on insulin secretion in both human and rodent islets in vitro (35). Beyond this, however, we found that the glucagon-producing α-cell is a primary target of IL-6. Islet α-cells express the IL-6 receptor and functionally respond to IL-6 kinetically prior to β-cells. IL-6 was found to increase glucagon secretion under fasting conditions (low glycemia) in isolated islets and when systemically administered in vivo. Furthermore, IL-6 promoted α-cell proliferation and prevented α-cell apoptosis due to metabolic stress while exacerbating β-cell apoptosis. Thus, in contrast to the negative effects on the β-cell, IL-6 acts as a growth and survival factor and promotes glucagon secretion in the α-cell.

Further studies in vitro supported this hypothesis. For this, we studied the role of IL-6 in the setting of obesity and insulin resistance by feeding wild-type and IL-6 KO mice HFD. Although HFD increased systemic IL-6 levels in wild-type animals, this did not occur in IL-6 KO animals. Most striking, IL-6 KO mice did not show increased α-cell mass under these conditions, demonstrating that IL-6 signaling is necessary for the stimulatory effect of HFD on α-cell mass. Consistent with these α-cell-specific findings, IL-6 KO animals displayed reduced fasting glucagon levels relative to wild-type animals on HFD. However, in contrast to the expected improvement in glucose tolerance in these animals, IL-6 KO mice on HFD displayed fed hyperglycemia, impaired glucose tolerance, and impaired glucose-stimulated insulin secretion compared with diet-matched wild-type animals. This effect has previously been published using IL-6 KO animals from the same source that we used (11). Since insulin sensitivity was similar among genotypes, the phenotype could be attributed to impaired β-cell function and suggests a role for the α-cell in maintaining β-cell function in vivo. Indeed, recent reports support this notion. Thus α-cell expression of prohormone convertase 1-3 (allowing the α-cell to produce GLP-1) or overexpression of the glucagon receptor on β-cells promotes improved insulin secretion (25, 69), thus supporting the hypothesis that the pancreatic α-cell can regulate β-cell function in vivo in a paracrine manner. That α-cell mass expansion is an important feature of the pathology of Type 2 diabetes was shown in Type 2 diabetic baboons, in which increased α-cell proliferation and mass together with hyperglucagonemia was recently described as part of the islet remodeling process (26).

Thus IL-6 regulation of the pancreatic α-cell represents a novel endocrine loop in the regulation of glucose homeostasis. Although it appears that this mechanism may exist to compensate for impaired β-cell function in the setting of obesity and/or Type 2 diabetes, it cannot be ignored that elevated IL-6 levels may also drive the relative hyperglucagonemia of diabetic patients. How this pathway contributes to the IL-6-mediated effects during physiology [e.g., during exercise, where systemic IL-6 levels are elevated (23)] or during the pathophysiology of obesity and diabetes in humans remains to be examined.

**Role of Insulitis in Obesity and Type 2 Diabetes: From Islet Adaptation to Failure**

Inflammation is not in itself a disease but a manifestation of a disease. Initially, it has beneficial effects such as preventing infection. However, excessive inflammation can exacerbate diabetes, similar to how an immune system that, in the case of Type 1 diabetes, fails to tolerate endocrine pancreas islets, may adapt to continue the survival of its functional components in a paracrine manner. That IL-1β and inflammatory signaling via NF-κB were previously reported to both promote insulin secretion and the β-cell response because of its functional components may lead to β-cell failure and decrease FPIR functions, which are potentially deleterious to the β-cell mass in a vicious cycle. Interestingly, we have found evidence of enhanced recruitment of innate immune cells, including macrophages and neutrophils, to islets, supporting that the increased IL-1β and other cytokines (e.g., TNF-α) may be critical in the development of the β-cell mass and other secondary inflammation in the β-cell mass itself. That the phenotype can be attributed to impaired β-cell function and suggests a role for the α-cell in maintaining β-cell function in vivo. Indeed, recent reports support this notion. Thus α-cell expression of prohormone convertase 1-3 (allowing the α-cell to produce GLP-1) or overexpression of the glucagon receptor on β-cells promotes improved insulin secretion (25, 69), thus supporting the hypothesis that the pancreatic α-cell can regulate β-cell function in vivo in a paracrine manner. That α-cell mass expansion is an important feature of the pathology of Type 2 diabetes was shown in Type 2 diabetic baboons, in which increased α-cell proliferation and mass together with hyperglucagonemia was recently described as part of the islet remodeling process (26).

Thus IL-6 regulation of the pancreatic α-cell represents a novel endocrine loop in the regulation of glucose homeostasis. Although it appears that this mechanism may exist to compensate for impaired β-cell function in the setting of obesity and/or Type 2 diabetes, it cannot be ignored that elevated IL-6 levels may also drive the relative hyperglucagonemia of diabetic patients. How this pathway contributes to the IL-6-mediated effects during physiology [e.g., during exercise, where systemic IL-6 levels are elevated (23)] or during the pathophysiology of obesity and diabetes in humans remains to be examined.

**Clinical Variations and Consequences**

Based on the above data, we initiated a series of experiments to further investigate the role of IL-1β. In collaboration with colleagues at the University of California, San Francisco, we treated female C57Bl6 mice with an acute intraperitoneal injection of IL-1β or a placebo control injection. We found that IL-1β treatment significantly increased FPIR, with both a marked increase in acute FPIR and a persistence of the effect for at least 7 days. Remarkably, acute FPIR improved glucose tolerance to a similar extent as the chronic treatment with agents like metformin, which is currently used to just palliate Type 2 diabetes.
Sustained hyperglycemic events that would provoke \( \beta \)-cell production of very low concentrations of IL-1ß followed by low concentrations of IL-1ß and in the presence of FLIP, Fas engagement would lead to \( \beta \)-cell proliferation and enhanced function via NF-\kappa B and PDX1 (36). Indeed, NF-\kappa B has been reported to have beneficial effects on both insulin secretion and \( \beta \)-cell proliferation (27, 48). If this response becomes excessive due to prolonged or repetitive exposure to nutrients, this initially adaptive process may become deleterious. IL-1ß will then decrease FLIP and Fas engagement and switch to pro-motile deleterious effects. In addition, IL-1ß initiates the vicious cycle of inducing itself and promoting an enhanced release of chemokines, which leads to recruitment of macrophages (2). Possibly, these macrophages then produce a high amount of IL-1ß (67) and other cytokine factors, which then impair the function of the \( \beta \)-cell. It is important to note that these mechanisms may be responsible for both decreased \( \beta \)-cell mass and impaired function. Depending on duration and magnitude of the effect as well as the individual regenerative capacity, the functional impairment may predominate over the more definitive decrease in \( \beta \)-cell mass. Interestingly, such an auto-inflammatory process occurs also in the insulin-sensitive tissues and in end organs such as kidney, eye, and the vasculature. Therefore, tissue inflammation may not only underlie \( \beta \)-cell failure and insulin resistance but also participate directly in the complications of diabetes, such as nephropathy, retinopathy, and cardiovascular disease.

Clinical Validation and Therapeutic Consequences

Based on the above-described predominant role of IL-1ß, we initiated clinical trials of IL-1 antagonist in Type 2 diabetes. In a proof-of-concept study, the naturally occurring antagonist of IL-1ß, IL-1Ra, was tested in a placebo-controlled study of 70 patients (38). At 13 wk, glycated hemoglobin was significantly improved due to enhanced \( \beta \)-cell secretory function. Remarkably, the improvement promoted by IL-1ß blockade lasted for at least 39 wk following treatment withdrawal (37), thus reflecting the disease-modifying potential of this therapy. Novel therapeutic approaches designed to modulate IL-1 are under development with agents lasting a month or longer (18). Rather than just palliating hyperglycemia, IL-1 antagonism may represent a novel treatment principle directed against the pathogenesis that underlies diabetes mellitus, whereby the progressive decline in functional \( \beta \)-cell mass could be prevented or even reversed. Due to the auto-inflammatory nature of the whole metabolic syndrome and based on preclinical studies, it is expected that IL-1 antagonism will also enhance insulin sensitivity and prevent complications like blindness, cardiovascular events, and nephropathy. Numerous ongoing clinical studies are based on this assumption.

References

5. Cerasi E, Luft F. Inhibitors of pro-inflammatory cytotoxic factors, which then impair the function of the \( \beta \)-cell. It is important to note that these mechanisms may be responsible for both decreased \( \beta \)-cell mass and impaired function. Depending on duration and magnitude of the effect as well as the individual regenerative capacity, the functional impairment may predominate over the more definitive decrease in \( \beta \)-cell mass. Interestingly, such an auto-inflammatory process occurs also in the insulin-sensitive tissues and in end organs such as kidney, eye, and the vasculature. Therefore, tissue inflammation may not only underlie \( \beta \)-cell failure and insulin resistance but also participate directly in the complications of diabetes, such as nephropathy, retinopathy, and cardiovascular disease.

Clinical Validation and Therapeutic Consequences

Based on the above-described predominant role of IL-1ß, we initiated clinical trials of IL-1 antagonist in Type 2 diabetes. In a proof-of-concept study, the naturally occurring antagonist of IL-1ß, IL-1Ra, was tested in a placebo-controlled study of 70 patients (38). At 13 wk, glycated hemoglobin was significantly improved due to enhanced \( \beta \)-cell secretory function. Remarkably, the improvement promoted by IL-1ß blockade lasted for at least 39 wk following treatment withdrawal (37), thus reflecting the disease-modifying potential of this therapy. Novel therapeutic approaches designed to modulate IL-1 are under development with agents lasting a month or longer (18). Rather than just palliating hyperglycemia, IL-1 antagonism may represent a novel treatment principle directed against the pathogenesis that underlies diabetes mellitus, whereby the progressive decline in functional \( \beta \)-cell mass could be prevented or even reversed. Due to the auto-inflammatory nature of the whole metabolic syndrome and based on preclinical studies, it is expected that IL-1 antagonism will also enhance insulin sensitivity and prevent complications like blindness, cardiovascular events, and nephropathy. Numerous ongoing clinical studies are based on this assumption.

References

1. Donath MY, Ehses JA, Schub FC; Donath MF. Free fatty acid induce a pro-inflammatory response in vitro, the adiposocyte factor1 receptor. J Clin Endocrinol Metab 95: 3720–3723, 2010.
2. Donath MY; Schub FC; Donath MF; Donath MY. Inhibitors of interleukin-1 (IL)-1beta messenger ribonucleic acid expression in beta-cells of individuals with Type 2 diabetes and regulation of IL-1beta in human islets by glucocorticoid induction. J Clin Endocrinol Metab: 119: 4056–4074, 2007.
5. Cerasi E, Luft F. Inhibitors of pro-inflammatory cytotoxic factors, which then impair the function of the \( \beta \)-cell. It is important to note that these mechanisms may be responsible for both decreased \( \beta \)-cell mass and impaired function. Depending on duration and magnitude of the effect as well as the individual regenerative capacity, the functional impairment may predominate over the more definitive decrease in \( \beta \)-cell mass. Interestingly, such an auto-inflammatory process occurs also in the insulin-sensitive tissues and in end organs such as kidney, eye, and the vasculature. Therefore, tissue inflammation may not only underlie \( \beta \)-cell failure and insulin resistance but also participate directly in the complications of diabetes, such as nephropathy, retinopathy, and cardiovascular disease.


