How biologics targeting the IL-1 system are being considered for the treatment of type 2 diabetes

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Metabolic diseases are associated with activation of the innate immune system in various tissues and characterized by elevated inflammatory factors and the presence of immune cells. Type 2 diabetes develops when islet beta cells are deficient in producing sufficient insulin to overcome peripheral insulin resistance. Intra-islet IL-1 β activity diminishes beta cell function and survival and governs islet inflammation. Targeting the IL-1 system with the IL-1 receptor antagonist IL1Ra improved insulin secretion, glycaemia and reduced systemic inflammation in a proof of concept study with patients with type 2 diabetes. Currently, long lasting and specific IL-1 β blocking antibodies are being evaluated in clinical trials and this may lead to a novel cytokine-based treatment for type 2 diabetes.

Introduction to diabetes and global epidemics

Diabetes is a chronically progressing metabolic disease leading to severe complications such as kidney failure, blindness and cardiovascular events. Currently 366 million people worldwide are affected by diabetes and according to the International Diabetes Federation the numbers are expected to rise to 552 million by the year of 2030 (International Diabetes Federation, available from <http://www.idf.org/>, press release of 14 November 2011). Major risk factors are a sedentary lifestyle, over nutrition and obesity [1]. Rapid economic development in Asian countries increasingly contributes to the global epidemic. Thus, in China the incidence of diabetes increased from 1980 to 2008 from 1% to 10% of the population [2]. Type 2 diabetes (T2D), the most common form of diabetes (80–95% of all diabetes cases), is associated with obesity and insulin resistance and is characterized by a lack of adequate insulin release to compensate for this increased demand [3, 4]. While insulin resistance is highly prevalent in obese individuals or in certain ethnic groups, it is the declining mass and function of the pancreatic insulin producing beta cells, which dictates onset and progression of the disease. In the longitudinal Whitehall II study it was observed that insulin sensitivity gradually decreases 3 years prior to the diagnosis, while insulin secretion first increases and then rapidly

declines 2 years prior to the onset of diabetes [5]. The notion that pancreatic beta cell dysfunction and death plays a major role in T2D development is further supported by whole genome wide association studies, which revealed that the majority of genes associated with T2D are genes, expressed in islet beta cells [6, 7]. Currently established therapies for T2D target either the insulin secretory pathway to increase transiently the insulin secretion or sensitize peripheral tissues to the action of insulin. However, there is a need for pharmacological interventions that prevent the progression of beta cell dysfunction and loss.

Type 2 diabetes as an auto-inflammatory disease

A novel treatment concept was proposed based on an underlying mechanism of glucose toxicity in islet beta cells [8]. In contrast to most other cells types, chronically elevated glucose concentrations are toxic for islet beta cells and lead to impaired insulin secretion and apoptosis [5, 9]. Investigating the mediator of glucotoxicity, it was reported that reduced insulin secretion *in vitro* can be partly reversed with the IL-1 β antagonist IL1Ra and that elevated glucose concentrations promote IL-1 β cytokine expression in islets *in vitro*. Further, islets of T2D patients

and of the gerbil *Psammomys obesus*, an animal model of T2D, stained positive for IL-1 β in immunohistochemistry while control islets were IL-1 β negative. Treatment of these diabetic animals with phlorizin provoked a reduction of circulating glucose concentrations by glucosuria and reduced islet IL-1 β expression and thus provided *in vivo* evidence that elevated glucose concentrations upregulated intra-islet IL-1 β expression [8]. These observations in islets linked for the first time IL-1 β , a major effector of the innate immune system, to T2D. Gene array and real time PCR data of beta cells isolated with laser capture microdissection from frozen sections of pancreata of type 2 diabetic and control subjects showed that beta cells from diabetics express increased IL-1 β mRNA levels and that the beta cells themselves are able to produce IL-1 β [10]. These *ex vivo* IL-1 β expression levels of beta cells from diabetic subjects correlated with their blood glucose concentrations. Further, studies on the regulation of IL-1 β mRNA expression in purified beta cells revealed that the strongest inducer of IL-1 β expression is IL-1 β itself, pointing to an auto-stimulated signal amplification process.

Besides elevated glucose, other nutrients such as free fatty acids, which are typically increased in T2D, promote IL-1 β expression in islets via Toll-like receptor (TLR) engagement and subsequent signal amplification through the IL-1 pathway [11]. High glucose concentrations lead to elevated production of reactive oxygen species (ROS), which in turn triggers the formation of inflammasomes in islet beta cells [12]. These multiprotein platforms activate caspase-1 and process the biologically inactive proIL-1 β protein to secreted, mature IL-1 β . Inflammasomes assemble when cells sense danger and stress signals, such as urea crystals in gout, asbestos fibres, LDL-cholesterol, ROS (for review see [13]) or amyloid deposits, which are typically observed in most islets from patients with T2D [14].

IL-1 β secreted upon inflammasome activation not only induces itself, but also acts as a master cytokine inducing many other pro-inflammatory factors such as the chemokine IL-8 or the cytokine IL-6 [10]. These chemokines attract immune cells to islets, which further contribute to the development of tissue inflammation. Indeed, increased numbers of macrophages are present in and around islets from patients with T2D [15, 16]. The picture that finally emerged from the study of the IL-1 system in islets was that an oversupply of nutrients constitutes a metabolic stress signal to islet beta cells which results in local activation of the innate immune system governed by IL-1 β , infiltration of immune cells and subsequent beta cell dysfunction and death [17].

Similar inflammatory processes were also observed in various tissues in obesity and T2D [18, 19]. In fat tissue a variety of pro-inflammatory cytokines are upregulated and there is an increased infiltration and activation of immune cells, mainly macrophages and T cells.

Along with inflammation in various tissues there are elevated levels of pro- and anti-inflammatory factors in the

circulation of obese and prediabetic subjects [20–22]. These include various chemokines, cytokines, C-reactive protein, fibrinogen and serum amyloid A. Interestingly, the IL-1 receptor antagonist, IL1Ra, is also increased prior to the onset of T2D and it has been speculated that this reflects an attempt to limit the ongoing metabolic disturbance [22]. Altogether, the observation of systemic sterile inflammation in various tissues led to the concept that T2D is an auto-inflammatory disease [23].

IL-1 antagonism in type 2 diabetes: proof of concept study

Based on the observed islet inflammation governed by IL-1 β and on the central role of beta cell failure in the pathogenesis of T2D, a proof of concept study was performed where IL-1 β was blocked [24]. IL-1 mediated actions are normally counterbalanced by the natural IL-1 receptor antagonist, IL1Ra, which binds to the IL-1 receptor without inducing signalling [25]. An imbalance of the IL-1 : IL1Ra ratio is the underlying cause for various chronic inflammatory conditions, such as inflammatory arthritis, gout or psoriasis. The IL-1 blocker anakinra (Kineret), a recombinant, nonglycosylated version of the human IL1Ra with an additional amino terminal methionine, was at that time already on the market for the treatment of adult rheumatoid arthritis. It is delivered as subcutaneous injections of 100 mg per single dose. A double-blind, two centre study was conducted with 70 patients with T2D, 34 received anakinra and 36 placebo as a daily injection over 13 weeks. The primary endpoint was the change in glycated haemoglobin (HbA1c), which serves as a measure of the mean blood glucose concentrations over the past 12 weeks. The main outcome was that HbA1c was reduced along with improved beta cell secretory function and a reduction of the systemic pro-inflammatory markers C-reactive peptide and IL-6. Of note, insulin sensitivity in peripheral tissues as measured with a euglycaemic and hyperinsulinaemic clamp, was not increased by anakinra pointing to a preferential targeting of the IL-1 antagonist to the islet beta cells. This 'islet specificity' may be best explained by the observation that islet beta cells express the highest levels of IL-1 receptors of all tissues tested [11]. Of note, a follow-up examination of the patients from this study showed that the beneficial effects on insulin secretion and systemic pro-inflammatory markers were still evident 39 weeks after cessation of IL-1 blockage [26]. In another trial with anakinra in prediabetic subjects, IL1Ra also improved beta cell function without changes in insulin sensitivity [27]. A main safety concern is the possibility of increased numbers of infections upon IL-1 blockage. However, the use of IL1Ra in around 100 000 patients with rheumatoid arthritis showed no significantly increased rate and severity of infections. Presumably, other master cytokines, such as TNF α , may compensate for the lack of IL-1 activity during host

defense from infections. Indeed, in trials with TNF α blockage opportunistic infections were described [28].

Long lasting IL-1 β specific inhibitors

The IL-1 receptor antagonist used for the above described proof of concept study has several features which make it not suitable for the long term treatment of patients with T2D. It has a short half-life of 4–6 h requiring daily to twice daily injections and injection site reactions occur in around 50% of the cases [29]. Another point of consideration, is that IL-1 receptor inhibition blocks not only IL-1 β but also IL-1 α , with unclear consequences.

Two alternative approaches to the treatment with the IL-1 receptor antagonist are currently used in clinical trials that block the IL-1 system in T2D (see Figure 1). The first approach targets the NF- κ B pathway using salsalate, a downstream effector of the IL-1 receptor signalling. The second approach directly targets the receptor IL-1 receptor ligand IL-1 β . While NF- κ B blockage is a more general anti-inflammatory approach lacking specificity for IL-1 signalling [30], antibodies against receptor ligands are highly specific. Therefore, long lasting humanized anti-IL-1 β antibodies were developed by several companies and are currently being tested in phase II and phase III clinical trials [31–34].

A dose escalation trial conducted with gevokizumab, an IL-1 β specific antibody which neutralizes IL-1 β with a K_d of 0.3 pM [35], showed that a single antibody injection resulted in improved HbA1c [34]. The placebo corrected mean reduction of HbA1c was –11.1 %, –0.44 % ($P = 0.071$) and –0.85 % ($P = 0.049$) after 1, 2 and 3 months, respectively. Further, there was a trend to increased insulin

production and significantly reduced circulating inflammatory markers. The antibody had a half-life of 22 days and showed no adverse side effects. These results show that the effects observed in the proof of concept study with IL1Ra on insulin secretion and circulating pro-inflammatory factors, were mainly mediated by IL-1 β and not by IL-1 α . Interestingly, the dose–response was U-shaped, the best improvement was obtained with an intermediate antibody dose while the highest antibody doses showed no toxicity but a reduced efficacy. A possible explanation could be that the high doses of antibody fully block IL-1 signalling and thus not only block the pathological effects of IL-1 β but also the physiological effects, that can be observed at low cytokine concentrations. Indeed, it was reported that IL-1 β has a dual effect in islets. At very low concentrations IL-1 β (low pg ml $^{-1}$ concentrations) promotes beta cell survival and function while higher concentrations and prolonged exposure induce beta cell dysfunction and death [17, 36]. Similar to the safety trial with gevokizumab, studies with two other anti-IL-1 β antibodies also revealed improvements in HbA1c (–0.4, $P = 0.045$) after 12 weeks of treatment along with a reduction in CRP [32] and a modest increase of insulin secretion rates 4 weeks after a single anti IL-1 β antibody injection [31].

Potential effects of IL-1 β on insulin sensitivity

Besides improvements of beta cell function, possible improvements of insulin sensitivity may contribute to the reduced HbA1c observed with IL-1 β inhibitors [37]. Indeed, chronic treatment of isolated fat cells with IL-1 β resulted in

Figure 1

Targets of IL-1 blockage. (A) IL-1 action is blocked with the IL-1 receptor antagonist IL1Ra, (B) IL-1 β is blocked with specific, humanized anti-IL-1 β antibodies and (C) IL-1 signalling is blocked by the non-steroidal anti-inflammatory drug (NSAID) salsalate. cIL-1 α ; cellular IL-1 α , sIL-1 α ; soluble IL-1 α ; IL1RI; IL-1 receptor 1, IL1RacP; IL-1 receptor associated protein

reduced insulin sensitivity [38, 39] and fat cell derived IL-1 β mediated insulin resistance in liver cells [40]. Further, numerous rodent models deficient in IL-1 production point to a role of the IL-1 system in regulating insulin sensitivity in peripheral tissues [41–44]. Production of bioactive IL-1 β requires the formation of inflammasomes to process proIL-1 β and mice genetically deficient in the inflammasome components Nalp3 or AIM or in caspase-1 are protected from the deleterious effects of high fat feeding and from the development of insulin resistance [42–44]. A prevention study with IL1Ra in the GK rat, a genetic model for T2D, also led to improved insulin sensitivity [41]. However, until today in humans IL1Ra intervention in type 2 diabetics and prediabetics has not uncovered significant changes in insulin sensitivity [24, 27]. It is speculated that specific IL-1 inhibition with more potent IL-1 blockers will show improvements of insulin sensitivity in humans. Additional and prolonged studies will be required to answer conclusively whether IL-1 β inhibition in humans not only improves beta cell function but also sensitizes to insulin, as expected by the above described animal and *in vitro* studies.

Outlook

Possible long term effects of anti IL-1 β therapy are now examined in the large phase III clinical trial CANTOS (Canacinumab Anti-inflammatory Thrombosis Outcomes Study) [33]. The primary endpoint of the CANTOS study will be cardiovascular events and secondary endpoints include new onset T2D and diabetes specific markers. This study is based on the numerous preclinical observations that causally link IL-1 β to inflammatory processes leading to atherothrombosis [45, 46]. Animal models deficient in the IL-1 receptor or IL1Ra or inflammasome components display accelerated atherosclerotic plaque formation. Further, cholesterol crystals and minimally oxidized LDL present in atherosclerotic plaques induce the formation of inflammasomes, which regulate IL-1 β maturation and release [47]. The acute phase protein CRP, which was strongly reduced in the circulation of patients with T2D by IL-1 blockage [24], is a predictor for cardiovascular events [48] and cardiovascular diseases are also the leading cause of death in T2D. Seventeen thousand two hundred patients will be included in the study and treated with various doses of anti IL-1 β antibody every 3 months and followed up over 4 years. Such large and long term trials could affirm the auto-inflammatory nature of metabolic disorders and thus lead to a cytokine-based therapy in the clinic.

Competing Interests

There are no competing interests to declare.

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