Interleukin-Targeted Therapy for Metabolic Syndrome and Type 2 Diabetes

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Abstract Interleukin-1β (IL-1β) is a key regulator of the body's inflammatory response and is produced after infection, injury, and an antigenic challenge. Cloned in 1984, the single polypeptide IL-1β has been shown to exert numerous biological effects. It plays a role in various diseases, including autoimmune diseases such as rheumatoid arthritis, inflammatory bowel diseases, and Type 1 diabetes, as well as in diseases associated with metabolic syndrome such as atherosclerosis, chronic heart failure, and Type 2 diabetes. The macrophage is the primary source of IL-1β, but epidermal, epithelial, lymphoid, and vascular tissues also synthesize IL-1. Recently, IL-1β production and secretion have also been reported from pancreatic islets. Insulin-producing β-cells within the pancreatic islets are specifically prone to

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IL-β-induced destruction and loss of function. Macrophage-derived IL-1β production in insulin-sensitive organs leads to the progression of inflammation and induction of insulin resistance in obesity. This chapter explains the mechanisms involved in the inflammatory response during diabetes progression with specific attention to the IL-1β signal effects influencing insulin action and insulin secretion. We highlight recent clinical studies, rodent and in vitro experiments with isolated islets using IL-1β as a potential target for the therapy of Type 2 diabetes.

Keywords β-Cell · IL-1β · Diabetes · Inflammation · Obesity · Interleukin-1 receptor antagonist

1 Introduction: The IL-1 Family

Twenty-five years ago, IL-1β was cloned in the lab of Charles Dinarello (Auron et al. 1984). Meanwhile, 11 ligands and 10 receptors of the IL-1 family have been discovered. The proinflammatory and agonistic ligands are IL-1α, IL-1β, IL-18, FIL-1ε, IL-1H2, IL-1ε, and IL-33; and the anti-inflammatory and antagonistic ligands are IL-1Ra, FIL-1δ, IL-1H4, and IL-1Hy2 (Dinarello 2009). IL-1α, IL-1β, and IL-1Ra bind to IL-1R1; IL-1β and the IL-1β precursors bind to IL-1R2; IL-33 binds to IL-1R4; IL-18 and IL-1H4 to IL-1R5; FIL-1ε, IL-1H2, and IL-1ε to IL-1R6; and IL-1R8, IL-1R9 and TIR8 remain orphan receptors (Boraschi and Tagliabue 2006). IL-1β is mainly produced by activated macrophages. Production and secretion of IL-1β have been linked not only to various autoimmune and autoinflammatory diseases, but also to metabolic dysregulation (Dinarello 2009). Signaling pathways of IL-1β have been shown to result in impaired insulin secretion and action (Maedler et al. 2009). Clearly, other cytokines and chemokines are involved in the inflammatory responses; however, this chapter focuses on the possibility of blocking only IL-1β as a target for improving glycemia in T2DM.

A recent paper showing that genetic variation in the IL-1 gene family is associated with hyperglycemia and insulin resistance provides another proof for the involvement of IL-1β in the pathogenesis of diabetes (Luotola et al. 2009).

2 IL-1β Links Obesity and Diabetes

Chronic subclinical inflammation is present in obesity, insulin resistance, and T2DM. The diseases related to metabolic syndrome are characterized by abnormal cytokine production, including elevated circulating IL-1β, increased acute-phase proteins, e.g., CRP (Koenig et al. 2006), and activation of inflammatory signaling pathways (Wellen and Hotamisligil 2005).

Proinflammatory cytokines can cause insulin resistance in adipose tissue, skeletal muscle, and liver by inhibiting insulin signal transduction. The sources of

cytokines in insulin-resistant states are the insulin target tissues themselves, primarily fat and liver, but to a larger extent the activated tissue resident macrophages (de Luca and Olefsky 2008).

While macrophage infiltration in adipose and brain tissue has been shown in many studies (Schenk et al. 2008), increased islet macrophage infiltration has only recently been observed in pancreatic sections from patients with T2DM (Ehses et al. 2007; Richardson et al. 2009) and in T2DM animal models, such as the GK rat (Homo-Delarche et al. 2006), the HFD and *db*/*db* mouse (Ehses et al. 2007), and the hyperglycemic Cohen diabetic rat (Weksler-Zangen et al. 2008). While IL-1β signals induce destruction and impaired insulin secretion in the β-cells, insulin signaling is disturbed in the insulin target tissues (Fig. 1).

Insulin receptor signaling is complex. To summarize shortly, signaling downstream of the insulin receptor involves phosphorylation of IRS1/2 and the activation of the PI3K–AKT pathway (responsible for insulin action on glucose uptake) and the Ras-mitogen-activated protein kinase (MAPK) pathway (responsible for suppression of gluconeogenesis, reviewed in (Taniguchi et al. 2006)). Due to inflammation, IRS1 can be alternatively phosphorylated on serine 307, which leads to downstream activation of the NF-κB pathway, phosphorylation of C-jun N-terminal kinase 1 (JNK1), and activation of the JNK/AP-1 pathway and thus disturbed insulin signaling. Furthermore, IL-1β induces suppressor of cytokine signaling (SOCS), which leads to degradation of insulin receptor substrate (IRS) proteins (Rui et al. 2002).

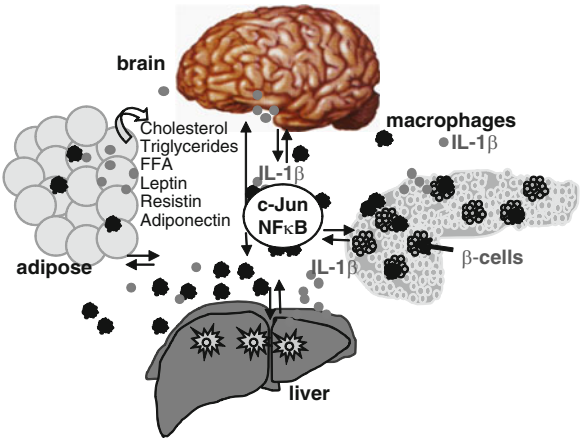

Fig. 1 The inflammatory axis in metabolic diseases and interplay between macrophage-derived IL-1β and its action in adipose tissue, brain, pancreas, and liver. Macrophages migrate into insulin-sensitive organs and produce proinflammatory signals, which change the cell fate. In adipose tissue, this leads to increased production of cholesterol, triglycerides, cytokines, and the adipokines lepin and resistin, while adiponectin is decreased. Insulin sensitivity is impaired and glucose uptake disturbed. Mediated through intracellular signaling cascades, NF-κB and c-Jun are activated and insulin resistance in the liver and brain and impaired insulin secretion in the β-cells develop [adapted from Maedler et al. (2009)]

2.1 IL-1β in Adipocytes

Infiltration of macrophages in adipose tissue is tightly correlated with obesity in mice and humans (Weisberg et al. 2003; Xu et al. 2003). Important modulators of inflammation are the adipocytokines, i.e., leptin, resistin, and adiponectin, which play a central role in the regulation of insulin resistance and β-cell function (Koerner et al. 2005; Tilg and Moschen 2006).

In obesity, not only circulating free fatty acids (FFA) and lipids but also leptin and resistin are increased; whereas adiponectin, which is known to prevent inflammation (Tilg and Moschen 2006) and is negatively correlated with insulin resistance, is decreased (Rasouli and Kern 2008). Leptin has been shown to exert pro- as well as anti-inflammatory properties, probably dependent on its dose and exposure time. While in vivo, leptin overexpression normalizes glycemia in the diabetic NOD mice as well as in STZ- and alloxan-induced diabetes (Yu et al. 2008), chronic leptin incubation in vitro leads to impaired β-cell function and survival (Maedler et al. 2004; Roduit and Thorens 1997; Seufert et al. 1999). Leptin has been shown to manipulate levels of IL-1β and IL-1Ra. While leptin acutely induces IL-1Ra expression in islets and monocytes (Gabay et al. 2001; Maedler et al. 2004), there is a chronic reduction of IL-1Ra and induction of IL-1β secretion.

IL-1Ra expression is increased in white adipose tissue in obese individuals with increased circulating FFA and lipids (Juge-Aubry et al. 2003). In contrast, daily IL-1Ra injections in HFD-fed mice normalize circulating FFA, lipids, as well as adipokines. Although the percentage of macrophages in a given adipose tissue depot is positively correlated with adiposity and adipocyte size (Weisberg et al. 2003), the normalization of lipids and adipokines by IL-1Ra seems to be independent of fat mass, since IL-1Ra treatment neither influences fat mass nor adipocyte size. In contrast, mRNA levels of the inflammatory cytokines IL-1β and TNF-α, the macrophage marker F4/80, and the proinflammatory macrophage marker CD11c are increased by the HFD in wild-type mice but reduced by IL-1Ra overexpression (Sauter et al. 2008). Interestingly, specifically the marker of the "classically activated" macrophages M1 (Lumeng et al. 2007) is highly induced by the HFD and normalized by IL-1Ra. Thus, the HFD-induced proinflammatory state of adipocytes may be the reason for the increased adipokines (resistin and leptin) and lipid production.

Undoubtedly, the effect of IL-1Ra on adipocyte-derived factors plays a protective role at the level of the β-cell.

2.2 IL-1β in the Liver

The bone marrow-derived macrophage cells in the liver are the Kupffer cells. Kupffer cells secrete cytokines, among them IL-1β, NO, and free radicals, which could, per se, induce β-cell failure (Barshes et al. 2005). This is specifically

deleterious in the environment of transplanted islets in the liver. Cytokines (IL-1β, IFN-γ, and TNF-α) are particularly elevated after islet transplantation (Bottino et al. 1998), and liver tissue macrophages participate in cell injury and graft failure (Kaufman et al. 1990, 1994). Strategies to inhibit IL-1β-induced β-cell failure, e.g., by salicylate treatment of the islets (Tran et al. 2002; Zeender et al. 2004) may therefore improve graft survival.

Similar to the role of macrophages in obese adipose tissue, secretion of IL-1β by the Kupffer cells could be central to hepatic insulin resistance in obesity. Cytokine-induced JNK phosphorylation and activation of the NF-κB pathway are indicative of insulin resistance in the liver, e.g., depletion of JNK in myeloid cells (including Kupffer cells) in mice leads to HFD-induced hepatic steatosis without an increase in inflammatory markers in the liver and no development of insulin resistance (Solinas et al. 2007). Furthermore, hepatocyte-specific inhibition of NF-κB (Cai et al. 2005) or of IKK-β (Arkan et al. 2005) in myeloid cells improves hepatic insulin sensitivity. These studies show that independent of obesity, the inflammatory status in the liver primarily regulates insulin sensitivity.

2.3 IL-1β in the Brain

In the healthy brain, members of the IL-1 family are expressed at low or undetectable levels (Allan et al. 2005). During neuro-inflammation, IL-1β is dramatically upregulated by various local and systemic brain insults including ischemia, trauma, hypoxia, and neurotoxic inflammatory stimuli (Allan et al. 2005).

IL-1β in the brain is produced primarily by microglia, which also express caspase-1 (Touzani et al. 1999). To a lesser extent, astrocytes, oligodendroglia, neurons, cerebrovascular cells, and circulating immune cells after infiltrating the brain under inflammatory conditions produce IL-1β (Rothwell and Luheshi 2000).

IL-1β has a number of diverse actions in the CNS to modify feeding behavior, fever (Dinarello and Wolff 1982), central pain modulation (Wolf et al. 2003), stress responses (Goshen et al. 2003) memory (Schneider et al. 1998), and neuroendocrine responses, mainly through actions in the hypothalamus (Sims and Dower 1994).

There is evidence of a hypothalamic control of insulin sensitivity, which is disturbed when elevated levels of proinflammatory cytokines are circulating. Studies in mice show that HFD promotes hypothalamic resistance to the main anorexigenic hormones, leptin and insulin, leading to the progressive loss of the balance between food intake and thermogenesis and, therefore, resulting in body mass gain (De Souza et al. 2005; Milanski et al. 2009; Munzberg et al. 2004). HFD feeding of rats resulted in hypothalamic induction of IL-1β, TNF-α, IL-6, and IL-10. Activation of the toll-like receptor 4 signaling induces local cytokine expression in the hypothalamus and promotes endoplasmic reticulum stress and insulin resistance (Milanski et al. 2009).

The structural and metabolic damage found in Alzheimer's disease is in part due to sustained elevation of IL-1β (Holden and Mooney 1995; Vandenabeele and

Fiers 1991; Zuliani et al. 2007). It upregulates expression of β-amyloid precursor protein (β-APP) and stimulates the processing of β-APP, resulting in amyloidogenic fragments in neurons (Goldgaber et al. 1989). Similarly, the β-APP deposits found in the Alzheimer brain share the same molecular structure as the amylin oligomer deposits found in the pancreatic β-cells in T2DM and are equally neurotoxic (Haataja et al. 2008). On the basis of the observations in the human islet amyloid polypeptide transgenic rat (Butler et al. 2004), there is evidence that IL-1β is expressed within the islets after the induction of severe hyperglycemia (unpublished observation), indicating that IL-1β expression can only be observed at high glucose levels. It remains to be elucidated if the toxicity of amylin oligomers on the β-cell involves IL-1β signals.

Possibly, the activation of cytokine-induced proinflammatory pathways (e.g., JNK) plays a major role in the modulation of neurodegeneration (Borsello and Forloni 2007). In line with this hypothesis, JNKs are negatively regulating insulin sensitivity in the obese state.

Four different pathways are shown in the brain as a consequence of diet-induced activation of inflammatory signaling: (1) induction of suppressor of cytokine signaling-3 (SOCS-3) expression (Howard et al. 2004), (2) activation of c-Jun N-terminal kinase (JNK) and I-kappa kinase (IKK) (De Souza et al. 2005), (3) induction of protein tyrosine phosphatase 1B (PTP1B) (Bence et al. 2006), and (4) activation of TLR4 signaling (Milanski et al. 2009). Thus, obesity and HFD induce activation of proinflammatory pathways in the brain, which may directly develop insulin resistance and lead to diminished glucose regulation by the insulin target tissues.

3 IL-1β Signaling in the β-Cell

Only when the β-cell compensates for the higher insulin demand during insulin resistance, normoglycemia can be maintained. A relative insulin deficiency leads to diabetes. From numerous in vitro studies from isolated islets and β-cell lines, we know that the β-cell is especially sensitive to cytokines. Consequently, circulating cytokines are likely to rapidly affect β-cell function and survival.

Soon after the cloning of IL-1β, Mandrup-Poulsen and colleagues observed that IL-1β impairs β-cell function (Mandrup-Poulsen et al. 1985, 1986). In addition to impaired insulin secretion, IL-1β was found to induce β-cell death, which was potentiated by the cytokines IFN-γ and TNF-α (Eizirik 1988; Pukel et al. 1988). In the pancreatic islet, IL-1R1 is present in the β-cells (Deyerle et al. 1992) and not in the α-cells (Scarim et al. 1997), and thus the β-cells are a target for IL-1a, IL-1β, and IL-1Ra.

Surprisingly, IL-1R1 is highly expressed in the β-cell; more than tenfold higher expression of IL-1RI mRNA was observed in isolated islets than in total pancreas, which is attributed to the expression in the β-cell. Furthermore, β-cell IL-1R1 expression levels are higher than in any other tissue. (Boni-Schnetzler et al.

2009), which may explain the high sensitivity of the β-cell to IL-1. Blocking IL-1β with specific IL-1β-neutralizing antibodies protected from the cytotoxic effects induced by activated mononuclear cell conditioned medium (Bendtzen et al. 1986), indicating that IL-1β may play an important role in the molecular mechanisms underlying autoimmune β-cell destruction.

Since then, IL-1β signaling and the underlying mechanisms of IL-1β-induced β-cell destruction have been investigated. Importantly, IL-1β induces its own and the expression of other cytokines, e.g., IL-2, -3, -6, and interferons (Dinarello 1988). In turn, cells that produce IL-1β also respond to IL-1β (Warner et al. 1987). IL-1β initiates signal transduction by binding to IL-1R1 in the β-cell. This leads to docking of the IL-1RAcP to the IL-1/IL-1R1 complex, which is followed by recruitment of the adaptor protein MyD88. IRAK-4, Tollip, and IRAK-1 are then recruited, allowing IRAK-1 to activate TRAF6, which in turn triggers activation of TAK1. TAK1 is able to stimulate two main pathways: the IKK–NF-κB pathway and the mitogen-activated/stress-activated protein kinase (MAPK/SAPK) pathway (Frobose et al. 2006). In addition to TAK1, MEKK1 seems to participate in the activation of both NF-κB and SAPK in β-cells (Mokhtari et al. 2008). Phosphorylation of I-κB, a cytosolic inhibitor of *NF-κB*, by IKK leads to I-κB degradation and NF-κB translocation to the nucleus, thus regulating the transcription of many target genes, such as iNOS expression and NO production, a toxic reactive radical. Consistently, interfering with NF-κB activation decreases IL-1β-induced β-cell death (Giannoukakis et al. 2000; Kim et al. 2007).

IL-1β can also activate protein kinase C delta, which leads to β-cell apoptosis presumably through iNOS expression (Carpenter et al. 2001, 2002). Notably, IL-1β induces *Fas* expression on β-cells (Augstein et al. 2003; Stassi et al. 1995), increasing their sensitivity to FasL and accelerating apoptosis via cleavage of downstream caspases [see Fig. 2 and reviewed in Donath et al. (2003)]. A distal consequence of IL-1β signaling in β-cells is the induction of endoplasmic reticulum (ER) stress. IL-1β depletes ER Ca^{2+}, leading to ER stress and induction of several ER stress markers including CHOP. The induction of ER stress by IL-1β can be prevented by inhibition of iNOS, suggesting that NO mediates ER stress (Cardozo et al. 2005). This is consistent with the notion that a chemical NO donor causes ER Ca^{2+} depletion and ER stress (Oyadomari et al. 2002). What is currently unclear is the importance of ER stress in IL-1β-induced β-cell impairment. Studies addressing the role of ER stress-induced CHOP so far indicate that ER stress and CHOP do not contribute to cytokine-induced β-cell death (Akerfeldt et al. 2008). Thus, while there is little doubt that ER stress is induced in β-cells by IL-1β, it is uncertain whether ER stress contributes to apoptosis or whether it may simply be a secondary effect and thus only plays a minor role, if any, in IL-1β-mediated apoptosis.

The MAPK/SAPK pathways consist of ERK1/2, p38, and JNK1/2, all of which are activated by IL-1β in β-cells (Larsen et al. 1998; Welsh 1996). Using both pharmacological and molecular inhibitor approaches, NF-κB, ERK1/2, p38, and JNK1/2 have been demonstrated to be involved in IL-1β-induced β-cell apoptosis (Abdelli et al. 2007; Bonny et al. 2001; Larsen et al. 1998; Pavlovic et al. 2000; Saldeen et al. 2001).

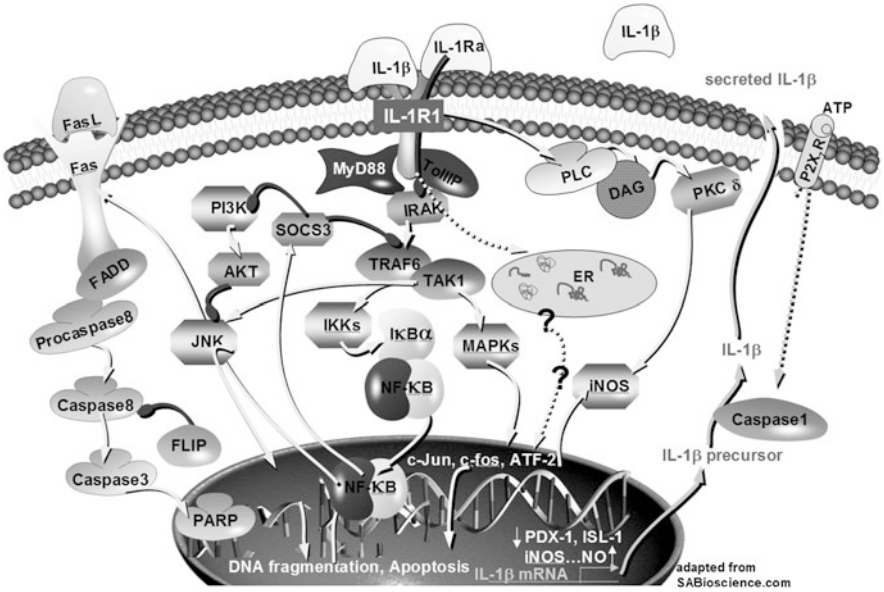

Fig. 2 Mechanisms of IL-1β signaling in the β-cell. Details are described in the text [adapted from Maedler et al. (2009)]

Another target of IL-1β signaling in β-cells is the survival kinase pathway PI3K–Akt. IL-1β reduces both PI3K (Emanuelli et al. 2004) and Akt (Storling et al. 2005) activation. Since Akt is a negative regulator of JNK/SAPK in β-cells (Aikin et al. 2004), reduced Akt signaling may allow increased and sustained proapoptotic JNK activation.

In general, signal transduction initiated by a ligand binding to membrane receptors leads to activation or induction of negative feedback mechanisms to ensure only transient signaling. This is also true for signal transduction evoked by proinflammatory cytokines such as IL-1β. IL-1β induces expression of SOCS-3 in β-cells (Emanuelli et al. 2004; Karlsen et al. 2001). SOCS-3 is a member of a family of proteins that function to terminate cytokine signaling, thereby constituting a negative feedback loop (Ronn et al. 2007). Although IL-1β induces SOCS-3 expression in β-cells, this induction seems to be insufficient to completely terminate IL-1β signal transduction, since prolonged NF-κB and MAPK/SAPK signaling is observed in β-cells exposed to IL-1β (Aikin et al. 2004; Larsen et al. 1998; Ortis et al. 2006). Putatively, either the amount of SOCS-3 induced by IL-1β in β-cells is too low to effectively block signaling or the kinetics of SOCS-3 induction by IL-1β may be abnormally slow in β-cells. In any case, forced SOCS-3 overexpression effectively inhibits IL-1β signaling at the level of TRAF6, leading to dampening of both the NF-κB and MAPK/SAPK pathways, thus protecting against apoptosis (Frobose et al. 2006; Ronn et al. 2008). Interestingly, IL-1β-induced endogenous SOCS-3 targets insulin signaling in the β-cell by associating with the insulin

receptor (IR), thereby preventing activation of IRS and PI3K (Emanuelli et al. 2004). By this mechanism, SOCS-3 induction is likely to contribute to IL-1β-induced desensitization of insulin signaling, which is important for optimal β-cell function. One may speculate whether IL-1β-induced SOCS-3 expression is preferentially directed toward IR signals while leaving the IL-1β signaling cascade unaffected. The IL-1β signaling pathways are shown in Fig. 2.

4 IL-1β Secretion

The primary sources of IL-1β are blood monocytes, tissue macrophages, and dendritic cells. B lymphocytes and NK cells also produce IL-1β (Dinarello 2009). The release of the leaderless cytokine, IL-1β, cannot be initiated through the Golgi apparatus. Inactive pro-IL-1β precursor accumulates in the cytosol and is processed by caspase-1 (also named Interleukin-converting enzyme, ICE) into the mature secreted IL-1β. The maturation occurs in a large multiprotein complex. ATP activates the $P2X_7$ receptor, which forms a pore in response to ligand stimulation and regulates cell permeability and cytokine release (Narcisse et al. 2005).

Resident islet macrophages are fundamental in the development of autoimmune diabetes (Arnush et al. 1998; Lacy 1994) and it is postulated that IL-1β secreted from such intra-islet macrophages results in β-cell destruction (Arnush et al. 1998). Recent studies show that the β-cells themselves are able to secrete IL-1β, which is induced by double-stranded RNA, a mechanism by which viral infection may mediate β-cell damage (Heitmeier et al. 2001) by elevated glucose concentrations (Boni-Schnetzler et al. 2008; Maedler et al. 2002) and by free fatty acids (Boni-Schnetzler et al. 2009).

A recent study shows that glucose-induced IL-1β secretion involves Caspase-1 activation mediated by the NALP3 inflammasome. The inflammasone is activated by bacterial toxins and endogenous stress signals (e.g., ATP and β-amyloid) through the formation of reactive oxygen species (Schroder et al. 2010; Zhou et al. 2009). Glucose-induced IL-1β secretion is prevented in $NALP3^{-/-}$ mice, indicating that IL-1β is generated through glucose-induced ROS production and oxidative stress (Zhou et al. 2009). The thioredoxin (TRX)-interacting protein (TXNIP), which has been linked to insulin resistance (Parikh et al. 2007), functions as an activator of NALP3. In line with this data, another recent study shows that TXNIP is highly increased by elevated glucose in β-cells and that TXNIP-deficient islets are protected against glucose toxicity (Chen et al. 2009).

Despite the high expression of IL-1R1 in β-cells, expression of the NALP3 inflammasone components NALP3, ASC, and Caspase-1 show relatively low expression levels (Zhou et al. 2009), which may explain the modest release of IL-1β from islets.

Upregulation of the Fas receptor plays a central role in the mediation of β-cell death (Cnop et al. 2005; Donath et al. 2005). IL-1β rapidly induces Fas upregulation, whereas glucose only induces Fas in chronic conditions (Elouil et al. 2005).

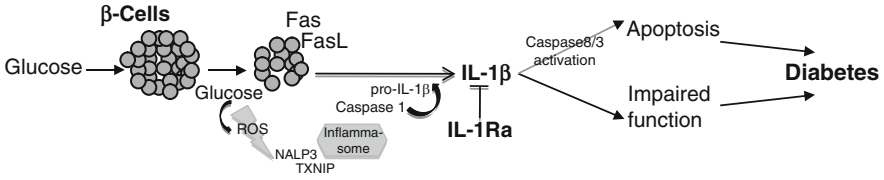

Fig. 3 Dual role of glucose on β-cell turnover. Stimulation of β-cells with glucose induces insulin secretion and β-cell proliferation. In contrast, chronic glucose exposure leads to upregulation of the Fas receptor and ligation with FasL to caspase activation, apoptosis, and impaired function, which contributes to β-cell failure in diabetes. Under such conditions, IL-1β is produced and secreted by the β-cell. This is mediated through ROS-induced induction of the NALP3 inflammasome, which activates Caspase-1 and maturation of active IL-1β from pro-IL-1β. Preincubation of the islets with the naturally occurring IL-1 antagonist interleukin-1 receptor antagonist (IL-1Ra) inhibits glucose-induced apoptosis and improves β-cell function and could therefore be a valuable tool for diabetes therapy

The dual role of glucose on β-cell turnover is illustrated in Fig. 3. While glucose promotes insulin secretion and β-cell survival in the short term, chronic glucose induces Fas upregulation, IL-1β secretion, which leads downstream to caspase cleavage, β-cell death, and loss of insulin secretion.

In two animal models, *Psammomys obesus* and Goto-Kakizaki (GK) rat, pancreatic β-cells express IL-1β under hyperglycemic conditions (Maedler et al. 2002; Mine et al. 2004). In *P. obesus*, normalizing hyperglycemia with phlorizin, an inhibitor of the renal tubular glucose reuptake, inhibited intra-islet IL-1β expression (Maedler et al. 2002). In contrast, Jorns et al. found no IL-1β expression within the islets (Jorns et al. 2006). IL-1β production by islet cells was confirmed in several studies (Boni-Schnetzler et al. 2008; Venieratos et al. 2010; Welsh et al. 2005; Zhou et al. 2009). While glucose-induced IL-1β mRNA production was not found in human islets that had been preincubated in suspension for 3–5 days (Welsh et al. 2005), Boni-Schnetzler et al. show that glucose response in islets is negatively correlated with basal IL-1β expression levels (Boni-Schnetzler et al. 2008). These studies show that IL-β may also mediate β-cell destruction in Type 2 diabetes [T2DM, reviewed in Donath et al. (2005)]. It is tempting to suggest IL-1β as a target for the treatment of diabetes. However, whether changes in circulating cytokines are physiologically relevant in the face of locally produced inflammatory mediators remains unknown.

5 Blocking IL-1β Signals Protects the β-Cell

As described above, IL-1β has been shown to impair insulin release, to induce Fas expression, thus enabling Fas-triggered apoptosis in rodent and human islets (Corbett et al. 1993; Giannoukakis et al. 1999, 2000; Loweth et al. 1998, 2000; Maedler et al. 2001; Mandrup-Poulsen et al. 1985, 1986, 1993; Rabinovitch et al.

1990; Stassi et al. 1997), and to share similarities with glucose-induced apoptosis (see Fig. 3). In parallel to the essential role of glucose in mediating insulin secretion and proliferation, a low concentration of IL-1β also stimulates insulin release and proliferation in rat and human islets (Maedler et al. 2006; Schumann et al. 2005; Spinas et al. 1986, 1987, 1988). The beneficial IL-1β effects seem to be partly mediated by the increased secretion of the naturally occurring anti-inflammatory cytokine and antagonist of IL-1α and IL-1β, the interleukin-1 receptor antagonist (IL-1Ra). Since it was discovered in 1987 (Dinarello 2000; Seckinger et al. 1987a, b), four forms of IL-1Ra have been described, of which three are intracellular proteins (icIL-1Ra I, II and III) and one is secreted (sIL-1Ra) (Arend and Guthridge 2000). Similar to IL-1β, IL-1Ra binds to type 1 and 2 IL-1 receptors but lacks a second binding domain. Therefore, IL-1Ra does not recruit the IL-1 receptor accessory protein, the second component of the receptor complex.

Endogenous production and secretion of IL-1Ra limits inflammation and tissue damage (Dinarello 2009). In vivo, exogenous IL-1Ra counteracts low-dose streptozotocin-induced diabetes (Sandberg et al. 1994) and autoimmune diabetes (Nicoletti et al. 1994) and promotes graft survival (Nicoletti et al. 1994; Sandberg et al. 1997; Stoffels et al. 2002; Tellez et al. 2007) and islet survival after transplantation (Satoh et al. 2007).

We have recently shown that IL-1Ra is secreted from the β-cell and expressed in β-cell granules (Maedler et al. 2004). IL-1Ra protects cultured human islets from the deleterious effects of glucose (Maedler et al. 2002) as well as IL-1β (Mandrup-Poulsen et al. 1993; Sandberg et al. 1997, 1993; Stoffels et al. 2002; Tellez et al. 2005). Inhibition of IL-1Ra with small interfering RNAs or long-term treatment with leptin leads to β-cell apoptosis and impaired function, which may provide a further link between obesity and diabetes.

The definite secretion and regulation mechanisms of IL-1Ra are unknown. Like IL-1β, IL-1Ra may also be secreted by a leaderless pathway via activation of the $P2X_7$ receptor (Glas et al. 2009; Wilson et al. 2004). In pancreatic islets from obese individuals, $P2X_7$ receptors are highly expressed and these receptors were almost undetectable in T2DM (Glas et al. 2009). In accordance with the $P2X_7$ receptor expression levels, increased IL-1Ra serum levels correlate with obesity and insulin resistance (Abbatecola et al. 2004; Meier et al. 2002; Ruotsalainen et al. 2006; Salmenniemi et al. 2004), but IL-1Ra is decreased in T2DM (Marculescu et al. 2002). Recent results from the Whitehall Study show that IL-1Ra levels are increased before the onset of T2DM (Herder et al. 2008), which are consistent with findings in mice fed with a high fat/high sucrose diet (HFD). IL-1Ra levels were increased after 4 and 8 weeks of diet together with an increase in β-cell mass and body weight. Serum concentrations of IL-1Ra are influenced by adipose tissue, which is a major source of IL-1Ra (Juge-Aubry et al. 2003). After 16 weeks, when the HFD-fed mice displayed glucose intolerance and β-cell apoptosis, IL-1Ra levels were lower than in the normal diet-fed mice. Mice deficient for the $P2X_7$ receptor were unable to compensatorily increase β-cell mass in response to the HFD feeding and had no adaptive increase in IL-1Ra levels (Glas et al. 2009).

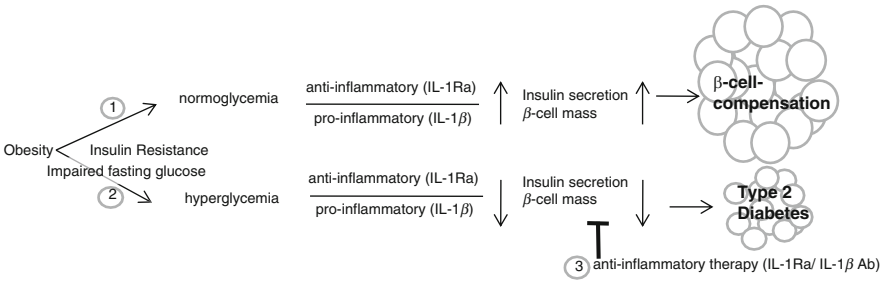

Fig. 4 Our hypothetical model illustrating the consequence of obesity on the development of Type 2 diabetes. (1) When IL-1Ra is highly expressed in the β-cell and the IL-1Ra/IL-1β balance is toward the protective IL-1Ra, β-cell mass and insulin secretion increase. The β-cell is able to adapt to a situation of higher insulin demand. (2) On the other hand, decreased β-cell expression of IL-1Ra, together with hyperglycemia-induced β-cell production of IL-1β, shifts the balance toward the proapoptotic IL-1β, leading to decreased β-cell mass, impaired β-cell function, and increased β-cell apoptosis. Glucose levels can no longer be regulated. This results in a vicious cycle and Type 2 diabetes develops. (3) But overexpression of IL-1Ra could reverse the process and protect from hyperglycemia-induced β-cell apoptosis [adapted from Maedler et al. (2009)]

The increased IL-1Ra could be an attempt of the body to counteract the deleterious effects of IL-1β and to preserve β-cell survival, insulin secretion, and insulin sensitivity. It is hypothesized that IL-1Ra could have an additional metabolic effect that leads to insulin resistance. However, when we treated mice daily for 12 weeks with IL-1Ra, we did not observe changes in insulin sensitivity at any time point (Sauter et al. 2008).

Whether serum IL-1Ra levels would explain the progression of diabetes in obese individuals and whether serum IL-1Ra affects IL-1Ra expression in the β-cell is not known. We hypothesize that a decreased β-cell IL-1Ra expression could trigger the progression from obesity to diabetes and high IL-1Ra expression could possibly protect the β-cell and enable it to adapt to conditions of higher insulin demand; this is illustrated in the cartoon shown in Fig. 4.

5.1 Lessons from IL-1 Mouse Models

Having shown the deleterious effects of IL-1β on the β-cell, one would hypothesize that the IL-1β-knockout mouse would be the ideal model for improved β-cell survival and function. Conversely, IL-1β-KO mice show impaired glucose tolerance, decreased β-cell mass, and decreased expression of β-cell transcription factors (e.g., PDX-1 and Pax-4) (Maedler et al. 2006), indicating that IL-1β has a dual role in the β-cell and activated pathways, e.g., FLIP, Fas, and NF-κB might be needed for insulin secretion and survival (Maedler et al. 2006; Liadis et al. 2007; Schumann et al. 2007). In line with these data, Caspase-8-knockout (Liadis et al. 2007) and Fas-deficient mice (Schumann et al. 2007) show impaired glucose

tolerance. NF-κB is for a long time known to be responsible for IL-1β-induced β-cell destruction (Flodstrom et al. 1996). In contrast, NF-κB also induces activation of the antiapoptotic gene A20, which protects against cell death (Liuwantara et al. 2006) and promotes insulin secretion (Hammar et al. 2004). β-Cell-specific NF-κB depletion accelerates diabetes in the NOD mouse (Kim et al. 2007).

Despite their basally impaired glucose tolerance, IL-1β-KO mice are protected against the diabetogenic effects of the HFD as well as against glucotoxicity (Maedler et al. 2006), which supports the concept that IL-β mediates nutrient-induced β-cell dysfunction during the development of T2DM.

In NOD mice, IL-1R deficiency slows but does not prevent diabetes progression (Thomas et al. 2004), and caspase-1 (interleukin-converting enzyme) deficiency has no effect on diabetes progression (Schott et al. 2004), although both IL-1R subtype 1 and caspase-1 are highly expressed in islets from wild-type NOD mice (Jafarian-Tehrani et al. 1995). It is possible that pathways other than IL-1β signals are involved in diabetes in NOD mice since it was shown that IL-10 promotes diabetes in NOD mice independent of Fas, perforin, TNFR 1, and TNFR 2 (Balasa et al. 2000).

5.2 Blocking IL-1β Signals In Vivo Inhibits Diabetes Progression

Recently, the hypothesis that blocking IL-1β as a successful strategy for the therapy of T2DM has been proved by several studies. Daily injection of IL-1Ra in mice fed an HFD improved glycemia, glucose-stimulated insulin secretion, and survival (Sauter et al. 2008), reduced hyperglycaemia, and reversed the islet inflammatory phenotype in the GK rat (Ehses et al. 2008). Treatment with an IL-1β antibody also improved glycemic control in diet-induced obesity in mice (Owyang et al. 2010; Osborn et al. 2008).

Importantly, results from a recent clinical study in patients with T2DM showed that IL-1Ra improved glycemic control and β-cell function (Larsen et al. 2007). After 13 weeks of treatment, C-peptide secretion was increased and inflammatory markers, e.g., interleukin-6 and C-reactive protein were reduced in the IL-1Ra group. HbA1c was significantly lower in the IL-1Ra compared to the placebo group, which correlated with the body surface area in the IL-1Ra group. The dose of 100 mg IL-1Ra was given daily to the patients without weight adjustment. Currently, ongoing trials that include dose adjustment to the body weight may result in better glycemic control in the higher body surface area group. The effect of interleukin-1 antagonism on β-cell function is currently tested in patients with recent onset of T1DM (Pickersgill and Mandrup-Poulsen 2009). Both IL-1Ra and anti-IL-1β antibody Xoma 052 do not completely block IL-1β signaling. While IL-1Ra is a competitive antagonist to IL-1β, XOMA 052 has a novel mechanism of action that reduces IL-1β activity by 40- to 50-fold rather than completely blocking it (Donath et al. 2008; Owyang et al. 2010). Given the dual

role of IL-1β on β-cell survival and insulin secretion, this may be an important characteristic of both drugs.

As shown by these recent studies, blocking IL-1β signaling may be a powerful new treatment for T2DM, which does not rely on replacing insulin exogenously but acts at the level of the β-cell to improve β-cell survival and to improve endogenous insulin secretion and action. Moreover, blocking IL-1β may also improve insulin sensitivity. Further studies will be necessary to clarify the contradiction of IL-1Ra's modulation of insulin sensitivity and the impact of IL-β on β-cell survival in T2DM.

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