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Are Obesity-Related Insulin Resistance and Type 2 Diabetes Autoimmune Diseases?

Diabetes 2015;64:1886–1897 | DOI: 10.2337/db14-1488

Obesity and associated insulin resistance predispose individuals to develop chronic metabolic diseases, such as type 2 diabetes and cardiovascular disease. Although these disorders affect a significant proportion of the global population, the underlying mechanisms of disease remain poorly understood. The discovery of elevated tumor necrosis factor-α in adipose tissue as an inducer of obesity-associated insulin resistance marked a new era of understanding that a subclinical inflammatory process underlies the insulin resistance and metabolic dysfunction that precedes type 2 diabetes. Advances in the field identified components of both the innate and adaptive immune response as key players in regulating such inflammatory processes. As antigen specificity is a hallmark of an adaptive immune response, its role in modulating the chronic inflammation that accompanies obesity and type 2 diabetes begs the question of whether insulin resistance and type 2 diabetes can have autoimmune components. In this Perspective, we summarize current data that pertain to the activation and perpetuation of adaptive immune responses during obesity and discuss key missing links and potential mechanisms for obesity-related insulin resistance and type 2 diabetes to be considered as potential autoimmune diseases.

Traditional autoimmune diseases involve a wide spectrum of clinical pathology and include diseases such as systemic lupus erythematosus, multiple sclerosis, Sjögren's syndrome, rheumatoid arthritis, and type 1 diabetes. A disease is considered autoimmune if its pathology is dictated by a self-antigen–specific adaptive immune response. Immunologists have adapted Koch's postulates, originally conceived to establish a causative link between microbes and infectious diseases, to define key criteria that would qualify an autoimmune disease (1,2):

1) Evidence of disease-specific adaptive immune response in the affected target tissue or organ
2) Demonstration of the ability of autoreactive T and B cells and/or autoantibodies to transfer disease to healthy individuals or animals through adoptive transfer or autoantigen immunization
3) Elimination of the autoimmune response dampens disease progression

Based on the above criteria, diseases with relatively well-established pathophysiology, such as type 1 diabetes and multiple sclerosis, are undisputedly classified as autoimmune. Key autoantigens have been identified and autoreactive specificities have been proven pathogenic through approaches such as adoptive transfer, autoantigen immunization, and transgenesis (3–6). Loss of tolerance toward self is supported by ample evidence pointing toward defective immune regulation, manifested as a result of combined environmental and predisposing genetic factors (4,7). Furthermore, researchers have devised immunotherapeutic strategies based on these findings, many of which are being tested clinically as potential treatment for these autoimmune diseases (8).

For many other chronic inflammatory conditions, however, the involvement of an autoimmune response

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Received 29 September 2014 and accepted 25 January 2015.

in disease development or progression is less clear. Type 2 diabetes and obesity-related insulin resistance are examples of such. Previously thought to be an inflammatory disease mediated predominantly by macrophages infiltrating metabolic tissues, such as the liver and visceral adipose tissue (VAT), obesity-associated adipose inflammation has only recently been tagged as having an adaptive immune component (9,10). A recent series of studies showed that, similar to macrophages, T and B cells are found to infiltrate the VAT in obese humans and mouse models, with their numbers and inflammatory status closely paralleling the degree of insulin resistance. In addition, alterations in some subclasses of circulating IgGs are also seen during obesity-related insulin resistance (11). Furthermore, transfer of $CD8^+$ T cells (12,13) or high-fat diet (HFD)-induced IgG antibodies (11) can aggravate insulin resistance without affecting obesity, while T- or B-cell depletion or genetic deficiency improves insulin resistance in diet-induced obese (DIO) mice (11–14). Through these and other observations, a link between adaptive immunity and obesity-associated inflammation and insulin resistance has been established, and it is now well accepted that adipose tissue inflammation in obesity results from an integrated dialogue between multiple cell types, encompassing metabolic cells as well as both innate and adaptive immune cells. These findings have raised the possibility that obesity-related insulin resistance has a defined autoimmune component to it. Nonetheless, little is known pertaining to the exact nature of the adaptive response mobilized during obesity, such as whether it actively targets self-antigens or foreign antigens, whether it is primarily a bystander, or whether antigen-specific responses are required for β-cell failure in type 2 diabetes. Here, we discuss the potential of obesity-associated inflammation and type 2 diabetes as autoimmune diseases, following the above-mentioned criteria for autoimmunity, and highlight recent clues that will help resolve this intriguing issue.

EVIDENCE OF DISEASE-SPECIFIC ADAPTIVE IMMUNE RESPONSE IN THE AFFECTED TARGET TISSUE OR ORGAN

The presence of a disease-specific adaptive immune response in the target organ can be indicative of autoimmune pathogenesis. For prototypical autoimmune diseases such as type 1 diabetes, inflammation is largely organ specific, involving antigen-specific pancreatic β-cell destruction mediated by autoreactive T cells. Studies in murine models or patients with type 1 diabetes show increased prevalence of autoreactive T cells, B cells, and autoantibodies in the circulation and in situ within the pancreatic islets (7,15–18). Interestingly, increased prevalence of B cells, $CD8^+$ T cells, and T helper (Th)1 and Th17 T cells has also been described in obesity-related insulin resistance (11,13). These cell types have been previously ascribed pathogenic roles in multiple autoimmune and inflammatory disorders and are also found to participate in obesity-linked inflammation. However, in contrast to type 1 diabetes, multiple tissues and organs, including the liver, VAT, muscle, pancreas, cardiovascular tissue, and hypothalamus, are affected by the low-grade inflammation that accompanies obesity (19,20), making it difficult to identify potential dominant tissue-specific target antigens. These adaptive immune pathways are thought to contribute to whole-body insulin resistance and impact several processes, such as β-cell function, energy storage and expenditure, and feeding behavior (19,21). Adaptive immune cells have been described in the VAT, muscle, liver, and pancreas during insulin resistance, but involvement by adaptive immune cells in other inflamed tissues and their antigenic specificities await future investigations.

T Cells in the VAT

Adaptive immune responses in the VAT are considered important players in the inflammatory events that accompany obesity-related insulin resistance. In mice, HFD feeding promotes a shift in VAT immune cells toward a proinflammatory phenotype, decreasing the proportion of resident $CD4^+Foxp3^+$ regulatory T cells (Tregs) (12,13,22), while increasing the proportion of Th1 $CD4^+$ T cells (13,23–25) and $CD8^+$ T cells (12,26). In obese VAT, Th1 $CD4^+$ T cells and $CD8^+$ T cells secrete high levels of the Th1 cytokine interferon-γ (IFN-γ) that can directly induce insulin resistance in adipocytes (23) or polarize resident macrophages to an inflammatory M1 subtype. In humans, evidence also indicates the participation of T cells in obesity-associated metabolic disorder. Compared with healthy control subjects, obese individuals harbor increased numbers of activated circulating Th1 T cells that correlate with the degree of insulin resistance (27), increased infiltration of $CD4^+$ T cells in subcutaneous adipose tissue (25,28–30), and increased ratio of Th1 and Th17 to Treg in the VAT (13,31).

Interestingly, VAT-infiltrating T cells display a predominantly activated, effector/memory phenotype ($CD44^{hi}$ $CD62L^{lo}$) as compared with T cells from secondary lymphoid organs, such as the spleen and the peripheral lymph nodes (25,26), and secrete increased amounts of IFN-γ (26). Furthermore, T-cell receptor (TCR) spectratyping shows that VAT-associated $CD4^+$ T cells have a biased TCR repertoire compared with splenic $CD4^+$ T cells, and that this phenomenon is further accentuated in obese VAT $CD4^+$ T cells (25). The presence of VAT-specific TCR gene bias is striking and indicative of two potential processes: a clonal expansion of VAT T cells upon specific antigenic cues and/or the recruitment and retention of T cells carrying a specific set of TCRs, potentially in response to certain VAT-associated antigenic cues. Such observations also directly point to the importance of T cell:antigen-presenting cell (APC) interactions.

APCs in the VAT

It remains unclear whether VAT T cells are activated in regional draining lymph nodes, directly in situ in the VAT or elsewhere. The VAT environment in HFD-fed animals can support the activation and proliferation of $CD4^+$ and $CD8^+$ T cells (26,32), where macrophages (32,33), B cells, dendritic cells (DCs) (34), and potentially the adipocytes themselves (35,36) are all candidate professional APC types that can process and present antigens for T-cell activation. Macrophages, being the predominant cell type in the VAT (accounting for up to 50% of the stromal vascular fraction) (33), are prime candidates for activating VAT T cells. A subset of macrophages bearing CD11c is found to infiltrate the VAT, and diphtheria toxin–mediated ablation $CD11c^+$ cells, including macrophages and DCs, resulted in improved insulin resistance (37). Macrophages are found in crown-like structures surrounding dying adipocytes, rendering them well poised to sample adipocyte-derived antigens and present them to T cells. Indeed, isolated VAT macrophages are able to capture and proteolytically cleave ovalbumin antigens and activate antigen-specific $CD4^+$ T cells in vitro (32). DCs are another highly specialized subset of APCs present in the VAT. While the role of DCs in modulating autoimmunity in type 1 diabetes has been well documented, with DC subsets contributing to both pathogenesis and tolerance under different circumstances, the role of DCs in type 2 diabetes is less understood. HFD feeding induces the accumulation of $CD11c^{hi}$, $CX3CR1^+$ DCs in the VAT that are capable of inducing Th17 differentiation ex vivo (34). Similar observations also were made in obese human patients, whose adipose tissues harbor increased numbers of $CD11c^{hi}$ $CD1c^+$ DCs (34). In another study, adipose tissue DCs were shown to participate in the recruitment of macrophages in DIO mice, and DC deficiency confers protection against obesity-induced insulin resistance (38).

Closely related to this point is the issue of relative timing of entry of T cells versus other cell types, such as APCs into the VAT upon induction of obesity. Recent time course studies in mice approximate an initial recruitment of T and B cells at 2–6 weeks on HFD (12,13,29,39,40), preceding the macrophages at 6–16 weeks (12,29,39). In such a scenario, early autoimmune-based antigen presentation could potentially occur from the adipocytes themselves, B cells, or resident macrophages (35). On the other hand, contradictory reports suggested the rise in M1-like macrophages in the VAT at less than 1 week on HFD (40–42), which would be consistent with a more typical time course of antigen presentation by immune APCs, followed by T-cell activation. The observed discrepancies in timing may be reflective of the sensitivity of the detection methods (such as real-time PCR vs. flow cytometry), as well as the differences in diet and environmental factors.

B Cells in the VAT

B cells constitute another adaptive immune subset within the crown-like structures in the VAT (43). B cells, in particular the B2 subset, have a predominantly pathogenic role in obesity-related insulin resistance, fulfilled through the secretion of inflammatory cytokines and antigen-specific antibodies and through promoting T-cell activation and IFN-γ or interleukin (IL)-17 secretion (11,14,43). B cell deficiency in IgM-heavy chain–deficient μMT mice reduces VAT inflammation, VAT recruitment of $CD8^+$ T cells (14), and VAT $CD8^+$ T cell expression of IFN-γ and CD107a (11). Evidence suggests that the antigen-presenting function of B cells is critical in mediating these inflammatory effects. B cells interact with T cells in the VAT in a contact-dependent, MHC class I– and class II–dependent manner (11,14). In addition, HFD feeding induces B cells to undergo class switching, presumably in a T-cell–dependent manner, to produce proinflammatory IgG2c that can promote macrophage TNF-α production and induce insulin resistance, consistent with the Th1-skewed phenotype of obesity-linked inflammation (11). The notion that B cells require T cells in an MHC-dependent manner for full pathogenicity raises the prospect of important T-cell–dependent antigens, some of which may be self-derived or possibly bacterial derived and could help drive antibody and cytokine production in insulin resistance. Further studies utilizing models of restricted B-cell repertoires in the setting of HFD exposure will lend new insights into the roles of B-cell antigen-specific immunity in insulin resistance.

Adaptive Immune Responses in Islets

In addition to VAT inflammation, the pancreas is an organ found to be infiltrated with adaptive immune cells during obesity-linked inflammation and type 2 diabetes (44). Patients with type 2 diabetes display heightened pancreatic islet inflammation, initially characterized by increased expression of inflammatory cytokines derived from innate immune cells, such as TNF-α, IL-1β, and IL-12 (44,45), as well as deposition of islet amyloid polypeptide (46). These observations initially led researchers to propose that islet inflammation in type 2 diabetes is distinct from that in type 1 diabetes and is predominantly mediated by innate cells (47). Our understanding of the nature of islet inflammation in type 2 diabetes, however, is only starting to emerge. Studies found an increased prevalence of islet-associated antigen-specific antibodies (48–51) and T-cell responses (52,53) in patients with type 2 diabetes, targeting autoantigens, such as glial fibrillary acidic protein (GFAP), GAD65, IA2, and proinsulin. Furthermore, a recent report documented an increased proportion of B cells within the islets of patients with type 2 diabetes compared with healthy control subjects (44). These studies provide evidence for a potential islet-specific adaptive immune process in type 2 diabetes.

Numerous factors inherent in the obesity-associated insulin-resistant state can contribute to β-cell stress, dysfunction, and demise. These may include lipotoxicity; glucotoxicity (54); dysregulated K_{ATP} channels (55); chronic inflammatory stimuli, such as increased IL-23, IL-24, and

IL-33, leading to oxidative and endoplasmic reticulum (ER) stress (56); or increased β-cell workload as a compensatory response to insulin resistance and hyperglycemia. Presentation of antigens from dying β-cells under inflammatory stimuli can, in turn, trigger a secondary autoimmune response that further perpetuates this negative cycle, leading to an accelerated loss of β-cell mass and function. This scenario is supported by studies that found a positive correlation between the presence of islet autoimmunity and reduced β-cell mass and function in patients with type 2 diabetes (49,57), although a causal relationship between local (islet) autoimmunity and impaired β-cell function has not been established.

Adaptive Immune Responses in Other Tissues

In obesity, inflammation occurs in several tissues and evidence suggests that adaptive immune cells are also present. HFD feeding–induced hepatic inflammation is associated with a drop in Treg numbers and an increase in macrophage and $CD8^+$ T-cell infiltration (58,59), and genetic deficiency in the B7 costimulatory pathway, which diminishes Treg development, exacerbates obesity-induced liver inflammation (58). Increased T-cell infiltration has also been documented in the skeletal muscle after 12 weeks of HFD feeding (60). Furthermore, hypothalamic inflammation characterized by microglia accumulation has been shown to contribute to insulin resistance (61,62). While adaptive immune cells have not been seen infiltrating the brain during HFD feeding, a recent report demonstrated that HFD exposure can induce IgG antibody deposition in the hypothalamus of rodents (63). Whether these responses are tissue specific and driven by local antigens and how they contribute to systemic insulin resistance require further characterization.

DEMONSTRATION OF THE ABILITY OF AUTOREACTIVE T AND B CELLS AND/OR AUTOANTIBODIES TO TRANSFER DISEASE TO HEALTHY INDIVIDUALS OR ANIMALS THROUGH ADOPTIVE TRANSFER OR AUTOANTIGEN IMMUNIZATION

The pathogenic nature of T cells in type 1 diabetes was initially demonstrated in adoptive transfer experiments where bulk pathogenic $CD4^+$ or combined $CD4^+$ and $CD8^+$ T cells caused rampant β-cell destruction when injected into immunodeficient NOD.*scid* mice (3). Subsequent cloning experiments demonstrated the antigen-specific nature of such destruction (64,65), and antigen-specific TCR-transgenesis further confirmed the autoimmune nature of β-cell destruction in type 1 diabetes. Interestingly, in obesity-linked insulin resistance, bulk $CD8^+$ T cells as well as B2 B cells and HFD-induced total IgG antibodies can also transfer metabolic dysfunction to healthy, obese animals (11–13). Although one can argue that bulk T and B cells or IgG may exert bystander proinflammatory effects in these settings, it remains possible that these cell subsets and antibodies are enriched for autoreactive specificities that can worsen disease (11).

Potential Autoantigen Targets

An expanding list of self-antigen targets is reported for obese, insulin-resistant individuals with type 2 diabetes, predominantly from studies that assayed serum antibody reactivity or peripheral blood mononuclear cells against panels of self-antigens. Increased prevalence of positive autoantibody and T-cell responses are found to target a spectrum of self-antigens, including islet autoantigens but also autoantigens expressed in multiple cell types and tissues (11,49,53,66–68). Among these are Golgi SNAP receptor complex member 1 (GOSR1) transcript variant 1, a protein involved in trafficking between the ER and Golgi compartments, phosphogluconate dehydrogenase, and GFAP. Autoantibody responses against these proteins are prevalent among insulin-resistant individuals and are found in 30–70% of the subjects tested (11,48). Certain aspects of these proteins make them attractive candidate autoantigens. GOSR1, for instance, has multiple transcript variants, and it is possible that its localization renders it vulnerable to ER stress–associated changes in transcription, splicing, or translation, with effects on antigenicity. Phosphogluconate dehydrogenase is highly expressed in adipocytes and may be potentially targeted by VAT immune cells. Finally, the GFAP present in the glial tissue enveloping islets in the pancreas has been identified as an autoantigen for type 1 diabetes (69) and may represent a critical antigenic link between the low-grade inflammation seen in the hypothalamus as well as in the pancreatic islets during obesity (63).

Other less prevalent autoantibody specificities have been identified, some of which may be linked to the pathology of metabolic syndrome. For instance, autoantibodies against a modified epitope in ApoB or agonistic autoantibodies against G-protein–coupled receptors have been associated with endothelial dysfunction and vascular complications (66,67). Some autoantibody targets may emerge after bacterial or viral infection. Autoantibodies against protein disulfide isomerase, also linked to ER stress pathways, are elicited following streptococcal infection and can contribute to insulin resistance (70). In another study, viral infections by a rhinovirus and a respiratory syncytial virus preceded glucose intolerance and onset of type 2 diabetes in a single individual (71). These viral infections triggered the appearance of autoantibodies targeting potential insulin receptor–binding molecules, such as DOK6, as well as self-proteins previously described in insulin resistance such as BTK and GOSR1 (11). These findings highlight the potential role for environmental cues, in addition to diet, that work together to shape potentially pathogenic autoimmunity during the course of insulin resistance.

ELIMINATION OF THE AUTOIMMUNE RESPONSE DAMPENS DISEASE PROGRESSION

In line with the above-mentioned adoptive transfer data, genetic deficiencies in B cells (11,14), $CD8^+$ T cells (12),

and MHC class II expression (which impairs $CD4^+$ T-cell development) (35) conferred protection against HFD-feeding–induced inflammation and insulin resistance. In addition, therapy with anti-CD3 mAb, a monoclonal antibody that has shown efficacy in reverting autoimmune type 1 diabetes in mouse models by targeting polyclonal T cells for deletion while expanding Tregs, also shows promise as an immunotherapy that dampens insulin resistance in DIO mice (13). Similarly, antibody-mediated depletion of $CD8^+$ T cells (12) or B cells (11) improves both glucose tolerance and insulin sensitivity in DIO mice. If these B- and T-cell responses are indeed autoimmune in nature, they pose as promising targets for antigen-specific immunotherapy as an alternative or adjunct approach to other anti-inflammatory therapies that are being tested, including the use of salsalate (72) and inhibitory therapy against IL-1β (73). In place of broad-acting therapies that block entire immunological pathways or effector molecules that are important for our own defense against foreign pathogens or cancer, antigen-specific immunotherapies offer a disease-targeted approach that minimize side effects of compromised systemic immunity.

Taking into consideration the evidence outlined above (Fig. 1), an autoimmune component in the pathology of obesity-linked insulin resistance and type 2 diabetes is entirely possible. In terms of the pathogenesis of obesity-associated insulin resistance, a key missing link is whether any of the identified targeted autoantigens drive the inflammatory response in key sites such as the VAT. Adoptive transfer data attest to the pathogenic nature of subsets of adaptive immune cells, which are further supported by subset-specific deletion or modulation. However, whether these subsets are enriched for autoreactive specificities and how and where such autoreactive responses arise during obesity are as yet intriguing unknowns. Experiments used to clarify the role of autoreactive T cells in type 1 diabetes, such as tissue-specific T-cell and B-cell cloning, antigen discovery, as well as other transgenic approaches, will lend invaluable insights to this issue.

Pathways to Autoimmune Responses During Obesity

Unlike classical autoimmune diseases such as type 1 diabetes, which follows a chronic, irreversible course of self-tissue destruction, obesity-associated insulin resistance is reversible through weight loss from lifestyle changes or surgical means (74). This notion implies that whichever stimuli that propagate the adaptive immune responses accompanying obesity may be removed when a lean state is restored. The question then becomes how obesity alters antigen expression, processing, or presentation and modulates adaptive immune cell activation, leading to loss of tolerance against self-tissues. Looking at classical autoimmune diseases, several intrinsic mechanisms are common in promoting loss of tolerance: genetic predisposition to defective antigen presentation on MHC molecules, defective autoantigen expression during central tolerance, defective cytokine pathways leading to Treg dysfunction and effector cell hyperactivation, and defective antigen clearance pathways. Evidence for such genetic predisposition is lacking in obesity-associated insulin resistance and type 2 diabetes, with little overlap found between genetic associations of type 2 diabetes and those of other autoimmune diseases (75,76), though some studies show correlation with Toll-like receptor 4 (TLR4) polymorphisms and progression of complications with type 2 diabetes (77). Nonetheless, in place of the lack of overall genetic predisposition to immune dysregulation, environmental factors, as well as the obese state itself, may provide the needed stimuli.

For all autoimmune diseases, the effects of genetic predisposition are compounded to additional conditioning environmental factors, such as diet, lifestyle, and presence of infectious agents that elicit a nonspecific response through mechanisms such as molecular mimicry (78). Environmental stimuli may prove all the more important for obesity-related insulin resistance and type 2 diabetes given the lack of known immune predispositions. We propose two overarching pathways highlighted in current literature, which could directly contribute to autoreactive adaptive immune activation through environment stimuli: *1*) dietary fat accumulation inducing changes in metabolic tissues, especially in adipose tissue with associated adipocyte cell death, and *2*) alteration of the gut microbiota and mucosal immunity (Fig. 2).

Inflammatory Changes in Adipocytes and Lipid Excess Elicit Adaptive Immunity

A large body of evidence supports the concept that the initial trigger for the chronic inflammation in obesity is metabolic in nature (19). Long-term caloric excess causes white adipocytes to become hypertrophic, accompanied by increased oxidative stress and ER stress as well as activation of the NLRP3 inflammasome, that culminates in the proinflammatory death of adipocytes (79). The efflux of fatty acids and aberrant production of adipokines and chemoattractants by degenerating adipocytes or from insulin resistance–associated lipolysis, in turn, contribute to the recruitment and activation of both innate and adaptive immune cells. For instance, adipocyte-secreted chemoattractants, such as MCP-1 and RANTES, engage their receptors on macrophages and T cells to effect their recruitment into the VAT, while increased levels of other inflammatory adipokines or cytokines, such as TNF-α, IL-6, and RBP4, can directly activate macrophages to promote VAT inflammation (80–85).

HFD-induced adipocyte death itself can trigger VAT inflammation and insulin resistance. Genetic inhibition of a key proapoptotic molecule Bid (86) or adipocyte-specific deletion of proapoptotic Fas (87) protected DIO animals from developing insulin resistance. In dying in a proinflammatory manner, adipocytes may serve as a reservoir of self-antigens for local B and T cells, as well as a source of costimulatory signals that help activate APCs to initiate

↑	Evidence favoring autoimmune pathogenesis
↓	Evidence against autoimmune pathogenesis
–	Evidence is inconclusive. More studies are needed.

	Type 1 diabetes			Type 2 diabetes		
Evidence of disease-specific adaptive immune response in the affected target tissue or organ						
Presence of T cells in target organs	↑	Infiltration of autoreactive T cells in islets	(17, 18)	–	Infiltration of T cells in the VAT with unknown specificity; evidence of oligoclonal expansion	(12, 13, 25)
				–	Infiltration of T cells in islets	(44, 52, 53)
				–	Infiltration of T cells in muscle and liver with unknown specificity	(58–60)
Presence of T cells in circulation	↑	Increased autoreactive T cells in peripheral blood	(53)	–	Increased circulating Th1 T cells correlate with disease	(27)
Presence of B cells in target organs	↑	Infiltration of autoreactive B cells in islets	(15, 16)	–	Infiltration of B cells in the VAT with unknown specificity	(11, 39, 44)
Presence of autoantibodies in circulation	↑	Presence of islet autoantibodies is predictive of disease	(4)	↑	Elevated autoantibodies present in circulation with unclear role in disease	(13, 52)
Transfer of disease via autoreactive T and B cells and/or autoantibodies						
T cell transfer worsens disease	↑	Polyclonal $CD4^+$ T cells, combined $CD4^+$ and $CD8^+$ T cells, and autoreactive T-cell clones transfer disease to NOD.*scid* mice	(3, 4)	–	Polyclonal $CD8^+$ T cells worsen disease in $CD8\alpha^{null}$ DIO mice	(12, 13)
Serum antibody transfer worsens disease	–	Total serum Ig does not worsen disease	(7)	–	HFD-induced IgG of unknown specificity worsens disease	(11)
Elimination of autoimmune response dampens disease progression						
Genetic deficiency in all adaptive immune cells dampen disease	↑	NOD.*scid* and NOD.$RAG2^{null}$ mice fail to develop type 1 diabetes	(6, NA)	↓	DIO C57BL/6.$RAG2^{null}$ or *scid* mice develop worse disease	(12, 116)
T-cell–specific genetic deficiency or immunotherapy blunts disease	↑	NOD.$TCR\beta^{null}$ mice fail to develop T1D; anti-CD3 mAb blunts disease	(NA, 4)	↑	$CD8\alpha^{null}$ mice and $TCR\beta^{null}$ mice are protected from DIO IR; anti-CD3 and anti-CD8α mAb blunts disease	(12, 13, 60)
B-cell–specific genetic deficiency or immunotherapy blunts disease	↑	NOD.μMT mice fail to develop T1D; anti-CD20 mAb blunts disease	(7)	↑	C57BL/6.μMT mice are protected from DIO IR; anti-CD20 mAb blunts disease	(11, 14)
Antigen-specific immunotherapy blunts disease	↑	Autoantigen-based immunotherapies blunt disease	(8)	–	Insufficient information for disease-driving autoantigen	NA

Figure 1—Evidence of autoreactivity in T1D and T2D according to modified postulates. Due to the extensive literature describing type 1 diabetes pathogenesis, we reference a number of review articles that can point readers to primary literatures on the different aspects. IR, insulin resistance.

a self-propagating inflammatory loop. Dietary fats may further enhance these processes by altering membrane organization important for antigen receptor signaling (88,89) or signaling through TLR2 and TLR4 (90–92) to induce ER stress and other inflammatory changes. Such stressors to adipocytes may alter folding and processing

of cell constituents, resulting in the generation of protein-, lipid-, or carbohydrate-based neo-antigens. Similar changes in response to lipotoxicity may happen over time in other metabolic cells, such as hepatocytes and β-cells of the pancreas. Some stressors have been shown to induce cell senescence in adipocytes and hepatocytes, inducing a senescence-activated secretory phenotype that may produce cytokines to attract T cells (93). In addition, given that TLR4 is expressed on relevant cell types involved in adaptive immunity, including B cells, adipocytes, and other APCs, such signals may provide the costimulation needed to break tolerance in B and T cells in the inflammatory environment of metabolic tissues. For instance, TLR4 stimulation on B cells causes increased secretion of natural IgM, which forms immune complexes that can facilitate autoantigen presentation to B cells in a manner dependent on apoptosis inhibitor of macrophage (52).

Activated B and T cells may, in turn, contribute to metabolic tissue inflammation through the secretion of inflammatory cytokines and antibodies or through the recruitment of other immune cells. This sequence of events (Fig. 2) is compatible with the timing of B- and T-cell recruitment to the VAT upon HFD feeding (11,39), which coincides with the onset of insulin resistance (29). In addition to increasing T- and B-cell recruitment and activation, inflammatory disturbances in the VAT can lead to reductions in local Treg numbers and function (13,22). Treg cells have been shown to exhibit phenotypic instability in the face of chronic inflammation, and elevated levels of adipokines, such as leptin, or hyperinsulinemia may further impact Treg homeostasis and their function in braking VAT inflammation (94,95).

Environmental Status in the Gut Conditions VAT Inflammation

Alterations in the gut microbiota and gut-associated immune responses are shown to accompany obesity in both humans and mice (96,97). Disturbances in the gut microbiome inside obese individuals and rodents may contribute to insulin resistance via participating in obesity-linked inflammation through a number of potential pathways. One such pathway involves inflammatory alterations in gut epithelial integrity, leading to increased "leakage" of bacterial products, including endotoxins such as lipopolysaccharides, across the intestinal epithelium. An alternative pathway has also been proposed involving a chylomicron-dependent process that delivers gut-derived lipopolysaccharide into the bloodstream and fat depots (98). Elevated systemic endotoxin and other gut bacterial components can, in turn, trigger an inflammatory response through binding pattern recognition receptors, such as TLRs and nucleotide-binding oligomerization domain-containing protein (NOD) on innate immune cells and adipocytes alike to mediate insulin resistance (99,100). Elevated gut-derived endotoxins can signal through TLR4 and provide the stimulation needed to break tolerance as outlined above. In addition to gut-derived factors with adjuvant effects, gut-derived antigens or dietary factors can also potentiate an obesity-associated inflammatory response. For instance, Western diet composition, such as high salt content, has the potential to skew immune responses toward a Th17 bias and promote autoimmunity (101). Some organisms found in obese guts, such as the segmented filamentous bacteria, have the capacity to induce organism-specific IL-17 responses that exacerbate obesity-associated liver inflammation and damage (102). Furthermore, dietary imbalance that results from the lack of dietary fibers can result in the reduction of beneficial metabolites such as butyrate, which has been shown to promote tolerance by inducing Tregs (103–105).

Another important but less well-studied aspect is how the gut-microbe interface may allow microbial and oral antigens to gain access to the adaptive immune system through being uptaken by APCs. This process may occur in nearby draining lymph nodes or mesenteric adipose tissue (106,107). Alternatively, gut antigens can be accessed by adaptive immune cells in local gut lymphoid structures, which can then leave the bowel and migrate to other tissues (92). Indeed, IgG antibodies that are immunoreactive against extracts of gut microbes have been detected in obese individuals with diabetes and are indicative of microbial antigen-specific B-cell activation (108). Nonetheless, it remains to be determined whether such microbe-specific adaptive immune responses have any bearing on the inflammation that is ongoing in obese metabolic tissues, such as the VAT, and whether antigenic mimicry between obesity-associated gut-derived bacteria and self-antigens exists and contributes to breakdown of self-tolerance during obesity.

Mucosal immune responses in the gut may indeed be intimately linked to VAT-associated immune responses and exert a direct impact on insulin resistance. Aside from studies documenting a heightened inflammatory activity in the bowels of obese rodent models and humans (109,110), bowel-VAT immune cross talks also have been implicated in inflammatory bowel diseases, where patients with Crohn disease exhibit features of increased visceral adipose tissue expansion, or "creeping fat," and potentially increased inflammation (111). The nature of this bowel-VAT immune network, how it operates, and how it can be manipulated for therapeutic benefits are areas that warrant future investigations.

CLINICAL IMPLICATIONS

Insights into the immune aspects of type 2 diabetes pathogenesis will undoubtedly be invaluable for the design of novel diagnostic and immunotherapeutic strategies to effectively manage the disease. Autoantibody diagnostics might potentially be used as surrogate markers for insulin resistance or markers for predisposition to diabetes and/or its complications (43), while an autoimmune pathophysiology would open metabolic

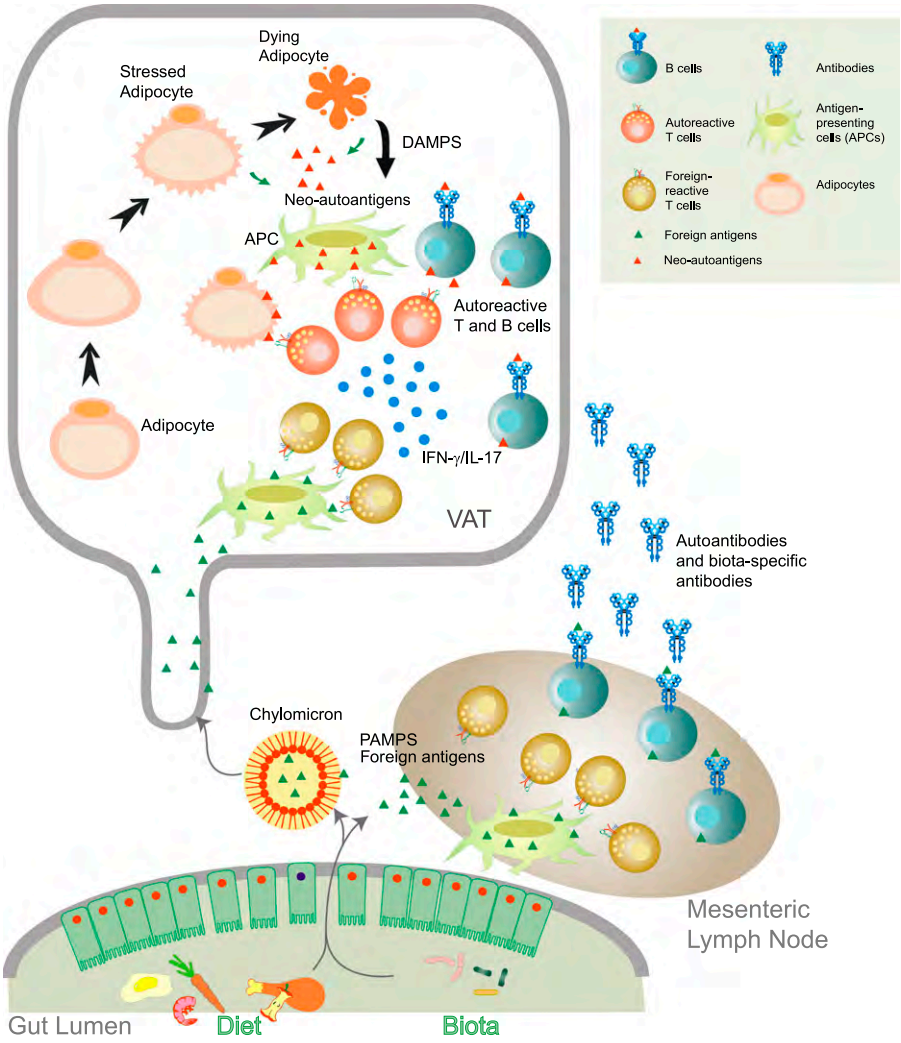

Figure 2—Proposed pathways, centered in the VAT, to autoimmune responses during obesity. Intrinsic inflammatory changes cooperate with obesity-associated dysbiosis in the gut to initiate self- or microbe-specific adaptive immune responses in the VAT, generating a feed-forward inflammatory loop that worsens insulin signaling. Long-term caloric excess causes hypertrophy and ER stress in white adipocytes, leading to the release of adipokines and chemoattractants that help activate and/or recruit innate cells, such as macrophages, and adaptive immune cells, such as B and T cells, to the VAT. Obesity-associated dysbiosis contributes to increased gut permeability, facilitating leakage of microbial products and oral antigens across the gut epithelium. Together with lipid excess and dying adipocytes, these serve as potential sources of antigens and costimulatory signals for the activation of VAT B and T cells, a process that can potentially take place in the draining lymph nodes or locally in the VAT. Activated B and T cells, in turn, contribute to VAT inflammation through the secretion of inflammatory cytokines and antibodies or through cross talk with other immune cells. DAMPs, danger-associated molecular patterns. PAMPs, pathogen-associated molecular patterns.

disease up to a number of immunomodulatory therapies. Some of these therapies might include cell-based therapies with regulatory B- or T-cell transfers, depletion of inflammatory T and B cells, blockage of the migration of pathogenic immune cells into metabolic tissue, or possibly dampening of pathogenic B cells and antibodies with fragment crystallizable receptor modulation. These therapies might replace or complement existing approaches aimed at targeting inflammatory pathways, such as with salicylates and cytokine-neutralizing biologics (72,73), though the implementation of these novel approaches would have to be carefully balanced by proper risk assessment of immunodeficiency-related side effects. In addition, as autoimmunity implies antigen specificity, self-antigen–specific immune responses might be curbed one day by better tolerated antigen-specific immunotherapies, with approaches that overcome current technical obstacles associated with the development of antigen-specific immunotherapy in humans (8). Advances that shed light on the relationship between gut microbiome and gut-associated immune pathways in obesity have opened up yet another avenue of therapeutic strategies —improving insulin resistance through the manipulation of diet, gut biodiversity, and potentially the gut immune pathways. Animal models, such as DIO C57BL/6 mice, provided a foundation on which these proof-of-concept strategies can be tested, but therapies tested in mice do not always translate in humans. Thus, the bulk of the

effort still remains in that equivalent immunological circuits will need to be better defined in human patients to enable clinical translation.

ARE OBESITY-RELATED INSULIN RESISTANCE AND TYPE 2 DIABETES AUTOIMMUNE DISEASES?

Tissue damage coupled to an inflammatory milieu can result in the loss of tolerance toward self-antigens and the initiation of an autoimmune response. It is therefore not surprising to find obesity as a risk factor for other autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis (112,113), as it provides fuel for an already dysregulated immune response. However, can obesity-related insulin resistance itself or type 2 diabetes be considered as bona fide autoimmune diseases? This distinction would be important given the above clinical implications.

Unlike many classical autoimmune diseases, obesity-associated immune responses are "low grade" in nature and do not manifest immediate clinical symptoms. Such low-intensity characteristics may be reflective of the lack of genetic predisposition to tolerance defects, as no dominant genetic association has been identified linking obesity-associated insulin resistance and type 2 diabetes to dysregulated immune pathways that are common in classical autoimmune diseases.

Yet chronic low-grade inflammation is not unlike the drawn-out silent inflammation in autoimmune individuals that can remain undetected for years and may or may not precipitate into clinical presentation, depending upon complex interactions between immunological and environmental triggers. An example is shown in the spectrum of islet autoimmunity, ranging from the aggressive β-cell destruction in type 1 diabetes to latent autoimmune diabetes in adults (114) to the insulitis found in autoantibody-positive, otherwise healthy individuals (115). All three scenarios carry autoimmune components with varying severity. Thus, a disease with latent autoimmune components such as type 2 diabetes cannot be strictly excluded from such a spectrum without ascertaining its pathologic contribution.

Closely related to the contention of whether type 2 diabetes is an autoimmune disease is the question of whether obesity-related VAT inflammation and insulin resistance/type 2 diabetes originate from an activated adaptive immune response or whether such adaptive immune responses evolve from chronic metabolic inflammation. One piece of evidence that stands against the former hypothesis is the fact that DIO rodent models do not require intact T- and B-cell responses to develop obesity-associated insulin resistance (13,116), although the relevancy of the animal models used and how closely they recapitulate human disease is in question here. For instance, the complete lack of T and B cells would mean the absence of regulatory subsets, such as the $Foxp3^+$ $CD4^+$ Tregs and the IL-10–producing regulatory B cells, which play pivotal roles in modulating adaptive immune responses. Furthermore, cell subset ablation can significantly affect gut-associated immunity, causing microbial imbalances that further affect VAT inflammation. Thus, future experiments are needed to tease out the cause-and-effect aspects of self-specific and gut-specific adaptive immune responses in obesity.

Fundamentally, available evidence is insufficient to support or dismiss the classification of metabolic syndrome and type 2 diabetes as typical autoimmune diseases. Following the criteria outlined above, obesity-associated inflammation and insulin resistance show evidence of disease-specific adaptive immune response in the affected target tissue or organ, primarily in the VAT. Although isolated T and B cells and/or antibodies have been demonstrated to transfer disease and T- and B-cell–targeting strategies dampen disease progression, whether these responses target specific self-reactive antigens remain to be demonstrated. On the other hand, the presence of distinct autoantibodies linked to the insulin-resistant or type 2 diabetes state suggests that there is a defined autoimmune component to these diseases. Future studies will be required to assess whether such findings are secondary effects of the disease or whether such autoimmunity represents a true driving pathology, as seen in classical autoimmune diseases.

Funding. Studies of obesity-associated adaptive immune responses in the laboratory of the authors were supported in part by Canadian Institutes of Health Research grant 119414 (D.A.W.), Canadian Diabetes Association grants OG-3-12-3844 and CS-5-12-3886 (D.A.W.), and the University of Toronto Banting & Best Diabetes Centre Sun Life New Investigator Award (D.A.W.). S.T. is a recipient of a Canadian Institutes of Health Research Banting Postdoctoral Fellowship. X.S.R. is the recipient of a Banting & Best Diabetes Centre Fellowship in Diabetes Care (funded by Eli Lilly Canada).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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