OPINION

Type 2 diabetes mellitus—an autoimmune disease?

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Abstract | Inflammation-induced inhibition of the insulin signalling pathway can lead to insulin resistance and contribute to the development of type 2 diabetes mellitus (T2DM). Obesity and insulin resistance are associated with a chronic but subclinical inflammatory process that impairs insulin action in most tissues and could also hamper pancreatic β-cell function. The involvement of monocytic cells and the profiles of the chemokines and cytokines induced by this inflammation suggest an innate immune response. However, emerging data indicate that elements of the adaptive immune system could also be involved. As activation of an adaptive response requires antigen specificity, some researchers have hypothesized that T2DM evolves from an innate immune response to an autoimmune condition. In this Perspectives article, we present the arguments for and against this hypothesis and discuss which mechanisms could be involved in a putative switch from innate immunity to autoimmunity.

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Introduction

Type 2 diabetes mellitus (T2DM) is among the most prevalent diseases in modern societies, affecting over 340 million people in the world.[1] Obesity is by far the most important predisposing factor for T2DM, and the rapid increase in the prevalence of obesity is expected to lead to a similar rise in the prevalence of T2DM.

The consumption of energy-dense and fat-rich diets is the main environmental factor leading to obesity.[2] Clinical and molecular studies from the past 20 years have provided undisputed evidence for the role of diet-induced subclinical inflammation as an important link between obesity and T2DM.[3] Dietary fats activate signal transduction through Toll-like receptors (TLRs) 2 and 4, and induce endoplasmic reticulum stress (ERS) in adipose tissue, liver and the hypothalamus.[4–7] TLR and ERS signalling induce inflammatory activity, which activates intracellular serine–threonine kinases that inhibit insulin signal transduction.[8,9] In addition, TLR and ERS signalling induce inflammatory gene transcription, resulting in the production and secretion of cytokines such as tumour necrosis factor (TNF) and IL-1β that, through an extracellular feed-forward loop, boost intracellular inflammatory signalling and insulin resistance.[8] Induction of ERS by saturated fats contributes to activation of inflammatory mediators[10] and triggers the dysfunction and death of pancreatic β cells in patients with T2DM.[9,10]

Macrophages and TNF are important for both induction and perpetuation of the inflammatory activity linked to obesity, which led to the concept that insulin resistance results from an anomalous activation of the innate immune system.[3,8,9,11] However, other studies suggest that components of the adaptive immune response also participate in progression of the inflammatory response associated with obesity.[12–14] Activation of an adaptive immune response requires processing and presentation of specific antigens through interaction between the major histocompatibility complex (MHC) and the T-cell receptor (TCR). No infectious agents are known to trigger inflammation in either obesity or T2DM. Thus, endogenous antigens or exogenous molecules (originating, for example, from dietary components) might be presented, act as antigens or anomalously modulate the immune response and thereby activate subsets of lymphocytes that target host cells and tissues. If evidence of such a mechanism could be obtained, obesity (and perhaps T2DM) might have an autoimmune component.

Our objective in this Perspectives article is to discuss the nature of the immune response in T2DM. We also compare the inflammatory processes occurring in T2DM with those of the well-defined autoimmune disease type 1 diabetes mellitus (T1DM).

Autoimmunity in T1DM and T2DM

The autoimmune diseases are a diverse group of chronic illnesses characterized by an immune response directed against specific antigens in the body. Well-known autoimmune diseases include rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus and T1DM. Our understanding of autoimmunity has evolved considerably since the first attempt was made to define this term in 1957,[15] and continues to be debated. In our view, a disease is considered to have an autoimmune aetiology if most of the following criteria are met: pathology is associated with loss of tolerance to specific antigens; transfer of pathogenic immune cells and/or antibodies replicates the disease in previously unaffected individuals; immunosuppression or immunomodulation modifies the natural history of the disease; animal models point to an autoimmune aetiology (including disease transfer by immune cells); and the disease is associated with genes that regulate the immune system, such as *HLA*.

The evidence suggesting an autoimmune mechanism of disease in T1DM includes loss of tolerance to several β-cell antigens, such as insulin, glutamate decarboxylase 2 (also known as GAD-65), receptor-type tyrosine-protein phosphatase N2 (also known as phogrin) and zinc transporter 8.[16] Moreover, animal models of T1DM, such as nonobese diabetic (NOD) mice and biobreeding (BB) rats, have a clear autoimmune cause of diabetes mellitus,[17] and T1DM can be 'transferred' into immune-deficient animals by T-cell transfer. Furthermore, in humans, bone marrow transplantation between HLA-identical siblings can transfer

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T1DM, and specific HLA variants can either protect against or predispose to T1DM.[18] Finally, therapies that inhibit or modulate T-lymphocyte activity delay the progressive loss of β-cell mass, although they do not prevent it.[19] T1DM also has a strong inflammatory component, and inflammation could contribute to early stages of the induction and amplification of the immune reaction against β cells. Furthermore, in later stages of this immune response, cross-talk between invading immune cells and the target β cells could lead to the progressive loss of β cells.[20]

Whether the pathogenesis of T2DM has an autoimmune component is less clear. So far, no potential autoantigenic target for T lymphocytes has been identified in this setting, but several reports describe potential targets for IgG antibodies associated with insulin resistance[21] and autoantibodies against pancreatic islet antigens in patients with T2DM.[22] The insulin resistance phenotype is not reported to be transferred following bone marrow transplantation, although glucose intolerance and insulin resistance develop in recipients of IgG antibody transfers in rodents.[21] In humans, T-lymphocyte inhibition has no proven therapeutic or preventive role in T2DM; however, in mouse models, inhibition of either B cells[21] or T lymphocytes[14] can attenuate the progression of obesity-related insulin resistance. Although no clear evidence of autoimmunity has been described in animal models of T2DM, targeting components of the adaptive immune system, such as IFN-γ-expressing type 1 T helper cells and B lymphocytes, can improve insulin resistance.[14,21] Of note, the overlap between candidate genes for T1DM and T2DM is very limited; only *GLIS3* (which encodes a zinc finger protein) is associated with both diseases, among over 50 candidate genes identified.[23,24] Moreover, none of the known candidate genes for other inflammatory or autoimmune diseases, such as, *IL23R*, *IL2RA*, *PTPN2* and a number of *HLA* alleles, are associated with T2DM.[25,26] Most genes linked to obesity are postulated to act on neuroendocrine circuits that regulate energy balance and have not been implicated in either innate or adaptive immunity.[27] While these genetic variants explain only a small fraction of the heritability of obesity and T2DM, they do not provide evidence for a role of autoimmunity in these two metabolic conditions.

T1DM (in common with several other autoimmune conditions) is associated with an increased risk of other autoimmune diseases, but the same cannot be said of T2DM. However, antibodies against G-protein-coupled receptors have been detected in sera from a subgroup of T2DM patients with an increased risk of hypertension and cardiovascular complications.[28] In addition, Rho-kinase-activating autoantibodies are present in sera from T2DM patients with maculopathy and macroalbuminuria,[29] and autoantibodies against IL-6 have been detected in sera from 2.5% of Danish patients with T2DM.[30]

Adiposity and inflammation

The stromal vascular fraction of the adipose tissue is populated by macrophages and other cells of the immune system, including T and B lymphocytes.[31,32] In lean individuals, immune cells residing in the perivascular space of the adipose tissue provide a first line of defence against potential pathogens. However, as adipose tissue mass increases in individuals with obesity, these macrophages and adaptive immune cells become activated even in the absence of a pathogenic threat.[31,33] Increased adiposity is accompanied by increased numbers of both $CD4^+$ and $CD8^+$ T lymphocytes in the adipose tissue,[31,33] recruited partly by C-C motif chemokine 5 (also known as T-cell-specific protein RANTES).[31] In obese mice, the increase in numbers of $CD8^+$ cells precedes the increase in $CD4^+$ cells and macrophages.[34] In addition, depletion of $CD8^+$ lymphocytes protects mice from diet-induced insulin resistance, but not from obesity, whereas adoptive transfer of $CD8^+$ lymphocytes can induce adipose tissue inflammation and insulin resistance in lean, $CD8^+$-depleted mice.[34] Upon stimulation, $CD8^+$ lymphocytes from obese mice produce more IFN-γ than do $CD8^+$ lymphocytes from lean mice, and adipocytes from obese mice express more MHC class I molecules than do those of lean mice.[33] These data suggest that, during the early development of obesity, antigens in the adipose tissue could be presented in an anomalous way and trigger an adaptive immune response, preferentially through $CD8^+$ lymphocytes.

In line with this apparent key role for $CD8^+$ cells in the inflammatory adaptive immune response in hypertrophic adipose tissue, one study has shown a reduction in the $FOXP3^+CD4^+$ subpopulation in the visceral fat depots of obese mice and humans.[13] If a similar subset of cells is experimentally activated in leptin-deficient $Lep^{ob/ob}$ mice, inflammatory infiltration of the adipose tissue is reduced and hyperglycaemia is partially corrected.[35] Regulatory T cells have an important role in the control of inflammatory responses, and downregulation of these cells might drive the unrestrained inflammatory response that is driven by $CD8^+$ T cells in obesity.[13] In lean mice, the proportion of regulatory T lymphocytes is high; however, the diversity in their TCR specificity is restricted.[36] During the development of obesity, the number of regulatory T cells in adipose tissue is reduced, and their TCR diversity is further restricted, suggesting the presence of potential adipose tissue autoantigens.[13,36]

Anomalous activation of B lymphocytes is also involved in the pathogenesis of obesity-linked insulin resistance.[14] Increased numbers of B lymphocytes infiltrate the adipose tissue of obese mice, a change accompanied by an increased blood concentration of IgG_{2c},[14] and depletion of B lymphocytes protects mice from obesity-linked insulin resistance without affecting body fat mass. Moreover, IgG antibodies purified from obese, insulin-resistant mice can transfer the glucose-intolerance phenotype.[14]

Taken together, these findings indicate that cells and molecules of the adaptive immune system have a role in the inflammatory activity linking obesity and insulin resistance. The characterization of this phenomenon has potential clinical relevance, as disorders related to innate immunity might respond best to cytokine antagonism, whereas disorders related to autoimmunity might preferentially respond to therapies that target T and B cells.[37] Indeed, treatment with anti-inflammatory drugs (including TNF blockers, IL-1 receptor antagonists and salicylate) is beneficial in animal models of T2DM,[3,38] but resulted in no or modest reductions in HbA_{1c} (≤0.5%) in patients with T2DM.[39,40]

Metabolic inflammation in T2DM

Obesity-associated inflammation is not restricted to adipose tissue; inflammatory processes also affect other tissues involved in whole-body energy homeostasis, and could promote the development of glucose intolerance and insulin resistance.[8] For example, insulin-resistant individuals with obesity can have inflammatory activity in the liver[41] and skeletal muscle.[42] In the hypothalamus, signs of inflammation are detected as early as 1 day after introducing a high-fat diet to rodents.[43] Genetic or pharmacological targeting of this inflammatory process

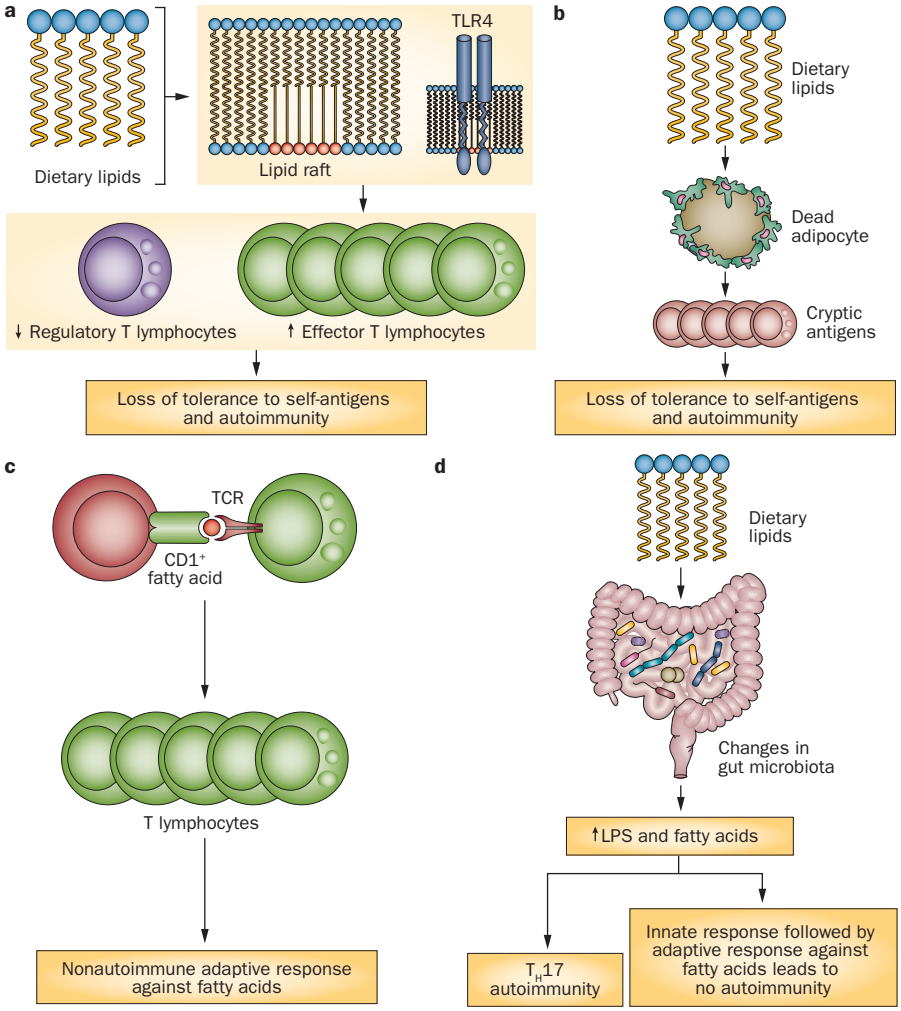

Figure 1 | Putative pathways of progression from innate to adaptive immune responses in obesity and type 2 diabetes mellitus. **a** | Dietary lipids could act as immunomodulators through various mechanisms: changing the composition of lipid rafts or activating signal transduction through TLR2 and TLR4. As a result of immunomodulation, inhibition of regulatory T lymphocytes and stimulation of effector T lymphocytes could result in loss of tolerance to self-antigens and autoimmunity. **b** | Cell death, induced by innate inflammation in response to fatty acids, could lead to release of cryptic antigens followed by loss of tolerance to self-antigens and autoimmunity. **c** | Dietary lipids could be presented to T lymphocytes in the context of CD1–TCR signal transduction, leading to a nonautoimmune adaptive response. **d** | Dietary lipids might induce changes in gut microbiota, resulting in increased blood levels of LPS and fatty acids. This mechanism could either modulate the immune response through an anomalous T_H17 response, contributing in some individuals to autoimmunity, or induce an innate response followed by a nonautoimmune adaptive response against fatty acids. Abbreviations: TLR, Toll-like receptor; TCR, T cell receptor; LPS, lipopolysaccharide; T_H17, type 17 T helper cells.

ameliorates not only the obese phenotype (reviewed elsewhere[44]) but also the defective regulation of hepatic glucose production,[45] the impairment of pancreatic β-cell function[46] and hypertension.[47]

The presence of low levels of cytokines and mild tissue infiltration by immune cells indicates that inflammation is chronic but low-level, characteristics that are important aspects of the inflammatory process in metabolic tissues. In contrast to the classic inflammatory process occurring in most autoimmune conditions, metabolic inflammation is not associated with the typical signs of inflammatory activity, such as heat, oedema, redness and pain, in individuals with obesity and/or T2DM.[48] Moreover, instead of increased energy expenditure, metabolic inflammation results in reduced whole-body energy expenditure.[48] Despite these major differences from classic inflammatory processes, however, cryptic antigens could still be exposed as a result of chronic low-level inflammation and lead to an adaptive autoimmune response, as proposed elsewhere.[49]

β cells, inflammation and T2DM

The inflammatory process in adipose tissue seems to be similar in all insulin-resistant individuals with obesity, regardless of whether or not they go on to develop T2DM.[50] Individuals with obesity will only develop diabetes mellitus when their pancreatic β cells fail to compensate for insulin resistance. Evidence for a role of innate and adaptive immunity in β-cell failure in patients who develop T2DM remains controversial. The presence of macrophages in pancreatic islets (determined by counting the number of $CD68^+$ cells per islet) increased from an average of 0.5 cells in nondiabetic individuals to 1.5 cells in people with T2DM.[51,52] The proportion of islets containing at least five immune cells increased from 0.6% in nondiabetic control individuals to 5.6% in patients with T2DM.[52] The presence of these macrophages has been linked to viral infection of islets[52] and expression of human islet amyloid polypeptide;[53] however, their role remains unclear. Microarray analysis of laser-capture microdissected β cells showed a minor increase (twofold to threefold) in levels of the chemokines CCL2, CCL11, CCL13, and CXCL1 and in the cytokines IL-1β and IL-8 (but not IFN-γ) in cells from patients with T2DM, compared with those from nondiabetic controls.[54] These cytokine and chemokine profiles indicate mild inflammation, which is consistent with an innate but not an adaptive immune response. A similar response was elicited *in vitro* by exposing human islets to the saturated fatty acid palmitate or synthetic ERS inducers, and this process was dependent on IL-1β production.[54] Blocking IL-1β with an IL-1 receptor antagonist prevented palmitate-induced inflammation but not β-cell apoptosis.[54] Consistent with these findings, the results of microarray analyses of islet cells from patients with T2DM linked a group of coexpressed genes (among which many were IL-1-related genes) to reduced insulin secretion.[55]

An autoimmune response to pancreatic β cells is present in adults with latent autoimmune diabetes mellitus, a condition that shares many features with T1DM and is often misdiagnosed as T2DM.[56] In some autoantibody-negative patients with T2DM, responses to islet-reactive T cells were observed by measuring mononuclear cell responses to human islet proteins

blotted onto nitrocellulose.[57] This method of evaluating T-cell activation, however, is under debate, as it might reflect unspecific inflammation and not autoimmunity, owing to lack of control tissues or specific identification of target antigens. The findings suggesting T-cell responses against islet proteins in patients with T2DM remain to be confirmed by other research groups using conventional assays based on specific β-cell antigens. In contrast to T1DM, in which nearly all β cells are eventually destroyed by the autoimmune response, the decrease in β-cell mass in patients with T2DM is modest (around 30–60%). This crucial finding suggests that the mechanisms of β-cell loss are different in T1DM and T2DM.[58]

Possible pathways to T2DM

Accumulating evidence suggests that innate (and, perhaps, adaptive) immunity have a role in the development of obesity-related insulin resistance. For example, several tissues involved in the control of metabolic functions are affected by complex subclinical inflammatory activity. Moreover, the insulin-resistance phenotype can be partly or completely rescued (depending on the stage of obesity) by targeting either the innate or the adaptive components of inflammation.[8,13,14,21,36,44,48,59]

In this Perspectives article we raise the questions of whether autoimmunity has a pathogenic role in the onset or progression of the inflammation associated with obesity and insulin resistance and whether autoimmunity influences the development of T2DM. Although current available data are not sufficient to give definitive answers to these questions, we propose four possible pathways that could lead to the onset and/or progression of the inflammatory response in both obesity and T2DM (Figure 1).

Dietary fatty acids could modulate immune activity and lead to activation of an anomalous adaptive immune response against self-antigens by, for example, changing the composition of lipid rafts[60] or by activating signal transduction through TLR2 and TLR4.[4,6] In this pathway, fatty acids could negatively modulate regulatory T lymphocytes and/or positively modulate effector T lymphocytes in metabolically relevant tissues, resulting in loss of tolerance to self-antigens, thus leading to autoimmunity (Figure 1a).

Alternatively, fatty acids could trigger an innate immune response and lead to cell death in relevant tissues, such as adipose tissue, exposing cryptic antigens and activating an anomalous adaptive immune response against self-antigens (Figure 1b). Dietary lipids activate the innate immune response in most metabolically relevant tissues,[8–10,44] and chronic inflammation can result in the death of key cell types, including adipocytes and neurons, in at least some of these tissues.[8,44] In this pathway, the cryptic antigens released as a consequence of inflammation-induced cell death could activate an adaptive immune response against self-antigens and thereby lead to autoimmunity.

Another possibility is that dietary fatty acids activate an anomalous adaptive immune response without the development of autoimmunity (Figure 1c). Endogenous and exogenous lipids can be presented to T lymphocytes, and the CD1–TCR signalling system would have a central role in this process.[61,62] In this pathway, dietary fatty acids could trigger T-lymphocyte activation through CD1-mediated antigen presentation, and the ensuing adaptive immune response would target dietary fats without leading to autoimmune activity.

Finally, changes in gut microbiota could result in increased blood levels of lipopolysaccharide and/or modulation of immune activity, which might lead to activation of either nonautoimmune, adaptive responses against fatty acids or of autoimmune responses against cryptic antigens (Figure 1d). Changes in the gut microbiota influence both obesity-linked systemic inflammation and insulin resistance.[63] The inflammation associated with diet-induced changes in microbiota can result from increased gut transposition of lipopolysaccharides as well as changes in the absorption of nutrients, particularly lipids.[63–65] Moreover, changes in microbiota can modify IL-17 production in the gut, which modulates systemic immune activity.[66] This pathway can have two possible outcomes: in the first, changes in lipopolysaccharide and lipid absorption in the gut could result in increased innate immune activity, followed by the activation of an adaptive immune response against dietary lipids, with no autoimmune activity; in the second, changes in immune regulation caused by upregulation of type 17 T helper cells (which increases IL-17 production) favours the development of autoimmunity.[67]

Another interesting possibility is that multiple pathways might be involved: for example, the direct activation of an innate immune response by fatty acids (as proposed in Figure 1b), could occur in parallel with lipid presentation through CD1–TCR, resulting in an innate immune response as well as nonautoimmune adaptive immune activity. Other pathways could possibly also explain the immune response in obesity and T2DM. The results of well-controlled experiments in the future will indicate whether autoimmunity is indeed activated in the pathogenesis of T2DM.

Conclusions

The presence of autoimmune activity in the inflammation linked to obesity and insulin resistance remains elusive. Even if adaptive immunity is indeed present, it might not necessarily have a pathogenic role in the development of T2DM. Failure of the β cell is central to the pathogenesis of T2DM; however, although considerable evidence supports a pathogenic role for islet inflammation and autoimmunity in T1DM, no conclusive data suggest that autoimmunity has any role in β-cell death in T2DM. The autoimmune response in T1DM targets mainly the pancreatic β cells. By contrast, the chronic, systemic low-grade inflammation in T2DM affects a variety of tissues, including adipose tissue, liver, the hypothalamus, β cells and the cardiovascular system. This broad spectrum of activity suggests the presence of a metabolically driven innate immune response rather than an autoimmune disease. Although an innate immune response evolve into an adaptive immune response in adipose tissue, it has not been shown to do so in β cells in models of obesity and T2DM.[54,58] Thus, currently, T2DM cannot be characterized as an autoimmune condition. Further studies are required to clarify this important and therapeutically relevant question.

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Author contributions
The authors contributed equally to all aspects of this article.