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Scleroderma Related Lung Disease: Is There a Pathogenic Role for Adipokines?

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Abstract

Scleroderma is a systemic autoimmune disease of unknown etiology whose hallmark features include endothelial cell dysfunction, fibroblast proliferation and immune dysregulation. Although virtually any organ can be pathologically involved in scleroderma, lung complications including interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are the leading cause of death in patients with this condition. Currently, the molecular mechanisms leading to development of scleroderma-related lung disease are poorly understood; however, the systemic nature of this condition has led many to implicate circulating factors in the pathogenesis of some of its organ impairment. In this article, we focus on a new class of circulating factors derived from adipose-tissue called adipokines, which are known to be altered in scleroderma. Recently, the adipokines adiponectin and leptin have been found to regulate biological activities in endothelial, fibroblast and immune cell types in lung and in many other tissues. The pleiotropic nature of these circulating factors and their functional activity on many cell types implicated in the pathogenesis of ILD and PAH suggest these hormones may play a mechanistic role in the onset and/or progression of scleroderma-related lung diseases.

Keywords

Scleroderma; Adipokines; Adiponectin; Leptin; Interstitial lung disease; Pulmonary fibrosis; Pulmonary hypertension

Introduction

Scleroderma is a progressive, systemic disease characterized by vasculopathy and excessive collagen deposition in the skin and internal organs. Scleroderma can affect almost any organ in the body but lung manifestations, including PAH and ILD, are its most serious complications[1]. It is estimated that 60% of scleroderma-related deaths are attributable to lung involvement, and currently there are few effective treatments for these conditions[2].

The systemic nature of scleroderma as well as its involvement of tissues from diverse vascular beds has led many to implicate serum-derived factors in its pathogenesis. In the 1990's, the observation that an adipose tissue-derived hormone called leptin regulates appetite in the brain led to the immediate recognition of adipose tissue as an important endocrine organ[3]. Since that time, many other adipose-derived signaling factors have been

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Compliance with Ethics Guidelines
Conflict of Interest
Shannon Haley, Dilip Shah, Freddy Romero, and Ross Summer declare that they have no conflict of interest.

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This article does not contain any studies with human or animal subjects performed by any of the authors.

identified and these hormones are now collectively referred to as adipokines. Adipokines act on virtually all tissues and regulate biological processes important in metabolism, immune regulation, vascular homeostasis and cell proliferation[4–8]. Although much of what we know about the functional role of adipokines is linked to obesity it is now increasingly apparent that endocrine function of adipose tissue is also altered in many other chronic conditions including connective tissue diseases[9–11]. This observation has led to emerging interest in understanding how adipose tissue dysfunction contributes to disease pathogenesis in non-obese individuals.

In this review, we will focus on the potential role of the adipokines adiponectin and leptin in ILD and PAH pathogenesis. We have elected to limit our discussion to adiponectin and leptin, the two most abundant hormones produced by adipose tissue, because each has well-documented activities in lung homeostasis[12–14]. The primary goal of this review is to stimulate further discussion on the possible role for adipokines in ILD and PAH pathogenesis and to promote further research in this new and exciting area of lung biology.

Interstitial Lung Disease and Pulmonary Arterial Hypertension

ILD and PAH are highly complex diseases and a full discussion of these conditions is beyond the scope of this review. For a more complete understanding of either disease, we refer the reader to one of several recent review articles[15–18].

Importantly, ILD is a non-specific term that refers to any chronic inflammatory disease of the lung interstitium. However, in patients with scleroderma, the term ILD often connotes a more serious condition that is associated with progressive scarring of the lung and portends a poor prognosis. The precise incidence of ILD in patients with scleroderma varies depending on how it is defined; more sensitive measurements such as high resolution CT scanning of the lung suggest that interstitial lung abnormalities are present in most patients with this disease[2]. Fortunately, life-threatening ILD occurs in only one-fifth of individuals with scleroderma [19]. Although immunosuppressive agents have been shown to slow the progression of ILD in some patients with scleroderma the overall efficacy of these treatments is quite limited[20].

In contrast to ILD, PAH is a disease that is confined to the pulmonary vasculature and is diagnosed based on sustained elevations in pulmonary artery pressures. In patients with scleroderma, PAH has a well-documented increased morbidity and mortality. The prevalence of PAH in scleroderma varies depending on whether patients have limited or diffuse disease but overall it is estimated that one-quarter of patients develop this condition[21]. Recent studies suggest that new treatments have improved mortality for PAH over the last decade [22]. However, despite the availability of these new pharmacological therapies, response to treatment is often transient and three-year mortality for scleroderma-associated PAH remains very high (25%) [22–24].

Scleroderma lung diseases: Are ILD and PAH connected?

As highlighted above, ILD and PAH are ostensibly very different conditions and for this reason are usually discussed in separate contexts. However, the fact that they often co-exist in scleroderma, and in other diseases, strongly suggests a pathogenic link between these conditions. Relevant to this, when direct comparisons are made between these conditions (Figure 1) several striking similarities emerge. First, ILD and PAH are both diseases that involve predominantly cells of mesenchymal origin (e.g. fibroblast, myofibroblast, endothelial and smooth muscle cell types)[15,17]. Second, chronic inflammation plays an important role in both conditions and similar types of immune cells and pro-inflammatory cytokines are observed in pathological specimens from patients with these diseases[25].

Moreover, ILD and PAH share many pathogenic mechanisms including altered endothelial cell function, enhanced cell proliferation, increased apoptotic cell death and impaired tissue remodeling further suggesting a commonality between these two conditions[15,17]. Although the precise molecular signals linking these two diseases are unknown, the possibility that adipokines adiponectin and leptin modulate processes central to the pathogenesis of ILD and PAH will be discussed below.

Adiponectin

Adiponectin is perhaps the most important adipokine secreted from adipose tissue because of its well-documented role in regulating metabolism, inflammation, vascular homeostasis and tissue remodeling[8,26–29]. The ability of adiponectin to regulate diverse biological processes in many different cells (Figure 2) is attributable in part to its unique collagen-like domain that enables protein monomers to form small, medium and large complexes that possess distinct functional capabilities[30].

Interestingly, and for reasons that are unclear, the concentration of adiponectin in the plasma far exceeds that of most other circulating hormones[31]. Moreover, plasma levels of adiponectin in healthy individuals are remarkably stable over time suggesting that maintenance of high serum concentrations is somehow important for organ homeostasis[32]. Consistent with this hypothesis, adiponectin production is down-regulated in response to pro-inflammatory cytokines and oxidative stress in obese subjects, and this reduction has been shown in mice to contribute, at least in part, to the pathogenesis of many obesity-related diseases including type II diabetes, systemic hypertension and peripheral vascular disease[33,34]. Relevant to this review, adiponectin production is also impaired in scleroderma and other connective tissue diseases; however, the impact of these changes on disease progression is currently not understood [35–37].

In addition to having well-described anti-diabetic properties, one of the most recognized functions of adiponectin is its ability to suppress vascular inflammation [8,27,29]. Although adiponectin has been shown to inhibit inflammatory responses in virtually every cell type the importance of adiponectin in controlling vascular homeostasis is highlighted by studies in adiponectin-deficient mice. Targeted deletion of the adiponectin gene leads to the development of a spontaneous lung phenotype characterized by activated lung endothelium, age-dependent increases in perivascular immune cell infiltration and increased pulmonary artery pressures[12]. In addition, adiponectin deficient mice also display an exaggerated eosinophilic inflammatory vascular response to allergic lung challenge that results in increased muscularization of the pulmonary arteries and worsening pulmonary hypertension[28]. Importantly, blocking immune cell infiltration in this model attenuates the development of pulmonary hypertension suggesting that anti-inflammatory actions of adiponectin are important for limiting the development of PAH. To our knowledge, no human studies have yet to explore the relationship between adiponectin and PAH in scleroderma.

As discussed above, adiponectin's anti-inflammatory activities are also mediated outside the vascular compartment. This is likely attributable to the fact that adiponectin has been shown to readily accumulate within most tissues[38,39]. Interestingly, high concentrations of adiponectin are reported in the airway lining fluid from the human and murine lung, and its accumulation has been shown to be dependent on the expression of T-cadherin in the lung endothelium[38,40]. Studies in mice demonstrate that deficiency of lung adiponectin leads to spontaneous activation of alveolar macrophage and to architectural distortion of distal airspaces of the lung[41]. Although structural changes are presumably related to increased pro-inflammatory cytokine production from alveolar macrophages it is equally plausible that changes result from direct loss of adiponectin actions on the lung's epithelium. Indeed,

adiponectin receptor 1 has been shown to be expressed on lung epithelium suggesting that adiponectin may be important for regulating epithelial cell homeostasis[40]. This ability of adiponectin to modulate cellular processes in both the intra and extravascular compartments of the lung provide, at very least, a plausible explanation for how adiponectin could serve as a molecular link for two anatomically distinct lung diseases.

In addition to its role in controlling inflammation, there is now strong evidence that adiponectin is also an important regulator of tissue remodeling and cell proliferation in the lung[28,29,42,43]. For example, recent studies have demonstrated that deficiency in adiponectin promotes pulmonary artery smooth muscle proliferation in the setting of vascular inflammation and chronic hypoxia[42]. The molecular signals mediating these effects are poorly understood but several different mechanisms have been proposed including 1) direct activation of pathways that inhibit growth factor-mediated activation, 2) inhibition of the differentiation of smooth muscle cells into a proliferative phenotype, and 3) binding growth factors and hindering their bioavailability at a receptor level[5,29,44,45].

Importantly, adiponectin is also likely to influence tissue remodeling in the lung by its effects on non-smooth muscle cell types. This is supported by numerous studies demonstrating that adiponectin effectively inhibits tissue remodelling in many other tissues. For example, adiponectin has been shown to inhibit hepatic stellate cell proliferation and attenuate liver fibrosis, and to prevent myocardial fibrosis associated with pressure overload and ischemia[37,46]. Relevent to scleroderma, tissue levels of adiponectin have been shown to inversely correlate with skin scores in patients with diffuse disease[47]. Moreover, adiponectin has been demonstrated to suppress the expression of type I collagen in both normal and scleroderma fibroblasts, and to attenuate the stimulation of pro-fibrotic responses elicited by TGF-β through activation of adenosine monophosphate-activated protein kinase[48]. These findings suggest hypoadiponectinmia might be an important stimulus for pro-fibrotic responses (e.g. increased collagen production) in scleroderma.

Leptin

Leptin is also a multi-functional hormone involved in metabolism, immune regulation and tissue remodeling [5]. Leptin's metabolic actions are important for down-regulating feeding impulses in the hypothalamus of the brain. In lean individuals, leptin levels are reduced in the blood during fasting and production rapidly increases after eating[49]. Somewhat paradoxically, circulating levels of leptin are markedly increased in obese subjects and this is ascribed to receptor resistance and the loss of leptin's actions in the brain[50]. Relevant to this review, independent of body mass index, plasma levels of leptin are also impaired in patients with scleroderma suggesting that synthesis and/or activity is influenced by this disease[9].

The structural homology of leptin to the IL-6 family of cytokines led to early speculation about its immune-regulatory activities [51]. Since that time, it is now widely recognized that leptin functions as an important immune modulating protein. Overall, the predominant actions of leptin are in enhancing pro-inflammatory responses. Leptin has been shown to activate monocytes, dendritic cells and macrophages and to stimulate their production of pro-inflammatory cytokines[4,7,52]. In addition, leptin has been found to promote phagocytosis and augment the chemotaxis of antigen presenting cells into tissue [4,5]. Interestingly, although leptin is considered mostly a mediator of the innate immune system, studies in mice have found that leptin augments the development of chronic autoimmune diseases through its ability to modulate T-regulatory cell function[53].

The pleiotropic actions of leptin in immune regulation have led investigators to implicate leptin in the pathogenesis of many chronic inflammatory conditions[14,54] (Figure 2). To

date, there are surprisingly very few studies that have investigated the role of leptin in the pathogenesis of scleroderma lung diseases. However, the limited data that is available suggests that leptin levels are increased in patients' scleroderma and these findings correlated with other measures of inflammation (e.g. tumor necrosis factor alpha)[9]. While these findings provide only an association between leptin and scleroderma lung disease it is tempting to speculate that higher circulating levels may somehow act to exacerbate the pro-inflammatory state in these conditions.

Leptin receptors are ubiquitous in the lung and are found on many parenchymal cell types including endothelium, fibroblasts and the proximal and distal lung epithelium[55,56]. The functional role for these receptors appears to have less to do with promoting pro-inflammatory responses and more to do with enhancing cellular proliferation and tissue remodeling[7,57,58]. Leptin has been shown to augment cell growth in endothelial, fibroblast and epithelial cell populations but signaling pathways mediating these effects have not been well-characterized[58–60].

In addition to controlling proliferation, leptin also appears to play a role in enhancing tissue remodeling. This was exemplified in a recent study using mice with defective leptin receptor signaling (db/db). These mice were found to be resistant to the development of bleomycin-induced lung fibrosis[58]. Consistent with these findings, treatment of human lung fibroblasts with leptin in culture was found to enhance TGF-β–mediated expression of many profibrotic genes. Interestingly, leptin-induced expression of pro-fibrotic genes was not observed in fibroblast deficient in PPAR-γ activity suggesting that leptin's effects are dependent on PPAR-γ signaling. Since adiponectin expression is induced by PPAR-γ, these findings suggest there is a reciprocal relationship between leptin and adiponectin on signaling in fibrotic diseases [26].

Conclusions and Implications

Scleroderma related lung disease is a major cause of morbidity and mortality, but despite decades of research the mechanisms leading to the development of ILD and PAH remain poorly understood. The shared pathogenic mechanisms between these conditions have prompted investigators to search for new factors that might provide a link between these diseases. In this review, we discuss the possible role for the adipokines adiponectin and leptin in ILD and PAH pathogenesis. While this area of investigation is arguably in its infancy the pleiotropic nature of adiponectin and leptin suggest that future research in this area will provide valuable insight into the pathogenesis of these conditions.

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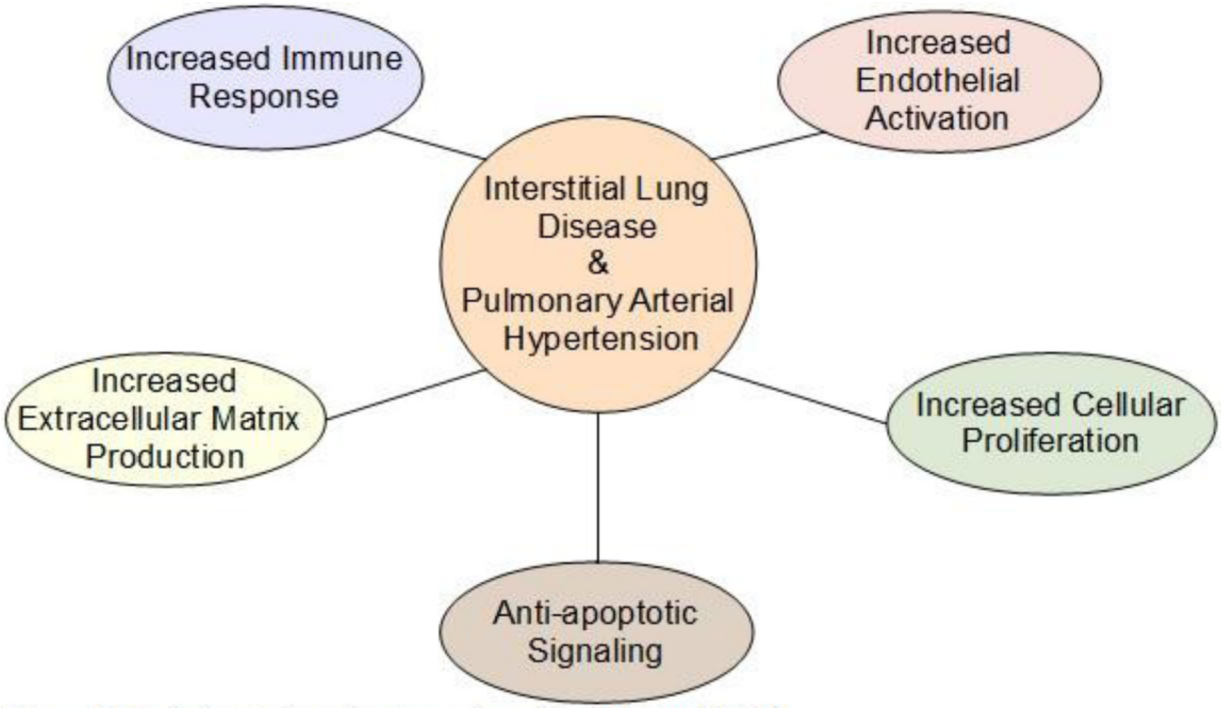

Figure 1.
Pathological mechanisms shared by ILD and PAH.

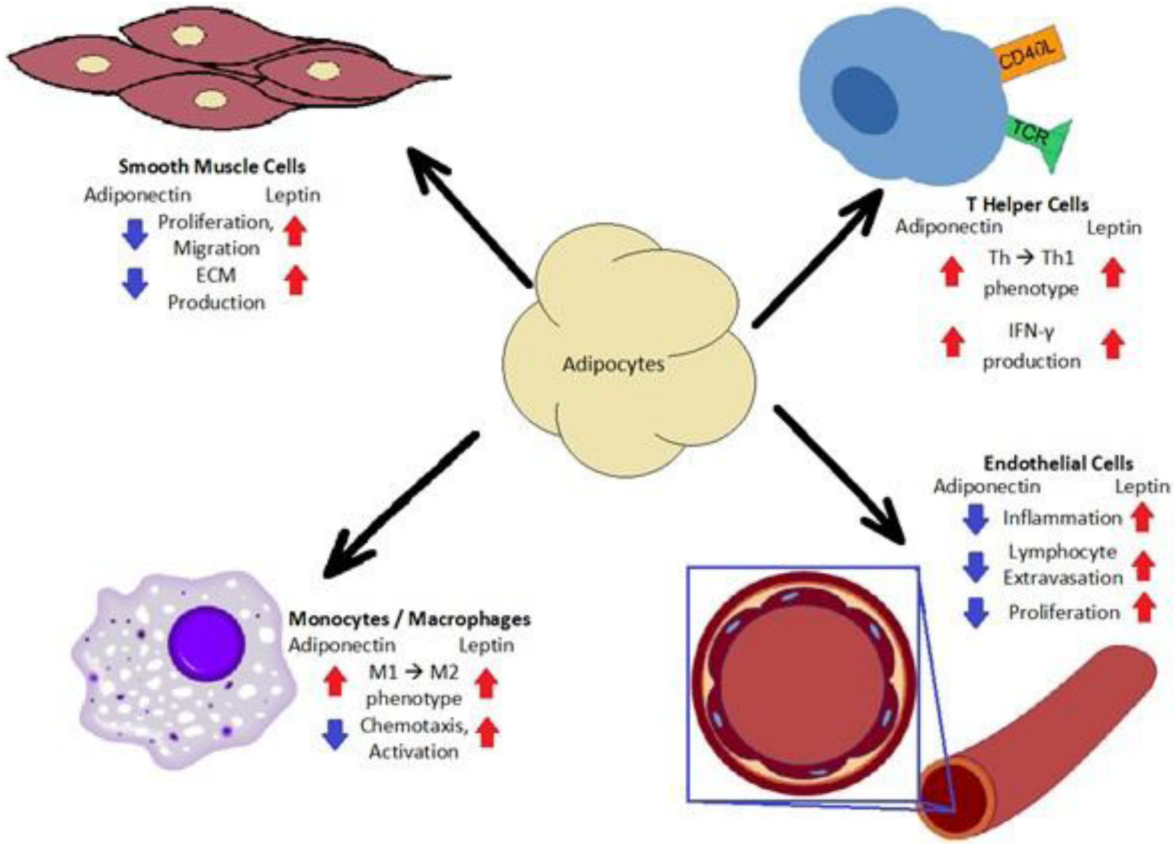

Figure 2.
Schematic depicting the pleiotropic effects of adiponectin and leptin.