JEM Journal of Experimental Medicine

REVIEW

The pleiotropic roles of leptin in metabolism, immunity, and cancer

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The discovery of the archetypal adipocytokine leptin and how it regulates energy homeostasis have represented breakthroughs in our understanding of the endocrine function of the adipose tissue and the biological determinants of human obesity. Investigations on leptin have also been instrumental in identifying physio-pathological connections between metabolic regulation and multiple immunological functions. For example, the description of the promoting activities of leptin on inflammation and cell proliferation have recognized the detrimental effects of leptin in connecting dysmetabolic conditions with cancer and with onset and/or progression of autoimmune disease. Here we review the multiple biological functions and complex framework of operations of leptin, discussing why and how the pleiotropic activities of this adipocytokine still pose major hurdles in the development of effective leptin-based therapeutic opportunities for different clinical conditions.

Introduction

In 1950, Ingalls et al. (1950) at The Jackson Laboratory described a mouse that they named *ob/ob* as its excessive eating made it become morbidly obese. 15 yr later, another obese and hyperphagic mouse was identified in the same laboratories (named *db/db*; Hummel et al., 1966). For decades, the existence of a "satiety factor" was only assumed on the basis of a presumed absence in obese mice (Coleman, 2010) until the *obese* (*ob*) gene was positionally cloned by Jeffrey Friedman and collaborators (Zhang et al., 1994). The encoded product was named leptin from the Greek word λεπτός (*leptòs*) that means "lean," and its receptor was cloned soon after (Tartaglia et al., 1995). Following a detailed description of the *ob/ob* and *db/db* mouse strains as not only morbidly obese but also insulin-resistant, infertile, and lethargic (Chen et al., 1996; Halaas et al., 1995; Pelleymounter et al., 1995), the field started to grow significantly. Leptin was found to be a blood-borne hormone produced by the adipose tissue that communicated the metabolic status to the central nervous system, modulating appetite through a negative feedback loop centered in the hypothalamus (Coleman, 2010). The subsequent discovery of leptin receptors (LEPRs) in other brain regions and in different organs and tissues led to appreciation of broader roles of leptin in the physiological control of glucose homeostasis, immune responses, hematopoiesis, angiogenesis, reproduction, and even mental processes such as memory and learning (Bennett et al., 1996; Chehab et al., 1996; Ducy et al., 2000; Sierra-Honigmann et al., 1998).

Here we summarize >25 yr of studies on the biology of leptin, its involvement in physiological and pathological processes related to metabolism, immunity, and cancer, and its potential use as a therapeutic target in the numerous studies that flourished after its identification in the mid-1990s.

Intracellular signaling

In mice, leptin is encoded by the *ob* gene, located on chromosome 6, and is a 167–amino acid nonglycosylated protein; in *ob/ob* mice, a nonsense mutation in codon 105 blocks protein synthesis with resulting hyperphagia, early development of gross obesity, insulin resistance, and infertility (Zhang et al., 1994). The human *OB* gene, located on chromosome 7, shares high sequence identity with the mouse orthologue (Green et al., 1995; Zhang et al., 1994).

Structurally, leptin is a four-helix bundle characteristic of the long-chain helical cytokine family, and nonmammalian leptin, even if dissimilar in primary amino-acidic sequence, appears as functionally conserved through convergent tertiary structures (Zhang et al., 1997). The cognate LEPR is a single-transmembrane-domain molecule that belongs to the class I cytokine receptor super-family (which includes the receptors of IL-1, IL-2, IL-6, and growth hormone). A single transcript produces several variants of the LEPR protein through alternative splicing: a long-form containing the cytoplasmic domain (LEPRB) is the only one capable of transducing downstream signals, four short isoforms,

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and a soluble isoform (Baumann et al., 1996; Bjørbæk et al., 1997; Frühbeck, 2005; Lee et al., 1996).

Leptin binding to LEPR, unlike other cytokine receptors, does not promote receptor dimerization but rather a conformational change that leads to the autophosphorylation and activation of JAK-2 (which is bound constitutively to the membrane proximal portion of the LEPR; Kloek et al., 2002). Activated JAK-2 phosphorylates three tyrosine residues of LEPRB (Tyr985, Tyr1077, and Tyr1138), which recruit cytosolic proteins to transduce cell signaling (Banks et al., 2000). Phospho-Tyr1138 engages STAT-3, which, upon JAK-2–dependent phosphorylation, translocates to the nucleus to promote expression of mRNAs, including for suppressor of cytokine signaling–3 (SOCS-3; Banks et al., 2000; Bjørbæk et al., 1999; Vaisse et al., 1996). Phospho-Tyr985 activates the ERK signaling pathway and also serves as a docking site for the inhibitory activity of SOCS-3 (Banks et al., 2000; Bjørbæk et al., 1999), while phospho-Tyr1077 promotes recruitment and activation of STAT-5, which also activates target gene transcription after dimerization (Gong et al., 2007). The pattern of LEPR-mediated STAT activation is similar to that observed for IL-6–downstream intracellular events (Sadowski et al., 1993), although signaling differences exist. While receptor complexes for the IL-6 family of cytokines share homo- or hetero-dimerization of glycoprotein (GP130) as a critical component for activation of associated cytoplasmic tyrosine kinases and signal transduction (Taga and Kishimoto, 1997), LEPR signaling was not inhibited by blockade of GP130 (Baumann et al., 1996). Nonetheless, leptin and IL-6 may converge on overlapping metabolic processes, since IL-6 is expressed both in adipose tissue and in hypothalamic nuclei and IL-6 knockout mice developed mature-onset obesity, which was counteracted by increased energy expenditure upon intracerebroventricular IL-6 treatment (Wallenius et al., 2002).

LEPR can also activate mitogen-activated protein kinase (MAPK) signaling cascade either directly or through an SH2-containing protein tyrosine phosphatase-2–mediated recruitment of growth factor receptor-bound protein-2 (Zhang et al., 2004). In addition, leptin signaling activates phosphoinositide 3 kinase (PI-3K) through insulin receptor substrate phosphorylation (Tong et al., 2008). In turn, PI-3K can activate the mechanistic target of rapamycin (mTOR), thus driving intracellular anabolic pathways (Cota et al., 2006; Hill et al., 2008). The major signaling events downstream of LEPR are depicted in Fig. 1. The specificity by which these well-delineated molecular pathways activated by LEPR engagement translate into defined systemic effects is still a matter of intense investigation.

Role of leptin in metabolism

Two milestone studies described how leptin tunes appetite and energy expenditure, thus regulating body weight (Halaas et al., 1995; Pelleymounter et al., 1995). Expressed and released by the white adipose tissue proportionally to its mass, leptin levels increase upon food intake (Ahima et al., 1996; Lönnqvist et al., 1995); differently from the broad diurnal quantitative variations of other hormones like ghrelin, though, the steadier levels of leptin appear to mirror the overall availability of energy to the host rather than acute changes in energy balance, thus reflecting states of malnutrition and obesity rather than hunger and satiety (de Candia and Matarese, 2018; Korbonits et al., 1997; Serrenho et al., 2019). Albeit there is no consensus on the underlying mechanisms, it is believed that leptin, once released in the bloodstream, can cross the blood–brain barrier through multiple routes including the fenestrated capillaries in the median eminence and/or endothelial and choroid plexus cells expressing the LEPR (Balland et al., 2014; Di Spiezio et al., 2018; Harrison et al., 2019; Sinha et al., 1996).

LEPR is expressed in many areas of the brain, and is particularly abundant in the arcuate and ventromedial nuclei of the hypothalamus, where it controls feeding by acting on multiple neuronal populations and by modulating both orexigenic and anorexigenic peptides (Burguera et al., 2000; Klok et al., 2007). The central activity of leptin is believed to derive from the concerted activation of pro-opiomelanocortin (POMC)-expressing neurons and the inhibition of neuropeptide Y/agouti-related peptide–expressing neurons in the arcuate nucleus of the hypothalamus (Friedman, 2019). While the leptin-mediated mechanism(s) of POMC depolarization of neurons remains to be unveiled, the hyperpolarization of the hypothalamic neurons seems to be mediated by an ATP-sensitive potassium channel that fosters an outward potassium current (Spanswick et al., 1997; Takahashi and Cone, 2005) leading to the neuronal regulation of appetite (Andermann and Lowell, 2017; Atasoy et al., 2012; Wu et al., 2009b). In addition to the adipose tissue, leptin is produced in low quantities by organs/tissues such as the placenta, skeletal muscle, brain, P/D1 cells in the stomach (which also produce ghrelin), and T cells (Bado et al., 1998; Chan et al., 2006; De Rosa et al., 2007; Maymó et al., 2011; Wang et al., 1998; Wiesner et al., 1999). LEPR expression in the white and brown adipose tissues, skeletal muscle, and pancreas, and its capability to promote β-oxidation and lipolysis while inhibiting insulin secretion, suggest the existence of a brain-independent regulation of peripheral energy expenditure by leptin (Friedman, 2019; Muoio and Lynis Dohm, 2002).

The paradoxical role of leptin in obesity

The critical role of leptin in energy homeostasis was enshrined by two observations: (1) human subjects with homozygous inactivating leptin or LEPR mutations were extremely hyperphagic and morbidly obese, with a metabolic imbalance closely resembling that of *ob/ob* and *db/db* mice (Clément et al., 1998; Montague et al., 1997); and (2) the administration of recombinant leptin to the above mutant mice and humans normalized food intake and substantially reduced body weight (Farooqi et al., 1999; Halaas et al., 1995). Intriguingly, only the very small proportion of obese individuals with a genetic deficiency of leptin suffers from leptin loss; the other majority displays elevated concentrations of circulating leptin and, when treated with the methionyl-recombinant leptin (r-metHuLeptin) analogue, these obese individuals only show limited weight loss (Chou and Perry, 2013). This apparent paradox, considering that elevated leptin levels should maintain metabolic homeostasis (Considine et al., 1996; Heymsfield et al., 1999; Maffei et al., 1995; Ravussin et al., 1997), demonstrates that leptin resistance represents the main obstacle to broader advantageous effects from

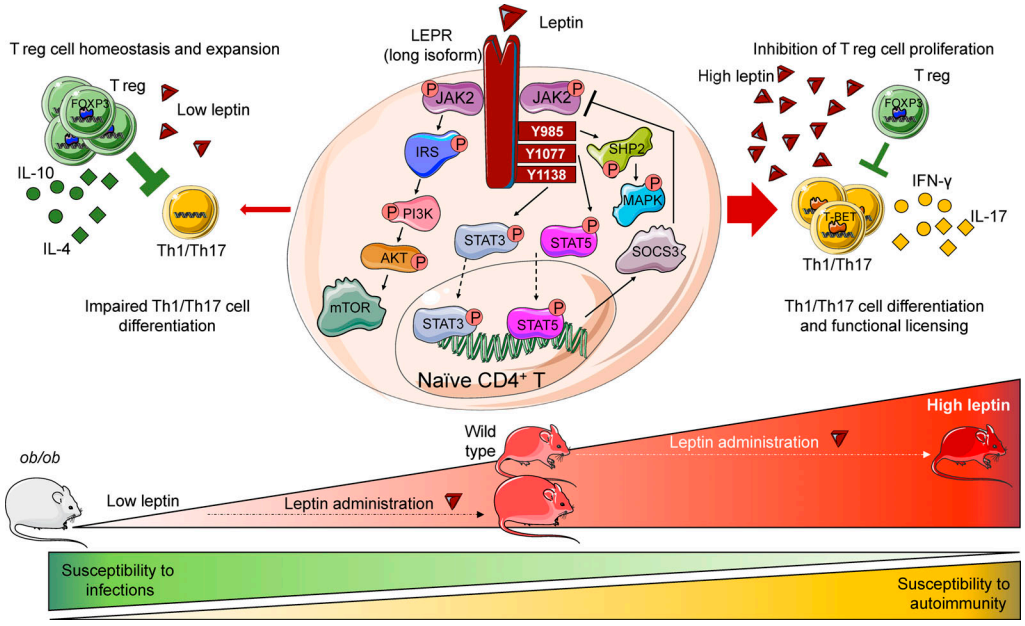

Figure 1. **Leptin-dependent regulation of immune homeostasis and function.** In a naïve CD4⁺ T cell, the LEPR-dependent intracellular signaling enhances the differentiation toward pro-inflammatory Th1/Th17 cells while inhibiting the proliferation of FOXP3⁺ T reg cells. Furthermore, at absent/low levels of leptin the growth and function of Th1/Th17 is impaired, while T reg cells expand more efficiently and release more regulatory-type cytokines. The opposite occurs when leptin levels are aberrantly high and enhance Th1/Th17 differentiation and growth on one side and inhibit T reg cell proliferation on the other. This different cellular response to leptin depends on the different sensitivity of Th1/Th17 and T reg cells to either physiologically fluctuating LEPR-mTOR activation (low/normal leptin) or consistent hyperstimulation of the same pathway (high leptin). The two opposite situations are correlated with either higher susceptibility to infections (low leptin: effector arm inefficient, elevated immune suppression) or enhanced susceptibility to autoimmunity (high leptin: effector arm hyperactive, inefficient immune regulation). Schematic figures were created with images adapted from Smart Servier Medical Art (http://www.servier.fr/servier-medical-art). P, phosphorylated.

leptin supplementation (DePaoli et al., 2018; Gruzdeva et al., 2019; Heymsfield et al., 1999). Mechanistically, leptin resistance in animal models of obesity and hyperleptinemia (Halaas et al., 1997; Knight et al., 2010) relies on the induction of the key leptin signaling rheostat SOCS-3, which attenuates the capability of leptin to induce STAT-3 phosphorylation and POMC activation and to decrease food intake and body weight (Buettner et al., 2006; Gao et al., 2004; Mori et al., 2004; Reed et al., 2010). STAT-3 phosphorylation and the hypothalamic response to leptin are also inhibited by fatty acid/TLR-induced low-grade inflammation, in a fashion similar to the insulin resistance in the adipose tissue and the liver (Prattichizzo et al., 2018). Additional mechanisms of reduction of leptin signaling are the induction of matrix metalloproteinase–2 in the hypothalamus of obese rodents (which promotes LEPR degradation; Mazor et al., 2018) and the saturable nature of leptin transport across the blood–brain barrier (Halaas et al., 1997; Schwartz et al., 1996).

In sum, although leptin agonism can exert beneficial effects by restraining food intake and promoting metabolic homeostasis and weight loss, these effects can be canceled in most obese patients by hyperleptinemia-induced leptin resistance.

The role of leptin in immunity

Leptin-dependent induction of immune functions

Even before leptin was identified, it was recognized that *ob/ob* and *db/db* mice had altered immune competence, hypotrophic thymus and spleen, and markedly reduced cytotoxic responses and antibody production when compared with lean mice (Chandra, 1980; Fernandes et al., 1978). After the discovery of leptin, it was demonstrated that multiple types of immune cells express detectable levels of LEPR, and features of the immune system dysregulation present in both *ob/ob* and *db/db* mice were thoroughly described (Lord et al., 1998; Lord et al., 2001; Procaccini et al., 2012b). Importantly, it was demonstrated that the impaired immunity associated with undernutrition, which predisposed mice to infectious diseases, was directly linked to low body weight–dependent reduction of leptin, and the administration of exogenous leptin, reversed the immunosuppressed phenotype and thymic atrophy in those mice (Howard et al., 1999; Lord et al., 1998). The key role of leptin in supporting a normal immune function was further confirmed by the finding that a large percentage of obese individuals with homozygous missense leptin mutation succumbed to infections during childhood (Ozata et al., 1999).

Multiple lines of experimental evidence have demonstrated that leptin activates innate responses to infection. In neutrophils, leptin sustains IL-1β, intracellular adhesion molecule-1, and chemokines that promote their chemotaxis at infection sites (Rummel et al., 2010) and stimulate the oxidative burst that is necessary for effective bacterial killing (Bruno et al., 2005; Caldefie-Chezet et al., 2001; Caldefie-Chezet et al., 2003; Park et al., 2009). Neutrophils are known to express the short form of the LEPR, which is unable to stimulate the JAK-STAT signaling, but instead is sufficient to activate the MAPK pathway and

prevent apoptosis (Bjørbæk et al., 1997; Zarkesh-Esfahani et al., 2004). In macrophages, leptin promotes phagocytic function, pro-inflammatory cytokine secretion, and leukotriene synthesis with a resulting increase in host survival, as shown in a mouse model of pulmonary bacterial infection with *Streptococcus pneumoniae* (Gainsford et al., 1996; Loffreda et al., 1998; Mancuso et al., 2002; Mancuso et al., 2011). Leptin-induced macrophage activation seems to mostly depend on PI-3K activity, which links a sensing of systemic leptin to macrophage lipid metabolism through the activation of mTOR (Maya-Monteiro et al., 2008). Leptin also regulates natural killer cell differentiation and cytotoxic activity, as exemplified by severely reduced numbers and markedly increased apoptotic rate of these cells in the bone marrow of *db/db* mice (Lo et al., 2009; Tian et al., 2002). In human natural killer cells, both long and short isoforms of LEPR are functional and, through the STAT signaling pathway, lead to the activation of IL-2 and perforin gene expression (Zhao et al., 2003). Finally, the leptin-mediated release of TNF-α from monocytes able to activate neutrophils shows the capability of leptin to stimulate the cross-cellular communication among the innate immune cells (Zarkesh-Esfahani et al., 2004).

The observations that LEPR is significantly up-regulated on mouse $CD4^+CD8^+$ T cells and B cells upon activation and leptin signaling promotes lymphocyte survival and function (Papathanassoglou et al., 2006) indicate a role for leptin in the adaptive immune response as well. Lack of responsiveness to leptin in *db/db* mice associates with reduced $CD4^+$ T cell proliferative responses (Papathanassoglou et al., 2006) and B cell hypo-responsiveness in terms of IgM production and differentiation into effector B cells (Jennbacken et al., 2013). The presence of detectable *LEPR* mRNA in B cells has indicated that, besides indirect effects through the activation of cellular immunity, leptin may also exert a direct effect on these lymphocytes (Busso et al., 2002). When circulating leptin levels are low, such as in undernutrition or during fasting, $CD4^+$ T helper 17 (Th17) cells produce less inflammatory cytokines (i.e., IFN-γ and IL-17) and are less glycolytic, with decreased lactate production and mitochondrial respiration, compared with Th17 cells from ad libitum–fed mice (Gerriets et al., 2016; Saucillo et al., 2014). The administration of leptin to fasting animals rescues T cell functional and metabolic defects by cell-intrinsic mechanisms (Gerriets et al., 2016; Saucillo et al., 2014). Furthermore, leptin modulates the cross-talk between innate and adaptive immunity by affecting dendritic cell number, maturation, cytokine production, and capacity to induce $CD4^+$ T cell proliferation (Macia et al., 2006; Moraes-Vieira et al., 2014).

Experimental evidence directly implicates leptin in the recruitment of immune cells to the adipose tissue. Leptin is indeed a potent chemoattractant for monocytes and macrophages, with leptin-mediated chemotaxis necessitating the presence of full-length LEPRs and the functional activation of JAK/STAT, MAPK, and PI-3K pathways in migrating cells (Gruen et al., 2007). In both *ob/ob* and *db/db* mice, the degree of adipose macrophagic infiltration was lower than expected due to their obesity, advocating leptin participation in recruitment of immune cells to the adipose tissue (Weisberg et al., 2003; Xu et al., 2003). Obesity due to high-fat diet in mice was shown to substantially increase the number of adipocytes in the bone marrow, resulting in an uptick of leptin, but not other cytokines and growth factors, expression. This leptin dysregulation possibly fostered the increase in the proportion of lymphocytes in marrows from obese compared with lean animals, suggesting that adipocyte-derived paracrine leptin can unbalance immune cells also outside the adipose tissue (Trottier et al., 2012). It will be relevant to identify the participation of paracrine leptin in the depot function of the bone marrow for the physiological maintenance of memory T cell survival and/or homeostatic proliferation (Di Rosa, 2016).

In sum, leptin plays a relevant role in activating an efficient and coordinated innate and adaptive immune response and normal leptin levels are necessary for an efficient clearance of infection (Fig. 1). Leptin influences on both the innate and the adaptive immune systems are summarized in Table 1.

Effects of leptin on immunological self-tolerance

The expression of the long form of LEPR on T lymphocytes (particularly in $CD4^+$ Th cells) strongly suggests the capability to activate the JAK-STAT pathway (Kim et al., 2010; Lord et al., 1998). Notwithstanding the general ability to promote proliferation in these cells, though, the engagement of the leptin pathway may result in different outcomes depending on the specific T cell subset. On the one hand, leptin promotes the proliferation and differentiation of pro-inflammatory $CD4^+CD25^-FOXP3^-$ conventional T cells (Lord et al., 2002; Yu et al., 2013), while on the other, it hampers the proliferation and homeostasis of $CD4^+CD25^+FOXP3^+$ regulatory T (T reg) cells (De Rosa et al., 2007; Reis et al., 2015). Leptin levels have indeed been inversely correlated with T reg cell number in autoimmune disease (Wang et al., 2017) and in nonclassical autoimmune inflammatory conditions, such as chronic obstructive pulmonary disease (Bruzzaniti et al., 2019).

A very recent study has demonstrated that the intensity of leptin-dependent STAT-3 phosphorylation is significantly higher in $CD4^+CD25^-$ effector T cells than in T reg cells, associated with a marked down-regulation of the cell cycle inhibitor p27 kIP1 in the former but not in the latter cells (Marrodan et al., 2021). As described above, mTOR is also activated by leptin and differently controls T cell responsiveness and survival, FOXP3 expression, and de novo differentiation of T reg cells (Delgoffe and Powell, 2009; Haxhinasto et al., 2008). The differences in response to leptin among the T cell subsets can actually be ascribed to the dynamic differences in dependence on mTOR signaling in these cells. In pro-inflammatory T effector cells, leptin-dependent mTOR activation impinges on the signaling pathways and transcriptional signatures involved in cell activation and growth, and leptin blockade super-imposes a transcriptional and biochemical response over rapamycin treatment (Procaccini et al., 2012a). On the other hand, the hypo-responsive state of the T reg cells in vitro depends on an elevated activity of the mTOR pathway. Treatment with rapamycin or leptin blockade imparts an oscillatory phenomenon characterized by early down-regulation of the LEPR-mTOR pathway followed by an increased activation of mTOR that is necessary for the T reg cells to expand (MacIver et al., 2013; Procaccini et al., 2010).

Table 1. **Biological effects of leptin on the different cell populations of the innate and the adaptive immune system**

Cell type	Effect of leptin	Reference
Innate immune system		
Neutrophils	Stimulation of chemotaxis and release of oxygen radicals, inhibition of apoptosis; indirect activation via monocyte-derived TNF-α	Caldefie-Chezet et al., 2003; Bruno et al., 2005; Zarkesh-Esfahani et al., 2004
Macrophages	Activation of phagocytosis, secretion of pro-inflammatory cytokines and leukotriene synthesis	Loffreda et al., 1998; Mancuso et al., 2002
Natural killer cells	Control of differentiation, proliferation and cytotoxicity	Tian et al., 2002
Dendritic cells	Enhancement of cell maturation, cytokine production and ability to induce $CD4^+$ T cell proliferation	Moraes-Vieira et al., 2014
Adaptive immune system		
B cells	Induction of differentiation and IgM production	Papathanassoglou et al., 2006; Jennbacken et al., 2013
Naïve T cells	Stimulation of proliferation and release of pro-inflammatory cytokines	Lord et al., 2002
Memory T cells	Growth inhibition	Lord et al., 2002
Th1/Th17	Promotion of cell proliferation, survival, and cytokine release	Papathanassoglou et al., 2006
T reg	Inhibition of proliferation and homeostasis	De Rosa et al., 2007

T reg cells represent a relevant fraction of the $CD4^+$ T cells resident in the murine adipose tissue, and the release of anti-inflammatory mediators may directly affect the tissue microenvironment (Feuerer et al., 2009): resident T reg cells were actually shown to ameliorate inflammation in the adipose tissue, but also liver fat accumulation, blood glucose, and insulin resistance (Eller et al., 2011; Ilan et al., 2010). Consistently, in human samples, there exists a correlation between body mass index and the drop in T reg cells in omental fat (Deiuliis et al., 2011; Feuerer et al., 2009). Since T reg cells express high levels of LEPR and also release leptin, they are exposed to high concentrations of the adipokine in the adipose tissue, especially in obesogenic conditions (Barbi et al., 2013; De Rosa et al., 2007; MacIver et al., 2013; Matarese et al., 2014; Wang and Green, 2012). The dysregulated leptin levels may thus fuel local and systemic inflammation by also further inhibiting the function of adipose-resident T reg cells.

The increase of adipose-resident conventional $CD4^+$ and $CD8^+$ T cells showing an activated pro-inflammatory phenotype is consistently observed in both obesity and aging (Bapat et al., 2015; Lumeng et al., 2011). Intriguingly, while adipose-resident T reg cells are decreased in obesity, as discussed above, they instead constantly rise during aging and demonstrate an enhanced expression of a set of transcripts that may promote the local adaptation of these cells to the lipophilic, hypoxic adipose tissue (Bapat et al., 2015; Cipolletta et al., 2015; Feuerer et al., 2009; Kohlgruber et al., 2018). In fact, T reg cells in aged adipose tissue seem to have lost their ability to curb inflammation: their depletion indeed stimulated insulin sensitivity compared with control mice, suggesting a detrimental role of adipose-resident T reg cells in age-associated insulin resistance (Bapat et al., 2015; Feuerer et al., 2009). The identification of a differential cell response to leptin (which is increased in both obesity and aging) as a driving factor for the accumulation and phenotypes of T reg cells in adipose tissue during aging may help to better elucidate the pathological bases of age-related dysmetabolic and inflammatory conditions.

In all, these data show that dysregulated increases of leptin favor exaggerated inflammatory responses by licensing the functional activation of pro-inflammatory T effector cell subsets while inhibiting T reg cells, and thus implicate that leptin may significantly perturbate immunological self-tolerance and foster autoimmunity (Fig. 1).

Leptin-dependent susceptibility to autoimmune diseases and allergic responses

The hypothesis that leptin may promote autoimmune diseases has found repeated experimental confirmations. First of all, mouse genetic deficiency of leptin inhibited the induction and progression of experimental autoimmune encephalomyelitis (EAE, a model of human multiple sclerosis [MS]; Constantinescu et al., 2011) and reduced production of autoantibodies and renal disease by increasing T reg cell frequency in systemic lupus erythematosus (SLE; Fujita et al., 2014; Lourenço et al., 2016). Consistently, in NZB/W lupus-prone mice, fasting-induced hypoleptinemia ameliorated the inflammatory state by inducing T reg cell expansion, a phenomenon reversed by leptin replacement (Liu et al., 2012). On the other hand, the severity of autoimmune diseases in mouse models have been closely associated with the systemic levels of leptin in those animals. Leptin administration skewed $CD4^+$ T cell phenotypes and cytokines and restored susceptibility to EAE in *ob/ob* mice (Matarese et al., 2001a; Matarese et al., 2001b; Sanna et al., 2003). Moreover, it increased EAE and SLE severity by enhancing T cell autoreactive responses in wild-type mice (Amarilyo et al., 2013; De Rosa et al., 2006; Galgani et al., 2010; Lourenço et al., 2016; Sanna et al., 2003; Yu et al., 2013). In SLE, leptin may also favor disease progression by stimulating phagocytosis of apoptotic cells by macrophages, which results in an increased availability of self-antigens promoting autoimmune responses (Amarilyo et al., 2014).

For humans, the unprecedented increase of obesity in Western countries has been paralleled by upticks in autoimmune diseases in the past few decades (De Rosa et al., 2017). The literature provides strong evidence that obese subjects are at increased risk of developing MS, psoriasis, rheumatoid and psoriatic arthritis, type 1 diabetes (T1D), inflammatory bowel disease, and thyroid autoimmunity, and suggests leptin involvement in obesity-dependent disease and response to medical treatment (Versini et al., 2014). In obese MS patients, for example, elevated leptin levels were predictive of a worsened disease progression (Carbone et al., 2014; Emamgholipour et al., 2013; Lanzillo et al., 2017; Lock et al., 2002; Matarese et al., 2005; Stampanoni Bassi et al., 2020), while leptin decreases due to metformin or pioglitazone treatments were associated with reduced disease activity (Negrotto et al., 2016). Similarly, in patients with rheumatoid arthritis (RA), leptin was recognized as parameter of high disease activity index (Cao et al., 2016), and beneficial effects from low caloric intake in RA patients could be linked to fasting-induced reduction of pro-inflammatory $CD4^+$ T cell activity associated with a drop of circulating leptin (Lago et al., 2007). Elevated levels of leptin were suggested to participate in the pathology of cartilage, synovium, and bone in RA (Gómez et al., 2011; Olama et al., 2012; Otero et al., 2006) and the formation of inflammatory infiltrates in psoriatic patients (Johnston et al., 2008). Human studies, consistently with mice observations, connect this pathogenic role of leptin with its capability to induce immune effector cells and pro-inflammatory mediator release and thus enhance the auto-immune disease (Johnston et al., 2008; Wang et al., 2018).

The increased susceptibility to allergic asthma in obese individuals was also linked to a leptin-dependent increase of Th2 cell proliferation, activation, and survival (Zheng et al., 2016), and elevated circulating leptin correlated with pro-allergic Th2 cell cytokine signatures and Th2 cell imbalance in children with allergic rhinitis and in patients with allergic asthma (Dias et al., 2019; Zeng et al., 2018). The key immunopathological role of leptin in allergic reactions has also been linked to its effect on human eosinophils in which the engagement of the LEPR activates MAPK-dependent pathways, hampers the caspase cascade and cell death, and induces release of pro-inflammatory cytokines and chemokines (Conus et al., 2005; Wong et al., 2007).

To recapitulate, by linking the nutritional status with a plethora of immunological activities, leptin is able to create a pathogenic systemic circuit that connects metabolic dysregulation with aberrant immune responses (Abella et al., 2017; Tsigalou et al., 2020).

Leptin signaling at the intersection of metabolic, immune, and vascular regulation

Leptin-mediated production of cytokines by immune cells (Faggioni et al., 2000; Shen et al., 2005; Tsiotra et al., 2013) and C-reactive protein by hepatocytes (Chen et al., 2006), in addition to endogenous and exogenous pro-inflammatory mediators of leptin release that include IL-1β and the endotoxin LPS (Faggioni et al., 1998; Landman et al., 2003), suggest a positive feedback loop between increased leptin levels and systemic low-grade inflammation, which has been suggested to aggravate leptin resistance (Chen et al., 2006). Taking into consideration the central role of low-grade inflammation in promoting the development of metabolic diseases such as type 2 diabetes (T2D; Donath and Shoelson, 2011) and cardiovascular diseases (CVDs; Libby, 2006; Prattichizzo et al., 2020), it is conceivable that chronic leptin elevation can play a deleterious role in those contexts. Indeed, elevated longitudinal leptin levels predict development of T2D, even when adjusted for adiposity parameters (McNeely et al., 1999; Wannamethee et al., 2007; Welsh et al., 2009). However, the relationship between leptin and CVDs is less straightforward. Increased levels of leptin have been associated with the development of atherosclerosis (Spiroglou et al., 2010) and, by triggering the extrinsic coagulation cascade, leptin may also be involved in thrombotic effects in hyperleptinemic-associated clinical disorders (Rafail et al., 2008).

To better understand the intersection of the metabolic and the immunological effects of leptin, we need to dissect central leptin resistance compared with leptin resistance in immune cells. The expression of both the short and the long isoforms of LEPR was found reduced in human peripheral blood mononuclear cells from obese compared with normal-weight individuals, suggesting a differential action of circulating leptin on these cells in dysmetabolic conditions (Tsiotra et al., 2000). A recent study in diet-induced obesity mice shed more light on this issue. While the injection of leptin in high-fat diet–fed mice was not able to reduce food intake or glycemia compared with saline-injected controls, demonstrating the loss of the hypothalamic actions of leptin (i.e., central leptin resistance), immune cells instead maintained their responsiveness to leptin stimulation in these obese animals, confirming the persistence of peripheral leptin signaling in the immune cell compartment (Souza-Almeida et al., 2020). Consistent results were obtained in obese rats, strengthening the evidence that obesity impairs the hypothalamic branch of leptin signaling, but not for the peripheral immune–metabolic one (Haas et al., 2008). While the biological mechanisms behind this phenomenon needs to be further elucidated, it is conceivable that leptin may keep fueling the inflammatory status in obesity, thus further exacerbating dysmetabolic conditions and the development of CVDs.

Role of leptin in cancer

Leptin effect on tumor progression

Mounting evidence supports the notion that obesity increases the risk of developing cancer and hampers therapeutic efficacy in the clinic (Calle et al., 2003; Font-Burgada et al., 2016). Pathological accumulation and dysfunction of adipose tissue, and chronic inflammation—characteristics of obesity—are well-recognized mediators of cancer. Dysmetabolic conditions such as hyperglycemia and insulin resistance further promote tumor growth (Deng et al., 2016). In addition, adipocyte-secreted proinflammatory factors, including leptin, regulate the expression of genes associated with cancer progression (adhesion, invasion, angiogenesis, signal transduction, and apoptosis), suggesting that adipocytes present in the tumor microenvironment directly support its growth (Carter and Church, 2012; Cascio et al., 2008). LEPR is highly abundant in many tumors as compared with normal tissues, e.g., leptin-responsive mammary

carcinoma and gastrointestinal malignancies (Howard et al., 2010; Ishikawa et al., 2004), and leptin signaling also synergizes with a plethora of different oncogenes, cytokines, and growth factors that impinge on the same signaling pathways (i.e., JAK-2/STAT, MAPK/ERK1/2, and PI-3K/AKT-1; Sánchez-Jiménez et al., 2019).

Significant research effort has been dedicated to unveiling the involvement of leptin in breast cancer (leptin involvement in the pathogenesis of other cancer types has been reviewed elsewhere; Garofalo and Surmacz, 2006). After correcting for body weight differences, females have higher leptin levels than males (premenopausal higher than post-menopausal), possibly related to estrogen and androgen regulation (Rosenbaum et al., 1996). The pronounced proliferative/anti-apoptotic response induced by leptin entangled with the estrogen pathway highlights obesity-associated hyperleptinemia as a risk factor for breast cancer (Dubois et al., 2014). Notably, the association of leptin levels with breast cancer risk persists after adjustment for obesity indices, suggesting that leptin may exert an independent role in breast tumorigenesis (Wu et al., 2009a).

Leptin expression in breast cancer, proposed as a relevant biomarker for grade, stage, lymph node involvement, relapse, and prognosis (Khabaz et al., 2017), was shown to regulate key pathways of proliferation and inhibition of apoptosis, tumor neo-angiogenesis, and invasion (Gonzalez et al., 2006; Knight et al., 2011; Mauro et al., 2007; Nepal et al., 2015; Saxena et al., 2008; Saxena et al., 2007; Fig. 2). This pro-tumorigenic action of leptin, which reflects its general role as mitogenic and pro-inflammatory factor, would make it a useful therapeutic target in cancer if leptin did not exert important parallel effects on anti-tumor immunity.

Leptin effects on tumor-infiltrating lymphocytes: Impact on immunotherapy

Since leptin has a recognized role in activating effector immune responses, it is reasonable to speculate that its action may enhance anti-cancer immunity. When oncolytic viruses (which replicate in tumor cells and induce cellular lysis/death and immune priming) were engineered to express leptin, their utilization resulted in complete tumor clearance in tumor-bearing mice, explained with the capability of leptin to reprogram tumor-infiltrating T cell metabolism and effector function (Rivadeneira et al., 2019). Leptin overexpression at the tumor site was able to increase mitochondrial capacity and cellular activation and induce an effector memory gene expression signature in tumor-infiltrating $CD8^+$ T cells that was reflected in successful tumor rejection upon rechallenge of tumor-bearing survivors (Rivadeneira et al., 2019). These results underline the validity of leptin up-regulation as a promising strategy for the stimulation of anti-cancer T cell fitness and immunity (Harjes, 2019; Kroemer and Zitvogel, 2019; Fig. 2). However, conflicting results showed that leptin is likewise linked to an impairment of anti-tumor efficacy by up-regulation of programmed cell death (PD)-1 on $CD8^+$ T cells and subsequent decreased proliferation and functional exhaustion in the tumor environment (Wang et al., 2019; Zhang et al., 2020). Across multiple species and tumor models, obesity-dependent leptin signaling appeared to be involved in higher PD-1 expression and T cell aging on one side, and augmented response to anti–PD ligand-1 checkpoint blockade on the other. The observation provides a mechanism by which this therapeutic strategy appears more efficient for obese compared with nonobese cancer patients, augmenting both their progression-free and overall survival (Wang et al., 2019).

To summarize, while important information has been gained, the balance of leptin effects on either immune anti-tumor activity or cell exhaustion and the response to anti–PD ligand-1 therapeutics in different tumor types and/or contexts (such as the patient's metabolic background) still remain elusive.

Leptin-based therapeutics

Leptin agonism in genetic and acquired leptin deficiencies

The discovery of the hormone leptin was welcomed as a cure for obesity (Campfield et al., 1995), especially since the proof of concept of regulation of appetite and the correction of obesity following daily injections of recombinant leptin in a child with leptin deficiency (Farooqi et al., 1999). Subsequent administration of leptin to additional patients with congenital leptin deficiency resulted in an increased ability to curb the wanting response to well-liked foods and not only exerted beneficial effects on appetite, fat mass, metabolic parameters, and pubertal development timing but also reversed T cell numeral and phenotypic abnormalities (Farooqi et al., 2007; Farooqi et al., 2002).

Besides genetic leptin deficiency, other conditions that warrant leptin replacement therapy are the lipodystrophy syndromes. In both genetic and acquired lipodystrophies, the pathological loss of adipose tissue leads to leptin reduction, which in turn results in hyperphagia and metabolic dysregulation (Garg, 2004). In these patients, the administration of r-metHuLeptin significantly lowered daily caloric intake and triglyceride levels while improving glycemic control (Diker-Cohen et al., 2015; Oral et al., 2002). Recombinant leptin can also come to the aid of women with hypothalamic amenorrhea whose reproductive cycles have been interrupted by strenuous exercise, eating disorders, or other social, environmental, and psychological abnormalities (Yen, 1993). Leptin treatment was shown to not only reactivate the menstrual cycle and correct neuroendocrine abnormalities but also stimulate $CD4^+$ T cell survival and proliferation and thus sustain immune reconstitution, demonstrating a better recovery than that obtained by changes in lifestyle (Chou et al., 2011; Matarese et al., 2013; Welt et al., 2004).

While a note of caution comes from a study that reported aggravation of concurring Crohn's disease in a patient with acquired generalized lipodystrophy upon leptin replacement (Ziegler et al., 2019), other observations revealed instead that this therapy did not sensibly alter the clinical course of autoimmune disease or clinical efficacy of immunosuppressive treatments (Lebastchi et al., 2015). Furthermore, the development of T cell lymphoma in patients with lipodystrophy has been associated with the higher risk for lymphoma in those patients, rather than with the use of exogenous leptin (Brown et al., 2016; Brown et al., 2018).

In conclusion, leptin replacement mostly causes adverse effects consistent with the biological function of the hormone such

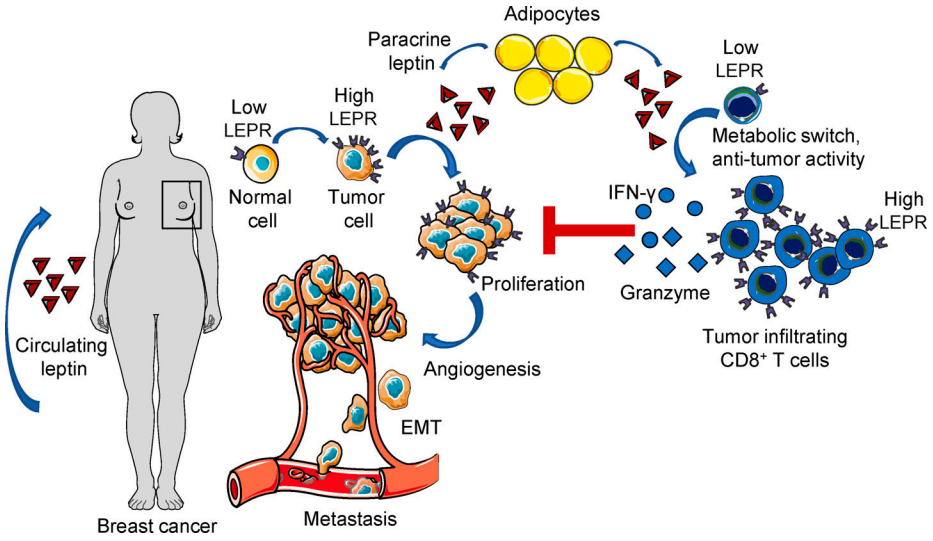

Figure 2. **Divergent effects of leptin on tumor progression.** In breast cancer, both circulating and paracrine leptin have a pro-tumor effect by enhancing cell transformation, proliferation, neo-angiogenesis, epithelial-to-mesenchymal transformation (EMT), and metastatic evolution. At the same time, leptin is able to activate the anti-tumor immune response by stimulating a metabolic switch and functional enhancement (secretion of cytokines and granzymes) of tumor-infiltrating $CD8^+$ T cells, able to kill tumor cells and hamper tumor progression. Schematic figures were created with images adapted from Smart Servier Medical Art (http://www.servier.fr/servier-medical-art).

as weight decrease, hypoglycemia, and decreased appetite (Brown et al., 2018; Oral et al., 2019), but it is very efficacious in restoring conditions of leptin deficiencies. In addition, the consistent and long-lasting decrease in food intake and weight loss after leptin injection, not only in *ob/ob* but also in wild-type animals (Pelleymounter et al., 1995), suggested the use of leptin also to regulate weight in individuals without leptin-related genetic disorders.

Leptin agonism in obesity

A very recent study has reported that short-term leptin administration decreased food intake after fasting, while long-term leptin treatment was able to reduce fat mass and body weight and modulated levels of circulating free fatty acids in lean normo- or mildly hypo-leptinemic individuals (Chrysafi et al., 2020). However, unlike in leptin-deficient subjects, leptin therapy failed to be a panacea in fighting obesity in subjects with normal genes for leptin and its receptor but with high leptin levels and leptin resistance. The significant increase of serum leptin after r-metHuLeptin treatment in obese subjects promoted the generation of anti-leptin antibodies and did not lead to weight loss beyond that achieved by hypocaloric diet alone (Shetty et al., 2011). Also, in the presence of obesity and T2D, r-metHuLeptin reduced hemoglobin A_{1c} albeit only marginally, but did not modulate body weight or circulating inflammatory markers, possibly due to the saturable nature of leptin signaling pathways (Moon et al., 2011).

This emerging knowledge has prompted the use of leptin-pathway modulators to overcome leptin resistance, such as islet amyloid polypeptide (IAPP or amylin), a pancreatic peptide cosecreted with insulin, shown to restore leptin-dependent STAT-3 phosphorylation in the hypothalamus (Roberts et al., 1989; Roth et al., 2008), and glucagon-like peptide-1 receptor agonists, able to promote leptin sensitivity and enhance leptin-induced weight loss in mice (Clemmensen et al., 2014). Nonetheless, more studies are needed to design optimal therapeutic strategies to ameliorate the anorexic effects of leptin in obese subjects.

Leptin modulation in T1D

T1D, characterized by insulin deficiency due to the autoimmune destruction of pancreatic β-cells (Eisenbarth, 1986), is the prototypical disease in which the contrasting beneficial and detrimental effects of leptin pleiotropy coexist. On the one side, a spontaneous single-base mutation in the *Lepr* of nonobese diabetic (NOD) mice (designated as NOD/db-5J) resulted in obesity and metabolic disturbances resembling a T2D syndrome but also drastically hampered intra-islet insulitis, thus down-regulating T1D autoimmunity and causing diabetic remission (Lee et al., 2006; Lee et al., 2005). In these mice, the genetic blockade of leptin signaling has an effect on disease onset and mostly reveals the pro-inflammatory nature of leptin in NOD/wild-type mice. Consistently, leptin administration early in life to prediabetic NOD females significantly augmented IFN-γ production by T cells and accelerated immune-mediated pancreatic destruction (Matarese et al., 2002).

On the other side, experimentally induced hyperleptinemia in NOD mice blocked hyperglucagonemia, improved glucose utilization in skeletal muscle, normalized hemoglobin A_{1c}, reduced plasma and tissue lipids, and reversed insulin deficiency, rescuing animals from ketoacidosis and death, since leptin is very powerful in allowing glucose entrance in tissues (Wang et al., 2010; Yu et al., 2008). The pleiotropic effects of leptin on T1D onset and progression are depicted in Fig. 3, and the summary of leptin-based therapeutic results is reported in Table 2.

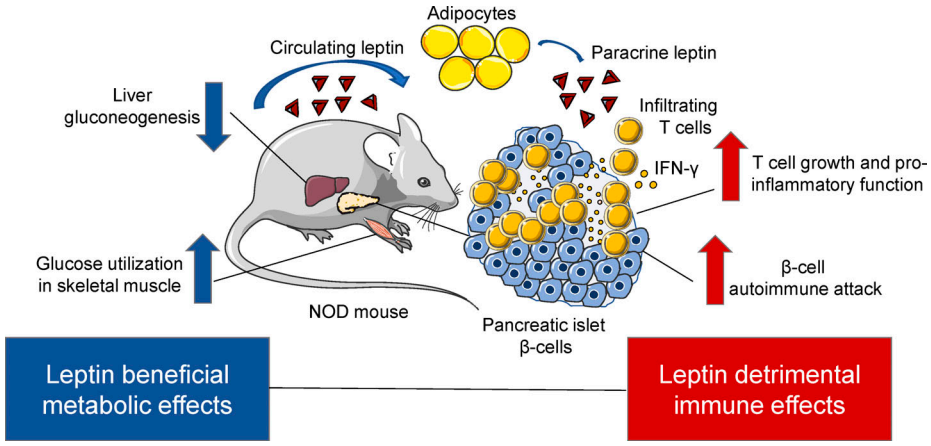

Figure 3. **Leptin as pro-inflammatory molecule but able to reduce hyperglycemia in T1D.** In NOD mice (disease model for human T1D), both circulating and paracrine leptin have a pro-autoimmune detrimental function, since they are able to stimulate the growth and the function of pancreatic islet infiltrating T cells, fueling local inflammation and β-cell destruction. In NOD mice at later stages of diabetic progression, the beneficial metabolic effects of leptin (enhancement of glucose entrance and utilization by peripheral tissues and decrease of liver gluconeogenesis) may take over, thus reducing hyperglycemia. Schematic figures were created with images adapted from Smart Servier Medical Art (http://www.servier.fr/servier-medical-art).

The capability of leptin to correct metabolic imbalance in the NOD mouse model led to consideration of this molecule in T1D therapy (Buettner, 2010). Recently, r-metHuLeptin was reported to reduce body weight and the daily insulin dose, although modestly, but failed to improve glycemic control in patients with T1D (Vasandani et al., 2017). The small number of patients in this pilot study (five female and three male patients) warrants studies of larger cohorts to draw more definitive conclusions.

Leptin antagonism: Lights and shadows

In specific pathological conditions, antagonizing leptin signaling can represent a therapeutic strategy to block leptin-mediated detrimental enhancement of autoreactive immune cells (autoimmune diseases) or tumor progression (Zabeau et al., 2014). In 1997, a prototypical antagonistic molecule, able to bind the receptor but knock out the signaling, led to a progressive increase of body weight in wild-type mice, and was proposed as potentially useful in the treatment of anorexia and cachexia (Verploegen et al., 1997). Optimized antagonistic leptin molecules have then been shown to attenuate inflammation and clinical severity in mouse models of chronic liver fibrosis (Elinav et al., 2009), chronic experimental colitis (Singh et al., 2013), RA (Otvos et al., 2011b), EAE (De Rosa et al., 2006), and SLE (Yu et al., 2013). Administration of a LEPR antagonist peptide significantly extended the average survival time in a mouse xenograft model of aggressive breast cancer (Otvos et al., 2011a), while in rats with transplanted acute myelocytic leukemia, a neutralizing anti-LEPR antibody halved the number of bone marrow leukemic cells and significantly blocked tumor angiogenesis (Iversen et al., 2002), demonstrating beneficial effects of leptin-antagonistic approaches also in models of cancer.

Notwithstanding the encouraging results in animals, the problematic drawback of the use of leptin antagonism to treat autoimmune diseases and cancer (Ray and Cleary, 2010) is that it also impacts the beneficial metabolic effects of leptin, mainly at the central level of the hypothalamus, with an inevitable, undesired weight gain. Moreover, in the case of cancer, additional studies are necessary to reveal the balance between the beneficial effects of leptin antagonism on slowing tumor growth and the detrimental effects possibly exerted on antitumor immunity.

Concluding remarks

Leptin may have been positively selected evolutionarily to prompt the pursuit of food during periods of famine, and to provide a defense against pathogens. As such, it may convey an evolutionary advantage and/or promote fertility/reproduction (Prentice et al., 2008). As for other pleiotropic genes, this selective force may have worked for leptin-dependent advantages at a young age irrespective of the disadvantages at older ages (Williams, 1957). The current increase in human lifespan, mainly attributable to the widespread availability of multiple therapeutics, antibiotics, vaccines, and hygiene measures, has uncovered the long-term deleterious effect of leptin on aging, inappropriate feeding states, and the development of metabolic diseases. Furthermore, the contemporary abundance of food and the alarming obesity epidemic in the Western world have further promoted the detrimental action of leptin on the development of autoimmune diseases and cancer. While leptin administration remains the gold standard therapy for leptin-deficient individuals, its success as a weight-regulator drug in obesity is dramatically hampered by leptin resistance. Furthermore, leptin pleiotropy makes it a powerful molecule on a biological perspective but a hurdle for its therapeutic modulation; all leptin modulation strategies will thus need to dissect its beneficial versus detrimental effects in the specific pathological contexts.

Table 2. **Effects of exogenous leptin replacement or leptin antagonism in animal models and in human diseases**

Leptin agonism			
Background	**Features**	**Clinical outcome**	**Reference**
Mouse			
ob/ob	Obesity, excessive food intake, infertile	Decrease of body weight, food intake, serum insulin and glucose level; normalization of body fat percentage; increase of total activity and lean mass	Pelleymounter et al., 1995; Halaas et al., 1995
db/db	Obesity, excessive food intake, infertile, hyperglycemia	Not responding	Halaas et al., 1995; Farooqi et al., 1999
Human			
Congenital leptin deficiency	Early-onset obesity, hyperphagia, alteration of the immune function	Weight loss, decreased basal metabolic rate, increased physical activity level, increased basal and stimulated serum gonadotropin concentration	Farooqi et al., 1999
Acquired leptin deficiency (lipodystrophy)	Generalized lack of body fat, insulin resistance, hypertriglyceridemia, polycystic ovary syndrome	Decreased average triglyceride level, glycosylated hemoglobin, and plasma glucose level; improved metabolic control	Oral et al., 2002; Santos and Cortés, 2020
Mutation in the *LEPR* gene	Early-onset obesity, hyperphagia, impaired pubertal development, reduced secretion of growth hormone and thyrotropin	Not responding (other possible therapies: bariatric surgery or setmelanotide treatment)	Clément et al., 1998
General obesity	Dysmetabolic syndrome, leptin resistance	Not responding	
Leptin antagonism (rodent studies only)			
Pathology	**Antagonizing molecule**	**Clinical outcome**	**Reference**
Inflammation and Autoimmunity			
Chronic liver fibrosis	Mutated leptin	Reduced IFN-γ levels, attenuated liver fibrosis, improved survival	Elinav et al., 2009
Chronic experimental colitis	Mutated leptin	Reduced systemic and mucosal pro-inflammatory cytokines and clinical severity; increased T reg cell number	Singh et al., 2013
EAE	Neutralizing leptin antibody or soluble LepR chimera	Slowed disease progression, reduced relapses, $FOXP3^+CD4^+$ T cell induction and pro-inflammatory T cell proliferation blockade	De Rosa et al., 2006
SLE	Neutralizing leptin antibody	Hampered pro-inflammatory Th17 cell response	Yu et al., 2013
Cancer			
Aggressive breast cancer	LepR antagonist	Increased average survival time	Otvos et al., 2011a
Acute myelocytic leukemia	Neutralizing LepR monoclonal antibody	Decreased leukemic cell number and angiogenesis within the bone marrow	Iversen et al., 2002

Acknowledgments

G. Matarese is supported by Fondazione Italiana Sclerosi Multipla (grants 2016/R/18 and 2018/S/5), Progetti di Rilevante Interesse Nazionale (2017 K55HLC 001), and the Italian Ministry of Health (RF-2019-12371111). P. de Candia is funded by Fondazione Italiana Sclerosi Multipla (grant 2018/R/4). This work has also been supported by the Italian Ministry of Health Ricerca Corrente to Istituto di Ricovero e Cura a Carattere Scientifico MultiMedica.

Author contributions: G. Matarese conceived the original idea, wrote the initial draft, provided oversight and leadership responsibility for this paper, and edited the manuscript. P. de Candia collected the literature to be cited, wrote the manuscript, and prepared the figures. A. La Cava substantially edited the manuscript and gave key advice. F. Prattichizzo wrote part of the initial draft, contributed with useful discussions, and reviewed the final manuscript. S. Garavelli helped with preparing the tables and the figures and revised the final draft. C. Alviggi contributed to the initial draft and revised the final manuscript. All authors gave consent to the final version of the work.

Disclosures: C. Alviggi reported personal fees from Merck outside the submitted work. G. Matarese reported grants from Merck, personal fees from Merck, grants from Biogen, personal fees from Biogen, personal fees from Roche, personal fees from Novartis, and grants from IBSA outside the submitted work. No other disclosures were reported.

Submitted: 18 December 2020
Revised: 10 March 2021
Accepted: 11 March 2021

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