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Review

Obesity in autoimmune diseases: Not a passive bystander

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ABSTRACT

In the last decades, autoimmune diseases have experienced a dramatic increase in Western countries. The involvement of environmental factors is strongly suspected to explain this rise. Particularly, over the same period, obesity has followed the same outbreak. Since the exciting discovery of the secretory properties of adipose tissue, the relationship between obesity and autoimmunity and the understanding of the underlying mechanisms have become of major interest. Indeed, the fat tissue has been found to produce a wide variety of "adipokines", involved in the regulation of numerous physiological functions, including the immune response. By conducting a systematic literature review, we extracted 329 articles regarding clinical, experimental and pathophysiological data on the relationship between obesity, adipokines – namely leptin, adiponectin, resistin, visfatin – and various immune-mediated conditions, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), multiple sclerosis (MS), type-1 diabetes (T1D), psoriasis and psoriatic arthritis (PsA), and thyroid autoimmunity (TAI), especially Hashimoto thyroiditis (HT). The strongest levels of evidence support an increased risk of RA (OR = 1.2–3.4), MS (OR = 2), psoriasis and PsA (OR = 1.48–6.46) in obese subjects. A higher risk of IBD, T1D and TAI is also suggested. Moreover, obesity worsens the course of RA, SLE, IBD, psoriasis and PsA, and impairs the treatment response of RA, IBD, psoriasis and PsA. Extensive clinical data and experimental models demonstrate the involvement of adipokines in the pathogenesis of these autoimmune diseases. Obesity appears to be a major environmental factor contributing to the onset and progression of autoimmune diseases.

Contents

Abbreviations: ACPA, Anti-citrullinated protein antibodies; ACR, American College of Rheumatology; AIM, apoptosis inhibitor of macrophage; Anti-Tg, anti-thyroglobulin antibodies; Anti-TPO, anti-thyroperoxydase antibodies; BMI, body mass index; CCL, chemokine ligand; CD, Crohn's disease; CSF, cerebro-spinal fluid; CRP, C-reactive protein; EAE, experimental autoimmune encephalomyelitis; ESR, erythrocyte sedimentation rate; Foxp3, Forkhead box protein 3; HAQ, Health Assessment Questionnaire; HLA, human leukocyte antigen; HT, Hashimoto thyroiditis; HR, hazard ratio; IBD, inflammatory bowel disease; IFNγ, interferon gamma; IL, interleukin; iNK cells, invariant natural killer T cells; MS, multiple sclerosis; NLRP3-inflammasome, NOD-like receptor protein 3-inflammasome; OR, odds ratio; PASI, Psoriasis Area and Severity Index; PBMC, peripheral blood mononuclear cell; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RR, relative risk; SLE, systemic lupus erythematosus; T1D, type-1 diabetes; T2D, type-2 diabetes; TAI, thyroid autoimmunity; Th17 cells, T-helper 17 cells; TNFα, tumor necrosis factor alpha; Treg cells, T-regulatory cells; TSH, thyroid-stimulating hormone; UC, ulcerative colitis; WAT, white adipose tissue.

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1. Introduction

For several decades, industrialized countries face an increased prevalence of immune-mediated diseases [1,2]. Most of these inflammatory conditions result from a complex interaction between genetic background and multiple environmental factors [3–8]. Since genetic basis has remained constant over time, there is increasing recognition that environmental factors, especially the Western lifestyle, have a preponderant role in this growing prevalence [9]. Westernization is accompanied by profound changes in dietary habits, promoting high-fat, high-sugar, high-salt foods [10] with excess calorie intake, leading to obesity outbreak over the past 20 years [11,12]. Therefore, the links between obesity and autoimmunity were questioned and the involvement of obesity in the rise of autoimmune conditions was strongly suggested. This link became even more fascinating in recent years since the discovery of the remarkable properties of adipose tissue. Indeed, the white adipose tissue (WAT), long regarded as an inert energy storage tissue, has been recognized to be an essential endocrine organ, secreting a wide variety of soluble mediators termed "adipokines" or "adipocytokines" [13]. Initially identified for their metabolic and appetite regulation activities, adipokines are known to be involved in various processes including immunity and inflammation [14]. By their pro-inflammatory action, these molecules contribute to the so-called "low-grade inflammatory state" in obese subjects, resulting in a cluster of comorbidities such as metabolic syndrome, diabetes, or cardiovascular complications [13]. On this basis, it is now of major interest to clarify the relationship between obesity and autoimmune/inflammatory diseases. In this review, following a short overview of the main mechanisms highlighted so far to link obesity and autoimmunity, we will detail metabolic and immunological activities of the main adipokines. Then, we shall focus on obesity and more precisely adipokines involvement, in the development and prognosis of several immune-mediated conditions.

2. Connecting obesity and autoimmunity

Obesity corresponds to an abnormal accumulation of adipose tissue within the body. According to World Health Organization (WHO), approximately 35% of the world population is estimated to be overweight (body mass index, BMI 25–30 kg/m^2) or obese (BMI > 30 kg/m^2) [12]. As mentioned above, it is widely known that obese persons exhibit a subclinical chronic state of inflammation leading to multiple metabolic disorders [13]. Moreover, as will be discussed further below, a large number of studies found a significant correlation between obesity and a higher prevalence or a worse prognosis of many immune-mediated conditions. Therefore understanding the underlying immune disorders in obesity that promote inflammatory autoimmune diseases is a major topic of research. Thus, to date, several mechanisms have been postulated. These mechanisms are schematically illustrated in Fig. 1.

First, numerous studies have documented the properties of WAT as a crucial site in the generation of soluble mediators named "adipokines", most of which carry a pro-inflammatory activity. These include classical cytokines such as interleukin (IL)-6 and Tumor Necrosis Factor alpha (TNFα), and specific molecules such as leptin and adiponectin [13]. These mediators are secreted by adipocytes as well as by a diverse set of immune cells found to abundantly infiltrate adipose tissue under obese conditions [15,16]. As will be discussed later in this review, adipokines appear to be key players in the interactions between adipose tissue and the immune system.

Recently, several authors have also highlighted the role of the apoptosis inhibitor of macrophage (AIM) in the pathogenesis of obesity-associated autoimmune diseases [17,18]. AIM is produced by tissue macrophages and was initially found to promote the survival of macrophages against various apoptosis-inducing stimuli [19]. Briefly, it was demonstrated that lipolysis induced by increased blood AIM under obese conditions releases large amounts of saturated fatty acids from adipocytes. The latter stimulate chemokine production in adipocytes via TLR4 activation, which results in increased M1-macrophage infiltration in adipose tissue. Moreover, AIM forms immune complexes with natural auto reactive IgM associated with autoantigens. Thus, AIM promotes their retention on follicular dendritic cells and autoantigens presentation to follicular B-lymphocytes, leading to production of IgG autoantibodies.

The T-helper 17 cells (Th17) are a recently discovered subset of CD4 effector T lymphocytes. Th17 cells secrete IL-17 and are now recognized for their involvement in the pathogenesis of autoimmune diseases [20]. Recently it has been reported that obesity may predispose induction of Th17 cells, at least in part in an IL-6-dependent process, which exacerbates auto inflammatory diseases like multiple sclerosis and colitis in several mouse models [21]. Paradoxically, IL-17 has also been shown to inhibit adipogenesis [22,23]. The precise role of Th17 cells and IL-17 in obesity-associated inflammatory conditions needs to be clarified.

Another exciting field of investigation is the contribution of nutrients, especially the influence of a high-salt, high-fat diet, on immune-mediated conditions [10,24]. Indeed, recent studies suggest that Western diet may cause dysbiosis, an alteration of intestinal microbiome. This modification induces profound modulation of extra intestinal immune responses, including Th17/Treg imbalance [25]. However, it is not yet clear if dysbiosis contributes to or is a consequence of autoimmune diseases. In the same area, another possibility involves the higher prevalence of vitamin D deficiency among obese subjects [26]. Vitamin D regulates many processes, including immune response. Thus, it has been shown to increase Treg cells and inhibits Th1 and Th17 differentiation [27]. Hence, some studies report an association between vitamin D deficiency and the development of autoimmune diseases, although these observations are still controversial [28,29].

Some areas still require further investigations. It has been demonstrated that the NLRP3 (NOD-like receptor protein 3)-inflammasome, a highly regulated protein complex involved via its secretion of IL1β and IL18 in the pathogenesis of many autoimmune diseases, can be activated in macrophages by numerous factors associated with obesity,

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