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REVIEW

Metabolic link between obesity and autoimmune diseases

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ABSTRACT. The abnormal accumulation of visceral adipose tissue in obesity is associated with metabolic changes that include altered glucose tolerance, insulin resistance, hyperlipidemia, and metabolic syndrome. Obesity also coincides with increased incidence of autoimmune diseases. Accumulating evidence suggest that prolonged metabolic overload related to overnutrition, influenced by genetic and epigenetic factors, might affect immunologic self-tolerance through changes in the energy metabolism of immune cells, particularly regulatory T (Treg) cells. A strong activation of nutrient-energy signaling pathways blocks the induction of the transcription factor forkhead P3 (FOXP3), a master regulator of Treg cells, consequently inhibiting their generation and proliferation, thereby promoting proinflammatory response. Expanding our knowledge on the topic, particularly on metabolic T cell flexibility *in vivo* will provide new insights that can be used to develop therapeutic strategies for various inflammatory diseases, including obesity and autoimmune diseases. Targeting specific metabolic pathways is emerging as an important approach to control immune response and maintain immunological homeostasis.

Key words: obesity, autoimmunity, immunometabolism, lymphocyte metabolism, cytokines

Autoimmune diseases, such as many other complex disorders, are believed to arise from a combination of genetic and environmental factors. The most common hypothesis on etiology of autoimmune diseases states that polymorphisms in various genes that are mostly involved in immunity result in defective regulation or reduced threshold for lymphocyte activation, and environmental factors initiate or augment activation of self-reactive lymphocytes that have escaped central thymic control and are poised to react against self-antigens. Although the genetic origins, environmental factors, and clinical manifestations of autoimmunity are vast, many autoimmune diseases share common features that contribute to pathogenesis, such as activation and generation of pathogenic effector $CD4^+$ and $CD8^+$ T cells. The consensus is that various cytokines present in the microenvironment such as interleukin-1β (IL-1β), IL-6, IL-23, and tumor growth factor-β directly affect T cell differentiation into pathogenic effector cells, by promoting T helper 17 (Th17)-cell differentiation while blocking regulatory T (Treg)-cell differentiation [1]. Effector T cells are highly dependent on macronutrients, such as carbohydrates, proteins, and lipids, which derive from their microenvironment, and limited nutrient availability can constrain effector T cell response and promote a tolerogenic environment [2]. Availability of metabolites therefore affects metabolic pathway usage and differentiation of effector T cells, reciprocally influencing the microenvironment.

Autoimmune diseases affect approximately 5% to 9.4% of the EU and US populations, more frequently women than man, and often congregate in families, suggesting genetic predispositions [3, 4]. Their incidence and prevalence between 1985 and 2005 showed a net percent increase per year in incidence (19.1 ± 43.1%) and prevalence (12.5 ± 7.9%) [3, 5]. The proposed explanation for recent rapid increase in incidence and prevalence of autoimmune diseases is the change of various environmental factors, including the decrease in infectious diseases due to improved hygienic standards, increased exposure to environmental pollutants and low vitamin D intake, among others [6, 7]. The list of environmental factors also includes an increased daily caloric intake of processed foods [8]. Since the 1970s, there has been an average increase of approximately 35% in the availability of calories per capita, in kilocalories per day, which corresponds to about 2800 kilocalories per day [9]. Industrialized or western food has often a high content of the so-called "holy triad", namely sugar, fat, and salt, which hyperactivate intracellular nutrient-energy-sensing pathways [10]. For obvious reasons, prolonged overnutrition has also been linked to the dramatic

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increase in prevalence of obesity, although other factors, both genetic and environmental, contribute to this global health problem. In 2016, more than 1.9 billion adults, representing 39% of the world's adult population, were affected by overweight, of whom over 650 million (13%) had obesity, with obesity rates surpassing 50% in many countries [11]. A high number of children and adolescents are also affected: in 2016, some 41 million children under the age of 5 years and 340 million (18%) of those aged 5 to 19 years had developed overweight or obesity.

Numerous epidemiologic studies have shown the association between an elevated body mass index and a waist-to-hip ratio, the commonly used anthropometric estimates of fatness, and autoimmune diseases, including type 1 diabetes (T1D), multiple sclerosis (MS), psoriasis, psoriatic arthritis, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel diseases, etc. [12-17]. Excessive adiposity is frequently accompanied by a low-grade chronic inflammatory state marked out by increased systemic markers of inflammation [18]. Although the initial trigger for this inflammation is not fully understood, it is reportedly associated to a homeostatic stress caused by a positive energy balance. Under the prolonged overnutrition conditions, the sensors on the immune cells can directly recognize increased nutrient availability, resulting in their aberrant activation [19]. The locally induced inflammation characterized by elevated secretion of proinflammatory cytokines and adipokines produced by adipose tissue promote immune responses by Th1 and Th17 cells, decrease the level of Treg cells and enhance M1-macrophage polarization [20] (*figure 1*). This proinflammatory microenvironment in turn favors bystander activation of other immune cells, including lymphocytes with autoreactive potential [21]. Obesity-induced adipose-tissue inflammation is associated with broad metabolic changes that include altered glucose tolerance, insulin resistance, hyperlipidemia, and metabolic syndrome. Similar metabolic alterations at a systemic and/or local level are also observed in autoimmune diseases [22]. This review is aimed to explore the association between obesity and autoimmunity, focusing particularly on the emerging metabolic link.

OBESITY-ASSOCIATED ALTERATIONS IN T CELL METABOLISM AND FUNCTION

The discovery of intracellular nutrients and energy sensors that react on changes in both the extracellular and intracellular environment has shed new light on association between metabolism and T cell differentiation and function. Crucial pathways involved in sensing the presence of nutrients necessary for the generation of energy and maintenance of cellular processes include mechanistic target of rapamycin (mTOR), adenosine monophosphate-activated protein kinase (AMPK), and general-controlled nonrepressed kinase [23, 24]. They sense not only essential nutrients, such as glucose, amino acids, and lipids, but also growth factors linked to nutrition. By controlling the metabolic switching among specific intracellular processes, such as glycolysis, fatty acid oxidation, and oxidative phosphorylation, they have a critical impact on metabolism, immune responses, and inflammation both at the intracellular and at the systemic level [23, 24]. mTOR is involved in the control of anabolic pathways, glycolysis, and nucleotide synthesis. It also suppresses the key catabolic process of autophagy and maintains homeostasis in response to changing availability of nutrients, growth factors (e.g., insulin), and adipocytokines, such as leptin [24]. It has been shown that propagation and integration of T-cell stimulation and costimulation critically depends on the phosphoinositide 3-kinase (PI3K)-AKT-mTOR signaling axis [25]. Naive CD4 activated T cells can differentiate into multiple effector Th-cell lineages, including Th1, Th2, Th17, and T-follicular helper cells, whereas $CD8^+$ T cells primarily differentiate into cytotoxic T lymphocytes (CTLs) (*figure 2*). Activation of the PI3K-AKT-mTOR signaling pathway is essential for the generation and metabolic reprograming of

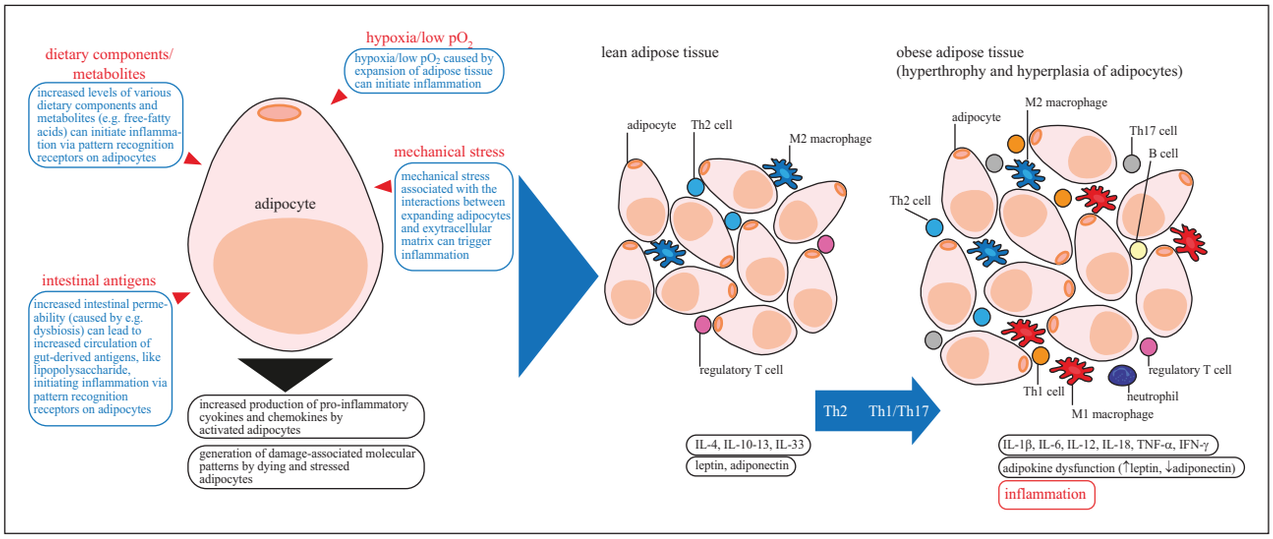

Figure 1
Chronic low-grade systemic inflammation in obesity [20].
Il: interleukin; IFN: interferon; Th: T helper; TFN: tumor necrosis factor.

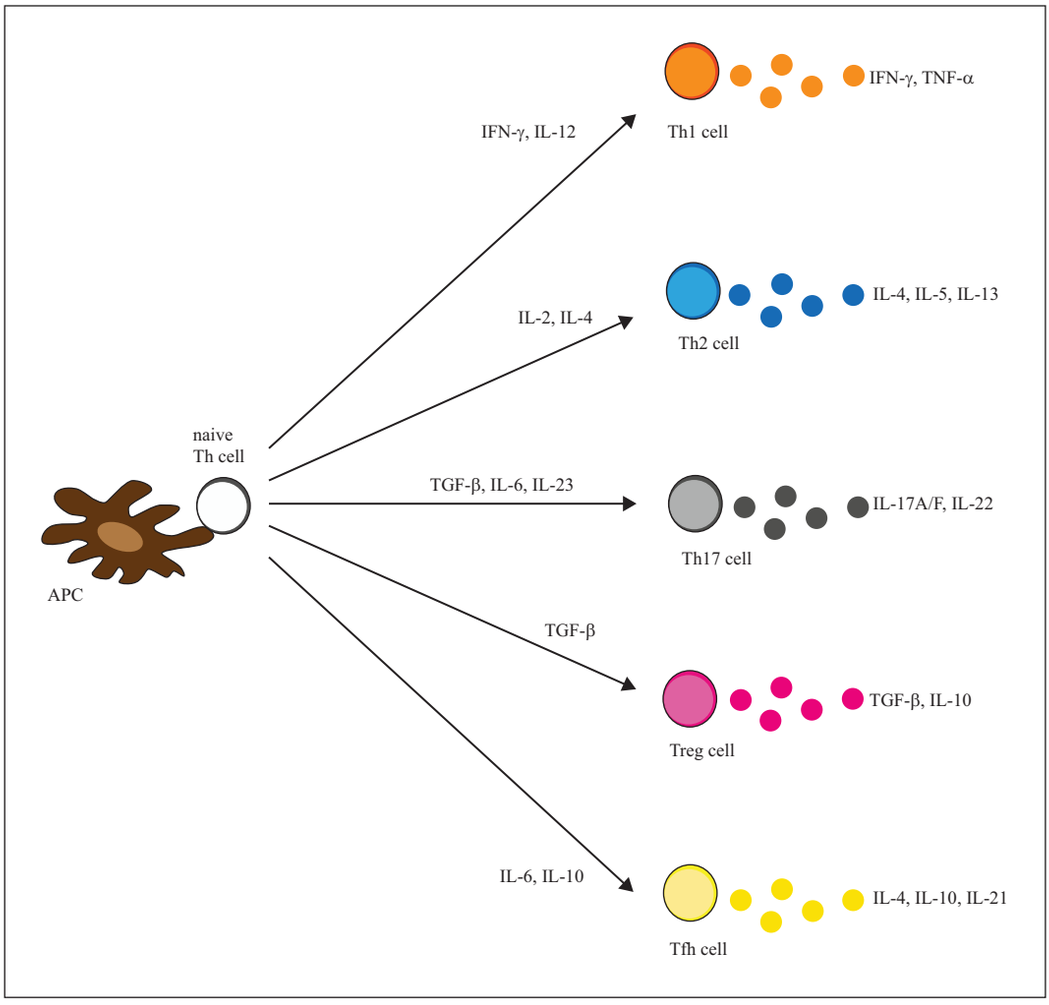

Figure 2
T-helper cell differentiation and key cytokines involved.
APC: antigen-presenting cell; IFN: interferon; IL: interleukin; TFH: T-follicular helper; TGF: transforming growth factor; Th: T helper; TNF: tumor necrosis factor; Treg: regulatory T.

$CD4^+$ T cells and cytotoxic T cells, playing a critical role in the differentiation of proinflammatory Th1 and Th17 cells and anti-inflammatory Treg cells [26]. Two important mTOR-dependent metabolic pathways that fuel the elevated energy and biosynthetic demands of effector $CD4^+$ and $CD8^+$ T cells are aerobic glycolysis and glutaminolysis [27]. Treg cells and Th2 cells, which are typically present in lean adipose tissue, have an anti-inflammatory effect on the surrounding tissue [28, 29]. By contrast, $CD8^+$ T cells and Th1 cells that migrate to, and are activated in, obese adipose tissue, promote the proliferation of proinflammatory M1 macrophages [29-31]. *Ex vivo*, these cells from adipose tissue exhibit higher proinflammatory cytokine production following restimulation [32]. It has been shown that an overabundance of glucose and lipids in obese tissue can impact T cell activation and differentiation directly *via* the modulation of nutrient sensor activity [29, 33]. Various studies have demonstrated a glucose-dependent increase in the production of proinflammatory cytokines, such as tumor necrosis factor-α, IL-1β, and IL-6, as well as the expression of insulin or growth factor receptors and their adaptors, including insulin receptor substrate 1, insulin signal peptide (INSP), also known as insulin receptor (IR) and insulin-like growth factor 1 receptor [34, 35]. Higher cytokine release by naive T cells is caused by increased chromatin decondensation, which requires glycosylation and product-specific receptor (advanced glycation end product receptor [AGER], also known as receptor for advanced glycation end products [RAGE]) signaling and p38 mitogen-activated protein kinase (MAPK) activity [35]. Hyperglycemia can also directly affect epigenetic modifications in cells by modulating the activity of sirtuins, a group of NAD-dependent protein deacetylases, by increasing histone acetyltransferase and acetyl-CoA expressions for use in histone acetylation [36, 37]. Furthermore, glucose concentration also affects activity of various transcription factors, including liver X receptor, forkhead box protein O1, wingless-related integration site (WNT) signaling, and energy-sensing kinase AMPK in different cell types, which are crucial for effector T cell generation, migration, and memory maturation [27]. Diet rich in saturated fatty acids (SFAs) has been associated with visceral adiposity and the development of type 2 diabetes [38]. SFAs can trigger pancreatic islet β-cell activation *via* toll-like receptor 4 (TLR4), leading to the upregulation of CC-chemokine ligand 2, followed by the recruitment of proinflammatory M1 macrophages to the site [39]. Free fatty acids in turn have been demonstrated to impact Th1-, Th17-, and

Treg-cell differentiation [40]. It has been shown that exposure of $CD4^+$ T cells to short-chain fatty acids (SCFAs) promotes Treg-cell differentiation, whereas medium-chain fatty acids and long-chain fatty acids (LCFAs) increase Th1- and Th17-cell differentiation *via* p38 MAPKs and Jun NH2-terminal kinase 1 (JNK1) [41]. It has been observed that acetyl coenzyme A carboxylase 1 (ACC1) expression in memory $CD4^+$ T cells from obese individuals correlate with the level of circulating Th17 cells [42]. Deletion of ACC1 inhibits Th17-cell differentiation, which can be restored by adding the exogenous fatty acids [42]. A high-fat diet or direct exposure to SCFAs during immune priming suffices to generate proinflammatory CXC-chemokine receptor 3 (CXCR3)-expressing $CD4^+$ T-effector memory cells *via* activation of phosphatidylinositol 3 kinase and AKT/protein kinase B (PI3K/AKT) signaling [43]. It is unclear, however, whether these cells are Th1 or Th17 cells, given that $CXCR3^+$ T cells are capable of producing both interferon gamma (IFN-γ) and IL-17A/E. The precise molecular mechanism responsible for SCFAs modulation of T cell differentiation is not known, although it involves TLR4 signaling [44]. Increased migration of $CXCR3^+$ T cells could intensify inflammation in tissues that regulate metabolic homeostasis, such as adipose tissue, muscle, and liver. In case of Th17-cell differentiation, the process depends on the master transcription factor RAR-related orphan receptor gamma (RORγt), a nuclear hormone receptor, whose binding to target DNA response elements is modulated by the availability of cholesterol-derived biosynthetic intermediates [27]. Lipid biosynthesis mediated by sterol regulatory element-binding protein is markedly increased in activated $CD4^+$ and $CD8^+$ T cells [27]. The resulting increase in cholesterol and fatty acid metabolism in obesity generates metabolites that are crucial for modulation of RORγt binding to target gene promoters. In this context, it is worth to note that PPARγ, a nuclear receptor that binds to ϖ-polyunsaturated fatty acids, is a central regulator of lipid uptake and storage in numerous cell types, including T cells [27]. PPARγ has been implicated in both the promotion and inhibition of T cell proliferation [45]. Data indicate that agonists of PPARγ downmodulate IFN-γ production by $CD4^+$ and $CD8^+$ T cells, and PPARγ activity controls the generation of visceral adipose tissue (VAT)-resident Treg cells [45]. Importantly, obesity is associated with a reduced level of VAT-resident Treg cells in adipose tissue [46, 47]. This unique Treg population has been recently defined and its main role is to keep the vast depot of adipose tissue quiescent in terms of inflammation to maximally sensitize insulin signaling [48]. VAT-resident Treg cells comprise 40% to 80% of VAT $CD4^+$ T cells, and are slightly distinct from lymphoid tissue-associated Treg cells which comprise only 5% to 15% of $CD4^+$ T cells [49]. As mentioned, VAT-resident Treg cells are highly dependent upon PPARγ [distal to T cell receptor (TCR) signaling] and have a unique transcriptome with many lipid metabolism genes upregulated compared to lymphoid tissue-associated Treg cells [49]. It has been shown that overactivation of mTOR, as happens under the conditions of lost fluctuations in diet and leptin during nutritional overload, reduces the proliferation of Treg cells, inhibits the differentiation of conventional T cells into Treg cells, and promotes the differentiation of the proinflammatory Th1/Th17 cell lineage, thus leading to defective immunoregulation [50, 51]. It has been shown that a strong activation of PI3K-kinase AKT-mTOR pathway restrains the induction of the transcription factor forkhead box protein 3, a master regulator of Treg cells, consequently inhibiting their generation and proliferation [52]. In line with this evidence, elevated and tonic activity of mTOR and the S6 ribosomal kinase maintained in naive $CD4^+$ T cells by genetic manipulation, results in lower levels of Treg cells, which in turn leads to the accumulation of proinflammatory T cells, including autoreactive T cells [53]. Treg cells show high sensitivity to oscillatory fluctuations in leptin and circulating nutrients, and rapidly adapt to microenvironmental changes such as low glucose and high lactate, which is typical for inflamed and ischemic tissues [8]. It seems that mTOR signaling needs to be rapid, oscillatory, and of low or intermediate strength to promote the proliferation and homeostasis of Treg *in vivo* and *in vitro*. Altogether, these data indicate that alterations in serum lipid content and abundance in obese individuals influence T cell differentiation, promoting Th17 and Th1 differentiation. It is also worth noting that a nutrient-mediated activation of innate immune cells residing in adipose tissue can further contribute to an inflammatory microenvironment, additionally amplifying T cell activation [54].

LYMPHOCYTE METABOLISM IN AUTOIMMUNE DISEASES

As mentioned, an obesity-associated overabundance of lipids, glucose, and amino acids impacts T cell activation and differentiation directly *via* the modulation of nutrient sensor activity [33]. Similar changes in lymphocyte metabolism are observed in autoimmunity [55] (*figure 3*).

For instance, an increased glucose uptake by T cells with overexpressed glucose transporter 1 (GLUT1) is sufficient to promote IFN-γ and IL-2 production following *in vitro* stimulation and promotes antibody deposition in glomeruli [56]. Moreover, deletion of GLUT1 reduces glycolytic activity in $CD4^+$ T cells and effector $CD4^+$ T cell generation, protecting against colitis [57]. Reduced GLUT1 mobilization to the plasma membrane due to increased lysosomal degradation of GLUT1-containing vesicles in WASP homolog-deficient T cells also leads to a reduction in T cell proliferation and decreased severity of experimental autoimmune encephalomyelitis (EAE, the mouse model for MS) [58]. Naive $CD4^+$ T cells from lupus-prone mice show higher glycolytic rates than those of age-matched control cells [59].

An increased glycolysis rate is a common feature for both effector $CD4^+$ T cells (Th1, Th17) and $CD8^+$ CTL cells [60, 61]. It has been demonstrated that inhibition of glucose metabolism in $CD4^+$ T cells cultured under Th1/Th17 polarizing conditions leads to significantly reduced differentiation into both lineages, whereas

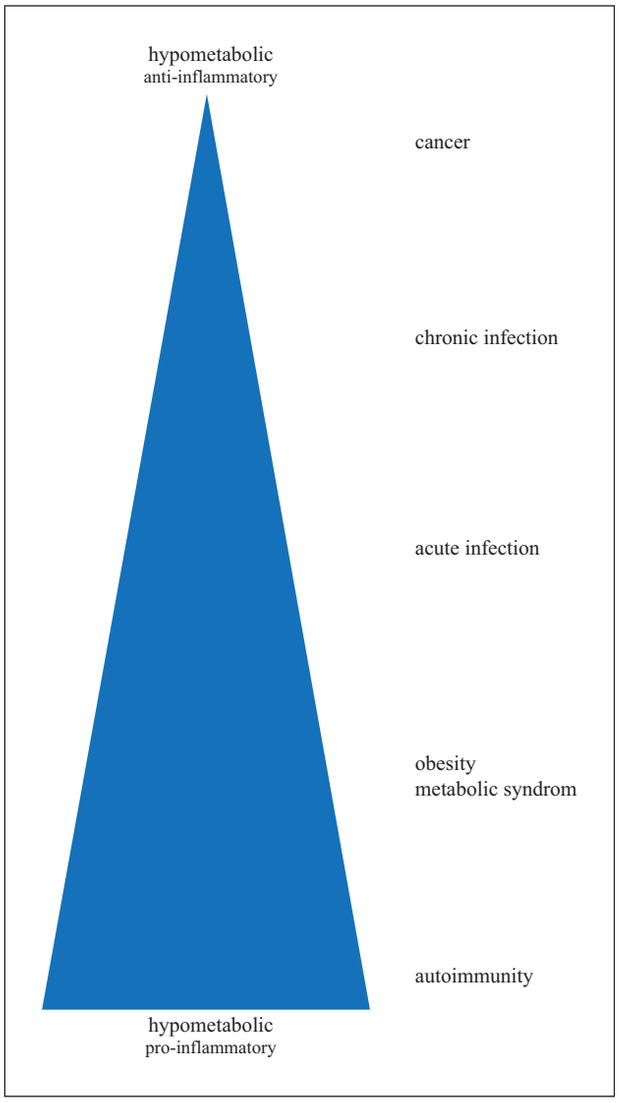

Figure 3
T-cell metabolic states in various diseases.

differentiation into inducible Treg cells is increased under glucose-limiting conditions [60, 62]. Furthermore, blocking glycolysis at the level of hexokinase improves clinical outcome in mice with EAE [60]. It seems therefore that glycolysis is enhanced in all effector T cell populations, but these cells have distinct glucose metabolism signatures.

During an inflammation, immune cells also require increased intracellular pools of amino acids to support broad range of cellular processes, as they are needed as substrates in protein and nucleic acid synthesis, as well as in the synthesis of other amino acids [63, 64]. Increased amino acid availability has been shown to upregulate signal transduction by mTOR1 and to induce stress-response pathways in T cells, whereas restriction differently affects T cell activation, proliferation, and clonal expansion [65]. For instance, halofuginone, an alkaloid that activates the amino acid starvation response by increasing uncharged tRNA levels and activating the amino-acid-sensing kinase general control nonderepressible 2, decreases Th17-cell differentiation [66]. Similar observations have been reported in case of amino acid restriction, including Met, Cys, Leu, as well as inhibition of tryptophanyl-tRNA charging [66, 67]. Interestingly, neither Th1- nor Th2-cell polarization is affected after activation of the amino acid response pathway, further indicating that effector $CD4^+$ Th-cell lineages have distinct sensitivities to amino acid restriction. In line with these findings, halofuginone reduces Th17-cell level in the central nervous system and disease severity in mice with EAE, but does not affect Th1-cell level or IFN-γ production [68]. In addition, leucine and other branched-chain amino acids activate mTORC1 [69]. T cell activation under glutamine-restricted conditions or following inhibition of small neutral amino acid transporters (SNATs) blocks T cell proliferation and IL-2 and IFN-γ production [70, 71]. Glutamine restriction promotes the differentiation of naive $CD4^+$ T cells toward Treg-cell lineage, whereas it does not affect the Th2-cell differentiation [72]. In support of these findings, deletion of Slc1a5 which encodes a glutamine transporter, limits Th1- and Th17-cell generation and reduces EAE development [73], whereas SNAT blocking inhibits T cell proliferation and IFN-γ production [71]. Serine deficiency has also been found to significantly reduce proliferation of effector T cells, particularly $CD8^+$ T cells [72, 74]. Serine is primarily used in the one-carbon metabolism cycle for purine biosynthesis. It seems plausible that methotrexate (MTX) used for the treatment of various autoimmune diseases, might be responsible for blocking Th17-cell differentiation *via* inhibition of folate-dependent one-carbon metabolism, which is critical for nucleotide biosynthesis [75]. It has been suggested that serine restriction could be used in conjunction with MTX to treat autoimmune diseases such as RA, leading to inhibition of Th17 differentiation and effector function [72].

High levels of circulating lipids associated with obesity might also promote differentiation of $CD4^+$ T cells into Th1 and Th17 cells. Rapidly proliferating cells require *de novo* fatty acid and cholesterol synthesis for incorporation into the plasma membrane and lipid membranes of organelles. Targeting glucose-derived *de novo* lipogenesis with an acetyl CoA carboxylase inhibitor blocks Th17 cell differentiation and proliferation, while promoting Treg-cell formation [76]. It is in line with the fact that *de novo* fatty acid and cholesterol synthesis are required for rapidly dividing T cells [72]. It has been found that in a relapsing-remitted model of EAE, linoleic acid and cholesterol metabolism are increased [77]. Dyslipidemia is also observed in individuals with RA, SLE, and MS [55, 78]. It remains unclear how altered lipid abundance promotes autoimmunity. Inhibition of cholesterol synthesis with statins (HMG-CoA reductase inhibitors) has been found to stop EAE progression [79]. Statins can directly modulate immune pathogenesis by inhibiting Th17 cell differentiation while promoting Treg-cell differentiation [80]. Importantly, use of statins was found to lower mortality in patients with RA [81]. It is also worth to note that diet-derived LCFAs and SCFAs have opposite effects on Th17 cell differentiation [41]. LCFAs promote the generation of pathogenic Th1 and Th17 cells, whereas SCFAs promote Treg-cell differentiation. Accordingly, an LCFA-rich diet exacerbates pathology in mice with EAE.

OBESITY AS AN AUTOIMMUNE DISEASE

Obesity itself displays various autoimmune characteristics, in which adipose tissue antigens are targeted by autoreactive T cells [82]. For instance, overweight and obese individuals exhibit: (i) the presence of inflammatory cell infiltrates, including Th1 and Th17 cells, $CD8^+$ T cells, and M1-polarized macrophages in adipose tissue which is a target organ; (ii) a reduced level of anti-inflammatory Th2 and Treg cells in the adipose tissue; and (iii) circulating auto-antibodies to adipose tissue and apoptosis of adipocytes [28, 29, 83-85]. The activity of several apokines involved in the control of food intake and Th1 responses, such as leptin, has been associated with autoimmune pathogenesis, including RA, SLE, MS, and T1D [86-88]. As mentioned, obesity often coexists with autoimmune diseases in the same individual, possibly as a result of concurrent analogous mechanisms of preferential differentiation of Th cells into pathogenic Th1 and Th17 cells and altered immunotolerance that operate in that individual but affect different organs.

It has been found that adipose tissue T cells display antigenic bias in their TCR diversity, implying that they undergo prior clonal expansion in response to specific, yet unidentified, autoantigens [29]. It has been suggested that the high levels of oxidized lipids might modify self-proteins and thus generate autoimmune responses [8]. The progression of obesity after ingestion of high-fat diet increases the concentration of "natural" immunoglobulin M (IgM) which results from the activation of TLR4 on B cells [84]. IgM and an apoptosis inhibitor of macrophage (AIM) play an important role in obesity-associated insulin resistance [89]. Higher serum levels of AIM have been found in obese individuals with coexisting autoimmune diseases in sharp contrast to individuals suffering from obesity only, implying that AIM may be used as a potential biomarker for obesity-related autoimmune disorders [84].

As mentioned, evidence suggests that an obesogenic diet significantly contributes to the production of autoantibodies, presumably *via* CD40L signaling, which intensifies the production of inflammatory mediators by adipocytes [90, 91]. Defects in B-cell tolerance have been associated with most of autoimmune diseases and are illustrated by the production of autoantibodies that target self-antigens. Some of these autoantibodies are pathogenic because they interfere with the function of the molecules they recognize, such as the acetylcholine receptor/muscle-specific tyrosine kinase in myasthenia gravis [92], and the aquaporin-4 water channel in neuromyelitis optica spectrum disease [93]. Others target nucleic acids or their associated proteins, allowing the formation of immune complexes that deposit in various organs and induce organ damage, like in systemic SLE [94]. These immune complexes also allow the activation of myeloid cells expressing FcRs-binding autoantibodies and TLRs, including TLR7, TLR8, and TLR9 that recognize autoantibody-bound nucleic acids and lead to cell activation, thereby intensifying inflammation [94]. As B cells have been demonstrated to be essential for the development of diabetes in the NOD mouse model, additional investigation revealed that B cells promote diabetes by recognizing self-antigens with their autoreactive B-cell receptors (BCRs) and presenting self-antigens *via* MHC class II molecules to T cells [95, 96]. Therefore, self-antigen presentation by autoreactive B cells that escape tolerance may initiate the development of autoimmune diseases [97].

Results from animal and human studies support the concept of pathogenic IgG antibody production directed against specific array of self-antigens in obesity, including: (i) the GOSPR1-Golgi apparatus, which is highly associated with insulin resistance in obese males; (ii) IgG2c antibodies with yet unidentified specificity in mice; and (iii) reduction of B-cell antibody responses in young and elderly individuals with obesity [98, 99]. In addition to the secretion of pathogenic antibodies in VAT [99], a production of autoreactive IgG antibodies in subcutaneous adipose tissue (SAT) in obese individuals has been demonstrated as well. During the development of obesity, reduced oxygen and subsequent hypoxia and cell death all result in the release of proinflammatory cytokines, peptide self-antigens, cell-free DNA, and lipids. Together, these factors may stimulate B-cell class switching and the production of autoimmune IgG antibodies. Fat-specific IgG antibodies are secreted by B cells in the SAT, whereas B cells express mRNA for the transcription factor T-bet and the membrane marker CD11c, both implicated in the production of autoimmune IgG antibodies [99-101].

CONCLUSIONS

The abnormal accumulation of VAT in obesity is associated with metabolic changes that include altered glucose tolerance, insulin resistance, hyperlipidemia, and metabolic syndrome. Obesity also coincides with increased incidence of autoimmune diseases [98], although other factors can influence these changes [102-104]. Accumulating evidence suggest that prolonged metabolic overload related to overnutrition, influenced by genetic and epigenetic components, might affect immunologic self-tolerance through changes in the energy metabolism of immune cells, particularly Treg cells. A strong activation of PI3K-kinase AKT-mTOR axis blocks the induction of transcription factor FOXP3, a master regulator of Treg cells, consequently inhibiting their generation and proliferation, and promoting Th1/Th17 response (metabolic programs regulating other T cell subsets, including Th9 and Th22 are still elusive and require further investigation [26]). Autoimmunity therefore might result from the impaired generation of thymus-derived Treg cells early in life and/or reduced generation of peripheral Treg cells by overstimulation of nutrient-energy sensing pathways. Expanding our knowledge on the topic, particularly on metabolic T-cell flexibility *in vivo*, will provide us with new insights that can be used to develop therapeutic strategies for various inflammatory diseases, including obesity and autoimmune diseases. Targeting specific metabolic pathways is emerging as an important approach to control immune response and maintain the immunologic homeostasis.

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