BIOLOGY

THE EMERGING ROLE OF ADIPOSE TISSUE-DERIVED LEPTIN IN INFLAMMATORY AND IMMUNE RESPONSES IN OBESITY: AN UPDATE

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Leptin, an adipocyte-secreted peptide, has a dual role acting as hormone in central regulation of metabolism and energy homeostasis, and as cytokine to regulate the innate and adaptive immune response in normal and pathological conditions. This review provides a synopsis of recent advances regarding the emerging role of leptin as a modulator of inflammatory and immune responses in adipose tissue in obesity. Scientific databases (Medline and PubMed) have been used to acquire the most recent and valuable reports about this issue. Recent findings indicate that leptin in adipose tissue acts to promote adipogenesis and angiogenesis processes, to enhance proliferation and production of pro-inflammatory cytokines by T-cells, macrophages and dendritic cells, and to negatively regulate the proliferation and expansion of regulatory T-cells, a specific lymphocytes subset involved in the control of immune responses. New therapeutic strategies based on developing leptin- or leptin-receptor neutralizing antibodies have been proposed as molecular tools in treating chronic inflammation and immunity response.

Key words: Leptin; Adipose tissue; Obesity; Inflammation; Immune response.

INTRODUCTION

Obesity, a heterogeneous condition arising from the interaction between genetic predisposition, environmental factors and lifestyle modification is associated with metabolic and cardiovascular disorders (CVD). Visceral adipose tissue accumulation triggers pathological events that incite metabolic and immune responses in obesity, leading to insulin resistance, Type 2 diabetes mellitus and CVD1-3.

The classical view of adipose tissue as a passive “reservoir” of free fatty acids (FFA) has been changed during last years being replaced with the concept that fat is a highly active endocrine organ, a source for hormones, growth factors, cytokines, and chemokines that regulates whole-body metabolism and immune function5. In physiological conditions in lean people, adipocytes control and maintain the balance between lipid storage and function. Chronic nutrient overload and impaired adipogenesis result in enhanced occurrence of dysfunctional hypertrophic adipocytes resistant to insulin actions, and with a pro-inflammatory secretory profile. Adipocytes and cells of stromal-vascular fraction, such as fibroblasts-like cells, preadipocytes, endothelial cells (ECs), and pericytes produce soluble mediators (adipokines) that not only influence energy homeostasis but also inflammatory-mediated immune response. Conversely, adipose tissue infiltrated immune cells secrete cytokines and chemokines that affect the activity of adipocytes. Thus, the function of adipose tissue as endocrine and immune system is dependent on the cross-talk between adipose tissue cells that is mediated either by cell-cell contact5, 6 and/or by secreted adipokines.

Leptin, an adipocytes-secreted hormone that shares structural and functional similarities with the inflammatory cytokines, may directly and indirectly contribute to initiation of immune response inside adipose tissue in overnutrition
circumstances. In this review we focus on the effects of the leptin on adipose tissue cells that mediate the pathological aspects of the inflammatory reaction and immune response in obesity, and on possible terapies that use leptin to modulate such responses.

**LEPTIN BIOLOGY AND LEPTIN SIGNALING**

*Leptin* (from the Greek *leptos*, meaning thin) is a 16 kDa non-glycosylated peptide hormone, encoded by the obese (*ob*) gene located on mouse chromosome 6 and on human chromosome 7q31.3 (*LEP* – the human homolog of the *ob* gene). The *ob*/ob or obese mouse has a recessive mutation in the *ob* gene and can not produce leptin. Mutant mice are indistinguishable from their unaffected littermates at birth, but gain weight rapidly, and become obese developing also insulin resistance and endocrine disorders. The administration of recombinant leptin to *ob*/ob mice decreases food intake and serum insulin concentration, and leads to significant body mass reduction. In humans, rare cases of *LEP* monogenic disorders have been reported in families with elevated prevalence of morbid obesity.

In chemical terms, leptin molecule possesses a tertiary structure with a four long-chain helical bundle motif; from this perspective leptin belongs to the type I cytokine family, including IL-6, IL-11, IL-12 or LIF. Leptin is predominantly expressed in adipose tissue (especially in subcutaneous depots), but it is also found at lower levels in many other tissues such as placenta, mammary gland, testes, ovary, endometrium, stomach, hypothalamus, and hypophysis. Circulating leptin levels positively correlate with body fat mass and adipocyte size, and are altered by nutritional status, i.e., falling with starvation and rising with excess calory intake. Leptin concentrations are dramatically elevated in obese subjects, who exhibit hyperleptinemia and leptin resistance. The hormone is secreted in a pulsatile fashion with significant diurnal-nocturnal variation, and has a sexual dimorphism with high levels in women. The expression of leptin can be upregulated by insulin and glucocorticoids, and pro-inflammatory cytokines while mediators of acute infection decrease the secretion of leptin from adipocytes.

Leptin exerts its effects by binding to specific receptors with a widespread tissue distribution. The leptin receptor (Ob-R) is encoded by the diabetes (*db*) gene on mouse chromosome 4, while in humans the homologous is *LEPR* gene (in chromosome 1p31). The Ob-R receptor is a single membrane-spanning protein that belongs to the class I cytokine receptor family, which also includes the gp130 subunit of the IL-6 receptor, the granulocyte-colony stimulating factor (G-CSF) and the leukemia-inhibitory factor (LIF). As a result of alternatively splicing of *db* gene, six isoforms of OB-R have been identified so far, i.e, a long isoform (OB-Rb), 4 short isoforms (OB-Ra, OB-Rc, OB-Rd, and OB-Rf), and a soluble isoform (OB-Re). Soluble Ob-Re is the secreted form of the leptin receptor that binds free leptin and regulates its concentration in circulation. All contain an identical extracellular binding domain, but only OB-Rb has an extended intracellular domain which comprises the typical structural elements of cytokine receptors. OB-Rb isoform is responsible for leptin’s key functions, including regulation of food intake and energy expenditure, neuroendocrine and immune function, and modulation of glucose and fat metabolism by improving insulin sensitivity and reducing intracellular lipids. OB-Rb is also found on immune cells, including subpopulations of T cells, B cells, dendritic cells (DC), monocytes, macrophages, neutrophils, and natural killer (NK) cells.

The leptin and leptin receptor genes have been investigated for gene variants potentially related to the pathophysiology of obesity, diabetes and its associated complications. A leptin gene polymorphism consisting in G to A substitution at nucleotide (nt) -2548 upstream of the ATG start site in the *LEP* gene promoter, *LEP* G-2548A, has been associated with adipocytes increased leptin production and secretion. Interestingly, as for *LEPR* gene polymorphism, the A to G transition in exon 6 at nt 668 from the start codon 223 (Q223R) was associated with impaired leptin-binding activity. The associations of the *LEP* G-2548A and *LEPR* Q223R gene variants with the incidence of obesity, and the potential involvement of genetic predisposition in the pathological processes linking obesity with other features of the metabolic syndrome have been analyzed in a large sample of Romanian population. The results indicated that *LEP* G-2548A and *LEPR* Q223R single nucleotide polymorphisms might not be considered as
important genetic risk factors for developing obesity in Romanian population. However, **LEP** -2548GG genotype is correlated with leptin levels, whereas the **LEPR** 223R allele predisposes healthy subjects to develop metabolic disturbances throughout their lives.

Related to the **leptin signal transduction**, it has been demonstrated that Ob-Rb associates with Janus kinase 2 (JAK2) to acquire a tyrosine kinase activity, and to initiate intracellular signaling. Upon leptin binding, Ob-Rb forms homodimers and leads to activation of STAT family transcription factors, extracellular signal-regulated kinases (ERK), phosphoinositol-3 kinase (PI3-K), and AMP-activated kinase (AMPK). After phosphorylation of membrane-distal Y1138 of Ob-Rb by JAK2, STATs are recruited via the SH2 (Src homology) domain and become substrate for JAK2 (Figure 1). Activation of STAT1, STAT3, STAT5, and STAT6 (in various cell types) regulates the expression of several genes that mediate the effects of leptin on proliferation and activation of immune cells. Phosphorylated STAT3 dimerizes, translocates to the nucleus inducing the expression of carnitine palmitoyltransferase-1 (CPT-1), acetyl CoA oxidase (ACO), PPARγ coactivator -1 (PGC-1) involved in fatty acid oxidation, and of the suppressor of cytokine signaling 3 (SOCS3). Leptin signaling may be inhibited by SOCS3 taking part in a feedback loop by binding tyrosine residues (Y985 and Y1077) in Ob-Rb receptor.

Phosphorylated JAK2 also activates PI3-K/Akt pathway via insulin receptor substrates (IRSs) (Fig. 1). The PI3-K/ Akt engage the downstream pathways involved in **glucose uptake and metabolism**, and mediates effects of various pro-inflammatory cytokines and bacterial stimuli in immune cells. By stimulating the uptake of glucose through ERK1/2 and PI3K-dependent pathways, leptin might help to restore the impaired T-cell function. Leptin activates AMPK by increasing intracellular AMP content; this, in turn, phosphorylates and inactivates acetyl CoA carboxylase (ACC) leading to reduction of malonyl-CoA formation and rescue CPT1 activity, a rate limiting step for long-chain fatty acids transport into the mitochondria and for fatty acid oxidation. Protein Tyrosine Phosphatase-1B (PTP-1B) localized on the surface of the endoplasmic reticulum is also involved in negative regulation of leptin signaling by dephosphorylation of JAK2 apparently after internalization of the leptin-Ob-Rb complex (Fig. 1).

![Fig. 1. Intracellular signaling transduction pathways triggered by leptin binding to Ob-Rb.](image)
Leptin acts as an afferent satiety signal by binding to the Ob-Rb in the arcuate nucleus of hypothalamus, thereby suppressing food intake and stimulating energy expenditure. Obese subjects are hyperleptinemic compared with lean persons, and are either tolerant or resistant to the central hypothalamic effects of leptin. Several mechanisms have been proposed to induce leptin resistance: alterations in the transport of leptin across the blood-brain barrier, decreased leptin-induced activation of STAT-3, as well as increased SOCS-3 expression—all suppressing leptin signaling. PTP-1B dephosphorylation of JAK-2, and the subsequent inhibition of leptin is another potential mechanism for leptin resistance.

LEPTIN EFFECTS ON ADIPOCYTES: FROM LIPID METABOLISM TO INFLAMMATION-MEDIATED IMMUNE RESPONSE

Under physiological conditions leptin limits lipid deposition in fat cells by different mechanisms, such as: decrease the binding of insulin to its receptor, impairs insulin signaling, reduces the metabolic actions of insulin (related to glucose uptake, glycogen synthesis, and lipogenesis) as well as the incorporation of glucose into lipids in adipocytes). Additionally, the expression of fatty acid synthase (FAS) and ACC by adipocytes has been shown to be reduced by leptin. In circumstances of overnutrition the adipose tissue secretes high concentration of leptin to store the extra-calories in adipocytes, and to prevent ectopic lipid deposition in non-adipose tissues. Leptin achieves lipid partitioning by (1) restraining the level of overnutrition, not exceeding the available adipocyte storage space, and (2) enhancing oxidation of any ectopic lipid overflow. The leptin action to promote energy dissipation has been assessed in rats by the increased glucose and fatty acids oxidation, lypolysis, and by augmented expression of ACO, CPT1, uncoupling protein-2 (UCP2), and PGC-1, an upregulator of mitochondrial biogenesis that transforms the adipocytes into “fat-oxidizing machines.” Leptin also function in reversing preadipocytes differentiation. High locally adipose tissue concentration of leptin observed in human obesity and in animal models of obesity can not prevent the excessive lipid storage in adipocytes. The possible suppressive mechanism that impairs leptin autocrine and paracrine action in fat tissue is related to SOCS-1 and 3 proteins that blocks STAT-3 phosphorylation induced by leptin. Leptin resistance increases adiposity, dyslipidemia, and insulin resistance suggesting that this peptide hormone may be the molecular link between obesity and type 2 diabetes.

Although the role of leptin in metabolic pathways is well documented, little is understood about its role in inflammation. Leptin could represent a key player bridging adiposity-to-inflammation in obesity.

Free fatty acids (FFA) released by hypertrophied adipocytes have an essential role in initiation of the inflammatory-mediated immune response. FFA bind to Toll-like receptors (TLRs), a family of membrane-spanning receptors known to activate JNK and NF-KB signaling pathways, and to initiate the inflammation processes. TLRs are mostly expressed on macrophages, and also on pre-adipocytes and mature adipocytes. The activation of TLRs (mostly TLR4) in adipocytes results in the synthesis of pro-inflammatory factors, such as TNF-α or IL-6, and of chemokines such as MCP-1, CCL5 or CCL11. When murine preadipocytes cell line, 3T3-L1, expressing TLR4 were treated with LPS, an increased TNF-α secretion and up-regulation of TLR2 protein expression was observed. Interestingly, mouse adipocytes “activated” by leptin express TLR1 to TLR9 together with higher inflammatory cytokine production upon stimulation with leptin. Moreover, adipocytes isolated from diet-induced obese (DIO) mice or genetically obese animals (ob/ob or db/db mice) exhibited increased TLRs expression together with higher inflammatory cytokine production upon stimulation with leptin. Recently, the presence of functional TLR2 and TLR4 was reported on human adipocytes isolated from subcutaneous fat tissue.

Taken together, the expression of functional TLRs on adipocytes classifies adipose tissue as a new member of innate immune system that is able to respond specifically to microbial or physical insults.

LEPTIN EFFECTS ON INNATE AND ADAPTATIVE IMMUNE CELLS IN ADIPOSE TISSUE

First evidences on leptin role in immunity come from the observations that ob/ob mice have an impaired immune response during starvation, and
the db/db obese mice suffer from thymus atrophy. Moreover, it has been shown that fat from DIO mice contains an increased number of macrophages than adipose tissue of mice fed a normal diet. In humans, it has been found that leptin levels in overnutrition or starvation periods contribute to inflammatory and immune response, and variation in circulating leptin levels influence the behaviour of immune cells.

In innate immunity, leptin can stimulate macrophages, monocytes, dendritic cells, neutrophils and natural killer cells. Accumulation of adipose tissue macrophages (ATMs) has been well-described in obese mice and humans. Reportedly, infiltrating ATMs localize around dying adipocytes, and aggregate in ‘crown-like structures’ that envelope and ingest the large dead adipocytes. The ATM number and phenotype is changing during the development of obesity in mice fed with high-fat diet. The ATMs shift from a reparative resident phenotype (“alternatively activated” macrophages AAMs, or M2) in lean animals to inflammatory (“classically activated” macrophages, or M1) newly recruited ATM in obesity. In humans, ATMs possess a proliferative capacity associated with a pro-angiogenic phenotype - the hallmark of cells involved in chronic inflammation. M1-macrophages induced by mediators such as LPS and IFN-γ secrete high levels of pro-inflammatory cytokines (TNF-α, IL-6, IL-12), and oxidative stress-mediated chemokines (such as MCP-1) - all being involved in the development of insulin resistance. M2 macrophages secrete low levels of pro-inflammatory cytokines and high levels of anti-inflammatory cytokines (II-10, IL-17). Recent evidence shows that the majority of the ATMs accumulated in obese adipose tissue are pro-inflammatory, expressing the cell surface markers F4/80, CD11b, CD11c, and are M1-like. Interestingly, ATMs which display F4/80 and CD11b, but not express the cell surface marker CD11c, do not exhibit inflammatory pathway activation, and are M2-like. When activates macrophages, leptin increases lipoprotein lipase expression through oxidative stress- and PKC-dependent pathways, and induces them to produce eicosanoids, nitric oxide, leukotriene B4, cholesterol acyltransferases-1, and cyclooxygenase 2, as well as other pro-inflammatory cytokines.

In human monocytes leptin stimulates in vitro proliferation and activation of monocytes, promoting the expression of CD69, CD25, CD38, and CD71, in addition to increasing the expression of monocytes surface markers, such as HLA-DR, CD11b, and CD11c. Leptin induces also the secretion of IL-1 receptor antagonist and upregulates interferon-gamma-inducible protein (IP-10). Moreover, leptin was shown to stimulate the oxidative stress in monocytes.

Leptin acting on dendritic cells (DCs) in fat induces differentiation, maturation, and survival of these cells. Leptin important action on DC is to induce the expression of CD40 and to up-regulate their immunostimulatory function in driving T cell proliferation. Markers of activation such as CD1a, CD80, CD83, or CD86 were identified on the leptin-treated DCs which presented an increased secretion of pro-inflammatory cytokines IL-8, IL-12, IL-6, and TNF-α, whereas MIP-1-α production was decreased. In db/db mice, dysfunctional signaling on the PI3K/Akt pathway, as well as STAT-3 and IκBα, markedly reduces expression of co-stimulatory molecules, and lower the Th2-type cytokine profile, diminishing the capacity to stimulate allogenic T cell proliferation. Moreover, the reduced number of DCs in db/db bone marrow in culture was attributed to significantly increased apoptosis, which was associated with dysregulated expression of Bcl-2 family genes.

Leptin stimulates chemotaxis of neutrophils through an indirect mechanism: it activates blood monocytes to secrete TNF-α, that in turn act on neutrophils to express CD11b. Infiltration of neutrophils in adipose tissue was mediated by CD11b and ICAM1 expressed on endothelial cells and on adipocytes. In addition, leptin protects neutrophils from apoptosis by delaying cleavage of Bid and Bax, the mitochondrial release of cytochrome c, and the activation of caspases. Interesting results were obtained when leptin stimulated in vitro neutrophil chemotaxis without increasing intracellular [Ca^{2+}] levels and without activating oxidative metabolism or granule exocytosis. Moreover, leptin inhibits action of two classical chemoattractants, on neutrophils such as IL-8 and C5a.

Leptin promotes natural killer (NK) cell proliferation, differentiation, activation, and cytotoxicity. Very recently, it has been showed
that a subset of NK cells, NKT cells (innate-like T lymphocytes that recognize glycolipid antigens and are capable of rapidly producing a mixture of T-helper type 1 (T_H1) and T_H2 cytokines), play a crucial role in the development of adipose tissue inflammation in diet-induced obesity. Thus, NKT cells can act as a bridge between the innate and adaptive immune systems72.

Recently, a study on DIO mice has supported the hypothesis that T lymphocytes come first at site of inflammation since presence of these cells is associated with insulin resistance in fat before accumulation of macrophages73. Adipose tissue contains many T cells, among these the CD8+ fraction increases during the progression of obesity74, while the CD4+ and regulatory T cell (T_reg) fractions are diminished. The CD4+ effector T cells (T helper type 2 (T_H2) cells) and T_reg cells found in human adipose tissue75 restrict, in part, inflammatory responses via production of the anti-inflammatory cytokine IL-10. It seems that a strong cell – to – cell contact of adipocytes / preadipocytes with lymphocytes represents an immunomodulatory mechanism in which: (i) CD8+ T cells are inhibited in their responsiveness to pro-inflammatory stimuli, and (ii) reactive CD4+ T cells are depleted from the immune response6.

Leptin has either proliferative effects in naïve T cells, or anti-proliferative effects on memory T cells76. Leptin promotes T cell activation and shifts the T-cell cytokine production towards a T_H1 response, increasing the production of interferon (IFN)-γ and IL-2, and suppressing the expression of IL-4 by T_H2 cells77,78. Apoptosis of T cells that normally accompanies fasting is prevented by leptin through up-regulation of anti-apoptotic protein bcl-xL79. Moreover, T cells and adipocytes within obese adipose tissue express high levels of the chemokine CCL5/“Regulated on Activation, Normal T-cell Expressed and Secreted” (RANTES) and of its receptor CCR5 capable to induce activation and migration of monocytes/macrophages, and differentiation of macrophages80. Immunological or genetic depletion of CD8+ T cells in DIO mice and ob/ob mice reduced macrophage infiltration and inflammatory cytokine expression in adipose tissue, and ameliorated systemic insulin resistance. The vicious cycle involving T cells, macrophages, and adipocytes in obese adipose tissue propagates local inflammation.

LEPTIN – A KEY PLAYER IN THE ANGIogenic PROCESS INSIDE ADIPOSE TISSUE

Visceral adipose tissue enlargement in obesity has been characterized by an increased presence of hypertrophic adipocytes, occurrence of localized hypoxia, and augmented angiogenic/ adipogenic responses81,82. Inflammation and angiogenesis are two processes that have long been coupled in many chronic disorders, and are triggered by the same molecular events, further strengthening their association. The endothelial cells in angiogenic vessels produce various growth factors and cytokines that promote, in a paracrine fashion, adipocytes’ growth and expansion82. Vascular pericytes behind endothelial layer in newly formed capillaries can differentiate into preadipocytes and adipocytes, thus supporting adipogenesis82. In adipose tissue, the fenestrated microvessels might play an essential role in local and systemic effects of adipokines. Hypoxia in adipose tissue induces high levels of hypoxia-inducible transcription factors 1 (HIFs), which increases the expression of angiogenesis-related factors (including vascular endothelial growth factor A (VEGF-A), leptin, TNF-α, IL-6, IL-8, and chemokines), and downregulates endogenous inhibitors of angiogenesis59,83. Intricate interplay between endothelial cells and adipocytes suggests that dysfunction of either compartment would have a substantial impact on the adipose tissue function.

The effects of leptin on angiogenic process (studied by cornea pocket and chorioallantoic membrane assays CAM)84 are mediated by FGF-285,86. Leptin influences the endothelial cells migration, proliferation, survival, and apoptosis, and stimulates the endothelial expression of matrix metalloproteinases (MMPs)86. On the other hand, leptin increases smooth muscle cell proliferation and migration that benefit the stabilization of newly shaped vessels88. Leptin may also potentiate VEGF-mediated angiogenesis, being able to stimulate endothelial VEGF secretion in a dose-dependent manner89. Similarly to VEGF-A, leptin induces formation of fenestrated capillaries, as confirmed by the lack of fenestrations in leptin deficient ob/ob mice89. In adipose tissue, enhanced expression of adhesion molecules and chemokines in endothelial cells together with increased permeability of newly formed microvasculature promote infiltration of immune cells, contributing to insulin resistance. From then on, a vicious cycle
The emerging role of adipose tissue-derived leptin exacerbate disturbances leading to an inflammatory-mediated immune in adipose tissue in obesity.

The functional influences of leptin in the physiopathology of both chronic inflammation and angiogenesis in adipose tissue are summarized in Figure 2.

**FUTURE DIRECTIONS: LEPTIN AS NEW POTENTIAL THERAPEUTIC TARGET**

Because of its dual role, leptin could represent an attractive therapeutic target for pharmacology of pathologies associated with chronic inflammation in obesity. Moreover, data from clinical trials using leptin as a therapeutic approach for weight reduction of obese persons were disappointing. The poor clinical efficacy of leptin in clinical studies might result from its short circulating half-life, low potency and poor solubility, demanding large and frequent doses to obtain modest clinical benefit.

Taking into account the detrimental effect of hyperleptinemia or leptin resistance on immune cells, the current efforts are directed to control the amount of bioavailable leptin by using a specific soluble receptor. Thus, three approaches have been employed to antagonize leptin activity: (1) binding free leptin in the circulation, (2) competitive Ob-R binding by mutants of leptin protein that do not cause signaling activation, and (3) specific anti–Ob-R monoclonal antibodies.

Alternatively, other targets could be found among molecules involved in the signaling pathways activated by leptin. SOCS3 is an important factor of leptin resistance and negative feedback, and increasing interest is focused on elucidating the mechanisms of how SOCS3 could contributes to the development of obesity and diabetes. PTP1B dephosphorylates JAK2 on leptin receptor and is an effective target for the treatment of both type 2 diabetes and obesity. Shp2 downregulates the STAT3 pathway while promoting ERK activation, and has a critical role in leptin signaling.

Fig. 2. Schematic overview of cells and factors involved in the inflammatory and immune response initiated by leptin in adipose tissue.
The recent proposal of nanobodies (an unique form of antibodies that is characterized by a single antigen-binding domain and generally does not cross the blood–brain barrier) may lead to an antagonist that could selectively inhibit peripheral activities of leptin. These forms of leptin antagonist might be clinically useful, as they can target peripheral adverse effect of leptin without inducing central weight gain.

Further insights into the cellular and molecular mechanisms regulating central and peripheral activities of the leptin and other adipokines might be of great advantage for therapeutic approaches of obesity-induced inflammatory diseases.

CONCLUSION

There is increasing evidence that leptin, besides its central effects on food intake and energy expenditure, is involved (per se or by synergistic action with other cytokines) in the pathogenesis of inflammatory and immune diseases. Recently reported data on leptin signaling deficiency that impairs innate and adaptive immune responses and attenuates inflammatory processes, support the notion that a strategy focused on blocking leptin activity might have therapeutic benefits to combat the metabolic and cardiovascular complications of obesity.

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