Immunol Res (2016) 64:820–830
DOI 10.1007/s12026-016-8808-8

REVIEW

Emerging role of adipokines in systemic lupus erythematosus

Hong-Miao Li[1,2] · Tian-Ping Zhang[1,2] · Rui-Xue Leng[1,2] · Xiang-Pei Li[3] · Xiao-Mei Li[3] · Hai-Rong Liu[4] · Dong-Qing Ye[1,2] · Hai-Feng Pan[1,2]

Published online: 17 June 2016

Abstract Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by multisystem organ involvement and unclear pathogenesis. Several adipokines synthesized in the adipose tissue, including leptin, adiponectin, resistin, and chemerin, have been explored in autoimmune rheumatic diseases, especially SLE, and results suggest that these mediators may be implicated in the pathogenesis of SLE. However, the current results are controversial. In this review, we will briefly discuss the expression and possible pathogenic role of several important adipokines, including leptin, adiponectin, resistin, and chemerin in SLE.

Keywords Systemic lupus erythematosus · Adipokines · Leptin · Adiponectin · Resistin

Hong-Miao Li and Tian-Ping Zhang have contributed equally to this work and should be considered co-first authors.

✉ Hai-Feng Pan
panhaifeng1982@sina.com

Dong-Qing Ye
ydqahmu@gmail.com; ydq@ahmu.edu.cn

[1] Department of Epidemiology and Biostatistics, School of Public Health, Anhui Medical University, 81 Meishan Road, Hefei 230032, Anhui, People's Republic of China

[2] Anhui Provincial Laboratory of Population Health and Major Disease Screening and Diagnosis, Hefei, People's Republic of China

[3] Department of Rheumatology, Anhui Provincial Hospital, Hefei, People's Republic of China

[4] Graduate School, Wannan Medical College, West of Wenchang Road, University Park, Wuhu 241002, Anhui, People's Republic of China

Introduction

Systemic lupus erythematosus (SLE) is a chronic, multisystem, inflammatory connective tissue disorder. The etiology and pathogenic mechanisms of SLE have not yet been clearly elucidated. Currently, the adipose tissue has been considered as an organ with immune functions, and it produces several mediators, such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), interleukin 1 (IL-1), chemokine ligand 2 (CCL2), complement components, all of which participate in the innate immune response as pro-inflammatory mediators [1]. Thus, the white adipose tissue (WAT) is regarded as the largest endocrine organ, secreting a variety of mediators called adipokines (also known as adipocytokines) [2]. Adipokines include a variety of cytokines, peptide hormones, and enzymes mainly synthesized and secreted by adipocytes and immune cells which infiltrate adipose tissue that play a role in a wide variety of biological functions, especially in inflammatory and immune processes [3]. In SLE patients, metabolic alterations are often observed, which may be due to the disease, the genetic background, or the treatment [4]. Given the function of adipokines during inflammatory responses, numerous studies regarding the role of adipokines in SLE as well as other autoimmune and inflammatory-related diseases are emerging. While there are conflicting reports, most studies have shown increased serum/plasma levels of leptin, adiponectin, and resistin in SLE patients [5–15]. The levels of adipokines may be influenced by metabolic status—metabolic syndrome, diabetes mellitus type 2, insulin resistance (IR), and nonalcoholic fatty liver disease. In this review, we briefly summarize our current understanding on the role of the most widely studied adipokines, including adiponectin, leptin, resistin, and chemerin, in the development and metabolic alterations of SLE.

Adipokines

Adipose tissue had been regarded only as the body energy storage, mechanical defense against injuries, and a thermoregulator for many years [16]. With the discovery of adipokines, many scientists showed great interest in the contribution of adipose tissue to body homeostasis. The so-called adipokines or adipocytokines are proteins mainly produced by the WAT. More recently, WAT is described as an active endocrine organ, which secretes a wide variety of adipokines, including both ubiquitous molecules (such as TNF-α and IL-6) and specific molecules (such as adiponectin, leptin, resistin, and visfatin) [17]. Later studies revealed that adipokines play an important role in many metabolic processes, not only the regulation of appetite, energy homeostasis, vascular hemostasis, blood pressure, the metabolism of carbohydrates and fats, but also the regulation of immune response and systemic inflammatory processes [3]. According to their action on inflammation, these adipokines can be classified into two types, one is mainly act as pro-inflammatory effects, like leptin, resistin, IL-6, TNF-α, and the other is predominantly anti-inflammatory effects, such as adiponectin and IL-10 [18].

Studies have revealed that obesity is a risk factor for many inflammatory and autoimmune diseases like SLE, in terms of incidence, disease severity, and outcomes, as well as for the overall cardiovascular risk [17]. Obesity is a state of chronic low-grade systemic inflammation that brings about the release of lipids, aberrant adipokines, and pro-inflammatory cytokines from adipose tissue [19]. Adipokines are pleiotropic molecules that contribute to this low-grade inflammatory state creating a cluster of metabolic disorder and autoimmune diseases [20]. Dysfunction of the adipose tissue characterized by adipocyte hypertrophy and dysfunction has been linked to chronic inflammation and IR, which caused the dysregulation of the expression of adipokines [19]. The expression and pathogenic role of adipokines including leptin, adiponectin, resistin, and chemerin have been assessed in several autoimmune rheumatic diseases, especially SLE and RA. Studies have shown increased levels of leptin and adiponectin in SLE, but correlation with disease activity is questionable. In RA, studies have also revealed elevated levels of leptin and adiponectin, and correlation with disease activity and joint erosion, but the results are contradictory [2, 15, 21].

Immunological functions of adipokines

Leptin

Leptin was the first identified adipokine and was initially dubbed the "antiobesity hormone." Leptin is a 16-kDa nonglycosylated polypeptide hormone discovered by positional cloning of a single gene mutation in the ob/ob mouse in 1994 [22]. It is encoded by the *obese* (*ob*) gene, the murine homolog of human *LEP* gene. Leptin is mainly produced by WAT, consisting of a bundle of four α-helices, and its circulating levels are positively correlated with body mass index (BMI) [23]. It decreases food intake and stimulating energy expenditure by acting on specific hypothalamic nuclei, where leptin induces anorexigenic factors as cocaine amphetamine-related transcript (CART) and suppressing orexigenic neuropeptides such as neuropeptide Y (NPY) [24]. Leptin exerts its biological actions through the activation of leptin receptor (OB-R), which belong to the class 1 cytokine receptor superfamily and are encoded by the *diabetes* (*db*) gene [25]. Alternative splicing of the *db* gene produces six different isoforms of leptin receptors, but only the long isoform Ob–Rb appears to be necessary for the signal transduction of the leptin [26]. Leptin and its receptors are expressed in different tissues including the central nervous and the cardiovascular systems, and in immune system cells [27]. Serum concentrations of leptin are positively related to body fat or energy balance of adipocytes, and associated with food intake, insulin levels, and sex hormones with higher concentrations in women than in men [28].

As a hormone with pleiotropic actions, leptin is involved in a variety of physiological functions, including fertility, bone metabolism, angiogenesis, inflammation, and immune responses, especially in several autoimmune diseases [26]. Investigations have shown that leptin is increased during acute infection and inflammation, indicating that leptin is act as a pro-inflammatory cytokine. It enhances macrophages phagocytosis activity and induces them to produce several pro-inflammatory cytokines, such as IL-1, IL-6, and TNF-α [29]. Recently, Laetitia et al. [30] observed that leptin and the stimulated production could disturb the immune system via different signaling pathways such as JAK2/STAT3 and mTOR, allowing tumor growth. Furthermore, it can stimulate the proliferation of T cells, promotes memory T cells differentiation toward T-helper 1 (Th1), and protects T cells from corticosteroid-induced apoptosis [31, 32]. Leptin can also inhibit the differentiation of CD4+ T cells into regulatory T cells and affect dendritic cell (DC) maturation and function, while it could lead to impaired cytotoxicity of NK cells [33].

Adiponectin

Adiponectin, a 244-amino acid protein, is also called adipocyte complement-related protein of 30 kDa (acrp30), adipose most abundant gene transcript 1 (apM1), adipoQ, or gelatin-binding protein of 28 kDa (GBP28) [34]. Adiponectin is one of the most abundant peptide hormones derived from adipose tissue. It belongs to the collagen super family, sharing

homologies with type VIII and type X collagens and complement factor C1q [29]. It is mainly synthesized by WAT, circulating as low molecular weight trimers (LMW) in plasma. LMW isoform may assemble through disulfide bonds to form a middle molecular weight (MMW) isoform or a high molecular weight (HMW) isoform. The multimeric forms as well as the globular form of adiponectin are found in the circulation while monomeric adiponectin is only occurred in adipocytes [35]. Adiponectin exerts its action via three specific receptors (AdipoR1, AdipoR2, and T-cadherin). AdipoR1 is predominantly expressed in skeletal muscle, AdipoR2 is found more abundantly in the liver, while T-cadherin is mainly expressed in the cardiovascular system [36]. The human *adiponectin* gene is located on 3q27 chromosome, a locus linked with susceptibility to diabetes and cardiovascular diseases [37, 38]. Ablation of the *adiponectin* gene has no dramatic effect in knockout mice on a normal diet, but when placed on a high-fat sucrose diet they develop severe IR and exhibit lipid accumulation in muscles [39].

Circulating adiponectin levels tend to be low in obese patients and increase with weight loss [40, 41]. Many studies have revealed that adiponectin produced anti-inflammatory effects. Adiponectin is an insulin-sensitizing adipokine [35]. Higher adiponectin levels could enhance insulin sensitivity, while low adiponectin plasma levels are associated with type 2 diabetes mellitus, dyslipidemia, hypertension, and coronary artery disease [42]. It also promotes glucose uptake and free fatty acid oxidation in skeletal muscle and the liver. Moreover, it inhibits the expression of TNF-α and modulates transformation of macrophages into foam cells to exert the protective effects on the vascular wall [29]. Furthermore, adiponectin also exhibits its anti-inflammatory effects on immune system. It suppresses differentiation and activation of M1 macrophages by downregulating pro-inflammatory cytokines, such as TNF-α and IL-6 in macrophages, while it promotes M2 macrophage proliferation and expression of anti-inflammatory M2 markers like IL-10 [43]. Interestingly, both TNF-α and IL-6 suppressed adiponectin production, suggesting the existence of a negative feedback between adiponectin and pro-inflammatory cytokines [44]. Recently, adiponectin has been shown to activate major signaling pathways that suppress cancer cell proliferation and to induce apoptosis [45].

However, some other reports demonstrate pro-inflammatory action of adiponectin [26, 27]. Serum concentration of adiponectin is elevated in patients with classic autoimmune inflammatory conditions. The anti- and pro-inflammatory effects of adiponectin may in part result from the changes in the relative proportion of its various isoforms. It has been confirmed that HMW adiponectin mainly exerts pro-inflammatory effects and serves as a marker for severity of CAD, suggesting that the ratio of the isoforms may determine adiponectin action.

Resistin

Resistin, known as adipocyte-secreted factor (ADSF) or found in inflammatory zone 3 (FIZZ3), is a 12.5-kDa cysteine-rich proteins that belongs to the resistin-like molecules (RELMs) family [46]. It was discovered in 2001 and was initially described as a mediator of IR [47]. There are marked interspecies differences in the source of production and structure of this protein. The production of resistin is restricted to adipocytes in rodents, while in humans it is mainly produced by circulating and WAT-resident peripheral blood mononuclear cells (PBMCs). Resistin receptor and its signaling pathways have not been identified, but toll-like receptor (TLR) 4 was proposed to mediate resistin inflammatory responses in human cells [48]. Serum resistin levels are known to increase with obesity in both mice and humans, so that it has been proposed as potential link between obesity and diabetes [46].

To date, resistin has consistently been shown to promote IR in animal models. However, the effect of this adipokine in humans is still controversial [48]. In humans, resistin may instead be involved in inflammatory processes rather than in the modulation of glucose homeostasis [29]. Krysiak et al. [42] found that resistin induces the production of IL-6, IL-1β, and TNF-α by PBMCs. Additionally, several pro-inflammatory cytokines increase resistin expression, indicating that resistin can increase its own activity by a positive feedback mechanism. Resistin also increases the expression of cytokines and adhesion molecules in vascular endothelial cells, thus contributing to atherogenesis [29]. Moreover, high plasma resistin levels were found to correlate with impaired renal function in patients with chronic kidney disease [49].

Chemerin

Chemerin, also known as tazarotene-induced gene 2 (TIG2) and retinoic acid receptor responder 2 (RARRES2), is a novel identified chemoattractant adipokine. It is an 18-kDa inactive proprotein mainly expressed in adipose tissue, and it is activated by posttranslational C-terminal cleavage [50]. Chemerin acts via the G-protein-coupled receptor chemokine-like receptor 1 (ChemR23 or CMKLR1) [51]. ChemR23 is expressed in various leukocyte families, including monocytes and macrophages, myeloid dendritic cells (mDC) and plasmacytoid dendritic cells (pDC), microglial cells and NK cells [52–54]. In macrophages, ChemR23 is downregulated by pro-inflammatory cytokines and TLR ligands, but upregulated by TGF-β, suggesting a potential involvement of chemerin in the recruitment of macrophages with an anti-inflammatory phenotype, during the resolution phase of inflammation and wound healing [55, 56]. In vitro experiments showed that

chemerin acts as a chemotactic factor for plasmacytoid DCs [57]. So it may plays dual roles as a broad spectrum antimicrobial protein and as a leukocyte attractant for macrophages, dendritic cells, and NK cells in host defense [58]. In addition to leukocyte families, ChemR23 expression was also observed in a growing number of non-leukocyte cell populations, including preadipocytes and adipocytes, chondrocytes, osteoclasts, skeletal muscle cells, and endothelial cells [53, 59–61]. In chondrocytes, chemerin and its receptor are expressed and increase the production of several pro-inflammatory cytokines, like TNF-α, IL-1β, and IL-6 [53]. In endothelial cells, ChemR23 is significantly upregulated by pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) [61].

Circulating levels of chemerin are increased in chronic inflammatory diseases such as ulcerative colitis (UC) and Crohn's disease (CD) [54]. A recently study showed that in human skin cultures, chemerin is significantly downregulated by IL-17 and IL-22, whereas it is upregulated by acute phase cytokines oncostatin M and IL-1β. Thus, it may play an important role in skin barrier defense against microbial pathogens [62]. Chemerin levels also correlate with serum concentrations of TNF-α, IL-6, and CRP and may reflect the inflammatory status associated with obesity [63]. In animal models, obesity and diabetes were associated with elevated circulating chemerin levels [64]. (Table 1).

Adipokines in SLE

SLE is a chronic inflammatory connective tissue disorder with multiple cellular and serological alterations and poorly understood pathogenesis. It is generally accepted that SLE may attribute to a combination of genetic and environmental factors with a prominent autoimmune component. The disease is characterized by a multitude of autoantibody production, formation of immune complexes, tissue inflammation in multiple organs, and high levels of pro-inflammatory cytokines in blood. Patients with SLE often have a series of clinical manifestations like malar rash, oral ulcer, renal damage, nervous system disorders. SLE patients often have the symptom of metabolic syndrome, accelerating the development of atherosclerosis and higher prevalence of IR [65]. It has been found that SLE is associated with increased risk of cardiovascular diseases (CVDs), and the incidence of CVDs is increased when obesity is present in patients with SLE. The significance of adipokines in these disorders suggests that it may play an important role in the development and progression of SLE.

Leptin and SLE

Previous studies on leptin have provided important information on the relationships between metabolic state and immune system function. Not only the endocrine system, but also the immune response, is influenced by adipocytes through numerous adipokines. Recently, emerging evidence suggests that leptin is implicated in the pathogenesis of many autoimmune diseases like SLE. However, the role of leptin in this disease is controversial. Serum/plasma leptin expression levels in SLE patients have been investigated in many studies, but with contradictory results (Table 2). Several studies indicated that higher serum leptin levels might contribute to systemic inflammation in SLE patients [6, 8, 14, 66–68]. Leptin levels are increased in pediatric systemic lupus [11, 69]. Chung et al. [5] found

Table 1 Potential role of adipokines in SLE

Adipokines	Potential role in SLE	Pro- or anti-inflammatory
Leptin	Upregulate IL-1, IL-6, and TNF-α	Pro-inflammatory
	Secret cytokine	
	Activate monocytes and macrophages	
	Regulate CD4+ T cells	
	Regulate dendritic cell	
Adiponectin	Downregulate TNF-α, MCP-1, and IL-6	Anti-inflammatory
	Express anti-inflammatory cytokines Arg-1, Mgl-1, and IL-10	
	Decrease T cell recruitment	
Resistin	Upregulate IL-6, IL-1β, and TNF-α	Pro-inflammatory
	Upregulate cytokines and adhesion molecules	
	Lipid accumulation	
Chemerin	Upregulate TNF-α, IL-1β, and IL-6	Pro-inflammatory
	Chemotactic function for macrophages, dendritic cells, and NK cells	
	Skin barrier defense	

Table 2 Serum/plasma leptin expression levels in SLE

Author	Study year	Disease	Parameter	Increase/decrease compared with controls	Correlation with disease activity
Afroze et al. [6]	2014	Human SLE	Serum leptin levels	Increase	NA
Al et al. [70]	2009	Children SLE	Serum leptin levels	Increase	No correlation
Barbosa et al. [67]	2014	Human SLE	Serum leptin levels	Increase	NA
Chung et al. [5]	2009	Human SLE	Plasma leptin levels	Increase	No correlation
De Sanctis et al. [4]	2008	Human SLE	Serum leptin levels	Decrease	No correlation
Elwakkad et al. [11]	2007	Juvenile SLE	Serum leptin levels	Increase	No correlation
Garcia-Gonzalez et al. [14]	2002	Human SLE	Serum leptin levels	Increase	No correlation
Hutcheson et al. [68]	2014	Human LN	Serum leptin levels	Increase	NA
Kim et al. [8]	2010	Human SLE	Serum leptin levels	Increase	No correlation
McMahon et al. [72]	2011	Human SLE	Plasma leptin levels	Increase	NA
Ryan et al. [93]	2006	Mice SLE	Plasma leptin levels	Increase	NA
Sada et al. [66]	2006	Human SLE	Plasma leptin levels	Increase	NA
Vadacca et al. [71]	2009	Human SLE	Serum leptin levels	Increase	Positive correlation
Vadacca et al. [85]	2011	Human SLE	Serum leptin levels	Increase	Positive correlation
Wislowska et al. [10]	2008	Human SLE	Serum leptin levels	No significant difference	No correlation

NA not available, *SLE* systemic lupus erythematosus

that patients with SLE have increased concentrations of leptin independent of age, race, sex, and BMI, suggesting that additional factors drive leptin production or alter the relationship between obesity and leptin in SLE. They also showed an association between leptin and IR, the metabolic syndrome, CRP, erythrocyte sedimentation rate (ESR), LDL cholesterol, and triglycerides in SLE. Similarly, Vadacca et al. [70] demonstrated that leptin correlated with insulin levels, HOMA-IR, MeS, triglycerides, BMI, weight to height (W/H) ratio, systolic and diastolic blood pressure, and disease activity index (SLEDAI) among SLE patients and positively correlated with vascular stiffness. Moreover, they found that leptin level was an independent risk factor for coronary heart disease and could be a useful tool in evaluating the importance of CVD risk factors. Another similar study showed that high leptin levels greatly increase the risk of subclinical atherosclerosis in SLE and are also associated with an increase in inflammatory biomarkers of atherosclerosis such as pro-inflammatory HDL, Lp(a), and OxPL/apoB100 [71]. Leptin receptor gene (*LEPR*) polymorphism and elevated leptin levels are associated with increased susceptibility of SLE in Kashmiri population [6]. High leptin levels may help to identify patients with SLE at risk of atherosclerosis. It is possible that leptin might promote atherosclerosis based on the mechanism that leptin has been shown to increase accumulation of cholesterol esters in foam cells, especially in hyperglycemic conditions [72]. It also activates circulating monocytes, induces monocyte proliferation [73], and upregulates endothelial cell production of monocyte chemoattractant protein [74]. In vitro, leptin treatment stimulates monocyte production of TNF-α and IL-6 [75]. In addition, leptin has been shown to promote Th1 responses in normal human CD4+ T cells and in (NZB XNZW) F1 lupus-prone mice through inducing RORγ transcription, whereas its neutralization in these autoimmune-prone mice inhibits Th17 responses. Another study showed that leptin directly reduces the number of regulatory T cells and increases the number of Th17 cells, providing a mechanism by which leptin deficiency ameliorates SLE lesions [76]. Chen et al. [77] showed that leptin and NAP-2 act synergistically to promote MSC senescence through enhancement of the PI3K/Akt signaling pathway in SLE patients. Furthermore, the short form ObRa has the capacity in vitro to activate JAK2 and ERK2 and to phosphorylate IRS-1 in a leptin-dose manner, thus indicating its important role in SLE pathogenesis [78].

Nevertheless, other groups have demonstrated lower or unchanged circulating leptin levels in SLE patients compared to healthy control [4, 10]. Wislowska et al. [10] showed that no correlation was found between serum leptin levels and disease activity of SLE, nor between serum leptin levels and disease damage index. De Sanctis et al. [4] demonstrated that leptin levels were significantly lower in patients with SLE. Our recent meta-analysis demonstrates no significant difference in plasma/serum leptin levels between the entire group of SLE patients and controls. However, plasma/serum leptin levels are significantly higher in the subgroup of SLE patients from an Asian population $\geq$40 years of age and with a BMI < 25 [15]. The differences among these studies may be due to differing disease severity and treatment modalities. According

to above data, the role of leptin in SLE is controversial, but most studies were prone to think that this adipokine is positively correlated with inflammatory status of SLE patients.

Adiponectin and SLE

Several studies have shown elevated levels of this adipokine in SLE patients [4, 5, 12]. Toussirot et al. [7] found that serum adiponectin levels were significantly higher in patients with SLE than controls. There was no significant correlation between adiponectin and fat mass measurements. Additionally, the relationships between ESR and adiponectin were found to be negatively correlated, whereas no relationship was observed between adiponectin and CRP or IL-6 levels. Adiponectin is an insulin-sensitizing adipokine. It can decrease plasma glucose and increase insulin sensitivity by inhibiting gluconeogenesis in the liver and by activating fatty oxidation in skeletal muscles. Despite higher adiponectin levels, patients with SLE were more insulin-resistant and had a higher prevalence of T2D and hypertension compared with controls [66]. Sada et al. [66] found that although adiponectin levels were higher in SLE patients than controls, patients with IR showed significantly lower adiponectin levels than patients without IR. Serum levels of adiponectin were inversely correlated with HOMA-IR in SLE patients, suggesting that adiponectin plays an important role in developing IR in SLE. In addition, adiponectin was significantly higher in the SLE patients with plaque, and it was found to serve as independent predictors of carotid plaque [79, 80]. It is now well known that adiponectin has beneficial effects on endothelial cells and endothelial function and is also cardioprotective. Adiponectin inhibits macrophage to foam cell transformation and reduces intracellular cholesteryl ester content in human macrophages. It protects against myocardial ischemia and helps to limit the inflammatory response to acute myocardial injury [36]. For unknown reasons, the endothelial dysfunction characteristic of SLE drives a higher adiponectin level, which nevertheless is not effective in protection. Therefore, increased adiponectin concentration could represent a compensatory mechanism to existing vascular damage [81]. Adiponectin also induces the production of anti-inflammatory mediators such as IL-10 and IL-1 receptor antagonist. Furthermore, adiponectin may suppress IL-2 induced NK cytotoxicity and inhibit B cell lymphopoiesis in stromal cell culture through the activation of prostaglandin synthesis [25]. Inflammatory cytokines such as TNF-α and IL-6 are able to inhibit *adiponectin* gene expression and protein secretion [36]. On the other hand, there is now some evidence that high molecular weight (HMW) adiponectin exerts pro-inflammatory biological functions inducing the secretion of IL-6 by monocytes [82]. More recently, adiponectin has been related to SLE renal involvement. Urinary levels of adiponectin are significantly elevated in SLE patients with renal involvement. Noteworthy is the fact that only HMW adiponectin isoform has recently been found in urine of patients with active lupus nephritis (LN), but not in urine of healthy individuals, and its content correlated with SLE severity. Because HMW isoform has been demonstrated to induce IL-8 and monocyte chemotactic protein (MCP)-1 production, higher amounts of this isoform may result in pro-inflammatory properties of adiponectin in this group of patients. Adiponectin is better to use as a supplemental index for assessment of renal function comparing with other diagnostic parameters such as anti-dsDNA antibodies in SLE patients [83, 84]. But only one study showed positive association between adiponectin levels and SLEDAI scores, suggesting that this cytokine in SLE might be involved in disease activity and also inducing related complications [83]. By contrast, some other studies found no significant difference in adiponectin levels between SLE patients and controls and its correlation with clinical manifestations or SLEDAI [67, 70, 71, 85]. Table 3 shows studies on serum/plasma levels of adiponectin in SLE patients. In summary, adiponectin may exert bidirectional effects of pro- and anti-inflammatory in SLE. The pro-inflammatory effects of adiponectin are specifically caused by its HMW isoform, while LMW adiponectin does not seem to affect inflammatory cytokine production.

Resistin and SLE

There is no agreement as for concentrations and function of resistin in SLE, because of a limited number of studies and their inconsistent results. Baker et al. showed the correlation between serum resistin levels and the severity of inflammation in SLE patients [86]. The diagnosis of SLE was significantly associated with increased resistin levels independent of age, race, renal function, body mass index (BMI), high-sensitivity CRP (hsCRP), hypertension, diabetes, and steroid use. In SLE patients, the resistin level was positively correlated with glomerular filtration rate (GFR), hsCRP, ESR, homocysteine, and disease duration [86]. They also reported that resistin level had no significant correlation with markers of IR or body adiposity, including homeostatic model assessment or BMI. Furthermore, resistin levels were significantly higher in SLE cases with coronary artery calcification (CAC) compared to those without CAC [86]. The mechanism by which resistin is increased in patients with SLE remains unknown, but postulated explanations include changes in renal function, direct effects of inflammatory mediators on resistin production, alterations in fat distribution, or some combination of these mechanisms [86]. In other studies, no significant differences in resistin concentrations were found between

Table 3 Serum/plasma adiponectin expression levels in SLE

Author	Study year	Disease	Parameter	Increase/decrease compared with controls	Correlation with disease activity
Al et al. [70]	2009	Children SLE	Plasma adiponectin levels	No significant difference	No correlation
Barbosa et al. [67]	2014	Human SLE	Serum adiponectin levels	No significant difference	NA
Chung et al. [5]	2009	Human SLE	Plasma adiponectin levels	Increase	No correlation
De Sanctis et al. [4]	2008	Human SLE	Serum adiponectin levels	Increase	No correlation
Grönwall et al. [80]	2014	Human SLE	Plasma adiponectin levels	Increase	NA
Loghman et al. [83]	2014	Human SLE	Urinary adiponectin levels	Increase	Positive correlation
McMahon et al. [71]	2011	Human SLE	Plasma adiponectin levels	No significant difference	NA
Reynolds et al. [79]	2010	Human SLE	Plasma adiponectin levels	Increase	NA
Rovin et al. [12]	2005	Human SLE	Plasma and urinary adiponectin levels	Increase	NA
Rovin et al. [84]	2006	Human SLE	Adiponectin levels of cell culture supernatants	Increase	NA
Sada et al. [66]	2006	Human SLE	Plasma adiponectin levels	Increase	NA
Toussirot et al. [7]	2010	Human systemic autoimmune diseases	Serum adiponectin levels	Increase	NA
Vadacca et al. [70]	2009	Human SLE	Plasma adiponectin levels	No significant difference	NA
Vadacca et al. [85]	2011	Human SLE	Serum adiponectin levels	No significant difference	No correlation

NA not available, *SLE* systemic lupus erythematosus

SLE patients and control subjects [4, 5, 70]. However, one study has revealed a relatively weak association between resistin and ESR but no association with CRP, IL-6, and TNF [5]. Although resistin measurements did not differ between patients and controls, resistin was clearly associated with general inflammation, renal disease, treatment with glucocorticosteroids, and bone loss [9]. There are also data indicating that resistin levels are inversely associated with renal function and possibly contribute to a low-grade inflammation in patients with chronic renal dysfunction [49]. However, our recent meta-analysis suggests that there was no significant difference in serum resistin level between SLE patients and normal controls [21]. Due to the small number of studies and different patient selection criterion, the correlation between resistin and SLE remains to be further elucidated.

Chemerin and SLE

Chemerin is abundant in human epidermis and plays a determinant role in skin inflammatory processes. It seems to support many anti-bacterial activities in the exudates from primary skin cultures [8, 14]. These data suggest that chemerin may contribute to skin defense by both recruitment of DCs and acting as an anti-bacterial agent in epidermis. Interestingly, the use of a chemerin peptide has been proposed to help wound closure and re-epithelialization [87]. William et al. [52] showed that recombinant chemerin induced the transmigration of plasmacytoid and myeloid DCs across an endothelial cell monolayer. ChemR23+ DCs were also observed in dermis from normal skin, whereas Langerhans cells were negative. Chemerin expression was selectively detected on the luminal side of high endothelial venules in secondary lymphoid organs and in dermal endothelial vessels of lupus erythematosus skin lesions. This finding, together with the selective expression of the cognate ligand on the luminal side of high endothelial venules and inflamed endothelium, suggests a key role of the ChemR23/chemerin axis in directing plasmacytoid DC trafficking. Similarly, Yin et al. [88] found that skin pDC and chemerin production were increased in response to ultraviolet B irradiation among mouse model. Thus, elevated chemerin expression positively correlates with pDC accumulation in UVB-irradiated skin and are closely involved in the development of skin lesions of lupus erythematosus patients.

Available evidences also suggest that chemerin plays a significant role in renal homoeostasis. It has been shown that chemerin presence in tubular and lymphatic epithelial cells in the kidney may serve as a marker of LN occurrence, and that its circulating levels correlate with renal function both in patients with normal glomerular filtration rate and in patients with renal disease [89–91]. Giuseppe et al. [90] found that ChemR23-positive DCs could infiltrate the kidney tubulointerstitium in patients with severe LN, suggesting that the ChemR23/chemerin axis may play a role in the recruitment of DCs within the kidney in LN patients. Collectively, these findings suggest a role of the

chemerin/ChemR23 system in the recruitment of pDCs in the development of SLE.

Adipokines as potential therapeutic targets for SLE

Due to its crucial roles in inflammation and proliferation cascade, adipokines may have promise as a potential therapeutic target for SLE. As leptin promotes macrophage phagocytosis of apoptotic bodies in SLE and subsequent availability of apoptotic-derived antigen to T cells, an inhibition of this process via leptin blockade might be helpful to improve clinical symptoms in SLE. A recent study found that leptin-treated mice had a significant increase in macrophage phagocytosis of apoptotic cells when compared to control mice that had been treated with vehicle [92]. In addition, leptin-deficient mice demonstrate decreased Th17 cells and elevated Treg cells [76, 93]. These results imply that limiting the leptin signaling could have effects in the modulation of autoimmune responses in SLE. More recently, Amarilyo et al. [94] revealed that leptin can promote T cell survival by modulating T cell apoptosis via an increased expression of Bcl-2 and can favor the proliferation of autoreactive T cells in NZB/W lupus-prone mice. This ability of leptin to promote lupus T cell autoimmunity suggests the possibility of a therapeutic targeting of leptin in SLE. Vilà et al. [95] indicated that, although metabolic alterations, mainly leptin resistance in the BWF1 mice, slow down the progression of autoimmunity, the presence of hyperinsulinemia and the sustained insulin stimulation of organs that remain insulin sensitive, such as the liver and potentially the kidneys, facilitates the overexpression and activity of the mTOR system and the appearance of the clinical symptoms of SLE. If these findings can be extrapolated to humans, subclinical IR, sustained over time, could be the key factor for the development of clinical SLE in subjects with an autoimmune-prone genetic background. It also has been reported that mice with experimental lupus that lack adiponectin develop more severe disease than wild-type mice, suggesting the involvement of adiponectin in regulating disease activity [96]. The current findings showed that the deficiency of adiponectin in a lupus model results in exacerbated disease [96, 97]. It is also possible that autoimmune disease states result in the development of "adiponectin resistance" that leads to an elevation of adiponectin levels. Thus, adiponectin deficiency in the context of a mouse model of established autoimmunity leads to more robust disease when compared to adiponectin-sufficient controls [98]. All these above findings suggest that treatment strategies targeting adipokines signalings may have some positive effects in patients with SLE and other autoimmune diseases. However, it should be noted that we are still very far from a therapeutic application, firstly because the data are still scarce and because the pleiotropic role of these adipokines to block them may have many unintended consequences.

Conclusion

Although much remains to be explored about roles of adipokines in SLE, the data from in vitro and in vivo models are now accumulating to support the potential effect of adipokines in this disease. However, patients with SLE often coexist with primary liver disorders, and non-alcoholic fatty liver diseases (NAFLD) are the most common attributed cause for liver biochemical abnormalities. Recent studies showed that obesity patients with SLE are more likely to develop liver diseases [99, 100]. Moreover, chronic hepatitis may disturb adipokines synthesis and change their serum levels and tissue expression. Indeed, current studies are still controversial, and many of these demonstrated their pathogenic action in SLE mostly through their pro- or anti-inflammatory properties. With the insights we have gained, however, there is evidence that adipokines may have great influence on SLE and it may become useful to develop novel interventions with the aim of improving outcomes for SLE patients. Therefore, further studies are required, especially in human systems, to comprehensively explore the role of adipokines in SLE.

Acknowledgments This work was supported by Grants from the National Natural Science Foundation of China (81573222, 81473058).

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

References

1. Tilg H, Moschen AR. Adipocytokines: mediators linking adipose tissue, inflammation and immunity. Nat Rev Immunol. 2006;6(10):772–83.
2. de Barbosa VS, Rego J, Antonio da Silva N. Possible role of adipokines in systemic lupus erythematosus and rheumatoid arthritis. Rev Bras Reumatol. 2012;52(2):278–87.
3. Korek E, Krauss H. Novel adipokines: their potential role in the pathogenesis of obesity and metabolic disorders. Postepy Hig Med Dosw. 2015;69:799–810.
4. De Sanctis JB, Zabaleta M, Bianco NE, Garmendia JV, Rivas L. Serum adipokine levels in patients with systemic lupus erythematosus. Autoimmunity. 2009;42(4):272–4.
5. Chung CP, Long AG, Solus JF, Rho YH, Oeser A, Raggi P, et al. Adipocytokines in systemic lupus erythematosus: relationship to inflammation, insulin resistance and coronary atherosclerosis. Lupus. 2009;18(9):799–806.

6. Afroze D, Yousuf A, Ali R, Kawoosa F, Akhtar T, Reshi S, et al. Serum leptin levels, leptin receptor gene (LEPR) polymorphism, and the risk of systemic lupus erythematosus in Kashmiri population. Immunol Invest. 2015;44(2):113–25.
7. Toussirot E, Gaugler B, Bouhaddi M, Nguyen NU, Saas P, Dumoulin G. Elevated adiponectin serum levels in women with systemic autoimmune diseases. Mediators Inflamm. 2010;2010:938408.
8. Kim HA, Choi GS, Jeon JY, Yoon JM, Sung JM, Suh CH. Leptin and ghrelin in Korean systemic lupus erythematosus. Lupus. 2010;19(2):170–4.
9. Almehed K, d'Elia HF, Bokarewa M, Carlsten H. Role of resistin as a marker of inflammation in systemic lupus erythematosus. Arthritis Res Ther. 2008;10(1):R15.
10. Wislowska M, Rok M, Stepien K, Kuklo-Kowalska A. Serum leptin in systemic lupus erythematosus. Rheumatol Int. 2008;28(5):467–73.
11. Elwakkad AS, Said RN, Muhammad SI, Saleh MT, Elhamshary A. Role for leptin and prolactin in human juvenile rheumatic diseases. Pak J Biol Sci. 2007;10(12):1984–9.
12. Rovin BH, Song H, Hebert LA, Nadasdy T, Nadasdy G, Birmingham DJ, et al. Plasma, urine, and renal expression of adiponectin in human systemic lupus erythematosus. Kidney Int. 2005;68(4):1825–33.
13. Harle P, Pongratz G, Weidler C, Buttner R, Scholmerich J, Straub RH. Possible role of leptin in hypoandrogenicity in patients with systemic lupus erythematosus and rheumatoid arthritis. Ann Rheum Dis. 2004;63(7):809–16.
14. Garcia-Gonzalez A, Gonzalez-Lopez L, Valera-Gonzalez IC, Cardona-Munoz EG, Salazar-Paramo M, Gonzalez-Ortiz M, et al. Serum leptin levels in women with systemic lupus erythematosus. Rheumatol Int. 2002;22(4):138–41.
15. Li HM, Zhang TP, Leng RX, Li XP, Li XM, Pan HF. Plasma/serum leptin levels in patients with systemic lupus erythematosus: a meta-analysis. Arch Med Res. 2015;46(7):551–6.
16. Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. Am J Clin Nutr. 2006;83(2):461S–5S.
17. Gremese E, Tolusso B, Gigante MR, Ferraccioli G. Obesity as a risk and severity factor in rheumatic diseases (autoimmune chronic inflammatory diseases). Front Immunol. 2014;5:576.
18. Toussirot E, Streit G, Wendling D. The contribution of adipose tissue and adipokines to inflammation in joint diseases. Curr Med Chem. 2007;14(10):1095–100.
19. Xu L, Kitade H, Ni Y, Ota T. Roles of chemokines and chemokine receptors in obesity-associated insulin resistance and nonalcoholic fatty liver disease. Biomolecules. 2015;5(3):1563–79.
20. Gomez R, Lago F, Gomez-Reino J, Dieguez C, Gualillo O. Adipokines in the skeleton: influence on cartilage function and joint degenerative diseases. J Mol Endocrinol. 2009;43(1):11–8.
21. Huang Q, Tao SS, Zhang YJ, Zhang C, Li LJ, Zhao W, et al. Serum resistin levels in patients with rheumatoid arthritis and systemic lupus erythematosus: a meta-analysis. Clin Rheumatol. 2015;34(10):1713–20.
22. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature. 1994;372(6505):425–32.
23. Otero M, Lago R, Lago F, Casanueva FF, Dieguez C, Gomez-Reino JJ, et al. Leptin, from fat to inflammation: old questions and new insights. FEBS Lett. 2005;579(2):295–301.
24. Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E, et al. Role of leptin in the neuroendocrine response to fasting. Nature. 1996;382(6588):250–2.
25. Stofkova A. Leptin and adiponectin: from energy and metabolic dysbalance to inflammation and autoimmunity. Endocr Regul. 2009;43(4):157–68.
26. Scotece M, Conde J, Gómez R, López V, Lago F, Gómez-Reino JJ, et al. Beyond fat mass: exploring the role of adipokines in rheumatic diseases. Sci World J. 2011;11:1932–47.
27. Beltowski J. Leptin and atherosclerosis. Atherosclerosis. 2006;189(1):47–60.
28. Krysiak R, Okopien B, Herman ZS. Adipose tissue: a new endocrine organ. Przegl Lek. 2005;62(9):919–23.
29. Versini M, Jeandel P-Y, Rosenthal E, Shoenfeld Y. Obesity in autoimmune diseases: not a passive bystander. Autoimmun Rev. 2014;13(9):981–1000.
30. Delort L, Rossary A, Farges M-C, Vasson M-P, Caldefie-Chézet F. Leptin, adipocytes and breast cancer: focus on inflammation and anti-tumor immunity. Life Sci. 2015;140:37–48.
31. Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. Nature. 1998;394(6696):897–901.
32. Stavropoulos-Kalinoglou A, Metsios GS, Koutedakis Y, Kitas GD. Obesity in rheumatoid arthritis. Rheumatology (Oxf). 2011;50(3):450–62.
33. Naylor C, Petri WA. Leptin regulation of immune responses. Trends Mol Med. 2016;22(2):88–98.
34. Li L, Wu LL. Adiponectin and interleukin-6 in inflammation-associated disease. Vitam Horm. 2012;90:375–95.
35. Okamoto Y, Kihara S, Funahashi T, Matsuzawa Y, Libby P. Adiponectin: a key adipocytokine in metabolic syndrome. Clin Sci (Lond). 2006;110(3):267–78.
36. Toussirot É, Binda D, Gueugnon C, Dumoulin G. Adiponectin in autoimmune diseases. Curr Med Chem. 2012;19:5474–80.
37. Stumvoll M, Tschritter O, Fritsche A, Staiger H, Renn W, Weisser M, et al. Association of the T–G polymorphism in adiponectin (exon 2) with obesity and insulin sensitivity: interaction with family history of type 2 diabetes. Diabetes. 2002;51(1):37–41.
38. Scotece M, Conde J, Gómez R, López V, Pino J, González A, et al. Role of adipokines in atherosclerosis: interferences with cardiovascular complications in rheumatic diseases. Mediat Inflamm. 2012;2012:1–14.
39. Whitehead JP, Richards AA, Hickman IJ, Macdonald GA, Prins JB. Adiponectin—a key adipokine in the metabolic syndrome. Diabetes Obes Metab. 2006;8(3):264–80.
40. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K. Adiponectin and adiponectin receptors in obesity-linked insulin resistance. Novartis Found Symp. 2007;286:164–76 **(discussion 76–82, 200–203)**.
41. Oh DK, Ciaraldi T, Henry RR. Adiponectin in health and disease. Diabetes Obes Metab. 2007;9(3):282–9.
42. Krysiak R, Handzlik-Orlik G, Okopien B. The role of adipokines in connective tissue diseases. Eur J Nutr. 2012;51(5):513–28.
43. Luo Y, Liu M. Adiponectin: a versatile player of innate immunity. J Mol Cell Biol. 2016;8(2):120–8.
44. Fantuzzi G. Adiponectin and inflammation: consensus and controversy. J Allergy Clin Immunol. 2008;121(2):326–30.
45. Nagaraju GP, Rajitha B, Aliya S, Kotipatruni RP, Madanraj AS, Hammond A et al. The role of adiponectin in obesity-associated female-specific carcinogenesis. Cytokine Growth Factor Rev. 2016. doi:10.1016/j.cytogfr.2016.03.014.
46. Steppan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, et al. The hormone resistin links obesity to diabetes. Nature. 2001;409(6818):307–12.

47. Stofkova A. Resistin and visfatin: regulators of insulin sensitivity, inflammation and immunity. Endocr Regul. 2010;44(1):25–36.
48. Abella V, Scotece M, Conde J, López V, Lazzaro V, Pino J, et al. Adipokines, metabolic syndrome and rheumatic diseases. J Immunol Res. 2014;2014:1–14.
49. Yaturu S, Reddy RD, Rains J, Jain SK. Plasma and urine levels of resistin and adiponectin in chronic kidney disease. Cytokine. 2007;37(1):1–5.
50. Zabel BA, Allen SJ, Kulig P, Allen JA, Cichy J, Handel TM, et al. Chemerin activation by serine proteases of the coagulation, fibrinolytic, and inflammatory cascades. J Biol Chem. 2005;280(41):34661–6.
51. Wittamer V, Franssen JD, Vulcano M, Mirjolet JF, Le Poul E, Migeotte I, et al. Specific recruitment of antigen-presenting cells by chemerin, a novel processed ligand from human inflammatory fluids. J Exp Med. 2003;198(7):977–85.
52. Vermi W, Riboldi E, Wittamer V, Gentili F, Luini W, Marrelli S, et al. Role of ChemR23 in directing the migration of myeloid and plasmacytoid dendritic cells to lymphoid organs and inflamed skin. J Exp Med. 2005;201(4):509–15.
53. Berg V, Sveinbjornsson B, Bendiksen S, Brox J, Meknas K, Figenschau Y. Human articular chondrocytes express ChemR23 and chemerin; ChemR23 promotes inflammatory signalling upon binding the ligand chemerin (21–157). Arthritis Res Ther. 2010;12(6):R228.
54. Bondue B, Wittamer V, Parmentier M. Chemerin and its receptors in leukocyte trafficking, inflammation and metabolism. Cytokine Growth Factor Rev. 2011;22(5–6):331–8.
55. Zabel BA, Ohyama T, Zuniga L, Kim JY, Johnston B, Allen SJ, et al. Chemokine-like receptor 1 expression by macrophages in vivo: regulation by TGF-β and TLR ligands. Exp Hematol. 2006;34(8):1106–14.
56. Zabel BA, Silverio AM, Butcher EC. Chemokine-like receptor 1 expression and chemerin-directed chemotaxis distinguish plasmacytoid from myeloid dendritic cells in human blood. J Immunol. 2005;174(1):244–51.
57. Gonzalvo-Feo S, Del Prete A, Pruenster M, Salvi V, Wang L, Sironi M, et al. Endothelial cell-derived chemerin promotes dendritic cell transmigration. J Immunol. 2014;192(5):2366–73.
58. Zabel BA, Kwitniewski M, Banas M, Zabieglo K, Murzyn K, Cichy J. Chemerin regulation and role in host defense. Am J Clin Exp Immunol. 2014;3(1):1–19.
59. Ernst MC, Sinal CJ. Chemerin: at the crossroads of inflammation and obesity. Trends Endocrinol Metab. 2010;21(11):660–7.
60. Sell H, Laurencikiene J, Taube A, Eckardt K, Cramer A, Horrighs A, et al. Chemerin is a novel adipocyte-derived factor inducing insulin resistance in primary human skeletal muscle cells. Diabetes. 2009;58(12):2731–40.
61. Kaur J, Adya R, Tan BK, Chen J, Randeva HS. Identification of chemerin receptor (ChemR23) in human endothelial cells: chemerin-induced endothelial angiogenesis. Biochem Biophys Res Commun. 2010;391(4):1762–8.
62. Ryffel B, Banas M, Zegar A, Kwitniewski M, Zabieglo K, Marczynska J, et al. The expression and regulation of chemerin in the epidermis. PLoS One. 2015;10(2):e0117830.
63. Tan BK, Chen J, Farhatullah S, Adya R, Kaur J, Heutling D, et al. Insulin and metformin regulate circulating and adipose tissue chemerin. Diabetes. 2009;58(9):1971–7.
64. Ernst MC, Issa M, Goralski KB, Sinal CJ. Chemerin exacerbates glucose intolerance in mouse models of obesity and diabetes. Endocrinology. 2010;151(5):1998–2007.
65. Chung CP, Avalos I, Oeser A, Gebretsadik T, Shintani A, Raggi P, et al. High prevalence of the metabolic syndrome in patients with systemic lupus erythematosus: association with disease characteristics and cardiovascular risk factors. Ann Rheum Dis. 2007;66(2):208–14.
66. Sada K-E, Yamasaki Y, Maruyama M, Sugiyama H, Yamamura M, Maeshima Y, et al. Altered levels of adipocytokines in association with insulin resistance in patients with systemic lupus erythematosus. J Rheumatol. 2006;33:1545–52.
67. Barbosa VdS, Francescantônio PL, Silva NAd. Leptina e adiponectina no lúpus eritematoso sistêmico: correlações clínicas e laboratoriais. Rev Bras Reumatol. 2015;55(2):140–5.
68. Hutcheson J, Ye Y, Han J, Arriens C, Saxena R, Li QZ, et al. Resistin as a potential marker of renal disease in lupus nephritis. Clin Exp Immunol. 2015;179(3):435–43.
69. Al M, Ng L, Tyrrell P, Bargman J, Bradley T, Silverman E. Adipokines as novel biomarkers in paediatric systemic lupus erythematosus. Rheumatology. 2008;48(5):497–501.
70. Vadacca M, Margiotta D, Rigon A, Cacciapaglia F, Coppolino G, Amoroso A, et al. Adipokines and systemic lupus erythematosus: relationship with metabolic syndrome and cardiovascular disease risk factors. J Rheumatol. 2009;36(2):295–7.
71. McMahon M, Skaggs BJ, Sahakian L, Grossman J, FitzGerald J, Ragavendra N, et al. High plasma leptin levels confer increased risk of atherosclerosis in women with systemic lupus erythematosus, and are associated with inflammatory oxidised lipids. Ann Rheum Dis. 2011;70(9):1619–24.
72. O'Rourke L, Gronning LM, Yeaman SJ, Shepherd PR. Glucose-dependent regulation of cholesterol ester metabolism in macrophages by insulin and leptin. J Biol Chem. 2002;277(45):42557–62.
73. Santos-Alvarez J, Goberna R, Sanchez-Margalet V. Human leptin stimulates proliferation and activation of human circulating monocytes. Cell Immunol. 1999;194(1):6–11.
74. Bouloumie A, Marumo T, Lafontan M, Busse R. Leptin induces oxidative stress in human endothelial cells. FASEB J. 1999;13(10):1231–8.
75. La Cava A, Matarese G. The weight of leptin in immunity. Nat Rev Immunol. 2004;4(5):371–9.
76. Fujita Y, Fujii T, Mimori T, Sato T, Nakamura T, Iwao H, et al. Deficient leptin signaling ameliorates systemic lupus erythematosus lesions in MRL/Mp-Faslpr mice. J Immunol. 2014;192(3):979–84.
77. Chen H, Shi B, Feng X, Kong W, Chen W, Geng L, et al. Leptin and neutrophil-activating peptide 2 promote mesenchymal stem cell senescence through activation of the phosphatidylinositol 3-kinase/Akt pathway in patients with systemic lupus erythematosus. Arthritis Rheumatol. 2015;67(9):2383–93.
78. Xu W-D, Zhang M, Zhang Y-J, Liu S-S, Pan H-F, Ye D-Q. Association between leptin and systemic lupus erythematosus. Rheumatol Int. 2013;34(4):559–63.
79. Reynolds HR, Buyon J, Kim M, Rivera TL, Izmirly P, Tunick P, et al. Association of plasma soluble E-selectin and adiponectin with carotid plaque in patients with systemic lupus erythematosus. Atherosclerosis. 2010;210(2):569–74.
80. Grönwall C, Reynolds H, Kim JK, Buyon J, Goldberg JD, Clancy RM, et al. Relation of carotid plaque with natural IgM antibodies in patients with systemic lupus erythematosus. Clin Immunol. 2014;153(1):1–7.
81. Song H, Chan J, Rovin BH. Induction of chemokine expression by adiponectin in vitro is isoform dependent. Transl Res. 2009;154(1):18–26.
82. Neumeier M, Weigert J, Schaffler A, Wehrwein G, Muller-Ladner U, Scholmerich J, et al. Different effects of adiponectin isoforms in human monocytic cells. J Leukoc Biol. 2006;79(4):803–8.
83. Loghman M, Haghighi A, Broumand B, Ataipour Y, Tohidi M, Marzbani C et al. Association between urinary adiponectin level

and renal involvement in systemic lupus erythematous. Int J Rheum Dis. 2014. doi:10.1111/1756-185X.12284.
84. Rovin BH, Song H. Chemokine induction by the adipocyte-derived cytokine adiponectin. Clin Immunol. 2006;120(1):99–105.
85. Vadacca M, Zardi EM, Margiotta D, Rigon A, Cacciapaglia F, Arcarese L, et al. Leptin, adiponectin and vascular stiffness parameters in women with systemic lupus erythematosus. Intern Emerg Med. 2011;8(8):705–12.
86. Baker JF, Morales M, Qatanani M, Cucchiara A, Nackos E, Lazar MA, et al. Resistin levels in lupus and associations with disease-specific measures, insulin resistance, and coronary calcification. J Rheumatol. 2011;38(11):2369–75.
87. Albanesi C, Scarponi C, Pallotta S, Daniele R, Bosisio D, Madonna S, et al. Chemerin expression marks early psoriatic skin lesions and correlates with plasmacytoid dendritic cell recruitment. J Exp Med. 2009;206(1):249–58.
88. Yin Q, Xu X, Lin Y, Lv J, Zhao L, He R. Ultraviolet B irradiation induces skin accumulation of plasmacytoid dendritic cells: a possible role for chemerin. Autoimmunity. 2014;47(3):185–92.
89. Pfau D, Bachmann A, Lossner U, Kratzsch J, Bluher M, Stumvoll M, et al. Serum levels of the adipokine chemerin in relation to renal function. Diabetes Care. 2010;33(1):171–3.
90. De Palma G, Castellano G, Del Prete A, Sozzani S, Fiore N, Loverre A, et al. The possible role of ChemR23/Chemerin axis in the recruitment of dendritic cells in lupus nephritis. Kidney Int. 2011;79(11):1228–35.
91. Yamamoto T, Qureshi AR, Anderstam B, Heimburger O, Barany P, Lindholm B, et al. Clinical importance of an elevated circulating chemerin level in incident dialysis patients. Nephrol Dial Transplant. 2010;25(12):4017–23.
92. Amarilyo G, Iikuni N, Liu A, Matarese G, Cava AL. Leptin enhances availability of apoptotic cell-derived self-antigen in systemic lupus erythematosus. PLoS One. 2014;9(11):1–5.
93. Ryan MJ, McLemore GR, Hendrix ST. Insulin resistance and obesity in a mouse model of systemic lupus erythematosus. Hypertension. 2006;48(5):988–93.
94. Amarilyo G, Iikuni N, Shi F-D, Liu A, Matarese G, La Cava A. Leptin promotes lupus T-cell autoimmunity. Clin Immunol. 2013;149(3):530–3.
95. Vilà L, Roglans N, Baena M, Barroso E, Alegret M, Merlos M, et al. Metabolic alterations and increased liver mTOR expression precede the development of autoimmune disease in a murine model of lupus erythematosus. PLoS One. 2012;7(12):1–12.
96. Aprahamian T, Bonegio RG, Richez C, Yasuda K, Chiang LK, Sato K, et al. The peroxisome proliferator-activated receptor gamma agonist rosiglitazone ameliorates murine lupus by induction of adiponectin. J Immunol. 2009;182(1):340–6.
97. Takemura Y, Ouchi N, Shibata R, Aprahamian T, Kirber MT, Summer RS, et al. Adiponectin modulates inflammatory reactions via calreticulin receptor-dependent clearance of early apoptotic bodies. J Clin Invest. 2007;117(2):375–86.
98. Parker J, Menn-Josephy H, Laskow B, Takemura Y, Aprahamian T. Modulation of lupus phenotype by adiponectin deficiency in autoimmune mouse models. J Clin Immunol. 2010;31(2):167–73.
99. Huang D, Aghdassi E, Su J, Mosko J, Hirschfield GM, Gladman DD, et al. Prevalence and risk factors for liver biochemical abnormalities in Canadian patients with systemic lupus erythematosus. J Rheumatol. 2011;39(2):254–61.
100. Liu Y, Yu J, Oaks Z, Marchena-Mendez I, Francis L, Bonilla E, et al. Liver injury correlates with biomarkers of autoimmunity and disease activity and represents an organ system involvement in patients with systemic lupus erythematosus. Clin Immunol. 2015;160(2):319–27.