CHAPTER

2

Physiology and Pathophysiology of Adipose Tissue-Derived Cytokine Networks

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OUTLINE

Although cytokines are most frequently studied as discrete variables, emerging data highlights the importance of elucidating the regulation

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and functional consequences of complex cytokine networks at the organ and/or tissue level, as well as in interorgan connections.

Beside its primary role in long-term storage of energy excess, the adipose tissue (AT) has also important endocrine functions through a complex network of secreted factors (called adipokines), which are key mediators in interorgan crosstalks; thereby enabling the organism to adapt to diverse physiological or pathophysiological situations such as aging, starvation, excessive/insufficient calorie intake, stress, cancer, or infection.

The purpose of the present chapter is to review the current knowledge on the functional pleiotropism exhibited by the AT, which notably relies on its ability to synthesize and release a variety of local and systemic signals acting in networks or cascades.

We will first define and describe some basic facts about the AT. Then we will propose a general scheme of cytokine networking in the AT and its role both in physiological and in pathological (i.e., obesity) states, focusing on two major adipokines: leptin and adiponectin. Finally we will show the most salient data supporting the notion that the AT—through its secretions—may play a largely neglected and underestimated role in lung development and respiratory diseases such as bacterial and viral pulmonary infections.

BASIC FACTS ABOUT ADIPOSE TISSUE HETEROGENEITY

The biological diversity of AT—both in terms of differences between depots and in the type of cells which are present within the tissue—has lately become a fundamental issue due to AT role in health and disease. Indeed chronic and excessive growth of AT (such as encountered in obesity) plays an important role in the development of metabolic syndrome so as, strikingly, its lack, loss, or abnormal anatomical distribution (such as encountered in lipodystrophy).[1] A mechanism whereby AT may foster the development of metabolic syndrome is through the release of different adipose-derived bioactive molecules having distinct metabolic and inflammatory effects on the AT itself and on distant organs.

Different Flavors of Adipose Tissue: White, Brown, Beige/Brite, and Pink

In mammals, ATs were formerly classified into two main types characterized by different anatomical locations, morphological/histological structures, functions, secretions, and regulations[2]: The white adipose

tissue (WAT; which stores energy as triglycerides for release as free fatty acids (FFAs) during fasting periods) and the brown adipose tissue (BAT; which dissipates energy and generates heat to maintain thermal homeostasis).

However, recent emerging evidence supports the existence of two additional categories of AT: The beige/brite (brown-in-white) AT (which corresponds to the development of brown-like adipocytes with thermogenic properties within WAT depots[3]) and the pink AT (which arises during pregnancy and corresponds to adipocyte-derived milk-producing mammary gland alveolar epithelial cells[4]). These reversible transdifferentiation properties of adipocytes (from white to brown for beige/brite adipocytes and from white to milk secretory epithelial cells for pink adipocytes) add to the enormous plasticity of the AT for volume and cell-type/number variations.

White Adipose Tissue: Distribution Matters

The WAT develops at multiple anatomical sites with major depots residing in the subcutaneous and the visceral regions. The subcutaneous adipose tissue (SCAT) is found just beneath the skin—constituting the major cellular component of the hypodermis—where it acts as a barrier against dermal infections, an insulator to prevent heat loss and a cushion to protect against external mechanical stress. The visceral adipose tissue (VAT) is found around all vital organs within the peritoneal cavity and the rib cage (i.e., omental, mesenteric, mediastinal, and epicardial AT). The distribution of VAT and SCAT differs from individuals and is dependent of several factors such as age, nutrition, gender, and genetics.[5–7] Importantly each anatomical depot differs in metabolic and hormonal profiles and, thus, has different physiological roles. In 1956, Vague was the first to notice that visceral obesity (android or "apple shape") is more frequently associated to metabolic disturbances than peripheral obesity (gynoid or "pear shape").[8] Since this initial observation numerous epidemiological and physiological studies have documented a close association between excessive VAT accumulation and a cluster of different metabolic diseases.[9] Recently a large-scale metaanalysis showed that different AT distribution patterns have distinct genetic components; with genes implicated in adipogenesis, angiogenesis, and insulin resistance playing a key role in determining AT distribution.[7]

Among the differences that could account for the association between AT distribution and metabolic diseases, the most obvious is SCAT and VAT respective anatomical localizations. The "portal hypothesis" proposes that the liver, via the portal vein circulation, is directly exposed to VAT-released metabolites such as FFAs and adipokines.[10] However,

data obtained in humans[11] and from murine models[12,13] suggest that this might be an over simplification. In fact the divergent metabolic effects of excessive SCAT and VAT also rely on intrinsic, cell-autonomous differences between both tissues. Indeed, comparative analyses of gene expression and secretome of SCAT and VAT revealed major differences between the two AT depots.[14–16]

Visceral and Subcutaneous Adipose Tissues Have Different Adipokine Secretion Patterns: A Focus on Leptin and Adiponectin

Since the report of tumor necrosis factor alpha (TNFα) production by the AT in 1993[17] and the discovery of the leptin and adiponectin hormones the following years,[18,19] AT has been recognized as a major endocrine organ secreting a wide array of hormones, cytokines, growth factors, and vasoactive substances; collectively called adipokines. Adipokines exert pleiotropic effects on different tissues/organs such as AT, brain, skeletal muscle, heart, liver, pancreas, intestine, bone, reproductive organs, blood vessels, and lungs; thus regulating several vital functions like appetite, insulin sensitivity and secretion, fat distribution, lipid and glucose metabolism, endothelial function, blood pressure, hemostasis, neuroendocrine functions and, last but not least, immunity.[20] To date hundreds adipokines constituting the adipose secretome have been identified; including the hormones leptin and adiponectin, and the proinflammatory cytokines TNFα, interleukin (IL)-6, and monocyte chemoattractant protein (MCP)-1. Most adipokines identified so far are proinflammatory and are upregulated in the obese state, while only few have antiinflammatory activities (adiponectin).

There is evidence that adipokines are differently expressed in, and secreted from, SCAT and VAT,[14–16] reinforcing the opposite role of these depots in the development of obesity and its comorbidities.[8,9] Generally the expression of proinflammatory adipokines is higher in VAT whilst leptin expression is higher in SCAT. Several comprehensive reviews on AT secretions have been already published,[21,22] we have thus chosen to focus here on the two prototypical adipokines leptin and adiponectin for four reasons. First, leptin and adiponectin are two of the most abundant circulating adipokines. Second, leptin and adiponectin have opposite inflammatory properties (respectively, pro- and antiinflammatory) and both play pivotal roles in the pathogenesis of obesity. Third, leptin and adiponectin secretions differ between SCAT and VAT depots. This is an important issue since, as mentioned previously; visceral adiposity is associated with low grade, chronic inflammation that contributes to the development of obesity-associated diseases, whereas

subcutaneous obesity is not. Fourth, as will be evoked in the last part of the chapter, leptin and adiponectin have been reported to participate in lung homeostasis as well as in the pathophysiology of several pulmonary diseases; paving the way for a secret talk between AT and lungs within a "fat-to-lung axis."

In vivo removal or transplantation of AT in mice allowed to assess SCAT and VAT respective metabolic features and highly suggested that AT functionality per se, rather than anatomical site of accumulation, is the major determinant for the association with metabolic disorders.[13,23,24] Beside adipogenic potential and ability to store and release selective lipids, the other intrinsic factor that differentiates SCAT and VAT is adipokine secretion, notably of leptin and adiponectin. However, it should be borne in mind that the secretome of whole AT (SCAT vs VAT) is not simply the sum of each of its components but rather the result of paracrine interactions between the multiple cell-types within the AT.

The discovery of leptin, the product of the obesity gene (*ob*),[18] led to the description of a previously unknown bidirectional communication network between AT and brain. Indeed leptin, secreted from AT into the bloodstream, can act in the central nervous system (CNS) to inhibit food intake by signaling the extent of AT mass.[25] Even if the AT is the major site of leptin production (more particularly the mature adipocytes within), the hormone is also produced in lower amounts by other tissues[26] such as BAT, stomach, skeletal muscle, placenta, possibly the brain, and lungs. If SCAT and VAT depots both express the *ob* gene, there are differences between sites in the relative *ob* mRNA expression levels. Indeed, SCAT seems to have an exclusive role in leptin secretion, since its mass correlates with plasma leptin levels, both in rodents[27] and humans.[28] Importantly, blood leptin levels are markedly increased in obesity, as noted in human studies and in different animal models of obesity.[25]

Initially considered as a satiety factor through its direct action on anorexigenic hypothalamic neurons, leptin has also substantial effect on food intake, activity-independent thermogenesis, glucose and lipid metabolism, insulin secretion, hematopoiesis, fetal growth, behavior, reproduction, and immunity.[26] Leptin exerts its effects via the Ob-R receptor[29] encoded by the *db* gene, which has several different splicing variants in mouse (from a to f); the full-length isoform (Ob-Rb) mediating most of the actions of leptin, notably in the CNS.[25] Beside specific regions of the brain (such as choroid plexus, leptomeninges, and hypothalamic arcuate nucleus)[30] Ob-R is also expressed in several tissues, including e.g., AT,[31] lungs[32] as well as on innate and adaptive immune cells.[33–35]

Despite its pivotal role in body weight regulation, through food intake inhibition and stimulation of energy expenditure by increased thermogenesis, leptin is much more than a simple adipostat. Indeed

leptin participates to immune homeostasis;[33–35] as revealed by thymic atrophy, T-lymphocyte diversity constriction, and immunodeficiency occurring in leptin-deficient (*ob/ob*) and leptin receptor-deficient (*db/db*) mice. Leptin can also modulate the onset and progression of inflammatory immune responses. Structurally wise leptin resembles proinflammatory cytokines such as IL-6 and IL-12, thus its overall action on the immune system is a proinflammatory effect; activating proinflammatory cells, promoting T-helper 1 (Th1) responses and mediating the production of other proinflammatory cytokines. Moreover, the expression of leptin and its receptor are upregulated by proinflammatory signals such as TNFα and IL-1. This is in accordance with the observation that blood leptin levels are increased during infection and acute inflammation. In contrast to acute stimulation of the inflammatory system, chronic inflammation causes a reduction in leptin levels. As such, leptin links metabolism to inflammation and immunity; inspiring the recent emergence of a new fascinating field of investigation: Immunometabolism.[36]

Identified in 1995,[19] adiponectin (also referred to as AdipoQ, Acrp30, apM1, or GBP28) is predominantly synthesized and secreted by adipocytes. In fact, AdipoQ is one of the most abundant adipokines considering its concentration in plasma relative to many other hormones. Posttranslational modifications result in three secreted isoforms that may vary in efficacy regarding their effects on target tissues: Low-, medium-, and high-molecular weight (LMW, MMW, and HMW, respectively) complexes.[37] The latter is considered the most bioactive and proinflammatory isoform in regulating insulin resistance. From a structural point of view, AdipoQ is related to the complement 1q/TNFα superfamily and contains a collagen-repeat domain. Mainly expressed by adipocytes, AdipoQ is also expressed at the mRNA and/or protein level by BAT, liver, skeletal muscle, bone marrow, and lungs.[38]

Contrary to leptin, blood adiponectin levels are high in lean individuals and markedly decreased with increasing obesity; especially AdipoQ HMW multimer levels.

Adiponectin modulates a wide range of metabolic processes such as food intake and energy expenditure, glucose and lipid metabolism, and insulin sensitivity.[39] In addition to its metabolic actions, AdipoQ is also reported to possess antiatherogenic and antiinflammatory properties.[40] Such effects are mediated by three different receptor types: AdipoR1 (almost ubiquitously expressed and abundantly so in skeletal muscle and brain), AdipoR2 (highly present in liver and AT), and the more recently found nonclassical receptor T-Cadherin (CDH13, expressed in endothelial, epithelial, and smooth muscle cells).[41] While AdipoQ is mostly produced by the AT, its receptors are expressed in AT as well as in brain hippocampus, hypothalamus, and brainstem, as well as in, e.g., liver, skeletal muscle, colon, and lungs.[42]

Adiponectin is a predominantly antiinflammatory adipokine that inhibits proinflammatory cytokines (TNFα, IL-6) while also stimulating the production of antiinflammatory cytokines (IL-10, IL-1 receptor antagonist (IL-1RA)) by different innate and adaptive immune cells.[40] In return, proinflammatory cytokines down regulate AdipoQ expression in adipocytes; resulting in decreased blood adiponectin levels. However, under certain conditions (i.e., asthma, arthritis), AdipoQ may have proinflammatory effects as well.[43]

Thus, balanced production of these two countering adipokines has to be maintained to ensure proper metabolic and immune homeostasis. Dysregulation of this equilibrium may signify the early development of inflammatory diseases such as obesity and any attempt to temper this axis may represent an opportunity to correct disease processes.

ADIPOSE TISSUE AUTOCRINE, PARACRINE, AND ENDOCRINE CROSS-TALK SCENARIOS

Adipokines can act in an autocrine/paracrine or endocrine manner thereby putting the AT at the center of a complex and multidirectional network of crosstalks within the tissue itself as well as between organs such as liver, intestine, brain, bone, pancreas, skeletal muscle, and lungs. In the present section, we will summarize the autocrine/paracrine and endocrine functions of two of the most abundant circulating adipokines: leptin and adiponectin.

Autocrine and Paracrine Functions of Leptin and Adiponectin

The long and short isoforms of the Ob-R are expressed in adipocytes[31]; suggesting that leptin may have direct autocrine/paracrine effects on adipocyte development and function. Few studies have been reported that examine the autocrine/paracrine actions of leptin on adipocytes. A recent review, however, focused on the effects of leptin on adipocyte metabolism.[44] Briefly, in vivo, in vitro, and ex vivo studies showed that leptin has direct inhibitory effects on adipocyte lipogenesis and insulin responsiveness whilst enhancing lipolysis; consequently leading to a reduction in adipocyte size. In vivo leptin treatment markedly reduces AT triglyceride stores. Additionally, leptin administration to leptin-deficient (*ob/ob*) and lean mice increases glycerol release. In in vitro experimental settings, leptin has been reported to inhibit accumulation of lipids in adipocytes by increasing triglyceride turnover, inhibiting de novo lipogenesis and promoting FFAs oxidation. However, in human adipocytes from either lean or obese healthy

subjects, leptin treatment failed to modulate lipolysis.[45] If leptin reduces adipocyte size, its direct effect on adipocyte number and/or preadipocyte differentiation into lipid-laden mature adipocytes is still debated. Leptin also interferes with insulin signaling and decreases insulin-mediated glucose uptake in mouse or rat adipocytes. As was noted for lipolysis, these findings are not reflected in human cells.[45]

In addition, leptin can also modulate the secretory function of adipocytes, as mainly shown in in vitro models. It has been proposed that leptin, at least in part, regulates its own release by AT, based on findings in mice deficient in Ob-R; which present high circulating leptin levels. Furthermore, leptin stimulates adiponectin expression and release by adipocytes and murine AT both ex vivo and in vitro.[46] Finally, in view of AT expansion in obesity, leptin is known to promote angiogenesis in several experimental models.[47]

In contrast to leptin, adiponectin levels negatively correlated with obesity and its metabolic complications. Adiponectin receptors are expressed in adipocytes; therefore it is tempting to speculate paracrine effect of adiponectin in AT and these effects are regulated at the level of adiponectin receptor gene expression. Indeed, it has been reported that AdipoQ increases basal glucose uptake in adipocytes and enhances insulin-stimulated glucose uptake.[48] Overexpression of adiponectin in 3T3-L1 adipocytes resulted in increased expression of GLUT-4 and enhanced insulin-mediated glucose uptake. In 3T3-L1 cells, adiponectin overexpression promotes preadipocyte proliferation and accelerated the expression of adipogenic transcription factors and adipogenesis. Adiponectin exerts antiinflammatory effects on adipocytes.[43] As a result, release of a number of proinflammatory cytokines (IL-6, IL-8, and MCP-1) by adipocytes is significantly suppressed. Like leptin, AdipoQ is also able to induce angiogenesis.[49]

Besides mature adipocytes and their precursors, AT also contains several other cell-types including fibroblasts, endothelial cells, and immune cells. During the progression of obesity, in addition to changes in adipocyte number, size, and secretory function (in which leptin and adiponectin play important roles, cf. supra), modifications in the number and activity of AT immune cells also occurred. The dramatic changes in AT immune cell composition and function arising during the development of obesity have been extensively reviewed.[50–52] Specifically, adipocytes—via their secretions—interact with certain immune cells and directly regulate their activation and proliferation state.

Leptin has proinflammatory functions and plays important roles in the immune system.[33–35] Ob-R is ubiquitously expressed on the surface of both innate (neutrophils, macrophages, mast cells, eosinophils, natural killer (NK) cells, innate NKT (iNKT) cells) and adaptive (T cells such as regulatory T cells (Tregs), and Th17 cells, B cells) immune cells

present in the AT. Leptin induces IL-6 and TNFα synergizing with LPS (lipopolysaccharide) in monocytes, a relevant cell type involved in inflammatory response. Leptin is also able to modulate the survival of autoreactive $CD4^+$ T cells and the activity of regulatory T cells.

Adiponectin also exerts relevant actions on the innate and adaptive immune systems.[40,43] There is a consensus that AdipoQ has antiinflammatory effects on several immune cell types such as monocytes and macrophages, as well as on the systemic regulation of T cell responses. Adiponectin inhibits IL-6 and TNFα production by macrophages and increases the production of antiinflammatory factors such as IL-10 or IL-1RA by monocytes, macrophages, and dendritic cells. Thus adiponectin-mediated effects on AT immune cell function and phenotype may contribute to its role in reducing inflammation within the tissue.

Endocrine Functions of Leptin and Adiponectin

Leptin primarily identified function is to inform the brain of changes in AT mass and Ob-R was found in hypothalamic nuclei involved in food intake control.[25] However, Ob-R is also expressed in several peripheral tissues including skeletal muscle, liver, pancreas, and lungs, as well as endothelial cells and immune cells. Moreover, besides the AT, the stomach, placenta, brain, and lungs are able to synthesize leptin. The appreciation of leptin as a major regulator of many, if not all, endocrine systems such as food intake, reproduction, growth behavior, mood, bone metabolism has been frequently reviewed.[53,54]

Adiponectin is mainly produced by AT and acts to reduce insulin resistance but, alike leptin, it also exerts actions on other tissues that expressed either AdipoR1 or AdipoR2 such as reproductive tissues, skeletal muscle, liver, and lungs. The endocrine effects of AT-derived AdipoQ are conventionally believed to regulate many physiological processes and several studies have reported strong correlations between adiponectin levels and various disease states such as obesity and diabetes, cardiovascular disease, certain types of cancer, hepatic fibrosis, reproduction, bone mass density, and inflammation.[55] In addition, emerging evidence suggests that adiponectin can also be expressed and secreted by skeletal muscle, cardiomyocytes, liver, and lungs.[56]

FROM ADIPOSE TISSUE TO LUNGS: THE ADIPOKINE CONNECTION

Beyond storing energy and participating to inflammatory processes, AT is also a key player in the regulation of several lung homeostatic

processes such as development, respiratory system mechanics, breathing regulation, and immunity. The association between AT and lungs is still incompletely understood, however, adipokines—notably leptin and adiponectin—have been reported to have substantial respiratory effects.

As previously mentioned, leptin is also synthesized and secreted by fetal lung tissue. In addition leptin receptors, including the signaling isoform Ob-Rb, are expressed in the fetal lungs of a variety of mammalian species; suggesting a role for leptin in lung growth and/or maturation during prenatal development.[57] Indeed, in vitro studies using fetal rat lung tissue showed that leptin treatment induced the division and maturation of type II pneumocytes; thus favoring surfactant protein synthesis and secretion, which will improve lung compliance.[58] Leptin is also involved in lung postnatal development, as revealed by decreased alveolar number and delayed alveolar enlargement in leptin-deficient *ob/ob* mice.[59]

In human, Ob-Rb is expressed by human bronchial and alveolar epithelial cells, bronchial smooth muscle cells, and bronchial submucosa.[60] Overweight and obese subjects, with high blood leptin levels, are more likely to have respiratory symptoms than lean individuals, even in the absence of demonstrable lung disease. Indeed obesity is often accompanied by pulmonary diseases such as obstructive sleep apnea hypopnea syndrome (OSAHS), obesity hypoventilation syndrome (OHS), chronic obstructive pulmonary disease (COPD), and asthma. While it has been proposed that OSAHS might correspond to a central leptin-resistant state due to impaired leptin transport through the blood brain barrier,[61] accumulating evidence suggest that leptin is involved in the local inflammatory response occurring in the airways of COPD patients. Indeed leptin levels are elevated in COPD patients during acute exacerbation. Smoking, which is the leading cause of COPD, also increases the expression of leptin/leptin receptor in lungs. It has also been reported that leptin may augment allergic airway responses partly through the induction of eosinophil accumulation and the enhancement of inflammatory processes in the lung.

Leptin has been reported to increase cell proliferation, differentiation, survival, migration, and invasion responses in several in vitro and in vivo cancer model systems; mainly through promotion of tumor vascularization. However, the role of leptin in lung cancer initiation and progression remains controversial. Terzidis et al. reported that elevated serum leptin concentration in nonsmall-cell lung cancer (NSCLC) patients may favor the tumorigenesis process.[62] Others, however, showed that mice deficient in leptin or its receptor had increased number of metastatic lung carcinoma cells, which was decreased upon leptin administration.[63]

Leptin is also involved in lung infectious diseases such as pneumonia, tuberculosis, and flu. Following intratracheal challenge with *Klebsiella*

pneumoniae, leptin levels were increased in whole lung homogenate, bronchoalveolar fluid, and serum.[64,65] In addition, leptin-deficient *ob/ob* mice were more susceptible to *K. pneumoniae* infection than control mice. Leptin-deficient mice also displayed reduced survival after *Streptococcus pneumoniae* infection and leptin administration improved pulmonary bacterial clearance and survival.[66] However, it has to be noted that other authors failed to detect differences between *ob/ob* and controls regarding lung inflammation and bacterial outgrowth during pneumoniae. Leptin plays a role in the early immune response to pulmonary infection with *Mycobacterium tuberculosis* through favoring the proinflammatory Th1 response and suppressing the antiinflammatory Th2 response. A chronic deficiency in leptin leads to an altered host defense against *M. tuberculosis*.[67] These observations might explain the increased susceptibility of lean individuals to develop active tuberculosis compared to obese patients who are able to better control the infection.[68]

Besides its role during bacterial infections of the lung, leptin has also been reported to play a key role in pneumoniae post-Influenza A virus (IAV) infection through its direct role on neutrophils.[69] In diet-induced obese mice infected with the H1N1pdm09 IAV strain, preexisting high levels of circulating leptin were shown to contribute to the development of severe lung injury.[70] Radigan et al. reported reduced viral clearance and worse outcome of Influenza A virus (A/WSN/33 [H1N1]) infection in leptin receptor-deficient mice.[71] Indeed epidemiological data showed that, during H1N1 2009 outbreak, obese or morbidly obese patients were more susceptible to infection and exhibited higher death rates among all patients.[72]

Adiponectin and its receptors are both expressed on multiple pulmonary cell-types; which make lungs a target tissue for adiponectin signaling. Similar to leptin, AdipoQ is involved in lung development, as deduced from abnormal postnatal alveolar development in normal-weight adiponectin-deficient mice.[73]

Allergen bronchoprovocation in sensitized mice reduced serum adiponectin levels as well as the expression of adiponectin receptor mRNAs in the lung.[74] Likewise, adiponectin attenuates allergic airway inflammation and airway hyperresponsiveness in mice but not in human, through the inhibition of proinflammatory cytokines.[75] Adiponectin levels have been found to be elevated in COPD patients compared to controls.[76] To support its antiinflammatory activity; it was shown that alveolar macrophages from AdipoQ-deficient mice display increased production of TNFα. In a dose- and time-dependent manner, it was demonstrated that AdipoQ reduced cytotoxic effects of TNFα and IL1β and induced the expression of the antiinflammatory IL-10 cytokine in lung epithelial cells; thus improving cell viability and decreasing apoptosis.[77] Overexpression of adiponectin has been shown to protect mice from developing pulmonary arterial hypertension in

response to inflammation and hypoxia through its antiinflammatory and antiproliferative properties.[78] Importantly, adiponectin administration reversed the detrimental effects of obesity on the lung endothelium via increasing the expression of vascular barrier-enhancing molecules; thus attenuating lung injury.[79] Whether this protective effect of AdipoQ on acute lung injury could be translated to human is still questioned. In a population of critically ill patients requiring mechanical ventilation 21% of whom had Acute Respiratory Distress Syndrome (ARDS), high serum adiponectin levels at admission were associated with increased mortality.[80] Therefore it remains unclear whether circulating adiponectin is really involved in the pathogenesis of ARDS, in humans.

Adiponectin was shown to facilitate the uptake of apoptotic cells by macrophages and increase the production of IL-8 in the presence of LPS; thus suggesting its role as modulator of the immune response.[81] It was reported that several tumor cell lines express adiponectin receptors, thus suggesting a potential effect of AdipoQ on tumor cells. However, studies evaluating the association between adiponectin and lung cancer are still scarce. Petridou et al. showed in patients with lung cancer that adiponectin levels were not significantly different from controls, but rather lower concentrations were detected in advanced disease stage; thus suggesting that AdipoQ might be a potential marker of lung cancer progression.[82] In advanced NSCLC patients, serum adiponectin levels did not show significant differences when compared to controls, thus not allowing the use of this parameter for overall survival estimation.[83]

Finally regarding the role of adiponectin in pulmonary infectious diseases, it has been reported that high AdipoQ levels might indicate activity and severity of *M. tuberculosis* infection.[84] However, additional studies are required to understand the role of adiponectin during lung viral or bacterial infections.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

The WAT produces a network of various adipokines—leptin and adiponectin being the best-studied of these—that function to regulate its own microenvironment and to communicate with organs such as, brain, muscle, pancreas, bone, intestine, heart, and liver, as well as with both innate and adaptive immune cells (Fig. 2.1A).

The association between leptin and adiponectin—which have respectively pro- and antiinflammatory activities—and pulmonary diseases, is still largely unexplored. Nevertheless, the existence of an AT–lung axis has been suggested. Here we focused on the current literature reporting

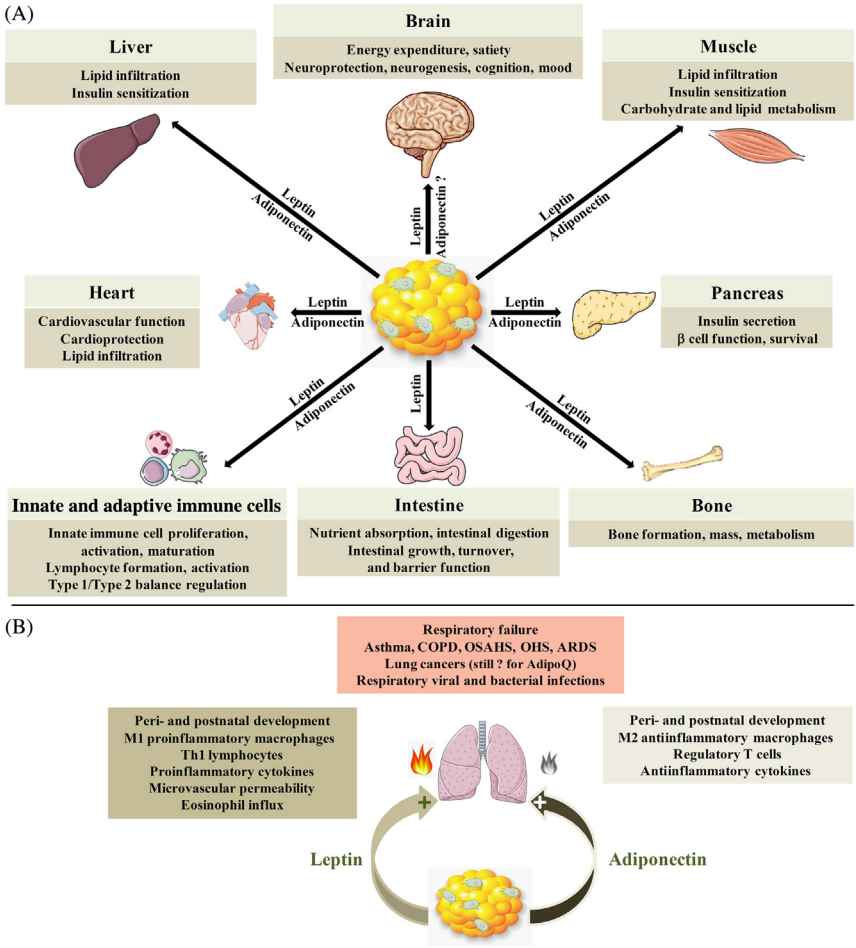

FIGURE 2.1 Intertwined interactions between the white adipose tissue (WAT) and remote organs and tissues via leptin and adiponectin. (A) *Leptin and adiponectin in the inter-organ communication network*. Adipose tissue (AT)-derived leptin and adiponectin regulate the function of distant organs and tissues as diverse as brain, skeletal muscle, pancreas, bone, intestine, heart, and liver. Importantly, both adipokines also modulate innate and adaptive immune responses, notably through their proinflammatory and antiinflammatory properties, respectively. Of note: To our knowledge, contrary to leptin,[85] AT-derived adiponectin has never been reported to have a role on the gastrointestinal tract; and its role in brain is still debated since controversial results have been reported regarding its capacity to cross the blood brain barrier.[86,87] (B) *The fat-lung axis*. In this communication network, the WAT influences the lungs by secreting, e.g., leptin (proinflammatory) and adiponectin (antiinflammatory); as summed up in the lateral boxes. In the upper box are listed the lung diseases that have been shown to be associated with leptin or adiponectin (see text for details and abbreviations). Of note: The role of adiponectin in lung carcinogenesis remains controversial.[88] However, adiponectin and leptin seem to have opposing roles in cancer development; similar to their functions in metabolic disease and other diseases.

on the role of leptin and adiponectin in the pathogenesis of lung diseases (Fig. 2.1B).

However, there are several considerations and/or limitations to consider when addressing that specific point. (1) Both leptin and adiponectin are not secreted from AT only; thus defining the contribution of lungs versus AT production on the observed effects is a challenging issue. In addition, leptin and adiponectin can be produced by multiple cell types; (2) Leptin and adiponectin functions in the lung may not necessarily be similar to those well described in the AT or the brain; (3) Substantial study design differences and conflicting results from the existing literature preclude definitive conclusions on the role leptin and adiponectin could play in lung physiology and pathophysiology; these differences include species, gender, age, genetics, and ethnic differences in adipokine levels; (4) Given the vast number of AT-derived adipokines, their cumulative roles as classes of adipokines should also be questioned.

Therefore the current challenge in adipokine research remains to elucidate their function in their tissue targets, at both cellular and molecular levels. This knowledge may facilitate the future use of adipokines—such as leptin and adiponectin—as pharmacotherapies, drug targets, and/or predictors of disease initiation or progression, notably concerning lung inflammatory diseases.

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