Obesity, Type 1 Diabetes, and Psoriasis: An Autoimmune Triple Flip

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Key Words

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Abstract

Obesity, type 1 diabetes, and psoriasis are wide-ranging health problems. Genetics, epigenetics, and environmental factors together with immune disturbances are involved in these diseases. The white adipose tissue is an active endocrine organ, secreting a wide variety of soluble mediators called adipokines that have a central role in the relationship between adipose tissue and immune system. Inflammatory cytokines, including the IL-23/IL-17 and IL-18 axes, and microRNAs are involved in many processes, including immunity and inflammation, thus having a major role in the onset of these three diseases. In this review, we present an overview of the roles of adipokines, cytokines, and microRNAs in the pathogenesis and the progression of these three diseases.

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Introduction

The pathophysiology of autoimmune diseases involves genetics, epigenetics, and environmental factors, together with immune disturbances. Many literature data con-

cerning the association between diet and the risk of developing autoimmune diseases are available [1]. The 'Western lifestyle' and a diet characterized by the use of high-fat, high-sugar, high-salt foods are involved in the development of autoimmunity, and the lack of physical activity in combination with excess calorie intake causes a high prevalence of obesity in developed societies [2, 3]. Obesity, in turn, predisposes to different diseases, and it is becoming increasingly clear that the dietary habits in Western societies and a high body mass index (BMI) also constitute risk factors for autoimmune diseases [4].

Once considered as an inactive energy storage tissue, the white adipose tissue has been discovered as an active endocrine organ, secreting a wide variety of soluble mediators termed 'adipokines' or 'adipocytokines' [5]. This group of cytokines has a key role in different processes, including immunity and inflammation. In particular, most of them have proinflammatory action and are involved in the 'low-grade inflammatory state' in obese subjects [6]. The most relevant adipokines are leptin, adiponectin, resistin, and visfatin.

Leptin has a key role in energy homeostasis: it promotes satiety and stimulates energy expenditure [7]. Furthermore, its serum levels are strongly correlated with the body fat mass and adipocyte size. Obese individuals show high levels of leptin expression in adipose tissue and in the systemic circulation. However, these high leptin levels

fail to reduce excess adiposity, a pathophysiologic status known as leptin resistance [8].

Leptin, up-regulated by inflammatory mediators such as tumor necrosis factor (TNF), IL-1 β , and insulin, promotes the release of proinflammatory cytokines such as TNF, IL-12, and IL-6 [9, 10]. In obese individuals, increased leptin production leads to a reduction in adipose tissue-infiltrating regulatory T cells (T_{reg}), thus amplifying local inflammation [7, 11]. T_{reg} are a subset of CD4+ CD25+ T cells, known as crucial mediators of immune tolerance [12].

Adiponectin is involved in the metabolic regulation and, similarly to leptin, is an insulin-sensitizing adipokine. Adiponectin reduces the secretion and the activity of TNF and IL-6, and induces the production of anti-inflammatory mediators, such as IRAK-1 (IL-10 and IL-1 receptor antagonist), in macrophages, monocytes, and dendritic cells. Adiponectin also enhances the number of T_{reg} cells [13, 14]. This cytokine is a key link between obesity and autoimmunity: despite being secreted by the adipose tissue, its levels are decreased in the serum of overweight patients and increased with calorie restriction [15–17]. TNF and IL-6 are efficient inhibitors of adiponectin secretion, suggesting the presence of a negative feedback between adiponectin and proinflammatory cytokines [6].

Proinflammatory cytokines, such as TNF, IL-1 β , and IL-6, increase the expression of resistin in human peripheral blood mononuclear cells [6]. In both rodents and humans, resistin serum levels increase with obesity [18, 19]. Different studies in animal models have shown that resistin promotes insulin resistance. However, in humans, resistin may be involved in inflammatory processes instead of in the glucose homeostasis modulation.

Visfatin increases the leukocyte production of inflammatory cytokines IL-6, TNF, and IL-1 β . Furthermore, it is involved in the activation of T cells, stimulating the expression of costimulatory molecules, such as CD54, CD80, and CD40 on monocyte surface. Visfatin has an important role in the development of both B and T lymphocytes and it acts as chemotactic factor for lymphocytes and monocytes. Together with resistin, visfatin is up-regulated by inflammatory mediators [20].

Type 1 diabetes (T1D) is a chronic disease due to the autoimmune destruction of insulin-producing β cells in the pancreas, leading to an abnormal regulation of glucose homeostasis in T1D patients [21, 22]. It is supposed that 90% of insulin-secreting β cells are destroyed due to autoimmune mechanisms driven by CD8+ and CD4+ T lymphocytes and proinflammatory cytokines. Abroga-

tion of CD4+ CD25+ FoxP3+ T_{reg} cells can break tolerance towards islet cell antigens in the pancreas, provoking T1D [23]. More recently, T_H17-dependent immunity has been demonstrated to be involved in the onset of autoimmune diabetes in animal models. In nonobese diabetic (NOD) mice, a model of spontaneous autoimmune diabetes, inhibition of T_H17 cells has been shown to mitigate autoimmune diabetes [24, 25]. In humans, the role of T_H17-dependent immunity in T1D is not fully clarified [26], even if many data show that the up-regulation of the IL-17 response has been associated with other immune-mediated diseases, such as multiple sclerosis, psoriasis, rheumatoid arthritis, and inflammatory bowel diseases [27]. Furthermore, the participation of IL-1 β , IFN- γ , and TNF in T1D is well known [28]. TNF and IFN- γ , released by infiltrating macrophages, are involved in pancreatic β cell apoptosis through activation of calcium channels, which, in turn, induce caspase activation [29].

Psoriasis is a chronic inflammatory autoimmune-mediated skin disorder [30]. It can occur at any age, although it most commonly appears for the first time in late adolescence or early adulthood and then usually persists for life [31]. Abnormal keratinocyte function, as well as the T_H1-mediated condition due to the large number of IFN- γ -secreting T cells in the epidermis, are strictly involved in the onset of psoriasis [32]. In psoriatic lesions, the most represented T-cell populations are T_H1, T_H22, and T_H17 [32]. Several authors have shown that different cytokines, including transforming growth factor β (TGF β), IL-6, IL-1, and IL-21, are involved in the differentiation of T_H17 cells. Furthermore, IL-23 has been found to have a key role in the maintenance and proliferation of differentiated T_H17 cells [31]. In addition to the recruitment of inflammatory T cell subsets, elevated levels of T_{reg} cells have been observed in patients with psoriasis, and increasing levels of these cells correlate with disease severity [33, 34]. Authors have found that T_{reg}, in the presence of proinflammatory cytokines such as IL-1 β and IL-6, can produce the proinflammatory cytokine IL-17. Therefore, T_{reg} may have a role in perpetuating, rather than in suppressing, inflammatory processes [35]. Recently, it has been found that IL-6, IL-23, and IL-21 may induce signal transducer and activator of transcription 3 (STAT3) phosphorylation of T_{reg} cells in psoriasis. STAT3 pathway results in impaired function of T_{reg} cells, which produce IL-17, IFN- γ , and TNF [36].

A growing number of studies support an involvement of the IL-18 axis in the pathogenesis of psoriasis [37]. For reasons not fully understood, patients with an organ-specific autoimmune disease have increased risks of develop-

ing autoimmune responses against other organs or tissues. Patients with T1D have been shown to have a higher susceptibility to develop other autoimmune diseases, such as psoriasis [23]. Recent studies have shown that patients with psoriasis are more inclined to be obese than healthy controls and that obesity is more common in patients with severe rather than mild psoriasis [38]. Finally, several adipokines have a central role in the low-grade inflammatory state in obese subjects, inducing autoimmune and inflammatory diseases such as T1D and psoriasis [39, 40]. The aim of this review is to present an outlook of the roles of adipokines, cytokines, and micro-RNAs (miRNAs) in the onset and maintenance phases of these three diseases.

The IL-23/IL-17 Axis

The IL-23/IL-17 axis is strictly involved in the pathogenesis of obesity and psoriasis. Moreover, there is a growing evidence that this axis may also be involved in T1D. T_H17 cells mediate the inflammation associated with tissue-specific autoimmune diseases. Aberrant T_H17 responses have been implicated in a growing list of autoimmune disorders [41]. T_H17 cells can be activated through different pathways. TGF β , in synergy with IL-6, has a key role in generating de novo T_H17 cells [42]. TGF β is also implicated in the differentiation of Foxp3+ T_{reg} cells [43]. Interestingly, IL-6 can break the homeostasis in the immune tolerance inhibiting the TGF β -driven T_{reg} differentiation and, as already mentioned, promoting the T_H17 differentiation [44]. Moreover, it has been found that TGF β upregulates IL-23 receptor α chain expression (IL23R), thus conferring reactivity to IL-23 that can play a key role in the survival and commitment of T_H17 cells [45]. Other authors have also shown an IL-6-driven IL-23R up-regulation on naïve CD4+ T cells through STAT3, as well as a synergic function of IL-6 and IL-23 in promoting T_H17 differentiation [46]. IL-6 increases TGF β mRNA levels in naïve CD4+ T cells, thus underlining that IL-6- and IL-23-driven T_H17 activation is dependent on TGF β [42]. IFN- γ and IL-4 can inhibit the action of TGF β on T cells, representing an important pathway by which these cytokines suppress T_H17 differentiation [45]. Differentiated T_H17 cells produce cytokines such as IL-17A, IL-17F, IL-21, and IL-22 [47].

Recent studies have observed that serum levels of leptin, IL-17, and IL-23 are significantly higher in obese subjects compared with lean controls. In particular, a study based on obese women has shown a correlation be-

tween serum levels of IL-17, IL-23, and increased weight, thus underlining a role for IL-17 and IL-23 as potential markers of the inflammatory syndrome that characterizes obesity. Adipose tissue, together with its infiltrating immune cells, is an important source of proinflammatory mediators and represents a possible cellular source of IL-17 and IL-23 in obese patients [48, 49].

Several studies have indicated an increase in IL-17 production in humans with T1D, especially in the very early stages of disease [50]. Monocytes from T1D patients have shown increased levels of IL-6 mRNA, giving a potential explanation for increased IL-17 production [51]. β cell survival and function may be impaired by IL-1 β , which is also able to promote IL-17 production [52]. It has been shown that T cells isolated from pancreatic lymph nodes of T1D patients undergoing pancreas transplant had a higher frequency of T_H17 cells than healthy controls [53]. Interestingly, in autoimmune diseases, a separate population of T_H cells, the T_H1/T_H17 cells that co-produce both IL-17 and IFN- γ , has been found [54]. Several studies have found an increased polarization of IL-17+ cells to produce IFN- γ in children with T1D compared with healthy controls [55, 56]. Thus, the presence of T_H1/T_H17 cells could potentially be a hallmark of T1D, even if further investigation is required.

Psoriasis is a T_H1 - and T_H17 -driven disease [57]. Inflammatory stress signals from keratinocytes activate dendritic cells (DCs) that can switch naïve CD4+ T cells into T_H17 ones [58]. The IL-23/IL-17 axis plays a crucial role in the inflammatory and proliferative pathway of both psoriatic skin and joint tissues [33]. Moreover, IL-17 serum levels in psoriatic patients have been shown to be increased compared to healthy controls [59] and T_H17 cell levels were higher in psoriatic plaques than in controls [60].

The IL-18 Axis

IL-18 is a cytokine that plays an important role in the T_H1 response. Pleiotropic effects of IL-18, especially the induction of IFN γ , are essential for immunity against invading pathogens. However, improper regulation of IL-18 can potentially lead to inflammation and destruction of self. This cytokine is synthesized as an inactive form that requires to be processed by caspase-1 into its active form [37].

IL-18 is one of the cytokines that have been found to be produced and released from human adipose tissue [61, 62]. Many studies have shown a strong evidence that IL-

IL-18 also has an important role in regulating energy homeostasis. Adipocytes from obese subjects secrete more IL-18 than those from lean controls [63]. In humans, circulating IL-18 levels positively correlate with BMI, adiposity, type 2 diabetes, or insulin resistance, hypertriglyceridemia, and metabolic syndrome [64, 65]. Furthermore, it has been observed a strong relationship between the chronic low-grade inflammatory state and its associated metabolic syndrome disorders due to increased adipokine release from accumulating white adipose tissue [64, 66].

IL-18 has also been reported to be involved in both the pathogenesis and progression of T1D. Genes for both mouse and human IL-18 are located in genetic regions associated with susceptibility to T1D [67, 68]. Different studies have reported increased serum IL-18 levels in patients with T1D, and this increase was correlated with glycated hemoglobin (HbA_{1C}) levels, suggesting a link between hyperglycemia and IL-18 [69, 70]. In NOD mice, pancreatic β cells can produce IL-18, and enhanced expression of this cytokine results in destructive insulinitis in these mice [71]. IL-18 protein expression was also observed within the pancreatic islets of patients with fulminant T1D [72]. Furthermore, a significant association between elevated IL-18 serum levels and increased numbers of autoantibodies detected was shown in new-onset T1D patients [73].

Concerning psoriasis, many immunohistochemical studies have shown that keratinocytes from healthy and psoriatic skin samples constitutively express IL-18 [74, 75]. However, IL-18 levels were higher in active and progressive psoriatic lesions than in those from patients with stable disease [76]. In psoriatic patients, serum IL-18 levels were increased [77]. Epidermal DCs express IL-18 receptor and, after IL-18-driven stimulation, show actin polymerization, a sign of increased migratory tendency [78].

Role of the Epigenetic Control: miRNAs

miRNAs are small non-protein-coding RNAs that negatively regulate gene expression at the post-transcriptional level targeting the 3'-untranslated region of a specific mRNA transcript [79]. miRNAs are main regulators of cellular pathways and networks, performing key roles in different biological processes and diseases [80–82]. Molecular phylogenetic studies have shown that a large number of miRNA sequences are highly conserved among species, thus underlining their key role in molecular pathways crucial for cell survival [83].

Several miRNAs, such as miR-21 and miR-146a, are prevalently expressed in immune cells, including T_{reg} cells, which are known to be critical players in immune tolerance [84, 85]. Dysregulation of miRNA expression or mutation in miRNA genes or in their binding sites are associated with a wide variety of human diseases, including autoimmune and inflammatory disorders [86].

Many studies on murine models have found that miR-21 and miR-146a are potentially involved in adipocyte differentiation through targeting C/EBP β (CCAAT-enhancer-binding protein- β) [87] and apolipoprotein E, respectively [88]. miR-21 has been shown to play a central role in the differentiation and function of both white and brown adipose tissue, and it is positively correlated with BMI in subcutaneous adipose tissue [89]. In preadipocyte proliferation, miR-146b is able to promote the transition to terminal differentiation, thus enhancing adipogenesis [90].

Recent studies have found that the expression of miR-146a and miR-146b-5p was significantly lower in newly diagnosed T1D patients compared with controls. Six genes were identified as target genes of miR-146a and miR-146b-5p: *BCL11A*, *NUMB*, *STX3*, *KLF7*, *GRID1*, and *PBX2*. These genes are associated with the risk of diabetes [91]. In pancreatic β cells, c-Rel and p65 activate miR-21 gene promoter, thus increasing its RNA levels. miR-21 down-regulates PDCD4 (programmed cell death protein 4) levels, thus protecting cells from Bax family-mediated apoptosis. Thus, the miR-21-PDCD4 axis may play a crucial role in T1D, representing a potential therapeutic target for treating the disease [92].

miR-21 is significantly up-regulated in psoriatic skin lesions compared to healthy skin [93]. Moreover, a positive correlation between miR-21 levels in T cells from psoriatic patients and disease activity has been found [94]. Concerning this association, recent studies have shown that miR-21 expression in psoriatic skin inflammation is suppressed by UV therapy [95]. Increased level of miR-21 in psoriasis could be explained by its involvement in T_H17 polarization as shown in a model of experimental autoimmune encephalomyelitis [96]. Moreover, miR-21 is able to activate TACE (TNF α -converting enzyme) through the down-regulation of epidermal TIMP-3 (tissue inhibitor of matrix metalloproteinase 3), the natural inhibitor of active TACE [97]. miR-146a, expressed in monocytes and macrophages by various Toll-like receptor ligands and pro-inflammatory cytokines, has been found overexpressed in psoriatic skin compared to controls [98, 99]. miR-146a, through its targeting action on IRAK-1 and TRAF-6 (TNF receptor-associated factor-6)

Fig. 1. Schematic representation of interactions between cytokines/adipokines in adipose tissue and obesity, psoriasis, and T1D. In obese subjects, resistin, leptin, and visfatin levels are increased while adiponectin levels are decreased (a). Visfatin and leptin increase IL-6 levels (b). This cytokine decreases adiponectin levels (c) and enhances resistin levels (d), thus playing a central role in the T1D pathogenesis. IL-6, in synergy with TGF β , is able to promote T_H17 differentiation (e). Another T_H17 differentiation pathway involves TGF β and IL-23, whose levels are increased in obese subjects (f). Differentiated T_H17 cells play a crucial role in both psoriasis and T1D, and increased levels of T_H17 cells could exacerbate these diseases (g). IL-18 levels are increased in psoriasis, T1D, and obesity (h). TNF is not represented in order to simplify the reading of the scheme.

proteins, plays a central role in the TNF signaling pathway [100]. However, it is worthwhile to underline that the role of miR-21 and miR-146a in psoriasis, as in other autoimmune diseases, is unknown and remains to be investigated in detail.

T1D and Psoriasis

Psoriasis and diabetes are both associated with chronic inflammation due to TNF and other proinflammatory cytokines, such as IL-1 and IL-6 [101]. The beneficial effects that many drugs have on both psoriasis and T1D may underline the correlation between these diseases. First approved for the treatment of moderate-to-severe psoriasis, alefacept is a biological drug tested in the T1DAL (inducing remission in new-onset type 1 diabetes with alefacept) trial [102]. This study has shown that alefacept is able to target pathogenic effector T cells, preventing β cell destruction in patients with new-onset T1D [103]. In particular, the fusion protein alefacept binds CD2 on T cells, thus inhibiting its interaction with CD58 on antigen-presenting cells, blocking ultimately the T_H1 and T_H17 polarization required for the onset and maintenance of these diseases [104]. Ustekinumab is a

monoclonal antibody currently approved and validated in patients under psoriasis treatment. This antibody targets the shared p40 subunit of IL-12 and IL-23, thus inhibiting both IFN- γ and IL-17 signaling pathways, respectively [105]. IL-12 differentiates naïve T cells into the T_H1 phenotype, which is known to be involved in both psoriasis and T1D. Furthermore, IL-23-driven T_H17 polarization plays a critical role in the onset of both diseases [106].

Obesity and T1D

Adipokines play a crucial role in the relationship between T1D and obesity, since their action involves metabolism, immunity, and obesity. Leptin and adiponectin regulate glucose metabolism through different mechanisms, including promotion of insulin secretion and glucose storage [107]. Recent studies have found high levels of adipokines in patients with T1D, suggesting a compensatory mechanism secondary to hyperglycemia, as well as the loss of endogenous insulin secretion in T1D patients [108]. Adiponectin has also been shown to protect β cells from apoptosis and islet immunoreactivity [109], while resistin has been shown to decrease β cell

viability [110]. Resistin is also involved in insulin resistance and its levels have been found to be increased in T1D [111], suggesting that it may be involved in the pathogenesis of this disease. Indeed, leptin has proinflammatory effects and accelerates autoimmune destruction of β cells in murine models [112]. Thanks to this knowledge on adipokines, it is clear that the prevention of obesity may have substantial benefits for preventing late complications of T1D.

Obesity and Psoriasis

Many studies have shown that patients with psoriasis are more frequently overweight or obese than the general population. There are strong pieces of evidence suggesting that obesity is an independent risk factor for psoriasis [113]. Furthermore, it has been indicated that obesity is more prevalent in patients with severe psoriasis than in patients with the mild form, reinforcing the link between body fat mass and psoriasis [3]. Extensive data, acquired on the proinflammatory role of adipocytes, show the pathogenic role of obesity in the incidence of psoriasis and in its severity. Adipokines and other mediators secreted by adipocytes may contribute to the inflammatory state in psoriasis [114]. Many studies have found that both leptin and resistin levels were higher in psoriatic patients than healthy controls, with a strong correlation to the severity of the disease [115, 116]. Recent studies have started focusing on dermal adipose tissue, and preliminary data have shown that psoriasis might interact systemically with subcutaneous white adipose tissue or locally with dermal white adipose tissue [117]. Nevertheless, psoriasis and obesity may be not reciprocally or unidirectionally causal, and instead may derive from a shared pathophysiology [118].

Conclusion

In conclusion, as summarized in figure 1, literature data highlight the strong relationship between obesity, T1D, and psoriasis. In particular, the IL-23/IL-17 axis may be involved in the pathogenesis of these three diseases, highlighting the occurrence of a common causal link among these systemic inflammatory diseases. Furthermore, the IL-18 axis plays a central role in the link between these diseases, because it is involved in the regulation of energy homeostasis, its genes are associated with T1D susceptibility and its levels have been found higher in active and progressive psoriatic lesions. The combination of genetic, epigenetic, and environmental factors is highly suspected to promote this triple flip. There is strong evidence for the negative impact of obesity on several autoimmune diseases. The adipose tissue is an active endocrine organ that may play a central role in the onset as well as in the worsening of pathological conditions in obese subjects. Adipokines may contribute to the inflammatory state in psoriasis as well as their dysregulation may have an important effect on β cell viability. Furthermore, miR-21 and miR-146a have been found to have an important role in these diseases. The discovery of stable, reproducible, and tissue-specific miRNAs in serum supports the potential role for use as novel biomarkers.

Many studies have focused on the treatment of autoimmune diseases with immune system-regulating drugs. In particular, new drugs targeting common inflammatory pathways could be helpful in the treatment of these diseases. Conditions such as obesity, psoriasis, and/or T1D can interfere in the efficacy of treatment and have shown to have a huge effect on public health. Mechanisms underlying the shared pathophysiological events need further studies in order to help clinicians in the management of these patients.

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