Review Article

Leptin and systemic lupus erythematosus: A comprehensive review

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Abstract

Leptin, a cytokine-like hormone produced by adipocytes, modulates innate and adaptive responses of the immune system. Several reports have indicated that leptin exerts pro-inflammatory effects which significantly trigger autoimmune responses in chronic inflammatory diseases e.g. systemic lupus erythematosus (SLE), an inflammatory, multi-system disease characterized by the presence of auto-antibodies. Irrespective of contradictory results, many studies have indicated that leptin concentrations are increased in SLE patients. This might reflect genetic association, or a mechanism underlying the pathogenesis of SLE. To shed light on this possibility, recent studies investigated several polymorphism genes related to leptin in SLE patients from different ancestral groups. This review focuses on current understanding of the role of leptin in the pathogenesis of SLE and its immunomodulatory effects. This is expected to provide new leptin-based therapeutic interventions as modern approaches which are safer than the currently used ones for the treatment of SLE.

Keywords: Leptin, Systemic Lupus Erythematosus, Polymorphism, Gene expression

INTRODUCTION

Adipose tissue possesses endocrine and immune properties. It produces various cytokines such as IL-6 and TNF-α, as well as the adipokines leptin, adiponectin and resistin. These cytokines regulate a variety of physiological processes such as food intake, insulin sensitivity, atherosclerosis, immunity and inflammation [1]. Systemic lupus erythematosus (SLE) is an autoimmune disease (type III hypersensitivity reaction) due to the accumulation of immune complexes in different organs, resulting in multi-system damage and various clinical manifestations arising from loss of immunological tolerance and the presence of auto-antigens [2]. The etiopathogenesis of SLE is facilitated by environmental factors and sex hormones (especially estrogen) which might trigger abnormal autoimmune responses in genetically predisposed individuals [3]. Moreover, the severity and clinical manifestations of SLE are linked to altered production of multiple cytokines [2]. Leptin is a cytokine-like hormone with pro-inflammatory properties. Increasing evidence show that low and high levels of leptin play are involved in the pathogenesis of various autoimmune diseases [4]. Therefore, leptin has

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been studied as a target of new therapeutic approaches for autoimmune diseases [5].

LEPTIN AND SIGNAL TRANSDUCTION PATHWAYS

Leptin is a non-glycosylated peptide hormone (16-KD) encoded by the *obese* gene synthesized mainly in the adipose tissue, especially in differentiated mature adipocytes. It is also secreted in small amounts by the gastric mucosa, skeletal muscle, placenta and mammary epithelium [6]. Leptin is known as a satiety factor with multiple effects such as regulation of endocrine function, reproduction and immunity [7].

The three-dimensional structure of leptin is highly similar to that of members of the long–chain helical cytokines, for example interleukin-6 (IL-6). There are six different isoforms of leptin receptor (OB-R) due to alternating splicing of OB-R-mRNA [8]. The only isoform with signaling capabilities like IL-6 cytokine receptors is Ob-Rb. This isoform is expressed in the hypothalamus and cardiovascular system, and also in different types of immune cells. It is thought that the ubiquitous expression of Ob-Rb receptor might reflect the pleiotropic effect of leptin [9].

Upon binding to its receptor (OB-Rb), leptin activates Janus-family tyrosine kinase 2 (JAK2) signaling pathway by auto-phosphorylating specific tyrosine residues in the cytoplasmic domain. This leads to activation of SH2-containing tyrosine-specific protein phosphatase (SHP2) and signal transducer and activator of transcription 3 (STAT3). Then, STAT3 activates gene transcription of the suppressor of cytokine signaling 3 (SOCS3), which negatively regulates leptin signaling, and other target genes. In addition, leptin activates extracellular signal-regulated kinase (ERK)/MAPK pathway (Ras-Raf-MEK-ERK signaling cascade). Leptin also mediates in the activation of phosphatidylinositol-3-kinase (PI3K)/Akt via the insulin receptor substrate 1/2 (IRS1/2) and protein tyrosine phosphatase 1B (PTP1B), which also acts as a negative regulator of leptin signaling (Figure 1) [7].

LEPTIN AND IMMUNITY

Early studies of thymus atrophy in (*db*/*db*) mice revealed the regulatory role of leptin on the function of immune cells. Later studies confirmed that leptin is involved in modulating responses in innate immunity and adaptive immunity [8]. In innate immunity, leptin increases CD11b marker expression on the surface of leukocytes,
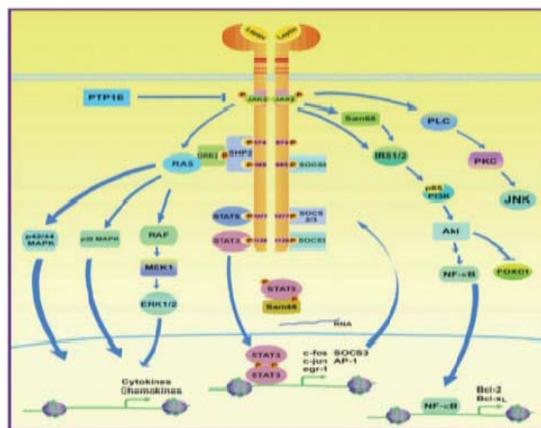

Figure 1: Signaling pathways of leptin (adapted from Zhou *et al*., 2013)

activates neutrophils by upgrading chemotaxis, and also activates natural killer (NK) cells, thereby increasing their cytotoxic capabilities. Moreover, leptin enhances the secretion of interleukin-2 (IL-2) via the activation of STAT3. Leptin also stimulates the proliferation of monocytes and macrophages, and increases their phagocytic effects and the release of pro-inflammatory cytokines [10].

With respect to its effect on adaptive immunity, leptin maintains thymic homeostasis by exerting anti-apoptotic influence on mature T cells and the precursors of hematopoiesis [11]. It also activates the proliferation of naïve T cells and secretion of IL-2 through the activation of MAPK and PI3K pathways [12]. Leptin enhances a shift in immune responses in the direction of T helper 1 (Th1)-cells by increasing the release of interferon-γ (IFN-γ) and TNF-α [13]. Leptin tends to suppress the proliferation of regulatory T-cells (Treg) $CD4^+CD25^+$ which are potent suppressors of autoimmunity [11,14]. Therefore, reduction in leptin concentrations leads to a decrease in proliferation of effector T cells, increased population of Treg cells, and downregulation of Th1 immunity [10].

ROLE OF LEPTIN IN PATHOGENESIS OF SLE

Systemic lupus erythematosus (SLE) is characterized by sex bias: females are predominantly more affected than males. This phenomenon is associated with differences in gene expression and sex hormones between the two sexes [15]. In healthy individuals, women have 5-10 times higher levels of leptin than men [16]. The increase in leptin concentration during inflammation points to its pro-inflammatory properties which might be responsible for systemic inflammation in SLE [17]. Indeed, circulating leptin levels are abnormally increased

in SLE [18]. Hyperleptinemia, which is associated with a direct increase in the number of Th17 cells, and decreases in the number of Treg cells, are considered as underlying factors in the development of SLE [19]. Studies have found that leptin stimulated proliferation of autoreactive T-cells in lupus-prone mice, thereby promoting autoimmunity [18].

Current advances in research on SLE have shown that the cytokine-like function of leptin may account for the molecular mechanism underlying the pathophysiology of SLE, and also revealed the possibility of using leptin as a predictor of severity of SLE, and serologic marker in identification of patients at risk of developing the active phase of the disease [20]. It is very likely that understanding how leptin modulates autoimmune responses in SLE might provide new possibilities for development of leptin-targeted therapies [21].

Amarilyo and coworkers have reported that abnormally high level of leptin in SLE triggers T-cell survival by increasing bcl-2 expression which modulates apoptosis in T-cells. Leptin also activates the proliferation of autoreactive T-cells in lupus-prone mice (NZBXNZW) F1 which carry an autoreactive T-cell repertoire. In addition, leptin may stimulate phagocytosis of apoptotic cells by macrophages in (NZBXNZW) F1 through modulating cAMP levels in macrophages [22]. This finding was linked to increased levels of apoptosis-derived antigens which favor the proliferation and responses of reactive T cell to the antigens. The authors suggested that that the inhibition of this process by blocking leptin may be of therapeutic application for SLE, since it may modulate SLE-associated autoimmune responses [22].

A more recent study by Lourenço and colleagues has shown that genetically-induced deficiency of leptin in mice protected the animals from developing SLE, and decreased the production of autoantibodies, specifically anti-dsDNA antibodies, and renal diseases [21]. Anti-dsDNA antibodies are produced mainly during the active phase of SLE and are associated with lupus nephritis [22]. These autoantibodies were leptin-dependent, since leptin blockade protected the mice model of lupus from developing autoantibodies, while administration of leptin promoted development of the active phase of disease. This finding suggests that leptin could possibly be exploited as new therapeutic intervention for SLE [23].

PLASMA or SERUM LEPTIN AND SLE

Despite availability of several studies on circulating levels of leptin in SLE patients, there are contradictory results on the association between plasma or serum leptin levels and SLE (Table 1). Many researchers reported elevated leptin in SLE patients, but failed to reach a clear conclusion on whether these increased levels were as a result of the disease, or were responsible for the pathogenesis of the disease. The results varied in patients according to demographic data, weight or dietary components, and disease markers such as anti-dsDNA antibodies [24]. For example, Lourenco and colleagues reported that leptin promoted the development of different types of autoantibodies, specifically anti-dsDNA antibodies [21], while another study found no association between anti-dsDNA antibodies and serum leptin levels [25]. In addition, there were variations in clinical manifestations, laboratory results and disease severity, with respect to leptin levels in SLE patients in the different studies. However, many of these studies failed to correlate the leptin levels with severity of SLE [24].

In order to provide a clearer picture of the relationship between plasma/serum levels of leptin and SLE, a study was conducted by Li and coworkers [24], in which eleven studies [20,25-33,35] were pooled through a meta-analysis. The study showed no significant difference in levels of leptin in plasma or serum between the whole groups of SLE patients and controls. However, analysis of leptin concentrations between subgroups of SLE patients revealed that plasma or serum leptin levels were significantly elevated in Asian SLE patients aged ≥ 40 years whose BMI values were < 25. Thus, the authors suggested that age, BMI, region and race might be associated with leptin levels in SLE patients, taking in consideration the effect of other factors such as clinical data, gender and environmental factors.

More recently, Badaway and colleagues [36] studied tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) and leptin concentrations in the sera of 90 SLE patients with anti-phospholipid syndrome (APS). The patients were divided into four groups: group A (30 SLE patients), group B (26 SLE patients with secondary APS i.e. SLE-APS), group C (14 SLE patients with primary APS i.e. pAPS), and group D control (n = 20). The authors reported significant increases in serum leptin and TWEAK in pAPS patients, when compared to other patients and control.

Table 1: Summary of studies on serum/plasma leptin levels in SLE patients

Year	Reference	Study type	Patients (n)	Controls (n)	Leptin concentration	*P*-value	Disease severity	Region	Observation
2014	Barbosa *et al* [25]	Case-control	52	33	Increased (serum)	<0.001	No correlation	Brazil	High leptin levels associated with renal diseases, while low levels associated with lupus anticoagulant and anticardiolipin
2014	Afroze *et al* [26]	Case-control	100	100	Increased (serum)	<0.001	Not done	India	
2011	Vadacca *et al* [27]	Case-control	60	29	Increased (serum)	0.035	Correlation	Italy	
2011	Mcmahon *et al* [20]	Case-control	250	122	Increased (plasma)	<0.001	NA	America	Serum leptin levels were associated with increased risk of atherosclerosis
2010	Kim *et al* [28]	Case-control	70	39	Decreased (serum)	<0.05	NA	Korea	High leptin concentrations were associated non significantly with malar rash, oral ulcers, alopecia, arthritis and renal disorders in SLE patients.
2009	De Sanctis *et al* [29]	Case-control	60	60	Decreased (serum)	<0.005	NA	Venezuela	
2009	Chung *et al* [30]	Case-control	109	78	Increased (serum)	<0.001	No correlation	America	There was a correlation between leptin levels and insulin resistance (IR) in SLE patients
2009	Al *et al* (31)	Cohort study	105	77	Increased (serum)	<0.05	No correlation	Canada	
2008	Wislowska *et al* [32]	Case-control	30	30	No difference (serum)	>0.05	No correlation	Poland	Low leptin levels associated with arthritis and CNS
2007	Elwakkad *et al* [33]	Case-control	12	21	Increased (serum)	<0.05	No correlation	Egypt	
2006	Sada *et al* [34]	Case-control	37	80	Plasma (increased)	<0.01	NA	Japan	The percentages of hypertension and DM higher in SLE patients than controls, 32% of SLE patients with IR showed higher incidence of hypertension and proteinuria than those without, Increased adiponectin in SLE patients, but inversely correlated with IR
2002	Garcia-Gonzalez *et al* 350	Cross-sectional study	41	23	Increased (serum)	0.023	No correlation	Mexico	

NA: Not assessed; DM: diabetes mellitus, IR: insulin resistance

The study investigated the feasibility of using these analyzed parameters as biomarkers for prediction of atherosclerosis. The results showed no significant correlation between TWEAK or leptin, and SLE. However, serum levels of leptin and TWEAK were significantly increased in pAPS patients, when compared to other patients and controls. They also found that cholesterol and triglyceride levels were significantly increased in SLE patients and pAPS group, relative to control, while HDL was markedly decreased in SLE, when compared to SLE-APS patients.

Diaz-Rizo and coworkers [37] investigated serum levels of leptin in 103 SLE women in relation to kidney damage, in a study involving 30 SLE patients who suffered from lupus nephritis (LN) and 73 SLE patients without LN. The study showed no difference in serum leptin levels between LN group and those without LN. On the other hand, there was a non-significant trend towards higher levels of serum leptin in SLE patients, but these levels were not related to the presence or severity of proteinuria.

In another study conducted by Mohammed and colleagues [38], leptin concentrations in sera collected from 40 SLE patients were correlated with laboratory results for CBC, ESR, ANA, anti-dsDNA, C3 and C4, as well as liver and kidney functions tests, and SLEDAI index. The study showed that serum leptin levels were significantly higher in SLE patients than in controls. In addition, the levels of these parameters were significantly associated with BMI and total cholesterol, but non-significantly with SLEDAI index and clinical features of SLE (malar rash, fever, and neuropsychiatric symptoms).

ASSOCIATION BETWEEN LEPTIN-RELATED POLYMORPHISMS AND SLE

Genetics play a key role in the pathogenesis of SLE, since many candidate genes tested in genetic association studies have been implicated in the pathogenesis of SLE [39]. However, only few gene association studies have focused on the association between leptin-related polymorphisms and SLE [40]. Afroze and colleagues [26] determined *LEPR* gene polymorphism (*LEPR Q223R*), a polymorphism in leptin gene (A>G transition) in 100 Kashmiri SLE patients. The A >G transition might alter signal transduction by impairing the binding of leptin to its receptor, thereby impairing *LEPR* expression. The study showed that *LEPR* gene polymorphism was associated with increased susceptibility to SLE in the Kashmiri population. In the study, carriers of variant genotype (A/G+

G/G) or the rare G allele were susceptible to developing SLE. However, there was a limitation in the study, in that it did not reach a conclusion on the association between Q223R polymorphism and SLE due to small size of the study sample of SLE patients with homogenous ethnicity.

Therefore, another study conducted by Zhao and coworkers [41] analyzed a larger number of SLE patients from multiple ancestral groups. The authors tested several single nucleotide polymorphisms (SNPs) within several leptin-related genes i.e. leptin gene (*LEP*), leptin receptor (*LEPR*), peroxisome proliferator-activated receptor (*PPAR*)-γ (*PPARG*), and growth hormone secretagogue receptor (*GHSR*).The SNPs were selected based on their relationship with the leptin gene and its receptor, and other genes association with the regulation of expression of leptin gene. Genetic variants of *LEP* may regulate the expression, function and catabolism of leptin. For *LEPR*, polymorphisms of all isomers were assessed since they may influence the catabolism of leptin, or induce sustained effect of leptin [42]. Polymorphisms of *PPARG* were analyzed because leptin downregulated *PPAR*-γ expression, leading to increased levels of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α) release [43]; while polymorphisms of *GHSR* exerted the opposite effects on leptin by inhibiting the release of these pro-inflammatory cytokines [44].

Zhao and colleagues performed the study by genotyping DNA samples collected from 13,706 participants (8,269 SLE patients and 7,437 controls) from four different ethnic groups to investigate the involvement of leptin pathway-related gene polymorphisms in the pathogenesis of SLE. Four ethnic groups were enrolled in the study: European Americans (3,966 SLE patients and 3,543 controls); African Americans (1,527 SLE patients and 1,812 controls); East Asians (1,272 SLE patients and 1,270 controls), and Hispanics (1,504 cases and 812 controls).The study used haplotype tag SNPs for genotyping the chosen genes, resulting in genotyping of 32 SNPs: 7 SNPs for *LEP*, 10 SNPs for *LEPR*, 3 SNPs for *GHSR,* and 12 SNPs for *PPARG.* These SNPs were subsequently passed through genetic association test. The study found an association between the A allele of rs12706832 in *LEP* and low susceptibility to SLE in African Americans, while the A allele of rs3828942 was linked to increased risk for SLE in the same group. For *LEPR*, the C allele of rs6690625 and the A allele of rs1892535 showed association with low susceptibility to SLE in Hispanics.

In *GHSR*, the G allele of rs2948694 showed an association with decreased risk of SLE in European Americans. For *PPARG*, the A allele of rs12633551 and A allele of rs3856806 were associated with low risk of SLE in European Americans. Although these data showed significant association signals at several loci, the associations did not remain significant after correction for multiple testing. Therefore, the study failed to confirm associations between any of the defined leptin-associated polymorphisms and increased susceptibility to SLE.

Li and his team [45] investigated the association between SNPs of *LEP* and *LEPR* with increased risk of SLE in a cohort of Chinese population. They genotyped four SNPs of *LEP* and nine SNPs of *LEPR* genes with improved multiple ligase detection reaction (iMLDR).

The study showed no significant differences between SLE patients and controls in the distribution of frequencies of alleles and genotypes of all tested SNPs. In addition, the effects of genotypes for the recessive, dominant and additive models showed no significant association with SLE. Subsequent analysis showed that the frequencies of TT genotype and T allele of the *LEP* rs2071045 polymorphisms were significantly increased in patients with pericarditis, while frequencies of genotype GA/AA and A allele of the rs1137100 polymorphism in *LEPR* were both linked to photosensitivity in SLE patients, in accordance with the distribution of genotype and allele of rs3806318 polymorphism. The study also showed no significant differences in serum leptin concentrations amongst SLE patients of different genotypes.

LEPTIN GENE EXPRESSION

There are increasing evidence of the involvement of leptin in maintenance of the immune system [46]. Leptin may stimulate activation and proliferation of peripheral blood mononuclear cells (PBMCs) through its receptors which are expressed on these cells. Leptin activates the JAK–STAT, IRS-1-PI3K and MAPK signaling pathways, and stimulates phosphorylation of tyrosine residues of the RNA-binding protein known as sterile motif (SAM), thereby modulating RNA metabolism [47]. Several factors might participate in regulating the expression of leptin gene, especially food intake and hormones such as insulin and sex hormones [48]. For example, it has been found that during feeding, insulin activates leptin secretion, while during starvation, a fall in insulin levels leads to a decrease in leptin release [49].The expression of leptin gene is also

increased by ovarian sex steroids, but it is inhibited by testosterone [50]. In addition, leptin release is increased during acute infection, sepsis, and inflammation due to the release of inflammatory mediators such as IL-1, TNF-α and LIF [51].

Several *in vitro* studies have been conducted on the immunomodulatory effect of leptin using PBMCs [52, 53]. These studies might provide an insight into leptin-targeted therapeutic interventions for SLE treatment, instead of the traditional treatment strategies. Brink and colleagues [52] have reported that exposure of PBMCs to leptin induced sustained phosphorylations of p38 MAP kinase and ribosomal protein S6 involved in initiation of mRNA translation. This finding may account for the molecular mechanisms underlying the observed immunomodulatory effect of leptin in PBMCs. Another study conducted by Zarkesh-Esfahani *et al* showed that leptin administration directly induced inflammatory responses and expression of its receptors in PBMCs [54].

Dixit and coworkers [55] showed that leptin induced the production of growth hormone by PBMCs by activating protein kinase C (PKC) and nitric oxide-dependent pathways. This effect might play an important role in immune homeostasis, thereby indicating the cytokine-like effect of this hormone on immune responses through regulation of the survival and proliferation of immune cells.

More recently, leptin gene expression was determined for the first time using PBMCs from healthy subjects [53]. However, there are no extant studies on the expression levels of leptin in SLE patients. This could be applied for development of new therapies for SLE based on leptin targeting. These therapies will be safer than the currently used methods which are toxic or cause adverse side effects in SLE patients.

CONCLUSION AND FUTURE PERSPECTIVES

Recent understanding of the role of leptin in immune responses and development of SLE, an autoimmune disease, provide a possibility for new leptin-targeted therapies that decrease leptin concentrations by repressing the expression of the leptin gene. These therapies are considered much safer than traditional treatment methods which produce adverse and toxic effects in SLE patients. This implies different therapeutic approaches for SLE, and use of leptin agonists which are effective in repressing enhanced T-cell immunity as a component of autoimmunity. Another therapeutic

possibility is to use drugs that reduce circulating levels of leptin, for example, drugs that activate peroxisome proliferator-activated receptor γ which functions as transcription factor when activated by its endogenous ligand (15-deoxy-$\Delta^{12,14}$- prostaglandin-J_2), resulting in the repression of the expression of *obese* gene [56].

DECLARATIONS

Acknowledgement

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

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