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Leptin in inflammation and autoimmunity

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Abstract

After its discovery as a key controller of metabolic function, leptin has been later extensively implicated in additional function including important modulatory activities on the innate and adaptive immune responses. This review analyzes the known implications of leptin in multiple inflammatory conditions, including autoimmune diseases, and how this knowledge could be instrumental in the design of leptin-based manipulation strategies to help restoration of abnormal immune responses.

Keywords

Leptin; inflammation; autoimmunity

1. Introduction

Leptin is a 16 kDa non-glycosylated protein that is mainly produced by adipocytes, for which reason it belongs to the group of cytokines that are commonly called adipocytokines or adipokines [1]. Leptin has a dual role as a hormone and a cytokine. As hormone, it influences multiple endocrine functions and bone metabolism, in addition to the key function of modulating energy homeostasis through mechanisms that include thermoregulation. As a cytokine, leptin promotes inflammatory responses. It derives that elevated levels of circulating leptin in obese patients contribute significantly to the low-grade inflammatory state that makes those individuals more susceptible to develop cardiovascular diseases, type II diabetes, or degenerative disease [2], in addition to autoimmune disease [3]. Conversely, reduced levels of leptin such as those found in malnourished individuals have been linked to increased risk of infection and reduced cell-mediated immunity [3], likely secondarily to an insufficient immune cell effector activity that cannot allow a proper control of pathogens (possibly concomitantly with an enhanced function of $CD4^+$ regulatory T cells (Tregs) that suppress effector immune responses) [4]. These data point to the fact that leptin, together with its role in the regulation of food intake and energy expenditure [5], also exerts a strong proinflammatory activity likely linked to its resemblance to IL-6 [6].

Leptin-deficient (*ob/ob*) and leptin receptor-deficient (*db/db*) mice not only have metabolic abnormalities and morbid obesity but also a series of marked abnormalities in neuroendocrine functions, angiogenesis, reproduction, insulin secretion, wound healing, hematopoiesis and lymphopoiesis, suggesting an involvement of leptin in the regulation of multiple important physiologic functions [7]. In addition to those disturbances, genetic deficiency in the leptin axis in both mice and humans associates with thymus atrophy and immune deficiency, in addition to an increased susceptibility to opportunistic infection [8–9]. Importantly, the impaired T-cell proliferation, reduced number of circulating $CD4^+$ T cells (particularly naïve T cells) and impaired cytokine production (lack of IFN-γ secretion and reduced IL-4 and IL-10 production) present in leptin-deficient subjects can all be reversed by the administration of recombinant leptin, demonstrating an important role of leptin on the physiology of the immune response [7].

2. Immune effects of leptin

Innate immune responses and inflammation are interwoven processes. As a first line of defense against infection, innate immunity operates to fight against pathogens to which it had no prior exposure. However, this limited lack of specificity in the effector immune response can lead to the production of inflammatory mediators that may harm the host, particularly if the response is prolonged or insufficiently controlled by the host's homeostatic mechanisms. The activation of innate immune cells including polymorphonuclear leukocytes (PMN) such as neutrophils, eosinophils, and basophils induced by proinflammatory insults favors the migration of these cells towards chemotactic stimuli produced at sites of inflammation. Once there, these cells produce powerful local mediators that cause harm to the pathogen but at the meantime can damage the host tissue. Together with the soluble mediators released by innate immune cells, macrophage phagocytosis, and dendritic cell (DC) presentation of antigens derived from the pathogen, adaptive immune responses ensue, with the recruitment of B and T lymphocytes. It derives that longer timeframes are required to mount an adaptive immune response (yet characterized by higher specificity and great efficacy also for the possibility to generate long-lasting immune responses available in case of subsequent encounters with the same pathogen). Interestingly, leptin provides a contribution to both the innate and adaptive immune response. Specifically, in monocytes/macrophages, leptin stimulates the expression of CD39, CD69, CD25, CD71 and IL-1Rα [10], and the production of proinflammatory cytokines IL-6 and TNF-α [11]. Moreover, it favors proliferation, phagocytosis through phospholipase activation [10], and the production of eicosanoids, nitric oxide, leukotriene B4 (LTB4) and cyclooxygenase 2 (COX-2) from these cells [12–13]. In neutrophils, leptin promotes chemotaxis and the release of reactive oxygen species [14]. It also protects neutrophils from apoptosis involving PI3K- and MAPK-dependent pathways, delays cleavage of Bid and Bax and mitochondrial release of cytochrome c and the activation of caspases [15], and upregulates the expression of several adhesion molecules and chemotaxis induced by the eosinophil chemoattractant RANTES [16].

In NK cells, leptin contributes to cell development, proliferation and cytotoxicity (this last function occurs via an upregulation of IL-2 and perforin expression through activation of STAT3) [17]. In DC, leptin promotes maturation and survival [18].

In general, leptin has proinflammatory properties and activities similar to other acute phase reactants, and upregulates the secretion of multiple inflammatory cytokines including TNF-α, IL-6, and IL-12 [6]. Moreover, after exposure to inflammatory stimuli such as LPS, TNF-α, and IL-1, the levels of circulating leptin and leptin expression in the adipose tissue increase [19–20]. Conversely, TNF-α and IL-1β increase the expression of leptin mRNA in the adipose tissue, creating a loop whose components influence each other in promoting inflammation [20]. Thus, proinflammatory mediators such as TNF-α and IL-1 - which upregulate leptin expression – can in turn contribute to the production of acute phase reactants that influence each other in promoting chronic inflammation, underscoring leptin's promoting effect on low-grade inflammation.

As mentioned before and as shown in Fig. 1, leptin affects both innate and adaptive immunity. In the adaptive immune response, leptin promotes T cell survival [21] by modulating the expression of anti-apoptotic proteins [22], partly explaining the reduced T cell numbers during fasting, where a significant drop in circulating leptin levels is observed [23].

While leptin enhances the proliferation and activation of T cells, it is noteworthy that it can exert differential effects on proliferation of naïve vs memory T cells or T effector cells (Teffs) vs. Tregs [24–25]. Specifically, leptin promotes naïve T cell survival and the production of IFN-γ and IL-2, and facilitates the differentiation and activity of Th1 cells while inhibiting Th2 cells [26]. It also promotes IgG2a switch and inhibits IgG_1 switch in B cells [6]. The activity of leptin on T cells also extends to proinflammatory Th17 cells, in which it promotes the expression of the master regulator transcription factor RAR-related orphan receptor **(**ROR)γt and leptin neutralization inhibits Th17 responses [27]. At the meantime, leptin represents a negative signal for the expansion of Tregs [24]. Leptin neutralization causes Tregs to proliferate and better suppress autoimmune responses, both in vitro and in vivo [24]. It is therefore expected that *ob/ob* and *db/db* mice display elevated numbers of Tregs [24].

Of note, freshly isolated Tregs produce leptin and express the leptin receptor, which is also expressed on additional immune cell subsets [28]. At the molecular level, leptin activates the mTOR pathway to control Tregs responsiveness [29] and Teffs functions [30]. More specifically, leptin inhibits rapamycin-induced proliferation of Tregs by increasing activation of the mTOR pathway [29]. Interestingly, leptin exerts opposite effects on Teffs, where it enhances their proliferation also through modulation of the mTOR pathway [30].

2.1 Leptin signaling in immune cells

Leptin receptor expression on multiple immune cell types makes the activity of leptin influential on different immune functions both in mice [31] and in humans [32]. The pleiotropic biological effects of leptin can be explained by the wide distribution of leptin receptors on different types of cells, not last those ones found in non-neural tissues and that take part in the immune response. In this context, the study of the biochemical events that follow the binding of leptin to its cognate receptors have been studied extensively and have been well characterized. Leptin receptors are class I cytokine receptors encoded by the *db* gene that vary in length due to alternative splicing. In mice, there are six different isoforms

that share a common extracellular and transmembrane domain, but differ in the length of their intracellular domain. They have characteristic extracellular motifs of four cysteine residues and contain the aminoacid sequence WSXWS (Trp-Ser-Xaa-Trp-Ser) and fibronectin type III domains [33]. Leptin receptors include a soluble form (Ob-Re), four short forms (Ob-Ra, Ob-Rc, Ob-Rd and Ob-Rf) and one long isoform (Ob-Rb) [34]. All have a common extracellular domain of more than 800 amino acids, a transmembrane domain of 34 amino acids, and a variable intracellular domain characteristic of each isoform. The main differences are in the intracellular amino acids: 302 for OB-Rb, and 34, 32 and 40, respectively, for the short forms OB-Ra, OB-Rc and OB-Rd. Signaling through Ob-Rb is considered the most important in conveying leptin effects, as this long isoform has the longest intracellular domain with 302 amino acids and is the only isoform containing functional Janus kinase (Jak)2 and signal transducers and activators of transcription (STAT) binding sites which are essential for signal transduction and transmission of leptin function [28]. On the other hand, the lack of cytoplasmic (short forms) or transmembrane components (soluble receptor) results in receptors that contribute to the regulation of plasma leptin levels by binding leptin without transducing intracellular signals [35]. From a biochemical standpoint, Ob-R does not have an intrinsic tyrosine kinase domain but a proline-rich box 1 motif that can bind Jak2. Leptin binding to Ob-Rb causes homo-oligomerization and binding to Jak which leads to autophosphorylation of Jak2 and the phosphorylation of intracellular Tyr985, Tyr1077, and Tyr1138 [36–37]. The phosphorylation of Tyr1138 is important for the recruitment of STAT proteins to the Ob-Rb/Jak2 complex, leading to transcription activation of target genes including the suppressor of cytokine signaling (SOCS)3 [38–42]. In addition to SOCS3, protein tyrosine phosphatase 1B (PTP1B) inhibits leptin-mediated signaling and acts by dephosphorylating Jak2 [43], whereas phosphorylated Jak2 activates the mitogen-activated protein kinase (MAPK) cascade via recruitment of src homology 2-containing tyrosine phosphatase (SHP2) to OB-Rb, which binds to GRB2 to signal through RAS, RAF and MEK1 for the activation of extracellular signal-regulated kinase (ERK)1/2, p38 MAPK and p42/44 pathways [37, 44–46]. An alternative pathway involves the interaction of SHP2 and GRB2 on Jak2 [47–48]. In any case, autophosphorylated Jak2 can phosphorylate insulin receptor substrate1/2 (IRS1/2) and activate phosphatidylinositol 3-kinase (PI3K)/Akt [49].

In humans, four splice variants of leptin receptor have been identified: a long OB-R isoform and three short isoforms designed huB219.1–huB219.3 [50]. Of those, the long isoform responsible for the anorexigenic effects of leptin is abundant in the hypothalamic centers regulating food intake and can also be found on immune cells [51–53], being capable to stimulate proliferation of peripheral blood mononuclear cells [54].

3. Leptin in non-autoimmune inflammation

Alone or in combination with IL-1, leptin promotes the expression of inducible nitric oxide (NO) synthase (iNOS) and COX-2 and the production of NO, prostaglandin E, IL-6, and IL-8. The effects of leptin are mediated through activation of the transcription factor nuclear factor-κB (NF-κB) and c-Jun NH_2-terminal protein kinase (JNK) (with subsequent phospholipase C (PLC) and protein kinase C (PKC) activation), having NO as a key mediator of the increased synthesis of those proinflammatory mediators [55–56]. These

events are responsible for leptin's stimulation of oxidative stress, and at the cardiovascular level they result in vascular inflammation and vascular smooth muscle hypertrophy – all factors that contribute to atherosclerosis, hypertension, coronary heart disease and thrombosis [57]. In other system, these events produce as well proinflammatory states that are discussed below.

3.1. Leptin and atherosclerosis

Leptin can contribute to atherogenesis [58–59] by promoting the recruitment of monocytes to the intima, eliciting foam cell formation, and favoring secretion of proinflammatory and atherogenic cytokines [60–61], in addition to altering cardiomyocyte structure and function [62]. This is because leptin receptors are present within lesions of atherosclerosis patients [63], and in fact; eptin-deficient *ob/ob* mice are resistant to atherosclerosis [64]. Also, low-density lipoprotein (LDL) receptor-deficient *ob/ob* (LDL-$R^{-/-/ob/ob}$) mice show a considerable reduction in atherosclerotic lesions as compared to LDL-$R^{-/-}$ mice with intact leptin signaling [65]. Leptin levels are also positively correlated with levels of fibrinogen, plasminogen activator inhibitor-1, von Willebrand factor, and factor VIIa, and negatively correlated with protein C and tissue plasminogen activator, thus affecting fibrinolysis and favoring arterial thrombosis [66–70].

3.2. Leptin and type 2 diabetes

Since leptin modulates glucose homeostasis and inhibits insulin synthesis and secretion, the development of type 2 diabetes in *ob/ob* and *db/db* mice is dramatically attenuated by leptin administration [71–72]. In addition to decreasing insulin secretion via a direct action on the pancreatic β cells, leptin also enhances glucose uptake and oxidation in skeletal muscle and suppresses the hepatic production of glucose [73–75]. At the molecular level, leptin signals in pancreatic β cells through Jak-STAT and interferes with cAMP and the activation of PI3 kinase [76]. A role of leptin in diabetic nephropathy is as well suggested by the observation that leptin deficient *ob/ob* mice are relatively resistant to the development of diabetic glomerulopathy, and by the finding leptin levels are increased in albuminuric type 2 diabetes patients (where urinary leptin positively correlates with urinary albumin-creatinine ratio and inversely correlate with glomerular filtration rate) [77].

In the metabolic syndrome - a combination of abdominal obesity, high blood pressure, high blood glucose, low HDL, elevated cholesterol and high triglycerides that increase the risk of heart disease and diabetes, high leptin levels predict disease worsening independently of obesity [78]. Those patients may also be affected by non-alcoholic steatohepatitis (a liver disease characterized by fat accumulation in hepatocytes), where leptin could contribute to fat accumulation through a reduced hepatic oxidation and an increased synthesis of free fatty acids that would cause liver inflammation and fibrosis through local lipid accumulation and peroxidation [79–81].

3.3. Renal inflammation

Leptin is mainly cleared by the kidney [82], which is an organ targeted by leptin activities [83]. Indeed, leptin-deficient *ob/ob* mice are protected from renal inflammation and nephrotoxic nephritis [84].

The direct and indirect effects of leptin on the kidney include natriuresis, increased sympathetic nervous activity, and the stimulation of reactive oxygen species [85]. Moreover, leptin is involved in the development of glomerulosclerosis through a paracrine TGF-β pathway (between glomerular endothelial and mesangial cells) that promotes deposition of extracellular matrix and proteinuria [86].

3.4. Chronic obstructive pulmonary disease (COPD)

Among the inflammatory conditions characterized by a strong tendency to chronicity, leptin has been considered an inflammatory marker of airway inflammation and a possible contributor to severity of COPD, a chronic inflammatory disease of the lung [87].

3.5. Behçet's disease

Also in Behçet's disease (a chronic, systemic inflammatory disorder with generalized vasculitis), the levels of serum leptin are increased, particularly in patients with long disease duration, where they correlate with disease activity [88].

3.6. Pelvic endometriosis

Leptin elevation in the peritoneal fluid of patients with endometriosis positively correlates with the clinical stage of the disease [89–90], although no differences are found in serum leptin concentration of endometriosis patients and controls [91]. Leptin's contribution to pelvic endometriosis could be related to the ability of leptin to promote neoangiogenesis and the production of proinflammatory cytokines [92].

3.7. Leptin and cancer

Given the immunomodulatory properties of leptin, considerations have been made on the possibility that leptin could influence tumorigenesis, particularly in hepatocellular carcinoma and prostate cancer [93]. The idea is that leptin might facilitate cancer cell progression by promoting inflammation, together with cell proliferation and migration while inhibiting apoptosis. Additionally, tumors and metastasis depend on angiogenesis, and leptin influences angiogenesis significantly [6]. However, insufficient information is currently available to draw conclusions, and further research and longitudinal studies are required to delineate both specific and additive effects of leptin in cancer [94].

3.8. Leptin and infection

In the course of acute inflammation, infection and sepsis, leptin levels increase favored by the presence of bacterial lipopolysaccharide and the increase in cytokines such as TNF-α, IL-6, and IL-1β [95]. In humans, plasma leptin is elevated in septic patients and positively correlates with patients' survival [96–97]. However, in some acute inflammatory conditions such as acute experimental endotoxemia and newborn sepsis, no increased levels of serum leptin are found [98–99].

In tuberculosis and pediatric HIV patients, leptinemia is reduced [100–101], and in HIV infection, highly active anti-retroviral therapy (HAART) associates with increased leptinemia, together with the amelioration of the clinical picture and improvement of $CD4^+$ T cell counts [102].

In bacterial infection, leptin proinflammatory activities (through TNF-α and IL-6 induction) seem to contribute to pathogens clearance. Leptin-deficient *ob/ob* mice develop severe disease and die of *Klebsiella* infection more rapidly than wild-type mice, and their elevated susceptibility to LPS-induced lethality can be reversed by leptin administration [103–107].

4. Leptin and autoimmunity

Elevated levels of circulating leptin have been associated with multiple autoimmune diseases, both in humans and in animal models of human autoimmunity [108], as discussed below.

4.1. Leptin and type-1 diabetes (T1D)

Leptin accelerates T1D onset and progression in nonobese diabetic (NOD) mice by stimulating autoimmune destruction of β-cells and by increasing IFN-γ production [109]. Also, a spontaneous mutation of ObR ($LepR^{db5J}$) in T1D-prone NOD mice inhibits T1D development [110]. Moreover, in *ob/ob* diabetic rats, systemic administration of leptin reversed ketoacidosis and normalizes blood glucose concentration by decreasing the delivery of glycerol and fatty acids to the liver, also reducing availability of acetyl-CoA (an inhibitor of the conversion of pyruvate to glucose) [111]. Although these data suggest a promoting role of leptin in T1D, also suggested by the finding of elevated circulating levels of leptin in T1D patients [112], recent data indicated that leptin treatment could reverse hyperglycemia in animal models of poorly controlled T1D (possibly through the suppression of glucagon production and/or responsiveness to this hormone) [111].

4.2. Leptin and multiple sclerosis

Leptin deficient *ob/ob* mice and leptin receptor-deficient *db/db* mice are resistant to the development of several experimentally-induced autoimmune diseases [6], among which experimental autoimmune encephalomyelitis (EAE) [113] – an animal model of human multiple sclerosis (MS). Resistance to EAE is reversed by leptin replacement while administration of leptin worsens EAE, indicating a key role of this adipokine in the disease susceptibility [113]. Furthermore, leptin neutralization improved clinical score and delayed EAE progression [114]. In MS patients, leptin production is increased in both serum and cerebrospinal fluid, and inversely correlates with the numbers of circulating Tregs [115].

4.3 Leptin and inflammatory bowel disease (IBD)

Although experimental colitis in rats resulted in increased leptin levels in association with weight loss [116], and *ob/ob* mice displayed resistance to acute and chronic intestinal inflammation [117], conflicting data and insufficient clinical studies may not allow at present to draw unequivocal conclusions on a possible role of leptin in IBD.

4.4 Leptin and autoimmune arthritis

ob/ob and *db/db* mice develop a milder form of antigen-induced arthritis than wild-type controls, and have markedly reduced antigen-specific autoreactive T cell proliferation and proinflammatory cytokine production [118]. In chondrocytes, leptin induces NOS activation,

in synergy with IFN-γ and IL-1 [119], in addition to metalloproteases activation, apoptosis, and chondrocyte phenotype loss [120].

However, the role of leptin in the pathogenesis of rheumatoid arthritis (RA) is controversial. High levels of leptin both systemically and in the joints have been reported by some authors - also correlating with disease activity [121] - but other studies found no changes or even low levels of leptin and no correlations with disease biomarkers or activity scores [122].

4.5 Leptin and systemic lupus erythematosus

Leptin increase in SLE does not correlate with disease activity but it can contribute to elevated cardiovascular risk [123] by inducing proinflammatory high-density lipoproteins and atherosclerosis [124]. The propathogenic effects of leptin in SLE can be ascribed, at last in part, to its promoting activities on proinflammatory Th17 cells [27] and the facilitated autoantibody production that is concomitant to the inhibition of immunoregulatory responses [125]. Other mechanisms include leptin's promotion of the activity and survival of autoreactive T cell via an increased expression of the anti-apoptotic molecule Bcl-2 [126–127]. Notably, leptin neutralization in lupus-prone mice inhibits proinflammatory responses and SLE manifestations [27, 125]. Similarly, a reduction in circulating leptin levels induced by fasting protects lupus mice from SLE via mechanisms that include an expansion of peripheral Tregs [128].

4.6. Leptin in psoriasis

Although an increase in leptin in psoriasis patients seems to parallel the severity of the disease, the data on a promoting role of leptin in the disease remain controversial [129–130].

5. Conclusions

Given the contribution of the proinflammatory activity of leptin to autoimmune and non-autoimmune inflammation, it has been suggested to limit leptin bioavailability in those conditions through antibody-based antagonism [3]. In non-autoimmune inflammatory conditions such cardiovascular and metabolic diseases, leptin inhibition could negatively influence the development and progression of the disease, whereas in autoimmunity it could reduce immune hyperactivity and slow the progression of chronic inflammation leading to target tissue damage.

It has nonetheless to be taken into account that lowered leptin levels could negatively affect effector immune responses during infection, and thus targeted approaches considering selective targeting of the leptin pathway might be considered to reduce this possibility. For example, useful leptin-based targets could be SOCS3 (an important factor of leptin resistance and negative feedback), PTP1B (which dephosphorylates Jak2 on OB-R), and SHP2 (which is critical for leptin signaling through downregulation of the ObRb-STAT3 pathway and the promotion of ERK signaling) [131–132].

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Highlights

- The cytokine activity of leptin is responsible for effects of this adipokine on both innate and adaptive immune responses
- Because of its pro-inflammatory actions, leptin contributes to the generation and maintenance of low-grade inflammation
- Leptin levels are elevated in multiple autoimmune diseases, and leptin blockade in experimental animal models has proven as beneficial in reducing autoimmune reactivity

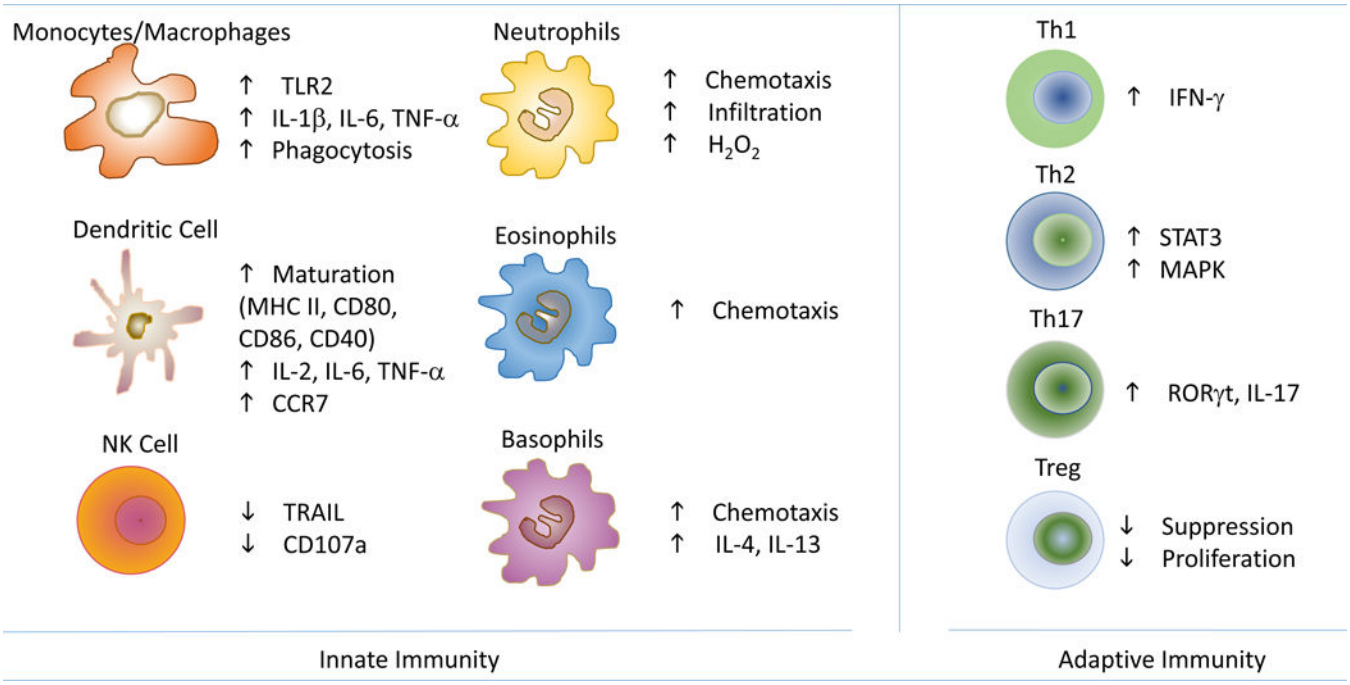

Figure 1.
Schematic representation of the multiple effects of leptin on different types of immune cells of the innate and adaptive immune systems.