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Leptin as regulator of pulmonary immune responses: Involvement in respiratory diseases

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Abstract

Leptin is an adipocyte-derived hormone, recognized as a critical mediator of the balance between food intake and energy expenditure by signalling through its functional receptor (Ob-Rb) in the hypothalamus. Structurally, leptin belongs to the long-chain helical cytokine family, and is now known to have pleiotropic functions in both innate and adaptive immunity. The presence of the functional leptin receptor in the lung together with evidence of increased airspace leptin levels arising during pulmonary inflammation, suggests an important role for leptin in lung development, respiratory immune responses and eventually pathogenesis of inflammatory respiratory diseases. The purpose of this article is to review our current understanding of leptin and its functional role on the different resident cell types of the lung in health as well as in the context of three major respiratory conditions being chronic obstructive pulmonary disease (COPD), asthma, and pneumonia.

Keywords

Leptin; Asthma; COPD; Pneumonia; Pulmonary immunity

1. Introduction

Leptin is a 16 kDa non-glycosylated polypeptide encoded by the ‘obese’ (*ob*) gene [1]. Originally described as a hormone secreted by adipocytes in proportion to total fat mass, leptin was implicated in early studies as a critical mediator of the balance between food intake and energy expenditure by signalling through its functional receptor (Ob-Rb) in the hypothalamus [2,3]. However, leptin belongs structurally to the long-chain helical cytokine family, which includes interleukin-6 (IL-6), G-CSF, and oncostatin M amongst others, and

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shares an extreme functional pleiotropy with many other members of this family. The near universal distribution of leptin receptors, including in the respiratory system, reflects a multiplicity of biological effects. Leptin has been reported to participate in diverse physiological functions in both the central nervous system and the periphery, including appetite and body mass control, metabolism, endocrine function, immune response, wound healing, reproduction, cardiovascular pathophysiology, and respiratory tissue development, remodelling, and function.

Adipocytes located in various fat depots are a major, but not sole source of leptin. Cells of the placenta [4], gastric mucosa [5], colon [6], mammary epithelium [7], pituitary, hypothalamus [8], skeletal muscle [9,10], bone [11] and bone marrow [12] have also been shown to produce leptin in certain circumstances [2]. Leptin expression has also been described in the lung tissues of humans [13], baboons [14], mice [15], seals [16], and even Xenopus [17]. Recent studies have shown leptin secretion by human lung epithelial cell types, including bronchial epithelial cells (BEC) [13,18], type II pneumocytes [13], and lipofibroblasts [19].

Leptin expression in adipocytes is regulated by food intake and circulating leptin levels have been shown to positively correlate with insulin levels. In addition, glucocorticoids appear to be potent regulators of leptin expression based on *in vitro* studies of isolated adipocytes [20], while a gender-related leptin regulation is suggested by the findings that leptin expression is increased by ovarian sex steroids and inhibited by testosterone [21–23]. Other modulators of leptin expression include a wide range of pro-inflammatory cytokines – including TNFα – which are known to acutely increase leptin synthesis in adipocytes [24,25], whereas chronic stimulation with such cytokines appears to lead to a suppression of leptin synthesis [26,27]. In the normal lung, numerous cell types display high levels of Ob-Rb [28,29], and specific leptin-binding sites have been identified in both bronchial and alveolar epithelial cells [30–32], airway smooth muscle cells, and (infiltrating) inflammatory cells. Multiple observations that leptin is actually present in induced sputum [33–35], proximal airway biopsies [18], bronchoalveolar lavage (BAL) fluid [36,37], and peripheral lung tissue [13] of patients with lung disease, strongly suggest the lung as a peripheral site of action for leptin. The present review aims to summarize our current understanding on leptin and its functional role in the respiratory system in homeostasis and inflammatory lung diseases.

2. Leptin signal transduction

Leptin acts via the Ob-R transmembrane receptor, which shares structural similarities with the class I cytokine receptor superfamily [38,39]. Members of this family have signature extracellular domains (so-called cytokine receptor homology or CRH domains) characterised by a set of four cysteine residues and the highly conserved Trp-Ser-Xaa-Trp-Ser motif. Several alternative splice isoforms of Ob-R exist in humans and rodents, designated Ob-Ra, Ob-Rb, Ob-Rc, Ob-Rd, Ob-Re (only in rats and mice) and Ob-Rf (only in rats). All isoforms contain the same extracellular domain of over 800 amino acids consisting of two CRH domains, separated by an immunoglobulin (Ig)-like domain and followed by two membrane-proximal fibronectin type III domains [38–40]. With the exception of Ob-Re which is a secreted receptor variant, they all share a similar transmembrane and

juxtamembrane JAK-binding domain of 34 and 29 amino acids respectively, followed by a variable intracellular domain. The isoforms can thus be classified into short isoforms (Ob-Ra, Ob-Rc, Ob-Rd and Ob-Rf), a full-length long isoform Ob-Rb, and a secreted isoform Ob-Re. Of note, the latter only exists in rodents. In man, a secreted Ob-R ectodomain is generated by proteolytic cleavage by the ADAM10 and ADAM17 metalloproteases [41]. Ob-Rb was initially considered to be the only functional isoform of the leptin receptor, based on its extended intracellular domain of approximately 300 residues containing various motifs required for activation of multiple signalling pathways [38]. Although signalling functions have been ascribed to short Ob-R isoforms in over-expression studies [42], their role in physiological leptin-mediated effects remains to be established.

The early recognition of Ob-R as a class I cytokine receptor rapidly led to the identification of the JAK/STAT pathway as the primary signalling route. Leptin-induced JAK-2 activation results in the rapid phosphorylation of three, conserved, cytoplasmic tyrosine-based motifs that act as binding sites for different signalling molecules, including STAT-1, STAT-3, STAT-5 and STAT-6. In addition to signalling through the JAK/STAT pathway, leptin is also able to induce alternative pathways, including the MAPK cascade, the PI3K/PDE3B/cAMP pathway, AMPK and mTOR. These different signalling cascades activated by leptin have extensively been reviewed by Wauman and Tavernier [2]. Given the multitude of signalling pathways activated via the Ob-R, leptin's effects on different cell types can be expected to be highly cell-specific. A very well studied, direct target of leptin-induced STAT-3 is SOCS-3, a key negative feedback regulator of Ob-R signalling [43]. Changes in SOCS-3 expression have been postulated to underlie the phenomenon of leptin resistance in the context of obesity [44]. Another negative regulator of leptin signalling is PTP1B, which acts primarily via dephosphorylation of JAK-2 [45,46].

To summarize, leptin signal transduction, especially the pathways that are activated upon Ob-R activation, how Ob-R expression is controlled and the molecular mechanisms leading to leptin resistance, are all well-characterized. However, it is not currently known whether these individual signalling routes can indeed be activated in the respiratory system.

3. Role of leptin in respiration and lung development

Multiple studies have shown that leptin participates in the regulation of pulmonary development and remodelling. Huang et al. characterized the effect of leptin deficiency on postnatal lung development in leptin-deficient (*ob/ob*) mice [47] and showed that the lung volume and alveolar surface area were lower in obese mice compared with wild-type and heterozygote (*ob/+*) mice, and that the alveolar size did not increase with age. Leptin replacement in *ob/ob* mice resulted in increased lung volume, enlarged alveolar size and surface area, suggesting a role for leptin in remodelling of lung parenchyma. Leptin receptor-deficient (*db/db*) mice [29] exhibit a 75% decreased rate of tracheal epithelial proliferation compared with wild-type littermates, emphasizing a potential role for leptin in pulmonary growth. Along these lines, leptin treatment was shown to increase the weight of the lungs in relation to the total body weight [48,49]. Insufficient maturation of the foetal lungs, a condition that can be characterized by the production of inadequate amounts of pulmonary surfactant by epithelial type II cells, is a leading cause of human neonatal

morbidity and mortality following premature birth. In this light, Torday, et al. reported that leptin was expressed by fibroblasts and that the leptin receptor was expressed by type II cells in foetal rat lung [19], suggesting a paracrine signalling mechanism in developing pulmonary tissue. Leptin receptor was also identified in foetal rabbit type II cells [31] and additional evidence supported correlations between leptin, maturation of the pulmonary epithelium and surfactant production. Furthermore, leptin is present in the foetal baboon lung and its receptor is enhanced during late gestation in type II cells responsible for the synthesis of pulmonary surfactant [14]. A mechanistically integrated link between leptin and its function in respiration and lung development was recently provided by the finding that leptin stimulates *Xenopus laevis* tadpole lung development [17]. However, a recent study by Sato et al. shows that neither leptin deficiency in *ob/ob* mice nor treatment with exogenous leptin in sheep and wild type mice influenced foetal lung maturation or surfactant production [50]. An explanation for these paradoxical results can be found in the different models that were used in these two studies. In addition, the responses of foetal lung to the leptin treatment might vary by dose, duration, dosing interval, route, and gestation age.

Gnanalingham investigated the impact of chronic leptin administration on the abundance of UCP2 in the neonatal lung [49]. UCP2, a recently discovered member of the inner mitochondrial membrane carrier subfamily, is highly abundant in the lung [51,52] and has postulated roles in energy regulation, reactive oxygen species production, and apoptosis, but its exact role and function in the neonatal lung have yet to be determined. Chronic leptin administration was shown to decrease the abundance of UCP2 protein in the lung, which might promote reactive oxygen species production and maintain host immunity through augmentation of alveolar macrophage phagocytosis and leukotriene synthesis [49]. The decrease in UCP2 with leptin administration on later lung function needs further study.

Leptin also has also been shown to participate in the regulation of respiratory function. In the *ob/ob* mouse, respiratory abnormalities including tachypnoea, decreased lung compliance, and aberrant respiratory muscle adaptations, such as alterations in diaphragmatic muscle MHC composition, are common with the obese phenotype [53]. Tankersley et al. showed that these respiratory abnormalities were attenuated following prolonged leptin administration [53]. Similarly, in wild-type mice that were obese due to a high-fat diet, respiratory depression was reversed by leptin treatment [54], suggesting a significant role of leptin as a neurohumoral modulator of central respiration, and in general pulmonary health as well.

Collectively, these findings suggest a modulatory role for leptin in pulmonary development and identify leptin receptor as a physiological marker of foetal lung maturity. In addition, there is increasing evidence showing that leptin is an important player in respiration, but additional research is needed in order to unravel the underlying mechanisms.

4. Role of leptin in inflammatory lung diseases

Numerous studies demonstrate that leptin has a potentiating role in the function of both innate and adaptive immunity [55], making it an ideal candidate for a central role in inflammatory respiratory diseases such as COPD, asthma, and pneumonia. Leptin is known

to stimulate neutrophil and macrophage chemotaxis and enhance functional responses such as oxidative burst [56], phagocytosis [57] and cytokine secretion [58,59]. Neutrophil chemotaxis response was shown to be blunted in leptin-resistant *db/db* mice as well as in mice with diet-induced obesity [60], which may indicate a crucial role for leptin signalling these cells. In addition, leptin promotes differentiation, survival, and immunostimulatory functions of dendritic cells (DCs), resulting in stronger heterologous T cell responses. Furthermore, leptin exerts proliferative [61] and anti-apoptotic effects [62] on T-lymphocytes and promotes Th1 cell differentiation [63]. The possible effects of leptin on the different (resident) cell types of the lung during inflammation will be discussed in the context of three major respiratory conditions: chronic obstructive pulmonary disease (COPD), asthma, and pneumonia.

4.1. COPD

Chronic obstructive pulmonary disease (COPD) is a leading and increasing cause of morbidity and mortality worldwide. COPD is recognized as a multi-organ disease [64], manifest by airflow limitation associated with both structural changes and an abnormal pulmonary inflammatory response to noxious particles or gases, including tobacco smoke [65], accompanied by various extra-pulmonary manifestations such as low-grade systemic inflammation [66] and an increased prevalence of cardiovascular co-morbidity [67].

4.1.1. Circulating leptin—The role of circulating leptin in the systemic manifestation of COPD is poorly understood and has in the past mainly been examined in male COPD patients with a low BMI (<21 kg/m^2) [68–70]. In women with COPD, serum leptin concentrations are increased compared to normal healthy women [71]. In addition, circulating leptin levels are higher in women with COPD than men with COPD, and increase with rising fat mass to a greater extent in women with COPD than in their male counterparts [71]. Moreover, Breyer et al. recently showed that there is a complex relationship between adipokine metabolism and low-grade systemic inflammation in COPD, with a significant relationship between circulating leptin and CRP and fibrinogen [72].

Both the BODE index (the body-mass index (B), the degree of airflow obstruction (O) and dyspnea (D), and exercise capacity (E), measured by the 6-minewalk test) [73] and fat-free mass index (FFMI) have been shown to be associated (positively and negatively, respectively) with circulating levels of leptin in COPD patients. In addition, leptin is the most significant predictor of low FFMI in those patients [74]. To date, however, longitudinal studies investigating the relationship between increased circulating leptin concentrations and clinical outcomes in COPD are lacking.

4.1.2. Pulmonary leptin—As the lung is highly vascularized, increased circulating levels of leptin may also contribute to the pathogenesis of lung inflammation and injury in COPD. Different types of inflammatory cells such as macrophages, neutrophils, dendritic cells, CD8+ T-lymphocytes have been implicated in the chronic inflammation associated with COPD, and a distinct inflammatory pattern has been described in each lung compartment [75]. In light of the immunomodulating effects of leptin, leptin may be a good candidate for the regulation of pulmonary immune function in COPD. Indeed, Broekhuizen and

colleagues demonstrated that leptin is present in induced sputum samples of mild-to-moderate COPD patients, and showed a strong correlation between sputum levels of leptin and both CRP and TNFα [33]. A more recent study on the expression of leptin in peripheral lung tissue of COPD patients, asymptomatic smokers, and never-smokers suggested that bronchial epithelial cells, type II pneumocytes, and alveolar macrophages are significant sources of pulmonary leptin [13]. Numbers of leptin-expressing bronchial epithelial cells and alveolar macrophages were markedly higher in smokers with and without COPD versus never-smokers, indicating that tobacco smoke may be a trigger for pulmonary leptin expression. This was confirmed by aireliquid interface cultures of primary epithelial cells, which demonstrated a dose-dependent increase in leptin mRNA expression and protein production after cigarette smoke concentrate stimulation [13]. Bruno et al. [18] also reported positive immunostaining for leptin protein in central airway epithelium from human bronchial biopsies, but found a decrease in leptin-positive epithelial cell counts in smokers and COPD patients compared to never-smokers. This difference may, however, be explained by different tissue specimens used in the two studies. Furthermore, in a more recent study, Bruno et al. [35] suggests that leptin plays a role in both pulmonary and systemic inflammation in current and former smokers with COPD. The leptin/Ob-R pathway may contribute to the improvement in host defence seen in COPD patients after smoking cessation, by augmenting neutrophil function. Lastly, associations between genetic polymorphisms in leptin and Ob-R genes and (severity of) COPD were investigated. Hansel et al. [76] examined the association between genetic variants in the Ob-R gene and lung function decline in European Americans selected from the National Heart Lung and Blood Institute Lung Health Study. significant associations between multiple SNPs in the Ob-R gene and lung function decline were identified and confirmed by haplotype analyses in a population of smokers with COPD. In addition, Ye et al. [77] recently showed a significant association between the polymorphism −2548 G/A in the leptin gene (linked to enhanced gene expression and increased circulating leptin levels [78] and the severity of COPD in a Chinese population.

In summary, increasing data suggest that leptin is present in induced sputum and lung tissue of COPD patients. Pulmonary leptin may be associated with greater disease severity in COPD.

4.1.3. Smoke-induced lung inflammation—Cigarette smoke is a profound stimulus of the innate immune response leading to inflammation that drives COPD pathogenesis. Subsequent host defence mechanisms appear to be altered, rather than suppressed. The functional role of leptin in smoke-induced lung inflammation and pathology is still under investigation. Specific leptin-binding sites have been identified in BEC and type II pneumocytes [30–32], suggesting a potential autocrine and/or paracrine pathway for leptin to activate epithelial cells in COPD. Indeed, leptin was shown to activate several intracellular signal transduction pathways in bronchial epithelial cells [13,79,80], including JAK/STAT and MAPK pathways. Interestingly, Woo et al. showed that leptin upregulates mucin production in human airway epithelial cells [79], hereby suggesting that leptin may contribute to mucus hypersecretion in inflammatory lung diseases. Further studies are clearly needed to determine additional effects of leptin on airway epithelial cells.

An interesting study published by Hansel and co-workers [76] showed a reduction in the expression of Ob-R receptor isoforms in the airspace and airway wall after 4 months of smoke exposure in AKR/J mice. It has yet to be determined whether these findings correspond to reduced leptin signalling in the lung. In another smoking mouse model, characterized by increased accumulation of neutrophils, DCs, macrophages, and lymphocytes in the lung, leptin expression in BEC and pneumocytes was significantly increased in cigarette smoke-exposed wild-type mice compared to air-exposed controls. Evidence that leptin is in fact involved in innate and adaptive immune cell recruitment is provided by studies of mice deficient in leptin signalling (*ob/ob* and *db/db* mice), which show significantly higher numbers of neutrophils and lower numbers of CD4+, CD8+ and dendritic cells compared to cigarette smoke-exposed wild-type mice [15]. Increases in neutrophil and monocyte chemoattractants CXCL1 and CCL2 seen in this model were significantly enhanced in the BALF of cigarette smoke-exposed *ob/ob* and *db/db* mice compared to wild-type mice.

To summarize, there is increasing literature showing the presence of the functional leptin receptor in the lung together with evidence of local leptin production in the respiratory compartment. Together, this supports the concept of autocrine and/or paracrine cross-talk between resident pulmonary epithelial cells and immune cells in response to inhaled noxious particles or gases. Further validation of this hypothesis by additional experimental and clinical studies is obviously needed to better understand the immunomodulating role of leptin in the pathogenesis of smoking-related COPD.

4.2. Asthma

Asthma is a prevalent and complex disorder that can occur in genetically predisposed individuals through a series of genee environment interactions [81]. Acute and chronic inflammation of the bronchi and the conducting airways plays a central role in the pathogenesis of asthma, and lead to airflow obstruction and the respiratory symptoms of the disease, such a wheezing, coughing, chest tightness, and dyspnea. inflammation is also important in the development of the airway hyperresponsiveness observed in asthmatics, as well as in the emergence of more permanent structural alterations to the airway walls, termed ‘airway remodelling’. Originally, a T_H1/T_H2 imbalance was proposed to explain the T_H2 mediated allergic airway inflammation in asthmatics. However, recent research has focused increasingly on the failure of endogenous tolerance mechanisms, including impaired function of regulatory T-cells (Tregs) [82] and airway epithelial cells [81].

4.2.1. Obesity and asthma—Over the past decade, the interaction between obesity and asthma pathogenesis has become apparent. Several epidemiological studies reported a higher prevalence and incidence of asthma in obese versus lean individuals [83–87]. Moreover, obesity appears to increase asthma severity and impair effective treatment and control of the disease [88,89]. However, the underlying mechanisms of this obesityeasthma relationship have not yet been elucidated. Several possibilities have been postulated [90], including common genetic and environmental factors [91], reduced lung volume and airway diameter in obese individuals [92], comorbidities of obesity such as sleeping-disordered breathing [93] and last but not least, the chronic low-grade systemic inflammation that accompanies

obesity [94]. The latter includes increased serum levels of cytokines, chemokines, acute phase proteins and energy regulating hormones such as leptin [95,96].

4.2.2. Mouse models—The possible role of leptin in allergic airways disease has been studied extensively in mouse models. Mice sensitized to and challenged with ovalbumin (OVA) exhibit many features of asthma, including increased airway hyperresponsiveness (AHR) to methacholine, increased airspace eosinophils, neutrophils and lymphocytes, and T_H2 cytokine expression, and increases in serum IgE. Interestingly, OVA-treated mice show increased serum levels of leptin, while exogenous administration of leptin augments OVA-induced AHR and serum IgE levels [97]. These augmenting effects of leptin on AHR may be due to a direct effect of leptin on airway smooth muscle (ASM) cells or may be related to the effects of leptin on IgE production. Cross-linking of high-affinity IgE receptors (FcεRI) on mast cells upon binding of allergen to IgE results in degranulation of these cells and subsequent release of mediators such as histamine, prostaglandin D_2 and cysteinyl leukotrienes, which are all powerful bronchoconstricting agents [98]. Importantly, exogenous administration of leptin has no apparent effects on the OVA-induced eosinophil recruitment to or T_H2 cytokine expression in the airways, suggesting that leptin is capable of augmenting AHR independently of T_H2 inflammation. This supports the hypothesis that leptin may instead be acting on the innate immune system. Along these lines, studies have shown that exogenous leptin increases the pulmonary inflammatory response following acute exposure to ozone (O_3) [99], a common trigger for asthmatic episodes, known to act through activation of Toll-like receptors [100]. These augmented responses to O_3 have also been observed in obese Cpe^{fat} mice [101] and in mice with diet-induced obesity [102], both of which manifest high circulating levels of leptin. However, as similar responses to O_3 are also observed in *ob/ob* [99] and *db/db* [101] mice, which lack leptin signalling, additional factors appear to be involved in the augmented response to O_3 in obese mice.

In conclusion, experimental mouse studies support an augmenting role for the leptin-axis in airway hyperresponsiveness, possibly independently of T_H2 inflammation but via a direct effect of leptin on airway smooth muscle.

4.2.3. Circulating leptin—Several human studies have reported on the relationship between serum leptin levels and the occurrence of asthma. Guler et al. found that serum leptin levels of asthmatic children and especially of asthmatic boys were increased compared to healthy controls, in spite of no difference in BMI levels [103]. In adult asthmatics, increased serum leptin levels compared to non-asthmatics have been described, however this association appeared stronger in women than in men [104]. Jartti et al. studied the link between leptin and asthma in individuals who were followed 21 years from childhood to adulthood. They found high serum leptin levels to be associated with asthma only in adulthood. However, this association did not persist when clinical data, such as age, parental asthma and active smoking status, were included in the statistical model [105]. Other studies have found no correlation between serum leptin levels and asthma [106,107]. Altogether, evidence of a link between asthma and serum leptin remains unclear and further studies are needed to elucidate whether leptin directly participates in the pathogenesis of asthma, perhaps in certain subsets of this heterogeneous disease, or whether increased serum

leptin levels are merely the result of the systemic inflammation that accompanies both asthma and obesity.

4.2.4. Pulmonary leptin—Although several studies have reported on the possible relationship between asthma and systemic levels of leptin, less is known regarding the presence and role of leptin in the pulmonary compartment. Expression of both leptin and its receptor has been described in the lung, especially in bronchial epithelial cells (BECs) and type II pneumocytes [13,29,108], but how these may be affected by obesity or allergic airway inflammation remains unclear. In mice, it has been shown that obese *db/db* mice, which lack the leptin receptor and show innate AHR, have higher leptin levels in bronchoalveolar lavage (BAL) fluid [109]. Moreover, these levels are modulated by PPARg ligands, which have been shown to reduce allergic inflammation and AHR. In humans, preliminary studies show increased BAL leptin levels in obese individuals compared to lean individuals, with positive correlations between BAL leptin levels and BMI, lung function, and BAL levels of TNFα, nitrates, and 8-isoprostanes, particularly in asthmatics [110–112]. In addition, Lugogo et al. recently demonstrated that primary alveolar macrophages derived from overweight/obese subjects with asthma are uniquely sensitive to leptin [110–112]. *Ex vivo* studies indicated that leptin alone was sufficient to induce production of pro-inflammatory cytokines from primary macrophages derived from overweight/obese subjects with asthma and pre-exposure to high-dose leptin enhanced the LPS-induced proinflammatory response [110–112]. This leptin-sensitive macrophage phenotype, in the context of higher levels of soluble leptin in the pulmonary compartment, may contribute to the pathogenesis of airway diseases associated with obesity.

On the other hand, Holguin et al. [36] showed that BAL adipokine levels (leptin and adiponectin) were not associated with the airway biomarkers of oxidation and inflammation. In addition, Bruno et al. reported a decreased expression of leptin and its receptor in BECs isolated from patients with mild or severe, uncontrolled asthma, compared to healthy individuals [108]. Moreover, these investigators found leptin and leptin receptor expression in isolated BECs to be inversely related to features of airway remodelling such as basement membrane thickening and TGF-β expression.

In summary, leptin is present in the pulmonary compartment of asthmatics. There is developing – but conflicting – literature suggesting a potential role for pulmonary leptin in inflammatory asthma. More studies are warranted to investigate mechanisms of leptin action in asthma and to determine whether modulation of pulmonary leptin may be helpful in asthma prevention or treatment.

4.2.5. Leptin and eosinophils—Important to review with respect to asthma pathogenesis are the effects of leptin on eosinophils as one of the major effector cells in asthma. Human eosinophils are known to express the leptin receptor Ob-Rb [113] and several studies investigated the role of leptin in the functioning of eosinophils. Leptin was shown to be a direct chemoattractant factor for eosinophils [114,115], possibly through the activation of the ERK1/2 and p38 MAPK signalling pathways. In addition, leptin has a priming effect on eotaxin-induced eosinophil migration [114,116]. Other studies suggest that

leptin is an activating factor for human eosinophils and may prolong eosinophil survival by suppressing eosinophil apoptosis [113,115].

However, as discussed previously, exogenous administration of leptin in mice has no apparent effects on the OVA-induced eosinophil recruitment to the airways [97]. Furthermore, leptin deficiency has recently been suggested to potentiate eosinophilopoiesis and the accumulation of eosinophils in the lung following OVA [117]. These apparent conflicting data may be explained by the fact that there are key differences between murine asthma and human asthma, and that human studies are limited by the greater heterogeneity among subjects while murine studies are controlled experiments.

In conclusion, current studies indicate a strong association between asthma and obesity, however the direction of causality is yet unclear. Adequately powered longitudinal and interventional studies are needed to establish a clear direction in association. The current evidence supports an emerging central immune modulating role for leptin in the pulmonary compartment. Further studies targeting leptin signalling are currently under way to clarify the role of pulmonary leptin in asthma pathogenesis.

4.3. Pulmonary infections

Pneumonia is most commonly caused by bacteria, viruses, or – less frequently – fungi or parasites. The associated symptoms, such as cough, chest pain, fever and dyspnea, are accompanied by an inflammatory response in the lungs. Malnutrition, which is often seen in patients with chronic diseases such as COPD or cancer, greatly increases the susceptibility to pulmonary infections [118,119]. The mechanisms responsible for this impaired host defence against infections are poorly understood, but may be related to reduced leptin levels. Furthermore, growing evidence suggests an effect of high BMI, and hence *leptin resistance*, on susceptibility to both bacterial and viral pulmonary infections [120–122], as highlighted by the recent H1N1 influenza epidemic [123,124].

4.3.1. Bacterial infections

The possible role of leptin in the immune response to pulmonary infections has mainly been studied in experimental murine models. Mice infected by intratracheal challenge with *Klebsiella pneumoniae*, a gram-negative bacteria, show increased leptin levels in serum, BAL fluid, and whole lung homogenates [125]. It is not clear whether increases in leptin in the pulmonary compartment are due to increased synthesis of leptin in the lung itself, or rather due to leakage of leptin from the circulation that may accompany pulmonary inflammation. Interestingly, leptin deficient *ob/ob* mice show impaired survival following administration of *K. pneumoniae*, *Streptococcus pneumoniae*, and *Mycobacterium abscessus*, suggesting that the presence of leptin is required for an effective immune response against diverse bacterial challenges [125–127]. The reduced bacterial clearance witnessed in leptin-deficient (*ob/ob*) mice does not appear to be due to impaired recruitment of inflammatory cells, but rather to result from defective macrophage and neutrophil phagocytosis of bacteria [57,125,126]. Moreover, macrophages from leptin-deficient mice show diminished leukotriene synthesis *in vitro*. Leukotrienes have been shown to enhance macrophage phagocytosis, and impaired leukotriene synthesis has been found in some

individuals found to be particularly susceptible to pulmonary infections [128,129]. Both the phagocytic response of macrophages and neutrophils and the synthesis of leukotrienes can be restored by exogenous administration of leptin in leptin-deficient mice [57,125,126].

More recently, Kordonowy et al. studied the effect of leptin on neutrophil trafficking in a sterile model of lipopolysaccharide (LPS)-induced lung injury [60]. Early airspace recruitment (2–6 h) was reduced in *db/db* mice, and neutrophils of uninjured mice demonstrated diminished chemotaxis towards the chemokine KC compared with control mice. In addition, adoptive transfer of *db/db* mouse neutrophils into injured control mice revealed a defect in airspace migration in these cells, suggesting that leptin is effective in driving alveolar airspace neutrophilia [60]. Herewith in line, Ubags and colleagues recently showed that pulmonary leptin is induced in injured lungs and that this cytokine is effective in driving alveolar airspace neutrophilia via a direct effect on neutrophils [130]. Further studies are warranted to better characterize and dissect the role of leptin in neutrophil recruitment and function in pneumonia and acute lung injury.

Experiments in lean mice fasted for 48 h, a physiological stimulus that reduces circulating leptin levels, show a 20-fold increase in *S. pneumoniae* burden compared to *ad libitum* fed mice [131]. Similar to leptin-deficient mice, macrophages from fasted animals exhibit defective phagocytosis of *S. pneumoniae*, while treatment with exogenous leptin restored bacterial clearance in fasted mice [131]. In recent studies, Mancuso and colleagues convincingly showed by means of mutant *s/s* and *l/l* mice deficient in leptin receptor-mediated STAT3 activation and ERK activation, respectively, that both signalling routes play an essential role in host defence against bacterial pneumonia and in leucocyte antibacterial effector functions [132,133]. In contrast to the above mentioned reports, Wieland et al. failed to detect differences between wild type and leptin deficient *ob/ob* mice in host response to both *K. pneumoniae* and *S. pneumoniae* [134]. This may be due to differing routes of bacterial administration (intratracheal versus intranasal) or to differences in mouse gender or age (with older, male mice being less susceptible to infections). However, the same group has also reported an increased susceptibility to infection with *Mycobacterium tuberculosis* in these mice [135]. Interestingly, the pulmonary response to *M. tuberculosis* was recently suggested to be affected by the host's nutritional status via the regulation on non-bone marrow-derived cells, and not through direct action of leptin on Th1 immunity [136]. Future studies are needed to better understand the role of non-bone marrow-derived cell like pulmonary epithelium involved in leptin-mediated immune regulation in bacterial infections.

4.3.2. Viral infections

To date, only a few studies report on the effects of obesity, and thus increased leptin levels and leptin resistance, on the immune response to viral infections. Diet-induced obese mice showed a higher mortality rate upon infection with influenza virus [137,138] and along with this increased mortality rate an altered immune response, including diminished NK-cell cytotoxicity and delayed pro-inflammatory cytokine expression [137]. The chronic leptin elevation in these mice appears to cause a state of leptin resistance [139], which may lead to an inadequate immune response and increased mortality upon viral infection. Zhang et al.

recently suggested that leptin has no effect on viral replication itself [140]. Furthermore, it has been shown that diet induced obesity results in selective impairment of DC functions and that obesity leads to delayed recruitment of mononuclear cells to the infected lung during influenza infection. In addition, while migration of antigenloaded DCs to the lymph node appears to be normal in obese mice, the ability of DCs to present antigens to $CD8^+$ T-cells is impaired, and this may be caused by a lack of co-stimulation by DCs [141]. Karlsson et al. showed that increased morbidity and mortality during a secondary influenza infection is due to impairment in the ability to generate and maintain functional influenza specific memory T-cells [142]. Furthermore, it has also been shown that diet-induced obesity can affect the maintenance of influenza-specific memory T-cell populations in the lung and this may be due to peripheral leptin resistance in the obese lung microenvironment affecting IL-15 function [143]. These studies highlight potentially different effects on the host's immune system seen in diet-induced obesity and obesity that arises from a leptin-deficient state.

In conclusion, there is a lack of – particularly clinical and translational – research, which is necessary to gain a more comprehensive understanding concerning the possible role of leptin in the human immune responses against bacterial or viral pulmonary infections.

5. Conclusions

The pleiotropic functions of leptin are of growing interest, and significant progress has been made in understanding leptin's role in inflammatory respiratory diseases and the underlying immune response. As a type-I cytokine, leptin appears to serve as far more than a satiety hormone for the regulation of food intake and energy expenditure. The presence of the functional leptin receptor in the lung on both leukocytes and lung epithelial cells together with evidence of local leptin production in the respiratory compartment, supports the concept that leptin plays an important role in respiration, lung development and the pathogenesis of diverse respiratory diseases.

Further studies are however needed to elucidate the functional – possibly autocrine and/or paracrine – targets and effects of leptin signalling in the respiratory system in homeostasis and disease. It will be critical to distinguish the effects of leptin signalling in both acute and chronic respiratory diseases, as it appears that leptin may have dichotomous effects depending on the acuity of the disease process. Furthermore, in order to fully understand the role of leptin in clinical disease, more longitudinal or weight-intervention studies are required that focus on the mechanisms by which human obesity – and hence leptin resistance – influences respiratory diseases, and in particular respiratory immunity. Future investigations that reveal the mechanisms by which leptin influences pulmonary inflammation may eventually contribute to the development of novel therapeutic interventions in respiratory diseases.

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Abbreviations

JAK	Janus kinase
STAT	signal transducers and activators of transcription
Tyr	tyrosine
PI3K	phosphoinositide 3-kinases
MAPK	mitogen activated protein kinases
DC	dendritic cell
Th	T-helper cell
IL	interleukin
IFN	interferon
CPE	carboxypeptidase E
SOCS	suppressor of cytokine signalling proteins
DIO	diet-induced obesity
COPD	chronic obstructive pulmonary disease
TNF-α	tumour necrosis factor alpha
CRP	C-reactive protein
BAL(F)	bronchoalveolar lavage (fluid)
BEC	bronchial epithelial cells
CD	cluster of differentiation
ASM	airway smooth muscle cells
NK	cells natural killer Cells

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