Does adiponectin play a role in pulmonary emphysema?

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Adiponectin is one of several recently described, circulating, secretory products synthesized by adipose tissue and known collectively as “adipokines” and/or “adipocytokines” (7, 22). Adiponectin plays an important role in energy homeostasis, regulating both glucose and lipid metabolism (14, 26). Adiponectin exerts its metabolic effects by binding to two receptors: AdipoR1, which is ubiquitously expressed, and AdipoR2, which is found predominantly in the liver (11, 29). Transduction of the adiponectin signal by its receptors involves activation of AMP-activated protein kinase and the transcription factor peroxisome proliferator-activated receptor-α, which, overall, increases fatty acid oxidation and glucose uptake in skeletal muscle, while reducing glucose production in the liver (12–14). Although expression of adiponectin is normally stimulated by insulin, both adiponectin and its receptors are downregulated in obesity-linked insulin resistance, hyperinsulinemia, and type 2 diabetes (12, 13).

Adiponectin is also an important anti-inflammatory molecule and has been implicated in the pathophysiology of obesity-related diseases (6, 12–15, 18, 19, 25, 26). Adiponectin is a collectin-like molecule that contains a collagen-like domain at the NH2 terminus and a globular, C1q-like domain at the COOH terminus, and shares structural characteristics with both the complement factor C1q and the TNF families of proteins (11, 26). Adiponectin forms trimers, hexamers, and higher-molecular-weight, multimeric complexes, which are found in the circulation of healthy individuals at relatively high concentrations (26). In humans, decreased circulating concentrations of adiponectin are associated with obesity, metabolic syndrome, insulin resistance, hyperinsulinemia, and type 2 diabetes, as well as with cardiovascular disease (12, 19, 26). In contrast, elevated serum levels of the proinflammatory adipokynes, TNF-α, IL-6, C-reactive protein (CRP), and leptin are increased in these syndromes (12, 19, 26). It is currently thought that chronic, low-grade inflammation of adipose tissue, due to macrophage infiltration, causes release of these proinflammatory cytokines, which then inhibit the local production of adiponectin in the adipocyte (26). Macrophages are the major source of TNF-α production by adipose tissue, whereas both adipose tissue and macrophages contribute to circulating IL-6 levels (7, 15). Adiponectin, in turn, acts as an anti-inflammatory molecule by modulating macrophage function through the inhibition of phagocytosis as well as by inhibiting TNF-α and IL-6 production (7, 15).

Paradoxically, serum levels of adiponectin appear to increase in autoimmune diseases and/or in chronic inflammatory conditions that are unrelated to obesity, such as rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes, and Crohn’s disease. In these diseases, increased serum levels of adiponectin are correlated with increased serum levels of IL-6, CRP, TNF-α, and leptin (8). In this regard, adiponectin is thought to attenuate or modulate the effects of these proinflammatory adipokynes (8).

Serum levels of adiponectin are also increased in patients with chronic heart failure, end stage renal disease, and anorexia nervosa, all diseases associated with cachexia, or body wasting (1, 2). Likewise, long-term caloric restriction in adult mice increases circulating adiponectin and insulin sensitivity (26). One explanation for these differences is that increased serum adiponectin levels appear to be correlated with positive energy balance (obesity), whereas decreased serum adiponectin levels are correlated with negative energy balance (cachexia). Interestingly, calorie restriction in rodents and starvation in humans cause alveolar loss in the lung, whereas refeeding in rodents results in alveolar regeneration (16). Although pulmonary emphysema has been reported in patients with anorexia nervosa (5), no correlative studies on caloric restriction, alveolar loss, and serum adiponectin levels have been conducted in experimental animal models.

While the role of adiponectin in energy metabolism and inflammation has been studied in a number of different human disorders, organ systems, tissues, and cells, little is known about its role in chronic lung disease. Chronic obstructive pulmonary disease (COPD) is a major, worldwide disease that results in progressive, irreversible airflow obstruction, or limitation. It is caused by chronic inflammation of the airways and the lung parenchyma in response to inhalation of environmental particles and gases, resulting in chronic bronchitis and pulmonary emphysema. In general, acute exacerbations of COPD (most often in response to bacterial infection) are associated with increased serum levels of CRP, IL-6, TNF-α, leptin, and adiponectin, as well as with increases in other factors associated with bacterial inflammation and infection (27). Recently, differences in body weight and serum adiponectin levels have been associated with the two major clinical phenotypes found in COPD. Pulmonary emphysema, which is characterized by destruction of the respiratory bronchioles, alveolar ducts, and mature alveoli, has been associated with cachexia, whereas chronic bronchitis, which results in disruption of the bronchial epithelium, smooth muscle hypertrophy, and fibrosis, has been associated with obesity. In a Japanese study of normal and underweight patients with emphysema, serum levels of adiponectin were elevated in both groups and were correlated with increased serum TNF-α and IL-6 levels, as well as with severity of lung disease (hyperinflation) (24). In contrast, while serum levels of TNF-α, IL-6, and leptin were significantly higher in a group of obese patients diagnosed with both COPD and metabolic syndrome, serum adiponectin levels were reduced and were associated with a less severe pulmonary phenotype compared with normal weight COPD patients (21). These studies suggest that adi-
Bronectin may be a better indicator of underlying metabolic and/or systemic disease than of chronic pulmonary inflammation in these patients.

Recently, genetically engineered mouse models of adiponectin deficiency have been used to examine the role of adiponectin in insulin resistance. Although adiponectin-deficient mice exhibited elevated plasma TNF-α concentrations and disturbances in free fatty acid catabolism, there was no evidence of insulin resistance when the mice were maintained on a normal diet (28). Likewise, there were no differences in food intake, growth rates, body weight, fat stores, or in the livers, skeletal muscle, or hearts of these mice. When challenged with a high-fat/high-sucrose diet, however, these mice developed a severe, diet-induced, insulin resistance with delayed clearance of free fatty acid from the plasma (28). These effects were reversed by the administration of exogenous adiponectin (28).

In their recent article, Summer et al. (20a) have taken advantage of these mice to study the role of adiponectin deficiency in the lungs of mice maintained on a normal diet. Since there were no differences in body weight or glucose metabolism in these animals, the authors were able to study the potential role of adiponectin in pulmonary inflammation and remodeling without the presence of these confounding factors. The authors report a number of interesting new findings in this model, which suggest that adiponectin plays a role in lung development and/or remodeling through the modulation of TNF-α and metalloproteinase (MMP) activity in alveolar macrophages. The authors show that adiponectin was easily detected in the bronchoalveolar lavage fluid (BALF) of wild-type mice and that loss of adiponectin resulted in increased expression of TNF-α, MMP-2, and MMP-12, in the lungs of adiponectin-deficient mice. These changes were associated with alveolar simplification and/or enlargement during postnatal development of the lung and with an increase in the number of activated alveolar macrophages found in the BALF. The authors show that alveolar macrophages isolated from adiponectin-deficient mice had higher levels of TNF-α and MMP-12 activity, both of which have been implicated in emphysematous remodeling of the lung (2, 4, 10, 23, 27). Pretreatment with adiponectin blocked LPS-stimulated TNF-α production in both wild-type and adiponectin-deficient macrophages, demonstrating that adiponectin has an anti-inflammatory effect on these cells. Together, these results suggest that circulating levels of adiponectin may have a protective effect on the lung through inhibition of alveolar macrophage function.

When using gene-targeted mice to study emphysema, it is important to distinguish between 1) alveolar enlargement due to an abnormality in lung development, or morphogenesis, and 2) alveolar enlargement caused by destruction of mature alveoli, normally associated with adult pulmonary emphysema. Lung development in the mouse is not complete until after birth. At birth, the lung is still in the saccular stage of lung development. Subsequent alveolarization of the lung, which involves subdivision, or septation, of the larger alveolar sacs into smaller alveolar units, takes place between postnatal day 5 and day 14, peaking at day 14 during this period, there is rapid proliferation of both epithelial and endothelial cells, as well as increased synthesis and deposition of extracellular matrix (ECM) molecules, such as collagen, elastin, and fibronectin. Summer et al. (20a) have shown that alveolar enlargement was established in adiponectin-deficient mice between postnatal day 6 and day 18, i.e., during the final stage of lung development. Adiponectin is detected in adipose tissue and serum by E16.5, at the end of branching morphogenesis in the fetal mouse, whereas serum levels of adiponectin normally peak at birth in the saccular stage of lung development (9). mRNA transcripts for adiponectin receptors 1 and 2 are detected as early as E12.5 in the embryonic mouse lung (9, 29, 30). Therefore, its tempting to speculate that disruption of the adiponectin signaling pathway in cells of the developing lung may have contributed to postnatal alveolar simplification in this model, perhaps through impaired prenatal differentiation of the lipofibroblast, a cell that shares many molecular similarities with adipocytes and also plays a role in maturation of the lung (18). On the other hand, MMPs are tightly regulated during lung development, and imbalances in these proteinases might contribute to disruptions in lung development during the postnatal period through the degradation of ECM components (10). Normally, endogenous levels of MMP-2 decrease in the lung between postnatal day 5 and day 21, whereas endogenous levels of MMP-9 and MMP-12 increase during this period (10). Summer et al. (20a) have shown that alveolar enlargement in the adiponectin-deficient mice is correlated with increased expression of MMP-2 and MMP-12 by postnatal day 18, which suggests that alterations in TNF-α-induced expression of MMPs during the postnatal period of lung development interfered with normal alveologenesis in the lungs of these mice. Therefore, this model appears to more closely resemble disruption of alveolar formation due to chronic inflammation in the neonate rather than destruction of mature alveoli associated with adult emphysema.

In this context, manipulation of the adiponectin-deficient mouse should be useful for further studies of the lung, focused to lung development, injury, and remodeling in the neonatal period. For instance, it might be of interest (and of therapeutic value) to see if exogenous administration, or replacement, of adiponectin can prevent or, more importantly, reverse this phenotype. Likewise, would a high-fat/high-sucrose diet potentiate this phenotype and, in this case, would adiponectin administration have any effects? Administration of TNF-α-neutralizing antibodies (3) or crossing the adiponectin-deficient mouse to the MMP-12-deficient (10, 23), MMP-2-deficient (10), or TNF-α receptor-deficient (4, 20) mice might also be of use in clarifying the role of these factors in alveolar simplification of the lung. Finally, the generation of an inducible mouse model of adiponectin deficiency might be valuable in determining the role of adiponectin in inflammation and remodeling in the adult lung (as well as in the neonate) in response to challenge with hyperoxia, LPS, smoke, or infection.

REFERENCES
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Editorial Focus


