Inflammatory stress in islet β -cells: therapeutic implications for type 2 diabetes?

Maria Lytrivi^{1,2}, Mariana Igoillo-Esteve¹ and Miriam Cnop^{1,2}

Type 2 diabetes is a common complex disease. Relatively little is known about the underlying pathophysiology. Mild islet inflammation has been suggested to play a pathogenic role; here we review the available evidence. Mild islet inflammation is histologically detected in pancreas sections of type 2 diabetic patients. In experimental models, it can be triggered by excess nutrients, amyloid, lipopolysaccharide, and endoplasmic reticulum and oxidative stress. Transcriptome studies do not consistently identify pro-inflammatory gene expression signatures in type 2 diabetic islets, and genetic evidence calls into question the causality of inflammation. Several anti-inflammatory medications confer a modest glucose-lowering effect, supporting the role for inflammation in type 2 diabetes. Whether these anti-inflammatory therapies target inflammation in islets or in other metabolically relevant tissues remains unknown.

Addresses

¹ ULB Center for Diabetes Research, Faculty of Medicine, Université Libre de Bruxelles, Brussels, Belgium

² Division of Endocrinology, Erasmus Hospital, Université Libre de Bruxelles, Brussels, Belgium

Corresponding authors: Lytrivi, Maria (mlytrivi@ulb.ac.be), Cnop, Miriam (mcnop@ulb.ac.be)

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Diabetes mellitus is a major public health problem, affecting 425 million people globally [1]. Both type 1 and type 2 diabetes (T2D) are characterized by functional defects of pancreatic β -cells and loss of β -cell mass, although the underlying mechanisms differ considerably [2]. Islet inflammation and autoimmune destruction of β -cells are pivotal in the pathogenesis of T1D. Over the past decade, several reports have suggested that islet inflammation may also play a role in T2D. In this review, we outline current evidence on islet inflammation and its potential triggers in T2D. We discuss recent therapeutic

trials that targeted inflammatory pathways or repurposed anti-inflammatory medications.

Evidence for islet inflammation in T2D

Histology

In pancreatic sections of T2D patients innate immune cells have been shown to infiltrate the islets [3–6]. The number of CD68⁺ cells (mainly macrophages) per islet increases from 0.5 in controls to 1.3 in T2D [3,6]. Inflammation, defined as >3 CD68⁺ cells per islet, is present in 20% of the T2D islets compared with 5% of non-diabetic islets [3,6]. Although macrophages are limited to the islet periphery in non-diabetic islets, intra-islet invasion is observed in T2D islets [6]. Macrophage islet infiltration has also been reported in rodent models of T2D (*db/db* mice, high-fat diet-fed C57BL/6J mice and GK rats) [3,7]. By contrast, data regarding lymphocyte infiltration in T2D islets are contradictory [5,8].

Transcriptome

While histological reports seem concordant on the presence of mild islet inflammation, transcriptomic studies have yielded discordant data on pro-inflammatory gene signatures. A microarray analysis of laser-capture microdissected β -cells from non-diabetic ($n = 9$) and T2D organ donors ($n = 10$) showed increased expression of the cytokines IL-1 β and IL-8 in T2D [9]. In the same laser-capture microdissected samples ($n = 10$ in both groups) we observed a non-significant induction of IL-1 β and IL-8 and increased expression of the chemokines CCL2 and CCL13 [10]. In a recent transcriptomic study of a large number of islet preparations, pro-inflammatory cytokines and chemokines were upregulated in islets isolated by enzymatic digestion from T2D organ donors, but not in laser-capture microdissected islets from pancreatectomized T2D patients [11[•]]. Single-cell transcriptomics did not report inflammation-related genes in T2D β -cells [12,13^{••}], but Segerstolpe *et al.* did identify an inflammatory gene signature in a subpopulation of acinar cells [13^{••}].

Genetics

To date, 400 loci associated with T2D risk have been identified [14^{••}]. Genome-wide association studies in African American and European populations identified one T2D locus associated to *HLA-B*, coding for major histocompatibility complex class I [15]. Because there is long-range linkage disequilibrium in this region the causality of HLA-B remains uncertain [15].

Mendelian randomization studies use genetic variants as an instrument to study association between an exposure (resulting from genetic variants) and an outcome. A Mendelian randomization study examined the impact of two common variants upstream of *IL1RN*, the gene encoding the IL-1 receptor antagonist (IL-1Ra), on T2D [16^{••}]. The variants increased IL-1Ra concentrations but did not associate with T2D (odds ratio 0.99). In a meta-analysis of 28 studies, a genetic variant in *IL6R* that impairs IL-6 signaling tended (non-significantly) to reduce T2D risk (odds ratio 0.97) [17].

For several gene variants identified in T2D genome-wide association studies, monogenic forms of diabetes exist that are caused by more damaging loss-of-function mutations in the same genes (e.g. *HNF1A*, *HNF4A*, *WFS1*). The existence of monogenic forms of diabetes caused by mutations in inflammation-related genes would provide support for a role of inflammation in T2D pathogenesis. No such reports exist to the best of our knowledge.

Potential triggers of islet inflammation in T2D

Nutrients, amyloid and humoral factors may elicit islet inflammation, and signal transduction in β -cells can amplify this process (Figure 1).

Non-esterified fatty acids (NEFA)

Obesity is associated with increased NEFA levels, due to increased lipolysis in the expanded fat mass and resistance to the anti-lipolytic effect of insulin [18]. High NEFA levels are predictive of diabetes development and induce β -cell dysfunction and apoptosis [19]. Palmitate, the most prevalent saturated NEFA, induces apoptosis to a greater extent than the unsaturated oleate, and when combined at equimolar concentrations, oleate protects from palmitate-induced apoptosis [20]. Boni-Schnetzler *et al.* [21] showed that NEFA treatment of human islets induces the pro-inflammatory cytokines IL-1 β , IL-6 and IL-8, with oleate inducing a stronger response than palmitate or the combination of oleate and palmitate. This response was IL-1R dependent and abrogated by IL-1Ra. We found that palmitate, but not oleate, induced expression of CCL2, CXCL1, IL-6, IL-8, IL-1 β and TNF- α in human islets [10]. We confirmed that IL-1 β mediated the chemokine/cytokine induction but blocking IL-1 β signaling did not protect from palmitate-induced apoptosis. Eguchi *et al.* provided further mechanistic insight in palmitate-induced islet inflammation [22]. Using elegant *in vitro* and *in vivo* models, they demonstrated that palmitate induces production of the chemokines CCL2 and CXCL1 by β -cells via Toll-like receptor 4 (TLR4), thereby recruiting M1-type pro-inflammatory macrophages/monocytes to the islets. Ablation of M1 macrophages/monocytes before ethyl palmitate infusion protected mice from β -cell dysfunction and preserved expression of key β -cell genes, pointing to important β -cell-immune cell interactions

[22]. NEFA induce secretion of damage-associated molecular pattern molecules by β -cells, which attract inflammatory macrophages [23].

Glucose

Chronic hyperglycemia, a hallmark of prediabetes and T2D, is β -cell toxic and exacerbates β -cell failure, causing a vicious circle [24]. Maedler *et al.* [25] suggested that human islet exposure to high glucose induced IL-1 β production by β -cells, leading to activation of the key transcription factor NF- κ B, Fas upregulation and β -cell dysfunction. Other studies [10,26] have failed to reproduce this change in IL-1 β expression or NF- κ B activation, arguing against a major role of IL-1 β in glucotoxicity.

Islet amyloid deposits

Deposition of islet amyloid, formed by aggregates of islet amyloid polypeptide (IAPP), is a pathologic feature of T2D and contributes to β -cell failure [27]. IAPP induces a pro-inflammatory response in macrophages, with release of IL-1 β and other cytokines/chemokines [28–30]. IAPP activates the NLRP3 inflammasome, a protein complex that activates caspase-1, which in turn cleaves pro-IL-1 β to mature IL-1 β [28]. This cytokine seems to mediate amyloid-induced islet inflammation and β -cell dysfunction. In transgenic mice expressing human IAPP (rodent IAPP not being amyloidogenic), treatment with IL-1Ra improved glucose tolerance and decreased amyloid extent and severity [29].

Systemic inflammation

Obesity and T2D are characterized by a state of systemic, low-grade inflammation, with mildly increased circulating pro-inflammatory cytokine levels. It is conceivable that, in addition to locally produced cytokines, circulating cytokines impact β -cell function/survival. While it is unclear whether low cytokine doses affect β -cells *in vivo*, some *in vitro* evidence supports this hypothesis. Exposure of mouse islets to cytokines at doses comparable to levels observed in T2D impairs calcium handling [31,32]. Cytokines decrease glucose-stimulated insulin secretion and increase cell death in islets of db/db mice [32].

Another humoral factor that may impact islet function is lipopolysaccharide (LPS). LPS is a component of the outer membrane of gram-negative bacteria. Diet-induced diabetes is associated with elevated circulating LPS levels through changes in the gut microbiota and increased gut permeability [33]. LPS causes weight gain, insulin resistance and glucose intolerance in animal models [34]. In islets, LPS decreases insulin gene expression through decreased PDX-1 and MafA expression [35], reduces glucose-stimulated insulin secretion [35,36] and induces inflammatory cytokines [36]. These phenomena are TLR4-dependent, leading to NF- κ B activation [35].

Figure 1

Potential triggers of pancreatic β -cell inflammation in type 2 diabetes. Hyperglycemia, increased circulating levels of non-esterified fatty acids (NEFA) and lipopolysaccharide (LPS) trigger mild inflammatory responses in pancreatic β -cells via direct activation of toll like receptor 4 (TLR4) or as a result of metabolically induced oxidative and endoplasmic reticulum (ER) stress. These pathways lead to the activation of the transcription factor NF- κ B and the upregulation of cytokines and chemokines. The released chemokines contribute to intra-islet macrophage recruitment. Aggregates of islet amyloid polypeptide (IAPP) trigger IL-1 β secretion by macrophages, which binds to the IL-1 receptor (IL-1R) and amplifies the inflammatory response. Whether this inflammatory response is adaptive or deleterious to pancreatic β -cells remains to be elucidated.

Endoplasmic reticulum (ER) stress and oxidative stress

Besides the direct activation of inflammatory pathways by specific triggers discussed above, secondary activation of inflammatory pathways may occur downstream of ER and oxidative stress. ER stress induces pro-inflammatory genes, through activation of NF- κ B and the JNK kinase (reviewed in [37]). Mild ER stress sensitizes β -cells to IL-1 β , amplifying the inflammatory response due to XBP1-s-mediated NF- κ B activation [38]. Oxidative stress is triggered in β -cells by glucose and NEFA overload [24], activating stress-sensitive kinases, such as JNK, PKC, p38-MAPK and IKK- β [39]. These in turn upregulate the expression of TNF- α , IL-6 and MCP-1 [39].

Therapeutic agents targeting inflammatory pathways in T2D

Several therapeutic interventions have been tested that target inflammatory pathways through different mechanisms of action (Table 1).

IL-1 β blockade

As *in vitro* data and data in rodent models suggested a central role of IL-1 β in islet inflammation, IL-1 β blockade emerged as a new therapeutic approach for T2D. In short-term phase 2 trials in T2D patients, daily subcutaneous injections of the IL-1Ra anakinra [40] or longer-acting IL-1 β neutralizing antibodies LY2189102 and gevokizumab [41,42] decreased HbA1c by 0.25–0.85%. In contrast to these encouraging proof-of-concept studies, the CANTOS phase 3 study with the anti-IL-1 β antibody canakinumab [43**] failed to demonstrate any benefit on diabetes. Study participants had a history of myocardial infarction and elevated CRP and 90% had (pre)diabetes. Canakinumab did not reduce the incidence of new-onset diabetes among prediabetic patients ($p = 0.8$). In diabetic patients, it modestly reduced HbA1c in the first 6–9 months of treatment, but this effect was lost with time [43**]. Canakinumab, at a dose of 150 mg, reduced the rate of cardiovascular events (nonfatal myocardial infarction, nonfatal stroke or cardiovascular death), but it

Table 1**Overview of therapeutic agents targeting inflammation in type 2 diabetes**

Therapeutic agent	Mechanism of action	Site of action	Trial	References
Anakinra	IL-1 antagonism	Increased insulin secretion (?)	Phase 2	[40]
LY2189102		No effect in phase 3 trial	Phase 2	[41]
Gevokizumab			Phase 2	[42]
Canakinumab			Phase 3 [CANTOS]	[43**,44]
Salsalate		Decreased insulin clearance	Phase 2	[47]
Diacerein	Decrease of IL-1 β and TNF- α	Increased insulin secretion	Phase 2	[48,49,50*]
Hydroxychloroquine	Increases adiponectin	Improved insulin sensitivity	Phase 2	[52]
	Other (?)			
Infliximab	TNF- α inhibition	Improved insulin sensitivity	No prospective trials	[54–56]
Etanercept			Observational data	
Adalimumab				

significantly increased fatal infection (in particular in diabetic patients), raising safety concerns [44].

Salsalate

Salsalate is an old, inexpensive salicylate drug used to treat joint pain. Salsalate inhibits I- κ B kinase, thereby inhibiting NF- κ B activation and inflammatory cytokine production. In prediabetic individuals salsalate treatment for up to 30 months decreased fasting glycemia and increased adiponectin levels [45,46]. Although the glucose-lowering mechanisms were not completely clear, salsalate decreased insulin clearance in the fasting state and did not affect insulin sensitivity [46]. A larger-scale study (TINSAL-T2D trial stage 2) was undertaken to evaluate the efficacy of salsalate in T2D [47]. Salsalate decreased HbA1c by 0.4% compared to placebo over 1-year follow-up. However, the salsalate-treated group showed increased LDL cholesterol and albuminuria, potentially implying adverse cardiovascular and renal outcomes and tempering enthusiasm about this drug.

Diacerein

Diacerein is an immunomodulatory drug used in osteoarthritis. Diacerein decreases the pro-inflammatory cytokines IL-1 β and TNF- α , through unknown mechanisms. Two small trials reported a remarkable efficacy of this drug in T2D patients, lowering HbA1c from 8.3 to 7% [48] and from 8.4 to 6.7% [49] after 2–3 months of treatment. Diacerein enhanced insulin secretion, with no changes in insulin sensitivity [48,49]. A larger trial confirmed the glucose-lowering effect of the drug, with a maximal decrease of HbA1c of 0.6% at 6 months [50*], but unfortunately the effect was not sustained after 1 year of treatment.

Hydroxychloroquine

Hydroxychloroquine is an anti-malarial drug, currently widely used in rheumatology given its anti-inflammatory properties. In a large observational study of rheumatoid arthritis patients, hydroxychloroquine reduced T2D risk, with a hazard ratio of 0.62 [51]. In a trial comparing hydroxychloroquine to pioglitazone as add-on treatment to metformin plus sulfonylurea in insufficiently controlled T2D

patients, hydroxychloroquine and pioglitazone similarly decreased HbA1c by 0.9% after 6 months [52]. Hydroxychloroquine had favorable effects on triglycerides and LDL cholesterol and did not induce weight gain. Intravenous glucose tolerance tests showed that hydroxychloroquine improves insulin sensitivity but not the acute insulin response to glucose [53]. Retinal toxicity with long-term use of this drug is a major limitation.

TNF- α inhibitors

TNF- α inhibitors improve insulin sensitivity in patients with inflammatory conditions [54]. A retrospective cohort study of rheumatoid arthritis and psoriasis patients found that TNF inhibitors reduced incident T2D, with a hazard ratio of 0.62, compared to non-biologic disease-modifying anti-rheumatic drugs [55]. Another retrospective study found that anti-TNF agents with concomitant hydroxychloroquine use conferred lower diabetes risk, but not when anti-TNF treatment was used without hydroxychloroquine [56].

Conclusions

Histological data consistently demonstrate mild islet inflammation in T2D. This is potentially triggered by excess nutrients, islet amyloid, humoral factors and other types of cellular stress. Islet inflammation does not necessarily have a pathogenic role, however. It could be an adaptive response aiming to restore homeostasis or an epiphenomenon. Transcriptome studies are discrepant and do not consistently identify pro-inflammatory gene expression signatures in T2D islets. Genetic evidence for causality remains scant. The efficacy of anti-inflammatory medications in T2D, albeit modest, supports the notion that inflammation—in a broad sense—contributes to T2D. Yet, it is difficult to determine whether these medications target inflammation in islets or in other metabolically relevant tissues. Studies in animal models could shed light on the glucose-lowering mechanisms of anti-inflammatory drugs and help elucidate the impact of islet inflammation on β -cell function. For example, β -cell-specific manipulation of genes with a key role in islet inflammation could provide insights. The development of imaging tools to assess pancreatic islet

inflammation [57] will help to conclusively confirm or infirm its role in human T2D.

Conflict of interest statement

Nothing declared.

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