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Leptin-based Adjuvants: An Innovative Approach to Improve Vaccine Response

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Abstract

Leptin is a pleiotropic hormone with multiple direct and regulatory immune functions. Leptin deficiency or resistance hinders the immunologic, metabolic, and neuroendocrinologic processes necessary to thwart infections and their associated complications, and to possibly protect against infectious diseases following vaccination. Circulating leptin levels are proportional to body fat mass. High circulating leptin concentrations, as observed in obesity, are indicative of the development of leptin transport saturation/signaling desensitization. Leptin bridges nutritional status and immunity. Although its role in vaccine response is currently unknown, over-nutrition has been shown to suppress vaccine-induced immune responses. For instance, obesity (BMI ≥ 30 kg/m²) is associated with lower antigen-specific antibody titers following influenza, hepatitis B, and tetanus vaccinations. This suggests that obesity, and possibly saturable leptin levels, are contributing factors to poor vaccine immunogenicity. While leptin-based therapies have not been investigated as vaccine adjuvants thus far, leptin's role in immunity suggests that application of these therapies is promising and worth investigation to enhance vaccine response in people with leptin signaling impairments. This review will examine the possibility of using leptin as a vaccine adjuvant by: briefly reviewing the distribution and signal transduction of leptin and its receptors; discussing the physiology of leptin with emphasis on its immune functions; reviewing the causes of attenuation of leptin signaling; and finally, providing plausible inferences for the innovative use of leptin-based pharmacotherapies as vaccine adjuvants.

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Disclosure

Dr. Poland is the chair of a Safety Evaluation Committee for investigational vaccine trials being conducted by Merck Research Laboratories. Dr. Poland offers consultative advice on vaccine development to Merck & Co. Inc., CSL Biotherapies, Avianax, Sanofi Pasteur, Dynavax, Novartis Vaccines and Therapeutics, and PAXVAX Inc. These activities have been reviewed by the Mayo Clinic Conflict of Interest Review Board and are conducted in compliance with Mayo Clinic Conflict of Interest policies. This research has been reviewed by the Mayo Clinic Conflict of Interest Review Board and was conducted in compliance with Mayo Clinic Conflict of Interest policies. All other authors have nothing to disclose.

Keywords

Adipokines; Leptin; Adjuvant; Receptors, Leptin; Vaccines; Obesity; Infectious Diseases; Communicable Diseases

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Introduction

Leptin circulates at levels proportional to body fat mass in humans and animals, with the exception of those with congenital leptin deficiency [1-3]. Congenital leptin deficiency results from mutations in the leptin (*LEP*) and/or leptin receptor (*LEPR*) genes [4]. Individuals with congenital leptin deficiency have a morbidly obese phenotype (BMI ~40 kg/m²) due to an inability to control food intake. Monogenic obesity, which includes congenital leptin deficiency, is rare and comprises less than 5% of the obese population. The majority of obesity is attributed to a positive energy balance (i.e., diet-induced obesity) and often results in leptin transport saturation due to hyperleptinemia [3, 5].

While leptin signaling is restored by regaining the energy balance achieved through diet and exercise, overconsumption of calorie-dense foods and a sedentary lifestyle is especially common in developed countries, such as the U.S. [6]. These unhealthy lifestyle choices have led to an obesity epidemic. It is estimated that 36% of adults and 17% of children (ages 2-19) in the U.S. are currently obese (BMI ~30 kg/m²) [7]. Worldwide, more than 10% of people are obese [8] with trends projected to increase in the near future [6].

Impairments of leptin signaling hamper the cooperative interplay of the immunologic, metabolic, and neuroendocrinologic processes necessary to mount protective immune responses against infections (i.e., influenza [9], human immunodeficiency virus (HIV) [10], and tuberculosis [11]), and possibly live attenuated and inactivated viral vaccines. It has recently been discovered that obesity is a significant risk factor for complicated influenza A/H1N1 disease [9] as well as poor influenza vaccine immunogenicity [12]. In addition, obese individuals are less protected against tetanus and hepatitis B infection following immunization [13]. While the underlying causes of these vaccine-induced immunologic dysfunctions are uncertain, nutritional status appears to be intricately connected to immunity. Leptin bridges metabolic and immunologic homeostasis [14]. In fact, leptin has multiple direct (i.e., increases thymopoiesis) and regulatory (i.e., modulates proinflammatory cytokines) immune functions [15]. Impairments of leptin signaling have been implicated in several innate and adaptive immune dysfunctions, such as impaired natural killer (NK) cell function and thymic atrophy [15, 16].

The use of leptin as a mucosal vaccine adjuvant has previously been shown to enhance immunity against *Rhodococcus equi*, a gram-positive bacterium that may potentially cause severe pneumonia in foals and immunocompromised humans [17]. In this study, pathogen-free mice received an intragastric or intranasal vaccine consisting of *Lactococcus lactis* as a delivery vector expressing the virulence-associated protein A (LL-VapA) from *R. equi* alone or in combination with a recombinant *L. lactis* strain that secretes leptin (LL-leptin). Only co-immunization of LL-VapA and LL-leptin via the intragastric route was capable of producing a protective immune response against *R. equi* challenge via the intragastric route. While LL-VapA vaccination via the intranasal route alone protected the mice from the bacterial challenge, co-immunization enhanced immunity. Intragastric leptin signaling is also associated with higher *Helicobacter pylori*-specific antibody titers following *H. pylori* vaccination of mice [18].

Leptin may also be recognized as an ideal candidate adjuvant for dendritic cell-based vaccines to treat cancers - as well as HIV - due to its abilities to prime helper T cells to a Th1 phenotype, promote dendritic cell survival and maturation, and enhance dendritic cell activation [19, 20]. Thus, the use of leptin-based adjuvant therapy alone or in combination with other adjuvants is feasible and worth investigation.

The purpose of this review is to briefly review the current literature on leptin, and discuss mechanisms whereby leptin-based therapy may enhance vaccine response. We will first concisely review the distribution and signal transduction of leptin and its receptors. Second, we will discuss the functions of leptin, focusing on its immune functions and any impairment to these functions. Third, we will outline the factors associated with attenuation of leptin signaling. Finally, we will provide plausible inferences for the potential use of leptin-based pharmacotherapies as vaccine adjuvants in select populations.

Leptin and Leptin Receptor Distribution and Signal Transduction

Leptin, a 16 kDa non-glycosylated protein, was the first discovered and well characterized adipokine (in 1994), and is produced almost exclusively by adipocytes [21]. Adipokines are adipocyte-derived cytokines and hormones that function at a local and/or systemic level to regulate and/or directly influence metabolic and physiologic processes, including inflammation and immunity. Other sites of leptin production, albeit nominal, include the placenta, mammary epithelium, skeletal muscles, and the gastric mucosa. While leptin is a hormone, it has cytokine-like properties. In fact, leptin and its receptors share functional and structural similarities with long-chain helical cytokines (and cytokine receptors) of the IL-6 superfamily [22].

The leptin receptor consists of two major isoforms: short form and long form, which result from differential splicing of the leptin receptor gene (mouse: *db*; human: *LEPR*) [22, 23]. There are four short-form isoforms (*LEPRa*, *c*, *d*, and *f*); one long-form isoform (*LEPRb*); and one soluble isoform (*LEPRs*). Circulating leptin is inactivated upon binding to the soluble leptin receptor. The soluble leptin receptor has no other known function. Recent evidence suggests that short-form leptin receptors are involved in transporting leptin across the blood-brain barrier [24]. The activated long-form isoform is responsible for most of leptin's effects [22, 23]. Receptor distribution is widespread and includes the spleen, thymus, brain, heart, liver, lung, muscle, pancreas, colon, and hemopoietic cells (i.e., T cells, B cells, NK cells, dendritic cells, and monocyte/macrophages) [15, 16, 23, 25]. However, leptin receptor expression on immune cell membranes is dependent upon the cell type. For instance, $25 \pm 5\%$ of monocytes and $12 \pm 4\%$ of neutrophils express the long form isoform of leptin receptor [26].

The downstream signal transducers of the leptin receptor are diverse. Activation of the leptin receptor results in conformational changes and consequential tyrosine phosphorylation and activation of janus tyrosine kinase-2 (JAK2) [27]. The phosphorylation of tyrosine-1138 acts as a docking site for signal transducer and activator of transcription-3 (STAT3), whereas the phosphorylation of tyrosine-985 acts as a docking site for SH2-containing tyrosine phosphatase (SHP2). JAK2/STAT3 is the major signal transduction pathway for leptin in immune cells [25]. Other lesser pathways triggered by leptin have been reported in immune cells and consist of SHP2-dependent mitogen-activated protein kinase (MAPK) and the phosphoinositide 3-kinase/serine/threonine protein kinase/mammalian target of rapamycin (PI3K/AKT/mTOR) [16, 22, 28].

Leptin Physiology and Pathology

The divergent signaling capacities of leptin in multiple tissues and cells reflect its ability to exert numerous biological responses both centrally and peripherally. For instance, leptin acts as a satiety signal, directing the hypothalamus to adjust accordingly for calorie consumption and expenditure [21]. Leptin levels decrease or increase rapidly to fasting or overconsumption, respectively. These rapid and transient circulating leptin level changes trigger the neuroendocrine response to either store energy in times of fasting or expend energy in times of overconsumption. Leptin also regulates bone metabolism, lipid metabolism, thermogenesis, insulin sensitivity, and the production of thyroid hormones [21, 23], as well as promoting angiogenesis and acting as a permissive factor for puberty and reproduction [21].

Leptin impacts the innate and adaptive immune systems in both a direct and regulatory manner. Leptin enhances the phagocytic activity of macrophages; promotes proliferation, differentiation, and migration of circulating monocytes and dendritic cells; prevents thymic apoptosis; and drives CD4⁺ T cell polarization toward a Th1 phenotype [25]. Leptin plays a role in maintaining lymphocyte survival by inhibition of Fas-mediated apoptosis; stimulating chemotaxis of neutrophils; and regulating lymphopoiesis. Leptin is capable of inducing proliferation of naïve CD4⁺CD45RA⁺ T cells, yet inhibits the proliferation of memory CD4⁺CD45RO⁺ T cells [29]. Furthermore, leptin acts as a negative regulator of Foxp3⁺ T regulatory cells (Treg), which are important in the control of inappropriate immune responses that are characterized by autoimmune disease [30]. Leptin can affect both the generation and proliferation of Treg cells resulting in reduced tolerance to self-antigens [31]. Experimental models of leptin and leptin receptor deficiencies increase the number and function of Treg cells with leptin administration returning the number and function of Treg cells to wild type levels [30-32]. Persistently high levels of leptin can result in chronic activation of mammalian target of rapamycin (mTOR) leading to inhibition of Treg cell proliferation [28, 33]. *In vivo*, rapamycin induced mTOR inhibition leads to increased proliferation of Treg cells and inhibits proliferation of T effector (Teff) cells [28, 33].

The direct and central adverse effects of aleptinemia or hyperleptinemia on immunity have been largely determined from leptin (*ob/ob*) and leptin receptor (*db/db*) knockout mice as well as diet-induced obese mice, respectively [15, 16, 34-36]. For instance, thymic atrophy, decreased circulating lymphocytes, increased circulating monocytes, impaired NK cell cytotoxicity, and decreased antigen-specific T cell proliferation have been reported in *ob/ob* and/or *db/db* mice [15, 16]. In addition, leptin levels differ between diet-induced obese and lean mice upon infection with influenza virus [34, 36]. A transient decrease in circulating leptin levels was reported in diet-induced obese mice infected with influenza virus [36]. The lungs of these obese mice had lower levels of IFN- α and IFN- β ; diminished NK cell cytotoxicity; and a six-fold higher mortality rate than the lean controls. In contrast, leptin levels increased in lean mice controls following influenza infection. In a separate study, diet-induced obese and lean mice were immunized with influenza A/H1N1 vaccine and challenged with influenza A/H1N1 viral infection [34]. Immunized obese mice had markedly suppressed neutralizing antibody activity and lower production of influenza-specific antibodies than lean controls. Following viral challenge, the innate immune response was delayed and the cellular immune response was reduced in obese animals, which led to a 100% mortality rate compared to a 14% mortality rate among immunized, lean control mice. Although leptin's specific role in these findings is currently unknown, leptin resistance, a term commonly used to describe a desensitization of leptin signaling, was proposed in both preclinical studies as a mechanism contributing to the observed immunologic impairments. Opportunistic infections are also significantly more pronounced in humans with malnutrition (very low leptin levels) as well as over-nutrition (very high

leptin levels), especially among those with co-morbidities, such as diabetes mellitus [37-39]. In addition, lower leptin concentrations in formula-fed babies versus breast-fed babies have been linked to decreased protection against infection, such as respiratory and gastrointestinal infections [40]. Thus far, it has been difficult to differentiate between the effects that nutritional and energy imbalances have and those that leptin directly has on immune function, as they are all interconnected. Nevertheless, recent evidence demonstrates that children with a specific leptin receptor polymorphism (Q223R) are four-times more susceptible to developing amoebiasis, an infection caused by the parasite *Entamoeba histolytica* [41]. The relationship between leptin and autoimmunity has been evaluated in a number of *ob/ob* and/or *db/db* mice studies [32, 42, 43]. Recently, *ob/ob* mice have been shown to be resistant to an experimental model of multiple sclerosis, autoimmune encephalomyelitis (EAE). This protection is reversed with leptin administration in adoptively transferred EAE [43, 44]. Leptin neutralization with antileptin mAb can prevent progression of transferred EAE. Furthermore, *ob/ob* and *db/db* mice have been studied with the animal model of immune mediated joint inflammation (AIA) [30]. Leptin and leptin receptor deficient mice had reduced synovial levels of IL-1 β and TNF- α compared to wild type [45]. There is no apparent increased risk of developing autoimmunity in the small number of human recombinant leptin trials to date [46-49]. Nonetheless, the potential role of leptin, nutritional status, or obesity in determining susceptibility to autoimmunity in humans is yet to be determined.

Factors Associated with an Attenuation of Leptin Signaling

Increased plasma concentrations of leptin are virtually synonymous with increased body fat [1, 2]. Although this has often been referred to as “leptin resistance,” it is more likely that leptin evolved as a survival signal to maximize feeding and store energy for later use during times of famine. Because leptin was evolutionarily adapted to prevent starvation and not to impede obesity, most adults probably operate at the maximal, or flat, slope of the central, and possibly peripheral, leptin dose-response curve [50, 51]. Viewed in this way, when leptin binding reaches a saturation point, any further increases in plasma leptin concentrations have no subsequent effect. In this manner, an attenuation of leptin signaling in relation to high serum leptin concentrations is due to leptin saturation [50, 52]. This theory is supported by the limited efficacy of exogenous leptin administration to reduce weight in obese persons [46, 51]. The lack of a CNS (appetite) response to elevated leptin concentrations associated with obesity may be due to several underlying mechanisms, resulting in reduced leptin signaling (Figure 1) [50, 52].

Leptin signaling may be diminished by an up regulation of suppressor of cytokine signaling-3 (SOCS3) [50, 53]. SOCS3 potently antagonizes leptin signaling. SOCS are a family of proteins (SOCS1-7) that negatively regulate signal transduction of various cytokines and growth factors by functioning as a pseudosubstrate to inhibit kinase activity [53]. A key pathway affected is JAK/STAT [53, 54]. SOCS3 binds specifically to the leptin receptor via phosphorylated tyrosine-985 (same binding site as SHP2), resulting in dephosphorylation of JAK2 [54]. SOCS3 expression is induced by leptin, whose levels are elevated in the obese state [54, 55]. Consequently, an upregulation of SOCS3 exacerbates leptin resistance by inhibiting leptin-induced STAT3 activation. It is worth noting that SOCS3 has also been shown to inhibit signaling of other cytokines and growth factors (e.g., IFN, IL-2, IL-6, G-CSF, and erythropoietin) [53].

Protein tyrosine phosphatases (PTPs) are a group of enzymes that catalyze the dephosphorylation of tyrosine residues [56]. There are multiple PTPs that impact leptin signaling. For instance, phosphatase and tensin homolog (PTEN) is a negative regulator of the PI3K pathway, a pathway activated by leptin. The receptor-type PTPe (RPTPe)

participates in a negative-feedback loop with leptin. Specifically, the activated leptin receptor permits tyrosine phosphorylation of RPTP ϵ , which activates RPTP ϵ to dephosphorylate JAK2. Finally, protein-tyrosine phosphatase 1B (PTP1B) is also capable of dephosphorylating JAK2. Its expression is elevated with a high-fat diet. T cell protein tyrosine phosphatase (TCPTP) is also elevated in obesity and has been shown to inhibit leptin-induced STAT3 phosphorylation.

An additional factor that contributes to the attenuation of leptin signaling is the downregulation of the short- and long-form isotypes of leptin receptors as a result of self-regulation in response to high circulating leptin levels [50, 52, 57]. The short-form isotypes are involved in the blood-brain barrier transport of leptin to the hypothalamus [57]. Downregulation of the short form isotype leptin receptors, in combination with high leptin levels, leads to a saturable transport system [50, 52, 57]. While downregulation of the long-form isotype in the hypothalamus has been reported to attenuate leptin signaling [57], there does not appear to be a significant downregulation of leptin receptors in immune cells [25].

Finally, chronic endoplasmic reticulum (ER) stress induces leptin resistance by inhibiting leptin-induced STAT3 phosphorylation [52, 58, 59]. PTP1B, but not SOCS3, has been found to mediate ER stress-induced leptin resistance, although the exact mechanism(s) is currently unknown [59]. ER homeostasis involves a balance of protein folding and secretion and ER folding and secretory capacities [60]. When demands exceed capacity, unfolded and misfolded proteins accumulate, resulting in ER stress. The ER is highly sensitive to energy status, and a positive energy balance (e.g., obesity) triggers ER stress, which in turn activates the unfolded protein response (UPR) [61, 58]. There are three main pathways of the UPR: inositol-requiring protein-1 (IRE-1), protein kinase-like ER kinase (PERK), and activating transcription factor- α (ATF- α) [60]. When activated, these pathways seek to restore protein folding by: diminishing protein translation until the issues regarding protein folding have been corrected; and promoting chaperone release. Chaperones stimulate accurate protein folding, and they target unfolded or misfolded proteins for rapid degradation. Chaperones also improve ER folding and secretory capacities, which have been shown to enhance leptin sensitivity. However, if ER stress persists, the UPR switches from a pro-survival to a pro-apoptotic response.

Understanding these multiple underlying and interconnected causes that impair leptin signaling extends the opportunities for discovering potential therapeutics to increase the range of leptin signaling. This knowledge may be used to treat obesity-induced illnesses and enhance vaccine response against infectious diseases.

Potential Adipokine-based Therapeutic Strategies

Continued innovation and technological advancements are leading to improved and novel vaccine/adjuvant development [62, 63]. The overall goal is to restore inflammatory and immune homeostasis without adversely affecting other physiological processes. This may be possible by restoring leptin sensitivity through leptin-based therapeutic strategies, such as synthetic and/or modified leptin, or drugs that selectively target a particular leptin-induced pathway. This review examines potential applications of leptin-based vaccine adjuvants.

In several prospective case studies, leptin replacement therapy has been shown to improve immune dysfunction in patients with lipodystrophy [64], or early onset obesity due to congenital leptin deficiency [65]. For instance, subcutaneous recombinant methionyl human leptin administration to individuals with severe lipodystrophy over four and eight months resulted in a normalization of both the number and percentage of T cell subsets and an enhancement of TNF- α expression [64]. In addition, leptin replacement therapy has been shown to increase STAT3 signaling [66]. Restoration of Th1/Th2 cytokine balance, along

with an increase in lymphocytes, neutrophils, and monocytes, has been reported after long-term leptin replacement therapy (up to four years) in two children diagnosed with congenital leptin deficiency [65].

While impairments attributed to leptin genetic mutations are treatable with replacement therapy, recombinant methionyl human leptin administration to individuals with obesity caused by dietary excess and/or a sedentary lifestyle has no apparent beneficial effects [46, 51]. This is most likely due to obesity-induced development of leptin transport saturation [5]. There are currently no pharmacotherapies on the market to enhance leptin signaling, although this is an active area of research with multiple prospective candidates [67-69]. In addition, no vaccine/adjuvant strategies have been applied to the obese population in an effort to enhance vaccine-induced immune response.

One promising type of pharmacotherapy candidate is chemical chaperones. In the ER, chaperones prevent protein unfolding and misfolding, avert nonfunctional protein aggregations, and direct properly folded protein trafficking from the ER to its final destination [60]. Administration of the chemical chaperones 4-phenylbutyric acid (4-PBA) and tauroursodeoxycholic acid (TUDCA) decreased ER stress in diet-induced obese mice [58]. As a result, up to a 10-fold increase in leptin sensitivity was observed, along with weight loss, despite a high-fat diet. PBA and TUDCA are currently FDA-approved drugs for treatment of urea-cycle disorders [70] and primary biliary cirrhosis [71], respectively. However, based on their leptin-sensitizing (and insulin-sensitizing) properties, they are currently being investigated as potential weight-loss and diabetic treatments [72, 73].

It is feasible that chaperones, such as TUDCA, could be used to simultaneously improve obesity-related health consequences (e.g., insulin resistance) and enhance vaccine response by not only indirectly restoring leptin sensitivity, but directly interacting with immune cells. It is worth noting that 4-PBA does not appear to have any immune functions. In contrast, TUDCA has been shown to inhibit influenza A viral replication by alleviating ER stress [74]. Influenza A, as well as other viral infections, induce ER stress [75]. IRE-1, a major pathway of the UPR, is critical for influenza A viral replication [74]. However, PERK and ATF- α , the other two major UPR pathways, are minimally or not involved. IRE-1 splices the transcription factor X-box-binding protein-1 (XBP-1), which in turn regulates expression of genes involved in UPR, such as chaperone genes [60, 75, 76]. Furthermore, IRE-1 and XBP-1 activation are critical for T and B cell development, especially plasma cell differentiation [76].

Molecular chaperones, such as heat-shock proteins (HSP), may also improve chronic ER stress induced by obesity. Plasma HSP60 expression is higher in obese versus lean males and is correlated to circulating leptin levels [77]. In addition, leptin has been found to stimulate HSP60 expression *in vitro*, suggesting that leptin modulates HSP60 expression [78]. HSP60 is associated with diabetes, cancer, and autoimmunity [79]. It is a natural ligand for TLR2 and TLR4 and, depending on its concentration, can act as a pro- or an anti-inflammatory mediator. Furthermore, it has previously been found to enhance immune response to peptides from West Nile virus [80] and cytomegalovirus [81]. It is currently unknown if TUDCA and 4-PBA could be used as effective adjuvants; however, their involvement in leptin sensitivity and immune function (TUDCA only), as well as the efficacy of other chaperones (i.e., HSP60) as vaccine adjuvants, make them promising candidates.

Another potential type of candidate to prevent obesity-related vaccine failure is SOCS3 antagonists. SOCS may potentially help regulate TLR signaling [82], and it has differential effects on B cell maturity [83]. For instance, low expression of SOCS3 is required to

maintain growth and differentiation of progenitor B cells in bone marrow, whereas higher levels of expression are needed to stimulate final B cell maturity and departure of mature B cells [83]. SOCS3's ability to suppress cytokine signaling has been shown to be important in controlling T cell proliferation and maintaining these cells in an inactive state, possibly by directly inhibiting CD28 [82]. In addition, STAT3 is important in the development and maintenance of memory T cells, and inhibition of STAT3 activity by SOCS3 impairs memory T cell responses [84]. Indeed, diet-induced obese mice infected with influenza virus had lower memory CD8⁺ T cell responses as well as increased levels of SOCS3 mRNA expression in the lungs compared to lean controls [85].

Viruses (e.g., influenza, hepatitis B, HIV, Epstein Barr) are capable of inducing SOCS3 to promote viral replication through inhibition of IFN- α/β JAK/STAT signaling [86-89]. This represents a mechanism to evade host immunity. While interferons have potent antiviral activity, they are also involved in the maturation and activation of dendritic cells, bridging innate and adaptive immunity. Therefore, an upregulation of SOCS3 expression by leptin and/or viral infection may impair both innate and adaptive immunity. Use of SOCS3 antagonists as viral vaccine adjuvants may help restore immune homeostasis, especially in individuals who have reduced leptin signaling.

While the possibilities of using vaccine adjuvants targeted to obese people are exciting, important questions must be answered and obstacles overcome before these, or other adjuvants, can be used successfully. A primary concern is currently there are no direct clinical measures to assess leptin signaling [90]. While circulating leptin concentrations are an approximation, they do not define actual leptin signaling capabilities. In addition, more research is required to understand the mechanisms by which leptin resistance impairs vaccine-induced immune responses. It is also important to identify the way in which these potential therapeutic candidates could be safely used as vaccine adjuvants. Finally, it will be necessary to determine that use of these, or other vaccine adjuvants, will not tip the Th1/Th2 balance in a pathological direction, causing anti-inflammatory or autoimmune-type responses. These questions and known challenges offer new research opportunities with potentially successful therapeutic avenues.

In conclusion, leptin plays an important role in numerous metabolic and immunologic processes. Impairments of leptin signaling appear to hamper these processes and possibly contribute to impaired vaccine-induced immune responses. Therefore, recombinant leptin administration or an improvement of leptin transport/signaling sensitivity could enhance vaccine response. While congenital leptin deficiency is rare, rates of obesity, especially childhood obesity, continue to rise in the U.S. and much of the world. The novel development of vaccines and/or adjuvants targeted to obese persons is imperative to protect this vulnerable population from the morbidity and mortality of infectious diseases.

Abbreviations

BMI	Body mass index
CRP	C-reactive protein
db/db	diabetic
ER	Endoplasmic reticulum
HSP	Heat shock proteins
JAK	Janus kinase
ob/ob	obese

LEPR	leptin receptor
MAPK	Mitogen-activated protein kinase
mTOR	mammalian target of rapamycin
NK	natural killer
PBA	4-phenylbutyric acid
PBMC	peripheral blood mononuclear cell
PI3K	Phosphatidylinositol 3-kinase
PTP1B	Protein-tyrosine phosphatase 1B
SOCS	Suppressor of cytokine signaling proteins
STAT	Signal transducer and activator of transcription
TLR	Toll-like receptor
TUDCA	Tauroursodeoxycholic acid
UPR	Unfolded protein response

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Highlights

Leptin deficiency/resistance impairs multiple immune functions.
An attenuation of leptin signaling may be associated with vaccine failure.
Chemical chaperones and inhibition of SOCS3 increase leptin sensitivity.
Leptin-based adjuvant therapy may enhance vaccine response.

Figure 1.

Overview of the development of obesity-induced impairments of leptin signaling.

An attenuation of leptin signaling despite high circulating leptin concentrations is a common consequence of obesity and has been shown to alter multiple immune functions, impairing both innate and adaptive immunity. Leptin signaling impairments are attributed to a combination of factors. 1.) In response to an excess of energy intake, adipose tissues hypertrophy, releasing pro-inflammatory cytokines, including leptin. 2.) In response to high circulating leptin levels, leptin self-regulates, which leads to a downregulation of the short- and long-form isotypes of leptin receptors. This causes a saturation of receptor-mediated transport across the blood-brain barrier. 3.) High leptin levels induce SOCS3 expression. 4.) SOCS3 binds to tyrosine-985 of the leptin receptor, the same docking site as SHP-2. Bound SOCS3 inhibits JAK2 phosphorylation. 5.) PTP1B also inhibits JAK2 phosphorylation. 6.) TCPTP inhibits STAT3 activity. 7.) Consequently, inhibition of STAT3 activation prohibits nuclear translocation and transcription. 8.) Chronic ER stress induces the UPR, which further inhibits leptin-induced STAT3 activation. 9.) If the chronic ER stress is unresolved, the UPR switches from pro-survival to pro-apoptotic, promoting a variety of immunological impairments.