Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2024**; 29(11): 373
https://doi.org/10.31083/j.fbl2911373

Review

Diverse Cytokines Secreted by Adipocyte in Linking Cardio-Metabolic Disorder and SLE

Min Lai[1,†], Kai Lin[2,†], Xiaofang Chen[1,*], Ye Cheng[1,*]

[1]Department of Cardiology, The Xiamen Cardiovascular Hospital of Xiamen University, 361000 Xiamen, Fujian, China
[2]Department of Interventional Clinic, The Xiamen Cardiovascular Hospital of Xiamen University, 361000 Xiamen, Fujian, China
*Correspondence: chenxiaofangheart@163.com (Xiaofang Chen); chengyeheart@163.com (Ye Cheng)
[†]These authors contributed equally.

Academic Editor: Amedeo Amedei
Submitted: 25 July 2024 Revised: 10 September 2024 Accepted: 19 September 2024 Published: 31 October 2024

Abstract

Systemic lupus erythematosus (SLE) is a multi-factorial autoimmune-mediated disease with hyper-stimulation of immune cells especially the T lymphocytes. By this method, it might facilitate the systematic damages in multiple tissues and organs. Otherwise, SLE is also correlated with diverse cardio-metabolic comorbidities, including dyslipidemia, insulin resistance, and hypertension. It is worth-noting that the risk of cardio-metabolic disorders is significantly higher compared with the healthy patients which was reported as approximately one-third of SLE patients were proved as obesity. Notably, current focus is shifting to implementing cardio-metabolic protective strategies as well as elucidating underlying mechanisms of lupus-mediated obese status. On the other hand, adipocyte, as the most abundant endocrine cell in fat tissue, are dysfunctional in obese individuals with aberrant secretion of adipokines. It is proposing that the adipokine might link the pathology of cardio-metabolic disorders and SLE, whereas the related mechanism is complicated. In the current review, the functions of adipokine and the potential mechanisms by which the adipokine link cardio-metabolic disorders and SLE was well listed. Furthermore, the recommendations, which identify the adipokine as the potential therapeutic targets for the treatment of cardio-metabolic disorders and SLE, were also summarized.

Keywords: systemic lupus erythematosus; cardio-metabolic disorders; inflammatory response; adipocyte; cytokine

1. Introduction

Systemic lupus erythematosus (SLE) is a multi-factorial autoimmune-mediated disease which is characterized by the hyper-stimulation of immune cells, especially the T lymphocytes, further facilitating the systematic damages and posing serious to human health [1]. Several organs, including renal, cardiovascular, and central nervous systems (CNS), could be influence aberrant under the disease's condition [2]. Importantly, the SLE patients presented a susceptibility of life-threatening complications, such as infections. Furthermore, the cardio-metabolic disorders, including dyslipidemia, hypertension, and obese, could explain the higher morbidity in SLE patients than that in health individuals [3]. As a consequence, emerging research interest in SLE since it embraces complex network of inflammatory response in the pathology of cardio-metabolic disorders.

Given that it has been firmly established that SLE is associated with cardio-metabolic disorders, attention is shifting into exploring the strategies as well as elucidating underlying mechanisms of lupus-related diseases. Accumulating evidence assumes that diverse adipokines might embrace vital roles in regulating the development of SLE and cardio-metabolic disorders [4]. As reported, the adipocyte is considered as a container for storing excess energy and a source of hormones [5]. Within metabolic syndrome, the adipocyte is enlarged and dysfunctional with excessive adipokine production into circulation. Some adipokines, such as leptin and tumor necrosis factor-α (TNF-α), have pro-inflammatory properties which modulates the inflammatory related disorders, such as psoriasis, rheumatoid arthritis (RA), and SLE. Other adipokines, such as adiponectin and omentin, display anti-inflammatory role. Imbalance of pro-inflammatory adipokines and anti-inflammatory adipokines in obese patients facilitate inflammation and oxidative stress, which amplifies cardio-metabolic disorders [6]. Concerning this notion, a positive relationship of SLE and obesity has been put forward to further explore the interaction between two diseases. Indeed, the prevalence of obesity in patients with SLE ranges from 3.3% to 45.2% and is increased by almost 2-fold when compared to the general population [7]. Nevertheless, the mechanism is not fully illustrated. In this review, the role of adipokines in linking cardio-metabolic disorders and SLE were well-summarized. In addition, the evidence identifying a potential therapeutic target aiming at cytokines for the clinical management of these two diseases were also listed.

2. Prevalence and Pathology of Cardio-Metabolic Disorder and SLE

Although not yet fully illuminated, several genetic pre-disposition-related or environmental related factors

contribute to the pathogenic progression of SLE. Subsequently, it was firstly reported that SLE has a greater tendency with cardio-metabolic diseases [8]. In 2005, Oeser *et al*. [9] conducted a clinical trial which contained 100 patients with SLE, aiming at exploring the relationship between body mass index (BMI) and the serum levels of pro-inflammatory cytokines, such as erythrocyte sedimentation rate (ESR) and interleukin-6 (IL-6). After analysis, the authors demonstrated that obese/over-weight patients embraced aberrant metabolic rate and higher serum levels of pro-inflammatory cytokines. Given that SLE is considered as a chronic systemic inflammatory disease induced by excessive production of pro-inflammatory cytokines, these results suggested that obesity was independently correlated with the progression of SLE. Thus, weight loss might improve functional capacity and decrease risk factors linking obesity and SLE [9]. Similar findings were shown in another clinical trial conducted by Correia and colleague. The authors enrolled 170 SLE women and found that about 92% patients were classified as being well nourished. Notably, in terms of BMI, malnutrition was found in 1.2% of the patients, overweight in 35.3%, and obesity in 27.8%, shedding lights on that the SLE individuals had inadequate nutritional status and food intake [10]. In 2019, Teh *et al*. [11] also re-examined the relationship between the prevalence between obesity and SLE. The trial contained 137 subjects and verified that obesity was significantly correlated with systemic lupus erythematosus disease activity index (SLEDAI) and current use rate of steroid. Meanwhile, the authors also demonstrated that obesity was correlated with disease activity, resultantly indicating that obesity might be strongly correlated with the prevalence of SLE which could be also considered as an important target for improving SLE outcomes [11]. More recently, a Mendelian randomization study conducted by Huang *et al*. [12] aiming to elucidate the causal relationship among pro-inflammatory cytokines, obesity, and SLE. After analysis, the authors found that obesity was associated with 25 cytokines, and 3 cytokines were associated with SLE, including chemokine (C-C motif) ligand 27 (CCL-27) and IL-18. In reverse, SLE was associated with 18 cytokines, and 2 cytokines were associated with obesity, including inflammatory protein-10 (IP-10) and macrophage inflammatory protein-1β (MIP-1β) [12]. As a consequence, these findings showed a strong relationship between the prevalence of obesity in SLE.

Aside from the established relationship between obesity and SLE, other obese related complications have been also considered for the pathogenic progression of SLE. Importantly, several obese related metabolic disorders, including hyperlipidemia, hypertension, and impaired fasting glucose, were shown to influence the prevalence of SLE in clinical trials from different countries. For instance, it is note-worthing that a meta-analysis enrolled 47 studies containing about 8500 subjects and showed that the prevalence of metabolic syndrome in SLE patients was 0.26. Comparing to the control individuals, the SLE patients presented a high risk of metabolic syndromes, indicating that SLE were more susceptible to cardio-metabolic disorders compared with the control population [13]. Another independent study proved that obesity could be a cause of auto-immune diseases although this finding remains controversial [14]. Owing to a high-fat diet (HFD) could induce the progression of over-weight, the association between a HFD and SLE should be recognized and considered. More recently, DelOlmo-Romero *et al*. [15] conducted a clinical trial to determine the prevalence of metabolic syndrome and the associations with SLE clinical characteristics in Spanish population. Notably, the authors demonstrated that metabolic syndrome were present in approximately 15% patients with SLE. In addition, patients with metabolic syndrome presented increased SLEDAI and the serum levels of complement C3, proposing that metabolic syndrome were associated with the progression of SLE [15]. Via using a microarray data set of SLE and metabolic syndrome from the Gene Expression Omnibus (GEO) database, Wang *et al*. [16] identified 153 genes enriched in immune- and metabolic-related pathways. As shown by the scRNA-seq results, *TNFSF13B* gene and *OAS1* gene possessed the highest diagnostic efficacy which were positive correlated with the pathways for the metabolism of cholesterol [16].

Conclusively, the status of cardio-metabolic disorder might importantly facilitate the SLE severity; simultaneously, SLE also occurs frequently in obese subjects. However, the mechanisms is not illuminated. Also, under the obese status, the quality as well as quantity of adipocytes might be also affected. This might also influence the progression SLE synchronously.

3. Different Adipokines in Regulating SLE and Cardio-Metabolic Disorders

The dysfunctional adipocyte could synthesize and produce multiple inflammatory related adipokines, such as adiponectin, resistin, and interlukin-1 (IL-1), which subsequently induces inflammatory response. Since the inflammatory response could be observed under the obese and SLE status, it is vital to find a fundamental understanding of these adipokines in linking SLE and cardio-metabolic disorders. On the other hand, given that SLE and metabolic syndrome shares the same risk factors, including inflammatory response and hyperlipidemia, it is reasonable to propose that the underlying mechanism in linking cardio-metabolic disorders and SLE might be explained by diverse adipokines. The roles of adipokines in linking cardio-metabolic disorders and SLE is summarized in Table 1 and Fig. 1.

3.1 Adiponectin

Adiponectin is exclusively synthesized and released by adipocyte which presents the function through three spe-

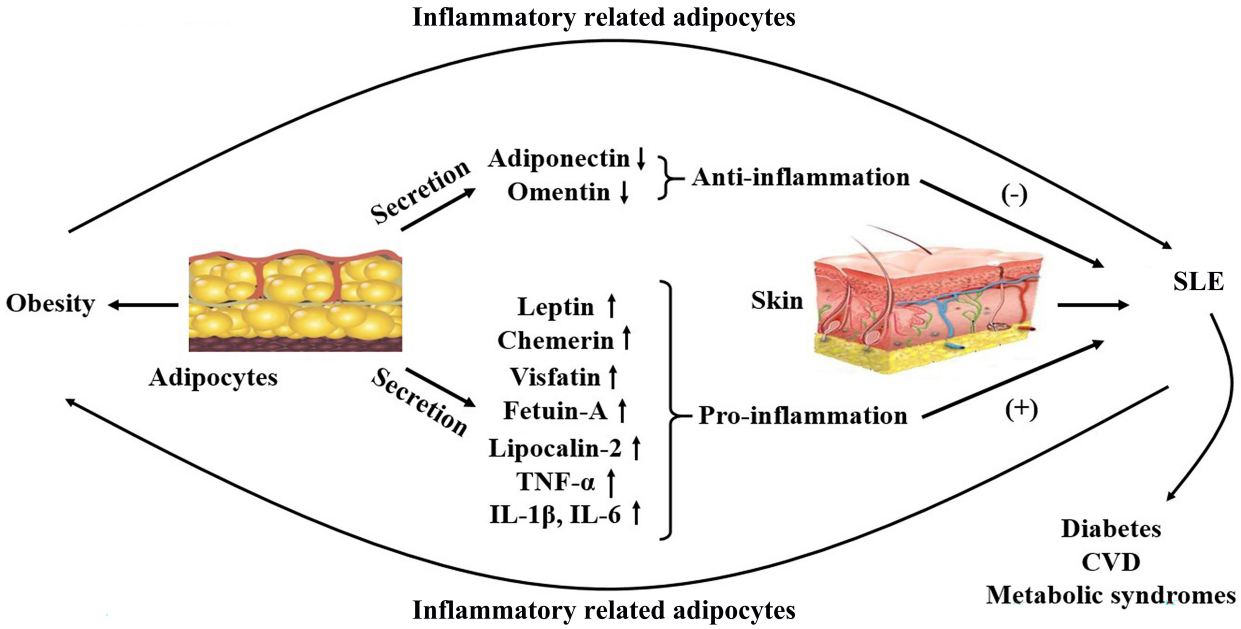

Fig. 1. The summary of the function of different adipokines in linking SLE and obesity. SLE-signature adipokines could modulate the metabolism of adipose tissue with triglyceride (TG) metabolism and thereby increase risk of obesity. Multiple inflammatory related adipokines, such as leptin, chemerin, fetuin-A, and lipocalin-2, could promote the inflammatory response and promote disease development; whereas other adipokines, including adiponectin, shows anti-inflammatory effects. The figure was produced via the Photoshop software 21.1.0.106. (https://www.adobe.com/cn/creativecloud/roc/business.html). Abbreviation: IL, interleukin; TNF, tumor necrosis factor; SLE, systemic lupus erythematosus; CVD, cardiovascular disease.

cific receptors, including receptor 1 (AdipoR1), receptor 2 (AdipoR2), and T-cadherin [17]. Notably, it has been shown that adiponectin could enhance insulin sensitivity and fatty acid oxidation, consequently reducing serum fatty acid concentrations and improving anti-inflammatory response. Since the important role of inflammatory response in obesity, type 2 diabetes mellitus (T2DM), and hyperlipidemia, adiponectin embraces a protective role in the pathogenic progression of metabolic syndrome [18].

Increasing evidence has shown the altered levels of adiponectin under obese status via basic experiment or clinical trials. For instance, Zhang *et al.* [19] demonstrated that the serum concentrations of adiponectin were significantly reduced; meanwhile, the authors also found that the levels of adiponectin were negatively associated with the serum levels of pro-inflammatory cytokines. Thereby, adiponectin could suppress the anti-inflammatory function on immune system. Notably, it is shown that adiponectin could exhibit the M1 macrophage simulation, whereas it could stimulate M2 macrophage proliferation by promoting the anti-inflammatory M2 markers expression, such as IL-10 [20]. On the other hand, adiponectin is also an insulin-sensitizing adipokine. It is demonstrated that higher serum adiponectin concentrations could enhance insulin sensitivity, while reduced adiponectin concentrations might facilitate the development of T2DM [21]. In another research, adiponectin is confirmed to promote the synthesis of nitric oxide (NO) in several endothelial cells, such as macrophage and hepatocyte, via stimulating the phosphatidylinositol-3 kinase/Akt (PI3K/Akt) pathway [22]. Similar results could be found in another independent research conducted by Liu *et al.* [23], which showed that in mice, adiponectin could protect against lipopolysaccharide (LPS)-related apoptosis during metabolic disorder by influencing the PI3K/AKT signaling pathways. Concerning on this notion, the reduced adiponectin contents could be identified as a risk factor for endothelial dysfunction. More recently, Samaha *et al.* [24] used the obese mice model and found that via adipo-Ron, as a new-discovered adiponectin receptor agonist, could positively modulate adiponectin expression with activation of adenosine monophosphate activated protein kinase (AMPK) pathway and subsequent improvement in inflammatory and oxidative signaling, indicating a novel therapeutic strategy for obesity.

On the other hand, the important role of adiponectin in SLE has also been given substantial attention. It has been confirmed that plasma adiponectin levels were increased in patients with SLE compared to healthy controls, a finding that was replicated in different research, suggesting that the adiponectin could affect the pathogenesis of SLE [25,26]. A meta-analysis, which was conducted by Zhang *et al.* [27] and enrolled 7 studies of SLE, also showed that serum concentrations of adiponectin in SLE patients were significantly higher compared with those in normal controls whe-

Table 1. Diverse adipokines and the function on obesity and SLE.

Adipokines	Basic function	Function on SLE	Function on obesity
Adiponectin	Anti-inflammatory Anti-atherogenic	Inversely correlated with SLE severity Increase in SLE patients Inhibit inflammatory response	Decreased in obese patients Protect against metabolic dysfunction Possess anti-inflammatory properties Inhibit the NF-κB signaling pathway
Leptin	Pro-inflammatory	Increased in SLE Increase Th-1 lymphocyte Decrease Th-2 lymphocytes Promote pro-inflammatory cytokines	Positively correlated with BMI Regulate feeding behavior through the central nervous system
Chemerin	Pro-inflammatory	Involved in the recruitment of pDC Promotes the pDC transmigration	Positively correlated with BMI Promote the adipogenesis differentiation
Visfatin	Pro-inflammatory	Enhance antimicrobial peptides in keratinocyte The gene is up-regulated in SLE patients Activate T lymphocytes in immune system	Positively correlated with obesity Induce dyslipidemia Inhibits the expression of metalloproteinases
Omentin	Anti-inflammatory	Lower levels in psoriatic patients compared to the healthy controls Increased after treatment of psoriasis Attenuate the TNF-α-induced adhesion molecule expression and monocyte adhesion	Increases insulin sensitivity in human adipocytes Risk factor for insulin resistance Omentin-1 is positively correlated with plasma level of adiponectin and is inversely correlated with BMI or WHR
Fetuin-A	Inhibit the lipid efflux Modulate inflammatory response	Induces pro-inflammatory adipokines Promotes transformation of M2-phenotype macrophages into M1-phenotype macrophages Increased in SLE patients	FFA could enhance the production of fetuin-A Reduce after treatment of weight loss
Lipocalin-2	A component of innate immune system Induces apoptosis Modulate inflammatory response	Increased in SLE patients Positively correlated with IL-1β	Increased in obese patients Positively correlated with BMI Induce dyslipidemia

Abbreviations: NF-κB, nuclear factor kappa B; BMI, body mass index; pDC, plasmacytoid dendritic cells; TNF, tumor necrosis factor; IL, interleukin; FFA, free fatty acid; WHR, waist hip rate; Th, T-help lymphocyte.

reas not in atherosclerotic patients. Similar results could be shown in another meta-analysis [28]. In addition, Loghman *et al*. [29] conducted a clinical trial and found that the urinary concentrations of adiponectin were increased in SLE patients with renal involvement. Concerning on this notion, the measurement of urinary adiponectin concentration might be helpful to discriminate impaired from normal renal function in SLE patients [29]. Another research conducted by Carbone *et al*. [30] demonstrated that high serum adiponectin was associated with accelerated carotid atherosclerosis in SLE young women, proposing a possible therapeutic target to improve vascular risk stratification in daily clinical practice. More recently, Kamel *et al*. [31] verified that the circulating adiponectin levels were correlated with the development of SLE. Taken together, given that the inflammatory response shares in both obesity and SLE, it might be reasonably to speculated that adiponectin could influence the pathological progression of those two diseases by inflammatory related signaling pathway.

On the contrary, Dan *et al*. [32] used the Mendelian randomization study which did not show a causal association between adiponectin and SLE. Similarly, some studies found no significant alteration of adiponectin levels in SLE patient [33,34]. Concerning on these inconsistent results, adiponectin might exert bidirectional effects in SLE. It is still required to have large-scale trials to further elucidate the accurate relationship between serum levels of adiponectin and the risk of SLE with the underlying mechanisms.

3.2 Resistin

Resistin, a 12.5-kDa cysteine-rich protein and discovered in 2001 which belongs to the resistin-like molecules family, has been considered as adipocyte-secreted factor and initially as a mediator of insulin resistance and its related metabolic disorders, such as type 2 diabetes mellitus and obesity [35]. As reported, resistin is prominently produced by white adipocyte and peripheral blood mononuclear cell in mammals, indicating a role of resistin in modulating obesity and inflammatory response. Indeed, it has shown that the circulating concentrations of resistin were significantly up-regulated in obese mice and in human beings [36]. Resistin expression is also shown to be associated with lipid profiles and inflammatory status in obesity and atherosclerotic groups [37]. Additionally, resistin has also consistently been demonstrated to induce insulin resistance and type 2 diabetic disorders in mice [38]. Nevertheless, the function of resistin in human beings is still controversial from the results. As demonstrated, resistin might participate in inflammatory response [14]. Multiple research has demonstrated that resistin could promote the synthesize and release pro-inflammatory adipokines, including IL-6 and IL-12 by peripheral blood mononuclear cell, indicating a vital role of resistin in modulating pathological progression of inflammation [39]. Reversely, it is verified that those inflammatory related cytokines could also up-regulate the expression content of resistin, suggesting a positive feedback mechanism whereby resistin regulates inflammatory response and its related disorders, such as SLE [40]. In addition, recent study showed another function of resistin as to facilitate the expression of adhesion molecules, resultantly might contributing to the atherosclerotic plaque formation and coronary artery diseases, highlighting resistin as a candidate therapeutic or diagnostic target for cardiovascular disease [41]. Also, another Multi-Ethnic Study of Atherosclerosis found that increased resistin concentrations were strongly correlated with heart failure, more prominently in HF with reduced ejection fraction than in heart failure with preserved ejection fraction. With in-depth research, it proposed a potential mechanism by which resistin controls the metabolic and cardiovascular related disorders is promoting the inflammatory response [42].

To date, since the inconsistent results, there is no agreement as for concentrations and function of resistin in regulating the risk of SLE. As shown, a study revealed that the risk of SLE was correlated with increased serum resistin concentrations independent of BMI, atherosclerosis, and steroid use history. Notably, the circulating resistin concentrations were positively associated with glomerular filtration rate, erythrocyte sedimentation rate, and homocysteine under the SLE conditions [43]. It is worth-noting that since insulin resistance is more prevalent in SLE patients than controls, one potential mechanism whereby resistin influence the risk of metabolic disorders and SLE might focus on the role of resistin in insulin resistance. Though the mechanism by which resistin is up-regulated under the SLE condition remains unclarified, multiple postulated explanations, such as affecting the renal function, altering the adipose distribution, or direct modulating the mediators on resistin production, could provide several potential mechanisms [44].

Similar with the discordant results showing the levels of adiponectin in SLE, no statistical discordance in resistin were observed between SLE patients and the healthy controls in some other clinical trials [25,45]. In this study, though the measurements of resistin did not alter significantly between the patients and the controls, resistin was strongly correlated with the systemic inflammatory response, renal failure, and the glucocorticosteroids use [46]. One meta-analysis confirmed no difference in serum resistin concentration between the SLE patients and the healthy controls [47]. Consistently, Duan *et al*. [48] used a two-sample univariable Mendelian randomization analyses demonstrated that the resistin was not identified as an independent risk factor for SLE, revealing no evidence to support that resistin as a risk factor for SLE. Conclusively, since the different subject enrolling criterion, the relationship between resistin with SLE still remains to be illustrated.

3.3 Leptin

Leptin is produced by adipocyte mainly in white fat tissue. Notably, leptin and its receptors were expressed in multiple diverse tissues, suggesting multiple functions of leptin in cardio-metabolic progressions including fertility, angiogenesis, and inflammatory response [28]. As reported, leptin is being identified as an essential modulator of whole-body energy homeostasis in mammals via affecting the food intake and enhancing the energy expenditure, suggesting that leptin has a vital role in metabolic related disorders [49]. Consistent with this notion, emerging evidence demonstrated that the circulating concentrations level of leptin were increased significantly in obese/over-weight subjects, which were also positively associated with BMI. Meanwhile, it is also revealed that the leptin levels were correlated with several inflammatory related skin diseases, including psoriasis, suggesting a regulatory role of leptin in linking obesity and inflammatory response. A meta-analysis evaluated the plasma levels of adipokines in psoriatic patients and confirmed that the leptin levels were significantly increased, either under the fasting or the postprandial condition, indicating that the increased leptin contents might originate from both adipocyte and keratinocyte and endothelial cell. Concerning on this notion, it is reasonably to speculate that leptin might influence the pathological development of obesity and skin diseases, such as SLE, via modulating the inflammatory response in multiple cell types. Indeed, it is shown that the circulating levels of leptin were significantly increased in patients with SLE which might also induce the inflammatory response [49,50]. Also, the similar alteration of serum leptin concentrations were also increased in pediatric systemic lupus [51].

In addition, another clinical trial confirmed that the serum leptin contents were significantly associated with insulin levels, BMI, and SLEDAI among SLE patients. Meanwhile, since the altered leptin concentrations were also positively associated with vascular stiffness, these findings indicated that leptin could be considered as an independent risk factor for coronary heart disease (CHD) and could be used for evaluating the cardio-metabolic risk factors [45]. Consistent with this finding, McMahon *et al*. [33] showed that the excessively production of leptin might up-regulate the risk of subclinical atherosclerosis in SLE via enhancing the inflammatory related biomarkers, including lipoprotein(a) and oxidated apolipoprotein-B100. Notably, leptin was shown to directly reduce the number of regulatory T lymphocyte and increase the number of T-help-17 (Th-17) lymphocyte, proposing a potential mechanism whereby leptin deficiency improve the skin lesions in SLE patients [52]. More recently, Chen *et al*. [53] found that the intervention of leptin and neutrophil-activating peptide-2 could promote the senescence progression of Mesenchymal stem cells via the enhancement of the PI3K/Akt signaling pathway in SLE patients, indicating the important role of leptin in SLE pathogenesis. However, the accurate association between leptin and SLE remains to be further elucidated.

3.4 Chemerin

Chemerin is a chemoattractant adipokine which involves in inflammatory response, atherosclerosis, and dyslipidemia [6]. Multiple cell types, such as adipocyte, endothelial cell, and keratinocyte, have been confirmed to regulate the serum levels of chemerin in human beings [54]. As a chemokine, chemerin presents the chemotactic feature through interacting with other receptors. For instance, chemerin could combine with both G protein coupled receptor 1 and chemokine CC-motif receptor-like 2 (CCRL2), which subsequently induces metabolic disorders. As shown, the CCRL2 receptors, which is expressed by the keratinocyte, could promote the cellular binding capacity and the transmigration of plasmacytoid dendritic cell, suggesting that the interaction between chemerin with CCRL2 might influence the inflammatory progression of multiple skin diseases, including psoriasis and SLE [55]. As an important adipokine, the serum concentrations of chemerin were well-established to be up-regulated under the obese conditions in mammals, with the positive association with BMI and serum obese related biomarkers, such as triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C), pointing to a regulatory function of chemerin in the pathological development of atherosclerotic related diseases [56]. Emerging evidence has shown that the gene expression contents of *CHEMERIN* were significantly up-regulated during the differentiation of pre-adipocyte; meanwhile, the increased circulating levels of chemerin might reversely induce the adipogenic differentiation, resulting in the hyperplasia and hypertrophy of adipocyte which indicated the important role of chemerin in modulating obese progression [57]. With in-depth investigation, Lin *et al*. [58] confirmed that the beige adipocyte was significantly restricted by the chemerin-CCRL2 axis via inhibiting the cyclic adenosine monophosphate (cAMP) signaling pathway, resultantly interrupting a feed-forward circuit between adipocyte and innate immunity which is required for cold-induced beige fat and thermogenesis.

On the other hand, chemerin could modulate the intracellular metabolism in keratinocyte and adipocyte, which might further promote inflammatory response in epidermis and fat tissue. Notably, to explore this hypothesis, the authors intervened the HaCaT cells and the human primary keratinocyte with recombinant chemerin protein and demonstrated that chemerin could promote the production and secretion of several inflammatory related adipokines, including IL-6, IL-12, TNF-α, which further stimulate the nuclear factor kappa B (NF-κB) signaling pathway. In addition, chemerin could significantly constrain the deacetylase activity of sirtuintype-1 (SIRT-1) through the augmentation of reactive oxygen species (ROS) production [59]. In

dermis, it has been shown that chemerin could promote the migration of plasmacytoid cell and modulate the extracellular regulated protein kinases 1 and 2 (ERK1/2) [60]. Similar with this finding, Yin *et al*. [61] confirmed that the skin plasmacytoid dendritic cell and chemerin production were increased in response to ultraviolet B irradiation in mice. Moreover, the increased gene expression of *CHEMERIN* was positively associated with the accumulation of plasmacytoid dendritic cell in ultraviolet-b (UVB)-irradiated skin, indicating a modulating role of chemerin in the development of skin lesions of SLE [61]. Recently, it is also suggested that chemerin might influence the renal homoeostasis. Indeed, the concentration of chemerin in lymphatic epithelial cell of kidneys is shown to serve as a marker of lupus nephritis occurrence which is also associated with the renal function [62]. Collectively, these findings provided the evidence showing a role of chemerin in the recruitment of plasmacytoid dendritic cell during the pathological progression of SLE. Taken together, the potential mechanism whereby chemerin links obesity and SLE might be the promotion of NF-κB signaling pathway through regulating of SIRT-1 activity and induce the inflammatory cascade response.

3.5 Visfatin

Visfatin is an inflammatory related adipokine which is significantly expressed mainly by adipocytes and macrophages. According to the results, visfatin is confirmed to play an important role in promoting cardiometabolic related disorders, such as cardiovascular disease, T2DM, and atherosclerosis [63]. Besides, visfatin also has multiple pro-inflammatory actions in multiple inflammatory related benign tumor or malignant tumor including breast cancer, lung cancer, and leiomyomas [64]. Via in-depth research, Zaidi *et al*. [63] used the breast cancer cell and verified that visfatin treatment could enhance both sphere diameter and the protein expression of octamer-binding transcription factor 4 (OCT4). The serum vascular endothelial growth factor (VEGF) contents were induced via visfatin therapy which were reduced via using the visfatin inhibitor, named FK866.

Visfatin is also confirmed to be strongly and positively associated with abdominal obesity, whereas the serum concentrations of visfatin is negatively associated with high density lipoprotein cholesterol (HDL-C) [65]. Chang *et al*. [66] conducted a systemic meta-analysis and found that the serum visfatin contents were higher in patients with metabolic syndrome, with pooled log odds ratios of 1.164 and 2.902, respectively. In addition, the visfatin concentrations were also positively correlated with insulin resistance. Given that insulin resistance might promote the obese progression, those findings could propose that the visfatin is promising for predicting obesity, diabetes, and metabolic syndrome [66]. Using male Wistar rats, Al-Suhaimi *et al*. [67] confirmed that thymoquinone significantly reduced the circulating concentrations of aspartate transaminase (AST), alanine transaminase (ALT), and visfatin whereas up-regulated the circulating adiponectin concentrations, revealing that in obese and diabetic conditions, visfatin deficiency inhibited the signaling pathway of Janus Kinase/Signal transducer and activator of transcription 3/PI3K (JAK/STAT3/PI3K) [67].

Aside from the role of visfatin in obesity, it is firstly demonstrated by Chung *et al*. [25] that the serum concentrations of visfatin were significantly higher in SLE individuals compared to those in healthy control individuals. The similar alteration of serum visfatin levels in SLE patients could be found in another clinical trial conducted by De Sanctis and the colleagues [68]. Via in-depth investigation, Ozgen *et al*. [69] explored the association between visfatin with carotid intima-media thickness (cIMT). However, the results might not show the causal relationship mentioned above [69]. More recently, Shaker *et al*. [70] also confirmed that the circulating visfatin concentrations in SLE patients with active lupus nephritis were higher compared with those in the healthy control subjects. In addition, the SLEDAI score and circulating visfatin concentrations were also demonstrated to be associated. Also, the circulating visfatin concentrations were up-regulated in SLE individuals with active lupus nephritis and were correlated with the disease severity scores. Taken together, the results suggested that the serum visfatin could be identified as a non-invasive biomarker for evaluating the severity and the risk stratification of SLE [70]. Given the well-established role of visfatin in affecting the pro-inflammatory adipokines, it is reasonably speculated that the underlying mechanism whereby visfatin links obesity and SLE might be promoting the progression of pro-inflammatory response.

3.6 Omentin

Omentin, also named intelectin, was first detected in adipocyte isolated from visceral omental tissue [71]. Accordingly, omentin is confirmed to have two isoforms, as omentin-1 and omentin-2, with omentin-1 being the main form in human circulation [72]. Emerging evidence showed omentin possessed multiple roles, including insulin resistance, inflammatory response, atherogenic plaque formation, and oxidative stress-decreasing effects, indicating an important function of omentin in modulating cardiometabolic disorders [73]. In details, omentin is positively associated with serum concentrations of adiponectin and is negatively correlated with BMI or waist-hip ratio (WHR), indicating a regulatory function in pathogenic progression of obesity [74]. Another clinical trial suggested omentin could be considered as an independent predictor of metabolic syndrome and obesity among adolescents in northeast China [75]. By analyzing the data from severely obese women undergoing intraoperative wedge liver biopsy during the bariatric surgery, the authors showed that the hepatic omentin-1 mRNA levels were lower in patients with advanced steatosis [76]. It is also verified that the cardio-

metabolic protective function of omentin is induced by the improved endothelial cell survival, including the progression of increased endothelial nitric oxide synthase (eNOS) and suppressed inflammation response or oxidative stress [77]. Concerning on this notion, omentin is currently identified as an excellent therapeutic target in several diseases, including T2DM, cardio-metabolic diseases, inflammatory diseases, and cancer.

Aside from the role in cardio-metabolic disorder, the function of omentin in inflammatory response has been given substantial attention in recent years. Omentin embraces a function in vascular smooth muscle cells which could attenuate the TNF-α-induced adhesion molecule expression and monocyte adhesion [78]. Similar results could be found in another independent research [79]. Otherwise, it should be noticed that besides the protective role against inflammatory response, omentin is also proposed to combine with the galactofuranosyl residues which locates on the walls of various bacteria [80]. Administering omentin-1 was shown to block cartilage degradation by inhibiting the production of pro-inflammatory cytokines, revealing omentin-1 is a potential therapy for the treatment for inflammatory related diseases [81]. Nonetheless, it is shown that the circulating concentrations of omentin-1 in SLE patients were not different from the healthy controls [82]. Also, the single nucleotide polymorphisms (SNPs) of *OMENTIN* gene were also not correlated with the genetic background of SLE in Chinese patients [83]. Whereas concerning on the modulatory function of omentin in inflammatory response and in producing pro-inflammatory cytokines, it is reasonably to infer that omentin might also influence the progression of SLE. Further studies focusing on the mechanisms whereby omentin links SLE and obesity are still required.

3.7 Chemerin

Chemerin is translated as a 163 amino acid preproprotein which is secreted as a 143 amino acid (18 kDa) proprotein following proteolytic cleavage of a signal peptide [84]. Currently, parallel lines of investigation supported that chemerin could be considered as a novel adipokine which might modulate adipocyte development and metabolic function. Emerging evidence from human experimental data indicated that circulating concentrations of chemerin were up-regulated in obese patients [85]. With in-depth research, it is shown that expression and secretion chemerin were increased dramatically with adipogenic progression. However, the loss of *CHEMERIN* gene expression in pre-adipocytes might disturb the differentiation into mature adipocytes [86]. Besides, chemerin is also confirmed to serve as a chemoattractant for multiple immune and inflammatory related cells which resultantly induce inflammatory response within white adipocyte under the obese condition [87]. On the other hand, the orphan G protein-coupled receptor chemokine-like receptor-1 (CMKLR-1) is shown to be expressed in human endothelial cells which might be up-regulated by the excessive production of pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β [57]. Recent study also demonstrated that chemerin could stimulate the key angiogenic pathways and promote the development of angiogenesis *in vitro* [58]. By using the adipocyte-specific endothelial nitric oxide synthase (eNOS/NOS3) knockout mice, the authors verified that despite less weight gain, those mice presented increased blood pressure, associated with exacerbated vascular dysfunction and remodeling [86]. Among the differentially expressed adipokines, the authors also found an up-regulation of chemerin, suggesting that deletion of NOS3 in adipocyte could potentiate hypertension and vascular remodeling via chemerin [86]. In conclusion, the findings indicated that chemerin could have an important role in multiple metabolic and inflammatory related pathway which might induce the pathological development of obesity and its related cardio-metabolic disorders.

Aside from the well-established role in obesity and metabolic disorders, increasing evidence also revealed chemerin is abundant in human epidermis which exhibited a modulatory function in inflammatory processes within skin cells. Though it is still required more large-scale clinical trial to explore the relationship between chemerin with the pathogenesis of SLE, several potential mechanisms whereby chemerin influences the cell metabolism which subsequently induces inflammatory response and SLE. For instance, it seems to support multiple anti-bacterial activities in the exudates from primary skin cultures, proposing that chemerin might contribute to skin defense through recruiting dendritic cells and acting as an anti-bacterial agent in epidermis [88]. Recombinant chemerin was also shown to promote the transmigration of plasmacytoid and myeloid dendritic cells across an endothelial cell monolayer. In addition, the expression level of chemerin was selectively detected on the luminal side of high endothelial venules in dermal endothelial vessels of skin lesions under the SLE condition [89]. These results, together with the cognate ligand on the luminal side of inflammatory endothelium, proposes an essential function of chemerin in plasmacytoid dendritic cell trafficking. Consistent with this notion, another independent research found that the plasmacytoid dendritic cell and chemerin concentrations were significantly up-regulated [61]. Taken together, the increased chemerin expression and concentrations is positively associated with plasmacytoid dendritic cell accumulation which are also strongly involved in the development of skin lesions under the status of SLE. Nevertheless, it is required to conduct more basic research or clinical trials to deeply investigate the relationship and the underlying mechanism by which chemerin links obesity and SLE.

3.8 Fetuin-A

Fetuin-A is synthesized by hepatocyte and adipocyte and secreted into circulation at high contents in human

beings [90]. The free fatty acids (FFA) in circulation could significantly promote the synthesis and production of fetuin-A in hepatocyte and adipocyte via stimulating the NF-κB signaling pathway [91]. Growing evidence showed the important role of fetuin-A in modulating cardio-metabolic disorders. For instance, reduced circulating concentrations of fetuin-A might directly inhibit the cardiac function via inducing the cardiac fibrosis and calcification, resultantly modulating the pathological progression of atherosclerotic plaque formation and cardiovascular diseases [92]. In addition, the serum levels of fetuin-A might be reduced in obese patients via the treatment of weight loss, indicating that fetuin-A might be correlated with the development of cardio-metabolic disorders [91]. With in-depth research, it is shown that fetuin-A not only induced inflammation in adipocyte but also acts as an upstream regulator of silent information regulator-1 (SIRT1) cleavage and AMPK stimulation [93]. Using human *in vitro* differentiated adipocytes, the authors found that fetuin-A could promote the low-grade chronic inflammatory response and could inhibit adiponectin production, suggesting a vital modulatory role of fetuin-A in the obese pathophysiology [94]. The similar crosstalk of fetuin-A and adiponectin could be found in another research [95].

Aside from the vital function in metabolic disorders, the role of fetuin-A in the inflammatory response, both the systemic and the tissue-specific, has gained substantial attention in the past several decades. As reported, fetuin-A induces the release of inflammatory related adipokines which inhibits the cholesterol efflux in macrophage [96]. The adipocyte-derived fetuin-A could also induce transformation of M2-phenotype macrophage into M1-phenotype macrophage, consequently facilitating the inflammatory response [97]. Since SLE is a well-reported systemic inflammatory disease, it is reasonably to speculate that fetuin-A might regulate the pathogenic of SLE. Indeed, Lee *et al*. [98] enrolled 76 SLE patients and found that among 1157 proteins quantified, 153 were differentially expressed in urine samples from SLE, including α-1-acid glycoprotein 1, fetuin-A, and ceruloplasmin. More recently, another independent case-control clinical trial revealed that fetuin-A were decreased in SLE patients, and the concentrations were negatively associated with cIMT. Moreover, there is a strong positive association between fetuin-A with anti-dsDNA and SLEDAI, proposing that fetuin-A level might be considered as a novel serum biomarker of disease activity in SLE patients [99].

3.9 Lipocalin-2 (LCN2)

Lipocalin-2 is a circulatory protein responsible for the transportation of small and hydrophobic molecules [100]. It is present in a large variety of cell types, including neutrophil, hepatocyte, adipocyte, macrophages, prostate, and renal cells. Different functions have been associated with lipocalin-2 which contain antibacterial, anti-inflammatory, and protection against cell stress [85]. Concerning on this notion, lipocalin-2 is identified as a biomarker for acute and chronic injury in different organs, including kidneys, heart, and lungs. For instance, using male mice, the authors demonstrated that lipocalin-2 could regulate the mitochondrial phosphor-lipidome remodeling, dynamics, and function in brown adipose tissue [101]. Recently, Javaid *et al*. [102] confirmed that the TNF-α-induced nitric oxide synthase (NOS)-like receptor thermal protein domain associated protein-3 (NLRP-3) inflammasome could significantly modulate the adipocyte dysfunction via adipocyte-derived lipocalin-2. On the other hand, lipocalin-2 is also identified as a key regulator of scavenger receptor-B1 (SR-B1) which might subsequently influence the HDL metabolism, inducing the pathological progression of atherosclerotic related coronary disease [103]. Through 12 weeks of high-intensity interval training, it is shown that the levels of lipocalin-2 might be improved in obese men [74].

It has been confirmed since 2010 that the neutrophil gelatinase-associated lipocalin-2 could be considered as a vital predictor of renal disease activity in SLE patients, and a significant predictor for flare in patients with a history of biopsy-proven nephritis [104]. Consistently, another independent research also showed that the 24-hour urinary excretions of neutrophil gelatinase-associated lipocalin-2 in the SLE group was significantly up-regulated [105]. Also, these findings have been replicated in several clinical trials [106,107]. Recently, Gómez-Puerta *et al*. [108] investigated whether levels of lipocalin-2 was the biomarkers to differentiate patients with lupus nephritis among SLE patients. Notably, the urinary lipocalin-2 was higher in patients with active lupus nephritis, suggesting that lipocalin-2 was a useful biomarker for the identification of renal involvement and discrimination of active lupus nephritis among SLE patients [108]. Since IL-1β promotes the development of obesity and SLE synergistically as mentioned above, it could be speculated that the regulatory feature of lipocalin-2 in linking SLE and obesity might be through inflammatory response.

4. Therapeutic Strategy for Obesity and SLE via Adipokines

Increasing evidence verified that the weight loss via diet control or daily exercise might effectively improve the development of SLE. To be more specific, the authors confirmed that a low fat diet (LFD) might reduce the plasma contents of leptin and increase the plasma contents of adiponectin, revealing that lifestyle modification might be the supplement for pharmacologic therapy in SLE individuals with cardio-metabolic disorders [109]. Notably, other research provided the notion that regulation inflammatory related adipokines might also improve obesity and SLE synchronously. A recent study revealed that the leptin-treated mice exhibited increased macrophage phagocytosis of apoptotic cells while compared with the control subjected

[110]. On the contrary, the *LEPTIN* gene-deficient mice presented decreased Th-17 cells and elevated Treg cells, implying that leptin could regulate the inflammatory responses in SLE and obesity [52]. Consistent with this finding, another study also showed that leptin could induce T cell survival by modulating T cell apoptosis via an increased expression of Bcl-2, proposing the possibility of a therapeutic targeting of leptin in SLE and obesity [111].

On the other hand, the SLE mouse models with lack adiponectin could facilitate more severe disease compared to the wild-type mouse models, indicating the involvement of adiponectin in regulating disease activity of SLE and obesity. As a result, the deficiency of adiponectin in the context of a mouse model of established auto-immunity could induce more robust disease while compared with the adiponectin-sufficient controls [112]. Importantly, Su *et al.* [113,114] also confirmed that recombinant apolipoprotein-A5 and apolipoprotein-A1 could significantly influence the differentiation of human adipose tissue-derived stromal cells into mature adipocytes. Since apolipoprotein-A1 is the main protein within HDL particle which plays a vital function in influencing the process of inflammatory response, the results suggested a potential therapeutic strategy for SLE and obesity which could use those two apolipoproteins. Concerning on the notion that some adipokines, such as leptin, chemerin, visfatin, and fetuin-A, have pro-inflammatory effects, further attention might be paid on create a biologic agent aiming at those pro-inflammatory cytokines. However, since there is short of the research on these novel adipokines, the ability for the novel agents in SLE therapy might be lower compared to the agent for the classical pro-inflammatory adipokines, such as IL-1β, IL-6, and TNF-α. Taken together, all the findings shed lights on that therapeutic strategies targeting inflammatory related adipokines might have positive functions in patients with SLE and obesity. Nevertheless, it should be noted that it is still far from a therapeutic application, since the data are scarce and the pleiotropic function of those adipokines might have multiple unintended consequences.

5. Conclusions

As mentioned in the current review, a strong association could be found between obesity, SLE, and adipokines. Accordingly, SLE and cardio-metabolic disorders might not be causal whereas could be a shared patho-physiological progression. Concerning on this notion, further basic experiments and clinical trials focusing on the elucidating the causal associations are significant. In the daily clinical practice, a final decision, which is made to select the therapeutic strategy, should be used to a SLE patient, and it seems vital to identify synchronously the weight management is also involved in the treatment. In a word, the patients with SLE might not only be assessed from a dermatological but also from a metabolic perspective feature, and the interactions of SLE with different comorbidities, especially cardio-metabolic disorders, might indicate the requirement for a multidisciplinary strategy in the treatment of the individuals with SLE and cardio-metabolic disorders.

Future research is necessary to fully illustrate the functions of diverse adipokines in the individuals with SLE and its comorbidities. As a consequence, the assessment of the serum inflammatory related adipokines concentrations, in well-phenotype individuals with SLE, is of great significance for the further understanding the disease in the clinical practice. According to the findings, diverse adipokines might be identified as the mediator of cutaneous inflammatory response, proposing a function of adipokines in the pathological development of SLE and cardio-metabolic disorders.

Author Contributions

ML, KL, XFC, and YC contributed to the study design. ML, KL, XFC, and YC wrote the manuscript. ML, KL, XFC, and YC reviewed drafts and approved the final version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This work was supported by grants from the project of Xiamen science and technology plan (No. 2022FCX012503010220 and 3502Z20244ZD1235), the Natural Science Foundation of Fujian Province (No. 2023J011685), the Health Research Project of Fujian Province (No. 2022QNB017).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Weinstein A, Alexander RV, Zack DJ. A Review of Complement Activation in SLE. Current Rheumatology Reports. 2021; 23: 16.

[2] Rice-Canetto TE, Joshi SJ, Kyan KA, Siddiqi J. Neuropsychiatric Systemic Lupus Erythematosus: A Systematic Review. Cureus. 2024; 16: e61678.

[3] Su X, Cheng Y, Chang D. The Important Role of Leptin in Modulating the Risk of Dermatological Diseases. Frontiers in Immunology. 2021; 11: 593564.

[4] Su X, Peng D. Adipokines as novel biomarkers of cardiometabolic disorders. Clinica Chimica Acta; International Journal of Clinical Chemistry. 2020; 507: 31–38.

[5] Song T, Kuang S. Adipocyte dedifferentiation in health and diseases. Clinical Science (London, England: 1979). 2019; 133: 2107–2119.

[6] Su X, Cheng Y, Zhang G, Wang B. Chemerin in inflammatory diseases. Clinica Chimica Acta; International Journal of Clinical Chemistry. 2021; 517: 41–47.
[7] Choo HMC, Cher WQ, Kwan YH, Fong WWS. Risk factors for cytomegalovirus disease in systemic lupus erythematosus (SLE): a systematic review. Advances in Rheumatology (London, England). 2019; 59: 12.
[8] Tian J, Luo Y, Wu H, Long H, Zhao M, Lu Q. Risk of adverse events from different drugs for SLE: a systematic review and network meta-analysis. Lupus Science & Medicine. 2018; 5: e000253.
[9] Oeser A, Chung CP, Asanuma Y, Avalos I, Stein CM. Obesity is an independent contributor to functional capacity and inflammation in systemic lupus erythematosus. Arthritis and Rheumatism. 2005; 52: 3651–3659.
[10] Borges MC, dos Santos FDMM, Telles RW, Lanna CCD, Correia MITD. Nutritional status and food intake in patients with systemic lupus erythematosus. Nutrition (Burbank, Los Angeles County, Calif.). 2012; 28: 1098–1103.
[11] Teh P, Zakhary B, Sandhu VK. The impact of obesity on SLE disease activity: findings from the Southern California Lupus Registry (SCOLR). Clinical Rheumatology. 2019; 38: 597–600.
[12] Huang AF, Zhou L, Xu WD. The causal associations of inflammatory cytokines with obesity and systemic lupus erythematosus: A Mendelian randomization study. International Journal of Rheumatic Diseases. 2024; 27: e15214.
[13] Sun C, Qin W, Zhang YH, Wu Y, Li Q, Liu M, *et al*. Prevalence and risk of metabolic syndrome in patients with systemic lupus erythematosus: A meta-analysis. International Journal of Rheumatic Diseases. 2017; 20: 917–928.
[14] Versini M, Jeandel PY, Rosenthal E, Shoenfeld Y. Obesity in autoimmune diseases: not a passive bystander. Autoimmunity Reviews. 2014; 13: 981–1000.
[15] DelOlmo-Romero S, Medina-Martínez I, Gil-Gutierrez R, Pocovi-Gerardino G, Correa-Rodríguez M, Ortego-Centeno N, *et al*. Metabolic syndrome in systemic lupus erythematosus patients under Mediterranean diet. Medicina Clinica. 2024; 162: 259–264.
[16] Wang Y, Huang Z, Xiao Y, Wan W, Yang X. The shared biomarkers and pathways of systemic lupus erythematosus and metabolic syndrome analyzed by bioinformatics combining machine learning algorithm and single-cell sequencing analysis. Frontiers in Immunology. 2022; 13: 1015882.
[17] Ruiyang B, Panayi A, Ruifang W, Peng Z, Siqi F. Adiponectin in psoriasis and its comorbidities: a review. Lipids in Health and Disease. 2021; 20: 87.
[18] Choi HM, Doss HM, Kim KS. Multifaceted Physiological Roles of Adiponectin in Inflammation and Diseases. International Journal of Molecular Sciences. 2020; 21: 1219.
[19] Zhang H, Park Y, Zhang C. Coronary and aortic endothelial function affected by feedback between adiponectin and tumor necrosis factor α in type 2 diabetic mice. Arteriosclerosis, Thrombosis, and Vascular Biology. 2010; 30: 2156–2163.
[20] Luo Y, Liu M. Adiponectin: a versatile player of innate immunity. Journal of Molecular Cell Biology. 2016; 8: 120–128.
[21] Krysiak R, Handzlik-Orlik G, Okopien B. The role of adipokines in connective tissue diseases. European Journal of Nutrition. 2012; 51: 513–528.
[22] Athari SS. Targeting cell signaling in allergic asthma. Signal Transduction and Targeted Therapy. 2019; 4: 45.
[23] Liu L, Yan M, Yang R, Qin X, Chen L, Li L, *et al*. Adiponectin Attenuates Lipopolysaccharide-induced Apoptosis by Regulating the Cx43/PI3K/AKT Pathway. Frontiers in Pharmacology. 2021; 12: 644225.
[24] Samaha MM, El-Desoky MM, Hisham FA. AdipoRon, an adiponectin receptor agonist, modulates AMPK signaling pathway and alleviates ovalbumin-induced airway inflammation in a murine model of asthma. International Immunopharmacology. 2024; 136: 112395.
[25] 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: 799–806.
[26] 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 International. 2005; 68: 1825–1833.
[27] Zhang MY, Dini AA, Yang XK, Li LJ, Wu GC, Leng RX, *et al*. Association between serum/plasma adiponectin levels and immune-mediated diseases: a meta-analysis. Archives of Dermatological Research. 2017; 309: 625–635.
[28] Dini AA, Wang P, Ye DQ. Serum Adiponectin Levels in Patients With Systemic Lupus Erythematosus: A Meta-analysis. Journal of Clinical Rheumatology: Practical Reports on Rheumatic & Musculoskeletal Diseases. 2017; 23: 361–367.
[29] 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. International Journal of Rheumatic Diseases. 2016; 19: 678–684.
[30] Carbone F, Montecucco F, Poggi A, Nobili F, Cacciapaglia F, Afeltra A, *et al*. Serum adiponectin levels are associated with presence of carotid plaque in women with systemic lupus erythematosus. Nutrition, Metabolism, and Cardiovascular Diseases: NMCD. 2020; 30: 1147–1151.
[31] Kamel SM, Abdel Azeem Abd Elazeem MEMI, Mohamed RA, Kamel MM, Abdel Aleem Abdelaleem EA. High serum leptin and adiponectin levels as biomarkers of disease progression in Egyptian patients with active systemic lupus erythematosus. International Journal of Immunopathology and Pharmacology. 2023; 37: 3946320231154988.
[32] Dan YL, Wang P, Cheng Z, Wu Q, Wang XR, Wang DG, *et al*. Circulating adiponectin levels and systemic lupus erythematosus: a two-sample Mendelian randomization study. Rheumatology (Oxford, England). 2021; 60: 940–946.
[33] 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. Annals of the Rheumatic Diseases. 2011; 70: 1619–1624.
[34] 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. Internal and Emergency Medicine. 2013; 8: 705–712.
[35] Lang H, Loudermilk EN, Clark WA, Marrs JA, Joyner TA, Wang L, *et al*. Inflammatory markers and body mass index amoung hispanic children. PloS One. 2024; 19: e0289523.
[36] Ozmen F, Şahin TT, Dolgun A, Ozmen MM. Changes in serum ghrelin and resistin levels after sleeve gastrectomy versus one anastomosis gastric bypass: prospective cohort study. International Journal of Surgery (London, England). 2024; 110: 5434–5443.
[37] Sabry MM, Dawood AF, Rashed LA, Sayed SM, Hassan S, Younes SF. Relation between resistin, PPAR-γ, obesity and atherosclerosis in male albino rats. Archives of Physiology and Biochemistry. 2020; 126: 389–398.
[38] Dotimas LG, Ojo B, Kaur A, Alake S, Dixon M, Rassi GDE, *et al*. Wheat germ supplementation has modest effects on gut health markers but improves glucose homeostasis markers in adults classified as overweight: A randomized controlled pilot study. Nutrition Research (New York, N.Y.). 2024; 127: 13–26.
[39] Gomez A, Parodis I, Sjöwall C. Obesity and tobacco smoking are independently associated with poor patient-reported out-

comes in SLE: a cross-sectional study. Rheumatology International. 2024; 44: 851–861.
[40] Gigante A, Iannazzo F, Navarini L, Sgariglia MC, Margiotta DPE, Vaiarello V, *et al*. Metabolic syndrome and adipokine levels in systemic lupus erythematosus and systemic sclerosis. Clinical Rheumatology. 2021; 40: 4253–4258.
[41] Zhou L, Li JY, He PP, Yu XH, Tang CK. Resistin: Potential biomarker and therapeutic target in atherosclerosis. Clinica Chimica Acta; International Journal of Clinical Chemistry. 2021; 512: 84–91.
[42] Cai X, Allison MA, Ambale-Venkatesh B, Jorgensen NW, Lima JAC, Muse ED, *et al*. Resistin and risks of incident heart failure subtypes and cardiac fibrosis: the Multi-Ethnic Study of Atherosclerosis. ESC Heart Failure. 2022; 9: 3452–3460.
[43] 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. The Journal of Rheumatology. 2011; 38: 2369–2375.
[44] García-Carrasco M, Mendoza-Pinto C, Munguía-Realpozo P, Etchegaray-Morales I, Vélez-Pelcastre SK, Méndez-Martínez S, *et al*. Insulin Resistance and Diabetes Mellitus in Patients with Systemic Lupus Erythematosus. Endocrine, Metabolic & Immune Disorders Drug Targets. 2023; 23: 503–514.
[45] 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. The Journal of Rheumatology. 2009; 36: 295–297.
[46] Dima A, Opris D, Jurcut C, Baicus C. Is there still a place for erythrocyte sedimentation rate and C-reactive protein in systemic lupus erythematosus? Lupus. 2016; 25: 1173–1179.
[47] 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. Clinical Rheumatology. 2015; 34: 1713–1720.
[48] Duan P, Tian S. Mendelian randomization analyses reveal no genetic causal effects of major adipokines on systemic lupus erythematosus. PloS One. 2024; 19: e0301699.
[49] Afifi AEMA, Shaat RM, Gharbia OM, Elhanafy M, Hasan ASG. Role of serum leptin levels and leptin receptor gene polymorphisms in systemic lupus erythematosus. Clinical Rheumatology. 2020; 39: 3465–3472.
[50] Yuan Q, Chen H, Li X, Wei J. Leptin: an unappreciated key player in SLE. Clinical Rheumatology. 2020; 39: 305–317.
[51] Elwakkad ASE, Said RN, Muhammad SI, Saleh MT, Elhamshary A. Role for leptin and prolactin in human juvenile rheumatic diseases. Pakistan Journal of Biological Sciences: PJBS. 2007; 10: 1984–1989.
[52] 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-Fas lpr mice. Journal of Immunology (Baltimore, Md.: 1950). 2014; 192: 979–984.
[53] 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 & Rheumatology (Hoboken, N.J.). 2015; 67: 2383–2393.
[54] Su X, Peng D. Emerging functions of adipokines in linking the development of obesity and cardiovascular diseases. Molecular Biology Reports. 2020; 47: 7991–8006.
[55] Tang C, Chen G, Wu F, Cao Y, Yang F, You T, *et al*. Endothelial CCRL2 induced by disturbed flow promotes atherosclerosis via chemerin-dependent β2 integrin activation in monocytes. Cardiovascular Research. 2023; 119: 1811–1824.
[56] Erdem NB, Kahramanoğlu Aksoy E, Dikmen D, Uçar Baş K, Ağaçdiken A, İlhan Esgin M, *et al*. Effects of low fat diet on inflammatory parameters in individuals with obesity/overweight and non-alcoholic fatty liver disease: A cross-sectional study. Medicine. 2024; 103: e37716.
[57] Singh A, Choubey M, Bora P, Krishna A. Adiponectin and Chemerin: Contrary Adipokines in Regulating Reproduction and Metabolic Disorders. Reproductive Sciences (Thousand Oaks, Calif.). 2018; 25: 1462–1473.
[58] Lin Y, Xiao L, Cai Q, Zhu C, Li S, Li B, *et al*. The chemerin-CMKLR1 axis limits thermogenesis by controlling a beige adipocyte/IL-33/type 2 innate immunity circuit. Science Immunology. 2021; 6: eabg9698.
[59] Hu S, Shao Z, Zhang C, Chen L, Mamun AA, Zhao N, *et al*. Chemerin facilitates intervertebral disc degeneration via TLR4 and CMKLR1 and activation of NF-kB signaling pathway. Aging. 2020; 12: 11732–11753.
[60] Gonzalvo-Feo S, Del Prete A, Pruenster M, Salvi V, Wang L, Sironi M, *et al*. Endothelial cell-derived chemerin promotes dendritic cell transmigration. Journal of Immunology (Baltimore, Md.: 1950). 2014; 192: 2366–2373.
[61] 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: 185–192.
[62] 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 International. 2011; 79: 1228–1235.
[63] Zaidi H, Byrkjeland R, Njerve IU, Åkra S, Solheim S, Arnesen H, *et al*. Adiponectin in relation to exercise and physical performance in patients with type 2 diabetes and coronary artery disease. Adipocyte. 2021; 10: 612–620.
[64] Rajput PK, Sharma JR, Yadav UCS. Cellular and molecular insights into the roles of visfatin in breast cancer cells plasticity programs. Life Sciences. 2022; 304: 120706.
[65] Zahedi AS, Zarkesh M, Sedaghati-Khayat B, Hedayati M, Azizi F, Daneshpour MS. Insulin resistance-related circulating predictive markers in the metabolic syndrome: a systematic review in the Iranian population. Journal of Diabetes and Metabolic Disorders. 2023; 23: 199–213.
[66] Chang YH, Chang DM, Lin KC, Shin SJ, Lee YJ. Visfatin in overweight/obesity, type 2 diabetes mellitus, insulin resistance, metabolic syndrome and cardiovascular diseases: a meta-analysis and systemic review. Diabetes/metabolism Research and Reviews. 2011; 27: 515–527.
[67] Al-Suhaimi EA, Shehzad A. Leptin, resistin and visfatin: the missing link between endocrine metabolic disorders and immunity. European Journal of Medical Research. 2013; 18: 12.
[68] De Sanctis JB, Zabaleta M, Bianco NE, Garmendia JV, Rivas L. Serum adipokine levels in patients with systemic lupus erythematosus. Autoimmunity. 2009; 42: 272–274.
[69] Ozgen M, Koca SS, Aksoy K, Dagli N, Ustundag B, Isik A. Visfatin levels and intima-media thicknesses in rheumatic diseases. Clinical Rheumatology. 2011; 30: 757–763.
[70] Shaker A, Fayed A, Morad MA, Labib S, Elmessiery RM, Salem KM, *et al*. Evaluation of Serum Visfatin as a Biomarker of Lupus Nephritis in Egyptian Patients with Systemic Lupus Erythematosus. Saudi Journal of Kidney Diseases and Transplantation: an Official Publication of the Saudi Center for Organ Transplantation, Saudi Arabia. 2023; 34: S170–S176.
[71] Hussein AA, Ahmed NA, Sakr HI, Atia T, Ahmed OM. Omentin roles in physiology and pathophysiology: an up-to-date comprehensive review. Archives of Physiology and Biochemistry. 2023; 1–14.
[72] Zoroddu S, Di Lorenzo B, Paliogiannis P, Mangoni AA, Carru C, Zinellu A. Resistin and omentin in breast cancer: A systematic review and meta-analysis. Clinica Chimica Acta; International

Journal of Clinical Chemistry. 2024; 562: 119838.
[73] Pan X, Kaminga AC, Wen SW, Acheampong K, Liu A. Omentin-1 in diabetes mellitus: A systematic review and meta-analysis. PloS One. 2019; 14: e0226292.
[74] Atashak S, Stannard SR, Daraei A, Soltani M, Saeidi A, Moradi F, *et al*. High-intensity Interval Training Improves Lipocalin-2 and Omentin-1 Levels in Men with Obesity. International Journal of Sports Medicine. 2022; 43: 328–335.
[75] Sun X, Li T, Tian Y, Ren S, Li L, Li P. Omentin as an Independent Predictor of Metabolic Syndrome and Obesity Among Adolescents in Northeast China. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2022; 15: 3913–3922.
[76] Waluga M, Kukla M, Zorniak M, Kajor M, Liszka L, Dyaczynski M, *et al*. Fibroblast growth factor-21 and omentin-1 hepatic mRNA expression and serum levels in morbidly obese women with non-alcoholic fatty liver disease. Journal of Physiology and Pharmacology: an Official Journal of the Polish Physiological Society. 2017; 68: 363–374.
[77] Lorenzo-Almorós A, Hang T, Peiró C, Soriano-Guillén L, Egido J, Tuñón J, *et al*. Predictive and diagnostic biomarkers for gestational diabetes and its associated metabolic and cardiovascular diseases. Cardiovascular Diabetology. 2019; 18: 140.
[78] Zhong X, Li X, Liu F, Tan H, Shang D. Omentin inhibits TNF-α-induced expression of adhesion molecules in endothelial cells via ERK/NF-κB pathway. Biochemical and Biophysical Research Communications. 2012; 425: 401–406.
[79] Zhui L, Yuling C, Hansheng W, Xiangjie L. Omentin reduces venous neointimal hyperplasia in arteriovenous fistula through hypoxia-inducible factor-1 alpha inhibition. Microvascular Research. 2024; 154: 104688.
[80] Colston JM, Chen YT, Hinson P, Nguyen NLH, Peñataro Yori P, Olortegui MP, *et al*. Enteropathy Markers in Early Life Were Associated with Adipokine, Apolipoprotein, and Cytokine Profiles Consistent with an Adverse Cardiometabolic Disease Risk Profile Later in Childhood in a Peruvian Birth Cohort. The American Journal of Tropical Medicine and Hygiene. 2022; 107: 754–765.
[81] Ko CY, Lin YY, Achudhan D, Chang JW, Liu SC, Lai CY, *et al*. Omentin-1 ameliorates the progress of osteoarthritis by promoting IL-4-dependent anti-inflammatory responses and M2 macrophage polarization. International Journal of Biological Sciences. 2023; 19: 5275–5289.
[82] Zhang TP, Li HM, Leng RX, Li XP, Li XM, Pan HF, *et al*. Plasma levels of adipokines in systemic lupus erythematosus patients. Cytokine. 2016; 86: 15–20.
[83] Zhang TP, Li HM, Li R, Zhang Q, Fan YG, Li XM, *et al*. Association of omentin-1, adiponectin, and resistin genetic polymorphisms with systemic lupus erythematosus in a Chinese population. International Immunopharmacology. 2020; 83: 106343.
[84] Ernst MC, Sinal CJ. Chemerin: at the crossroads of inflammation and obesity. Trends in Endocrinology and Metabolism: TEM. 2010; 21: 660–667.
[85] Recinella L, Orlando G, Ferrante C, Chiavaroli A, Brunetti L, Leone S. Adipokines: New Potential Therapeutic Target for Obesity and Metabolic, Rheumatic, and Cardiovascular Diseases. Frontiers in Physiology. 2020; 11: 578966.
[86] Man AWC, Zhou Y, Reifenberg G, Camp A, Münzel T, Daiber A, *et al*. Deletion of adipocyte NOS3 potentiates high-fat diet-induced hypertension and vascular remodelling via chemerin. Cardiovascular Research. 2023; 119: 2755–2769.
[87] Liu R, Han Y, Huang C, Hou M, Cheng R, Wang S, *et al*. Adipocyte-derived chemerin rescues lipid overload-induced cardiac dysfunction. iScience. 2023; 26: 106495.
[88] Mariani F, Roncucci L. Chemerin/chemR23 axis in inflammation onset and resolution. Inflammation Research. 2015; 64: 85–95.
[89] 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. The Journal of Experimental Medicine. 2005; 201: 509–515.
[90] Jirak P, Stechemesser L, Moré E, Franzen M, Topf A, Mirna M, *et al*. Clinical implications of fetuin-A. Advances in Clinical Chemistry. 2019; 89: 79–130.
[91] Mori K, Emoto M, Inaba M. Fetuin-A: a multifunctional protein. Recent Patents on Endocrine, Metabolic & Immune Drug Discovery. 2011; 5: 124–146.
[92] Icer MA, Yıldıran H. Effects of fetuin-A with diverse functions and multiple mechanisms on human health. Clinical Biochemistry. 2021; 88: 1–10.
[93] Chattopadhyay M, Mukherjee S, Chatterjee SK, Chattopadhyay D, Das S, Majumdar SS, *et al*. Impairment of energy sensors, SIRT1 and AMPK, in lipid induced inflamed adipocyte is regulated by Fetuin A. Cellular Signalling. 2018; 42: 67–76.
[94] Hennige AM, Staiger H, Wicke C, Machicao F, Fritsche A, Häring HU, *et al*. Fetuin-A induces cytokine expression and suppresses adiponectin production. PloS One. 2008; 3: e1765.
[95] Lee HJ, Lim Y, Yang SJ. Involvement of resveratrol in crosstalk between adipokine adiponectin and hepatokine fetuin-A in vivo and in vitro. The Journal of Nutritional Biochemistry. 2015; 26: 1254–1260.
[96] Miller C, Sask KN. Fetuin-A adsorption to tunable polydimethylsiloxane and subsequent macrophage response. Journal of Biomedical Materials Research. Part a. 2023; 111: 1096–1109.
[97] Chattopadhyay D, Das S, Guria S, Basu S, Mukherjee S. Fetuin-A regulates adipose tissue macrophage content and activation in insulin resistant mice through MCP-1 and iNOS: involvement of IFNγ-JAK2-STAT1 pathway. The Biochemical Journal. 2021; 478: 4027–4043.
[98] Lee JS, Lee EJ, Yeom J, Oh JS, Hong S, Lee CK, *et al*. Urine β-2-glycoprotein 1 as a biomarker for diagnosis of systemic lupus erythematosus. Lupus. 2021; 30: 1306–1313.
[99] Atta DS, Emera A, Ghoneim RS, Elnaggar AM. Serum level of fetuin-A in systemic lupus erythematosus patients: association with atherosclerosis and disease activity. Clinical Rheumatology. 2022; 41: 453–461.
[100] Jaberi SA, Cohen A, D'Souza C, Abdulrazzaq YM, Ojha S, Bastaki S, *et al*. Lipocalin-2: Structure, function, distribution and role in metabolic disorders. Biomedicine & Pharmacotherapy. 2021; 142: 112002.
[101] Su H, Guo H, Qiu X, Lin TY, Qin C, Celio G, *et al*. Lipocalin 2 regulates mitochondrial phospholipidome remodeling, dynamics, and function in brown adipose tissue in male mice. Nature Communications. 2023; 14: 6729.
[102] Javaid HMA, Ko E, Joo EJ, Kwon SH, Park JH, Shin S, *et al*. TNFα-induced NLRP3 inflammasome mediates adipocyte dysfunction and activates macrophages through adipocyte-derived lipocalin 2. Metabolism: Clinical and Experimental. 2023; 142: 155527.
[103] Hu S, Zhu Y, Zhao X, Li R, Shao G, Gong D, *et al*. Hepatocytic lipocalin-2 controls HDL metabolism and atherosclerosis via Nedd4-1-SR-BI axis in mice. Developmental Cell. 2023; 58: 2326–2337.e5.
[104] Rubinstein T, Pitashny M, Levine B, Schwartz N, Schwartzman J, Weinstein E, *et al*. Urinary neutrophil gelatinase-associated lipocalin as a novel biomarker for disease activity in lupus nephritis. Rheumatology (Oxford, England). 2010; 49: 960–971.
[105] Yang CC, Hsieh SC, Li KJ, Wu CH, Lu MC, Tsai CY, *et al*. Urinary neutrophil gelatinase-associated lipocalin is a potential biomarker for renal damage in patients with systemic lupus

erythematosus. Journal of Biomedicine & Biotechnology. 2012; 2012: 759313.

[106] El Shahawy MS, Hemida MH, Abdel-Hafez HA, El-Baz TZ, Lotfy AWM, Emran TM. Urinary neutrophil gelatinase-associated lipocalin as a marker for disease activity in lupus nephritis. Scandinavian Journal of Clinical and Laboratory Investigation. 2018; 78: 264–268.

[107] Elewa EA, El Tokhy MA, Fathy SE, Talaat AM. Predictive role of urinary neutrophil gelatinase-associated lipocalin in lupus nephritis. Lupus. 2015; 24: 138–146.

[108] Gómez-Puerta JA, Ortiz-Reyes B, Urrego T, Vanegas-García AL, Muñoz CH, González LA, *et al*. Urinary neutrophil gelatinase-associated lipocalin and monocyte chemoattractant protein 1 as biomarkers for lupus nephritis in Colombian SLE patients. Lupus. 2018; 27: 637–646.

[109] Seth M, Biswas R, Ganguly S, Chakrabarti N, Chaudhuri AG. Leptin and obesity. Physiology International. 2020; 107: 455–468.

[110] Amarilyo G, Iikuni N, Liu A, Matarese G, La Cava A. Leptin enhances availability of apoptotic cell-derived self-antigen in systemic lupus erythematosus. PloS One. 2014; 9: e112826.

[111] 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: e51118.

[112] Parker J, Menn-Josephy H, Laskow B, Takemura Y, Aprahamian T. Modulation of lupus phenotype by adiponectin deficiency in autoimmune mouse models. Journal of Clinical Immunology. 2011; 31: 167–173.

[113] Su X, Wang B, Lai M, Peng H, Song J, Huang H, *et al*. Apolipoprotein A1 Inhibits Adipogenesis Progression of Human Adipose-Derived Mesenchymal Stem Cells. Current Molecular Medicine. 2023; 23: 762–773.

[114] Su X, Weng S, Peng D. New Insights into Apolipoprotein A5 and the Modulation of Human Adipose-derived Mesenchymal Stem Cells Adipogenesis. Current Molecular Medicine. 2020; 20: 144–156.