Role of leptin in the pathogenesis of systemic lupus erythematosus

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ABSTRACT

Leptin is a 16 kDa adipocyte-secreted hormone that regulates weight centrally and links nutritional status to neuroendocrine and immune functions. Several studies indicate that leptin plays an important role in immune responses. Leptin affects both innate and adaptive immunity. It can stimulate dendritic cells (DC), monocytes, macrophages, neutrophils and natural killer cells. Leptin is involved in DC maturation and survival, and can skew the cytokine balance of a T helper (Th)1 profile. In adaptive immunity, leptin can promote naïve T cell survival and production of interferon-γ and interleukin-2, and activate Th1 cells while inhibiting Th2 cells. Leptin may play an important role in the regulation of the Th1/Th2 balance. As a survival factor, leptin has been shown to suppress B cell apoptosis. The role of leptin in the pathogenesis of systemic lupus erythematosus (SLE) is not fully determined yet. This review tries to link the role of leptin in immunity to the pathogenesis of SLE.

Leptin constitutes a hormone synthesized by the adipose tissue that binds with a receptor which is a member of the class I cytokine receptor family.[1-4] Leptin has been increasingly recognized as a cytokine-like hormone with pleiotropic actions in modulating immune responses. Leptin can activate monocytes, dendritic cells (DC), and macrophages and stimulate them to produce T helper (Th)1 type cytokines. Leptin also exerts activating effects on neutrophils and natural killer (NK) cells and stimulate their gene expressions. Importantly, leptin has been shown to modulate the adaptive immunity *via* enhancing T cell survival and stimulating their production of pro-inflammatory cytokines such as interferon (IFN)-γ and interleukin (IL)-2. Recent evidence demonstrates a detrimental involvement of leptin in promoting the pathogenesis of various autoimmune diseases. In respect of its diverse functions in immunity, leptin has been explored as a potential target for therapeutic development in treating autoimmune diseases.[5]

PATHOGENESIS OF SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease characterized by widespread inflammation affecting virtually every organ or system in the body. The disease is associated with the deposition of autoantibodies and immune complexes, leading to tissue damage.[6]

The exact patho-aetiology of SLE remains elusive. An extremely complicated and multifactorial interaction among various genetic and environmental factors is probably involved. Multiple genes contribute to disease susceptibility. The interaction of sex, hormonal milieu, and the hypothalamo–pituitary–adrenal axis modifies this susceptibility and the clinical expression of the disease. Defective immune regulatory mechanisms, such as the clearance of apoptotic cells and immune complexes, are important contributors to the development of SLE. The loss of immune tolerance, increased antigenic load, excess T cell help, defective B cell suppression, and the shifting of Th1 to Th2 immune responses lead to B cell hyperactivity and the production of pathogenic autoantibodies.[6-8] Prolonged periods of immune response to external/environmental factors such as UV radiation or viral infection can also cause immune system dysregulation.[9]

Cytokines have been implicated in regulating disease activity and the involvement of different organs in SLE. T helper cells can be divided into different subsets depending on their cytokine profile. The Th1 cells increase macrophage activation and produce IL-2, IFN-γ and tumor necrosis factor (TNF)-α. The Th2 cells stimulate antibody production and upregulate humoral immunity and allergic responses. They produce IL-4, IL-5, IL-6, IL-10 and IL-13. The Th3 cells are regulatory cells that can act to induce immune tolerance and characteristically produce transforming growth factor-β, IL-4 and IL-10. The Th0 cells can produce cytokines of all three types. The pattern of cytokine production in different disease states may be described as a Thl, Th2, or Th3 response based on the cytokines produced. Recent experimental observations suggest a key role for IL-10 in the pathogenesis of SLE as it has a particular ability to encourage B cells to make antibodies.[6] The pathogenesis of SLE is summarized diagrammatically in figure 1.

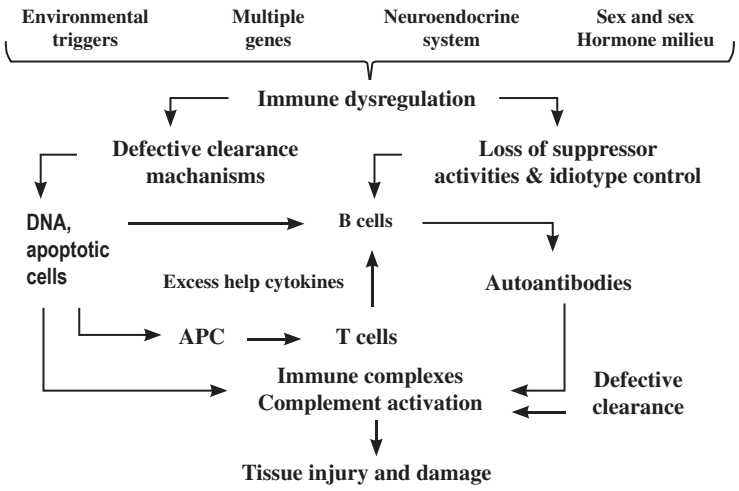

Figure 1 The pathogenesis of systemic lupus erythematosus. Multiple genes confer susceptibility to disease development. Interaction of sex, hormonal milieu, the hypothalamo–pituitary–adrenal axis, and defective immune regulation, such as clearance of apoptotic cells and immune complexes, modify this susceptibility. The loss of immune tolerance, increased antigenic load, excess T cell help, defective B cell suppression, and shifting of T helper (Th)1 to Th2 immune responses lead to cytokine imbalance, B cell hyperactivity, and the production of pathogenic autoantibodies. Finally, certain environmental factors are probably needed to precipitate the onset of the disease (adapted from Mok et al., 2003)[7]

STRUCTURE OF LEPTIN RECEPTOR

The discovery of leptin in 1994 completely changed the traditional view of white adipose tissue (WAT). Actually, WAT was considered for decades as only a triglyceride reservoir with a passive or null endocrine role. The discovery of leptin, followed by many other adipocyte-derived molecules, called adipokines, identifies the adipose tissue as one of the main endocrine organs with an active and relevant role in regulating energy homeostasis, metabolism, as well as immune-inflammatory processes.[10]

Leptin is derived from the Greek *leptos*, meaning thin. Leptin is a 16 kDa non-glycosylated peptide hormone encoded by the obese (*ob*) gene and mainly produced by adipocytes although low levels has been detected in the hypothalamus, pituitary, stomach, skeletal muscle, mammary epithelia, chondrocytes, and a variety of other tissues. Leptin is structurally and functionally related to the IL-6 cytokine family.[10-12]

The leptin receptor (Ob-R) is a cytokine receptor and belongs to the class I cytokine receptor family.[2-4,13] The Ob-R gene produces at least six transcripts designated Ob-Ra through Ob-Rf. Two of the isoforms have been described in only one species each, Ob-Rd in mice and Ob-Rf in rats. In humans, only expression of Ob-Ra, Ob-Rb and Ob-Rc mRNA have been reported.[11] Ob-R is encoded by the diabetes (*db*) gene. The OB-R shares the highest structural similarity and signaling capability with those of the IL-6 type cytokine receptors. It contains four fibronectin type III domains, four conserved cysteine residues and two cytokine-like binding motifs, Trp-Ser-Xaa-Trp-Ser, in the extracelullar region. The OB-R exists in a dimeric form even in the absence of leptin and is activated upon ligand binding. By alternative splicing, OB-R mRNA gives rise to six different isoforms that share identical extracellular binding domain but with cytoplasmic domains of different length which include one soluble form (OB-Re), four short forms (OB-Ra, OB-Rc, OB-Rd, and OB-Rf) and one long form (OB-Rb). The different isoforms have distinct biological activities. For example, OB-Ra is responsible for the transport of leptin across the blood-brain barrier whereas the soluble OB-Re serves as a regulator of circulating leptin levels. Among the six isoforms, only OB-Rb is most capable of transducing its signaling function and has been shown to be of prime importance in leptin-mediated signaling (fig 2).[5,14]

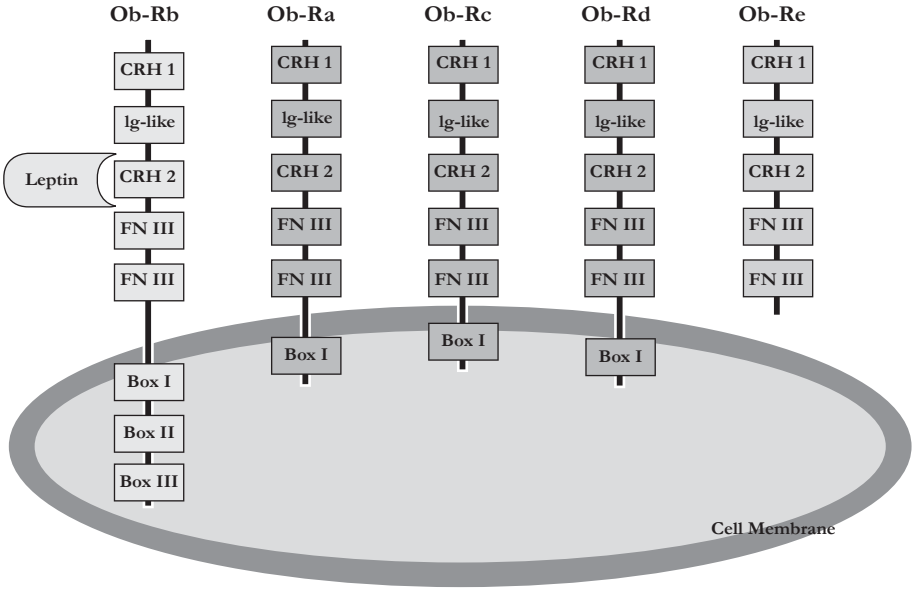

Figure 2 Structure and isoforms of mouse leptin receptor. The Ob-R gene produces at least six transcripts designated Ob-Ra through Ob-Rf. One soluble form (OB-Re), four short forms (OB-Ra, OB-Rc, OB-Rd, and OB-Rf) and one long form (OB-Rb). Cytokine receptor homology module (CRH)2 is the main binding site for leptin on the Ob-R. The immunoglobulin-like fold (Ig-like) and the fibronectin type III domain (FN III) domains are critically involved in Ob-R activation. Cytokine receptor homology module (CRH)2 is the main binding site for leptin on the Ob-R. The Ig-like and the FN III domains are critically involved in Ob-R activation (adapted from Bernotiene et al., 2006).[11]

LEPTIN SIGNALING TRANSDUCTION PATHWAYS

Intracellularly, all six OB-R isoforms contain a highly conserved proline-rich box 1 (intracellular amino acid 6-17) but only OB-Rb has an extended intracellular domain of approximately 300 residues. The major functions of all short isoforms except OB-Re are limited to leptin transportation, internalization, and degradation although some evidence suggests that they are capable of triggering certain signaling events. The long receptor OB-Rb, a fully functional receptor, does not have an intrinsic tyrosine kinase domain but its box 1 motif recruits and binds janus kinases (JAKs). The box 1 motif together with the immediate surrounding amino acids is essential for JAK activity. The extended intracellular domain in the distal part of OB-Rb is required for the induction of signal transducers and activators of transcription (STAT) signaling.[5]

Upon leptin binding, OB-Rb-associated JAK2 at the box 1 motif is activated which then auto-phosphorylates its own tyrosine residues and phosphorylates tyrosine residues on the intracellular domain of the receptor (Tyr 974, Tyr 985, Tyr 1077 and Tyr 1138) to provide docking sites for signaling proteins containing src homology 2 (SH2) domains (fig 3). The phosphorylated tyrosine residues Tyr 1077 and Tyr 1138 bind to the STAT proteins which are then activated and translocated to the nucleus to stimulate gene transcription.[5,15,16] Both Tyr 1077 and Tyr 1138 bind to STAT5 while only Tyr 1138 recruits STAT1 and STAT3. The other two phosphorylated residues Tyr 974 and Tyr 985 recruit SH2 domain-containing phosphatase 2 (SHP2) which activates the mitogen-activated protein kinase (MAPK) pathways including extracellular signal-regulated kinase (ERK1/2), p38 MAPK and p42/44 MAPK pathways through interaction with the adaptor protein growth factor receptor-bound protein 2 (GRB2).[5,17-19] The auto-phosphorylated JAK2 at the box 1 motif can phosphorylate insulin receptor substrate1/2 (IRS1/2) that leads to activation of phosphatidylinositol 3-kinase (PI3K)/Akt and the MAPK pathways.[5,16,20-22]

Leptin has also been shown to activate various isoforms of STATs including STAT1, STAT3, STAT5 and STAT6 in a variety of cell types[15,23,24] (Figure 3). Among various STAT proteins activated by OB-Rb, STAT3 has been most extensively reported to mediate effects of leptin on growth and function of normal and cancer cells as well as immune cells, primarily by inducing various gene expressions such as c-fos, c-jun, egr-1 and activator protein-1.[5,25,26] STAT3 has been shown to mediate the leptin signal in activating macrophages and in promoting the survival and activation of lymphocytes and peripheral mononuclear cells. Src associated in mitosis protein 68 (Sam68), an RNA binding protein involved in inhibiting cell proliferation, is tyrosinephosphorylated and forms a complex with activated STAT3 upon leptin stimulation in human peripheral blood mononuclear cells.[27-29] The phosphorylation on Sam68 leads to its dissociation from RNA and allows it to bind to proteins containing SH2 and SH3 domains.[30] On the other hand, STAT3 can induce activation of the negative-feedback regulator, suppressors of cytokine signaling 3 (SOCS3), which binds to the phosphorylated tyrosines (Tyr 985, Tyr1077 and Tyr 1138) on the receptor to inhibit leptin signaling.[31,32] The involvement of SOCS3 in the negative-feedback control of leptin signaling is suggested to underlie the development of leptin resistance commonly found in obesity.[17] Other proteins of the SOCS family that are induced by leptin include SOCS1 and SOCS2.[13,33] Based on the complex activation network of the STAT proteins, further analyses on their regulation by leptin signaling in immune cells will merit a fuller understanding of leptin-mediated immune modulation. Apart from the SOCS proteins induced by STATs to inhibit leptin signaling, protein tyrosine phosphatase 1B (PTP1B) is another negative regulator localized on the surface of endoplasmic reticulum and acts by dephosphorylation of JAK2 on OB-R. Moreover, overexpression of PTP1B has been shown to inhibit leptin-induced SOCS3 and c-fos expression.[5,34-36]

Leptin activates the MAPK cascade *via* the recruitment of SHP2 to OB-Rb, which then binds to GRB2 to activate further signaling steps including RAS, RAF and MEK1, leading to the activation of ERK1/2, p38 MAPK and p42/44 pathways.[17-19,37] The primary docking site for SHP2 is phosphorylated Tyr 974 and Tyr 985.[17] It has been reported that leptin can induce c-jun N-terminal protein kinase (JNK) *via* phospholipase C (PLC) and subsequently protein kinase C (PKC) activation.[38,39] In neutrophils, leptin activates chemotaxis *via* p38 MAPK pathway.[40] Leptin also stimulates TNF-α production *via* p38 and JNK MAPK pathways in LPS-stimulated kupffer cells.[41] Furthermore, leptin has been shown to activate the MAPK pathways to mediate anti-apoptotic effects in mononuclear cells.[18,30,42] The MAPK pathways are essential in regulating a wide range of immune functions. ERK1/2 and p38 MAPK pathways synergistically mediate cytokine production in DC and participate in the chemokine production in CD40L-stimulated macrophages.[5,43,44]

The PI3K/Akt pathway represents a key signaling cascade which mediates effects of a wide range of ligands in a variety of different cell types. The typical target of PI3K, Akt, is an integral part of a key signaling pathway that is necessary for inducing immune and inflammatory responses.[26] Akt is also the mediator of signals from pro-inflammatory cytokines and toll-like receptor ligands in a variety of immune cells. The PI3K/Akt pathway is the upstream regulator for a number of effectors including the antiapoptotic transcription factor NF-κB. Akt inhibits its downstream target pro-apoptotic forkhead transcription factor FOXO1 or FKHR-L1, which functions to induce the expression of Bim, a pro-apoptotic member of the Bcl-2 family proteins.[5]

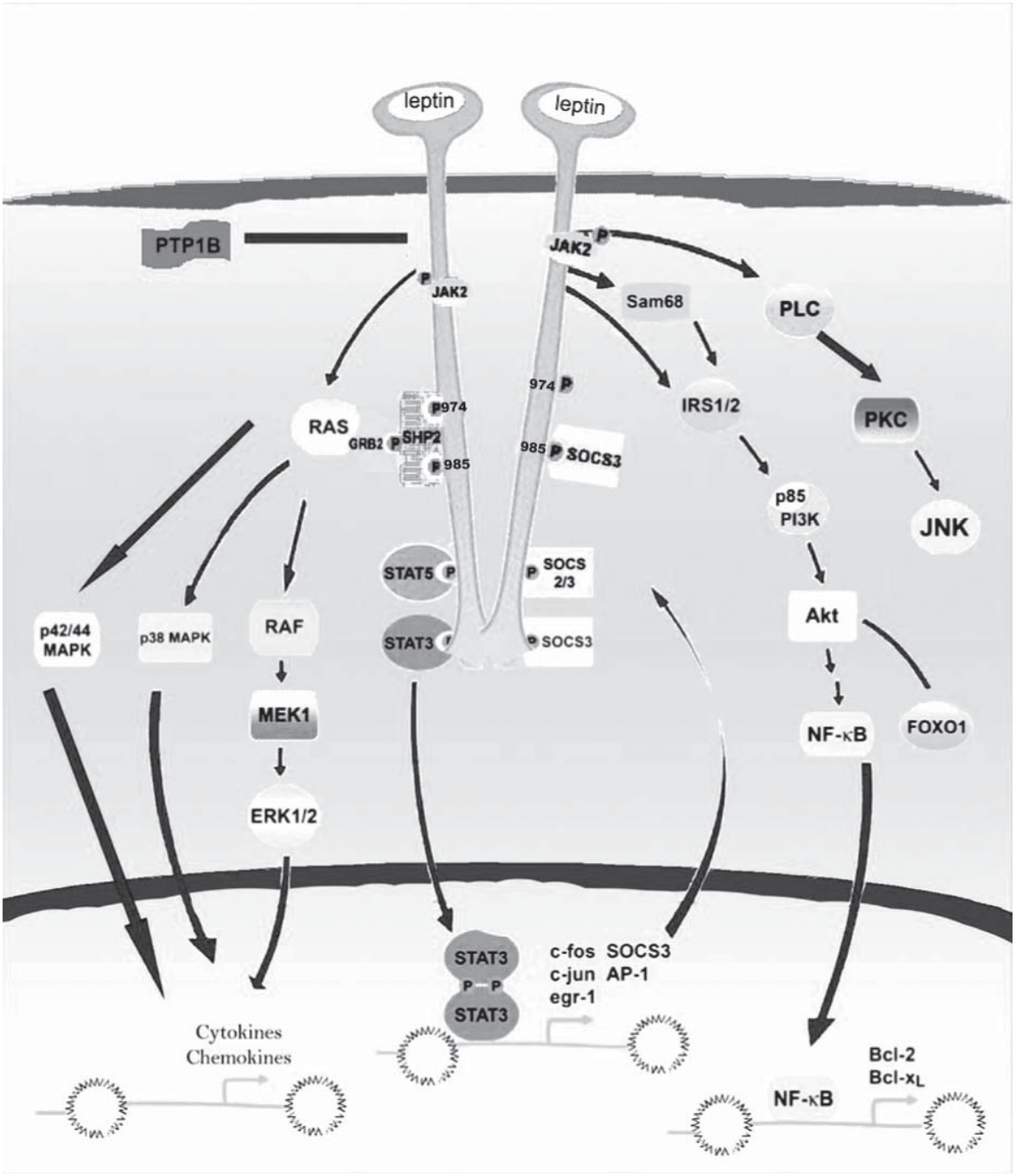

Figure 3 Signaling pathways activated by leptin. Only the long form of the leptin receptor (OBRb) can signal intracellularly. After binding leptin, OBRb-associated Janus-family tyrosine kinase 2 (JAK2) becomes activated by auto- or cross-phosphorylation and tyrosine phosphorylates the cytoplasmic domain of the receptor. Four of the phosphorylated tyrosine residues function as docking sites for cytoplasmic adaptors such as signal transducer and activator of transcription (STAT) factors, particularly STAT3. After subsequent dimerization, STAT3 translocates to the nucleus and induces the expression of suppressor of cytokine signalling 3 (SOCS3) and other genes such as c-fos, c-jun, egr-1, activator protein-1 (AP-1). SOCS3 takes part in a feedback loop that inhibits leptin signalling by binding to phosphorylated tyrosines. SRC homology 2 (SH2) domain-containing phosphatase 2 (SHP2) is recruited to Tyr985 and Tyr974 and activates extracellular signal-regulated kinase 1/2 (ERK1/2) and p38 mitogen-activated protein kinase (MAPK) pathways through the adaptor protein growth factor receptor-bound protein 2 (GRB2). Ultimately after leptin binding, JAK2 can induce phosphorylation of the insulin receptor substrate 1/2 (IRS1/2) proteins that are responsible for the activation of phosphatidylinositol 3-kinase (PI3K). Phosphotyrosine phosphatase 1B (PTP1B), which is localized on the surface of the endoplasmic reticulum, is involved in negative regulation of OBRb signalling through the dephosphorylation of JAK2. Activation of NF-κB by leptin binding has been shown to induce Bcl-2 and Bcl-XL expressions (adapted from Lam et al., 2007).[5]

EFFECTS OF LEPTIN ON INNATE IMMUNE RESPONSES

The role of leptin in innate immunity has been demonstrated by a wide range of leptin actions on antigen-presenting cells (APCs), NK cells, and neutrophils.[5] Congenital leptin deficiency in human displayed dysfunctional immune function such as an increased incidence of infection-related death during childhood and leptin therapy has been shown to correct multiple immune abnormalities in these patients.[45,46] Both *db/db* and *ob/ob* mice exhibit defective cell-mediated immunity and lymphoid atrophy with enhanced susceptibility to infection and injuries.[47] Peritoneal macrophages in *ob/ob* mice display impaired phagocytic capacity which rendered them unable to clear bacterial infection.[48] The findings that leptin expression can be induced rapidly by inflammatory stimuli such as LPS, IL-1, and TNF-α during the acute phase of immune response indicate a role for leptin acting as a mediator in regulating inflammatory activities.[48,49] Several studies have shown that leptin signaling participates in innate immunity by promoting the maturation and survival of DC. In the absence of leptin signaling, DC display a Th2-biased cytokine profile while exogenous leptin treatment skewed the cytokine balance of normal DC towards a Th1 profile.[5,50,51] The altered Th1:Th2 cytokine balance is associated with a corresponding change in the immuno-stimulatory capacity on T cells. In monocytes and macrophages, leptin has been shown to stimulate proliferation and phagocytosis, together with production of pro-inflammatory cytokines.[42] In macrophages, leptin can induce production of factors involved in regulating immune responses such as nitric oxide, leukotriene B4, cholesterol acyl-transferases-1 and cyclooxygenase 2.[49,52-54]

Leptin can stimulate DC, monocytes, macrophages, neutrophils, and NK cells. Leptin is involved in DC maturation and survival, and can skew the cytokine balance of a Th1 profile. In monocytes and macrophages, leptin has been shown to stimulate proliferation and phagocytosis, together with production of pro-inflammatory cytokines.[5] Leptin modulates the activity and function of neutrophils by increasing chemotaxis and the secretion of oxygen radicals (such as hydrogen peroxide, H_2O_2 , and superoxide, O_2^-) through direct and indirect mechanisms.[55,56] In humans, the action of leptin seems to be mediated by TNF secreted by monocytes.[57] Leptin increases phagocytosis by monocytes/macrophages and enhances the secretion of pro-inflammatory mediators of the acute-phase response and the expression of adhesion molecules.[42,58] On NK cells, leptin increases cytotoxic ability and the secretion of perforin and IL-2.[55,59]

EFFECTS OF LEPTIN ON ADAPTIVE IMMUNE RESPONSES

The functions of leptin in stimulating the pro-inflammatory cytokine production involved in innate immune responses can indirectly modulate the adaptive immunity. Early studies on *db/db* mice revealed that the development and maturation of both T and B cells are severely affected with reduced numbers of lymphocytes in peripheral lymphoid organs.[5,60] The immune abnormalities in immune responses are observed in *ob/ob* and *db/db* mice as well as T cells in the *ob/ob* mice indicating a protective role of leptin in enhancing T cell survival. In a recent study, treatment with pharmacologic doses of leptin in the *ob/ob* mice stimulates thymopoiesis even in the LPS-induced thymic atrophy.[61] Furthermore, leptin has been shown to promote the survival of both T and B lymphocytes by suppressing Fas-mediated apoptosis which may result from its induction of the anti-apoptotic proteins including Bcl-2 and Bcl-XL.[50,62,63] Leptin also increases the production of a variety of proinflammatory cytokines such as IFN-γ and IL-2 in T lymphocytes and modulates the immune response towards the Th1 phenotype by stimulating CD4 in mice with starvation-induced leptin deficiency.[5]

Thymic atrophy induced upon starvation was prevented by leptin replacement, and leptin also protected thymocyte apoptosis by maintaining thymic maturation of the double positive CD4+CD8+ T lymphocyte proliferation with activation of STAT3 and its DNA binding activity.[5,23,58] In Th1 cells, leptin increases their TNF-α and IFN-γ production and IgG2a switching by B cells. In contrast, leptin exerts inhibitory effects on Th2 cells by reducing IgG1 switching. Consistently, CD4+ T cells from *db/db* mice showed impaired proliferative capacity.[27] Notably, leptin can modulate specific aspects of T cell function with differential effects on distinct subpopulations of lymphocytes, as demonstrated by the findings that leptin can stimulate proliferation of CD4+CD45RA+ naïve T cells but inhibit anti-CD3-driven proliferation of CD4+CD45RO+ memory T cells while stimulating their production of IFN-γ.[64] These studies indicate the diverse actions of leptin in regulating immune homeostasis. Although the immunomodulatory role of leptin in immunity has become increasingly evident, the other major function of leptin as an endocrine hormone to regulate energy storage and metabolism has added complexity in ascertaining the leptin effects either in immune modulation or in metabolic functions. This requires cautious interpretations of the observed immune deficits in the *ob/ob* and *db/db* mice, as hyperglycemic and insulin resistant conditions that occur during their early adulthood can affect the immune system indirectly.[5]

Leptin is essential for thymic homeostasis by its anti-apoptotic functions and maintenance of thymic maturation.[5,65] Leptin can promote naïve T cell survival and production of IFN-γ and IL-2, and activate Th1 cells while inhibiting Th2 cells.[5,66] On Th1 cells, it increases their TNF-α and IFN-γ production, and IgG2a switching by B cells. In contrast, leptin exerts inhibitory effects on Th2 cells by reducing IgG1 switching. On memory T cells, leptin promotes the switch towards Th1-cell immune responses by increasing IFN-γ and TNF secretion, the production of IgG2a by B cells and delayed-type hypersensitivity (DTH) responses.[48,55] As a survival factor, leptin has been shown to suppress B cell apoptosis (fig 4).[5]

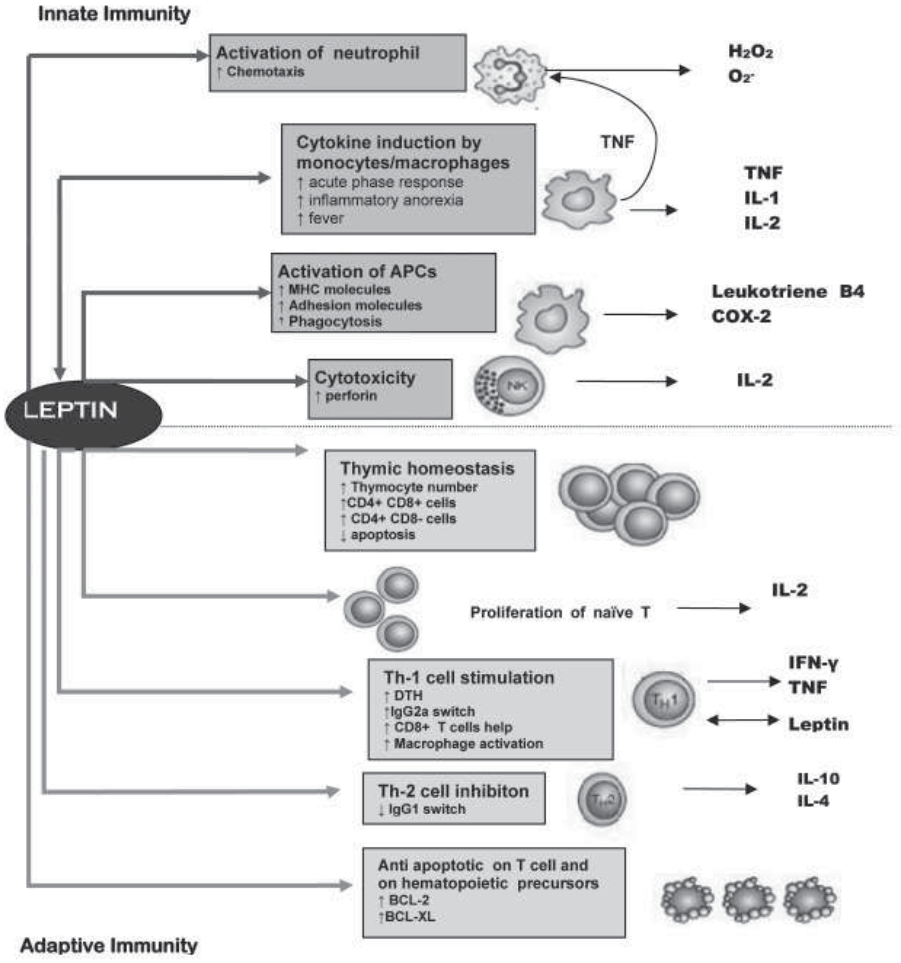

Figure 4 Effects of leptin on innate and adaptive immune responses. In innate immunity, leptin modulates the activity and function of neutrophils by increasing chemotaxis and the secretion of oxygen radicals through direct and indirect mechanisms. Leptin increases phagocytosis by monocytes/macrophages and enhances the secretion of pro-inflammatory mediators of the acute-phase response and the expression of adhesion molecules. On natural killer (NK) cells, leptin increases cytotoxic ability and the secretion of perforin and interleukin-2 (IL-2). In adaptive immunity, leptin affects the generation, maturation, and survival of thymic T cells by reducing their rate of apoptosis. On naive T-cell responses, leptin increases proliferation and IL-2 secretion. On memory T cells, leptin promotes the switch towards T helper (Th)1 -cell immune responses by increasing interferon-γ (IFN-γ) and TNF secretion. This process is then sustained by an autocrine loop of leptin secretion by Th1 cells. Leptin has anti-apoptotic effects on mature T cells and on haematopoietic precursors (adapted from La Cava et al., 2004).[55]

LEPTIN IN INFLAMMATION AND AUTOIMMUNITY

A growing body of evidence indicates that leptin acts as a pro-inflammatory cytokine in immune responses. Although pro-inflammatory factors are critical mediators of host defense mechanisms, these cytokines can negatively associate with the development of autoimmune diseases. Leptin has also been shown to enhance immune reactions in autoimmune diseases that are commonly associated with inflammatory responses. Recent evidence indicates that leptin is involved in the dysregulated balance between Th1 and Th2 cytokines and contributes to the pathogenesis of RA. In contrast, leptin deficiency has a protective effect on autoimmune diseases by altering the balance of Th1:Th2 cytokine production and promoting a Th2 response as shown in fasting RA patients exhibiting significantly improved clinical disease activity correlated with a marked reduction in serum leptin and a shift toward Th2 cytokine production.[5]

The immunomodulatory effects of leptin have also been linked to enhanced susceptibility to other autoimmune disease such as experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis.[67,68] Recent studies have shown that leptin is involved in the induction and progression of EAE.[69,70] The *ob/ob* mice are resistant to EAE induction with increased IL-4 and a lack of IFN-γ after myelin-specific stimulation of T cells. Interestingly, leptin replacement renders these mice to become susceptible to the disease accompanied by a shift to Th1 type cytokine pattern and reversal of IgG1, a Th2 dependent antibody, to the Th1 dependent IgG2a.[71] In both experimentally-induced colitis and hepatitis models, *ob/ob* mice exhibit a dramatic reduction of colitis severity along with reduced serum levels of TNF-α and IL-18.[72] Leptin replacement converts disease resistance to susceptibility with spontaneous release of proinflammatory cytokines in these mice. The influence of leptin deficiency has been examined on immune-mediated renal disease and accelerated nephrotoxic nephritis in the *ob/ob* mice which were found to be strongly protected from the disease.[73]

Leptin is produced by adipocytes that are present in the perilymphonodal adipose tissue and the lymph node itself. In the lymph node, leptin promotes the differentiation of Th1 cells, the activation of monocytes/macrophages and the secretion of cytokines of the acute-phase response and oxygen radicals.

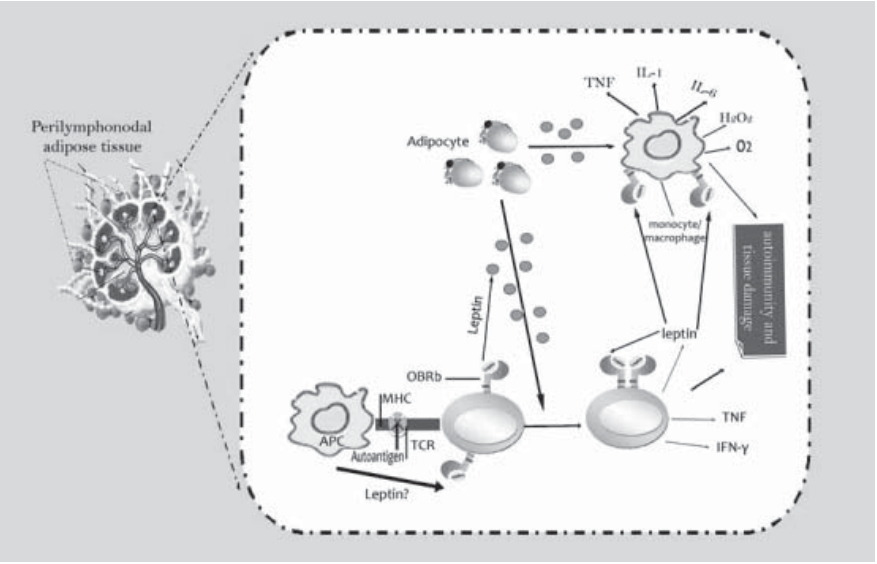

Figure 5 A model for the role of leptin in autoimmunity. In the lymph node, leptin promotes the differentiation of T helper 1 (Th1) cells, the activation of monocytes/macrophages and the secretion of cytokines of the acute-phase response and oxygen radicals. Autoantigens could be presented to Th0 cells that express the long form of the leptin receptor (OBRb). Leptin could then affect the priming of autoreactive T cells towards Th1-type pro-inflammatory responses. Leptin has autocrine effects on Th1 and paracrine effects on monocytes or macrophages leading to production of inflammatory cytokines by those cells and finally leading to autoimmunity and tissue damage (adapted from La Cava et al., 2004).[55]

Autoantigens could be presented to Th0 cells that express the long form of the leptin receptor (OBRb). Leptin could then affect the priming of autoreactive T cells towards Th1-type pro-inflammatory responses, for example, in experimentally induced autoimmune diseases that affect the central nervous system (CNS), the gastrointestinal mucosa, hepatocytes, pancreatic β-cells, synovial cells and cartilage. Paracrine effects of TH1 cells that produce leptin after activation with antigen could then sustain an autocrine loop of proliferation and T-cell survival (fig 5).[55,58]

In relation to the important role of leptin in autoimmunity, women have twice higher serum leptin levels than men adjusted for age and body mass index, and are predisposed to autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, and SLE. Therefore, leptin might play a part in the prevalence of autoimmune conditions in females.[1,5] The higher leptin levels in females are sustained by the reciprocal influence of estrogens on leptin secretion and the potentiation of leptin production by estrogens. In addition, APCs from females produce higher IL-12 than males. All these factors may contribute to the increased capacity of females to produce Th-1 pro-inflammatory immune responses and therefore to the increased cell-mediated autoimmune disease susceptibility (fig 6).[74]

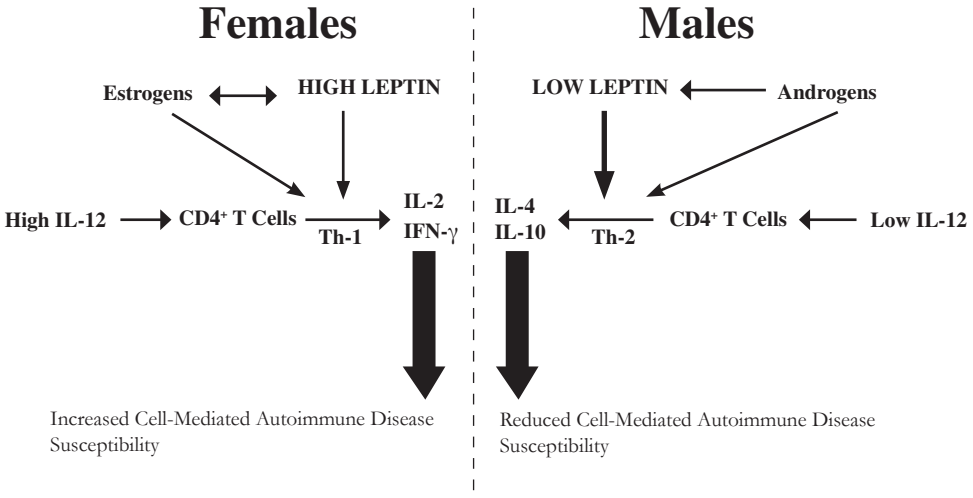

Figure 6 A model summarizing the reciprocal influence of leptin and sex hormones on the immune T cell function in females and males. Leptin might play a part in the prevalence of autoimmune conditions in females. The higher leptin levels in females are sustained by the reciprocal influence of estrogens on leptin secretion and the potentiation of leptin production by estrogens. In addition, APCs from females produce higher IL-12 than males. All these factors may contribute to the increased capacity of females to produce Th-1 pro-inflammatory immune responses and therefore to the increased cell-mediated autoimmune disease susceptibility (adapted from Matarese et al., 2002).[74]

LEPTIN IN HUMAN SYSTEMIC LUPUS ERYTHEMATOSUS

The role of leptin in the pathogenesis of SLE is not fully determined yet. A cross-sectional study done by Garcia-Gonzales et al[1] found that patients with SLE had higher serum leptin levels than those of the control group. A borderline negative correlation was observed between leptin levels and disease activity (MEX-SLEDAI score), but not statistically significant ($r = 0,3$; $p = 0,06$).

Wislowska et al[75] found that serum leptin levels in SLE patients with arthritis ($p < 0,05$) and CNS involvement ($p = 0,05$) were significantly lower in comparison with serum leptin levels in SLE patients without arthritis and CNS involvement. A positive correlation was found between serum leptin levels and the values of hemoglobin ($r = 0,44$; $p < 0,02$), but no correlation was found between serum leptin levels and the disease activity (SLEDAI score), nor between serum leptin levels and the disease damage index as measured by SLICC (Systemic Lupus International Collaborating Clinics). The serum leptin level was significantly lower in SLE patients with the presence of arthritis or neurological disorders, which suggests that active chronic inflammation may lower plasma leptin concentrations.

Our study (see original article in this journal titled 'Correlation between serum leptin concentration and disease activity in normal body mass index premenopausal women with systemic lupus erythematosus') found that the median of serum leptin levels in normal body mass index premenopausal women with SLE who had active disease (MEX-SLEDAI score greater than or equal to 2 points) was lower than that of patients with inactive disease (MEX-SLEDAI less than 2 points), but this difference was not statistically significant. A weak negative correlation was observed between serum leptin levels and MEX-SLEDAI score ($r = -0,22$; $p = 0,07$).

Systemic lupus erythematosus is characterized by a predominantly humoral response (Th2 type) leading to over expression of Th2 cytokines, such as IL-4 and IL-10, whereas in rheumatoid arthritis is thought to be provoked by a more cellular response (Th1 type).[76] Th2 immune responses lead to B cell hyperactivity and the production of pathogenic autoantibodies,[6,7,8] which finally lead to tissue injury and damage.[7] Leptin exerts inhibitory effects on Th2 cells,[5] leading to decreased production of IL-4 and IL-10 and then reduced activation of B cells. This circumstance may explain the discovery of the negative correlation between serum leptin levels and disease activity in several studies mentioned above. A scheme of hypothesis about the role of leptin in the pathogenesis of SLE (according to the author's opinion) is shown in figure 7.

SUMMARY

Leptin has been recognized as a cytokine-like hormone with pleiotropic actions in modulating immune responses. The exact role of leptin in the pathogenesis of SLE is not fully determined yet. Systemic lupus erythematosus is characterized by a predominantly humoral response (Th2 type), leading to over expression of Th2 cytokines, such as IL-4 and IL-10. Leptin has inhibitory effects on Th2 cells and may lead to decreased production of IL-4 and IL-10 and then reduced activation of B cells. Many studies are required to explore whether leptin has a protective effect or enhancement towards tissue injury and damage.

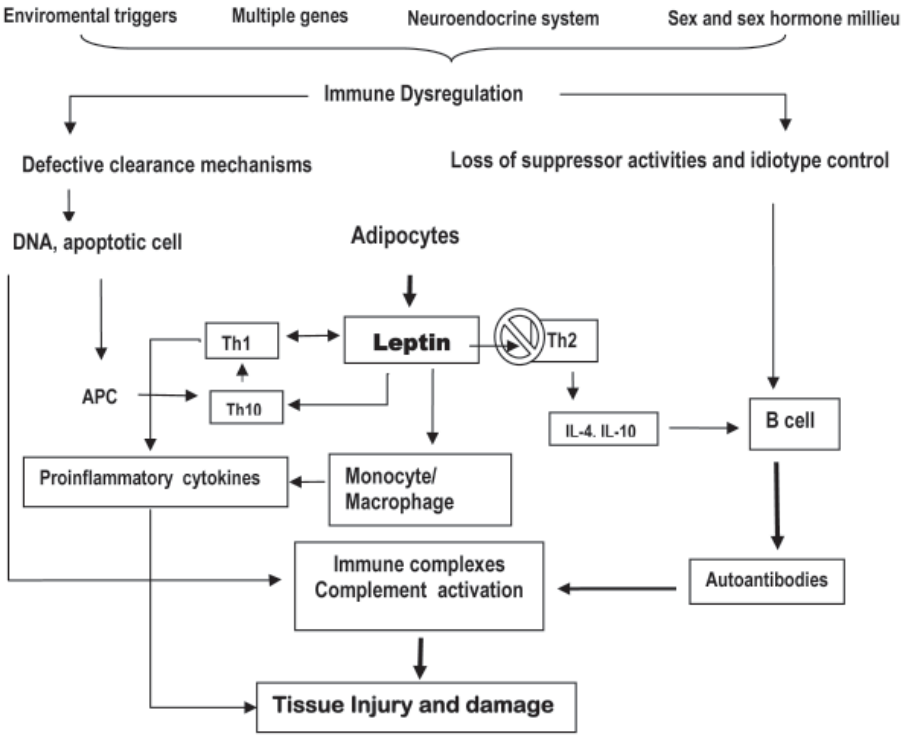

Figure 7 Hypothesis of the role of leptin in the pathogenesis of systemic lupus erythematosus (SLE). The SLE is characterized by a predominantly humoral response (Th2 type), leading to over expression of Th2 cytokines, such as IL-4 and IL-10. Th2 immune responses lead to B cell hyperactivity and the production of pathogenic autoantibodies, which finally lead to tissue injury and damage. Leptin has inhibitory effects on Th2 cells, leading to decreased production of IL-4 and IL-10 and then reduced activation of B cells and might have a protective effect on tissue injury and damage (author's opinion).

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