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Obesity: "Priming" the Lung for Injury

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Abstract

Acute lung injury (ALI) is a severe inflammatory condition that develops in response to local and systemic lung challenges. To date, specific risk factors for development of ALI remain poorly defined. Recent epidemiological studies have reported obesity as an important predisposing factor in the development of this condition. Although the pathogenic mechanisms linking obesity and ALI have not been well-elucidated, emerging scientific evidence has described factors secreted by adipose tissue that have important biological activities in lung and has suggested that altered secretion of these factors during obesity contributes to increased ALI susceptibility. The objective of this manuscript is to highlight recent clinical evidence supporting the association between obesity and ALI and to discuss the posited role for adipose tissue-derived factors in the pathogenesis of this condition.

Introduction

Acute lung injury (ALI) is a severe inflammatory lung process that develops in response to other serious medical conditions including sepsis, pneumonia, aspiration and trauma.[1,2] It is estimated that over 200,000 cases of ALI occur each year in the United States, and morbidity and mortality for this condition remain unacceptably high.[2]

It is generally accepted that ALI develops from excess production of pro-inflammatory factors that lead to local tissue destruction and to influx of proteinaceous fluid into the lung.[1,2] Despite significant advances in the understanding of this condition's pathogenesis, therapies to treat ALI are limited and consist largely of supportive measures. While additional treatments for established disease are clearly needed, it is now appreciated that prevention is equally important in limiting the burden of this condition. Prevention, however, requires knowledge of specific predisposing risk factors which contribute to the development of ALI.

One important predisposing condition recently identified in large epidemiological studies is increased body mass index (BMI).[3,4] Increasing BMI has been shown to correlate with the risk of developing both ALI and its most severe form, acute respiratory distress syndrome (Adjusted Odds ratio 1.72, 95% Confidence interval 1.25 to 2.36 for obese vs normal weight).[3] Moreover, this association has been found to persist even after adjusting for other ALI risk factors. Given the global increase in the prevalence of obesity, these findings suggest that BMI may be one of the most important modifiable risk factors for prevention of

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ALI. In fact, obesity is already being used in clinical prediction models to help physicians identify patients at high risk for developing ALI.[5]

Interestingly, despite increased incidence, clinical studies have not consistently demonstrated an association between BMI and mortality from ALI.[6,7] These findings suggest that obesity somehow "primes" the lung to develop ALI but does not negatively influence the natural history of established disease. Currently, the mechanisms contributing to this "priming" effect are largely unknown, and their elucidation will be important for developing effective strategies to reduce the prevalence of this life-threatening condition. This review will discuss the emerging scientific evidence implicating adipose tissue-derived factors in the pathogenesis of obesity-associated ALI.

Obesity, chronic inflammation and "priming" of the lung

Over the last decade, it has become well-established that obesity is a chronic inflammatory disease and that many health-related consequences result from its persistent, low-grade, systemic inflammation.[8–10] Chronic low-grade inflammation develops during obesity in part due to direct changes occurring in adipose tissue.[11] As body fat accumulates, alterations develop in adipose tissue's cellular composition. Infiltration by activated macrophages is a notable example of such a change, seen in the adipose of obese subjects.[12,13] These macrophages and adipocytes secrete large quantities of pro-inflammatory cytokines including IL-6 and TNF-α, factors whose chronic release into serum has been shown to contribute to the development of both obesity-related metabolic and cardiovascular diseases.[14,15]

Given the harmful effects of chronic inflammation on numerous systemic processes, it is tempting to speculate that elevated pro-inflammatory cytokine levels "prime" the lung of obese individuals for subsequent acute inflammatory response. This hypothesis is supported by clinical investigations demonstrating a strong correlation between transient elevations in pro-inflammatory cytokine levels (e.g. TNF-α, IL-6) and the risk of developing ALI in patients with critical illness (e.g. sepsis).[16–18] Additionally, experimental studies in mice have shown that acute increases in serum concentrations of TNF-α and IL-6 induce a wide range of effects in lung that mimic many of the early events of ALI including depletion of anti-oxidant stores, up-regulation of adhesion molecules on lung endothelium and enhanced susceptibility of endothelium to injury.[19,20] While these findings strongly support a link between acute inflammation and risk of developing ALI, future prospective clinical trials are needed to determine the association between chronic low-grade inflammation and incident ALI in obese individuals.

Adipokines in development of ALI

In addition to cytokines, adipocytes secrete numerous hormones called adipokines that are critical for controlling systemic inflammation as well as other key biological processes (e.g. metabolism).[21–23] However, during obesity, the secretory status of adipocytes is altered for a variety of unclear reasons, and the production of many (if not all) adiopkines is affected. The net result of these changes is an increase in production of adipokines that promote inflammation.[23] The impact of these hormonal changes on the development of many obesity-related diseases has been described previously in detail[23], but for the purposes of this review, discussion will be limited to the putative role of the pro-inflammatory adipokine leptin and the anti-inflammatory adipokine adiponectin in development of ALI.

Leptin

Leptin is a 16 KD protein that represents the product of the obese gene (*ob*) found on human chromosome 7.[24] It is synthesized and secreted almost exclusively by adipocytes and functions to down-regulate feeding behavior in the brain.[25] In lean, healthy individuals, leptin levels are low in the blood during fasting and transiently increase after consumption of food. Leptin levels also positively correlate with adipose tissue mass, with increased serum concentrations seen in obesity. This rise in circulating leptin is attributed to tissue resistance and the loss of leptin's anorexic response in the brain.[25]

Along with leptin's well-described role in energy homeostasis, accumulating evidence describes an important immune-modulating activity for this hormone.[26] This finding is consistent with leptin's structural homology to the IL-6 family of cytokines. The major immune-related actions of leptin are involved in augmenting pro-inflammatory responses. For example, leptin has been shown to stimulate production of pro-inflammatory cytokines, enhance phagocytosis and augment chemotaxis.[26]

Leptin's immune-related actions have implicated it in the pathogenesis of many obesity-related inflammatory diseases including ALI.[27–29] Evidence for such an association includes murine studies in which targeted deletion of either leptin or the leptin receptor protects against the development of hyperoxia and Bleomycin-induced ALI.[28,30] Furthermore, intra-tracheal administration of leptin in quantities observed in serum of receptor deficient mice induces many, if not all, of the pathological features characteristic of ALI in humans.[28] Although the role of leptin in development of human ALI has yet to be investigated, clinical studies have demonstrated that concentrations of leptin are increased in bronchoalveolar lavage fluid of patients with ALI when compared to mechanically-ventilated patients without this condition.[30] Taken together, these findings provide support for the concept that higher circulating concentrations of leptin contribute to ALI development and suggest that inhibition of leptin signaling may limit its development in obese individuals. Future prospective clinical studies are needed to confirm the association between leptin and ALI.

Adiponectin

Adiponectin is a 30 KD protein that is also secreted almost exclusively from adipose tissue and has both metabolic and immune-related activities.[31–33] However, in contrast to leptin, adiponectin is secreted constitutively at high concentration into the serum of lean, healthy individuals, while production decreases with increasing body fat [22]. Importantly, adiponectin expression is inhibited by oxidative stress and pro-inflammatory cytokines such as IL-6 and TNF-α, the presumed mechanism for the decreased production seen in obese individuals.[22]

Adiponectin was first described as an insulin-sensitizing hormone but is now equally recognized for its actions in modulating inflammation.[23] The predominant immune-related functions of adiponectin involve suppressing inflammation. Adiponectin is structurally similar to the collectin family of proteins which includes the serum complement factor C1q and the highly abundant surfactant proteins SpA and SpD in lung. These proteins partly function as pattern recognition molecules, able to bind oligosaccharide repeats on the surface of cells. Relevant to this, one key mechanism by which adiponectin has been shown to limit systemic inflammation is through aiding in the clearance of apoptotic cell debris by tissue macrophages.[34]

Adiponectin has additional immune-related functions mediated through receptor-dependent mechanisms. Currently, there are three well-characterized adiponectin receptors: adiponectin receptor 1, adiponectin receptor 2 and T-cadherin.[35,36] Binding of adiponectin to these

receptors has been shown to directly or indirectly activate various intracellular signaling pathways important in regulating metabolic and inflammatory processes.[35,37] Notably, adiponectin receptors are expressed in alveolar macrophages and endothelial cells within the lung, though their functional roles in lung homeostasis has yet to be determined.[38–40]

Recent findings indicate a key role for adiponectin in regulating lung immune responses.[39–42] For example, mice deficient in adiponectin have a propensity to develop spontaneous lung inflammation. Isolated alveolar macrophages and lung endothelium from these mice demonstrate upregulation of activated cell surface markers and express increased concentrations of pro-inflammatory genes, a pattern of "priming" similar to that seen in sepsis. These findings indicate that adiponectin acts to promote an anti-inflammatory phenotype in lung through tonic inhibition of immune and endothelial cell activation. This suggests that conditions leading to hypoadiponectinemia, such as obesity, may lead to "priming" of the lung, increasing its susceptibility to pro-inflammatory challenges. Consistent with this, a recent experimental study demonstrated that hypoadiponectinemia predisposes to development of lipopolysaccharide-induced ALI in mice.[43] The mechanisms leading to increased development of ALI have not been fully identified; however, it appears to relate in part to the loss of adiponectin's anti-inflammatory actions on lung endothelium.[43]

It is worth noting that a recent clinical study observed higher serum concentrations of APN were associated with increased mortality in patients with acute respiratory failure of diverse etiologies, a subset of which included ALI.[44] Although this report appears to contradict the hypothesis that hypoadiponectinemia predisposes to development of ALI, it is equally plausible, and probably more likely that higher serum adiponectin levels simply reflect the response to acute illness in patients with established disease and have little or no correlation with adiponectin levels prior to the onset of ALI. Regardless, these findings further support a possible role for adiponectin in lung immune homeostasis and provide the basis for future investigations examining its influence on the development of ALI.

Conclusion

Clinical studies indicate that obesity is an important risk factor for development of ALI, yet the mechanisms mediating this association are not well understood. Given the world-wide increase in the prevalence of obesity, elucidating such mechanisms is critical to reducing the burden of this life-threatening medical condition. Since it is well-established that adipose tissue-derived factors have a key role in regulating lung homeostatic mechanisms, it seems logical to begin focusing research efforts on understanding how altering their secretion, as occurs during obesity, affects the development of ALI. These studies will likely advance our understanding of ALI pathogenesis while also providing direction in the development of novel therapies to prevent and treat this disease.

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