

# Type 2 diabetes as an inflammatory disease

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**Abstract** | Components of the immune system are altered in obesity and type 2 diabetes (T2D), with the most apparent changes occurring in adipose tissue, the liver, pancreatic islets, the vasculature and circulating leukocytes. These immunological changes include altered levels of specific cytokines and chemokines, changes in the number and activation state of various leukocyte populations and increased apoptosis and tissue fibrosis. Together, these changes suggest that inflammation participates in the pathogenesis of T2D. Preliminary results from clinical trials with salicylates and interleukin-1 antagonists support this notion and have opened the door for immunomodulatory strategies for the treatment of T2D that simultaneously lower blood glucose levels and potentially reduce the severity and prevalence of the associated complications of this disease.

## Insulin resistance

A pathological condition in which insulin becomes less effective at lowering blood glucose levels.

## Endoplasmic reticulum stress

(ER stress). A response by the ER that results in the disruption of protein folding and the accumulation of unfolded proteins in the ER.

## Lipotoxicity

The toxic effects of elevated levels of free fatty acids. These detrimental effects may be functional and reversible, or may lead to cell death.

Major advances have been made in understanding the mechanisms that are involved in the pathogenesis of type 2 diabetes (T2D)<sup>1–5</sup>. A decrease in insulin-stimulated glucose uptake (insulin resistance) is associated with obesity, ageing and inactivity. The pancreatic islets respond to insulin resistance by enhancing their cell mass and insulin secretory activity. However, when the functional expansion of islet  $\beta$ -cells fails to compensate for the degree of insulin resistance, insulin deficiency and ultimately T2D develop. The onset of T2D leads in turn to the development of its long-term consequences: macrovascular complications (including atherosclerosis and amputations) and microvascular complications (including retinopathy, nephropathy and neuropathy). Insulin resistance is typically present throughout the progression from prediabetes to the later stages of overt T2D. By contrast, the onset of T2D and its progression are largely determined by the progressive failure of  $\beta$ -cells to produce sufficient levels of insulin. Interestingly, many insulin-resistant individuals do not become diabetic, because their  $\beta$ -cells are able to compensate for the increased demand for insulin. Only about one-third of obese, insulin-resistant individuals actually develop chronic hyperglycaemia and T2D. The reasons for this heterogeneity are incompletely understood, although genetics and epigenetics probably have roles.

The leading hypothesized mechanisms to explain insulin resistance and islet  $\beta$ -cell dysfunction in T2D have been oxidative stress, endoplasmic reticulum stress (ER stress), amyloid deposition in the pancreas, ectopic

lipid deposition in the muscle, liver and pancreas, and lipotoxicity and glucotoxicity (BOX 1). All of these stresses can be caused by overnutrition<sup>6–10</sup>, although it has been difficult to determine which mechanism is the most important in each tissue and in each model or individual with T2D. It is noteworthy, however, that each of these cellular stresses is also thought to either induce an inflammatory response or to be exacerbated by or associated with inflammation<sup>11–15</sup>.

This Review examines recent evidence that implicates the pathological involvement of the immune system in T2D, dissects potential underlying mechanisms and concludes that obesity is associated with inflammation and that the pathogenesis of T2D can be viewed as an autoinflammatory disease. We also review the recent results from clinical trials using anti-inflammatory drugs to lower blood glucose levels in patients with T2D.

## Evidence for T2D as an inflammatory disease

**Circulating inflammatory factors in obesity and T2D.** Cross-sectional and prospective studies have described elevated circulating levels of acute-phase proteins (such as C-reactive protein (CRP), haptoglobin, fibrinogen, plasminogen activator inhibitor and serum amyloid A) and sialic acid, as well as cytokines and chemokines, in patients with T2D<sup>16–19</sup>. Furthermore, elevated levels of interleukin-1 $\beta$  (IL-1 $\beta$ ), IL-6 and CRP are predictive of T2D<sup>17,20</sup>. Similarly, the serum concentration of IL-1 receptor antagonist (IL-1RA) is elevated in obesity and prediabetes<sup>21</sup>, with an accelerated increase in IL-1RA levels before the onset of T2D<sup>19,22,23</sup>. The expression

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**Glucotoxicity**

The toxic effects of hyperglycaemia. These detrimental effects may be functional and reversible, or may lead to cell death.

**Autoinflammatory disease**

A disease resulting from an attack by the innate immune system on the body's own tissues. By contrast, autoimmune diseases are caused by the pathological activation of adaptive immune responses. Autoimmune and autoinflammatory diseases have some characteristics in common, including shared effector mechanisms.

**M1-type macrophage**

A macrophage that is activated by Toll-like receptor ligands (such as lipopolysaccharide) and interferon- $\gamma$ , and that expresses inducible nitric oxide synthase, which generates nitric oxide.

of IL-1RA is induced by IL-1 $\beta$  and reflects the body's response to counterbalance increased IL-1 $\beta$  activity. Of particular interest is the increased CRP level, which is currently the best epidemiological biomarker for T2D-associated cardiovascular disease<sup>16–19</sup>. Most pro-inflammatory factors that are present at high levels in the blood of patients with T2D are IL-1 dependent, and blocking IL-1 activity has been shown to reduce their concentrations<sup>24–27</sup> (see below).

Elevated levels of circulating IL-1 $\beta$ , IL-6 and acute-phase proteins in T2D may reflect the activation of innate immune cells by increased nutrient concentrations, but the levels of these inflammatory markers may not necessarily reflect the degree of inflammation in individual tissues. For example, the total volume of the pancreatic islets is small compared with the blood volume. Thus, even a high level of islet inflammation is unlikely to demonstrably contribute to the circulating levels of these inflammatory factors. By contrast, the mass of adipose tissue in obese individuals is large, and can make up over half of the body weight in morbid obesity. The liver is also a relatively large organ and is the site for IL-6-induced production of CRP. Thus, the adipose tissue and the liver may disproportionately contribute to the circulating levels of inflammatory markers. Consistent with this, the circulating levels of inflammatory factors in obese individuals with prediabetes are similar to the levels in those with overt diabetes. Furthermore, the levels of circulating CRP or

IL-6 do not predict the efficacy of anti-inflammatory treatments directed towards insulin secretion or insulin resistance<sup>25,28</sup>. In summary, degrees of inflammation vary within individuals and between tissues, and circulating levels of inflammatory factors may not reflect the severity of inflammation within a specific tissue.

**Evidence for inflammation in insulin-sensitive tissues and islets.** The production of tumour necrosis factor (TNF) by cells in the adipose tissue of obese rodents provided early evidence of tissue inflammation in the pathogenesis of insulin resistance and T2D<sup>29</sup> (FIG. 1). Some animal studies<sup>30</sup> and several clinical trials using TNF blockade have failed to demonstrate beneficial effects on glucose metabolism<sup>31–36</sup> (see below). However, a few small studies conducted with obese individuals or patients being treated for alternative conditions suggest that TNF blockers may alter insulin sensitivity or glycaemic parameters, indicating that further prospective studies may be warranted<sup>37–40</sup>.

Despite the ongoing controversy over whether TNF blockade improves glycaemic parameters in patients with T2D, the identification of adipose tissue-derived TNF has been highly instructive. The source of TNF in adipose tissue was originally thought to be the adipocytes themselves in response to obesity. However, this notion has been revised by the discovery of macrophages in adipose tissue, and the finding that obesity results in increased numbers of macrophages and changes in the activation status of these cells. We now appreciate that adipose tissue macrophages produce a significant proportion of the inflammatory factors that are upregulated by obesity<sup>41,42</sup>. The increase in the number of macrophages in adipose tissue largely correlates with the degree of obesity.

Initial studies are beginning to characterize the macrophage subtypes in the adipose tissue under different conditions, including in lean or obese animals and individuals<sup>43,44</sup>, following rapid weight loss<sup>45</sup>, and in lipodystrophy (a condition of adipose tissue loss that is paradoxically associated with insulin resistance and T2D)<sup>46</sup>. Similar to resident macrophages in other tissues, adipose tissue macrophages adapt to their environment; for example, their genomic and proteomic expression profiles are highly distinct from those of resident macrophages in other tissues (H. Shapiro, J. Lee and S.E.S., unpublished observations). Furthermore, the genomic profile of adipose tissue macrophages from lean mice differed from the profile of macrophages that had been recently recruited to adipose tissue during the induction of diet-induced obesity. The recently recruited macrophages have a classically activated, pro-inflammatory phenotype (M1-type macrophages; expressing TNF and inducible nitric oxide synthase) compared with the alternatively activated phenotype (M2-type macrophages; expressing YM1 (also known as CHI3L3), arginase 1 and IL-10) of the resident adipose tissue macrophages from lean mice<sup>43</sup>. The authors proposed that during the progression to obesity, adipose tissue is associated with a phenotypic switch in macrophages from a M2 to a M1 phenotype and that these M1-type macrophages contribute to the

**Box 1 | Potential pathogenic mechanisms in type 2 diabetes**

Several mechanisms have been described to explain impaired insulin secretion and function in type 2 diabetes (T2D). Interestingly, each of these mechanisms, except for amyloid deposition, is thought to have a role in both insulin resistance and islet  $\beta$ -cell failure. Although listed separately, these mechanisms are strongly linked and contribute to tissue inflammation.

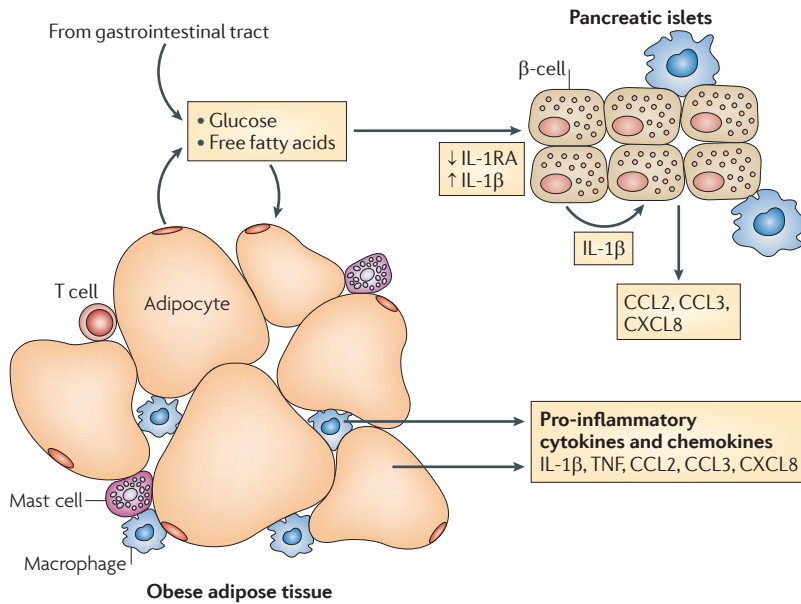
**Glucotoxicity.** Hyperglycaemia *per se* impairs insulin secretion<sup>116,117</sup> and induces  $\beta$ -cell death<sup>81</sup>. Of note, small changes in glucose concentrations, which are apparent years before overt T2D, are toxic for  $\beta$ -cells<sup>7</sup>. *In vivo* studies performed in patients with type 1 diabetes<sup>118</sup> and in rat models of the disease<sup>119</sup> have demonstrated that chronic hyperglycaemia also promotes insulin resistance.

**Lipotoxicity.** Similar to glucose, long-chain free fatty acid levels in the plasma are often increased in states of insulin resistance, impairing  $\beta$ -cell secretory function<sup>120,121</sup> and inducing  $\beta$ -cell apoptosis<sup>122,123</sup> and insulin resistance<sup>124</sup>. Interestingly, saturated fatty acids seem to be particularly toxic, whereas mono-unsaturated fatty acids are protective, and the combination of elevated glucose and free fatty acids has a potentiating effect on T2D (glucolipotoxicity)<sup>125</sup>. Lipotoxicity may act through the circulation or locally by ectopic tissue lipid deposition<sup>126</sup>.

**Oxidative stress.** Several cell stressors (including glucose in particular) lead to the generation of reactive oxygen species<sup>127</sup>.  $\beta$ -cells have very low levels of antioxidative enzymes and are therefore particularly vulnerable to oxidative stress. Oxidative stress is also central to the development of insulin resistance<sup>128,129</sup>.

**Endoplasmic reticulum stress.** In response to insulin resistance,  $\beta$ -cells dramatically increase insulin production. The flux of proteins through the endoplasmic reticulum (ER) of  $\beta$ -cells is quite high under physiological conditions and any further increase is expected to tilt the balance towards ER stress<sup>10,130,131</sup>. ER stress is also thought to have a role in insulin resistance<sup>132</sup>.

**Amyloid deposition.** Islet amyloid deposits are found in the islets of most patients with T2D. However, it remains unclear whether aggregation of human islet amyloid polypeptide is a cause or consequence of  $\beta$ -cell failure<sup>133</sup>.



**Figure 1 | Development of inflammation in type 2 diabetes.** Excessive levels of nutrients, including glucose and free fatty acids, will stress the pancreatic islets and insulin-sensitive tissues such as adipose tissue (and the liver and muscle, not shown), leading to the local production and release of cytokines and chemokines. These factors include interleukin-1 $\beta$  (IL-1 $\beta$ ), tumour necrosis factor (TNF), CC-chemokine ligand 2 (CCL2), CCL3 and CXC-chemokine ligand 8 (CXCL8). Furthermore, production of IL-1 receptor antagonist (IL-1RA) by  $\beta$ -cells is decreased. As a result, immune cells will be recruited and contribute to tissue inflammation. The release of cytokines and chemokines from the adipose tissues into the circulation promotes inflammation in other tissues, including the islets.

Cells of the adaptive immune system are also present in adipose tissue and may contribute to metabolic disruption. T cells generally accumulate in obese adipose tissue in parallel with macrophages<sup>49</sup>, although changes in the relative numbers and activities of CD4<sup>+</sup> and CD8<sup>+</sup> T cells and of T helper 1 (T<sub>H</sub>1), T<sub>H</sub>2 and forkhead box P3 (FOXP3)<sup>+</sup> regulatory T (T<sub>Reg</sub>) cells occur asynchronously and with distinct kinetics. In general, CD8<sup>+</sup> T cells and T<sub>H</sub>1 cells are thought to contribute to the insulin resistance phenotype, whereas T<sub>Reg</sub> cells and T<sub>H</sub>2 cells tend to counter it<sup>50,51</sup>. In this scenario, the macrophages would be the effector cells under the control of the T cells. One of the more interesting of the unanswered questions is whether the T cells recognize antigens that are present in the adipose tissue and, if so, what these antigens are.

T<sub>Reg</sub> cells are of special interest owing to their important role in the maintenance of self-tolerance and the suppression of potentially autoreactive T cells; through these functions they prevent the development of autoimmunity in experimental models in both mice and humans<sup>52,53</sup>. The number of T<sub>Reg</sub> cells in the adipose tissue of lean mice is unusually high at ~50% of the CD4<sup>+</sup> T cell compartment, but this number decreases dramatically in proportion with increasing obesity<sup>50</sup>. This contrasts with the increase in macrophage number that accompanies obesity, and suggests a potential relationship between these two cell populations in adipose tissue. Furthermore, adipose tissue T<sub>Reg</sub> cells express (and are thought to secrete) an unusually high amount of the anti-inflammatory cytokine IL-10, which in lean mice could help to suppress adipose tissue inflammation<sup>50</sup>. Targeted induction of T<sub>Reg</sub> cells improves circulating glucose levels and insulin sensitivity in obese mice, reduces macrophage numbers and TNF levels in adipose tissue, and decreases pancreatic islet hyperplasia<sup>50,51</sup>.

Tissue inflammation has also been detected in the islets of patients with T2D, along with increased levels of cytokines and chemokines<sup>54–56</sup>. Of note, patients with T2D and every animal model of T2D investigated to date display immune cell infiltration of the islets<sup>56</sup>. Islet tissue sections from patients with T2D also show fibrosis, which is found in conjunction with amyloid deposits, and this also argues for an inflammatory response in islets, as fibrosis is a hallmark of chronic inflammation. An interesting recent report shows that human islet amyloid polypeptide (IAPP) induces the secretion of IL-1 $\beta$  by bone marrow-derived macrophages, suggesting that IAPP may contribute to islet inflammation<sup>15</sup>.

Although the concept of insulinitis in T2D is recent<sup>14</sup>, it is well established in type 1 diabetes and is considered to be a characteristic of the disease. The precise aetiology of the insulinitis in both types of diabetes remains to be fully understood, but differences are known to exist; for example, the insulinitis in type 1 diabetes is driven by an autoimmune-mediated process, whereas in T2D it is now thought to be due to autoinflammation. However, a common final effector pathway involving IL-1 $\beta$  seems to be activated in both types of diabetes<sup>12</sup> (see below). Furthermore, additional overlap exists between both diseases (TABLE 1) and in many cases a clear classification is not feasible, arguing for an involvement of the immune system not only in type 1 diabetes but also in T2D.

development of insulin resistance<sup>47</sup>. But by comparing resident adipose tissue macrophages from lean mice with recently recruited immature macrophages from obese mice, these studies compared kinetically distinct populations, and this alone might account for their conclusions. A recent study by Shaul *et al.*<sup>44</sup> concluded that resident CD11c<sup>+</sup> adipose tissue macrophages in the fat pads of obese mice have a mixed M1/M2 phenotype that did not seem to be pro-inflammatory. Therefore, the precise phenotype of adipose tissue macrophages remains to be clarified, and most importantly, we need to know which macrophage phenotype (if any) is related to the development of insulin resistance.

Although macrophages are the most abundant leukocyte population in expanding adipose tissue, other immune cell types are present and their numbers and activities may change during the transition from lean to obese. For example, mast cells were shown to accumulate in subcutaneous adipose tissue during the induction of obesity in mice<sup>48</sup>. Moreover, obese mast-cell-deficient *Ki<sup>t</sup><sup>W-sh/W-sh</sup>* mice and obese mice treated with ketotifen, which blocks mast cell function, had improved insulin resistance compared with wild-type mice or untreated control mice, respectively<sup>48</sup>. However, the pathological role of mast cells in obesity and T2D remains to be clarified, as both of these approaches led to substantial weight loss relative to the control mice, which makes it difficult to distinguish the potential mechanisms, as weight loss itself promotes insulin sensitivity.

**M2-type macrophage**

A macrophage that is stimulated by interleukin-4 (IL-4) or IL-13 and that expresses arginase 1, the mannose receptor CD206 and the IL-4 receptor  $\alpha$ -chain.

***Ki<sup>t</sup><sup>W-sh/W-sh</sup>* mice**

The *Ki<sup>t</sup><sup>W-sh</sup>* (or *sash*) mutation abolishes KIT expression in mast cells, and the mutant mice are deficient in mast cells.

**Insulinitis**

Inflammation of the pancreatic islets during the progression of diabetes. Insulinitis in type 1 diabetes is caused by autoimmunity and in type 2 diabetes by metabolic stressors such as hyperglycaemia and elevated levels of free fatty acids.

Table 1 | Comparison of characteristics associated with type 1 and type 2 diabetes\*

	Type 1 diabetes	Type 2 diabetes	Refs
<b>Age of onset</b>	Mainly young but can occur at all ages	Usually associated with ageing but prevalence is increasing in younger individuals	134–136
<b>Insulin deficiency</b>	Absolute	Relative to the prevailing resistance to insulin	137
<b>Risk factors</b>	Genetics <sup>‡</sup> , obesity, insulin resistance	Genetics <sup>‡</sup> , obesity, insulin resistance	135, 138–140
<b>Insulinitis</b>	Autoimmune	Autoinflammatory	2,12
<b>Autoantibodies</b>	Present in 85–90%	May be present	134–136
<b>Treatment</b>	Insulin	Diet and exercise, oral agents such as metformin; insulin recommended early in the treatment	141

\*No single clinical feature or diagnostic parameter completely discriminates the two diseases<sup>142</sup>. <sup>‡</sup>Genetics are relevant to both type 1 and 2 diabetes, but different susceptibility genes have been identified in different families.

### Inflammatory mechanisms in T2D

The studies discussed above support the hypothesis that inflammation has a role in the pathogenesis of T2D. Here, we discuss some of potential mechanisms involved in the inflammatory response in this disease.

**Hypoxia.** It has been proposed that hypoxia in expanding adipose tissue may induce an inflammatory response. It is well established in oncology that rapidly growing tissue can expand faster than the vasculature that supports its oxygen and nutrient requirements. Hypoxia ensues as oxygen supplies become limited, and compensatory angiogenesis is induced through the production of various angiogenic factors in an attempt to restore the required levels of oxygen and nutrient delivery<sup>57</sup>. Hypoxia and neovascularization are also seen in rodent models of obesity in which the fat mass is rapidly expanding; for example during high-fat feeding<sup>58,59</sup>. Furthermore, hypoxia has been observed in human adipose tissue and contributes to adipose tissue dysfunction<sup>60,61</sup>.

Macrophages accumulate at sites of hypoxia or ischaemia, providing a pathological link between adipose tissue expansion and the induction of inflammation. The recruitment of macrophages to hypoxic or ischaemic tissues has been studied in greater detail in tumour growth, wounds and infections, atherogenesis and arthritis<sup>62</sup>, but the principles seem to be similar for expanding adipose tissue. Hypoxia induces the expression of numerous pro-angiogenic and pro-inflammatory genes in macrophages<sup>63</sup>, suggesting that the recruited macrophages have an important role in resolving hypoxia, possibly in an attempt to repair damaged tissue.

**Cell death.** Adipocyte expansion beyond oxygen and nutrient requirements also seems to lead to adipocyte cell death. This is readily apparent in mice fed a high-fat diet, as dead adipocytes are located throughout their fat pads<sup>64,65</sup>, whereas this is not observed in the fat pads of mice fed a normal diet. The most distinguishing feature of the dead adipocytes is that they are located individually and sporadically throughout the fat pads and are surrounded by macrophages to form what are referred to as ‘crown-like structures’<sup>64,65</sup>. There are higher numbers of crown-like structures in the gonadal white adipose tissue of male mice than in the subcutaneous white

adipose tissue. The high proportions of macrophages that are found in crown-like structures suggest that many of the monocytes that are recruited to expanding adipose tissue in obesity are there to remove cellular debris. However, it does not establish that recruited macrophages are causally linked to the development of insulin resistance.

In contrast to adipose tissue macrophages, islet macrophages were not detected in the vicinity of necrotic or apoptotic cells<sup>56</sup>. Furthermore, islet inflammation is an early event in the development of T2D and is apparent in mice after 8 weeks of high-fat feeding<sup>56</sup>, during which time  $\beta$ -cell function declines but  $\beta$ -cell mass increases without an increase in islet cell death. Therefore, it is unlikely that cell death has an important role in the recruitment of macrophages to the islets. This recruitment may instead be a consequence of islet-derived chemokines that are produced in response to metabolic stress (see below).

**The NF- $\kappa$ B and JNK pathways.** Many of the metabolic stresses that promote insulin resistance and T2D also activate the inflammation- and stress-induced kinases I $\kappa$ B kinase- $\beta$  (IKK $\beta$ ) and JUN N-terminal kinase (JNK)<sup>1,66,67</sup>, suggesting that these kinases may have key roles in the pathogenesis of these conditions. Indeed, IKK $\beta$  activates the transcription factor nuclear factor- $\kappa$ B (NF- $\kappa$ B), and obesity induces the expression of NF- $\kappa$ B target genes, such as pro-inflammatory cytokines, in the liver and adipose tissue<sup>1,66,67</sup>. These cytokines, including TNF, IL-6, and IL-1 $\beta$ , may promote insulin resistance in the tissues where they are produced, such as the liver and adipose tissue, and may also be transported through the circulation to affect more distant sites, including the vessel walls, skeletal and cardiac muscle, the kidneys and circulating leukocytes. The other potentially important kinase, JNK, activates transcription factors such as ELK1, ATF2 (activating transcription factor 2) and JUN, although the potential roles of these JNK-responsive transcription factors in obesity are not well established<sup>68</sup>. Nevertheless, bone marrow transplant and selective genetic ablation experiments have provided ample evidence to support a role for JNK in the inflammatory response to obesity and the development of insulin resistance (see below).

#### Ischaemia

A condition in which the flow of blood to a tissue or organs is less than normal, and which results in injury to that tissue or organ.

In fact, many of the same cytokines that are produced in response to NF- $\kappa$ B activation also activate both JNK and NF- $\kappa$ B in a feed-forward manner. This includes TNF and IL-1 $\beta$ , which activate JNK and NF- $\kappa$ B through the engagement of their specific cellular receptors. Other stimuli that promote insulin resistance and T2D, including free fatty acids (FFAs) and advanced glycation end-products, also act through specific cell surface receptors, such as Toll-like receptors (TLRs) and receptor for advanced glycation end-products (RAGE)<sup>69</sup>. All these extracellular stimuli bind cell surface receptors and activate intracellular pathways that converge on both IKK $\beta$ -NF- $\kappa$ B and JNK signalling.

Bone marrow transplant and selective genetic ablation methods have been used to assess the relative contribution of the JNK and IKK $\beta$ -NF- $\kappa$ B signalling pathways in haematopoietic and non-haematopoietic parenchymal cells in obesity-induced insulin resistance, and to identify the main tissue sites involved. The liver and adipose tissue are important sites for the activation of both pathways. In the liver, this activation occurs in both hepatocytes and myeloid cells such as macrophages, and upregulates the production of pro-inflammatory cytokines, including TNF, IL-6 and IL-1 $\beta$ <sup>66,67,70-72</sup>. Although these pathways are activated in both haematopoietic and non-haematopoietic cells, it is the leukocytes that account for most of the local production of pro- and anti-inflammatory cytokines in the liver and adipose tissue. However, in muscle cells, the activation of IKK $\beta$  and NF- $\kappa$ B results in wasting and cachexia through the activation of the E3 ubiquitin ligase TRIM63 (also known as MURF1)<sup>73</sup>, whereas in the hypothalamus it seems that the IKK $\beta$ -NF- $\kappa$ B pathway affects feeding behaviour and the leptin signalling axis<sup>74</sup>. Therefore, IKK $\beta$ -NF- $\kappa$ B activation in these tissues affects insulin resistance indirectly, through changes in body weight, as opposed to the more direct effects on insulin resistance that result from the activation of this pathway in the liver, adipose tissue and leukocytes.

NF- $\kappa$ B is also activated in islet  $\beta$ -cells through the actions of glucose and IL-1 $\beta$ , and inhibition of NF- $\kappa$ B seems to protect  $\beta$ -cells from various insults, including from the effects of glucotoxicity or multiple treatments with low-dose streptozotocin (a natural chemical that is particularly toxic to  $\beta$ -cells)<sup>55,75</sup>. The NF- $\kappa$ B and JNK pathways are thus activated in multiple tissues in obesity and T2D, and have central roles in promoting tissue inflammation. Accordingly, reducing the activity of these pathways may be of therapeutic benefit (see below).

**IL-6 and insulin resistance.** The roles of IL-6 signalling in insulin resistance have been controversial and at times paradoxical<sup>76,77</sup>. Concentrations of circulating IL-6 and CRP (the hepatic expression of which is induced by IL-6) are increased in obesity and predict the incidence of T2D in predisposed individuals<sup>20</sup>. Hepatic and adipose production of IL-6 are thought to promote insulin resistance<sup>67,76,78</sup>, whereas production of IL-6 by skeletal muscle, especially during intense exercise, is thought to be beneficial<sup>77</sup>. Analysis of hepatocyte-specific deletion of the IL-6 receptor in mice has added to the controversy, as these mice seem to be protected from both local and systemic insulin resistance<sup>79,80</sup>.

**The IL-1 system as a sensor of metabolic stress.** The earliest evidence for an inflammatory process in pancreatic islets arose from the observation that hyperglycaemia induces  $\beta$ -cell apoptosis<sup>81</sup>. By examining the underlying mechanism, it was shown that high glucose concentrations induce the expression of the pro-apoptotic receptor FAS (also known as CD95) on  $\beta$ -cells<sup>82</sup>, which is further upregulated by glucose-induced IL-1 $\beta$  production by  $\beta$ -cells<sup>55</sup>. Therefore, IL-1 $\beta$  and FAS contribute to both the glucose-induced impairment of  $\beta$ -cell secretory function and apoptosis<sup>55,83</sup>.

Additional mechanisms regulate IL-1 $\beta$  expression in islets (FIG. 2). FFAs (such as oleate, palmitate and stearate) stimulate IL-1 $\beta$  secretion and the production of IL-1 $\beta$ -dependent pro-inflammatory molecules in cultured human and rodent islets<sup>84-86</sup>. A combination of moderately increased glucose levels and FFAs was shown to induce an even stronger increase in cytokine production than just FFAs alone<sup>85</sup>.

The underlying mechanisms of 'nutrient' (that is, glucose and FFA)-induced activation of IL-1 $\beta$  are complex. FFAs may stimulate the production pro-inflammatory molecules by direct activation of TLR2 and TLR4, which can sense lipids, or indirectly through FFA metabolites such as ceramide<sup>86-89</sup>. Glucose-induced IL- $\beta$  production is thought to involve the NOD-, LRR- and pyrin domain-containing 3 (NLRP3; also known as NALP3) inflammasome. High concentrations of glucose induce the dissociation of thioredoxin-interacting protein (TXNIP) from thioredoxin under the influence of reactive oxygen species, allowing binding of TXNIP to the NLRP3 inflammasome. This leads to the activation of caspase 1 and the subsequent processing of pro-IL-1 $\beta$  and release of mature IL-1 $\beta$ <sup>90</sup>. Whether reactive oxygen species are indispensable in this process remains unclear.  $\beta$ -cells have very low levels of antioxidative enzymes and are therefore particularly vulnerable to oxidative stress; however, activation of the inflammasome in the absence of reactive oxygen species has been shown in patients with chronic granulomatous disease<sup>91,92</sup>.

Interestingly, deposition of amyloid in the islets is a hallmark of T2D, and human IAPP seems to contribute to the induction of IL-1 $\beta$  production in the islets through the NLRP3 inflammasome<sup>15</sup>. However, the induction of IL-1 $\beta$  secretion by IAPP has only been shown in macrophages, and *in vivo* amyloid deposition requires prolonged high-fat feeding (for a period of 1 year), whereas the first signs of islet inflammation are apparent after 8 weeks<sup>56</sup>, indicating that IAPP-mediated IL-1 $\beta$  secretion may be a late event in islet inflammation. It remains possible that the inflammasome may act as a sensor of metabolic danger<sup>93</sup>, resulting in IL-1 $\beta$  production and the induction of numerous cytokines and chemokines<sup>24,94,95</sup>. Therefore, activation of the inflammasome may contribute to the recruitment of immune cells, which can mediate a broad inflammatory response.

These initial mechanisms of IL-1 $\beta$  induction may be amplified by a cycle of autoinflammation. Indeed, human islets, particularly purified human  $\beta$ -cells, are very sensitive to IL-1 $\beta$  autostimulation<sup>84</sup>. This is probably a consequence of the abundant expression of IL-1

#### Cachexia

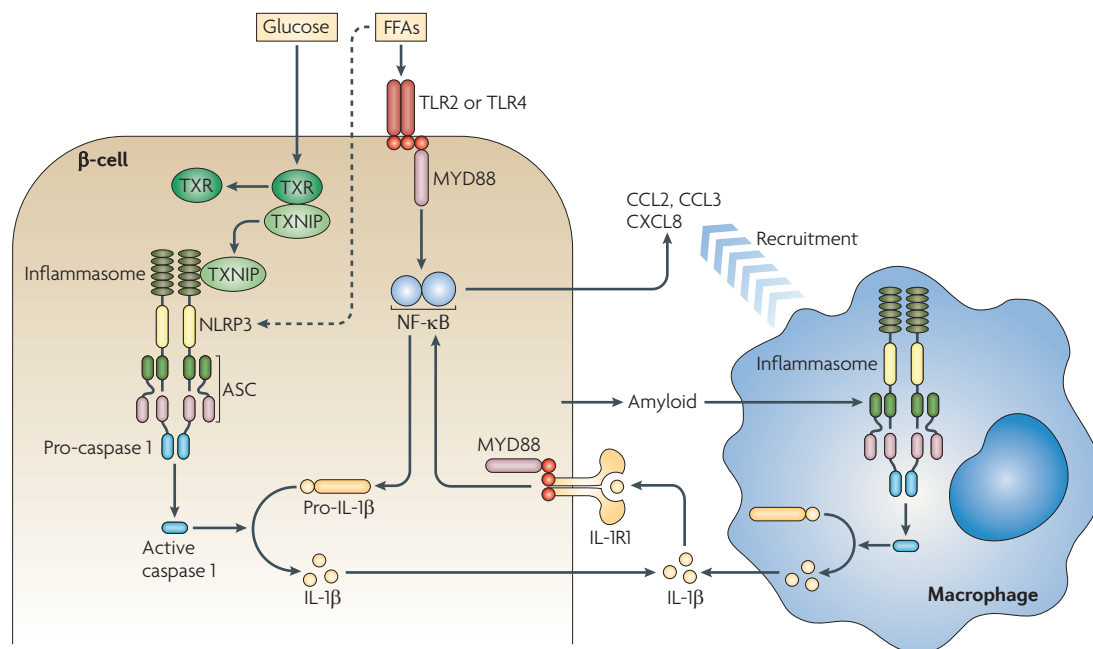
Severe weight loss, muscle wasting and debility caused by prolonged disease. It is thought to be mediated through neuro-immunoendocrine interactions.

#### Leptin

A protein hormone that regulates energy intake and expenditure. It is one of the most important adipose-derived hormones and its production correlates with the mass of adipose tissue.

#### Inflammasome

A molecular complex of several proteins that, when activated, results in the production of active caspase 1, which cleaves pro-interleukin-1 $\beta$  (pro-IL-1 $\beta$ ) and pro-IL-18 to produce the active cytokines.



**Figure 2 | Interleukin-1β-induced inflammation in islets of patients with type 2 diabetes.** High concentrations of glucose promote β-cell production of interleukin-1β (IL-1β) through the dissociation of thioredoxin-interacting protein (TXNIP) from its inhibitor thioredoxin (TXR), resulting in activation of the NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome, activation of caspase 1 and processing of pro-IL-1β into its mature form. IL-1β induces the production of a wide range of cytokines and chemokines such as CC-chemokine ligand 2 (CCL2), CCL3 and CXC-chemokine ligand 8 (CXCL8) through nuclear factor-κB (NF-κB) activation. This is enhanced by free fatty acid (FFA)-induced activation of Toll-like receptor 2 (TLR2) or TLR4 and leads to the recruitment of macrophages. FFAs may also directly activate the NLRP3 inflammasome. Islet-derived amyloid can activate the recruited macrophages through the NLRP3 inflammasome, increasing IL-1β production and the vicious cycle of IL-1β autostimulation through IL-1 receptor type 1 (IL-1R1). ASC, apoptosis-associated speck-like protein containing a CARD; MYD88, myeloid differentiation primary-response protein 88.

receptor type 1 (IL-1R1) by these cells. Analysis of IL-1R1 expression in numerous tissues showed that the highest levels were expressed in mouse islets and by the insulin-producing cell line MIN6 compared with 20 other mouse tissues, including immune tissues such as the spleen and thymus<sup>85</sup>. IL-1β autostimulation of islets can be prevented by reducing NF-κB activity or by blocking IL-1R1 signalling (with IL-1RA, by ligand neutralization or by the genetic elimination of the IL-1R1-associated signalling protein myeloid differentiation primary-response protein 88 (MYD88))<sup>84,85</sup>. Blocking IL-1R1 signalling also inhibits FFA- and glucose-induced upregulation of IL-1β<sup>84,85</sup>.

Another factor that promotes islet inflammation in T2D is a defect in an anti-inflammatory mechanism. IL-1RA is highly expressed in the endocrine pancreas of non-diabetic individuals but is decreased in the islets of patients with T2D, and this enhances the susceptibility of the β-cells to IL-1β<sup>84</sup>. The precise mechanisms responsible for this decrease remain to be elucidated but the adipose tissue-derived hormone leptin might be involved, as it decreases IL-1RA expression in human islets *in vitro*<sup>54</sup>.

Therefore, the IL-1 system is an integral part of the response to metabolic disturbance and IL-1 antagonism has therapeutic potential (see below).

**Chemokines.** Adipocytes may secrete chemokines such as CC-chemokine ligand 2 (CCL2; also known as MCP1), which recruits monocytes. Consistent with this hypothesis, the expression of CCL2 is increased in the adipose tissue of obese rodents and humans<sup>96-99</sup>. Mice with a targeted deletion of either *Ccl2* or its receptor CC-chemokine receptor 2 (*Ccr2*) have decreased numbers of macrophages in adipose tissue<sup>41,98</sup>, whereas transgenic upregulation of *Ccl2* expression in adipocytes results in increased macrophage numbers<sup>100</sup>. However, the metabolic consequences of diminished signalling through the CCL2-CCR2 axis are relatively small, possibly owing to the redundancy between chemokines that recruit monocytes<sup>101</sup>. In addition to CCL2, the expression of CCL3, CCL6, CCL7, CCL8 and CCL9 is increased in adipocytes from mice fed a high-fat diet compared with mice fed a normal diet, suggesting that these chemokines could also have a role in monocyte recruitment<sup>101</sup>. These findings are consistent with a potential increase in chemokine-mediated recruitment of monocytes to expanding adipose tissue, although other chemoattractants such as leukotrienes could also be involved.

Islet cells can also produce a wide range of chemokines in the context of T2D. *In vitro* treatment of islets with high concentrations of glucose and the saturated fatty acid palmitate increases the production of

several biologically active chemotactic factors (CXC-chemokine ligand 8 (CXCL8) and CCL3 in human islets; CXCL1 in mouse islets)<sup>56,85</sup>. Islets isolated from rodent models of T2D (Goto-Kakizaki rats, high-fat-fed mice and Zucker rats) also show increased production of various chemokines, including CXCL1, CCL2 and CCL3 (REFS 26,102). Importantly, the relevance of these findings for humans is supported by evidence for the upregulation of various chemokines in laser-captured nearly pure  $\beta$ -cells from patients with T2D<sup>103</sup>. Although most chemokines are produced by  $\beta$ -cells in the islets, some (for example, CXCL8) may also be produced by pancreatic  $\alpha$ -cells<sup>56</sup>.

The precise functions of the various chemokines remain to be clarified; however, they have a crucial role in tissue infiltration by immune cells in T2D.

**Adipokines.** Adipokines are hormones that are produced mainly or exclusively by adipocytes. Examples include leptin and adiponectin, both of which have potential immunomodulatory effects. Genetically obese *ob/ob* mice, which produce a mutated, non-functional form of leptin, show many of the same inflammatory changes as other models of obesity (including diet-induced obese mice), and *ob/ob* mice become both insulin resistant and diabetic. These results indicate that leptin may not have a particularly important role in obesity-induced inflammation. Adiponectin is considered to be an anti-inflammatory and cardioprotective protein. It may exert these effects in several ways; for example, by inducing anti-inflammatory cytokines such as IL-10 and IL-1RA<sup>104</sup>, through vascular mechanisms including enhancement of nitric oxide bioavailability<sup>105</sup>, or by reducing endothelial cell-leukocyte adhesion<sup>106</sup>.

In summary, multiple mechanisms may contribute to inflammation in T2D, some of which are general and others are tissue specific. Thus in the pancreatic islet cells, inflammation may be initiated by direct sensing of excess nutrients, leading to activation of the IL-1 system, whereas in adipose tissue, excess storage of fat causes hypoxia and inflammation. Common downstream mechanisms include the activation of NF- $\kappa$ B and JNK pathways and cytokine and chemokine release, leading to the recruitment of immune cells.

### Clinical trials and implications

Further evidence for roles of inflammation in T2D comes from clinical studies using either small molecule anti-inflammatory approaches or biological agents that target specific pro-inflammatory cytokine pathways to improve parameters of glucose control, such as glycated haemoglobin levels. To date, the most promising approaches include the selective blockade of IL-1R1 activation with either IL-1RA or specific antibodies, and inhibition of the NF- $\kappa$ B pathway with salicylate derivatives such as salsalate. Both approaches seem to lower blood glucose levels and improve  $\beta$ -cell secretory function and insulin sensitivity, as well as reducing evidence of systemic inflammation<sup>25,107</sup>. Of note, the improvement in insulin secretion lasted 39 weeks following the withdrawal of IL-1RA treatment<sup>108</sup>. Similarly, 3 months after a single

injection with an IL-1 $\beta$ -specific antibody, individuals with T2D showed sustained reductions in glycated haemoglobin levels and an improvement in insulin secretion by  $\beta$ -cells<sup>27</sup>. This probably reflects the interruption of IL-1 $\beta$  autoinduction<sup>84</sup>.

These proof-of-concept studies validate the potential approach of targeting of inflammatory mediators as a treatment for T2D and support a causative role for inflammation in the pathogenesis of this disease. They pave the way for new therapeutic approaches that could be disease modifying as opposed to palliative. This offers the opportunity to simultaneously target several features of the disease (including defective insulin secretion by  $\beta$ -cells, insulin resistance in adipose tissue, and microvascular and macrovascular complications) with anti-inflammatory drugs (either alone or in combination) to alter the course of the disease.

Based on preclinical studies, three anti-inflammatory approaches have been clinically tested: TNF antagonism, IL-1 $\beta$  antagonism and salsalate treatment (TABLE 2). In contrast to IL-1 $\beta$  antagonism and salsalate treatment, TNF antagonism has thus far failed to improve blood glucose levels in patients with T2D<sup>32-36</sup>. Improvements in glucose metabolism have been observed in patients being treated with TNF blockers for rheumatoid arthritis<sup>37,39,40,109-111</sup>, and a marginal effect of TNF blockers on fasting glucose levels was observed in obese individuals in a recent report<sup>38</sup>. Based on these latest findings additional clinical trials may aim to block TNF signalling, either alone or in conjunction with other cytokine-blocking approaches.

Current anti-inflammatory approaches to treating T2D focus on salsalate and IL-1 $\beta$  antagonism. Mechanistically these approaches may have similarities, including the modulation of IL-1R1 and NF- $\kappa$ B pathways<sup>1,55,67,112</sup>. IL-1 antagonists are large proteins that must be injected and have effects that may last for several weeks to months. By contrast, salsalate is an orally administered small molecule with a short half-life that requires more than once-a-day dosing. IL-1 antagonists are also designed to be highly specific for their targets, whereas salsalate and other non-acetylated forms of salicylate may have broader molecular actions. Thus in addition to the inhibition of NF- $\kappa$ B, they may inhibit other kinases<sup>113</sup>, upregulate the expression of heat shock factor protein 1 (REF. 114) and inhibit insulin clearance<sup>115</sup>.

In addition to having apparent efficacy and durability in lowering glucose levels, it is encouraging that both approaches also seem to have high margins of safety. Salicylates such as salsalate have been used to treat joint pain in millions of patients over many decades, and many of these patients may also have diabetes, cardiovascular disease or other metabolic conditions. Although not as broadly used, IL-1 antagonists have been used for several indications, including in more than 100,000 patients with rheumatoid arthritis. It is also encouraging that the rate and severity of infections are unaffected, and rare or unusual infections have not been reported for individuals taking either drug, in contrast to certain other immunomodulatory therapies.

#### Salsalate

A prodrug form of salicylic acid that has fewer side effects than sodium salicylate. Salsalate is approved for use in humans as a source of salicylic acid.

Table 2 | Clinical studies using anti-inflammatory approaches to treat type 2 diabetes or prediabetes

Mechanism	Drug	Trial Phase	Number of subjects	Treatment duration (weeks)	Main findings	Refs
IL-1 receptor blockade	Anakinra (Kineret; Amgen/Biovitrum)	II	69	13	↓ Glycated haemoglobin, ↓ CRP, ↑ insulin production	25
IKKβ–NF-κB inhibition	Salsalate	II	20	4	↓ FBG, ↓ CRP, ↑ insulin sensitivity, ↑ adiponectin	107
IKKβ–NF-κB inhibition	Salsalate	II	16	2–4	↓ FBG, ↓ FFA, ↓ triglycerides, ↓ CRP, ↑ adiponectin	143
IKKβ–NF-κB inhibition	Salsalate	II	40	1	↓ FBG, ↑ insulin	144
IKKβ–NF-κB inhibition	Salsalate	IIb	104	12	↓ Glycated haemoglobin, ↓ FBG, ↓ triglycerides, ↑ adiponectin	28
IL-1β-specific antibody	XOMA 052 (Xoma)	I	98	Single injection	↓ Glycated haemoglobin, ↓ CRP, ↑ insulin production	27
IL-1 receptor blockade	Anakinra (Kineret; Amgen/Biovitrum)	II	12	4	Ongoing, closed for recruitment	NCT00928876*
IL-1β-specific antibody	ACZ885 (canakinumab; Novartis)	II	231	Unknown	Ongoing, closed for recruitment	NCT00605475*
IL-1β-specific antibody	ACZ885 (canakinumab; Novartis)	II	140	48	Ongoing	NCT00995930*
IL-1β-specific antibody	ACZ885 (canakinumab; Novartis)	II	232	4	Ongoing, closed for recruitment	NCT01068860*
IL-1β-specific antibody	ACZ885 (canakinumab; Novartis)	II-III	600	17	Ongoing, closed for recruitment	NCT00900146*
IKKβ–NF-κB inhibition	Salsalate	III	284	48	Ongoing, closed for recruitment	NCT00799643*
IKKβ–NF-κB inhibition	Salsalate	II	80	12	Ongoing, closed for recruitment	NCT00330733*
IL-1β-specific antibody	XOMA 052 (Xoma)	II	325	26	Ongoing, closed for recruitment	NCT01066715*
IL-1β-specific antibody	XOMA 052 (Xoma)	II	80	48	Ongoing, closed for recruitment	NCT01144975*
IL-1β-specific antibody	LY2189102 (Lilly)	II	80	12	Ongoing, closed for recruitment	NCT00942188*
IL-1β-specific vaccine	CYT013-IL1bQb (Cytos Biotech.)	I	32	Unknown	Ongoing	NCT00924105*

Trials with tumour necrosis factor (TNF) antagonists<sup>31–40</sup> are not listed owing to the lack of effects in patients with type 2 diabetes. CRP, C-reactive protein; FBG, fasting blood glucose; FFA, free fatty acid; IKKβ, IκB kinase-β; IL-1, interleukin-1; NF-κB, nuclear factor-κB. \*ClinicalTrials.gov identifier.

**Outstanding questions and future directions**

Increasing data suggest a potential role for inflammation in the pathogenesis of T2D. This is supported by the results of both preclinical studies and new clinical trials using anti-inflammatory approaches to treat the disease. But these are early days and there are many unanswered questions. What is the relative contribution of inflammation to the development of T2D? How efficacious are the anti-inflammatory approaches at improving glycaemia and T2D complications, and how durable will the effects be? What will be the best therapeutic modality: life-long

treatment or short-term interventions aiming at breaking inflammatory flares? How do drugs such as salsalate and IL-1 blockers really work in T2D? Do anti-inflammatory strategies target the underlying mechanisms of the disease, and if so, would starting these therapies early prevent progression or even the overt manifestation of the disease? The early studies suggest that these strategies are well tolerated with few serious side effects and with little evidence of immunosuppression. From the numerous ongoing preclinical and clinical studies (TABLE 2), some of these questions should be addressed in the near future.

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**Competing interests statement**

The authors declare competing financial interests: see web version for details.

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