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The Many Faces of Asthma in Obesity

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ABSTRACT

Obesity is a major risk factor for the development of asthma, and causes severe, uncontrolled disease that responds poorly to therapy. The obese state alters early onset allergic asthma, and leads to the development of a novel form of late onset asthma secondary to obesity. The presentation of early onset allergic asthma is altered through effects on immune function. Factors such as mechanical loading, effects of adipokines on airways, altered diet, insulin resistance and altered metabolism of nitric oxide likely all contribute to increased airway reactivity in obesity, causing late onset asthma in obesity. Obesity also alters responses to environmental factors such as ozone and particulate matter. Focused studies to understand the importance of these factors in the pathogenesis of airway disease in obesity will be essential to develop therapies to intervene in this new epidemic of airway disease. J. Cell. Biochem. 115: 421–426, 2014.

KEY WORDS: ASTHMA; OBESITY; AIRWAY REACTIVITY; ADIPOKINES

Obesity is a major risk factor for the development of asthma, with an estimated 250,000 new cases of asthma per year in the United States related to obesity [Beuther and Sutherland, 2007]. Not only is obesity a risk factor for the development of asthma, but obese asthmatics tend to have more severe disease, do not respond as well to standard therapy and have a nearly five-fold risk of hospitalization due to asthma exacerbations [Pradeepan et al., 2013]. The obesity epidemic is leading to a major change in the type of asthma that is commonly encountered in clinical practice, and an urgent need to understand the mechanisms that link these two diseases.

Recent studies suggest that there are at least two distinct phenotypes of asthma in obesity [Wenzel, 2012]. There is one phenotype of patient that tends to be younger at the time of diagnosis, and have a higher prevalence of atopy and allergic disease; these patients are likely to have classic early onset allergic asthma that is complicated by the subsequent development of obesity. There is another phenotype of obese asthmatic with later onset disease, and a much lower prevalence of allergic disease, which occurs more commonly in women; these individuals have late onset asthma arising as a consequence of obesity. The purpose of this article is to discuss the mechanisms that link both early onset asthma complicated by obesity, and late onset asthma that develops as a direct consequence of obesity.

ALLERGIC ASTHMA COMPLICATED BY OBESITY

Early onset allergic asthma is a disease process characterized by Th2 driven lymphocytic inflammation with increases in cytokines such as interleukins 4 and 5 that promote airway eosinophilia, and interleukin 13 leading to mucus hypersecretion [Wenzel, 2012]. In severe asthma, Th17 pathways may be induced and associated with airway neutrophilia [Wenzel, 2012]. The airway epithelium is also involved in the pathogenesis of asthma, producing cytokines that are involved in the initiation and maintenance of the immune response, and undergoing remodeling which contributes to the pathophysiology of the disease. Atopic asthma is an inflammatory disorder characterized by accumulation of eosinophils, mast cells and CD4+ T lymphocytes, and remodeling of the airway.

When obesity was first recognized to be a risk factor for asthma it was assumed that obesity was likely contributing to enhanced allergic airway inflammation. However, epidemiological studies suggest that markers of allergic airway inflammation are actually *decreased* in proportion to obesity [Komakula et al., 2007]. To understand the effects of obesity on early onset allergic asthma, it is important to understand the perturbations in adipose tissue and the immune system that occur in obesity.

Adipose tissue produces a number of cytokines and adipokines which may affect the airway such plasminogen activator inhibitor-1,

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monocyte chemotactic factor-1, interleukins 6 and 8, and adipokines such as leptin and adiponectin. The precise role of many of these mediators in the pathogenesis of allergic airway disease is far from well known, but there have been a number of studies focused on the potential role of adiponectin (which is decreased in obesity), and leptin (which increases in obesity) in allergic asthma.

Leptin increases Th1 cytokine production, and promotes CD4 (+) T lymphocytes differentiation toward a Th1 phenotype [Procaccini et al., 2012]. In-vitro data suggest that leptin may augment eosinophil function: leptin is a chemoattractant for eosinophils, and suppresses eosinophil apoptosis [Wong et al., 2007; Takeda et al., 2012]. These disparate effects of leptin, augmenting eosinophil function yet promoting Th1 differentiation, make it hard to predict the in vivo effect of leptin on allergic asthma. One study modeling the in vivo effect of leptin in allergic asthma found that allergen challenge in normal weight mice supplemented with leptin increased serum IgE and airway reactivity, but had no significant effect on OVA-induced eosinophil recruitment to the airway [Shore et al., 2005]. This suggests that effects of leptin on asthma are not simply related to increases in allergic airway inflammation. Leptin may increase airway reactivity through other effects on the airway, as discussed in more detail below.

Another adipokine which has been studied for its role in allergic asthma is adiponectin. Adiponectin is significantly reduced in obesity. There have been a number of epidemiological studies investigating the relationship between serum adiponectin and asthma, many suggest that serum adiponectin is inversely associated with asthma (particularly among women who smoke) [Sood et al., 2012]. Adiponectin is known to ameliorate many inflammatory pathways by increasing the synthesis of interleukin 10, decreasing production of tumor necrosis factor-α and interleukin 6, and inhibiting activation of NF-κB [Villarreal-Molina and Antuna-Puente, 2012]. Mouse studies of increasing adiponectin in allergic asthma using exogenous adiponectin or over-expression suggest that adiponectin may decrease acute, but not chronic allergic inflammation [Shore et al., 2006; Verbout et al., 2013]. Adiponectin deficient mice develop increased allergic airway inflammation compared with wild-type mice in response to chronic allergen challenge associated with remodeling of pulmonary arteries [Weng et al., 2011]. These mouse studies suggest that decreases in adiponectin, as occurs in obesity, might exacerbate acute and chronic airway allergic inflammation and may also affect the pulmonary vasculature.

It is hard to reconcile mouse data suggesting that adiponectin deficiency augments allergic inflammation, and yet airway eosinophilic inflammation is reduced in proportion to BMI in people with asthma. These contradictory observations may be related to the fact that most human studies have included multiple phenotypes of obese asthmatics, in the future it will be important to separate out different phenotypes of obese asthma to understand the effects of adiponectin on allergic airway inflammation and disease activity in human asthma.

Obesity also has profound effects on the immune system that may be important in the pathogenesis of allergic asthma. As obesity develops, enlarging adipocytes secret chemokines that attract leukocytes into adipose tissue: there is accumulation of pro-inflammatory "M1 like" or "classically activated" macrophages producing pro-inflammatory mediators such as tumor necrosis factor-α, interleukin 6, interleukin 1β, and interleukin 12 [Mathis, 2013]. Mast cells and neutrophils also increased in adipose tissue in obesity [Liu et al., 2009; Talukdar et al., 2012]. In contrast, regulatory T cells decrease in obesity [Feuerer et al., 2009]. Adipose tissue in obesity is infiltrated with cells of the immune system that produce a pro-inflammatory change, contributing to medical complications of obesity such as the metabolic syndrome. Obesity appears to have complex systemic effects on adaptive immunity outside of the localized changes in adipose tissue. T and B-cell function may be impaired [Sato Mito et al., 2009] along with changes in proliferative capacity and T cell numbers [Yang et al., 2009]. Obesity produces profound changes in the immune system, and so it is perhaps to be expected that it will affect a complex immune disease such as allergic asthma.

There have been important insights into the effects of obesity on allergic asthma gained from studies of mouse models of obesity and allergic asthma [Mito et al., 2002; Johnston et al., 2007; de Vries et al., 2009; Calixto et al., 2010; Saraiva et al., 2011; Dietze et al., 2012; Lintomen et al., 2012], and these are summarized in Table I. Most studies show increased serum IgE in response to allergen challenge, and increased airway reactivity in the obese mice; however, most show reduced airway eosinophilia, and T cell function is reduced in mediastinal draining lymph nodes (but not the spleen). A few studies paradoxically report small increases in airway wall eosinophila, and have suggested that recruitment to the airway itself may be altered in obesity [Calixto et al., 2010; Lintomen et al., 2012]. A recent human study suggested that airway wall eosinophilia was increased in obese asthmatics despite low levels of sputum eosinophils, supporting an abnormality of eosinophil trafficking in obesity [Desai et al., 2013]. The animal studies suggest that the relationship between allergic asthma and obesity may depend on the both the mouse models of obesity and allergic asthma. The implication for clinical studies is that careful phenotyping of obese asthmatics will be necessary to understand the relationship between obesity and allergic asthma.

Obesity affects adaptive and innate immunity, and alters production of adipokines such as leptin and adiponectin. This is likely to have complicated effects on allergic airway disease (Table II).

TABLE I. Studies of Allergic Airway Disease in Obese Mouse Models

	Asthma model	Mouse	Main findings
Mito et al. [2002]	OVA	C57BL/6 high fat diet	Increased mast cells in tracheal mucosa of obese mice
Johnston et al. [2006]	OVA	Ob/Ob and Db/Db	Airway reactivity increased in obese mice airway inflammation decreased in obese mice
de Vries et al. [2009]	OVA	C57BL/6 high fat diet	Reduced airway eosinophilia and mediastinal T cell cytokine production in HFD mice
Calixto et al. [2010]	OVA	C57BL/6 high fat diet	Increased peribronchilar eosinophils, Delayed transit into airway
Saraiva et al. [2011]	OVA	A/J mice, HFD	Increased BAL eosinophils, Collagen and α-SMA
Lintomen et al. [2012]	OVA	Ob/Ob	Increase lung tissue, blood and bone marrow eosinophils
Dietze et al. [2012]	OVA	AKR/HFD	Increased serum antibodies, no difference in physiology, increase in airway eosinophils

TABLE II. The Myriad Effects of the Obese State on the Pathogenesis of Asthma in Obesity

Early onset TH2 high asthma	Late onset TH2 low asthma
Abnormal eosinophil trafficking	Innate increased responsiveness
Altered T-cell function	Mechanical loading
Factors contributing to innate increased responsiveness	Effects of adipokines on airway
Factors contributing to altered response to challenge	Diet
	Insulin resistance
	Altered NO metabolism
	Altered response to environmental challenge
	Ozone
	Particulates

Future studies, particularly in humans, will need to carefully phenotype obese asthmatics to allow a better understanding of the effects of obesity on allergic airway disease.

LATE ONSET ASTHMA DEVELOPING CONSEQUENT TO OBESITY

Late onset asthma developing in the setting of obesity appears to represent a unique phenotype of asthma. We are still in the very early stages of developing an understanding of the mechanistic basis underlying this form of airway disease. This type of asthma appears to be characterized by late onset disease with lower markers of airway eosinophila and Th2 inflammation than are typical of early onset allergic asthma, and this form of asthma is more common in women than men. There are a number of factors that could contribute to innate increases in airway reactivity with obesity, and also factors that could contribute to increased airway responses to environmental insults such as ozone, we will discuss both increased innate responsiveness and increased responses to environmental factors under this classification of late onset asthma developing consequent to obesity.

Airway hyperresponsiveness in non-atopic asthma could be caused by mechanical changes in the airway. Obese patients have reduced functional residual capacity because of the changes in mechanical loading of the chest wall and abdomen with adipose tissue. Breathing at the low lung volume increases airway responsiveness [Skloot et al., 1995]. It has been hypothesized that breathing at low lung volumes may lead to increased actin–myosin cross-linking in airway smooth muscle, effectively making the muscle stiffer, contributing to airway disease in obesity [Fredberg, 2000]. Tepper et al. have shown that stretch of smooth muscle is a critical determinant of airway reactivity in vivo, and in vitro modulates the expression of proteins in airway smooth muscle [Desai et al., 2011]. Exogenous stretch of smooth muscle with continuous positive airway pressure decreases airway reactivity in animal models, and in human asthmatics [Busk et al., 2012; Xue et al., 2013]. Thus breathing at low lung volumes, as occurs in the setting of obesity, promotes airway reactivity through effects on smooth muscle function.

Obesity may also have direct effects on airway caliber. Obesity certainly increases airway resistance through reducing lung volume, but airway caliber also appears to be reduced independently of reduction in lung volume [King et al., 2005]. Obese individuals also breathe close to the closing volume of the airways, which may promote airway closure during normal tidal breathing [Mahadev et al., 2013]. We have found that airway reactivity in obese late onset asthmatics is characterized particularly by airway closure which improves with weight loss. These data suggest that obesity may have direct effects on airway caliber and airway function that promote airway closure leading to airway disease in the setting of obesity.

Mediators produced by adipose tissue may be important in the pathogenesis of late onset asthma in obesity. We have previously reported that markers of adipose tissue metabolic inflammation are increased particularly in visceral fat of patients with this from of asthma [Sideleva et al., 2012]. This was not related to enhanced airway inflammation, suggesting that these metabolic mediators could be having direct effect on the airway. Indeed, leptin was significantly increased in visceral adipose tissue of obese asthmatics, and this was related to airway reactivity. Many studies have reported elevated serum leptin to be associated with asthma in obesity [Sood, 2010]. Prior work suggests that leptin may have multiple effects on the lung: leptin appears to be involved in lung development; leptin deficient *ob/ob* mice have decreased lung volume and alveolar surface area [Huang et al., 2008]; which increases with leptin replacement; mice deficient in leptin receptor have decreased proliferation of tracheal epithelium [Tsuchiya et al., 1999]; leptin has pro-fibrotic effects in a bleomycin mouse model [Jain et al., 2011]; and multiple cell type in the lung express receptors for leptin suggesting that leptin may have pleotropic effects on the lung [Vernooy et al., 2013]. Leptin may also be having some immuno-modulatory effects in these obese asthmatics; Lugogo et al. [2012] demonstrated that primary alveolar macrophages derived from the obese subjects with asthma are sensitive to leptin and demonstrate a pro-inflammatory phenotype. How these diverse actions of leptin could be involved in the pathogenesis of airway disease in the setting of obesity is under intense investigation.

Other factors produced by adipose tissue may play an important role in the increased airway responsiveness of obesity. TNF-α is increased in obesity. Signaling through TNFR2 may be critical for innate airway responsiveness in obesity: obese mice deficient in TNFR2 do not have the enhanced airway reactivity characteristic of obese mice [Williams et al., 2013], whereas those deficient in TNFR1 (with higher serum levels of TNF-α) have increased airway reactivity [Zhu et al., 2012]. Signaling through TNFR2 appears to increase expression of IL17-A, endothelin 1, and trkβ, suggesting that these pathways may be important in the innate airway responsiveness characteristic of obesity [Williams et al., 2013]. Much work remains to be done to understand the direct effects of adipose tissue derived adipokines and cytokines on the airway.

Metabolic changes may contribute to late onset asthma in obesity. The metabolic syndrome of insulin resistance, glucose intolerance, type 2 diabetes and dyslipidemia, is due to decreased tissue sensitivity to insulin. Many studies have found associations between insulin resistance and impaired lung function. There are many potential mechanisms that may link insulin resistance and asthma. Insulin acts on the nitric oxide–arginine signaling pathway regulating NO and endothelin-1 release. Depletion of nitric oxide in mice increases AHR

and collagen deposition [Wells et al., 2009]. Holguin et al. [2013] have shown that exhaled nitric oxide is decreased particularly in late onset obese asthmatics, and this is related to adverse effects on lung function, thus bioavailability of NO may be involved in the pathogenesis of asthma in obesity. Insulin also effects proliferation and differentiation of airway smooth muscle cells and fibroblasts [Papagianni et al., 2007], and can induce airway smooth muscle contraction via PI-3K/Akt pathway [Dekkers et al., 2009]. The insulin resistance that characterizes the metabolic syndrome may contribute to the development of late onset asthma in obesity.

Yet another factor that may contribute to the pathogenesis of asthma in obesity is diet. The obesity epidemic is not simply related to increased intake of nutrients, but with profound changes in diet and lifestyle. Typical Western Diets are high in saturated fatty acids. Wood et al. [2011] have shown that airway neutrophilia is increased, and response to bronchodilator is decreased following a meal high in saturated fats. This may be related to signaling through TLR-4 pathway inducing subsequent NFκB inflammatory pathways. Vitamin D is another dietary factor that has generated much interested for its potential role in obesity [Paul et al., 2012]. Vitamin D levels tend to be lower in obesity, and this may have pleotropic effects on pro-inflammatory pathways pertinent to asthma. While there have been many observational trials linking diet and asthma, there are few prospective-controlled interventional studies on diet and asthma. There have been a number of small studies suggesting that weight loss maybe a useful intervention in the treatment of obese asthma [Dixon et al., 2011; Scott et al., 2012] but the role of manipulating individual nutrients is unclear. One recent study suggested that increasing anti-oxidants in the diet may improve asthma control [Wood et al., 2012], the results of more controlled trials in different patient populations will be important to understand the role of specific nutrients in the pathogenesis of obesity associated asthma.

As discussed above, a number of different pathways may contribute to increased airway responsiveness in obesity; obesity may also alter responses to environmental insults, further contributing to the development of late onset asthma in obesity. Recent human studies suggest that the obese have increased responses to ozone and particulate matter [Alexeeff et al., 2007; Lu et al., 2013]. Shore et al. have modeled airway disease in obesity using ozone exposure in obese mice. Inflammatory responses to acute ozone exposure are increased in obese mice [Johnston et al., 2006]. Ozone induces IL13 and IL5 production in obese mice and airway neutrophilia. This airway neutrophilia (but not increased responsiveness) can be inhibited by blocking IL13. TNFR2 deficient obese mice exposed to ozone also have decreased airway neutrophilic inflammation, but actually have increased airway reactivity (which differs from the innate airway responsiveness characteristic of obesity noted above) [Williams et al., 2013]. Adiponectin deficiency in obesity may be another important factor altering response to ozone; sub-acute ozone exposure increases airway neutrophilia through an IL17 dependent mechanism [Kasahara et al., 2012]. All this suggests that the exposure to an agent that induces airway responsiveness likely acts through different pathways than those that induce increased airway reactivity in "naïve" obese subjects, and that environmental air pollution may be more problematic in obese than lean people.

CONCLUSIONS

Obesity is a complex disease state which produces pleotropic effects on the immune system, alters circulating factors which may affect the lung, and produces mechanical derangements which change pulmonary physiology. Obesity alters the pathogenesis of early onset allergic asthma, and also produces a unique phenotype of late onset asthma. Obesity also alters response to environmental perturbations such as ozone and particulate matter. The challenge will be to understand how the multiple perturbations associated with obesity interact to produce airway disease in obesity, and with this knowledge to intervene in this new patient population.

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