Preisverleihung 2014

STIFTUNG PROFESSOR DR. MAX CLOËTTA

Heft Nr. 42

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«Targeting Inflammation in the Treatment of Type 2 Diabetes: Time to Start»

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«The Evolution of Mammalian Gene Expression: Dynamics and Phenotypic Impact»

TARGETING INFLAMMATION IN THE TREATMENT OF TYPE 2 DIABETES: TIME TO START

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Abstract

The role of inflammation in the pathogenesis of type 2 diabetes mellitus and associated complications is now well-established. Islets of patients with type 2 diabetes display the typical features of an inflammatory process characterized by the presence of cytokines, chemokines, immune cell infiltration, impaired function and tissue destruction with fibrotic areas. Functional studies have shown that targeting inflammation may improve insulin secretion and sensitivity. In particular clinical proof of concept studies using antagonists of the IL-1β pathway demonstrated the role of the innate immune system in type 2 diabetes. This program has now entered the phase 3 of clinical development. In this article we discuss the mechanisms of islet inflammation in type 2 diabetes and review the opportunity of clinical translation.

According to the International Diabetes Federation, 382 million people were affected by diabetes in 2013 (http://www.idf.org/diabetesatlas)[1]. The prevalence of the disease is expected to rise to 592 million by 2035. Of note, it is a worldwide epidemic, although the vast majority (80 %) of people with diabetes lives in low-income and middle-income countries. Type 2 diabetes is a disease that tends to affect people as they age, especially those with genetic and epigenetic predispositions. It is strongly promoted by over-nutrition and physical inactivity. In predisposed individuals, an insulin secretion defect can be detected concomitantly with a reduced response to insulin-stimulated glucose uptake in fat, liver and adipose tissues, a condition known as insulin resistance[1-5]. At the individual level, insulin resistance remains relatively constant over time, and increases only mildly with age. By contrast, after an initial increase in insulin production, the onset and progression of type 2 diabetes is caused by a continuous deterioration of the insulin-secretory capacity of pancreatic β cells. Thus, insulin secretion no longer compensates for the increased peripheral insulin demand. The progression from prediabetes to diabetes is largely dictated by changes in islet secretory capacity, necessitating an increasing need for medication that culminates in insulin replacement (Figure 1).

Islet inflammation in type 2 diabetes

Multiple mechanisms underlie defective insulin secretion and responses in type 2 diabetes. These include glucotoxicity, lipotoxicity, oxidative stress, ER stress, alterations of the gut microbiota, endocannabinoids, and formation of amyloid deposits in the islet[6-10]. The relative contribution of each of these mechanisms remains unclear. They probably all participate in the pathology of the disease, with inter-individual differences depending on genetic background, nutrition, physical activity, the use of antibiotics, and other environmental factors. Interestingly, all of these mechanisms are associated with inflammatory responses[11-19]. In pancreatic islets, elevated glucose concentrations increase islet cell metabolic activity, leading to elevated ROS formation which promotes NLRP3 inflammasome and caspase 1 activation, thus enabling the production of ma-

[1] *Part of this text is reproduced from Donath MY: Nature reviews Drug discovery 2014, 13:465–76.*

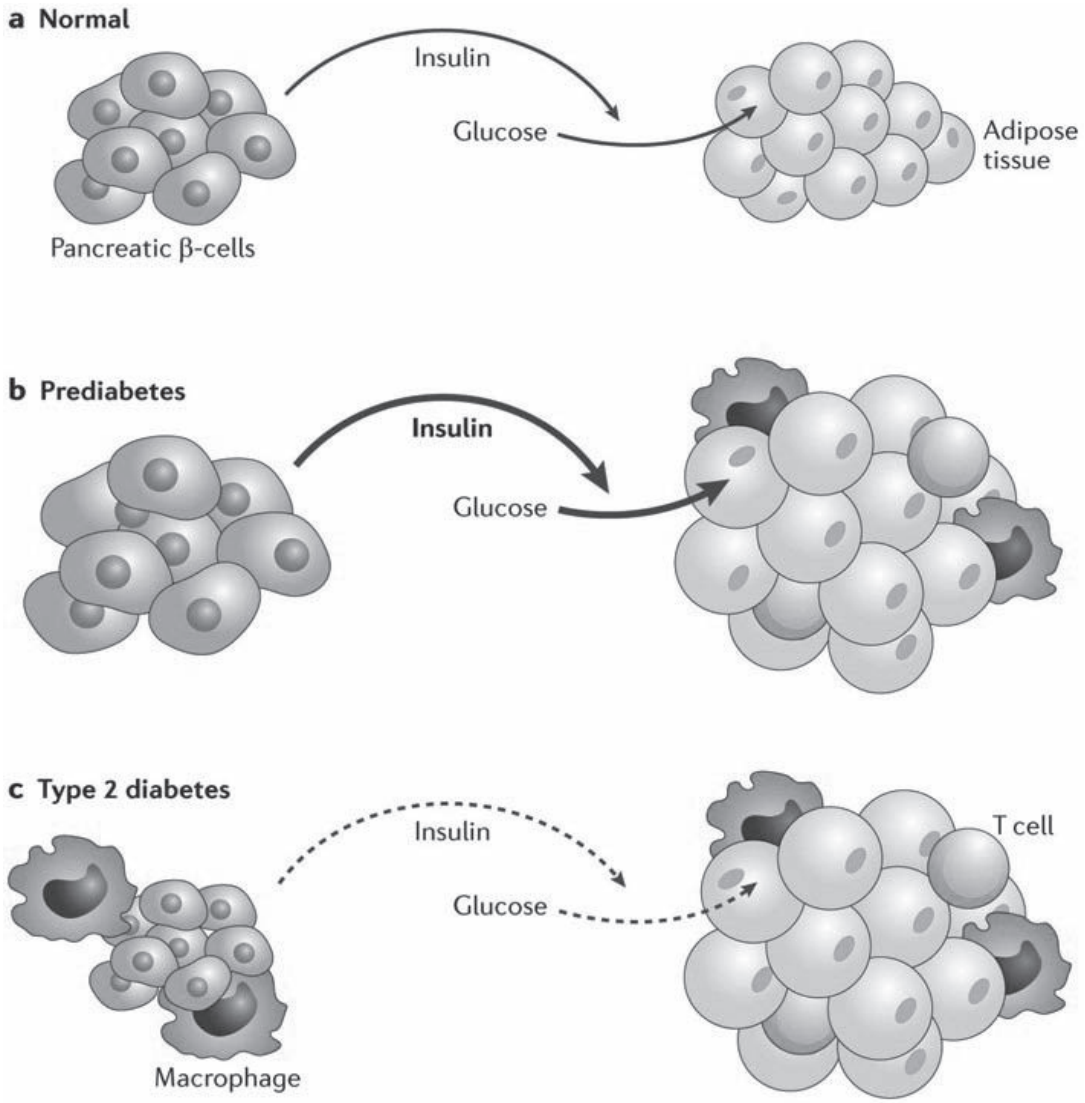

Figure 1. *Type 2 diabetes is caused by a continuous deterioration of the insulin-secretory capacity of pancreatic β-cells, which does not allow compensation for an increased peripheral insulin demand. In healthy individuals, insulin secretion by the pancreatic islet allows for normal glucose disposal in the insulin-sensitive tissues: fat, liver and adipose tissues (Upper panel). During prediabetes, genetic predisposition, overnutrition and physical inactivity reduce the response to insulin-stimulated glucose uptake that is compensated for by an increase in insulin production (Middle panel). In patients with type 2 diabetes insulin secretion no longer compensates for the increased peripheral insulin demand (Lower panel). The progression from prediabetes to diabetes is largely dictated by changes in islet secretory capacity while insulin resistance remains relatively constant over time. (Reproduced from Donath MY: Nature reviews Drug discovery 2014, 13:465–76)*

ture IL-1β[20, 21] (Figure 2). Increased insulin demand and production induces ER stress which also activates the inflammasome[18]. Furthermore,

lipopolysaccharides from bacterial cell walls (endotoxins) or free fatty acid bound to Fetuin-A activate TLR2 and TLR4, leading to NF-κB translocation and induction of inflammation[22, 23]. All these components will induce very low concentrations of islet-derived IL-1β. Initially this inflammatory process may be beneficial, promoting β-cell proliferation and insulin production that compensate for insulin resistance[24]. IL-1β will induce various cytokines and chemokines including IL-6, IL-8, TNFα and MCP1 that lead to the attraction of macrophages and other immune cells,[25-27] probably depending on the duration of IL-1β exposure and stress level. This recruitment of immune cells will be enhanced by the vicious cycle of IL-1β auto-stimulation[28]. Furthermore, islets produce amyloid polypeptide that aggregates to form amyloid fibrils in patients with type 2 diabetes. Recent data suggest that human islet amyloid polypeptide interacts with immune cells to promote the synthesis of IL-1β via the inflammasome[14-16]. Thereby, resident islet macrophages adopt a pro-inflammatory phenotype that induces islet dysfunction. Indeed, depletion of islet macrophages improves glucose metabolism in mice expressing human islet amyloid polypeptide,[14] and the IL-1 receptor antagonist improves glycemia in diabetic mouse recipients of islets isolated from mice expressing human islet amyloid polypeptide[15]. Finally, endocannabinoids which mediate satiety in the hypothalamus[29] and are upregulated in the liver during obesity[30], may also promote macrophage activation[17].

Blockade of IL-1 in the treatment of type 2 diabetes

Since the first observation assigning a role for IL-1β in the pathogenesis of type 2 diabetes[20], numerous observations[31, 32] and clinical studies[33-41] in humans suggest its involvement in impaired insulin secretion and in insulin resistance. An initial proof of concept clinical study randomly assigned 70 patients with type 2 diabetes to receive either anakinra (a recombinant human IL-1–receptor antagonist) or placebo for 13 weeks[34]. Anakinra improved glycaemia and β cell secretory function and reduced markers of systemic inflammation. In accordance with the initial protocol, after anakinra withdrawal, the patients were followed-up for 39 additional weeks in a blinded manner[33]. At that time, insulin secretion was still preserved and inflammation was still decreased, suggesting that IL-1 antagonism has long-lasting effects, possibly owing to an interruption of

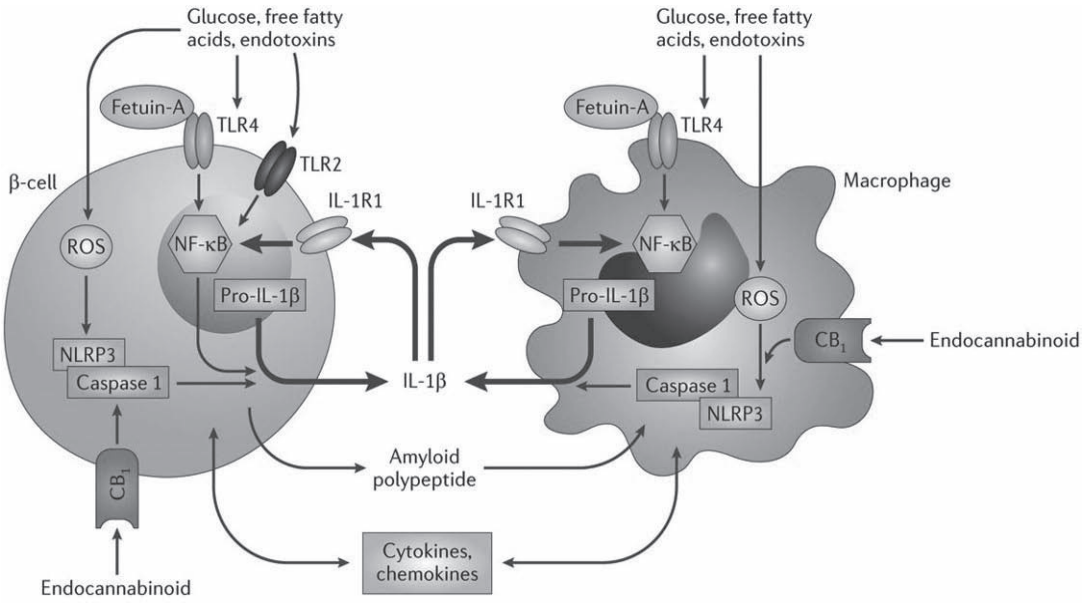

Figure 2. *Islet inflammation in type 2 diabetes. Prolonged exposure of pancreatic islet β-cells to elevated concentrations of glucose and free fatty acids increases islet cell metabolic activity leading to elevated ROS formation. This promotes NLRP3 inflammasome and caspase 1 activation, thus enabling the production of mature IL-1β. Lipopolysaccharides from the bacterial cell wall (endotoxins) or free fatty acid bound to Fetuin-A activate TLR2 and TLR4 and induce the expression of proinflammatory factors via NF-κB. Endocannabinoids may also activate the inflammasome via the CB1 receptor. IL-1β autostimulation further amplifies inflammation, engendering a vicious cycle (thick arrows). IL-1β induces various cytokines and chemokines that lead to the attraction of immune cells. Macrophages may then be activated by human islet amyloid polypeptide, high glucose, free fatty acids, endotoxins, and endocannabinoids leading to deleterious concentrations of IL-1β. (Reproduced from Donath MY: Nature reviews Drug discovery 2014, 13:465–76)*

the vicious cycle of IL-1 auto-induction[28]. Two interesting follow up studies using anakinra in pre-diabetic individuals[35] and in those with impaired glucose tolerance[37] showed that even at these very early stages of the disease, antagonizing the IL-1 system improves β cell secretory function and thus may prevent or delay the onset of type 2 diabetes. Furthermore, in a preliminarystudy in patients with type 1 diabetes who also have insulin resistance caused by obesity and elevated glucose concentrations (glucotoxicity), treatment with anakinra improved insulin sensitivity and glycemic control[36]. These proof of concept studies with anakinra demonstrate the role of IL-1 in the pathogenesis of defective insulin secretion and insulin resistance in type 2 diabetes. However, anakinra requires daily injections and often causes adverse effects at the in-

jection site. Humanized antibodies against IL-1β have therefore been developed by multiple groups and tested in various diseases, including type 2 diabetes. The half-life of these antibodies is around 3 weeks, allowing for monthly or less-than-monthly dosing. Each of these antibodies has had beneficial effects in patients with type 2 diabetes. A single dose of the anti-IL-1β antibody gevokizumab improved placebo-corrected glycated hemoglobin (a measure of blood glucose levels) by up to 0.9 % after 3 months. This single dose also enhanced insulin secretion and sensitivity, and reduced markers of systemic inflammation and of leukocyte activity (C-reactive protein and spontaneous and inducible pro-inflammatory cytokines)[38]. Two studies in patients with type 2 diabetes have been conducted with another anti-IL-1β antibody, canakinumab. The first study used a single dose of antibody in individuals with impaired glucose tolerance or with well-controlled (glycated hemoglobin of around 7.0 %) type 2 diabetes[40]. Although the number of patients was small (27–33 per arm), a trend towards an improved insulin secretion rate was observed. The second study aimed to find the optimal dose of canakinumab needed to improve glucose control in patients with type 2 diabetes[39]. A 4-month course of monthly canakinumab injections resulted in a numerical reduction in placebo-corrected glycated hemoglobin of 0.2 %. This seemingly modest improvement in glycaemia can be explained by the low starting glycated hemoglobin; most patients reached the treatment target of 7.0 %. Finally, weekly injections of the anti-IL-1β antibody LY2189102 for 12 weeks improved placebo-corrected glycated hemoglobin by 0.4 % and improved fasting and postprandial glycaemia and inflammatory biomarkers[41]. Importantly, similar to the original study using anakinra, long-lasting effects of IL-1 antagonism were observed after the end of treatment, with a placebo-corrected decrease in glycated hemoglobin of 0.6 % at week 24.

On the basis of these eight independent clinical studies, IL-1β has the capacity to improve glucose metabolism in patients with diabetes. Importantly, IL-1 antagonism was well-tolerated with no evidence of drug-related adverse events, apart from reactions at the anakinra injection site.

Challenges

Several questions remain in the development of anti-inflammatory drugs for the treatment of type 2 diabetes. These include the magnitude of the effects, safety of the drug, cost of treatment, and whether anti-inflammatory drugs can be used concomitantly for other indications.

To assess the magnitude with which drugs decrease glycaemia it is important to consider the starting level of blood glucose. Several studies of anti-inflammatory drugs were conducted in patients with near-normal glycated hemoglobin levels, which limits the possibility to uncover the maximum glucose-lowering effect as these drugs will not drive insulin secretion to cause hypoglycaemia. By contrast, sulfonylureas and exogenous insulin are equipotent at all blood glucose levels. Furthermore, very few studies with anti-inflammatory agents have been conducted in drug-naive patients. Taking these factors into account, the observed effects with anti-inflammatory drugs are in the same range as the effects obtained with the dipeptidyl peptidase 4 inhibitors that are approved as hypoglycaemic agents: linagliptin decreased glycated haemoglobin by 0.2 % from a baseline of 7.7 %[42]; saxagliptin reduced placebo-corrected glycated haemoglobin by 0.3 % from a baseline of 8.0 %[43].

Type 2 diabetes is a slowly progressing chronic disease. Accordingly, the long-term safety of therapeutic agents is critical. Several anti-inflammatory drugs being evaluated for the treatment of diabetes are already in use for other indications, so some safety data are already available. For example, >100,000 patients with rheumatoid arthritis have been treated with anakinra. Infections were rarely reported, despite concomitant use of other immunosuppressive drugs. Of note, tempering the IL-1 system may even improve the healing of diabetic wounds[44]. This apparently surprising observation can be explained by the normalization of an overactive immune system. This theory remains speculative, and possible adverse effects will have to be balanced with therapeutic benefits.

As the number of people with diabetes increases, the disease will require an increasing proportion of health-care budgets. Therefore, the cost of anti-diabetic drugs is a major issue. In low-income countries, diabetes

care can cost up to 25 % of a family's income (http://www.who.int/mediacentre/factsheets/fs236/en/). However, the most expensive item in diabetes expenditures appears to be hospital admissions for the treatment of long-term complications, not anti-diabetic medications. These hospital costs could be decreased by more efficient anti-diabetic drugs. Furthermore, the effects of some anti-inflammatory agents (such as antibodies) last for several weeks, reducing the amount of required drug.

Individualized clinical translation

An increasing number of diseases seems to be caused or promoted by pathological activation of the immune system[45]. Some of them appear to be driven by molecular pathways that also affect metabolism. Novel therapeutic approaches based on pathways underlying the pathogenesis of the disease rather than on the manifestation of symptoms belonging to a specific clinical discipline could therefore be developed. In several cases this can already be implemented. For example, the role of IL-1β is well-established in mediating acute gouty arthritis[46, 47] and IL-1β antagonism is highly effective to treat this condition[48]. In the large number of patients suffering from both gout and type 2 diabetes, IL-1β blockade may improve the manifestations of both dieases.

Future developments

The existing data support a role for inflammation in the pathogenesis of type 2 diabetes and anti-inflammatory drugs can improve glycaemia without the danger of hypoglycemia. Treatments addressing inflammation, the cause of the disease, could be used to prevent the progressive decrease in insulin secretion[34] and action[49, 50]. Although the adipose tissue and pancreas have been the mostly studied, in patients with type 2 diabetes, disease manifestation in the brain, liver, muscle, heart and periodontal tissues are also associated with signs of inflammation. Therefore treatment may benefit also these organs and improve multiple interconnected metabolic circuits. This interplay is also evident in animal models where the total body genetic or pharmacologic interventions have generate more consistent results compared to tissue specific genetic studies which may not resemble the real physiology.

However, several questions remain unanswered. The interruption of vicious cycles of IL-1β auto-induction (and possibly of other mediators), and the long half-life of some drugs, particularly those that are antibody-based, means that some drugs could have long-lasting effects[33]. The optimal dose and treatment duration therefore need to be carefully considered. Thus, it is conceivable that after restoration of normoglycaemia, some patients may require a boost of anti-inflammatory drugs only a few times per year, during recurrent flares. Future genetic and biomarker studies may profile patients with type 2 diabetes to identify those responding best to a specific anti-inflammatory drug. Inflammation is also an important pathogenic pathway in the development of diabetic complications, including cardiovascular disease[51, 52]. On the basis of this observation, a phase III trial of an IL-1β antagonist (canakinumab) has been initiated (http://www.clinicaltrials.gov/ct2/show/NCT01327846), to investigate the potential of this drug to protect patients from cardiovascular disease and to prevent or improve type 2 diabetes. Finally, some anti-inflammatory treatments (anti-IL-1β) seem to be more effective at improving insulin secretion, while others (anti-TNFα, salsalate) may primarily affect insulin-sensitive tissues, probably reflecting the different pathways involved in the immune response during the course of diabetes. Thus, by combining various anti-inflammatory drugs, broader and more efficacious therapeutic strategies could be developed. So judiciously adding or sequentially using these novel anti-diabetic treatments could provide a tailored solution to treat inflammation in patients with type 2 diabetes.

Table 1. Clinical studies using IL-1 antagonists to treat patients with type 2 diabetes

Mechanism	Drug	Treatment duration	Main findings*	Remarks/Limits	Source
IL-1 receptor blockade	Anakinra (Kineret)	13 weeks	HbA1c↓, leukocyte↓, CRP↓ insulin secretion↑	Dose not adapted to body weight	34
IL-1 receptor blockade	Anakinra (Kineret)	Follow up for 39 weeks	Sustained CRP↓, insulin secretion↑, insulin requirement↓	Follow up study of the one above (N Engl J Med. 356:1517-26; 2007)	33
IL-1 receptor blockade	Anakinra (Kineret)	4 weeks	insulin secretion↑	Prediabetic patients	35
IL-1β antagonsim	Single dose of anti-IL-1β antibody (gevokizumab)	13 weeks	HbA1c↓, CRP↓ insulin secretion↑	High basal HbA1c. Strong effects on gylcaemia	38
IL-1β antagonsim	Single dose of anti-IL-1β antibody (canakinumab)	4 weeks	insulin secretion↑CRP↓	Low basal HbA1c	40
IL-1β antagonsim	Anti-IL-1β antibody (canakinumab)	16 weeks	CRP↓, HbA1c↓ insulin secretion↑(not statistical significant),	Underpowered for low basal HbA1c	39
IL-1β antagonsim	Anti-IL-1β antibody (LY2189102)	12 weeks and follow up for 24 weeks	HbA1c↓, CRP↓ insulin secretion↑	Further improvement of HbA1c at week 24	41
IL-1 receptor blockade	Anakinra (Kineret)	1 week and follow up for 4 weeks	insulin sensitivity↑	Patients with type 1 diabetes and insulin resitance due to obesity and glucotocity.	36
IL-1 receptor blockade	Anakinra (Kineret)	4 weeks	insulin secretion↑ (1st phase insulin secretion improved)	Subjects with impaired glucose tolerance	37

HbA1c, glycated haemoglobin; IKKβ, IκB kinase-β; NF-κB, nuclear factor-κB; CRP, C-reactive protein; FBG, fasting blood glucose. (Modified from Donath MY: Nature reviews Drug discovery 2014, 13:465–76.)

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Acknowledgments
I like to thank my collaborators who contributed so much in all my studies, my mentors and supporters, in particular Professors Jürgen Zapf, Philippe Halban, Adriano Fontana and Michael Fried. The Swiss National Research Foundation for financial support. A very special thanks to the Professor Max Cloëtta Foundation for awarding me the prize 2014 and most importantly for the instrumental support I received in 1999 allowing me to create my research group.