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REVIEW

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An immune origin of type 2 diabetes?

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Abstract Subclinical, low-grade systemic inflammation has been observed in patients with type 2 diabetes and in those at increased risk of the disease. This may be more than an epiphenomenon. Alleles of genes encoding immune/inflammatory mediators are associated with the disease, and the two major environmental factors the contribute to the risk of type 2 diabetes—diet and physical activity—have a direct impact on levels of systemic immune mediators. In animal models, targeting of immune genes enhanced or suppressed the development of obesity or diabetes. Obesity is associated with the infiltration and proinflammatory activity of macrophages in adipose tissue, and immune mediators may be important regulators of insulin resistance, mitochondrial function, ectopic lipid storage and beta cell dysfunction or death. Intervention studies targeting these pathways would help to determine the contribution of an activated innate immune system to the development of type 2 diabetes.

Keywords Adipocytes · Beta cells · IL-6 · Innate immunity · Insulin resistance · Macrophages · Metabolic syndrome · Mitochondria · Type 2 diabetes · Subclinical inflammation

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Abbreviations CRP: C-reactive protein · FasL: Fas ligand · FLIP: Fas-associated death domain protein-like IL-1β converting enzyme-inhibitory protein · ICAM: intercellular adhesion molecule · MCP-1: monocyte chemotactic protein-1 · NF-κB: nuclear factor-κB · PAI-1: plasminogen activator inhibitor-1 · RANTES: regulated upon activation normal T cell expressed and secreted · SOCS: suppressor of cytokine signalling

Introduction

Type 2 diabetes is caused by the failure of beta cells to compensate for insulin resistance. Inflammatory or immunological factors are implicated in both insulin resistance and beta cell failure, and this review will consider evidence suggesting that these might be linked by a common mechanism.

Association of subclinical inflammation with type 2 diabetes

Subclinical systemic inflammation [1–6] and abnormalities of virtually all systemic indicators of inflammation have been reported in type 2 diabetes. These include increases in acute-phase proteins, cytokines and mediators associated with endothelial activation (Table 1), although it is important to note that the degree of immune activation is far below that seen in acute infections. For example, median plasma C-reactive protein (CRP) levels were only twice as high in patients with diabetes as compared with matched control subjects in a population-based German cohort, and serum levels of IL-6 largely overlapped (Fig. 1). We recently extended this study to include chemokines (C. Herder et al., unpublished results). Interestingly, we observed the selective upregulation of certain chemokines rather than a uniform upregulation of all inflammatory mediators. Systemic concentrations of RANTES (regulated upon activation normal T cell expressed and secreted) and IL-8 were elevated, whereas levels of monocyte chemotactic protein-1 (MCP-1) and eotaxin were not.

Table 1 Markers of subclinical inflammation in type 2 diabetes or the metabolic syndrome

Acute-phase proteins	
α-1 Acid glycoprotein	Haptoglobin
CRP	Fibrinogen
Serum amyloid A protein	Orosomucoid
Systemic cytokines/chemokines	
IL-6	Soluble IL-6 receptor
TNF-α	Soluble TNF-α receptors 1 and 2
IL-10	MIF
IL-1+IL-6	MCP-1
IL-18	RANTES
Blood/endothelial cell activation	
Soluble ICAM-1	Soluble VCAM-1
Soluble E-selectin	Soluble P-selectin
von Willebrand factor	Soluble CD40 ligand
TAFI	PAI-1
t-PA	Leucocyte count

All parameters exhibit increased levels in blood of patients with type 2 diabetes and/or in individuals with metabolic syndrome, except for systemic levels of IL-10 which are reported to be decreased [102, 105, 106, 183–188]

MIF Macrophage migration inhibitory factor, *TAFI* thrombin-activatable fibrinolysis inhibitor, *t-PA* tissue plasminogen activator, *VCAM-1* vascular cell adhesion molecule-1

The possibility that these inflammatory changes might be a consequence of type 2 diabetes rather than a contributor to its development can be rejected on two grounds. First, similar degrees of subclinical inflammation are seen in subjects with IGT and those with overt type 2 diabetes (Table 1). Second, prospective studies (Table 2) have reported subtle proinflammatory changes, including raised leucocyte counts and modest increases in circulating inflammatory mediators, many years before the diagnosis of type 2 diabetes [7–22] and at a stage when few would be expected to have IGT or impaired fasting blood glucose levels. Very high levels of CRP did not further increase diabetes risk [17].

Genetic studies support a pathogenic role for immune mediators

Although low-grade inflammatory changes precede type 2 diabetes by many years, immune activation might nonetheless simply reflect an underlying, but unrelated disease process. One way of assessing whether immune reactivity plays a causal or contributory role in the pathogenesis of type 2 diabetes is to search for an association between diabetes risk and immune genes. The number of immune genes identified as containing one or more alleles associated with type 2 diabetes is steadily increasing. However, most studies are small and are not population-based, and the reported associations have yet to be confirmed in different populations. Nonetheless, it is worth noting that alleles in HLA loci and in the genes encoding TNF-α, TNF-β, TNF-α receptor 80, IL-6, IL-6 receptor-α, CRP, TGF-β and plasminogen activator inhibitor-1 (PAI-1) have been reported to be associated with type 2 diabetes and/or the metabolic syndrome [23–36]. Most of these alleles are functional in that they modify the inflammatory response, and the concept of an inflammatory contribution to the pathogenesis of type 2 diabetes would indeed require functional alleles such as these to be associated with diabetes risk.

Lessons from animal models

Another way of investigating the relationship between inflammatory immune reactivity and type 2 diabetes is to study immune gene defects in animals to determine whether these cause or prevent the development of diabetes. While such studies do not allow firm conclusions to be drawn concerning the pathogenesis of human diabetes, they can provide the necessary proof of principle. Several of the immune genes associated with diabetes have been studied in animal models and, as shown in Table 3, immune gene disruption or transgenic overexpression in mice had a major effect on the risk of developing insulin resistance or dia-

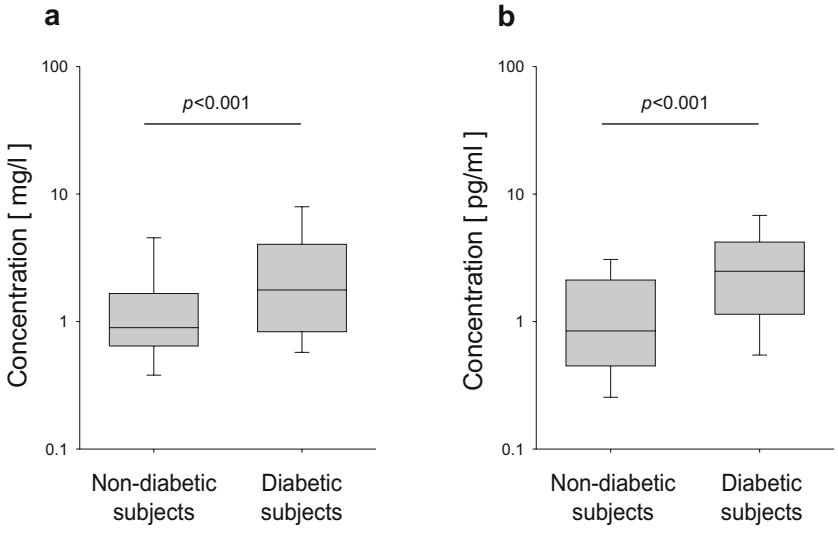

Fig. 1 Elevated systemic levels of CRP (**a**) and IL-6 (**b**) in type 2 diabetes. Comparison of patients with type 2 diabetes (n=152) with non-diabetic control subjects matched for age and sex (n=77) from a population-based sample. Modified after Müller et al. [218] *Box* and *whisker plots* show the 10th, 25th, 50th (median), 75th and 90th percentiles

Table 2 Prospective studies of incident type 2 diabetes

Study	Age at entry (years)	Number of subjects	Follow-up for diabetes	Incident diabetes (*n*)	Immunological risk factor
Atherosclerosis Risk in Communities Study (ARIC) [7, 8]	45–64	12,330	7 years	1,335	Factor VIII ↑ von Willenbrand factor ↑ Leucocyte count ↑ Orosomucoid ↑ Fibrinogen ↑ Sialic acid ↑ Serum albumin ↓
Women's Health Study (WHS) [9]	≥45	27,628	4 years	188	CRP ↑ IL-6 ↑
Cardiovascular Health Study (CHS) [10]	≥65	5,888	3–4 years	45	CRP ↑
Pima Indian Population [11]	≥5	2,088	15 years	695	γ-globulin ↑
Pima Indian Population [12]	18–50	272	5.5 years	54	Leucocyte count ↑
West of Scotland Coronary Prevention Study (WOSCOPS) [13, 189]	45–64	5,974	4.9 years	127	CRP ↑
National Health and Nutrition Survey Epidemiological follow-up Study (NHANES I) [14]	25–74	8,352	20 years	878	Leucocyte count ↑
Japanese male office worker study [15]	35–59	2,953	6 years	154 (263 IFG)	Leucocyte count ↑
Insulin Resistance Atherosclerosis Study (IRAS) [16]	40–69	1,047	5 years	144	PAI-1 ↑
Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Augsburg cohort Study [17]	45–74	2,052	7.2 years	101	CRP ↑
EPIC-Potsdam study [18]	35–65	27,548	2.3 years	188	IL-6 ↑, IL-6+IL-1 ↑
Mexico City Diabetes Study [19]	35–64	1,244	6 years	190 (metabolic syndrome)	CRP ↑ in women only
Hong Kong Cardiovascular Risk Factors Prevalence Study [20]	25–74	228 IGT 228 NGT	2 years	21	CRP ↑
Hoorn study [22]		279	6.4 years	54	CRP ↑ in men only
Nurses' Health Study [21]	30–55	32,826	10 years	737	TNF-α Rec 2 ↑ IL-6 ↑ CRP ↑

betes in response to a high-caloric diet [37–43]. A straightforward explanation is that, in these animal models, TNF-α, IL-6, intercellular adhesion molecule-1 (ICAM-1) or PAI-1 are either directly or indirectly involved in the development of severe obesity and diabetes. However, one important caveat is that, as previously observed [44], the phenotype caused by a gene defect strongly depends on the overall genetic background, i.e. a defective PAI-1 or ICAM-1 gene may not exhibit diabetes- or obesity-regulating properties if introduced onto another genetic background (S. Martin and H. Kolb, unpublished results). It should, however, be acknowledged that immune genes do affect diabetes risk.

Table 3 Animal models that prove the link between inflammatory/immune genes and type 2 diabetes

Inflammatory/immune defects that *cause* insulin resistance or type 2 diabetes in mice on a high-caloric diet
ICAM-1 gene disruption [38]
CD11b gene disruption [38]
IL-6 gene disruption [39]
Inflammatory/immune defects that *prevent* insulin resistance or type 2 diabetes in mice on a high-caloric diet
TNF-α/TNF-α receptors 1 and 2 gene disruption [37]
PAI-1 gene disruption [40, 41]
PAI-1 gene overexpression [42]
Inducible nitric oxide synthase gene disruption [43]

Immune mechanisms in diabetes pathogenesis: insulin resistance

No randomised controlled trial has provided formal proof that high-caloric diets and insufficient muscle work are the major environmental factors promoting the pathogenesis of obesity and type 2 diabetes, and it is unlikely that any such trial will ever be undertaken. The indirect evidence is, however, overwhelming, and we will assume that this concept is valid.

Environmental factors seem to act via two major targets. One is the processing of glucose, fatty acids and other metabolites, as regulated by insulin and other hormones in the majority of tissues, and the other is beta cell function. The resulting insulin resistance and impaired insulin secretion precede the onset of hyperglycaemia by many years, if not decades [45, 46]. The hypothesis of an immune origin of type 2 diabetes is based on the concept that immune inflammatory mediators are responsible for the effects of these environmental factors on insulin resistance and beta cell function. As depicted in Fig. 2, the metabolic concept of the pathogenesis of diabetes considers that tissue function is directly affected by the toxic effect of excess glucose, NEFA and triglycerides, probably mediated by increased oxidative stress. The immunological concept assumes that the production of proinflammatory immune mediators is an essential step in glucotoxicity and lipotoxicity. Conversely, anti-inflammatory immune mediators such as IL-10 would be expected to counteract glucotoxicity and lipotoxicity.

In animal models, both insulin resistance and diabetes can result from diverse genetic defects affecting the function of individual organs, including liver, fat, muscle, islet and neuronal tissue [47–67]. However, as described above, insulin resistance may also result from defects in various inflammatory/immune genes (Table 3). What mediates the effects of environmental factors on insulin resistance? There are indications that dietary effects may be immune mediated and that monocytes, endothelial cells and other cell types respond to elevated concentrations of glucose or NEFA by releasing inflammatory mediators, such as PAI-1, IL-6, TNF-α, soluble ICAM-1, prostaglandins, MCP-1 and IL-1β [68–75].

These responses can be suppressed by experimental strategies aimed at blocking the production or action of free radicals or superoxide [69, 72, 73, 76–79]. It has therefore been proposed that increased mitochondrial activity accounts for increased oxidative stress, which, in turn, causes the expression of several critical immune genes via redox-regulated transcription factors, such as nuclear factor-κB (NF-κB) or stress kinases. The recent observation of a close association between impaired mitochondrial function and insulin resistance or type 2 diabetes supports this concept [80, 81].

The upregulation of proinflammatory gene expression in response to high levels of glucose or fat has also been observed in vivo within a few hours of enteral uptake or parenteral administration of nutrients [82–87]. Furthermore, levels of circulating immune mediators, such as IL-6

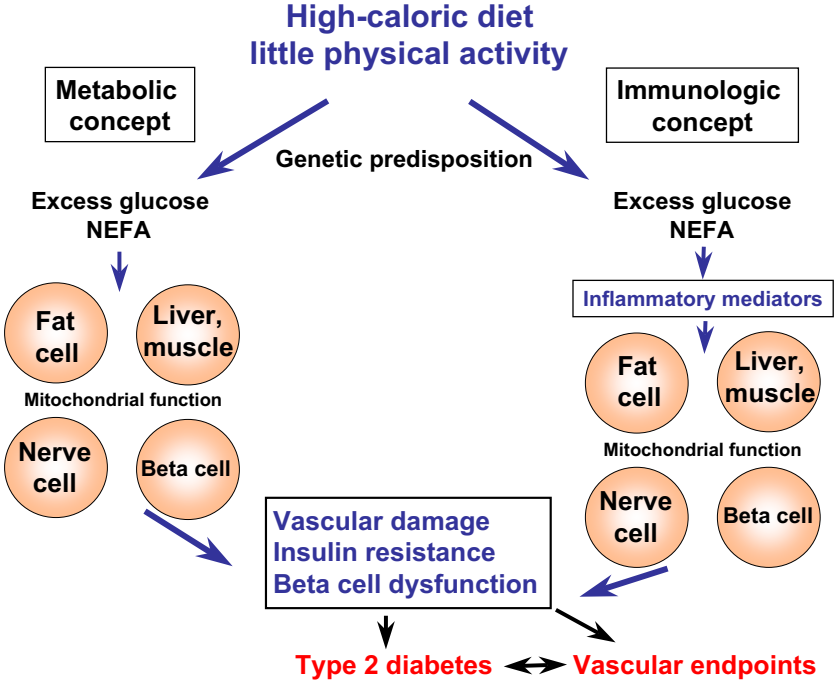

Fig. 2 Metabolic vs immunologic concepts of the pathogenesis of type 2 diabetes. The two major pathogenic factors causing type 2 diabetes appear to be insulin resistance of major peripheral tissues and impairment and gradual loss of beta cell function, both of which are closely associated with vascular damage. The metabolic concept assumes a direct detrimental effect of high levels of glucose and NEFA or triglycerides on target cells limited by the functional capacity of mitochondria. The immunological concept suggests that an essential step in macronutrient toxicity is the induction of inflammatory mediators, which regulate mitochondrial function and damage target cells. Without such an inflammatory response, excess macronutrient supply (including advanced glycation and lipoxation end products) would not be diabetogenic

or IL-18, released in healthy subjects in response to the macronutrient challenge were similar to those seen in type 2 diabetes. An additional, interesting argument is that western diets are usually rich in advanced glycation and lipoxation end-products. Both are glucose-derived compounds that have been shown to elicit a profound proinflammatory response in vitro as well as in vivo [88, 89].

It may be argued that the inflammatory response observed is only an epiphenomenon attributable to excess radical production in mitochondria, whereas the consequences of impaired or unbalanced mitochondrial activity relevant to diabetes are immediate functional defects in fat cells, hepatocytes, beta cells or other cells [90]. The only available experimental evidence to address this comes from animal studies. It has been shown that a high-calorie diet does not induce insulin resistance if certain proinflammatory genes, such as PAI-1 and TNF-α, are non-functional [37, 41]. Furthermore, deletion of other immune genes, such as ICAM-1, renders a high-caloric diet prodiabetic [38]. The intercellular adhesion molecule ICAM-1 is not expressed in mitochondria and is not considered to regulate mitochondrial function. Conversely, immune or inflammatory mediators such as PAI-1 appear to have major effects on mitochondrial function and ectopic triglyceride accumulation in non-adipocytes [41]. Many proinflammatory genes are induced by the transcription factor NF-κB. Impaired activation of NF-κB by deletion of the gene encoding IκB kinase-β in myeloid cells alone protected mice from high-fat-diet-induced insulin resistance in liver and muscle, indicating a key role for activated leucocytes [91]. We recently observed that cytokines modulate the expression of uncoupling protein-2, a major regulator of thermogenesis and substrate oxidation [92]. The capacity of mitochondria to process large quantities of substrate may therefore be modulated by low-grade inflammation.

The induction of low-grade inflammation by a high-caloric diet may also occur via the concomitant growth of adipocytes. The observation that systemic levels of many immune mediators are strongly correlated with BMI, fat mass and/or waist circumference [93] has led to the assumption that many circulating immune mediators originate from adipocytes; however, this view may be too simple. Two recent studies in mice and humans provide evidence that obese adipose tissue exhibits macrophage infiltration and that these macrophages are a major source of inflammatory mediators [94, 95]. Infiltrated macrophages account for almost all TNF-α expression and much of the IL-6 expression in adipose tissue. It should be noted that the upregulation of proinflammatory genes in macrophages occurs before circulating insulin levels increase (a marker of insulin resistance). The infiltration of adipose tissue by macrophages is strongly correlated with BMI in humans, suggesting that fat accumulation in adipocytes triggers the influx of macrophages and their activation. This may occur through the release of chemokines from adipocytes [94–96] and/or via the expression of stress proteins on the fat cell surface [97, 98]. Hence, obesity would only result in insulin resistance and type 2 diabetes if macrophage infiltration and activation—'adipositis'—evolved and persisted.

How do proinflammatory immune mediators cause insulin resistance? Many studies have analysed this question, and these will only be summarised here. Immune mediators such as TNF-α and IL-6 can directly interfere with insulin signalling [99–103], and the binding of these cytokines to their cognate receptor on muscle cells or hepatocytes has been shown to induce an intracellular response that interferes with the ability of the insulin receptor to phosphorylate its intracellular targets. The cellular response to insulin is dampened in consequence. One well-described example of this is the induction of the protein suppressor of cytokine signalling-3 (SOCS-3) by IL-6 in hepatocytes. This protein associates with the insulin receptor and suppresses insulin-dependent receptor autophosporylation and IRS-1 phosphorylation [100]. SOCS-3 also binds to IRS-1 and IRS-2, leading to their ubiquitination and proteasomal degradation [104]. Immune mediators also affect insulin sensitivity indirectly by modulating the regulatory function of fat, nerve or other cells, e.g. by influencing the release of leptin or by activating the hypothalamic–pituitary–adrenal axis [105–109].

One final aspect of immune-mediated insulin resistance to consider is the way in which physical exercise/muscle work might counteract insulin resistance. Muscle work is intimately linked with the production of certain immune mediators, and skeletal muscle expresses a large amount of IL-6, which is released into the circulation in response to exercise [110–112]. In contrast, the expression of low levels of TNF-α is unaltered [113]. The production of IL-6 is modulated by the glycogen content of muscle tissue [114], and IL-6 may also be released from the human brain during prolonged exercise [115]. Muscle-derived IL-6 may have beneficial effects, at least within a certain concentration range, since IL-6 inhibits low-grade TNF-α production and stimulates lipolysis and fat oxidation [116, 117]. Intra-arterial acute infusion of IL-6 does not impair whole-body glucose disposal in healthy humans [118]. Although IL-6 administration has been shown to induce hepatic and skeletal muscle insulin resistance in mice [119], the fact that IL-6 deficiency was associated with the development of diabetes in the same species cannot be ignored (Table 3). In obese subjects, IL-6 levels in the central nervous system are negatively correlated with fat mass, and intracerebroventricular IL-6 treatment decreases body fat in rats [120]. Taken together, these findings suggest that the glucose-lowering effect of exercise may indeed be immune mediated.

Immune mechanisms in diabetes pathogenesis: beta cell destruction

The other major issue in the pathogenesis of type 2 diabetes is whether and, if so, how immune mediators are involved in the steady loss of beta cell function which predates the onset of diabetes [121–123]. Metabolic stress resulting from a high-caloric diet and the concomitant detrimental effects of increased glucose or NEFA concentrations on beta cells are considered major contributors to beta cell loss

[74, 122, 124–127], which occurs mainly by apoptosis [128, 129]. The question at issue is whether beta cell damage and apoptosis are direct consequences of the increased mitochondrial generation of oxygen radicals or whether immune/inflammatory mediators are responsible (Fig. 3).

Evidence favouring oxidative stress as a mediator of beta cell apoptosis in type 2 diabetic patients has recently been published [130], and lipid peroxidation was shown to be increased in the islets of patients with type 2 diabetes as compared with control subjects. The islets of diabetic patients contained less cytoplasmic Cu/Zn superoxide dismutase, and there was a clear inverse correlation between oxidative DNA damage and islet beta cell volume density in these patients.

There is controversy as to whether in vitro exposure of human islets to high glucose levels leads directly to beta cell apoptosis [68, 131, 132]. High glucose increased TUNEL staining (evidence of apoptosis) in a dose-dependent manner, and increased expression of the Fas receptor, leading to cleavage of pro-caspase 3 and activation of caspase 3. This probably occurred through transactivation of Fas by Fas ligand (FasL) expressed constitutively by neighbouring islet cells [68, 131, 132]. In contrast, glucose oxidation was unaffected in human islets exposed to high glucose in vitro, and human islets transplanted to hyperglycaemic nude mice did not exhibit ultrastructural signs of apoptosis [68, 132]. One of the differences between the in vitro studies cited above is in the method used to culture human islets. In the former study, human islets were cultured on an extracellular matrix from bovine corneal epithelial cells, whereas in the latter the islets were cultured in free-floating organ cultures. Clarification is needed as to whether this methodological difference affected the outcome of these and other studies, and may explain discrepancies in the literature concerning the expression of FasL on human beta cells [131, 133].

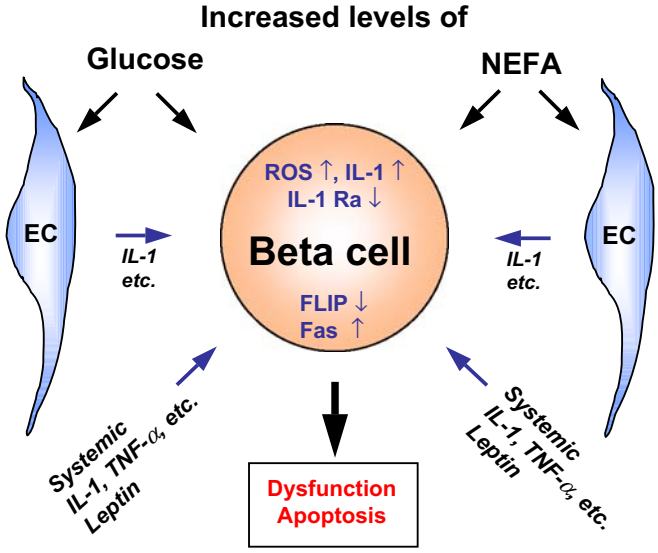

Fig. 3 A model for inflammatory beta cell dysfunction and apoptosis in (pre) type 2 diabetes. Metabolic stressors can cause beta cell dysfunction via increased cytokine action or reduced cytokine antagonist action, and increased free radical production. A reduced expression of the Fas/FasL signalling inhibitor FLIP may accelerate this phenomenon. Toxic actions may be enhanced by products of metabolically stressed endothelial cells and by increased systemic levels of beta cell toxic immune mediators. *IL-1 Ra* IL-1 receptor antagonist; *ROS* reactive oxygen species; *EC* endothelial cells

It is intriguing that glucose-stimulated IL-1 synthesis and secretion and high-glucose-induced beta cell apoptosis were prevented by an IL-1 receptor antagonist [134], although this observation requires independent confirmation. IL-1 expression has also been detected in pancreases from type 2 diabetic patients, but not in control subjects, as well as in *Psammomys obesus* fed a high-energy diet leading to hyperglycaemia [134]. In this model, IL-1 expression in islet beta cells was reversed by the administration of phlorizin, leading to normoglycaemia. It is surprising that IL-1, which usually does not cause beta cell apoptosis in human islets [133, 134], induced apoptosis in these experiments. It is not clear whether this relates to the culture conditions, or to the secretion of cytokines such as TNF-α or IFN-γ in these particular islet preparations. A very recent study from the same group suggested that an IL-1 receptor antagonist is a physiological regulator of beta cell viability, since small interfering RNAs directed against the IL-1 receptor antagonist increased the apoptotic rate, even at basal glucose levels at which beta cell IL-1 production is low [135]. In the same study, leptin, an important adipokine and a member of the IL-6 cytokine family, was shown to induce beta cell apoptosis in human islets by reducing levels of IL-1 receptor antagonist and increasing IL-1β synthesis and secretion [135].

The reduced level of the Fas-associated death domain protein-like IL-1β converting enzyme-inhibitory protein (FLIP) observed in the pancreases of type 2 diabetic patients may also contribute to glucose-induced apoptosis [136]. Interestingly, this inhibitor determines whether Fas-signalling will lead to apoptosis or cell proliferation. This concept is consistent with the observation that the signalling intermediates involved in glucose- and IL-induced beta cell apoptosis in human islets are strikingly similar [137]. The toxic actions of NEFA on beta cell function may be mediated by similar pathways; several lines of evidence point to this. Exposure to NEFA causes oxidative stress [76, 125, 127, 138–141] followed by apoptosis [142], and IL-1 potentiates NEFA toxicity [143]. Exogenous IL-1 or other toxic immune mediators from the islet endothelium [144–147] or from the circulation may act in concert with dietary fatty acids to damage beta cells, although the signalling pathways involved may differ in some respects. While cytokines induce activation of NF-κB and nitric-oxide-dependent endoplasmic reticulum stress, NEFA induce endoplasmic reticulum stress independently of NF-κB and nitric oxide in beta cells [148]. Since recent studies have questioned the role of nitric oxide in cytokine-induced beta cell destruction in vivo [149], and have emphasised mitochondrial perturbation as an important feature, the main effector mechanisms elicited by cytokines and metabolic factors may not differ to a great extent.

In conclusion, there is emerging, although controversial, evidence that metabolic factors—particularly glucose in

(pre) type 2 diabetes—may contribute to beta cell dysfunction and apoptosis. This is thought to occur via metabolic stress leading to the synthesis of inflammatory mediators that elicit intracellular responses that are largely similar to those involved in immune-mediated beta cell destruction in type 1 diabetes.

Immune or inflammatory?

As described above, low-grade inflammation in (pre) type 2 diabetes is generally considered to be a non-specific consequence of metabolic stress. This type of 'inflammatory' response would not require the infiltration of 'inflamed' tissues by (auto)antigen-reactive immune cells—the hallmark of classic inflammation. Although it is conceivable that inflammation is fuelled by non-antigen-specific reactions, we would like to point out that a chronic inflammatory state, such as that observed in (pre) type 2 diabetes, may be driven by antigens, and that chronicity may result from deficient anti-inflammatory feedback loops. Antigens known to be expressed on stressed cells or released from damaged cells, notably stress proteins or certain lipid compounds, are candidates for this role [97, 150–152]. Such stress antigens may drive inflammation in obese adipose tissue, islets or the vessel wall, and heat shock protein 60 and oxidised lipids have already been identified in animal models as antigens that either cause or maintain the atherosclerotic disease process in the vessel wall [153–155].

Limited data are available on islet histology in type 2 diabetes. Although a decrease in beta cell volume, an increased number of alpha cells and the deposition of islet amyloid have been reported, it is not known whether tissue macrophages, dendritic cells or endothelial cells exhibit a proinflammatory phenotype [128, 129, 139, 156–158]. In diabetic patients, the presence of extensive islet amyloidosis does not appear to be associated with the influx of macrophages [159]. However, there are no data on the type of morphological or inflammatory changes that occur in pancreatic islets prior to diabetes onset, for example, in obese individuals with IGT.

Intervention studies

The classical treatment modalities for type 2 diabetes are diet and exercise for weight reduction, and pharmacological intervention by oral hypoglycaemic drugs or insulin, all of which affect the inflammatory state. Weight reduction and/or physical exercise markedly reduce circulating levels of inflammatory mediators such as CRP and IL-6 (Table 4), a response that probably indicates the remission of macrophage-mediated inflammation in adipose tissue as a consequence of altered fat cell metabolism. It could be argued that the remission of systemic low-grade inflammation by lifestyle changes is an epiphenomenon, but, once again, genetic studies imply a causal relationship. For example, it was reported by the Finnish Diabetes Prevention Study that the protective effect of lifestyle changes was associated with polymorphisms in the promoters of the genes encoding TNF-α and IL-6 [160].

Table 4 Interventions that have an impact on the inflammatory state

Inflammatory mediators whose concentrations are reduced by weight loss and/or physical exercise [190–207]
CRP, TNF-α, soluble TNF-α receptor 2, IL-6, IL-18, MCP-1, PAI-1, t-PA, soluble ICAM-1, soluble VCAM-1, P-selectin
Inflammatory mediators whose concentrations are reduced by glucose-lowering drugs [186, 188, 208–217]
Sulphonylurea: TNF-α
Metformin: CRP
Glitazones: CRP, SAA, TNF-α, soluble CD40 ligand, PAI-1
Insulin: CRP, IL-1, IL-6, TNF-α, soluble ICAM-1, MCP-1, PAI-1

SAA Serum amyloid A, *t-PA* tissue plasminogen activator, *VCAM-1* vascular cell adhesion molecule-1

As shown in Table 4, all oral hypoglycaemic agents have anti-inflammatory properties. It is therefore conceivable that a dampening of innate immune reactivity contributes to their therapeutic effects and those of insulin. To date, the preventive or therapeutic potential of anti-inflammatory/immunosuppressive therapy has not been evaluated. Pilot trials with antibodies directed against TNF-α have not shown a beneficial effect on insulin action, in contrast to the observations in mice [161–164]. However, it is not known whether sufficiently high concentrations of TNF-α antagonist were reached in target tissues, or whether immune mediators other than TNF-α are more important for the induction of insulin resistance in humans. Recent studies with TNF-α infusion demonstrated its ability to cause insulin resistance in vivo [165]. The results of therapeutic studies on high-dose aspirin in type 2 diabetes patients are more encouraging: in parallel with a reduction of systemic CRP levels there was a 25% reduction in fasting blood glucose and an even larger decrease in serum triglyceride levels [166].

A clinical trial has been launched to investigate the importance of proinflammatory cytokines in the generation of insulin resistance and beta cell failure in type 2 diabetes. This will test the effect of subcutaneous human recombinant IL-1 receptor antagonist (100 mg/day) vs placebo in patients with type 2 diabetes (collaboration between M. Donath, Division of Endocrinology and Diabetes, University Hospital, Zurich, Switzerland and The Steno Diabetes Centre, Denmark).

Low-grade inflammation and health

Cross-sectional and prospective studies in the general population, the elderly, and centenarians have shown that mildly elevated levels of CRP and proinflammatory cytokines are associated with, or predict, atherosclerosis, myocardial infarction, stroke, depression and Alzheimer's disease, and that longevity is associated with decreased systemic inflammation [105, 167–171]. Here, again, polymorphisms in immune genes modulate risk, implying a pathogenetic significance for immune gene products

[171–173]. Where studied, the upregulation of inflammatory mediators was linked to increased oxidative stress, impaired mitochondrial function and abnormal cholesterol metabolism [174–176]. Interventions targeting cholesterol metabolism or oxidative stress also ameliorated inflammation [167, 177–182]. We therefore conclude that the metabolic concept and the immunological concept are simply two views of the same process, seen from different angles.

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